

Environmental Pollutants Used in Textiles, Food Packaging May Contribute to Poor Kidney Health

Effects may be especially dangerous for children

By Tracy Hampton



ertain highly pervasive environmental pollutants may have a variety of negative effects on kidney health, according to an analysis of all relevant studies published on this topic to date.

In the Clinical Journal of the American Society of

Nephrology analysis, researchers assessed studies on perand polyfluoroalkyl substances (PFAS), which are a large group of manufactured non-biodegradable compounds used to provide stain and grease repelling properties to consumer products including textiles, papers, and food packaging. PFASs are also used in aqueous fire-fighting foams. Recently, they have been detected on military bases, as well as in public water supplies from industrial contamination and in agricultural and crop products.

Because PFASs have been detected in soil, air, and water from all regions of the world, with bioaccumulation across entire ecological food chains, the compounds are now recognized as globally ubiquitous pollutants.

"The kidneys are very sensitive organs, particularly when it comes to environmental toxins that can get in our bloodstream," said John Stanifer, MD, a nephrologist and clinical researcher at Duke University. "Because so many people are now exposed to these PFAS chemicals, and to the newer, increasingly produced alternative PFAS agents such as GenX, it is critical to understand if and how these chemicals may be contributing to kidney disease."

Dr. Stanifer and his colleagues systematically searched

PubMed, EMBASE, EBSCO Global Health, World Health Organization Global Index, and Web of Science for studies from 1990 to 2018 on the epidemiology, pharmacokinetics, or toxicity of PFAS exposure and kidney-related health.

In the 74 studies identified (21 epidemiologic, 13 pharmacokinetic, and 40 toxicological studies), there were many adverse outcomes linked to PFAS exposure, including worse kidney function and dysregulated pathways linked to kidney disease. Those dysregulated pathways include oxidative stress pathways, peroxisome proliferators-activated receptor pathways, and NF-E2-related factor pathways.

Toxicology studies showed tubular histological and cellular changes from PFAS exposure, and pharmacokinetic studies demonstrated that the kidneys are the major routes of elimination.

"By searching all the known studies published on the topic, we concluded that there are several potential ways in which these chemicals can cause kidney damage," said Dr. Stanifer. "Further, we discovered that there have already been multiple reports suggesting that these chemicals are

Continued on page 3 💙

KIDNEY WEEK SCIENTIFIC SESSIONS

THURSDAY

Imaging Cellular Structure and Dynamics from Molecules to Organisms

State-of-the-Art Lecture: Eric Betzig

Cellular and Molecular Mechanisms of Action of Klotho *Jack W. Coburn Endowed Lectureship:* Chou-Long Huang

Defining Structure Function Relationship in Glomerular Failure across Disciplines and Diseases Barry M. Brenner Endowed Lectureship: Lawrence Holzman

Consolidation: Friend or Foe? Christopher R. Blagg, MD, Lectureship: Janis M. Orlowski

FRIDAY

Cell Atlases as Road Maps to Human Disease State-of-the-Art Lecture: Aviv Regev

Vascular Complications in Autosomal Dominant Polycystic Kidney Disease (ADPKD) Robert W. Schrier Endowed Lectureship: Terry J. Watnick

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Designing Innovative Alternatives to RRT: Patients as Partners Celeste Castillo Lee Memorial Lectureship: David M. White

SATURDAY

Sickle Cell Anemia: Yesterday, Today, and Tomorrow State-of-the-Art Lecture: Griffin P. Rodgers

Evolving Complexity of the Glomerular Basement Membrane

Michelle P. Winn Endowed Lectureship: Rachel Lennon

SUNDAY Improving Health Outcomes in the Era of Data Ubiquity State-of-the-Art Lecture: Robert M. Califf

Using Population Data to Inform Patient Care in Nephrology Donald W. Seldin Young Investigator Award: Morgan Grams

Inside

CKDu

A team from two NIH institutes discusses possible contributors to CKDu and the condition's continued increase around the world

ASN in Review

From establishing KidneyX to adding midcareer awards to its awards portfolio, ASN has made progress toward reaching its strategic plan goals.

Findings

Levosimendan improves GFR in cardiorenal syndrome





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¹Brunelli, SM et al. 2018. J Am Soc Nephrol. Apr;29(4):1336-1343. ²Hymes, JL et al. 2017. Am J Kidney Dis. Feb;69(2):220-227.

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ASN Kidney Week-New in 2018

Transforming Nephrology through Precision Health

Early Programs

ASN offers 10 Early Programs on Tuesday, October 23, and Wednesday, October 24, preceding the Annual Meeting (October 25–28).

Here are the new or biennial Early Programs:

- Advances in Research Conference: -Omics, Organoids, and Organs-on-Chips: Innovation Through Collaboration This year's conference presents critical recent advances in the biology of organoids and organs-on-chips as they relate to the human kidneys. The conference will include descriptions of how these in vitro systems can incorporate pharmacogenetics, gene expression profiles, multiple "-omics" technologies, and biomarker discovery and translation, all for enhanced molecular understanding of the human kidneys in health and disease.
- Clinical Nephro-Pharmacology Across the Spectrum of Kidney Diseases

This program is designed to review fundamental issues related to clinical pharmacology in kidney diseases, as well as to improve knowledge and skills in the areas of drug dosing and pharmacology across the spectrum of kidney function and disease states. Special focus is given to anticoagulants and the toxicity of cancer medications.

Evaluation and Management of Kidney Stones Nephrologists are often called to evaluate and manage patients with recurrent kidney stones. This program reviews the current

state-of-the-art with respect to evaluation and management of all forms of stone disease. Topics include the role of stone imaging modalities, as well as indications, risks, and benefits of various surgical approaches for stone removal.

 Polycystic Kidney Disease: Translating Mechanisms into Therapy

Recent advances in the pathophysiology and therapeutics for PKD will be the focus of this program. Reviews of recently completed clinical trials, including vasopression receptor antagonists, will be discussed, as well as new strategies to assess risk for ADPKD progression, which will likely play a key role in identifying patients who may benefit from therapeutic interventions.

Expanded Fellows-in-Training Bowl

Thursday, October 25, and Friday, October 26

Which nephrology training team will reign supreme? This year's competition is a two-day, single-Elimination Round on Thursday at 10:30 a.m. Eight teams will compete in Nephron Challenges that test medical knowledge and content retention—and buzzer skills.

- Semi-Finals on Friday at 10:30 a.m.—
 4 teams compete in case-based debates.
- Finals on Friday at 11:30 a.m.—

Final 2 teams complete in Nephron Challenges.

Visit the Exhibit Hall, and cheer on your favorite teams!

ASN TV

We are excited to announce the launch of ASN TV at Kidney Week 2018. ASN TV will bring a new element to the conference through the use of video to enhance your experience. View daily episodes with conference news (e.g., interviews, session highlights, attendees' insights and reactions) and in-depth leadership case studies.

ASN TV will be on screens around the convention center as well as available on select hotel channels. This content is available on the ASN website, on YouTube, as well as across social media channels.

iPosters

Your Annual Meeting registration includes complimentary access to iPosters, a cutting-edge technology resource that transforms the poster hall into an online and mobile experience—both during and after Kidney Week. iPoster features include:

- Interactive interface to browse uploaded posters
- Keyword search and multiple indices to quickly find uploaded posters
- Various communication tools

Access iPosters at www.asn-online.org/KWiPosters.

In addition to the new items here, don't forget to check out these events:

- Welcome Reception in the Exhibit Hall on Thursday, 6:30–7:30 p.m.
- Daily state-of-the-art lectures during the plenary sessions (Thursday–Sunday, 8:00–9:30 a.m.)
- Daily poster presentations with more than 3000 posters (Thursday–Saturday, 9:30 a.m.–2:30 p.m.)
- ASN Communities Lounge in the Exhibit Hall (Thursday–Saturday, 9:30 a.m.–2:30 p.m.)

Environmental Pollutants

Continued from page 1

associated with worse kidney outcomes."

Fan Fan Hou, MD, PhD, a researcher at Southern Medical University, in Guangzhou, China, noted that the findings add to previous studies on PFAS compounds.

"The increase in environmental pollution, a result of accelerated industrialization and urbanization worldwide, has become a global health challenge. Although there is evidence for the association between exposure to PFAS and kidney cancer, the impacts of PFAS exposure on non-cancer kidney outcomes are inconclusive," said Dr. Hou, who was not involved with this research. "Large prospective cohort studies with accurate exposure measurement and long follow-up period are required to better understand the renal adverse effect of PFAS."

Disproportionate effect on children, ethnic and racial minorities

Experts also stress that it is concerning that children are exposed to PFAS agents to a greater extent than adults. Lifecourse studies will be critical to understand the long-term health impact of this exposure.

"The study of the kidney effects of perfluorinated chemicals is especially relevant in pediatrics," said Howard Trachtman, MD, who is a pediatric nephrologist at NYU Langone Health. "Because of the persistence of these chemicals in the body for extended periods of time and the association between exposure and reduced GFR that we have documented in healthy pediatric participants in NHANES, children and adolescents may be especially vulnerable to the adverse renal consequences of exposure to perfluorinated chemicals over a lifetime."

Environmental risk factors contribute to the development and perpetuation of health disparities around the world, Dr. Langone and his team noted. Contaminants have been linked to higher burdens of chronic diseases and cancers, maternal and neonatal mortality, and developmental toxicity. Dr. Langone was not involved with the study.

Studies are needed to understand the role that environmental exposure to PFAS chemicals may play in driving kidney disease disparities, Dr. Langone said.

"Chronic kidney disease, which affects more than 30 million people in the United States and more than 500 million people across the world, disproportionately burdens ethnic and racial minorities and people living in poverty; yet exactly what causes these disparities is not fully known," he said.



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Kidney News Wins Design Award

ASN Kidney News has received an award honoring outstanding graphic communication for a healthcare publication.

Graphic Design USA's (GDUSA) 2018 Health + Wellness Design Awards honor the best of graphic design in the healthcare industry, including traditional medicine and healthcare, healthy lifestyles and nutrition, public health and community education, and the aging of society. Among the most selective of graphic design competitions, GDUSA noted that only 150 of the 1600 entries in the 2018 competition made the cut for a Health + Wellness Design Award.

"The 2018 winners showcase features 150 projects encompassing the big picture of health and wellness," GDUSA said in a statement. "For five decades, GDUSA has presented competitions that focus on areas of growth and opportunity for graphic design. In 2018, that's the perfect description of health and wellness, one of the fastest-growing segments of the economy and the epicenter of the national conversation."

Kidney News underwent a comprehensive redesign that launched in January 2018.

"With [the January 2018] issue, we present a fresh new design for the magazine, including a more eye-catching cover and easier navigation," *KN* Editor-in-Chief Richard Lafayette, MD, wrote at the time. "The table of contents has been refreshed to make it easier to find the information you desire. And we wished this to become a more visual experience, so illustrations and supporting figures and tables will be more prominent and frequent. We hope the new colors and fresher formatting are appealing as well."

KN's winning entry will be published in the Health + Wellness Design showcase, with full creative credits displayed in the print edition magazine, website, and digital app.

A sample is printed here.

ASN would like to thank *Kidney News* Design Editor Lisa Cain for her expert guidance and leadership in the redesign process.





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The PRISMAFLEX System is one of the best tools we've used in our ICU. And with Baxter's support, we can do so much for our patients now that we've implemented our Super User Program and CRRT Task Force."

Juan Carlos Aycinena, MD

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ASN IN REVIEW

ASN progress in achieving its five strategic goals since last year's Kidney Week

GOAL 1

Lead the kidney community by focusing on education, communications, policy, and collaboration

Announcing the Hidden Epidemic of Kidney Diseases Worldwide

More than 850 million people worldwide have some form of kidney disease—roughly double the number of people who live with diabetes and 20 times more than the prevalence of cancer. The global burden of kidney diseases was determined through concerted effort by the American Society of Nephrology (ASN), the European Renal Association—European Dialysis and Transplant Association (ERA-EDTA), and the International Society of Nephrology (ISN).

In addition to using high-impact data to communicate the kidney disease pandemic and raise awareness of kidney diseases, ASN/ERA-EDTA/ISN are collaborating to compare the realities across the global nephrology workforce and to prioritize ethical issues confronting nephrologists.

Transitioning to a New JASN EIC, Launching an Open Access Journal

JASN remains the most cited nephrology journal that publishes original research about the kidney and kidney diseases. Under the leadership of new Editor-in-Chief Josephine P. Briggs, MD, JASN introduced a new cover with a prominently displayed short Table of Contents, began publishing Letters to the Editor, and improved the time from submission to publication. *CJASN* introduced monthly Patient Voice editorials to provide the patient perspective on research articles, and now includes Visual Abstracts for all research articles. *CJASN's* impact factor rose by more than 20% over the past year.

The online versions of both journals were redesigned to provide easier navigation, greater search capability, and safer pay-per-view functionality.

In 2020, ASN will introduce Kidney360, an open access, online-only general kidney journal. Kidney360 will facilitate timely and broad dissemination of global kidney science, encourage data sharing, and incorporate innovative publishing tools to maximize discourse within the kidney field.

Expanding Social Media, Communities

ASN's social media presence is strong and growing. ASN's main twitter page @ASNKidney experienced a 28% growth in followers since 2017; @ASNadvocacy, @KidneyNews, @JASN_News, and @CJASN experienced even higher levels of growth. The society launched a twitter page for @Kidney_X in April 2018. #AskASN Twitter chats remain popular, attracting a growing number of nephrology fellows and trainees. ASN's social media users are mostly from the United States, the United Kingdom, Mexico, Canada, Spain, and India.

ASN Communities allow kidney health professionals to network, collaborate, and discuss issues facing the specialty on an online platform. ASN members from more than 130 countries composed approximately 17,000 posts across 19 Communities and Exchanges, led by 47 community leaders.

Broadening the Board Review Course & Update (BRCU)

BRCU now has an expanded leadership team of two Education Directors and an Education Deputy Director. The course's leaders have increased the number of female speakers from 4 in 2017 to 10 in 2018 and added a lecture, "How to Study for the Boards; How to Approach a Board Question."

Each week for the eight weeks between the conclusion of BRCU and the fall American Board of Internal Medicine Nephrology Board examination, ASN will email course participants a selection of nephrology "pearls of wisdom"—five things to know about important board topics. Each email will include seven "pearls" plus one nephrology diagnostic algorithm to help clarify thinking and focus studying.

GOAL 2

Transform kidney research through discovery and innovation to prevent, treat, and cure kidney diseases

Establishing KidneyX to Spur Innovation

Established in April 2018 with a Memorandum of Understanding between ASN and the U.S. Department of Health & Human Services, KidneyX seeks to improve the lives of the 850 million people worldwide currently affected by kidney diseases by accelerating the development of drugs, devices, biologics, and other therapies across the spectrum of kidney care including prevention, diagnostics, and treatment.

KidneyX will engage a community of patients, researchers, innovators, and investors to develop breakthrough therapies through a series of prize competitions. The first KidneyX prize competition, aimed at improving kidney replacement therapies for patients, launches on October 25, 2018. Learn more at KidneyX.org.

Continuing to Build the Kidney Health Initiative (KHI)

A public-private partnership among ASN, the U.S. Food and Drug Administration, and the nephrology community, KHI now includes more than 90 organizations and companies, making it the largest collaborative in the kidney arena. KHI workgroups and the KHI Patient and Family Partnership Council advance the collaborative's mission to enhance patient safety and foster innovation in kidney diseases.

KHI's signature initiative, "Developing a Roadmap for Innovative Alternatives in Renal Replacement Therapy," will be submitted to a top nephrology journal for publication in the coming months. KHI published eight additional articles this year, including "Prioritizing Symptoms of ESRD Patients for Developing Therapeutic Interventions" in the *Clinical Journal of the American Society of Nephrology*. Four new projects were launched, and work continues for six ongoing projects. To learn more, visit www.kidneyhealthinitiative.org.

Implementing Recommendations from the ASN Innovation and Discovery Task Force

The ASN Innovation and Discovery Task Force is working on several initiatives to support future innovators in nephrology, to educate clinicians about breakthrough treatments and approaches, and to identify mechanisms and funding sources to generate evidence for and success of cutting-edge clinical research about kidney diseases. Initiatives include support for the development of a clinical trial finder, mandatory clinical trial training during nephrology fellowships, and seed funding and advisement to small companies to help ideas progress to the proof-of-concept stage.

Supporting the Future through the ASN Foundation for Kidney Research

At ASN Kidney Week 2018, the ASN Foundation for Kidney Research will announce the results of the Securing the Future Campaign. The campaign raised more than \$22,600,000 in gifts and pledges from ASN, Keryx Biopharmaceuticals, Inc., Amgen, and individual donors. These funds were used to endow five career development grants in 2018, including one Joseph V. Bonventre Grant, two Carl W. Gottschalk Grants, one John P. Merrill Grant in Transplantation, and one Norman J. Siegel Research Scholar Grant.

GOAL 3

Encourage every kidney health professional in the world to contribute to, and benefit from, ASN

Expanding the ASN-Amos Medical Faculty Development Program

To address the shortage of scholars from historically disadvantaged backgrounds with academic and research appointments in nephology, ASN partners with the Robert Wood Johnson (RWJ) Foundation to administer the ASN–Amos Medical Faculty Development Program (ASN-AMFDP) award. The program offers four-year postdoctoral research awards. The first recipient is continuing his work on gene discovery in African Americans with familial focal segmental glomerulosclerosis.

ASN and RWJ announced a second ASN-AMFDP award finalist to be honored in 2019: Rasheeda Hall, MD, whose research aims to develop an evidence-based approach to deprescribe potentially inappropriate medications for older dialysis patients.

Initiating the LGBTQ and Ally Member Reception at Kidney Week; #IAmASN Promotion

ASN holds its first ever lesbian, gay, bisexual, transgender, queer and questioning (LGBTQ) and ally member reception at Kidney Week 2018. The event is meant to be an evening of networking and gathering to discuss ways of serving LGBTQ participants in ASN Kidney Week and supporting LGBTQ members of the kidney community.

In another effort to highlight the diversity of ASN's membership, #IAmASN buttons will be available at the ASN Services booth for pickup and display. Attendees are encouraged to put on a button, take a picture, and share on twitter @ASNKidney with the #IAmASN hashtag.

Providing Travel Support for the NIDDK NMRI and Exhibiting at SNMA and LMSA

ASN provides travel support to individuals conducting kidney-related research to ensure their attendance at the National Institute of Diabetes and Digestive and Kidney Diseases Network of Minority Health Research Investigators annual workshop. Over the past 4 years, ASN has supported 58 investigators.

ASN exhibited at the Latino Medical Student Association annual meeting for the first time in 2018 and, as it has done for the past 5 years, at the Student National Medical Association annual meeting. Fifty students interested in nephrology were provided ASN membership through this outreach to medical students at the Latino and Student National Medical Association meetings in 2018.

Partnering with Renal Fellow Network Blog, Increasing ASN Membership

Launched in 2008 as a forum for fellows to share experiences in training and kidney care, the Renal Fellow Network quickly grew and doubled its monthly visitors over a 7-year period. On the blog's 10th anniversary, ASN will partner with Renal Fellow Network to further increase its reach. Two nephrology or postdoctoral fellows will now serve 2-year terms as coeditors under the guidance of faculty advisors. The blog will also look to expand its pool of contributors to include PhD students, postdoctorates, medical students, and residents.

ASN membership shows continued growth. Nearly 20,000 kidney health professionals in more than 130 countries now contribute to ASN as members. Since 2014, membership has grown 30%.

GOAL 4

Foster career development for current and future kidney health professionals

Identifying Trends in Nephrology Training and Practice

The ASN Data Analytics program identifies trends in nephrology training and practice in order to provide the kidney community with data key to informed decision-making.

In collaboration with investigators at George Washington University Health Workforce Institute, ASN conducted the 5th annual Nephrology Fellow Survey, which provides leading indicators on the nephrology job market and perceptions of training and clinical practice. The Early Practice Survey (of nephrologists out of training between 2 and 10 years) found key distinctions between physicians in group practices and those based in academic centers.

Continuing research collaborations overseen by the program include the joint ASN/ERA-EDTA/ISN *Global Nephrology Workforce Survey* to characterize nephrology practice across the world and quantify how nephrologists' roles differ within and between regions. Other ongoing efforts include monitoring trends in the current nephrology training landscape by analyzing data collated in the ASN Nephrology GME Database. Future initiatives include the launch of the ASN Data Resource Center, a dedicated online repository for reports and other resources, and development of the biennial ASN *State of Nephrology Practice Survey*.

Launching the ASN Pre-Doctoral Fellowship Award Program

The ASN Foundation for Kidney Research launched the ASN Pre-Doctoral Fellowship program, which will award five two-year fellowships to nephrology PhD students annually.

In addition, the ASN Foundation funded 44 leading researchers who are working to cure kidney diseases, including 25 new projects and 19 projects continuing work begun in 2016 and 2017. The Foundation pro-

vides more than \$3 million in funding for members at all stages of their careers.

The Foundation funds the Career Development Grants Program, the Ben J. Lipps Research Fellowship Program, the William and Sandra Bennett Clinical Scholars Program, the American Society of Nephrology–Harold Amos Medical Faculty Development Program, and the new ASN Pre-Doctoral Fellowship Program.

Partnering with the American Physiological Society to Establish the APS/ASN Summer Conference Travel Support Program

In 2019, ASN will jointly present the American Physiological Society (APS) Renal Section's Summer Conference. In addition to co-presenting the conference, ASN will provide travel support for up to 30 participants to attend the conference via a new ASN Fundamental Science Travel Support Program. This program underscores ASN's continued commitment to expand opportunities for ASN members interested in basic, or fundamental, science.

Other ASN initiatives to support basic science include holding two summits for PhDs since 2013, initiating a new grants program for PhD students, funding research fellowship and career development grants in basic science, and expanding Kidney TREKS (Tutored Research and Education for Kidney Scholars) to include PhD students. ASN also recently assessed program content at ASN Kidney Week to confirm that the meeting now offers the same amount of basic science as in the past.

Planning to Start ASN Midcareer Awards in 2019

In April 2018, the ASN Council unanimously approved a proposal from the Career Advancement Committee to add midcareer awards to the ASN awards portfolio. These awards will honor healthcare providers between 10 and 20 years from completion of their professional training who have demonstrated impact in nephrology in the areas of clinical service, research, education, mentorship, and leadership.

ASN partnered with the American Heart Association Council on the Kidney in Cardiovascular Disease to dedicate the Young Investigator Award to Donald W. Seldin, MD, FASN. Dr. Seldin, who died earlier this year, helped establish nephrology as a medical specialty and create ASN, serving as the society's second president in 1967–1968.

GOAL 5

Assert the value of nephrology to health and science professionals, healthcare systems, and other stakeholders to ensure high-quality care for patients

Expanding Nephrologists Transforming Dialysis Safety (NTDS) to Include Human Factors Engineering

ASN's partnership with the Centers for Disease Control and Prevention engages nephrologists to take the lead in bringing about the cultural changes needed to transform infection prevention in dialysis facilities. NTDS expanded to include human factors engineering to identify barriers and facility adherence to infection prevention practices. Six facility observations will take place in 2019.

NTDS also contributed an infection prevention section to the ASN Virtual Mentor Curriculum, compiled an Ebola Gap Analysis, launched a vascular access initiative, published an infection prevention series of manuscripts in *CJASN*, and produced two webinars in the "Targeting Zero Infections" series: "Infectious Disease Reporting: State Requirements and Resources" and "Environmental Decontamination."

In its 3rd year, NTDS will offer two additional webinars, publish a Hepatitis Screening Algorithm, and present recommendations on blood culture standardization. It will further produce a NephSAP special edition on infection prevention and an infection prevention curriculum for fellows.

Asserting the Value of Nephrology with Community and Congressional Stakeholders

ASN convened the 4th Kidney Community Advocacy Day (KCAD) and 6th annual Kidney Health Advocacy Day (KHAD) in Washington, DC, to urge funding and legislation to improve care for kidney patients and innovation in kidney medicine. In partnership with the American Association of Kidney Patients, 49 patient and physician advocates met during KHAD with congressional delegations about the urgent need to accelerate innovations in kidney care.

At KCAD, 75 advocates from 15 organizations representing the spectrum of patient and professional groups in the kidney and transplant community called on their congressional delegations to increase funding for kidney research, support increased innovation in kidney medicine, including KidneyX, and pass the Living Donor Protection Act.

ASN opposed a proposal from the Centers for Medicare & Medicaid Services (CMS) that would reduce physician payment under Evaluation and Management codes. Coupled with a proposal to reduce the documentation burden—a concept ASN has long supported and favors overall—the proposed reimbursement changes could have wide-ranging effects. ASN is partnering with other medical specialties to urge CMS to work in collaboration to develop more nuanced, less harmful, policies.

Holding a Disaster Relief Summit

ASN convened a Disaster Relief Summit in June 2018 to address the current state of disaster preparedness and relief in the United States and Caribbean. The summit brought together experts in disaster preparedness and response from across the country, as well as a representative from the International Society of Nephrology Disaster Relief Task Force and a nephrologist from the Caribbean.

Participants identified challenges and gaps to achieving high quality performance in pre- and post-disaster situations and recognized ASN's role in setting policies concerning disaster preparedness and in helping to facilitate availability of healthcare professionals during and after disasters.

Bringing Together a Group of Division Chiefs to Discuss the Need to Reassert the Value of Nephrology

To assert the value of nephrology to a diverse array of stakeholders, the ASN Council is reimagining what the specialty will stand for in the future and articulating the aspects that are core to achieving that vision. The topic will be an area of focus at a Summit of Division Chiefs ASN will convene in late 2018, and numerous ASN committees are sharing their perspectives. Looking ahead, ASN plans to publish a manuscript defining the scope of nephrology practice and articulating a vision for nephrology in the future in a peer-reviewed journal in early 2019.



AKI Rates and Severity Are Highest in Winter

Inderstanding seasonal patterns of disease has important implications for clinical care. Yet for many years, little has been known about seasonal variations in acute kidney injury (AKI).

A new study shows that AKI does indeed show a seasonal pattern, with incidence and severity both being higher in the winter months.

Using a Japanese community hospital database, the researchers conducting the *Nephrology Dialysis Transplantation* study identified 81,279 hospitalized patients with AKI. Patients were identified according to Kidney Disease: Improving Global Outcomes serum creatinine criteria. The patients represented 14.6% of all patients admitted over the 3-year study period, from 2012 to 2014.

The investigators assessed associations between month of admission and AKI, with adjustment for patient characteristics and AKI risk factors. Seasonal variations in AKI severity and 30-day mortality were examined as well.

The proportion of patients with AKI varied by month, from a high of 16.7% in

January to a low of 13.4% in June: adjusted odds ratio 1.24. This seasonal pattern appeared to reflect community-acquired AKI in older adults hospitalized for cardiovascular and pulmonary disorders upon subgroup analyses.

Disease severity was also found to be higher in winter than in summer. Thirtyday mortality was 15.6% in autumn, 18.4% in winter, 16.4% in spring, and 14.5% in summer. Disease severity was determined based on AKI stage, proportion of patients receiving acute renal replacement therapy, and number of organ failures.

The new study shows significant seasonal effects in AKI, with incidence, severity, and mortality all being highest in winter. The findings have implications for clinical practice, including hospital resource utilization and preventive care in the community, the authors noted.

Iwagami M, et al. Seasonality of acute kidney injury incidence and mortality among hospitalized patients. *Nephrol Dial Transplant* 2018; 33:1354–1362.

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Evaluation, Postdonation Care Entail Significant Costs for Living Kidney Donors

hile most healthcare costs for living kidney donors are incurred during the perioperative period, there are also significant costs related to evaluation and follow-up care, reports a study in *Transplantation*.

The retrospective analysis included 1099 living kidney donors who donated at one Ontario transplant center between 2004 and 2014. All aspects of predonation and postdonation care were covered under Canada's universal health insurance program. Costs related to the donors' care were analyzed in three periods: predonation evaluation; perioperative care, including the nephrectomy and 30-day postoperative period; and follow-up to 1 year after donation. Incremental costs, compared to healthy matched donor controls, were expressed in 2017 CAD \$.

The estimated healthcare costs for living kidney donors were about CAD \$3596 for the evaluation period, CAD \$11,694 for the perioperative period, and CAD \$1011 for the follow-up period. The costs for evaluation were higher if the recipient started dialysis after the start of the donor evaluation period.

Overall, the costs associated with living kidney donation were higher for women, older donors, and over a longer predonation period. The investigators found that costs were lower in more recent years. They also found significant variation in costs during the perioperative period between transplant centers.

Having accurate estimates of the costs of living kidney donation is essential to encouraging more people to be living kidney donors. Many previous studies of this issue have looked only at the surgical costs of donation, without considering the costs of donor evaluation and follow-up care.

Habbous S, et al. Healthcare costs for the evaluation, surgery, and follow-up care of living kidney donors. *Transplantation* 2018; 102:1367–1374].

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RENAL TECHNOLOGIES

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Only one calcimimetic lowers and maintains key sHPT lab values with IV administration you control¹

Indication

Parsabiv[™] (etelcalcetide) is indicated for the treatment of secondary hyperparathyroidism (HPT) in adult patients with chronic kidney disease (CKD) on hemodialysis.

Limitations of Use:

Parsabiv[™] has not been studied in adult patients with parathyroid carcinoma, primary hyperparathyroidism, or with CKD who are not on hemodialysis and is not recommended for use in these populations.

Important Safety Information

Contraindication: Parsabiv[™] is contraindicated in patients with known hypersensitivity to etelcalcetide or any of its excipients. Hypersensitivity reactions, including pruritic rash, urticaria, and face edema, have occurred.

Hypocalcemia: Parsabiv[™] lowers serum calcium and can lead to hypocalcemia, sometimes severe. Significant lowering of serum calcium can cause QT interval prolongation and ventricular arrhythmia. Patients with conditions that predispose to QT interval prolongation and ventricular arrhythmia may be at increased risk for QT interval prolongation and ventricular arrhythmias if they develop hypocalcemia due to Parsabiv[™]. Closely monitor corrected serum calcium and QT interval in patients at risk on Parsabiv[™].

Significant reductions in corrected serum calcium may lower the threshold for seizures. Patients with a history of seizure disorder may be at increased risk for seizures if they develop hypocalcemia due to Parsabiv[™]. Monitor corrected serum calcium in patients with seizure disorders on Parsabiv[™].

Concurrent administration of Parsabiv[™] with another oral calcimimetic could result in severe, life-threatening hypocalcemia. Patients switching from cinacalcet to Parsabiv[™] should discontinue cinacalcet for at least 7 days prior to initiating Parsabiv[™]. Closely monitor corrected serum calcium in patients receiving Parsabiv[™] and concomitant therapies known to lower serum calcium.

Not an actual Parsabiv™ vial. The displayed vial is for illustrative purposes only.

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Measure corrected serum calcium prior to initiation of Parsabiv[™]. Do not initiate in patients if the corrected serum calcium is less than the lower limit of normal. Monitor corrected serum calcium within 1 week after initiation or dose adjustment and every 4 weeks during treatment with Parsabiv[™]. Measure PTH 4 weeks after initiation or dose adjustment of Parsabiv[™]. Once the maintenance dose has been established, measure PTH per clinical practice.

Worsening Heart Failure: In Parsabiv[™] clinical studies, cases of hypotension, congestive heart failure, and decreased myocardial performance have been reported. Closely monitor patients treated with Parsabiv[™] for worsening signs and symptoms of heart failure.

Upper Gastrointestinal Bleeding: In clinical studies, 2 patients treated with Parsabiv[™] in 1253 patient years of exposure had upper gastrointestinal (GI) bleeding at the time of death. The exact cause of GI bleeding in these patients is unknown and there were too few cases to determine whether these cases were related to Parsabiv[™].

Patients with risk factors for upper GI bleeding, such as known gastritis, esophagitis, ulcers or severe vomiting, may be at increased risk for GI bleeding with Parsabiv[™]. Monitor patients for worsening of common Parsabiv[™] GI adverse reactions and for signs and symptoms of GI bleeding and ulcerations during Parsabiv[™] therapy.

Adynamic Bone: Adynamic bone may develop if PTH levels are chronically suppressed.

Adverse Reactions: In clinical trials of patients with secondary HPT comparing Parsabiv[™] to placebo, the most common adverse reactions were blood calcium decreased (64% vs. 10%), muscle spasms (12% vs. 7%), diarrhea (11% vs. 9%), nausea (11% vs. 6%), vomiting (9% vs. 5%), headache (8% vs. 6%), hypocalcemia (7% vs. 0.2%), and paresthesia (6% vs. 1%).

Please see Brief Summary of full Prescribing Information on adjacent page.

IV = intravenous; sHPT = secondary hyperparathyroidism; PTH = parathyroid hormone; P = phosphate; cCa = corrected calcium. **Reference: 1.** Parsabiv[™] (etelcalcetide) prescribing information, Amgen.



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BRIEF SUMMARY OF PRESCRIBING INFORMATION



. 2.5mg/0.5mL | 5mg/1mL |

Please see package insert for full Prescribing Information.

INDICATIONS AND USAGE

PARSABIV is indicated for the treatment of secondary hyperparathyroidism (HPT) in adult patients with chronic kidney disease (CKD) on hemodialysis

Limitations of Use:

PARSABIV has not been studied in adult patients with parathyroid carcinoma, primary hyperparathyroidism, or with chronic kidney disease who are not on hemodialysis and is not recommended for use in these populations.

CONTRAINDICATIONS

Hypersensitivity

PARSABIV is contraindicated in patients with known hypersensitivity to etelcalcetide or any of its excipients. Hypersensitivity reactions, including pruritic rash, urticaria, and face edema, have occurred with PARSABIV [see Adverse Reactions (6.1) in PARSABIV full prescribing information].

WARNINGS AND PRECAUTIONS

Hypocalcemia

PARSABIV lowers serum calcium [see Adverse Reactions (6.1) in PARSABIV full prescribing information] and can lead to hypocalcemia, sometimes severe. Significant lowering of serum calcium can cause paresthesias, myalgias, muscle spasms, seizures, QT interval prolongation, and ventricular arrhythmia. QT Interval Prolongation and Ventricular Arrhythmia

In the combined placebo-controlled studies, more patients treated with PARSABIV experienced a maximum increase from baseline of greater than 60 msec in the QTcF interval (0% placebo versus 1.2% PARSABIV). In these studies, the incidence of a maximum post-baseline predialysis QTcF > 500 msec in the placebo and PARSABIV groups was 1.9% and 4.8%, respectively *[see Adverse Reactions (6.1) in PARSABIV* full prescribing information]. Patients with congenital long QT syndrome, history of QT interval prolongation, family history of long QT syndrome or sudden cardiac death, and other conditions that predispose to QT interval prolongation and ventricular arrhythmia may be at increased risk for QT interval prolongation and ventricular arrhythmias if they develop hypocalcemia due to PARSABIV. Closely monitor corrected serum calcium and QT interval in patients at risk receiving PARSABIV.

Seizures

Significant reductions in corrected serum calcium may lower the threshold for seizures. Patients with a history of seizure disorder may be at increased risk for seizures if they develop hypocalcemia due to PARSABIV. Monitor corrected serum calcium in patients with seizure disorders receiving PARSABIV.

Concurrent administration of PARSABIV with another oral calcium-sensing receptor agonist could result in severe, life-threatening hypocalcemia. Patients switching from cinacalcet to PARSABIV should discontinue cinacalcet for at least 7 days prior to initiating PARSABIV [see Dosage and Administration (2.4) in PARSABIV full prescribing information]. Closely monitor corrected serum calcium in patients receiving PARSABIV and concomitant therapies known to lower serum calcium

Measure corrected serum calcium prior to initiation of PARSABIV. Do not initiate in patients if the corrected serum calcium is less than the lower limit of normal. Monitor corrected serum calcium within 1 week after initiation or dose adjustment and every 4 weeks during treatment with PARSABIV [see Dosage and Administration (2.2) in PARSABIV full prescribing information]. Educate patients on the symptoms of hypocalcemia, and advise them to contact a healthcare provider if they occur.

If corrected serum calcium falls below the lower limit of normal or symptoms of hypocalcemia develop, start or increase calcium supplementation (including calcium, calcium-containing phosphate binders, and/or vitamin D sterols or increases in dialysate calcium concentration). PARSABIV dose reduction or discontinuation of PARSABIV may be necessary [see Dosage and Administration (2.2) in PARSABIV full prescribing information].

Worsening Heart Failure

In clinical studies with PARSABIV, cases of hypotension, congestive heart failure, and decreased myocardial performance have been reported. In clinical studies, heart failure requiring hospitalization occurred in 2% of PARSABIV-treated patients and 1% of placebo-treated patients. Reductions in corrected serum calcium may be associated with congestive heart failure, however, a causal relationship to PARSABIV could not be completely excluded. Closely monitor patients treated with PARSABIV for worsening signs and symptoms of heart failure.

Upper Gastrointestinal Bleeding

In clinical studies, two patients treated with PARSABIV in 1253 patient-years of exposure had upper gastrointestinal (GI) bleeding noted at the time of death while no patient in the control groups in 384 patient-years of exposure had upper Gl bleeding noted at the time of death. The exact cause of Gl bleeding in these patients is unknown, and there were too few cases to determine whether these cases were related to PARSABIV.

Patients with risk factors for upper GI bleeding (such as known gastritis, esophagitis, ulcers, or severe vomiting) may be at increased risk for GI bleeding while receiving PARSABIV treatment. Monitor patients for worsening of common GI adverse reactions of nausea and vomiting associated with PARSABIV [see Adverse Reactions (6.1) in PARSABIV full prescribing information] and for signs and symptoms of GI bleeding and ulcerations during PARSABIV therapy. Promptly evaluate and treat any suspected GI bleeding.

Advnamic Bone

Adynamic bone may develop if PTH levels are chronically suppressed. If PTH levels decrease below the recommended target range, the dose of vitamin D sterols and/or PARSABIV should be reduced or therapy discontinued. After discontinuation, resume therapy at a lower dose to maintain PTH levels in the target range [see Dosage and Administration (2.1) in PARSABIV full prescribing information].

ADVERSE REACTIONS

- The following adverse reactions are discussed in greater detail in other sections of the labeling:
- Hypocalcemia [see Warnings and Precautions (5.1) in PARSABIV full prescribing information]
- Worsening Heart Failure [see Warnings and Precautions (5.2) in PARSABIV full prescribing information]
- Upper Gastrointestinal Bleeding [see Warnings and Precautions (5.3) in PARSABIV full prescribing information]
- Adynamic Bone [see Warnings and Precautions (5.4) in PARSABIV full prescribing information]

Clinical Trials Experience

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

The data in Table 2 are derived from two placebo-controlled clinical studies in patients with chronic kidney disease and secondary hyperparathyroidism on hemodialysis. The data reflect exposure of 503 patients to PARSABIV with a mean duration of exposure to PARSABIV of 23.6 weeks. The mean age of patients was approximately 58 years, and 60% of the patients were male. Of the total patients, 67% were Caucasian, 28% were Black or African American, 2.6% were Asian, 1.2% were Native Hawaiian or Other Pacific Islander, and 1.6% were categorized as Other. Table 2 shows common adverse reactions associated with the use of PARSABIV in the pool of placebo-controlled studies. These adverse reactions occurred more commonly on PARSABIV than on placebo and were reported in at least 5% of patients treated with PARSABIN

Table 2: Adverse Reactions Reported in ≥ 5% of PARSABIV-Treated Patients

Adverse Reaction*	Placebo (N = 513)	PARSABIV $(N = 503)$
Blood calcium decreased ^a	10%	64%
Muscle spasms	7%	12%
Diarrhea	9%	11%
Nausea	6%	11%
Vomiting	5%	9%
Headache	6%	8%
Hypocalcemia ^b	0.2%	7%
Paresthesia⁰	1%	6%

*Included adverse reactions reported with at least 1% greater incidence in the PARSABIV group compared to the placebo group

Asymptomatic reductions in calcium below 7.5 mg/dL or clinically significant asymptomatic reductions in corrected serum calcium between 7.5 and

< 8.3 mg/dL (that required medical management)

Symptomatic reductions in corrected serum calcium < 8.3 mg/dL

Paresthesia includes preferred terms of paresthesia and hypoesthesia

Other adverse reactions associated with the use of PARSABIV but reported in < 5% of patients in the PARSABIV group in the two placebo-controlled clinical studies were:

• Hyperkalemia: 3% and 4% for placebo and PARSABIV, respectively.

• Hospitalization for Heart Failure: 1% and 2% for placebo and PARSABIV, respectively. Myalgia: 0.2% and 2% for placebo and PARSABIV, respectively.

• Hypophosphatemia: 0.2% and 1% for placebo and PARSABIV, respectively.

Description of Selected Adverse Reactions

Hypocalcemia

In the combined placebo-controlled studies, a higher proportion of patients on PARSABIV developed at least one corrected serum calcium value below 7.0 mg/dL (7.6% PARSABIV, 3.1% placebo), below 7.5 mg/dL (27% PARSABIV, 5.5% placebo), and below 8.3 mg/dL (79% PARSABIV, 19% placebo). In the combined placebo-controlled studies, 1% of patients in the PARSABIV group and 0% of patients in the placebo group discontinued treatment due to an adverse reaction attributed to a low corrected serum calcium.

Hvpophosphatemia

In the combined placebo-controlled studies, 18% of patients treated with PARSABIV and 8.2% of patients treated with placebo had at least one measured phosphorus level below the lower normal limit (i.e., 2.2 mg/dL).

QTc Interval Prolongation Secondary to Hypocalcemia

In the combined placebo-controlled studies, more patients treated with PARSABIV experienced a maximum increase from baseline of greater than 60 msec in the QTcF interval (0% placebo versus 1.2% PARSABIV). The patient incidence of maximum post-baseline predialysis QTCF > 500 msec in the placebo and PARSABIV groups was 1.9% and 4.8%, respectively.

Hvpersensitivity

In the combined placebo-controlled studies, the subject incidence of adverse reactions potentially related to hypersensitivity was 4.4% in the PARSABIV group and 3.7% in the placebo group. Hypersensitivity reactions in the PARSABIV group were pruritic rash, urticaria, and face edema.

Immunogenicity

As with all peptide therapeutics, there is potential for immunogenicity. The detection of anti-drug binding antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to etelcalcetide with the incidence of antibodies to other products may be misleading.

In clinical studies, 7.1% (71 out of 995) of patients with secondary hyperparathyroidism treated with PARSABIV for up to 6 months tested positive for binding anti-etelcalcetide antibodies. Fifty-seven out of 71 had pre-existing anti-etelcalcetide antibodies

No evidence of altered pharmacokinetic profile, clinical response, or safety profile was associated with pre-existing or developing anti-etelcalcetide antibodies. If formation of anti-etelcalcetide binding antibodies with a clinically significant effect is suspected, contact Amgen at 1-800-77-AMGEN (1-800-772-6436) to discuss antibody testing.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summarv

There are no available data on the use of PARSABIV in pregnant women. In animal reproduction studies, effects were seen at doses associated with maternal toxicity that included hypocalcemia. In a pre- and post-natal study in rats administered etelcalcetide during organogenesis through delivery and weaning, there was a slight increase in perinatal pup mortality, delay in parturition, and transient effects on pup growth at exposures 1.8 times the human exposure for the clinical dos of 15 mg three times per week. There was no effect on sexual maturation, neurobehavioral, or reproductive function in the rat offspring. In embryo-fetal studies, when rats and rabbits were administered etelcalcetide during organogenesis, reduced fetal growth was observed at exposures 2.7 and 7 times exposures for the clinical dose, respectively.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data Animal Data

There were no effects on embryo-fetal development in Sprague-Dawley rats when etelcalcetide was dosed at 0.75, 1.5, and 3 mg/kg/day by the intravenous route during organogenesis (pre-mating to gestation day 17) at exposures up to 1.8 times human exposures at the clinical dose of 15 mg three times per week based on AUC. No effects on embryo-fetal development were observed in New Zealand White rabbits at doses of etelcalcetide of 0.375, 0.75, and 1.5 mg/kg by the intravenous route (gestation day 7 to 19), representing up to 4.3 times human exposures based on AUC. In separate studies at higher doses of 4.5 mg/kg in rats (gestation days 6 to 17) and 2.25 mg/kg in rabbits (gestation days 7 to 20), representing 2.7 and 7 fold clinical exposures, respectively, there was reduced fetal growth associated with maternal toxicities of hypocalcemia, tremoring, and reductions in body weight and food consumption.

In a pre- and post-natal development study in Sprague-Dawley rats administered etelcalcetide at 0.75, 1.5, and 3 mg/kg/day by the intravenous route (gestation day 7 to lactation day 20), there was a slight increase in perinatal pup mortality, delay in parturition, and transient reductions in post-natal growth at 3 mg/kg/day (representing 1.8-fold human exposures at the clinical dose of 15 mg three times per week based on AUC), associated with maternal toxicities of hypocalcemia, tremoring, and reductions in body weight and food consumption. There were no effects on sexual maturation, neurobehavioral, or reproductive function at up to 3 mg/kg/day, representing exposures up to 1.8-fold human exposure based on AUC. Lactation

Risk Summary

There are no data regarding the presence of PARSABIV in human milk or effects on the breastfed infant or on milk production. Studies in rats showed [14C]-etelcalcetide was present in the milk at concentrations similar to plasma. Because of the potential for PARSABIV to cause adverse effects in breastfed infants including hypocalcemia, advise women that use of PARSABIV is not recommended while breastfeeding. Data

Presence in milk was assessed following a single intravenous dose of $\left[^{14}\text{C}\right]\text{-}$ etelcalcetide in lactating rats at maternal exposures similar to the exposure at the human clinical dose of 15 mg three times per week. [14C]-etelcalcetide-derived radioactivity was present in milk at levels similar to plasma.

Pediatric Use

The safety and efficacy of PARSABIV have not been established in pediatric patients. Geriatric Use

Of the 503 patients in placebo-controlled studies who received PARSABIV, 177

patients (35.2%) were ≥ 65 years old and 72 patients (14%) were ≥ 75 years old. No clinically significant differences in safety or efficacy were observed between patients ≥ 65 years and younger patients (≥ 18 and < 65 years old). No differences in plasma concentrations of etelcalcetide were observed between patients ≥ 65 years and younger patients (≥ 18 and < 65 years old).

OVERDOSAGE

There is no clinical experience with PARSABIV overdosage. Overdosage of PARSABIV may lead to hypocalcemia with or without clinical symptoms and may require treatment. Although PARSABIV is cleared by dialysis, hemodialysis has not been studied as a treatment for PARSABIV overdosage. In the event of overdosage, corrected serum calcium should be checked and patients should be monitored for symptoms of hypocalcemia, and appropriate measures should be taken [see Warnings and Precautions (5.1) in PARSABIV full prescribing information].

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PARSABIV[™] (etelcalcetide)

Manufactured for:

KAI Pharmaceuticals, Inc., a wholly owned subsidiary of Amgen, Inc. One Amgen Center Drive Thousand Oaks, California 91320-1799

Patent: http://pat.amgen.com/Parsabiv/

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MODELS FOR COMPREHENSIVE KIDNEY CARE

Kidney care delivery models are in flux as the kidney community aims to reduce silos of care, provide continuity of care across a patient's trajectory, and ensure incentives for kidney health practitioners. Kidney News Editorial Board member Glenda Payne, RN, asked three organizations—ASN, the National Kidney Foundation, and Dialysis Clinic, Inc., to discuss their care delivery models and the rationale behind them.

ASN Care Delivery Model Concept: Comprehensive Care across a Patient's Journey

By Rachel Meyer

ntegration across medical settings and disease phases, led by nephrologists serving as principal care providers, will improve care quality and patient outcomes in advanced kidney disease through renal replacement therapy, end-of-life care, or both.

This statement is the thesis for the kidney care delivery model that the American Society of Nephrology (ASN) is currently developing to submit to the Physician-Focused Technical Payment Advisory Committee (P-TAC), emphasizing that nephrology professionals can improve care, improve patient-centeredness of care, and add value to the healthcare system by spanning care settings and disease phases. In doing so, nephrologists can reinforce a healthcare system in which patients are at the center and their providers are with them.

Before diving into the details of the ASN concept, let's review the current care delivery and payment model policy. In 2015, Congress enacted the Medicare Access and Children's Health Insurance Program Reauthorization Act (MACRA), a bill that overhauled the physician payment system and put us on a path to rewarding value (how well patients do versus cost of care) instead of volume (how many patients receive care). MACRA created incentives, which will increase over time, for physicians to provide care through alternative payment models models that take on financial risk and provide more coordinated patient care. MACRA also created the P-TAC, an independent body of expert clinicians and health economists, to evaluate new suggestions for physicianled alternative payment models.

The kidney community was fortunate that the ESRD Seamless Care Organization (ESCO) program met the standards for qualifying as an alternative payment model, affording some nephrology health professionals the opportunity to test new ways of delivering kidney care (and, thanks to MACRA, receive a payment bonus along the way). The ESCO program has shown significant early success; ESCOs achieved \$75 million in savings and improved outcomes in the first year, signaling the potential for more coordinated care to benefit patients with kidney diseases.

However, one significant limitation of the ESCO program is that it starts and ends with dialysis care. Although important gains can be made in improving dialysis care and patient outcomes, the greatest gains for patients would likely occur earlier in the course of kidney disease by slowing the progression to the extent possible and by preparing patients for a smooth transition to a modality of their choice, including preemptive transplantation. Similarly, the ESCO model does not include patients who have received a kidney transplant—a missed opportunity to increase access to transplantation and to best prepare transplant recipients who experience graft loss for a smooth and safe transition back to dialysis.

ASN believes that the optimal kidney care delivery model would eliminate these "silos" of care between advanced kidney disease, kidney failure/dialysis, and transplantation—and provide palliative care as needed throughout. Led by nephrologists, such a model would focus on managing and slowing the progression of kidney diseases and other complex chronic conditions kidney patients commonly face, and it would emphasize preparation for and management of care transitions with shared decision-making.

Creating continuity across the current silos of care delivery and payment for advanced kidney disease, kidney failure/dialysis, and transplantation would align the incentives in such a manner that health professionals and providers are rewarded for doing what is best for patients. For example, preventing a patient from needing dialysis for even a few months provides substantial savings, but currently health professionals are not rewarded for that optimal patient outcome. Similarly, transplantation is less expensive than dialysis over time and significantly improves patient outcomes, but under the current structure there is no mechanism to identify those savings and reward the health professionals who facilitate this process. A comprehensive kidney care model that spans the current payment silos would better align incentives to do the right thing for patients at each stage of their kidney disease.

As currently envisioned, patients would become eligible for the model at an estimated GFR of 30 mL/min/1.73 m², and, unlike the ESCO and other proposed kidney care models (wherein patients are removed after receiving a kidney transplant), patients would never become ineligible for the model in the future. This ensures a smooth transition of care to transplantation and, if needed, back to dialysis, and it allows tracking the savings that result from a kidney transplantation.

ASN leaders are working through many questions on their way to developing a proposal for the P-TAC to consider. A topic of much consideration and debate is whether this model would best be developed as one that individual physicians could choose to participate in, or as a model that requires the participation of multiple stakeholders—building on the ESCO partnerships between dialysis organizations and nephrologists to include others, such as transplantation centers. Each approach offers upsides and downsides.

Regardless, moving from a conceptual model to an actual care delivery and payment plan to propose to the P-TAC is no small task. The ASN leadership will be working through a host of complicated questions and decision points in preparation for submission to the P-TAC. Your thoughts and input are welcomed: Please contact ASN Policy and Advocacy Specialist David L. White at dwhite@asn-online.org to share feedback.

Rachel Meyer is director of policy and government affairs at the American Society of Nephrology.

A Proposed Model for Comprehensive Chronic Kidney Disease Care from the National Kidney Foundation

By Jeffrey S. Berns, MD, and Tonya L. Saffer, MPH

ccessible healthcare that puts patients first is the most important goal that any new model for payment and care delivery should have at its center. The shift from a fee-for-service system toward reimbursement for delivering value has great potential to improve patient outcomes through better engagement. This shift in payment also creates opportunities for a more rewarding career environment for healthcare practitioners by providing the resources necessary to support earlier intervention and strengthen patient engagement. Early on, the National Kidney Foundation recognized the potential of value-based payment models as an opportunity to address a question that we hear from our patients who are living with ESRD. livery to patients at each point in their CKD journey, and encourage collaboration between primary care and nephrology practitioners to ease transitions for patients who experience progression toward ESRD.

Often in healthcare, particularly kidney care, we wait until a patient's condition is medically complex and costly to the healthcare system before intervening. Current models in kidney care have focused primarily on the care of dialysis patients to reduce the costs generated by this highly expensive population. The CKDintercept: Comprehensive Chronic Kidney Disease Care Model seeks to change this by providing primary care practitioners and nephrologists care management payments tied to quality measures to deliver targeted, individualized care to patients with CKD across the longitudinal spectrum of this condition.

In this model, not every patient with CKD would be viewed as being in a "predialysis" state, as is so common now. Instead, care would focus on delaying progression, avoiding complications, and engaging patients in shared decision-making and self-management. For patients who may ultimately experience progression to ESRD despite best efforts, this model promotes easier transitions and informed decision-making about treatment options in advance of kidney failure—including how treatment options such as transplantation, home dialysis, in-center dialysis, or supportive end-of-life care can help patients achieve their goals and be responsive to their values and preferences.

The CKDintercept model presents the opportunity for primary care and nephrology providers to form organizations and receive tiered monthly payments for tailored kidney care management. The model also allows patients to receive care in their current healthcare setting and promotes collaboration with nephrology practitioners in an evidence-based and cost-effective manner.

CKDintercept organizations (CKDi-O) would re-



Why did I not know I had kidney disease?

In June 2016, the National Kidney Foundation established a multidisciplinary workgroup that included patients, family physicians, internal medicine physicians, nephrologists, advanced practitioners, a dietitian, and a social worker to develop a payment model to improve earlier detection and treatment of chronic kidney disease (CKD), promote collaborative evidence-based care deceive per-beneficiary per-month payments (PBPM) for the management of CKD stages 3 through the transition to ESRD. This fee is intended to help support implementation of a multi-disciplinary care team to help with care coordination, remote monitoring, nutrition, and medication management. A Performance-based Incentive Payment (PBIP) would also be available, contingent on performance for CKD-related quality measures and lowering CKD-related expenditures. CKDI-Os would take on risk beginning in year two of the model, allowing those providers to achieve advanced alternative payment model (AAPM) participation status. Attribution in the model would be prospective assignment of beneficiaries based on plurality of primary care or nephrology claims to providers in the CKDI-O. Beneficiaries would also be allowed to voluntarily opt in by self-selecting a participating provider. Participation would be contingent on an appropriate percentage of the practitioner's attributed diabetic and hypertension population with an estimated GFR and urine ACR in alignment with the Kidney Disease: Improving Global Outcomes/Kidney Disease Outcomes Quality Initiative guidelines that successfully achieve selected measures specific to delivering CKD care.

CKDI-O providers would also need to participate in practice transformation activities, which is common for other AAPMs. Recommended activities include integrated mental health, nutrition counseling, advanced care planning, development of patient and family advisory councils, and use of shared decision-making tools.

The CKDintercept model is intended to allow primary care physicians (PCPs) and nephrologists to participate regardless of practice size or experience with APMs. For PCPs and nephrologists who are participating in other APMs, the model can be tailored to allow for crossparticipation. The National Kidney Foundation encourages the participation of community health centers and their practitioners because CKD has a disproportionate impact on individuals with social risk factors.

Value over volume

The CKDintercept model enhances care delivery by establishing a set of criteria to allow participants flexibility in designing the plan specifically to address each criterion during the application process (Table 1). The model defines which services would not be separately billable in fee for service. The criteria outline what is necessary to improve quality, lower costs, and enhance patient engagement while allowing participating practitioners flexibility in how they would address the criteria. Because the model proposes payment to practitioners up front monthly as opposed to a shared savings arrangement, the initial investments by practices to meet the criteria should be recovered in a relatively short time. This approach is similar to what is used in the Oncology Care Model.

We can, and we must, do better for patients now. We must develop and test new models of care that promote earlier detection of those at highest risk for the disease and improved treatment of those with it. As a kidney community we must stop looking at individuals with CKD as being in a "predialysis" state and focus on delivering the right care to the right patient at the right point in time. Delivering on this promise of earlier and better care will take the engagement of the primary care community and kidney community and a commitment to work together. The CKDintercept model is a work in progress. The organizations that represent these communities must come to the table to help shape the details for this model, support its testing, and solve the perceived challenges that a new model of care poses. Only through this coordinated effort can we truly improve the lives of kidney patients.

Full details of the National Kidney Foundation's proposed model, including the proposed quality measures and evidence base, can be found at https://www.kidney. org/sites/default/files/20171120-CKDintercept-Comprehensive-CKD-Care-Model_CMMI-RFI.pdf.

Jeffrey S. Berns, MD, FACP, FASN, is professor of medicine, Perelman School of Medicine, University of Pennsylvania, and associate chief, Renal-Electrolyte and Hypertension Division. Tonya L. Saffer, MPH, is senior health policy director at the National Kidney Foundation.

Examples of services included in the model (not separately payable)	CKD eGFR <60–30 ACR 30–299	CKD eGFR <30 ACR >300
Medical nutrition therapy by a dietitian	•	•
Office visits for evaluation (including evaluation of common comorbidities	•	•
Care coordination with patients' other healthcare practitioners	•	•
24/7 patient access to healthcare team	•	•
Longitudinal care management	•	•
Patient-centered care planning, addressing patient life goals, culture, and values	•	•
Evaluation of community/social services needs	•	•
Depression/anxiety assessment	•	•
Access to pharmacists for medication questions	•	•
Live or virtual kidney disease education sessions		•
Insurance navigation and coordination		•
Coordination with vascular access surgeon, transplantation center as appropriate		•

Table 1. Overview of the CKDintercept model

Abbreviations: eGFR = estimated glomerular filtration rate; ACR = albumin to creatinine ratio

The DCI REACH Program

By Doug Johnson

ialysis Clinic, Inc., has been providing care coordination to patients with chronic kidney disease (CKD) since 2010. This program was started in Spartanburg, South Carolina, and has since grown to care for more than 4000 patients in more than 15 locations in 12 states. In one location we have enrolled more than 400 patients under a program in a partnership with a local health plan. For all other programs, we provide this service free of charge to patients as a community benefit.

Four years ago we officially named our program REACH Kidney Care. REACH stands for Real Engagement Allowing Complete Health. As a nonprofit provider, we believe that when possible we should fully inform people with kidney diseases about their choices in care, and work with them to determine the course that best meets their culture, values, and life goals. More information about the REACH program is provided at http://www.reachkidneycare. org/. Below is a summary of our program.

Patient population

We serve patients with GFR below 30 mL/min per 1.73 m^2 and patients with GFR 30 to 59 mL/min per 1.73 m^2 , with albuminuria detectable on dipstick, exceeding 300 mg/g creatinine.

Primary goal

Our primary goal is to treat a patient with late-stage CKD, focusing care on meeting that patient's current clinical needs instead of treating the patient as someone who may need dialysis.

Secondary goals

For patients whose kidney disease has progressed to the point where GFR is below 20 mL/min per 1.73 m², we provide education on choices of care for renal replacement therapy (RRT), including transplantation, home dialysis, in-center dialysis with a permanent access, and medical management without dialysis. For a patient choosing a modality for RRT, we help the patient navigate the healthcare system to implement this choice.

We recognize that not all patients desiring transplantation will receive a transplant before they start dialysis. If a patient chooses transplantation, we also work with the patient to choose a dialysis modality to prepare the patient in case the patient does not receive a preemptive transplant. For a patient choosing medical management without dialysis, we follow and support the patient closely through this journey, let the patient and his or her family know that we will not abandon them, and add additional services as needed and requested, including palliative and hospice care.

Tertiary goal

For a patient who has chosen a modality for RRT, we follow the patient closely, in partnership with the patient's nephrologist, to allow a safe start of dialysis later in the progression of the patient's CKD. Nationwide, 11.7% of patients start with a GFR at or above 15 mL/ min per 1.73 m². In Spartanburg, only 3% of patients since January 1, 2014, have started with a GFR above 15 mL/min per 1.73 m², and 71% start with a GFR 5 to 10 mL/min per 1.73 m².

Frequency of visits

The frequency of visits depends on the clinical needs of

the patient. At a minimum, the nurse care coordinator sees the patient at the same frequency as the patient's nephrologist, with these visits alternated so that the patient is seen twice as often. In some instances, the patient is seen by the nurse care coordinator on a weekly basis. The nurse care coordinator sends a progress note for each visit to the patient's nephrologist and other physicians.

Staff

- Nurse care coordinator: role described above.
- Dietitian: helps the patient learn what she/he can eat, instead of providing a list of foods to be avoided. Specific attention is paid to include foods important to the patient's culture of origin.
- Social worker: educates the patient on available resources; provides supportive counseling.

Very advanced CKD

For patients with very advanced CKD who plan eventual dialysis, and who otherwise would have been referred to start dialysis but do not have a clinical need to start, we provide a framework of support and services for the patient to allow a safe transition to dialysis later in the progression of CKD, delaying the burden of thriceweekly dialysis. A patient could visit the care coordinator once a week to allow for close evaluation. We provide consistent support, close follow-up, and clear communication with the nephrology team. The level of care of a patient with late-stage CKD should be comparable with the care given to patients receiving dialysis, without the requirement for dialysis or thrice-weekly clinic visits.

Doug Johnson is Vice Chairman of the Board, Dialysis Clinic, Inc.



"

I now have protected time and financial stability to prepare for a career path that is focused not only on providing excellent care at the bedside but also on developing the research skills necessary to innovate nephrology care."

> Yuenting Diana Kwong, MD, 2018 Donald E. Wesson Research Fellow

With support from ASN members, industry partners, and leaders in the field, the ASN Foundation for Kidney Research stands committed to funding talented fellows and early-career researchers who are building the future of kidney care. By providing financial security and protected research time, ASN Foundation grants allow researchers to take chances, ask tough questions, and transform care.

Your gift to the ASN Foundation will help ensure the availability of funding that will open new avenues to care and cures. With 100% of every donation going directly towards research, every contribution gets us one step closer to preventing and curing kidney diseases. Please join us.

Want to learn more? www.asn-online.org/donate or click the "Donate" icon on the Kidney Week app. It is the generosity of individuals and companies within the kidney community that make change possible. A special thank you to the following donors* for their generous support of the ASN Foundation for Kidney Research:

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When you see risk factors of confirmed hyperkalemia...¹



Consider once-daily, sodium-free VELTASSA

IMPORTANT INFORMATION

Contraindications: VELTASSA is contraindicated in patients with a history of a hypersensitivity reaction to VELTASSA or any of its components.

Worsening of Gastrointestinal Motility: Avoid use of VELTASSA in patients with severe constipation, bowel obstruction or impaction, including abnormal post-operative bowel motility disorders, because VELTASSA may be ineffective and may worsen gastrointestinal conditions. Patients with a history of bowel obstruction or major gastrointestinal surgery, severe gastrointestinal disorders, or swallowing disorders were not included in clinical studies.

Hypomagnesemia: VELTASSA binds to magnesium in the colon, which can lead to hypomagnesemia. In clinical studies, hypomagnesemia was reported as an adverse reaction in 5.3% of patients treated with VELTASSA. Approximately 9% of patients in clinical trials developed hypomagnesemia with a serum magnesium value <1.4 mg/dL. Monitor serum magnesium. Consider magnesium supplementation in patients who develop low serum magnesium levels.

Adverse Reactions: The most common adverse reactions (incidence $\geq 2\%$) are constipation, hypomagnesemia, diarrhea, nausea, abdominal discomfort and flatulence. Mild to moderate hypersensitivity reactions were reported in 0.3% of patients treated with VELTASSA and included edema of the lips.

Please see Brief Summary of Prescribing Information on following page.



ACCESS TO VELTASSA IS BROAD AND IMPROVING²

VELTASSA is covered by **most insurance plans**, including Medicare Part D.



VELTASSA HAS BEEN PRESCRIBED TO OVER 50,000 PATIENTS SINCE **APPROVAL³**

Join thousands of physicians helping their patients by treating hyperkalemia with VELTASSA.



Policy Update

Nephrology Public Policy Developments Abound

Rall in Washington, DC, during election years is typically known for being a slow time in the nation's capital. For the kidney community, however, August and September of 2018 are proving to be anything but slow.

As the 2018 fiscal year for the federal government comes to a close on September 30, lawmakers are busy finalizing legislation to fund the government. In late August, the Senate passed a funding bill providing, among other provisions, the \$2 billion increase for the National Institutes of Health (NIH) that ASN has been advocating for, and House lawmakers are rumored to be keeping the Senate spending levels in their legislation.

ASN has also been working to secure inclusion of language with the funding bill that would support KidneyX, living donation, and further study of Medicare reimbursement policy for immunosuppressive medications. Increasing funding for the NIH, as well as support for groundbreaking initiatives like the Kidney Precision Medicine Project are among the messages the 75 advocates participating in Kidney Community Advocacy Day took to legislators in late September.

In a win for living donors, the Department of Labor issued clarification in August 2018 that people who donate organs are eligible to receive job protection under the Family and Medical Leave Act (FMLA). This change guarantees that organ donors may take time to recover after donation surgery without the risk of losing their job, a significant barrier many potential kidney donors face. Ensuring FMLA protection for living donors has been a longstanding policy priority of ASN.

VELTASSA® (patiromer) for Oral Suspension

Brief Summary of Prescribing Information. Please see Full Prescribing Information for complete product information.

INDICATION AND USAGE

VELTASSA is indicated for the treatment of hyperkalemia.

Limitation of Use: VELTASSA should not be used as an emergency treatment for life-threatening hyperkalemia because of its delayed onset of action.

CONTRAINDICATIONS

VELTASSA is contraindicated in patients with a history of a hypersensitivity reaction to VELTASSA or any of its components [*see Adverse Reactions*]. **WARNINGS AND PRECAUTIONS**

Worsening of Gastrointestinal Motility Avoid use of VELTASSA in patients with severe constipation, bowel obstruction or impaction, including abnormal post-operative bowel motility disorders, because VELTASSA may be ineffective and may worsen gastrointestinal conditions. Patients with a history of bowel obstruction or major gastrointestinal surgery, severe gastrointestinal disorders, or swallowing disorders were not included in the clinical studies.

Hypomagnesemia VELTASSA binds to magnesium in the colon, which can lead to hypomagnesemia. In clinical studies, hypomagnesemia was reported as an adverse reaction in 5.3% of patients treated with VELTASSA *[see Adverse Reactions].* Monitor serum magnesium. Consider magnesium supplementation in patients who develop low serum magnesium levels on VELTASSA.

ADVERSE REACTIONS

The following adverse reaction is discussed in greater detail elsewhere in the label:

• Hypomagnesemia [see Warnings and Precautions]

Clinical Trials Experience Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of VELTASSA cannot be directly compared to rates in the clinical trials of other drugs and may not reflect the rates observed in practice. In the safety and efficacy clinical trials, 666 adult patients received at least one dose of VELTASSA, including 219 exposed for at least 6 months and 149 exposed for at least one year. Table 1 provides a summary of the most common adverse reactions (occurring in $\ge 2\%$ of patients) in patients treated with VELTASSA in these clinical trials. Most adverse reactions were mild to moderate. Constipation generally resolved during the course of treatment.

Table 1: Adverse Reactions Reported in $\ge 2\%$ of Patients

Adverse Reactions	Patients treated with VELTASSA (N=666)
Constipation	7.2%
Hypomagnesemia	5.3%
Diarrhea	4.8%
Nausea	2.3%
Abdominal discomfort	2.0%
Flatulence	2.0%

During the clinical studies, the most commonly reported adverse reactions leading to discontinuation of VELTASSA were gastrointestinal adverse reactions (2.7%), including vomiting (0.8%), diarrhea (0.6%), constipation (0.5%) and flatulence (0.5%). Mild to moderate hypersensitivity reactions were reported in 0.3% of patients treated with VELTASSA in clinical trials. Reactions have included edema of the lips.

<u>Laboratory Abnormalities</u> Approximately 4.7% of patients in clinical trials developed hypokalemia with a serum potassium value < 3.5 mEq/L. Approximately 9% of patients in clinical trials developed hypomagnesemia with a serum magnesium value < 1.4 mg/dL.

DRUG INTERACTIONS

In clinical studies, VELTASSA decreased systemic exposure of some coadministered oral medications. Binding of VELTASSA to other oral medications could cause decreased gastrointestinal absorption and loss of efficacy when taken close to the time VELTASSA is administered. Administer other oral medications at least 3 hours before or 3 hours after VELTASSA.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

VELTASSA is not absorbed systemically following oral administration and maternal use is not expected to result in fetal risk.

Lactation

Risk Summary

VELTASSA is not absorbed systemically by the mother, so breastfeeding is not expected to result in risk to the infant.

Pediatric Use Safety and efficacy in pediatric patients have not been established.

Geriatric Use Of the 666 patients treated with VELTASSA in clinical studies, 59.8% were age 65 and over, and 19.8% were age 75 and over. No overall differences in effectiveness were observed between these patients and younger patients. Patients age 65 and older reported more gastrointestinal adverse reactions than younger patients.

Renal Impairment Of the 666 patients treated with VELTASSA in clinical studies, 93% had chronic kidney disease (CKD). No special dosing adjustments are needed for patients with renal impairment.

OVERDOSAGE

Doses of VELTASSA in excess of 50.4 grams per day have not been tested. Excessive doses of VELTASSA may result in hypokalemia. Restore serum potassium if hypokalemia occurs.

PATIENT COUNSELING INFORMATION

<u>Drug Interactions</u> Advise patients who are taking other oral medication to separate the dosing of VELTASSA by at least 3 hours (before or after) [see Drug Interactions].

<u>Dosing Recommendations</u> Inform patients to take VELTASSA as directed with or without food and adhere to their prescribed diets. Inform patients that VELTASSA should not be heated (e.g., microwaved) or added to heated foods or liquids and should not be taken in its dry form.

Manufactured for:

Relypsa, Inc.

Redwood City, CA 94063 Version 05; May 2018

References: 1. Weir MR, Bakris GL, Bushinsky DA, et al; for OPAL-HK Investigators.
Patiromer in patients with kidney disease and hyperkalemia receiving RAAS inhibitors. *N Engl J Med.* 2015;372(3):211-221. 2. Data on file as of December 2017. Relypsa, Inc.
3. Data on file as of March 2018. Relypsa, Inc.

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ASN leadership and staff have also been spending time with various institutes across NIH to discuss priorities for ASN in two areas: 1) new basic, translational, and clinical science research initiatives to spur innovation in the diagnosis, prevention, and treatment of kidney diseases; and 2) approaches to address the declining interest in academic careers in nephrology. ASN met with the National Heart, Lung and Blood Institute, the National Institute of Allergy and Infectious Diseases, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and the National Institute on Minority Health and Health Disparities. The society encouraged collaboration across institutes to ensure the success of innovative projects including the Kidney Precision Medicine Project, organized by NIDDK, and KidneyX, coordinated by ASN and the U.S. Department of Health and Human Services.

ASN will continue to meet with institutes across NIH as well as other federal research partners in the coming months to raise the profile of kidney diseases, promote more kidney-related research, and encourage more collaboration with NIDDK.

September also marked the conclusion of the comment period regarding proposed changes to physician payment as well as to the End-Stage Renal Disease (ESRD) Prospective Payment System (PPS) and Quality Incentive Program (QIP) proposed rule. The Centers for Medicare & Medicaid Services (CMS) proposed to ease documentation requirements for Evaluation and Management (E/M) coding and—in a troubling move to collapse payment for E/M code levels two through five into a single payment, among other proposed changes. ASN, together with virtually every other medical professional society, has identified a host of concerns with the E/M reimbursement proposals.

The society collaborated with a broad coalition of more than 40 societies to develop a coordinated response and speak with one voice to CMS on the issue. ASN also participated in a meeting with CMS Administrator Seema Verma and CMS Chief Medical Officer Kate Goodrich, MD, to discuss the proposed rule, a conversation that influenced a response strategy. ASN and the coalition urged CMS to finalize several of its proposals to ease the documentation burden now, but to work with the entire medical professional community over the coming year in a collaborative, transparent process to ensure appropriate reimbursement while minimizing unintended consequences before finalizing any changes to payment.

The PPS/QIP rule proposed several changes in line with recommendations ASN made in the past, including removing some measures from the QIP, creating a more predictable pathway to add new drugs to the bundle, and exploring efforts to increase transplantation and home dialysis. Other areas of concern remain, such as the flawed Bloodstream Infection measure and the lack of a pathway to add new devices to the bundle, and in these instances ASN provided constructive recommendations to the agency.

PEOPLE WITH KIDNEY DISEASE ARE MORE LIKELY TO HAVE GOUT.

Gout Awareness

The Alliance for Gout Awareness works to reduce stigma and empower patients by improving public understanding of gout.

COME LEARN MORE AT ASN KIDNEY WEEK BOOTH #2239

Findings

Steroid-Dependent Nephrotic Syndrome: Rituximab versus Tacrolimus

Rituximab appears more effective than tacrolimus in children with corticosteroid-dependent nephrotic syndrome (CDNS), reports a trial in *JAMA Pediatrics*.

The randomized, open-label trial included children and adolescents (aged 3 to 16 years) with CDNS. The patients, seen at a tertiary care center in India over a 16-month period, had received no previous corticosteroid-sparing therapy. They were randomly assigned to tacrolimus, along with tapering alternate-day prednisolone, for 12 months; or a single course of rituximab, two 375 mg/m² infusions. Twelve-month relapse-free survival was compared between groups.

Of 176 patients screened, 120 were enrolled in the study; all but 3 had 1-year follow-up data. The two treatment groups had similar characteristics. Fifty-three percent were boys, and the mean age was 7.2 years. Mean duration of CDNS was 2.5 years in the tacrolimus group and 2.3 years in the rituximab group; 25% of patients in both groups had a disease duration of less than 1 year. Both groups had a median of 4 relapses; mean cumulative prednisolone dose in the previous year was 246 mg/kg in the tacrolimus group and 239 mg/kg in the rituximab group.

The 12-month relapse-free survival rate was 90.0% for children assigned to the rituximab group, versus 63.3% for those assigned to the tacrolimus group. In a Cox proportional hazards regression model, the relative risk of relapse was five times higher with tacrolimus compared to rituximab.

The median time to first relapse was 40 weeks with rituximab versus 29 weeks with tacrolimus. Multiple relapses occurred in only 2 patients in the rituximab group, compared with 10 in the tacrolimus group.

Despite a higher rate of mild to moderate infections in the tacrolimus group (43.3% versus 21.7%), both treatments were well tolerated. The mean 12-month cumulative corticosteroid dose was 25.8 mg/kg with rituximab versus 86.3 mg/kg with tacrolimus.

The B-lymphocyte-depleting antibody rituximab has emerged as an alternative to the calcineurin inhibitor tacrolimus for children with CDNS. This trial-performed in an area with a high incidence of childhood idiopathic nephrotic syndrome—suggests that rituximab is more effective than tacrolimus as first-line corticosteroid-sparing therapy for pediatric CDNS. In addition to higher relapse-free survival, rituximab reduces corticosteroid exposure and is well-tolerated, without nephrotoxic effects [Basu B, et al. Efficacy of rituximab vs tacrolimus in pediatric corticosteroid-dependent nephrotic syndrome: a randomized clinical trial. JAMA Pediatr 2018; 172:757–764].

Second-Line Sulfonylureas Increase Risks in Type 2 Diabetes

Sulfonylureas are widely used as second-line oral antidiabetic therapy, despite potential cardiotoxicity and hypoglycemia risk. A new UK population-based cohort study suggests that such second-line treatment with sulfonylureas is associated with increased risks of myocardial infarction, death, and severe hypoglycemia. The study was published in the *British Medical Journal*.

Using the UK Clinical Practice Research Datalink, the researchers identified 77,138 patients with type 2 diabetes who started metformin monotherapy between 1998 and 2013. In a prevalent new-user design, the analysis included 23,592 patients who added or switched to sulfonylurea as secondline therapy and the same number of patients who remained on metformin.

The two groups were matched for highdimensional propensity score, hemoglobin A1c, and number of previous metformin prescriptions. The two groups were compared for risk of myocardial infarction, ischemic stroke, death from cardiovascular causes, death from any cause, or severe hypoglycemia. At a mean follow-up of 1.1 years, sulfonylurea therapy was associated with significant increases in myocardial infarction, hazard ratio (HR) 1.26; all-cause mortality, HR 1.15; and severe hypoglycemia, HR 7.60. There were also trends toward increased risk of ischemic stroke and cardiovascular death in patients receiving second-line sulfonylureas. Compared to patients who added sulfonylureas, those who switched to sulfonylureas were at increased risk of myocardial infarction, HR 1.51; and all-cause mortality, HR 1.51.



No Benefit of Tamsulosin for ED Patients with Small Ureteral Stones

Compared to metformin, second-line sulfonylurea therapy for type 2 diabetes was found to be associated with an increased risk of cardiovascular and hypoglycemic events, the authors said.

"Continuing metformin when introducing sulfonylureas appears to be safer than switching," the researchers write [Douros A, et al. Sulfonylureas as second line drugs in type 2 diabetes and the risk of cardiovascular and hypoglycaemic events: population based cohort study. *BMJ* 2018; 362: k2693. The α -adrenergic receptor blocker tamsulosin does not increase passage of small, symptomatic ureteral stones, reports a randomized clinical trial in *JAMA Internal Medicine*.

The two-phase trial included 512 adults seen in the emergency department with symptomatic ureteral stones. All patients had a symptomatic ureteral stone measuring less than 9 mm in diameter (mean 3.8 mm) on computed tomography. About three-fourths of patents were male and one-fourth were non-white; the

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mean age was 40.6 years.

Patients were assigned to 28 days of treatment with tamsulosin, 0.4 mg, or placebo. The main outcome of interest was stone passage by 28 days, determined by the patient's visualization or capture of the stone.

In 497 patients evaluated, there was no significant difference in stone passage rates: 50% with tamsulosin and 47% with placebo. The two groups were also similar in terms of secondary outcomes, including crossover to tamsulosin, time to stone passage, hospitalization, surgery, and repeated ED visits. Exploratory analysis showed no benefit of tamsulosin in patient subgroups according to stone location, size, or location.

Tamsulosin is widely used as "medical expulsive therapy" for patients with urinary stones seen in the ED. Some studies suggest that this treatment is effective mainly for larger stones, reflecting the high rate of spontaneous passage for smaller stones.

Continued on page 22

For the control of serum phosphorus levels in adult patients with chronic kidney disease on dialysis

AURYXIA[®] (ferric citrate), A NON-CALCIUM, NON-CHEWABLE CHOICE FOR CONTROL OF HYPERPHOSPHATEMIA

- Reduced mean serum phosphorus to 4.88 mg/dL in the pivotal study
- Starting dose of 2 tablets 3 times per day with meals
- Demonstrated safety and tolerability over 52 weeks



PREGNANCY AND LACTATION: Overdosing of iron in pregnant women may carry a risk for spontaneous abortion, gestational diabetes and fetal malformation. Rat studies have shown the transfer of iron into milk. There is possible infant exposure when AURYXIA is taken by a nursing woman

ADVERSE REACTIONS: In clinical trials, likely adverse reactions occurring in \geq 5% of patients treated with AURYXIA were discolored feces, diarrhea, constipation, nausea, vomiting, cough, abdominal pain and hyperkalemia

To report suspected adverse reactions, contact Keryx Biopharmaceuticals at 1-844-445-3799

Please see the Brief Summary including patient counseling information on the following page



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PP-AUR-US-0426

12/17

This placebo-controlled trial finds no increase in stone passage rate with tamsulosin prescribed to ED patients with symptomatic ureteral stones smaller than 9 mm. The investigators conclude: "Although tamsulosin may still play a role in medical expulsive therapy for larger stones, guidelines that recommend tamsulosin for ureteral stones may need to be revised" [Meltzer AC, et al. Effect of Tamsulosin on Passage of Symptomatic Ureteral Stones: A randomized clinical trial. JAMA Intern Med 2018; 178: 1051–1057].

Levosimendan Improves GFR in Cardiorenal **Syndrome**



Auryxia (ferric citrate) tablets

AURYXIA® (ferric citrate) tablets for oral use containing 210 mg of ferric iron equivalent to 1 g AURYXIA for oral use. INDICATION AND USAGE

AURYXIA is indicated for the control of serum phosphorus levels in adult patients with chronic kidney disease on dialysis.

CONTRAINDICATIONS

AURYXIA is contraindicated in patients with iron overload syndromes (e.g., hemochromatosis).

WARNINGS AND PRECAUTIONS

Iron Overload: Iron absorption from AURYXIA may lead to excessive elevations in iron stores. Increases in serum ferritin and transferrin saturation (TSAT) levels were observed in clinical trials. In a 56-week safety and efficacy trial evaluating the control of serum phosphate levels in patients with chronic kidney disease on dialysis in which concomitant use of intravenous iron was permitted, 55 (19%) of patients treated with AURYXIA had a ferritin level >1500 ng/mL as compared with 13 (9%) of patients treated with active control. Assess iron parameters (e.g., serum ferritin and TSAT) prior to initiating AURYXIA and monitor iron parameters while on therapy Patients receiving intravenous iron may require a reduction in dose or discontinuation of intravenous iron therapy.

Risk of Overdosage in Children Due to Accidental Ingestion:

Accidental ingestion and resulting overdose of iron-containing products is a leading cause of fatal poisoning in children under 6 y of age. Advise patients of the risks to children and to keep AURYXIA out of the reach of children.

ADVERSE REACTIONS

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 adverse reaction rates in the clinical trials of another drug and may not reflect the rates observed in practice. Hyperphosphatemia in Chronic Kidney Disease on Dialysis

A total of 289 patients were treated with AURYXIA and 149 patients were treated with active control (sevelamer carbonate and/or calcium acetate) during the 52-week, randomized, open-label, active control phase of a trial in patients on dialysis. A total of 322 patients were treated with AURYXIA for up to 28 days in three short-term trials. Across these trials, 557 unique patients were treated with AURYXIA; dosage regimens in these trials ranged from 210 mg to 2,520 mg of ferric iron per day, equivalent to 1 to 12 tablets of AURYXIA. Adverse reactions reported in more than 5% of patients treated with AURYXIA in these trials included diarrhea (21%), discolored feces (19%),

nausea (11%), constipation (8%), vomiting (7%), and cough (6%). During the 52-week, active-control period, 61 patients (21%) on AURYXIA discontinued study drug because of an adverse reaction, as compared to 21 patients (14%) in the active control arm. Patients who were previously intolerant to any of the active control treatments (calcium acetate and sevelamer carbonate) were not eligible to enroll in the study. Gastrointestinal adverse reactions were the most common reason for discontinuing AURYXIA (14%).

DRUG INTERACTIONS

Orally administered doxycycline has to be taken at least 1 hour before AURYXIA. Orally administered ciprofloxacin should be taken at least 2 hours before or after AURYXIA. Oral drugs that can be administered concomitantly with AURYXIA are: amlodipine, aspirin, atorvastatin, calcitriol, clopidogrel, digoxin, diltiazem, doxercalciferol, enalapril, fluvastatin, glimepiride, levofloxacin, losartan, metoprolol, pravastatin, propranolol, sitagliptin, and warfarin.

Oral medications not listed above

There are no empirical data on avoiding drug interactions between AURYXIA and most concomitant oral drugs. For oral medications where a reduction in the bioavailability of that medication would have a clinically significant effect on its safety or efficacy, consider separation of the timing of the administration of the two drugs. The duration of separation depends upon the absorption characteristics of the medication concomitantly administered, such as the time to reach peak systemic levels and whether the drug is an immediate release or an extended release product. Consider monitoring clinical responses or blood levels of concomitant medications that have a narrow therapeutic range.

USE IN SPECIFIC POPULATIONS Pregnancy:

Risk Summary

There are no available data on AURYXIA use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. Animal reproduction studies have not been conducted using AURYXIA. Skeletal and encephalic malformation was observed in neonatal mice when ferric gluconate was administered intraperitoneally to gravid dams on gestation days 7-9. However, oral administration of other ferric or ferrous compounds to gravid CD1-mice and Wistar-rats caused no fetal malformation.

An overdose of iron in pregnant women may carry a risk for spontaneous abortion, gestational diabetes and fetal malformation. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. Adverse outcomes in pregnancy occur regardless of the health of the mother or the use of medications. In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies are 2 to 4% and 15 to 20% respectively. Clinical Considerations

The effect of AURYXIA on the absorption of vitamins and other nutrients has not been studied in pregnant women. Requirements for vitamins and other nutrients are increased in pregnancy. Lactation:

Risk Summary

There are no human data regarding the effect of AURYXIA in human milk, the effects on the breastfed child, or the effects on milk production. Data from rat studies have shown the transfer of iron into milk by divalent metal transporter-1 (DMT-1) and ferroportin-1 (FPN-1). Hence, there is a possibility of infant exposure when AURYXIA is administered to a nursing woman. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for AURYXIA and any potential adverse effects on the breastfed child from AURYXIA or from the underlying maternal condition.

Pediatric Use: The safety and efficacy of AURYXIA have not been established in pediatric patients.

Geriatric Use: Clinical studies of AURYXIA included 292 subjects aged 65 years and older (104 subjects aged 75 years and older). Overall, the clinical study experience has not identified any obvious differences in responses between the elderly and younger patients in the tolerability or efficacy of AURYXIA.

OVERDOSAGE

No data are available regarding overdose of AURYXIA in patients. In patients with chronic kidney disease, the maximum dose studied was 2,520 mg ferric iron (12 tablets of AURYXIA) per day. Iron absorption from AURYXIA may lead to excessive elevations in iron stores, especially when concomitant intravenous iron is used.

In clinical trials, one case of elevated iron in the liver as confirmed by biopsy was reported in a patient on dialysis administered IV iron and AURYXIA.

PATIENT COUNSELING INFORMATION

Dosing Recommendations: Instruct patients to take AURYXIA as directed with meals and adhere to their prescribed diets. Instruct patients on concomitant medications that should be doesd apart from AURYXIA. Advise patients not to chew or crush AURYXIA because tablets may cause discoloration of mouth and teeth.

Adverse Reactions: Advise patients that AURYXIA may cause discolored (dark) stools, but this staining of the stool is considered normal with oral medications containing iron.

AURYXIA may cause diarrhea, nausea, constipation, vomiting, hyperkalemia, abdominal pain, and cough. Advise patients to report severe or persistent gastrointestinal symptoms to their physician. Accidental Ingestion: Advise patients to keep this product out of the reach of children and to seek immediate medical attention in case of accidental ingestion by a child.



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12/17

In patients with heart failure and renal impairment, the calcium sensitizer levosimendan is associated with improved kidney function, compared to no improvement with dobutamine, reports a randomized trial in the open-access Journal of the American Heart Association.

The double-blind trial included 32 patients with chronic heart failure, left ventricular ejection fraction (LVEF) less than 40%; and impaired renal function. Most patients were men in New York Heart Association class III; the most common cause of heart failure was dilated cardiomyopathy. The mean age was 58 years.

Patients were randomly assigned to receive levosimendan, loading dose 12 µg/ kg plus 0.1 µg/kg/min; or dobutamine, 7.5 $\mu g/kg/min)$ for 75 minutes. Mean LVEF was 27.2% in the levosimendan group and 26.0% in the dobutamine group; mean eGFR was 49.4 and 55.3 mL/min/1.73 m², respectively.

Both groups underwent measurement of systemic hemodynamics via pulmonary artery catheter. In addition, a renal artery catheter was placed for measurement of renal plasma flow by the infusion clearance technique for para-aminohippurate (PAH), corrected by renal extraction of PAH. Renal extraction of chromium ethylenediamine tetraacetic acid was used to assess filtration fraction. Changes in renal artery blood flow, GFR, and renal oxygenation were compared between groups.

The two treatments resulted in similar increases in stroke volume index, cardiac index, systemic oxygen delivery, and mixed venous oxygen saturation. Renal blood flow also increased to a similar extent in both groups: by 22% with levosimendan and 26% with dobutamine.

In contrast, levosimendan caused a 22% increase in GFR, compared to no change in the dobutamine group. There was no change in filtration fraction with levosimendan, compared to a 17% decrease with dobutamine. There were no serious adverse events.

Management of cardiorenal syndrome in patients with advanced heart failure poses difficult challenges. Inotropic drugs are an option for selected patients with severely reduced cardiac output with compromised perfusion of the kidney and other organs. In previous studies, levosimendan has shown beneficial effects on renal function in acute and chronic heart failure.

In this trial of short-term inotropic infusion for patients with heart failure and renal impairment, levosimendan and dobutamine produce similar increases in renal blood flow. However, levosimendan increases GFR, which dobutamine does not.

The results suggest "a preferential dilation of preglomerular afferent arterioles," the researchers write. They conclude: "Based on these findings, levosimendan may be the preferred inotropic drug for treatment of patients with the cardiorenal syndrome" [Lannemyr L, et al. Differential effects of levosimendan and dobutamine on glomerular filtration rate in patients with heart failure and renal impairment: A randomized double-blind controlled trial. J Am Heart Assoc 2018; DOI: 10.1161/ JAHA.117.008455].



2018 Scientific Exposition

Thursday, October 25 – Saturday, October 27

Exhibits and Posters Halls A-C | 9:30 a.m. - 2:30 p.m. daily

Highlights Include

- Over 150 Exhibiting Companies
- ASN Communities Lounge
- Career Fair
- Complimentary **Refreshment Breaks**
- Exhibitor Spotlights
- FIT Bowl
- Poster Sessions
- Welcome Reception
- Wi-Fi

Welcome Reception Thursday, October 25

6:30 p.m. - 7:30 p.m.

ASN welcomes you to San Diego with a reception in the exhibit hall the evening of Thursday, October 25.



Communities Lounge Aisles 1700 and 1800

A focal point of your exhibit hall experience, visit the lounge to learn more about ASN Communities online forum, meet the leaders, network with your peers, and unwind at the relaxation zone.



Thursday, October 25 10:30 a.m. – 12:30 p.m. Elimination Round

Which nephrology training team will reign supreme? Stop by and watch teams test their knowledge against their peers. The Fellows-In-Training (FIT) Bowl is a two-day, single elimination tournament held in Exhibit Hall A. Seating is limited.

> Friday, October 26 10:30 a.m. - 11:30 a.m. Semi-Finals

> 11:30 a.m. - 12:30 p.m. Finals

Exhibitor Spotlight Schedule

Join your colleagues for the latest advances in nephrology practices, products, services, and technologies presented in two theaters on the exhibit hall floor (no continuing education credit). Seating is limited and available on a first come, first served basis. All presentations include breakfast or lunch.

Thursday, October 25		Friday, Octobe	Friday, October 26		Saturday, October 27	
10:00 a.m. – 11:00 a.m.	Theater 1	10:00 a.m. – 11:00 a.m.	Theater 1	10:00 a.m. – 11:00 a.m.	Theater 1	
Diagnosing and Managing Fabry	Disease Presented by	2008T BlueStar Hemodialysis M Advancing Dialysis Care	2008T BlueStar Hemodialysis Machine – Advancing Dialysis Care		g from Clinical phrology	
SANOFI	GENZYME 🎝		Presented by		Presented by	
			FRESENIUS MEDICAL CARE		Daiichi-Sankyo	
11:00 a.m. – 12:00 p.m.	Theater 2	11:00 a.m. – 12:00 p.m.	Theater 2	11:00 a.m. – 12:00 p.m.	Theater 2	
A Silent Threat: Hyperkalemia in Diabetes, Heart Failure and CKE	Patients with	Survival After End Stage Renal F Preventing Cardiac Disease in E	- ailure: SRD Patients	Science to Solution: Expanded	Hemodialysis	
	Presented by		Presented by		Baytor	
	relypsa A Vifor Pharma Group Company		STAGE		Daxcer	
12:00 p.m. – 1:00 p.m.	Theater 1	12:00 p.m. – 1:00 p.m.	Theater 1	12:00 p.m. – 1:00 p.m.	Theater 1	
The Role of Parsabiv [™] (etelcalce Treatment of Secondary Hyperpa (HPT) in Adult Patients on Hemo	tide) in the arathyroidism dialysis	Rituxan (Rituximab) for the Treat Granulomatosis with Polyangitis	ment of (GPA) and MPA Presented by	Treating Hyperuricemia in Unco Patients with Chronic Kidney D	ontrolled Gout isease Presented by	
	Presented by		Genentech A Member of the Roche Group	1	HORIZON	
1:00 p.m. – 2:00 p.m.	Theater 2	1:00 p.m. – 2:00 p.m.	Theater 2	1:00 p.m. – 2:00 p.m.	Theater 2	
Thrombotic Microangiopathy Tea	m Approach Presented by	Long-Term Results of Treatment Range of Patients with Type 2 Di	Across a Broad abetes Presented by	Is it More Than a Kidney Stone Managing Patients with a Rare Primary Hyperoxaluria Type 1	: Identifying and Kidney Disease,	
×	LEXÍON °	Janss	en / Pharmaceutical companies of	•\	$\frac{1}{2}$	



The Kidney Health Initiative: Reflections and Future Perspectives

By Prabir Roy-Chaudhury

he Kidney Health Initiative (KHI) was created in September 2012 through the signing of a memorandum of understanding between the American Society of Nephrology and the U.S. Food and Drug Administration. It is important to give recognition here to Dr. Ronald J. Falk, who in his role as ASN President at the time, was the true visionary and champion behind the formation of KHI (together with strong support from FDA leadership).

The rationale behind the formation of KHI was simple. Despite the very significant morbidity, mortality, and economic cost associated with diseases of the kidney, there were almost no new therapies entering the kidney space. The mission for KHI, therefore, was well defined: to create an innovation substrate that would facilitate the passage of drugs, devices, and biologics into the kidney space, and to do so in a multidisciplinary fashion that would include all the diverse stakeholders in the field.

Starting from a small group of interested stakeholders, KHI today comprises over 90 member organizations that include all the different stakeholder groups in the kidney disease area: patients and patient organizations; industry partners including large pharma, small biotech, and dialysis organizations; health professional organizations; and federal agencies (which, in addition to the FDA, include the Centers for Medicare & Medicaid Services [CMS], National Institutes of Health [NIH], and Centers for Disease Control and Prevention [CDC]).

KHI creates an innovation substrate for the passage of safe and effective therapies into the kidney disease area through the coordination of member-driven projects in five priority areas, such that the output of these projects, which can include white papers, data standards, workshops, or roadmaps, will facilitate the passage of drugs, devices, and biologics into the kidney disease area for the benefit of our patients. The five priority areas are 1) Patient Partnerships, 2) Biomarkers and Pathogenesis, 3) Regulatory Interactions, 4) Clinical Trial Design, and 5) Clinical Trial Infrastructure.

A number of our projects, for example, have focused on the development of clinical trial end points (in vascular access, IgA nephropathy, FSGS, lupus nephritis, and primary hyperoxaluria). We hope that the published multi-stakeholder white papers in these areas (with FDA participation) will result in a better defined product development pathway, making it more attractive and less risky for both industry and academia to enter into these areas. Similarly, we hope that an ongoing project that focuses on the development of a patient-centered roadmap for innovative renal replacement therapy-with strong regulatory and reimbursement domains-will serve as a catalyst for interest, investment, and

disruptive innovation in the

dialysis area. A key distinguishing feature of KHI has been the placement of the patient perspective front and center in all of our activities. This has happened in large part owing to a strong and empowered Patient and Family Partnership Council (championed by the late long-time dialysis patient and advocate Celeste Castillo Lee; a Kidney Week Memorial Lectureship in her name is scheduled for Friday, October 26). The Patient and Family Partnership Council is closely involved in all KHI projects (from initial selection to implementation to dissemination of the output), and has been critical to the success and impact of KHI.

So what are the things that KHI has changed over the past 5 years?

At a tangible level I do believe KHI has shown the kidney community that diverse stakeholder groups can in fact work together toward a common achievable goal. In addition, the output from KHI projects is beginning to serve as a catalyst for therapeutic product development in the kidney disease area.

At a more intangible level, I strongly believe that the presence of an organization like KHI has given hope to our patients, created interest and excitement among healthcare professionals caring for kidney patients, and most important, has instilled enthusiasm and confidence in our industry partners. And, not surprisingly, I believe that these intangible benefits are likely to be far more important than the tangible benefits that have accrued as a result of the Kidney Health Initiative.

But what about the future?

My personal view is that the real impact of KHI is yet to come. We have been extremely successful over the past 5 years in bringing the renal community together and in doing projects that we hope will serve as a catalyst to steer interest, innovation, and investment (i³) into the kidney disease area. Having established ourselves as a respected and recognized entity, however, we now need to leverage our infrastructure and our members to do much more. Now is the time for us to be bold, to tackle head on some of the "grand challenges" that we face in kidney disease, such as clinical trial infrastructure, the need to create both a clinical urgency and a business imperative for the development of new therapies for kidney disease, and the targeted use of a combination of information technology and artificial intelligence, within every aspect of kidney disease, in order to develop an individualized precision medicine approach with better screening and stratification pathways. Now is the time for KHI to be the facilitator and convener, the large tent, if you will, for innovation in its broadest sense within the kidney disease area.

On a more personal level, it has been both an incredible honor and a humbling experience to have led the Kidney Health Initiative for the past five years. I owe KHI far more than I could ever have contributed to it. This is because KHI has allowed me to interact with an amazingly diverse and talented group of people, spurring my mind to grow and mature in ways I had never thought possible. I am a far more complete and holistic person today than before I joined KHI, and for that I will always remain grateful to KHI and to all the people who make KHI what it is (the KHI staff [with special mention of Melissa West, the KHI project director], the KHI Board of Directors, our member organizations, and our many friends and champions within FDA, NIH, and CMS who have worked so hard for KHI's success).

Finally, the most important message that I have learned personally from my association with KHI is this: KHI is basically a platform or meeting place for diverse stakeholders in the kidney disease space; the creation of such a meeting place, however, can result in wonderful and impactful progress in the field, in addition to long-lasting friendships.

Prabir Roy-Chaudhury, MD, PhD, FASN, is Professor of Medicine and the Division Director for Nephrology at the University of Arizona. He is departing the position of ASN Co-Chair of KHI in December 2018.



unrestricted and restricted diet periods. Ketorena is a Keto-analogue designed to offer CKD patients on LPD/VLPD

the nutrition that may be needed to avoid protein energy wasting, with reduced nitrogen and other nephrotoxic waste.

Patients can order Ketorena and learn more at ketorena.com or by calling 1-844-980-9933.

RAAS Blockers Linked to Increased Survival in Dialysis Patients

A ntihypertensive medications, including renin angiotensinaldosterone system (RAAS) inhibitors, have a small but significant survival benefit for hemodialysis patients, according to a study in *Kidney International*.

The researchers analyzed data from the International Dialysis Outcomes and Practice Patterns Study (DOPPS) phases 2 to 5 (2002-2015). The study included data on 11,421 patients with incident hemodialysis, over 120 days or less; and 11,421 with prevalent hemodialysis, over 120 days. The exposure of interest was baseline treatment with RAAS inhibitors: angiotensin-converting enzyme inhibitor, angiotensin-receptor blocker (ARB), aldosterone receptor antagonist, or direct renin inhibitor. The effects of treatment with RAAS inhibitors or other antihypertensive agents on allcause mortality were estimated by Cox regression analysis.

Overall, 39% of patients were taking a RAAS inhibitor at baseline. More than 95% of these prescriptions were for ACE inhibitors or ARBs. Prescription of RAAS inhibitors varied widely by region, duration of hemodialysis, and diabetes status, but not by history of congestive heart failure or coronary artery disease.

Prescription of a RAAS inhibitor was associated with a significant reduction in all-cause mortality: adjusted hazard ratio 0.89 in incident hemodialysis patients and 0.94 in the prevalent hemodialysis group.

Beta-blockers and calcium channel blockers were also associated with lower mortality. Among patients with a RAAS inhibitor prescription, the survival benefit appeared greater with ARBs versus ACE inhibitors.

Hemodialysis patients are less likely to receive RAAS inhibitor therapy, reflecting mixed data from clinical trials and concerns about hyperkalemia. This analysis of DOPPS data shows significantly lower all-cause mortality in hemodialysis patients receiving a RAAS inhibitor: by 11% in incident and 6% in prevalent hemodialysis patients.

The study shows no interaction between diabetes, coronary artery disease, or congestive heart failure and the survival benefit of RAAS inhibitors. Randomized trials are needed to clarify RAAS inhibitor prescribing criteria in patients receiving hemodialysis, the authors noted [Karaboyas A, et al. DOPPS data suggest a possible survival benefit of renin angiotensinaldosterone system inhibitors and other antihypertensive medications for hemodialysis patients. *Kidney Int* 2018; 94:589–598]

Physical Function and Walking Linked to Survival in CKD

Rease, self-reported measures of physical functioning and physical activity are independently associated with survival, reports a study in *Clinical Kidney Journal*.

Such self-reported measures of functioning and physical activity may be reasonable surrogates for objective assessments, the study authors noted.

The cohort study included 450 adult patients with CKD not requiring renal replacement therapy (RRT), enrolled in a study of physical therapy in CKD. Fifty-seven percent of the patients were men. The median age was 62 years, and the median eGFR was 29 mL/min/1.73 m².

At enrollment, patients completed questionnaires regarding physical function (the Duke Activity Status Index, or DASI) and habitual activity (the General Practice Physical Activity Questionnaire). Mortality was assessed at a median follow-up of 43 months; renal replacement (RRT) was evaluated as a competing event.

During follow-up, 74 patients died and 101 initiated RRT. For patients above a DASI cutoff score of 19.2, the adjusted subdistribution hazard ratio (SHR) for death was 0.51. Each 1-unit increase in DASI score was associated with a 3% reduction in mortality.

Increased walking was also associated with increased survival. Compared to no walking, adjusted SHRs for mortality were 0.48 for participants who walked less than 1 hour per week, 0.25 for those who walked 1 to 3 hours, and 0.48 for those who walked 3 or more hours per week. For those who reported a walking speed of 3 mph or faster, the adjusted SHR was 0.37, compared to less than 3 mph.

Decreased physical function is a risk factor for mortality in patients with CKD. Higher self-reported physical function, weekly walking time, and walking speed are independently associated with increased survival among CKD patients not initially requiring RRT. Used together with clinical information, the DASI and patient-reported walking behavior may provide useful prognostic information for identifying patients at risk of adverse events, the authors said.

Clarke AL, et al. Association of self-reported physical function with survival in patients with chronic kidney disease. *Clin Kidney J* 2018; DOI: 10.1093/ckj/sfy080.



Chronic Kidney Diseases in Agricultural Communities: A discussion with NIEHS and NIDDK



hronic kidney disease of uncertain origin (CKDu) has increased globally, particularly in agricultural communities. It is unclear whether this condition—also referred to as chronic kidney disease non-traditional etiology (CKDnt), Mesoamerican nephropathy (MeN), and chronic interstitial nephritis in agricultural communities (CINAC), among other terms—represents one common disease, or if it is a syndrome of related ones that differ by region.

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the National Institute of Environmental Health Sciences (NIEHS), both part of the National Institutes of Health (NIH), hosted a workshop on CKD in Agricultural Communities in June 2018 that brought together clinicians, basic scientists, epidemiologists, and public health officials to discuss current gaps in CKDu knowledge.

Bonnie Joubert, PhD, a program director in the Population Health Branch at NIEHS, Brian Berridge, DVM, PhD, Associate Director of the National Toxicology Program, and Susan Mendley, MD, a program director in the Division of Kidney, Urologic, and Hematologic Diseases at NIDDK, jointly answered questions about the condition and the future of related research.

What is CKDu?

CKDu is an increasingly common form of early onset CKD that occurs in specific agricultural regions, including Nicaragua, El Salvador, Sri Lanka, and likely additional areas as well. The numerous names for the condition indicate our lack of certainty of the cause, but nephrologists recognize that it is a primarily tubulointerstitial disease, and those affected do not have the traditional risk factors for CKD: diabetes, hypertension, and advanced age.

Over the past 20 years, the prevalence of CKDu appears to be increasing. It exacts a large death toll and a significant cost to public health systems.

What are the potential contributors to CKDu?

The causes of CKDu are unknown, and this was the guiding purpose for the recent workshop held in Bethesda, MD. There is strong consideration given to environmental exposures (including herbicides, pesticides, heavy metals, and other possibilities), heat stress and underlying genetic susceptibility, or interactions between several of these, but these theories require much more investigation.

Since CKDu is of "unknown origin," how do you define the disease for the purpose of research and for determining its prevalence?

A discrete and widely accepted "case defi-

nition" is, in fact, a gap in the field, which complicates our ability to accurately measure and document how common this disease is. CKDu is typically identified by the absence of traditional risk factors for chronic kidney disease, such as hypertension, diabetes, known causes of glomerulonephritis, or infections in individuals living in certain areas (e.g., Central, South America) and working in roles (e.g., sugarcane workers) known to predispose them to this condition. CKDu typically impacts individuals at younger ages than traditional chronic kidney disease.

In what populations is CKDu found?

CKDu is believed to have caused a serious public health problem in specific countries for decades. It gained global recognition with clearer characterization in the early 2000s, posing a notable burden in Sri Lanka, El Salvador, Guatemala, and Nicaragua, and in India, among others. Those affected are predominantly located in agricultural rural areas and in hot climates, such as along the Pacific coast of Central America and less in the mountains. However, the full extent of the disease is unclear, and more research needs to be done to accurately describe its prevalence and geographical reach.

Where is CKDu expected to be prevalent in the future?

Researchers are actively working to address this very question.

Are there populations with CKDu in the United States?

We are unsure if CKDu contributes to the development of chronic kidney disease among residents of the United States. Researchers are using the United States Renal Data System (USRDS) to look for trends or patterns suggestive of areas of the country with CKDu. There are immigrants in the U.S. from affected areas who may be more likely to have CKDu, as well as U.S.born residents with CKD that cannot be explained by traditional risk factors. However, more data is needed to determine whether these instances can be characterized as CKDu.

How does progression of CKDu differ from that for CKD?

An incomplete characterization of the course of the disease makes this difficult to know. Chronic kidney disease (particularly CKDu) is often not discovered early due to the "silent" progression that can occur over long periods of time. Patients who begin to show evidence of clinical illness may already be in the advanced stages of their disease. Lack of sufficient medical care once diagnosed can also affect our understanding of the prevalence and the rate of progression.

Are there other instances/ experiences of kidney diseases of unknown origin that could help inform research on CKDu?

Balkan Endemic Nephropathy is a chronic kidney disease described in men and women living in farming villages in valleys surrounding tributaries of the Danube River in Bosnia, Croatia, Romania, Bulgaria, and Serbia. Although the condition was recognized decades earlier in horses, the etiology of this disease was unknown until a toxic component (aristolochic acid) was identified in the seed of a local plant (Aristolochia clematitis) that contaminated wheat harvested for flour.

Experimental work has implicated aristolochic acid as a cause for chronic kidney disease in local residents and we now recognize it as an important cause of CKD among users of traditional herbal medicines. Millions more potential patients now encounter this toxin through herbal medication than through contaminated wheat. Investigations into Balkan Endemic Nephropathy considered many of the factors (for example, mycotoxins or heavy metals) that are also being considered as causes or contributors to the current epidemic of CKDu before the toxin was identified.

What could CKDu tell us about other kidney diseases?

CKDu appears to be a form of tubulointerstitial disease, and it is possible that toxicity to tubular cells may initiate the interstitial damage. This may be relevant to other forms of CKD and other tubular toxins. Further study of CKDu may elaborate pathways of tubular cell injury and may help us understand communication between tubular epithelial cells and cells of the interstitium.

Why is understanding of CKDu important to our understanding of the kidney overall?

Studying CKDu may ultimately provide insight into an underlying cause of kidney disease, and how multiple insults, including environmental exposures, can have an impact. among sugarcane and corn workers in El Salvador over a 30-month period.

- Katherine James, PhD, from the University of Colorado, Denver, is investigating CKD and possible CKDu in a rural Colorado population exposed to cadmium and arsenic. Her research is looking to investigate the association between environmental exposure to these materials.
- Lee Newman, MD, also from the University of Colorado-Denver, is looking at CKDu in Guatemalan sugarcane workers. His study looks at biomarkers of exposure and effect, including early biological change, and will advance our ability to identify factors that put individuals at risk for the development of CKDu and also detect illness at preclinical stages.
- Penny Vlahos, PhD, and Stephen L. Schensul, PhD, from the University of Connecticut, lead an interdisciplinary study identifying the environmental, behavioral, and healthcare factors associated with progression of CKDu in Sri Lanka.
- Benjamin D. Humphreys, MD, from Washington University in St. Louis, is investigating the cellular precursors of kidney fibrosis with the goal of targeting these cells with new and effective treatment.
- Sushrut S. Waikar, MD, from Harvard University, is studying blood and urine markers that are associated with kidney fibrosis, which will allow identification of patients at risk of kidney disease progression and will facilitate design of clinical trials to test new therapies.

Are NIDDK and NIEHS any closer to solving the "u" or "unknown" part of CKDu?

The June 2018 meeting entitled Chronic Kidney Diseases in Agricultural Communities brought a broad range of researchers together to address this issue in a multidisciplinary, strategic, and collaborative setting. NIEHS and NIDDK also engage

Studying CKDu may ultimately provide insight into an underlying cause of kidney disease, and how multiple insults, including environmental exposures, can have an impact.

What are the most promising studies about CKDu that NIDDK and NIEHS are undertaking?

NIEHS and NIDDK are actively funding research to understand potential environmental impacts of CKDu. Some examples include:

 Madeleine Scammell, PhD, from Boston University, is focusing on agricultural workers in Central America. She is studying how exposure to the herbicide glyphosate, heavy metals, and heat stress may affect kidney function in activities, such as a collaborative partnership with pathologists, discussion through other workshops, and engaging the agricultural community, to support research efforts in this field.

NIEHS also has a collaborative partnership with the World Health Organization (WHO) through the WHO Collaborating Centre for Environmental Health Sciences. Part of this collaboration involves activities specific to CKDu. For example, an international workshop is planned in partnership across the National Institutes of Health, and the WHO regional representatives Pan American Health Organization (PAHO) and South-East Asia Regional Office (SEARO), as well as the Consortium on the Epidemic of Nephropathy in Central America and Mexico/Consorcio de la Epidemia de la Nefropatía en Centroamérica y México (CENCAM). The workshop will take place March 20–22, 2019, in Costa Rica and will build on the June NIDDK/ NIEHS workshop and previous International Mesoamerican Nephropathy workshops organized by CENCAM.

Finally, the ongoing NIDDK consortium, the Kidney Precision Medicine Project (KPMP), uses renal biopsies from subjects with CKDu to investigate underlying mechanisms involved in progressive loss of renal function, and this will provide insights into chronic kidney diseases in agricultural communities.



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Thursday, October 25, 2018

PLENARY SESSION

Eric Betzig, PhD



scientist who won a Nobel Prize for his work in the area will deliver a state-ofthe-art lecture on "Imaging Cellular Structure and Dynamics from Molecules to Organisms" on Thursday, October 25.

The speaker, Eric Betzig, PhD, is a senior fellow at the Janelia Research Campus of the Howard Hughes Medical Institute in Ashburn, Va. He was co-recipient of the 2014 Nobel Prize in Chemistry for his role in developing superresolution microscopy, particularly his invention of photoactivated localization microscopy (PALM).

Dr. Betzig followed an interesting path to

this discovery. After earning a PhD in applied physics at Cornell University, he became a principal investigator at AT&T Bell Labs. There, he extended his thesis work on near-field optical microscopy, developing the first method to break the diffraction barrier in light microscopy. He explored many applications, including high-density data storage, semiconductor spectroscopy, and super-resolution fluorescence imaging of cells. By 1993, he held a world record for data storage density. He recorded the first super-resolution fluorescence images of cells and was the first to image single fluorescent molecules under ambient conditions, determining their positions to better than 1/40 of the wavelength of light.

Frustrated with technical limitations, Dr. Betzig quit science. In 1996, he became vice president of research and development at his father's machine tool company, where he developed a high-speed motion control technology based on an electrohydraulic hybrid drive with adaptive control algorithms. Commercial failure of this and the other technologies he developed there left him unemployed in 2003 and looking for new directions.

During this period, he teamed with his best friend and Bell Labs colleague, Harald Hess, to invent the super-resolution technique PALM that led to the Nobel Prize.

From 2005 to early 2018, he was a group leader at the Janelia Research Campus, where he continues to work developing new optical imaging technologies for biology.

Dr. Betzig holds 28 U.S. patents. His other honors include receiving the William L. McMillan Award from the University of Illinois and a National Academy of Sciences Award for Initiatives in Research.

Coburn Lecture Will Cover "Anti-Aging Protein" Klotho



Chou-Long Huang, MD, PhD

A research pioneer will deliver the Jack W. Coburn, MD, Endowed Lectureship, entitled "Cellular and Molecular Mechanisms of Action of Klotho," on Thursday, October 25.

The speaker will be Chou-Long Huang, MD, PhD, professor of medicine and director of the division of nephrology at the University of Iowa Carver College of Medicine in Iowa City.

His current research interests focus on WNK kinase in fluid and electrolyte regulation and the role and mechanism of klotho in CKD-mineral and bone disorder (CKD-MBD)

Dr. Huang describes his lecture targetklotho—as "an anti-aging protein predominantly

expressed in the kidney, parathyroid glands, and choroid plexus of the brain. It is a single-pass transmembrane protein with a large extracellular domain. Secreted klotho functions as a humoral factor that regulates several ion channels and transporters, and other processes, including insulin and insulin-like growth factor signaling."

His research has been funded by the National Institutes of Health for more than 20 years and has resulted in the publication of 77 original research articles, 25 invited reviews, and six book chapters.

He has served as an abstract reviewer for and served as co-chair of sessions at ASN annual meetings. He was international editor of Acta Nephrologica and on the editorial board of Current Hypertension Reviews. He is currently on the editorial boards of Frontiers in Renal and Epithelial Physiology and Translational Andrology and Urology.

Dr. Huang received his medical degree from Taipei Medical University in Taiwan and a PhD from the University of California, San Francisco (UCSF). He completed a residency in internal medicine at the University of Iowa and a nephrology fellowship at UCSF. He was on faculty at UCSF for three years, and then at the University of Texas Southwestern Medical Center in Dallas for 20 years, where he held the Jacob Lemann Professorship in Calcium Transport and the Ruth W. and Milton P. Levy, Sr., Chair in Molecular Nephrology. In 2017, he returned to Iowa for his current position as the Roy J. Carver Chair in Internal Medicine.

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

Be sure to visit the ASN Learning Center.

With hours of educational content from past Kidney Weeks, board review programs, and more, the Learning Center is a must-have resource for every nephrologist. Learn more at www.asn-online.org.

Glomerular Disease Expert to Give Brenner Lectureship



Lawrence Holzman, MD

Lawrence Holzman, MD, will speak on "Defining Structure Function Relationship in Glomerular Failure across Disciplines and Diseases" in the Barry M. Brenner Endowed Lectureship on Thursday, October 25.

Dr. Holzman is C. Mahlon Kline Professor of Medicine and chief of the renal, electrolyte, and hypertension division at the University of Pennsylvania in Philadelphia.

An expert in glomerular disease, he is known for his investigations of podocyte biology, where he has contributed to our understanding of the signaling mechanisms that govern podocyte cytoskeletal architecture in health and disease.

His laboratory has been a leader in characterizing the molecular components of the kidney glomerular filter. He established the first evidence to support the hypothesis that its junctional components participate in regulating podocyte morphology by modulating actin cytoskeletal dynamics. The lab has particularly focused on signaling functions of members of the cell adhesion molecules of the nephrin family. The researchers developed a transgenic mouse strategy for examining the functional biology of proteins and their interactions in the podocyte that is now used internationally.

Recognizing early the need to incorporate precision medicine approaches for glomerular disease patients, he helped found two National Institutes of Health (NIH)-sponsored national longitudinal observational studies of these patients: He teamed with Dr. Matthias Kretzler and Dr. Akinlolu Ojo to create the Nephrotic Syndrome Study Network (NEPTUNE) in 2008. He also helped found Cure Glomerulonephropathy (CureGN), a multicenter five-year cohort study of glomerular disease patients.

He has published more than 100 manuscripts, work made possible by the efforts of his talented students and collaborators and by continuous funding from the NIH and other organizations.

Dr. Holzman is also a dedicated educator and mentor. He served as the nephrology fellowship program director at the University of Michigan and directed its NIH-sponsored T32 training program. He currently directs the T32 program at the University of Pennsylvania.

Dr. Holzman has served on multiple NIH and foundation study sections. He served a term as associate editor of the *Journal of Clinical Investigation* and worked on the editorial boards of the *Journal of the American Society of Nephrology* and *Kidney International.* For ASN, he has served on the Grants Review Committee, on the Policy and Advocacy Committee, and as chair of the Glomerular Disease Advisory Group.

He received his MD from the New Jersey Medical School. He completed his internal medicine residency at the hospital of the Medical College of Pennsylvania and his nephrology fellowship at the University of Michigan Hospital. Over some 20 years, he rose to a full professorship at the University of Michigan Medical School. He left Michigan to join the University of Pennsylvania School of Medicine in 2011.

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

Policy Expert to Speak on Consolidation in Healthcare



Janis M. Orlowski, MD

A prominent physician and healthcare executive will deliver the Christopher R. Blagg, MD, Lectureship in Renal Disease and Public Policy on Thursday, October 25. Janis M. Orlowski, MD, will speak on "Consolidation: Friend or Foe²"

Dr. Orlowski is the chief healthcare officer at the Association of American Medical Colleges (AAMC) in Washington, D.C. In this role, she focuses on the interface between the healthcare delivery system and academic medicine, particularly how academic medical centers can leverage their expertise in research and innovation to support reforms. She advocates for academic medicine

as a change leader in healthcare.

She also leads the AAMC Council of Teaching Hospitals and Health Systems, which is composed of approximately 400 U.S. major teaching hospitals and health systems including 64 Veterans Affairs medical centers. Dr. Orlowski serves in a consulting role for several AAMC groups, such as the chief medical officers group and group on resident affairs.

Dr. Orlowski joined AAMC as chief healthcare officer in 2014 following 10 years at MedStar Washington Hospital Center. She began her tenure at MedStar in 2004 as senior vice president and chief medical officer, where she was responsible for clinical care, education, and research at an institution of more than 1500 physicians. In 2007, she was named chief operating officer and chief medical officer at MedStar, and assumed the operational responsibilities for ambulatory, medical, and perioperative services.

Before joining MedStar, Dr. Orlowski began her career at Rush University in Chicago, where she held a number of medical staff leadership positions and faculty appointments from 1985 to 2004, including serving as the associate vice president and executive dean of the medical school.

Board-certified in internal medicine and nephrology, Dr. Orlowski has been in practice for more than 25 years, specializing in acute renal care and transplantation. Her dedication and devotion to medicine has been recognized with numerous teaching excellence awards and appointments to several nationally prominent boards and committees, such as the D.C. Board of Medicine and the United Network for Organ Sharing committee on transplant policy. Dr. Orlowski also serves on the boards of trustees of the Medical College of Wisconsin, Marquette University, and Creighton University.

She received her medical degree with honors from the Medical College of Wisconsin and completed her residency and nephrology fellowship at Rush University Medical Center.

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



Friday, October 26, 2018

Systems Biologist to Speak

on Mapping Cells to Study

PLENARY SESSION



Aviv Regev, PhD

"ell Atlases as Road Maps to Human Disease" is the title of a state-of-the-art lecture to be delivered on Friday, October 26. The speaker will be Aviv Regev, PhD.

Dr. Regev is professor of biology at the Massachusetts Institute of Technology (MIT) in Cambridge, Mass., and director of the Klarman Cell Observatory and Cell Circuits Program at the Broad Institute of MIT and Harvard University. She is also an investigator with the Howard Hughes Medical Institute.

She co-founded and co-leads the international initiative to build a human cell atlas, with the mission to create comprehensive reference

maps of all human cells as a basis for understanding human health and diagnosing, monitoring, and treating disease.

Dr. Regev is a computational and systems biologist whose research centers on understanding how complex molecular circuits function in cells and between cells in tissues. Her lab has been a pioneer of single-cell genomics: inventing key experimental methods and computational algorithms for the field; demonstrating how to apply them to understand cell taxonomies, histological organization, differentiation, and physiological processes; and inferring the molecular and cellular circuits that control the function of cells and tissues in health and disease. Her research has led to the publication of more than 150 papers.

She is a member of the editorial boards of *Cell, Nature/EMBO Molecular Systems Biology*, and *Development*. She was formerly on the boards of *Genome Research* and *Genome Biology*. She serves as senior editor of *eLife* and was associate editor of *PLoS Computational Biology*.

She is on the scientific advisory boards of ThermoFisher Scientific and Syros Pharmaceuticals.

Dr. Regev has received the National Institutes of Health Director's Pioneer Award, the Overton Prize, and innovator prizes from the International Society for Computational Biology, the Earl and Thressa Stadtman Scholar Award from the American Society for Biochemistry and Molecular Biology, and the Paul Marks Prize for Cancer Research from Memorial Sloan Kettering Cancer Center.

Dr. Regev received her doctorate in computational biology from Tel Aviv University in Israel. Prior to joining the Broad Institute and MIT in 2006, she was a fellow at Harvard University, where she developed new approaches to the reconstruction of regulatory networks and modules from genomic data.

M. Amin Arnaout to Receive Homer W. Smith Award



M. Amin Arnaout, MD

Acclaimed physician-scientist M. Amin Arnaout, MD, FASN, will be presented the 2018 Homer W. Smith Award on Friday, October 26. This award recognizes outstanding contributions to understanding how kidneys function in normal and diseased states.

Dr. Arnaout will speak on "Integrins and Kidney Diseases: Basic Concepts and Clinical Implications."

Dr. Arnaout is professor of medicine at Harvard Medical School, principal investigator at the Harvard Stem Cell Institute, and a physician at Massachusetts General Hospital, where he directs the leukocyte biology/inflammation and the structural biology programs.

He has made seminal contributions to basic and translational medical research for more than three decades through more than 200 publications. His discovery of the cell adhesion receptors known as integrins formed a foundation for development of new anti-inflammatory, anti-thrombosis, and anti-fibrosis drugs for treating common diseases affecting the kidney, heart, and other organs.

Dr. Arnaout also made seminal discoveries in other kidney-related fields. He elucidated the autoantibody nature of C3 nephritic factor, revealed the molecular basis of hemodialysis leukopenia, identified neutrophil proteinase 3 as the target antigen of cytoplasmic antineutrophil cytoplasmic antibodies (c-ANCA), elucidated the role of polycystin 1 in the vasculopathy of autosomal dominant polycystic kidney disease, and developed a microfluidic kidney proximal tubule-on-chip device.

Dr. Arnaout served as chief of nephrology at Massachusetts General from 1998 to 2013. During his tenure, the division became the country's largest academic center for patient care, physician training, and research in kidney diseases, hypertension, and transplantation. The division's growth led to a tripling of clinical outpatient visits, a greater than 30% increase in the number of kidney transplants, and a tripling of federal research funding.

He started the hospital's annual Kidney Care day in 2002, a program that has been adopted worldwide. Dr. Arnaout trained generations of physician-scientists, doctoral students, and clinicians who have assumed leading positions at academic centers and in the biotech industry.

Dr. Arnaout has served the profession in many capacities, including as program chair of the 1998 ASN Renal Week and chair of the ASN Science Committee. He served as a council member of the International Society of Nephrology (ISN) and on study sections at the National Institutes of Health (NIH).

Dr. Arnaout's many awards include the ASN Presidential Medal for Excellence Award, the NIH Young Investigator Award, ISN Donald Seldin lectureship awards, and the 2017 Kuwait prize in science.

He received his medical degree from the American University of Beirut, followed by an internal medicine residency at its medical center. He completed nephrology and immunology fellowships at Johns Hopkins Hospital, Boston Children's Hospital, and Harvard Medical School.

ASN KIDNEYWEEK

Talk Will Focus on Vascular Complications in Polycystic Kidney Disease



Terry J. Watnick, MD

A leading researcher in polycystic kidney disease (PKD) will deliver the Robert W. Schrier Endowed Lectureship on Friday, October 26. Terry J. Watnick, MD, will speak on "Vascular Complications in Autosomal Dominant Polycystic Kidney Disease (ADPKD)."

Dr. Watnick is associate professor of medicine at the University of Maryland School of Medicine in Baltimore. She directs the Baltimore Polycystic Kidney Disease Research and Clinical Core Center, which provides a wide variety of research tools to ADPKD investigators.

Research in her laboratory focuses on understanding the biology of cystic kidney diseases. AD-

PKD is the most common of these disorders and is caused by mutations in two genes: *PKD1* (which provides instructions for making the protein polycystin-1) and *PKD2* (which controls the protein polycystin-2). ADPKD is a systemic disorder characterized by renal cysts, liver cysts, and a number of vascular complications. Dr. Watnick's research uses a variety of model systems and organisms to understand the biology of these proteins.

A particular focus is the vascular phenotype associated with *PKD1/2* mutations in humans and in mice. The lab has discovered new roles for polycystins in the vasculature, in both endothelial cells and vascular smooth muscle cells, in a quest to understand why mutations in PKD proteins result in vascular consequences such as aneurysms in humans as well as edema and hemorrhage in mutant mice.

The Baltimore Polycystic Kidney Disease Research and Clinical Core Center works to promote translational PKD research by providing unique tools and reagents to a diverse national and international group of investigators. The center has generated many of the reagents that have driven the PKD field forward and has assembled a bio-bank of clinical samples with detailed clinical information from more than 100 individuals with ADPKD.

Dr. Watnick served on the editorial board of *Advances in Chronic Kidney Disease* and is currently on the board of the *Journal of the American Society of Nephrology*. She serves as a peer reviewer for a half dozen other journals. She has served as an abstract reviewer for ASN Kidney Week and the International Society of Nephrology meeting as well as on the scientific advisory board of the PKD Foundation. She has published more than 50 peer-reviewed articles and four book chapters, presented 45 abstracts, and holds a patent on detection and treatment of PKD.

Her many awards include a physician-scientist award from the National Institutes of Health.

Dr. Watnick received her MD degree from the Yale School of Medicine and stayed on for an internal medicine residency at Yale New Haven Hospital. She then moved to Johns Hopkins where she completed both clinical and research fellowships in nephrology.

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

Transplant Recipient and Advocate to Examine Patients as Partners



David M. White

"Designing Innovative Alternatives to RRT: Patients as Partners" is the title of the Celeste Castillo Lee Memorial Lectureship, scheduled for Friday, October 26.

The speaker will be David M. White, a healthcare consultant with expertise in patient-centered care, patient engagement, and kidney disease awareness and prevention. He is a kidney transplant recipient and a veteran of six years of in-center, in-center nocturnal, and peritoneal dialysis. His expertise stems from advocacy for himself and others with kidney diseases.

Mr. White serves on the boards of directors of the American Association of Kidney

Patients, the Kidney Health Initiative (KHI), and the Veterans Transplantation Association. He chairs the KHI Patient and Family Partnership Council and co-chairs the Advisory Panel on Patient Engagement of the Patient-Centered Outcomes Research Institute.

He is a member of the American Society of Transplantation Transplant Community Advisory Council, the ESRD National Coordinating Center Health Services Advisory Group, the National Kidney Foundation Kidney Advocacy Committee, and the Quality Insights Mid-Atlantic Renal Coalition Patient Advisory Committee. He served as a technical expert panelist for the Centers for Medicare & Medicaid Services.

Professionally, Mr. White has many years of experience as an information technology consultant and office information systems manager. He has been a self-employed healthcare advocate for the past seven years. He is a frequent presenter at local, regional, and national conferences and has made regional and national television appearances as a patient advocate.

He studied mathematics and political science at Yale University and is a U.S. Army veteran. Mr. White lives in Hillcrest Heights, Md.

Visit the ASN Services booth in Lobby C to claim your CME credits for Kidney Week. ASN Services is open from 7:00 a.m. to the end of the business day. PLENARY SESSION

NIDDK Director to Speak on Sickle Cell Anemia



Griffin P. Rodgers, MD

"Sickle Cell Anemia: Yesterday, Today, and Tomorrow" is the title of a state-of-the-art lecture to be delivered by Griffin P. Rodgers, MD, director of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) on Saturday, October 27.

Dr. Rodgers was named NIDDK director in 2007, after serving as the institute's deputy director since 2001. In his position as director, he provides scientific leadership and manages a staff of over 600 employees and a \$2 billion budget.

Dr. Rodgers is widely recognized for research that led to the development of the first effective therapy for sickle cell anemia. The drug, hydroxyurea, was

the first approved by the Food and Drug Administration to treat the disease and has increased survival rates.

In addition, he and his collaborators have reported on a modified blood stemcell transplant regimen that is highly effective in reversing sickle cell disease in adults and is associated with relatively low toxicity. Early studies have found that more than half of patients treated were able to stop anti-rejection medications one year after the transplant, meaning they had achieved "stable mixed-donor chimerism," a condition in which a person has two types of cells in their blood.

His research has led to more than 250 original research articles, reviews, and book chapters. He has edited four books and monographs and holds three patents.

He has been honored for his research with numerous awards, including the Richard and Hinda Rosenthal Foundation Award, the Arthur S. Flemming Award from George Washington University, and the Legacy of Leadership Award from Howard University Hospital, among others.

Dr. Rodgers received his medical degree from Brown University. He performed his residency in internal medicine at Barnes Hospital at Washington University and chief residency in internal medicine at the John Cochran VA in St. Louis. His fellowship training in hematology was in a joint program of the National Institutes of Health with George Washington University. In addition to his medical and research training, he earned an MBA with a focus on the business of medicine and science from Johns Hopkins University.

Dr. Rodgers to Receive the ASN President's Medal

NIDDK Director Griffin P. Rodgers, MD, will be honored with the ASN President's Medal on Saturday, October 27. Dr. Rodgers' scientific leadership and management of NIDDK are widely recognized as providing a catalyst for generating discoveries that will ultimately cure kidney diseases. A tireless advocate for people with kidney diseases, he is also widely known for his work on sickle cell anemia. Each year, ASN awards the ASN President's Medal to individuals who have helped advance the society's mission to "lead the fight against kidney disease by educating health professionals, sharing new knowledge, advancing research, and advocating the highest quality care for patients."

ASN to Bestow Belding H. Scribner Award on John T. Daugirdas



John T. Daugirdas, MD

professional organizations.

Dr. Daugirdas has spent many years investigating how best to use various forms of dialysis to treat patients who have CKD. He has focused on two areas of critical importance to dialysis patients: dialysis adequacy and dialysis hypotension.

of Illinois at Chicago.

The Belding H. Scribner Award will be tendered

to John T. Daugirdas, MD, FASN, on Saturday,

October 27, for his career-long contributions

to the practice of nephrology. Dr. Daugirdas is

Clinical Professor of Medicine in the Division of

Nephrology and Hypertension at the University

ner Award is presented to individuals who have

made outstanding contributions to the care of

patients with renal disorders or have substan-

tially influenced the clinical practice of nephrol-

ogy. Dr. Daugirdas has made significant contri-

butions in patient care, research, and service to

Established in 1995, the Belding H. Scrib-

Under his leadership, the University of Illinois participated as a Clinical Center in the HEMO Trial, a major randomized trial looking at dialysis adequacy. He also participated in the Frequent Hemodialysis Network Trials, which evaluated the potential benefits of dialysis given more frequently than 3 times per week.

Dr. Daugirdas is co-editor of the *Handbook of Dialysis* and editor of the *Handbook of Chronic Kidney Disease Management*. In 1995, he founded a Web journal, *Hypertension, Dialysis* and *Clinical Nephrology*, which continues to highlight advances in nephrology including articles, abstracts, and meeting presentations. He is current editor of *Hemodialysis International*.

He serves on the editorial boards of the Journal of the American Society of Nephrology, American Journal of Chronic Kidney Disease, American Journal of Nephrology, and Nephron Clinical Practice. He has previously been on the editorial boards of Kidney International, International Journal of Artificial Organs, American Society for Artificial Internal Organs (ASAIO) Journal, Dialysis and Transplantation, Journal of Blood Purification, and American Journal of Kidney Diseases.

He has served on guideline-writing committees, the ASAIO program committee and membership committee, the International Society of Nephrology informatics committee, meeting planning committees of the National Kidney Foundation, National Institutes of Health committees, and Centers for Medicare & Medicaid Services technical expert panels.

Dr. Daugirdas is a graduate of Northwestern University's Honors Program in Medical Education at Chicago. He completed a surgical internship at Boston University, a surgical residency at McGill University in Montreal, and an internal medicine residency and nephrology fellowship at the Veterans Administration Hospital in Hines, Ill.

Nancy Day Adams to Be Given Robert G. Narins Award for Contributions in Education



Nancy Day Adams, MD

Nancy Day Adams, MD, will receive the Robert G. Narins Award on Saturday, October 27, for her many efforts in education and training the next generation of nephrologists.

Dr. Adams is professor emeritus after retiring as professor of clinical medicine in nephrology at the University of Connecticut Health Center in Farmington. She retired in March 2017 as chief of the division of nephrology, a position she held for more than 20 years. She was also training program director in nephrology for a similar time.

She has been active in medical education throughout her career, teaching in all four years of medical school. She headed the Liaison Committee on Medical Education task force for the school of medicine and was a women's liaison officer to the American Association of Medical Colleges. She was the founding director of electives for pre-clinical medical students, participating in curriculum reform. She has been involved in resident and fellow teaching and served as mentor, adviser, and career counselor for many future specialists.

For ASN, Dr. Adams served as director of education for fellowship training, chaired the training program directors' executive committee, and was a founding member of the Workforce and Training Committee. She served as point person for nephrology on the Association of Specialty Professors Council. She was program chair for two years of the joint Women in Nephrology–ASN professional development seminar. She also served on the education committee of the American Society for Bone and Mineral Research.

She was active in conducting patient-centered research, including retrospective reviews of dialysis care in prisoners and patients with genetic diseases.

John P. Peters Award to Honor William G. Couser



William G. Couser, MD, FASN

of the division of nephrology.

Dr. Couser's career is remarkable for the breadth and importance of his contributions to nephrology. His achievements include seminal research that changed the way in which the pathogenesis of glomerulonephritis is understood, important clinical studies, leadership of the two largest renal organizations in the world, editorship of the world's top-ranked nephrology journal, involvement in education and advancing nephrology in the developing world, and training nephrologists who have gone on to their own distinguished careers.

He has served as president of both ASN and the International Society of Nephrology (ISN). He directed the ISN Global Outreach Programs for five years, organizing educational events in 61 developing countries. As ISN president in 1996, he designated the second Thursday of March each year as World Kidney Day, an event now celebrated in over 100 countries.

Dr. Couser is internationally recognized for his research elucidating disease processes of the kidney, particularly immunologic mechanisms of kidney diseases and glomerulonephritis. His work was instrumental in changing the understanding of the pathogenesis of glomerulonephritis to the current concept that most forms are autoimmune diseases with injury resulting primarily from immune deposit formation.

He has published more than 340 peer-reviewed scientific articles, reviews, and book chapters; lectured in more than 60 countries; and won several teaching awards for his ability to depict complex mechanisms using unique animated slides he creates himself.

He is co-editor of the reference textbook Immunologic Kidney Diseases. From 2001 to 2007, he was editor-in-chief of the *Journal of the American Society of Nephrology*.

His many honors include the David Hume Award of the National Kidney Foundation and the Joel Kopple Award of the International Federation of Kidney Foundations.

Dr. Couser received his medical degree from Harvard Medical School. He completed residencies in internal medicine at the University of California in San Francisco and at Boston City Hospital and fellowship training in nephrology at the University of Chicago Pritzker School of Medicine before joining the faculty there in 1972. He was on the faculty at Boston University from 1973 to 1982, when he moved to the University of Washington in Seattle. He retired from clinical and administrative responsibilities in 2004 to devote full time to his editorial responsibilities and international promotion of nephrology.

ASN will recognize the wide-ranging contributions of William G. Couser, MD, FASN, with the presentation of the John P. Peters Award on Saturday, October 27.

The John P. Peters Award is given to those who have made substantial research contributions to the discipline of nephrology and have sustained achievements in one or more domains of academic medicine including clinical care, education, and leadership.

Dr. Couser is affiliate professor of medicine in the division of nephrology at the University of Washington School of Medicine in Seattle. From 1982 through 2004, he was the Belding H. Scribner Professor of Medicine and (through 2002) head

Glomerular Basement Membrane Will Be Lecture Subject



Rachel Lennon, MBBS, PhD, will discuss "Evolving Complexity of the Glomerular Basement Membrane" in the Michelle P. Winn Endowed Lectureship on Saturday, October 27.

Dr. Lennon is a Wellcome Trust senior research fellow in clinical science and professor of nephrology at the University of Manchester in the U.K. She is also a consultant pediatric nephrologist at the Royal Manchester Children's Hospital.

Her research is focused on understanding mechanisms of glomerular disease, the leading cause of

Rachel Lennon, MBBS, PhD

CKD in adults and children. Her overarching research question concerns how the glomerular filtration barrier is regulated in health and disrupted in disease.

Early in her career, she made a series of discoveries to support the concept that cells of the glomerular capillary wall respond to chemical and physical cues from their microenvironment.

Her research group has developed proteomic approaches to defining the molecular landscape of cell-matrix adhesion in the glomerulus and created a setting to explore disease processes in a global manner. The group aims to improve understanding of the mechanisms of disease as a step toward developing targeted treatment for glomerular disease.

Among its achievements, the research group has used tissue proteomics to define the human glomerular matrisome and discover structural and regulatory matrix proteins; identified a core network of matrix proteins that may be necessary for basement membrane assembly in the glomerulus; discovered that mice with susceptibility to glomerular insult have structural defects in their glomeruli well before they develop overt disease; and generated high-quality proteomic data sets that are available to the research community.

Her research has led to the publication of some 30 peer-reviewed articles, 12 reviews, and four book chapters.

Dr. Lennon is active in professional organizations as well, for example, serving as the research secretary for the British Association of Paediatric Nephrology and the lead of the clinical studies group.

Dr. Lennon graduated from Nottingham University Medical School and trained in clinical pediatrics in Nottingham and London. She completed subspecialty training in pediatric nephrology in Bristol. She was awarded a Wellcome Trust research training fellowship in 2004 and completed her PhD studying circulating mediators of kidney diseases. She was appointed to a National Institutes for Health Research academic clinical lectureship in 2007 and in 2008 began working at the Wellcome Trust Centre for Cell-Matrix Research in Manchester. In 2010, she was awarded a Wellcome Trust intermediate clinical fellowship to establish her research group. In 2016, she was awarded a Wellcome Trust senior research fellowship in clinical science.

ASN gratefully acknowledges Duke University School of Medicine, the school's Division of Nephrology, and several individuals for support of the Michelle P. Winn, MD, Endowed Lectureship.

Dr. Adams has spoken at annual meetings of the Group on Women in Medicine and Science, at the Connecticut State Medical Society women in medicine meeting, and at numerous universities and hospitals nationally.

Among many honors, she received the Laureate Award and the George Thornton Teaching Award from the Connecticut Chapter of the American College of Physicians. She was named Master of the American College of Physicians in 2017.

Dr. Adams is a graduate of the University of Oregon Medical School. She served as resident, chief resident, and nephrology fellow at the Medical College of Wisconsin in Milwaukee. During her fellowship, she spent six months as a clinical research registrar at the Churchill Hospital renal unit in Oxford, England. She began her career as a faculty member at the Medical College of Wisconsin and the University of Texas Health Science Center at San Antonio. She was recruited to the University of Connecticut School of Medicine in 1984. PLENARY SESSION

Lecture Explores Relationship of Data and Better Health Outcomes



Robert M. Califf, MD

mproving Health Outcomes in the Era of Data Ubiquity" is the title of a stateof-the-art lecture to be given on Sunday, October 28.

The speaker will be Robert M. Califf, MD, vice chancellor for health data science at Duke University and Donald F. Fortin, MD, Professor of Cardiology in the university's medical school. He is also director of Duke Forge, the university's center for health data science.

Dr. Califf served in the Obama administration as deputy commissioner for medical products and tobacco in the Food and Drug Administration (FDA) from 2015 through

2016, and as commissioner of food and drugs from 2016 through 2017. Prior to joining the FDA, Dr. Califf was a professor of medicine and vice chancellor for clinical and translational research at Duke University. He was the founding director of the Duke Clinical Research Institute.

A nationally and internationally recognized expert in cardiovascular medicine, health outcomes research, healthcare quality, and clinical research, Dr. Califf has led many landmark clinical trials and is one of the most frequently cited authors in biomedical science, with 1250 publications in the peer-reviewed literature.

He has served on numerous Institute of Medicine committees and was a member of the FDA Cardiorenal Advisory Panel and FDA Science Board Subcommittee on Science and Technology. Dr. Califf has been a member of advisory committees for the National Library of Medicine; National Cancer Institute; National Heart, Lung, and Blood Institute; National Institute of Environmental Health Sciences; and National Institute on Aging. He has also served on committees of the American College of Cardiology and American Heart Association and was editor-in-chief of American Heart Journal for a decade.

Dr. Califf has led major initiatives aimed at improving methods and infrastructure for clinical research, including the Clinical Trials Transformation Initiative, a public-private partnership co-founded by the FDA and Duke. He also served as the co-principal investigator of the National Patient-Centered Clinical Research Network (PCORnet). He currently chairs the board of the People-Centered Research Foundation, a nonprofit organization that supports the work of PCORnet.

Dr. Califf is a graduate of Duke University School of Medicine. He completed a residency in internal medicine at the University of California, San Francisco, and a fellowship in cardiology at Duke.

Young Investigator Recognized for Insights on Population Data in Patient Care

The Donald W. Seldin Young Investigator Award cosponsored by ASN and the

American Heart Association Council on

the Kidney in Cardiovascular Disease will

be presented to Morgan Grams, MD, PhD, MHS, who will speak on "Using Population

Data to Inform Patient Care in Nephrol-

cine and epidemiology in the division of nephrology at Johns Hopkins University

in Baltimore. She is director of nephrology

initiatives for the Chronic Kidney Disease

Prognosis Consortium, an 11-million par-

ticipant global consortium with a coordinat-

Dr. Grams is associate professor of medi-

ogy" on Sunday, October 28.



Morgan Grams, MD, PhD, MHS

ing center at Johns Hopkins.

She also maintains active research programs in the metabolomics and genomics of kidney diseases as well as drug safety in CKD. Research in the Morgan Grams Lab focuses on preventing and ameliorating the complications associated with CKD. Recent work includes examining the racial differences in and prognostic value of biomarkers of hyperglycemia. The researchers have also developed an online tool to help identify living kidney donor candidates by weighing a variety of factors to assess the long-term risk of end stage renal disease.

Dr. Grams has worked with several studies, including the Atherosclerosis Risk in Communities study and the Chronic Kidney Disease Prognosis Consortium.

She serves as associate editor of the American Journal of Kidney Diseases and is on the editorial board of the Clinical Journal of the American Society of Nephrology. She is a peer reviewer for eight journals, including the Lancet.

She has served as a professional development award grant reviewer for the National Kidney Foundation, abstract reviewer for the American Diabetes Association, and an abstract reviewer for ASN Kidney Week.

Dr. Grams received the Gold Humanism Award from the Columbia University College of Physicians and Surgeons and the Young Investigator Award from the American Transplant Congress.

She received her medical degree from Columbia University and her master's and doctoral degrees from the Johns Hopkins Bloomberg School of Public Health. She completed an internal medicine residency at New York Presbyterian-Columbia University and a nephrology fellowship at Johns Hopkins.

ASN thanks the American Heart Association's Council on the Kidney in Cardiovascular Disease for co-sponsorship of the Donald W. Seldin Young Investigator Award.



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STATE-OF-THE-ART LECTURE

SAVING AND SUSTAINING LIVES TOGETHER ASN KIDNEY WEEK 2018

JOIN US AND INVESTIGATE NEW POSSIBILITIES FOR RENAL PATIENTS AND THE THERAPIES THAT SUPPORT THEM

Baxter is proud to be participating in ASN Kidney Week 2018. As always, this event brings together the global renal care community to discuss, explore and discover ways to provide the best possible care for individual PD, HD and acute patients. We look forward to seeing you there!



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- Our latest ASN news and media
- Information on our ASN Spotlight sessions
- And much more!

GLBL/MG130/18-0001a



Learn more about slowing **ADPKD** progression at JYNARQUEhcp.com

INDICATION and IMPORTANT SAFETY INFORMATION for JYNARQUE[™] (tolvaptan)

INDICATION:

JYNARQUE is indicated to slow kidney function decline in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD).

IMPORTANT SAFETY INFORMATION:

WARNING: RISK OF SERIOUS LIVER INJURY

• JYNARQUE (tolvaptan) can cause serious and potentially fatal liver injury. Acute liver failure requiring liver transplantation has been reported

 Measure transaminases (ALT, AST) and bilirubin before initiating treatment, at 2 weeks and 4 weeks after initiation, then monthly for the first 18 months and every 3 months thereafter. Prompt action in response to laboratory abnormalities, signs, or symptoms indicative of hepatic injury can mitigate, but not eliminate, the risk of serious hepatotoxicity.

 Because of the risks of serious liver injury, JYNARQUE is available only through a Risk Evaluation and Mitigation Strategy program called the JYNARQUE **REMS** Program

CONTRAINDICATIONS:

- History, signs or symptoms of significant liver impairment or injury. This contraindication does not apply to uncomplicated polycystic liver disease
 Taking strong CYP3A inhibitors
 With uncorrected abnormal blood sodium concentrations
- Unable to sense or respond to thirst
- Hypovolemia

- Hypersensitivity (e.g., anaphylaxis, rash) to JYNARQUE or any component of the product
- Uncorrected urinary outflow obstruction
- Anuria

Serious Liver Injury: JYNARQUE can cause serious and potentially fatal liver injury. Acute liver failure requiring liver transplantation has been reported in the postmarketing ADPKD experience. Discontinuation in response to laboratory abnormalities or signs or symptoms of liver injury (such as fatigue, anorexia, nausea, right upper abdominal discomfort, vomiting, fever, rash, pruritus, icterus, dark urine or jaundice) can reduce the risk of severe hepatotoxicity. To reduce the risk of significant or irreversible liver injury, assess ALT, AST and bilirubin prior to initiating JYNARQUE, at 2 weeks and 4 weeks after initiation, then monthly for 18 months and every 3 months thereafter.

Hypernatremia, Dehydration and Hypovolemia: JYNARQUE therapy increases free water clearance which can lead to dehydration, hypovolemia and hypernatremia. Instruct patients to drink water when hypernatremia. Instruct patients to drink water when thirsty, and throughout the day and night if awake. Monitor for weight loss, tachycardia and hypotension because they may signal dehydration. Ensure abnormalities in sodium concentrations are corrected before initiating therapy. If serum sodium increases above normal or the patient becomes hypovolemic or dehydrated and fluid intake cannot be increased, suspend IXNAROUE until serum sodium hydration suspend JYNARQUE until serum sodium, hydration status and volume status parameters are within the normal range.

HELP CONSERVE NEPHRON FUNCTION BY SLOWING THE DECLINE OF KIDNEY FUNCTION WITH THE FIRST AND ONLY FDA-APPROVED TREATMENT FOR ADPKD

JYNARQUE[™] (tolvaptan) slows disease progression, so you can finally take a stand against ADPKD

ADPKD=autosomal dominant polycystic kidney disease.

Inhibitors of CYP3A: Concomitant use of JYNARQUE with drugs that are moderate or strong CYP3A inhibitors (e.g., ketoconazole, itraconazole, lopinavir/ritonavir, indinavir/ritonavir, ritonavir, and conivaptan) increases tolvaptan exposure. Use with strong CYP3A inhibitors is contraindicated; dose reduction of JYNARQUE is recommended for patients taking moderate CYP3A inhibitors. Patients should avoid grapefruit juice beverages while taking JYNARQUE

Adverse Reactions: Most common observed adverse reactions with JYNARQUE (incidence >10% and at least twice that for placebo) were thirst, polyuria, nocturia, pollakiuria and polydipsia.

Other Drug Interactions:

- Strong CYP3A Inducers: Co-administration with
- strong CYP3A inducers: co administration with strong CYP3A inducers reduces exposure to JYNARQUE. Avoid concomitant use of JYNARQUE with strong CYP3A inducers **OATP1B1/3 and OAT3 Transporter Substrates:** Patients who take JYNARQUE should avoid concomitant use with OATP1B1/B3 and OAT3 substrates (e.g., statins, bosentan, glyburide, nateglinide, repaglinide, methotrexate, furosemide), as the plasma concentrations of these substrates may be increased.
- **BCRP Transporter Substrates:** Tolvaptan is an inhibitor of BCRP. Patients who take JYNARQUE, should avoid concomitant use with BCRP substrates (e.g., rosuvastatin)
- /2-Receptor Agonist: Tolvaptan interferes with the V_2^2 -agonist activity of desmopressin (dDAVP). Avoid concomitant use of JYNARQUE with a V_2 -agonist.

Pregnancy and Lactation: Based on animal data, JYNARQUE may cause fetal harm. In general, JYNARQUE should be discontinued during pregnancy. Advise women not to breastfeed during treatment with JYNARQUE.

To report SUSPECTED ADVERSE REACTIONS, contact Otsuka America Pharmaceutical, Inc. at 1-800-438-9927 or FDA at 1-800-FDA-1088 (www.fda.gov/medwatch).

Please see Brief Summary of FULL PRESCRIBING INFORMATION, including **BOXED WARNING**, on the following pages.



Otsuka

Otsuka America Pharmaceutical, Inc. Manufactured by Otsuka Pharmaceutical Co., Ltd., Tokyo,

101-8535 Japan.

Distributed and marketed by Otsuka America Pharmaceutical, Inc., Rockville, MD 20850.

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Dialyze Direct Acquires Affiliated Dialysis Centers

ialyze Direct, LLC, a leading provider of staff-assisted home hemodialysis services in skilled nursing facilities with geriatric populations, has signed an agreement to acquire Affiliated Dialysis Centers, LLC, an established dialysis provider with corporate headquarters in Glen Ellyn, IL.

An independent regional provider of dialysis services serving more than 400 patients in Illinois and Ohio, Affiliated Dialysis Centers will effectively double its current patient count under the purchase agreement with Dialyze Direct, said Dialyze Direct CEO Josh Rothenberg.

This acquisition "will propel us as a leader across the nation in staffing for hemodialysis in skilled nursing facilities," said Alice Hellebrand, Dialyze Direct's chief nursing officer.

The acquisition will bring Affiliated's skilled nursing facility dialysis business the outcomes model and turnkey dialysis approach used by Dialyze Direct. Both companies also have a home-based hemodialysis component.

Hellebrand said in an interview that Dialyze Direct is benchmarked against national averages, and "we are defining the geriatric population that requires dialysis, particularly dialysis patients in skilled nursing homes.' She noted that the company has developed protocols and policies related to this specific patient population. The average patient age is above 65 years.

JYNARQUE[™] (tolvaptan)

The ability to improve patient health, assist the skilled nursing facilities in procedural work, and help them work with payers is helping Dialyze grow into an attractive business model. "We hope to expand into 6 more states by the end of 2019, Rothenberg said.

Dialyze Direct currently has operations in Florida, Texas, New York, New Jersey, Ohio, and Pennsylvania. Its purchase of Affiliated Dialysis Centers is expected to be complete in December 2018.

JYNARQUE™ (tolvaptan) tablets for oral use Brief summary of PRESCRIBING INFORMATION. See full prescribing information for Brief summa JYNARQUE.

WARNING: RISK OF SERIOUS LIVER INJURY

- DYNARQUE (tolvaptan) can cause serious and potentially fatal liver injury. Acute liver failure requiring liver transplantation has been reported Measure ALT, AST and bilirubin before initiating treatment, at 2 weeks and 4 weeks after initiation, then monthly for the first 18 months and every 3 months thereafter. Prompt action in response to laboratory abnormalities, signs, or symptoms indicative of hepatic injury can mitigate, but not eliminate, the risk of serious hepatotoxicity.
- Because of the risks of serious liver injury, JYNARQUE is available only through a restricted distribution program under a Risk Evaluation and Mitigation Strategy (REMS) called the JYNARQUE REMS Program.

INDICATIONS AND USAGE: JYNARQUE is indicated to slow kidney function decline in adults at

risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD). CONTRAINDICATIONS: JYNARQUE is contraindicated in patients:

- With a history, signs or symptoms of significant liver impairment or injury. This contraindication does not apply to uncomplicated polycystic liver disease Taking strong CYP 3A inhibitors With uncorrected abnormal blood sodium concentrations Unable to sense or respond to thirst

- Hypovolemia Hyporsensitivity (e.g., anaphylaxis, rash) to tolvaptan or any component of the product Uncorrected urinary outflow obstruction

WARNINGS AND PRECAUTIONS

Serious Liver Injury: JYNARQUE can cause serious and potentially fatal liver injury. Acute liver failure quiring liver transplantation has been reported in the post-marketing ADPKD experience iscontinuation in response to laboratory abnormalities or signs or symptoms of liver injury (such a tigue, anorexia, nausea, right upper abdominal discomfort, vomiting, fever, rash, pruritus, icterus, darl ine or jaundice) can reduce the risk of severe hepatotoxicity. fatigue, anorexia. na

In a 3-year placebo-controlled trial and its open-label extension (in which patients' liver tests were monitored every 4 months), evidence of serious hepatocellular injury (elevations of hepatic transaminases of at least 3 times ULN combined with elevated bilirubin at least 2 times the ULN) occurred in 0.2% (3/1487) of tolvaptan treated patients compared to none of the placebo treated patients.

To reduce the risk of significant or irreversible liver injury, assess ALT, AST and bilirubin pr initiation of JYNARQUE, at 2 weeks and 4 weeks after initiation, then monthly for 18 months and 3 months thereafter.

At the onset of signs or symptoms consistent with hepatic injury or if ALT, AST, or bilirubin increase to >2 times ULN, immediately discontinue JYNARQUE, obtain repeat tests as soon as possible (within 48-72 hours), and continue testing as appropriate. If laboratory abnormalities stabilize or resolve, JYNARQUE may be reinitiated with increased frequency of monitoring as long as ALT and AST remain

below 3 times ULN

below 3 times ULN. Do not restart JYNARQUE in patients who experience signs or symptoms consistent with hepatic injury or whose ALT or AST ever exceeds 3 times ULN during treatment with tolvaptan, unless there is another explanation for liver injury and the injury has resolved. In patients with a stable, low baseline AST or ALT, an increase above 2 times baseline, even if less than 2 times upper limit of normal, may indicate early liver injury. Such elevations may warrant treatment suspension and prompt (48-72 hours) re-evaluation of liver test trends prior to reinitiating therapy with more frequent monitoring.

more frequent monitoring. JYNARQUE REMS Program: JYNARQUE is available only through a restricted distribution program under a Risk Evaluation and Mitigation Strategy (REMS) called the JYNARQUE REMS Program winder a Risk Evaluation and Mitigation Strategy (NLWE) summer because of the risks of liver injury. Notable requirements of the JYNARQUE REMS Program include the following:

 Prescribers must inform patients recoving JYNARQUE about the risk of hepatotoxicity ass with its use and how to recognize the signs and symptoms of hepatotoxicity and the app with the second symptometry of the second symptoms of the second symptometry of the second symptoms of the sec actions to take if it occurs

Patients must enroll in the REMS program and co nply with ongoing monitoring requirer Pharmacies must be certified by enrolling in the REMS program and must only dispense to patients who are authorized to receive JYNARQUE.

Further inform

er information, including a list of qualified pharmacies/distributors, is available at: www.JYNARQUEREMS.com or by telephone at 1-877-726-7220.

Hypernatremia, Dehydration and Hypovolemia: JYNARQUE increases free water clearance and, as a result, may cause dehydration, hypovolemia and hypernatremia. Therefore, ensure abnormalities in sodium concentrations are corrected prior to initiation of therapy.

estuan concentrations are concerned prior to initiation of increapy. nstruct patients to drink water when thirsty, and throughout the day and night if awake. Monitor for veight loss, tachycardia and hypotension because they may signal dehydration.

In the two double-blind, placebo-controlled trials of patients with ADPKD, hypernatremia (defined as any serum sodium concentration >150 mEq/L) was observed in 4.0% versus 0.6% and 1.4% versus 0% of tolvaptan-treated versus placebo-treated patients, respectively. The rate of dehydration and hypovolemia in the two studies was 2.1% versus 0.7% and 2.3% versus 0.4% for tolvaptan-treated versus placebo-treated patients, respectively.

During JYNARQUE therapy, if serum sodium increases above normal range or the patient becomes hypovolenic or dehydrated and fluid intake cannot be increased, then suspend JYNARQUE until serum sodium, hydration status and volume status is within the normal range.

Co-Administration with Inhibitors of CYP 3A: Concomitant use of JYNARQUE with drugs that are noderate or strong CYP 3A inhibitors (e.g., ketoconazole, itraconazole, lopinavir/ritonavir, indinavir/ itonavir, ritonavir, and conivaptan) increases tolvaptan exposure. Use with strong CYP 3A inhibitors s contraindicated; dose reduction of JYNARQUE is recommended for patients while taking moderate

ADVERSE REACTIONS

The following adverse reactions are discussed in more detail in other sections of the labeling: • Serious Liver Injury

· Hypernatremia, Dehydration and Hypovolemia

riypernatremia, Dehydration and Hypovolemia
 Drug Interactions with Inhibitors of CYP 3A
 Clinical Trials 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 practice. JYNARQUE has been studied in over 3000 patients with ADPKD. Long-term, placebo-controlled safety information of JYNARQUE in ADPKD is principally derived from two trials where 1,413 subjects received tolvaptan and 1,098 received placebo for at least 12 months across both studies.

TEMPO 3:4 -NCT00428948: A Phase 3, Double-Blind, Placebo-Controlled, Randomized Trial in Early, Rapidly-Progressing ADPKD: The TEMPO3:4 trial employed a two-arm, 2:1 randomization to tolvaptan or placebo, titrated to a maximally-tolerated total daily dose of 60-120 mg. A total of 961 subjects with over rapidly progressing ADPKD were randomized to YNARQUE. Of these, 742 (77%) subjects who were treated with JYNARQUE remained on treatment for at least 3 years. The average daily dose in these subjects was 96 mg daily

A subjects in the placebo group. Aquaretic effects were the most common reasons for discontinuation of JYNARQUE. These included pollakiuria, polyuria, or nocturia in 63 (6.6%) subjects treated with JYNARQUE compared to 1 subject (0.2%) treated with placebo. Table 1 lists the adverse reactions that occurred in at least 3% of ADPKD subjects treated with JYNARQUE and at least 1.5% more than on placebo.

Table 1. TEMP 0 5.4, Treatment Emergent Adverse Reactions in 25 % of 5 TNARQUE Treated								
S	Subjects with Risk Difference ≥ 1.5%, Randomized Period							
	Tolvaptan (N=961)			Placebo (N=483)				
Adverse Reaction	Number of Subjects	Proportion (%)*	Annualized Rate [†]	Number of Subjects	Proportion (%) [*]	Annualized Rate [†]		
ncreased urination8	668	69.5	28.6	135	28.0	10.3		
Thirst [‡]	612	63.7	26.2	113	23.4	8.7		
Dry mouth	154	16.0	6.6	60	12.4	4.6		
Fatigue	131	13.6	5.6	47	9.7	3.6		
Diarrhea	128	13.3	5.5	53	11.0	4.1		
Dizziness	109	11.3	4.7	42	8.7	3.2		
Dyspepsia	76	7.9	3.3	16	3.3	1.2		
Decreased appetite	69	7.2	3.0	5	1.0	0.4		
Abdominal distension	47	4.9	2.0	16	3.3	1.2		
Dry skin	47	4.9	2.0	8	1.7	0.6		
Rash	40	4.2	1.7	9	1.9	0.7		
Hyperuricemia	37	3.9	1.6	9	1.9	0.7		
Palnitations	3/1	3.5	1.5	6	1.2	0.5		

*100x (Number of subjects with an adverse event/N) 100x (Number of subjects with an adverse event/Total subject years of drug exposure)

*Thirst includes polydipsia and thirst *Increased urination includes micturition urgency, nocturia, pollakiuria, polyuria

Increased urnation includes micrurition urgency, nocturia, poliakturia, polyuria <u>REPRISE-NCT02160145:</u> A Phase 3. A Randomized Withdrawal. Placebo-Controlled, Double-Blind, Trial in Late Stage 2 to Early Stage 4 ADPKD: The REPRISE trial employed a 5-week single-blind titration and run-in period for JYNARQUE prior to the randomized double-blind period. During the JYNARQUE titration and run-in period. 126 (8.4%) of the 1496 subjects discontinued the study, 52 (3.5%) were due to aquaretic effects and 10 (0.7%) were due to liver test findings. Because of this run-in design, the adverse

reaction rates observed during the randomized period are not described. *Liver Injury*: In the two double-blind, placebo-controlled trials, ALT elevations >3 times ULN were observed at an increased frequency with JYNARQUE compared with placebo (4.9% [80/1637] versus 1.1% [13/1166], respectively) within the first 18 months after initiating treatment and increases usually resolved within 1 to 4 months after discontinuing the drug.

Postmarketing Experience: The following adverse reactions have been identified during post-app use of tolvaptan. Because these reactions are reported voluntarily from a population of uncertain size not always possible to estimate their frequency reliably or establish a causal relationship to drug exper *Hepatobiliary Disorders:* Liver failure requiring transplant

Immune System Disorders: Anaphylaxis

DRUG INTERACTIONS

CYP 3A Inhibitors and Inducers

<u>CYP 3A Inhibitors and Inducers</u> <u>CYP 3A Inhibitors</u>: Tolvaptan's AUC was 5.4 times as large and Cmax was 3.5 times as large after co-administration of tolvaptan and 200 mg ketoconazole. Larger doses of the strong CYP 3A inhibitor would be expected to produce larger increases in tolvaptan exposure. Concomitant use of tolvaptan with strong CYP 3A inhibitors is contraindicated.

Dose reduction of JYNARQUE is recommended for patients while taking moderate CYP 3A inhibitors Patients should avoid grapefruit juice beverages while taking JYNARQUE

Strong CYP 3A Inducers: Co-administration of JYNARQUE with strong CYP 3A inducers reduces exposure to JYNARQUE. Avoid concomitant use of JYNARQUE with strong CYP 3A inducers.

OATPIBI/3 and OAT3 Transporter Substrates: The oxobutyric acid metabolite of tolvaptan is an inhibitor of OATPIBI/B and OAT3 in vitro. Patients who take JYNARQUE should avoid concomitant use with OATPIBI/B3 and OAT3 substrates (e.g., statins, bosentan, glyburide, nateglinide, methotrexate, furosemide), as the plasma concentrations of these substrates may be increased. BCRP Transporter Substrates: Tolvaptan is an inhibitor of BCRP. Patients who take JYNARQUE should avoid concomitant use with BCRP substrates (e.g., rosuvastatin).

 $V_2\text{-}Receptor Agonist: As a V_2\text{-}receptor antagonist, tolvaptan will interfere with the V_2\text{-}agonist activity of desmopressin (dDAVP). Avoid concomitant use of JYNARQUE with a V_2\text{-}agonist.$ USE IN SPECIFIC POPULATIONS

USE IN SPECIFIC POPULATIONS Pregnancy: <u>Risk Summary</u>: Available data with JYNARQUE use in pregnant women are insufficient to determine if there is a drug associated risk of adverse developmental outcomes. In embryo-fetal development studies, pregnant rats and rabbits received oral tolvaptan during organogenesis. At maternally non-toxic doses, tolvaptan did not cause any developmental toxicity in rats or in rabbits at exposures approximately 4 and 1-times, respectively, the human exposure at the maximum recommended human dose (MRHD) of 90/30 mg. However, effects on embryo-fetal development occurred in both species at maternally toxic doses. In rats, reduced fetal weights and delayed fetal ossification occurred at 17-times the human exposure. In rabbits, increased abortions, embryo-fetal death, fetal microphthalmia, open eyelids, cleft palate, brachymelia and skeletal malformations occurred at approximately 3-times the human exposure. Advise pregnant women of the potential risk to the fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage in the U.S. general population is 2-4% and 15-20% of clinically recognized pregnancies, respectively.

and 13-20% of clinically recognized pregnancies, respectively. Lactation: <u>Bisk Summary</u>: There are no data on the presence of tolvaptan in human milk, the effects on the breastfed infant, or the effects on milk production. Tolvaptan is present in rat milk. When a drug is present in animal milk, it is possible that the drug will be present in human milk, but relative levels may vary. Because of the potential for serious adverse reactions, including liver toxicity, electrolyte abnormalities (e.g., hypermatremia), hypotension, and volume depletion in breastfed infants, advise women not to breastfeed during treatment with JYNARQUE. Padiatric live: Softward affordiments of BOLIDEOUTIES.

Pediatric Use: Safety and effectiveness of JYNARQUE in pediatric patients have not been established. Geriatric Use: Clinical studies of tolvaptan did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. Other reported clinical

Reata Gets \$30 Million Milestone Payment

Reata Pharmaceuticals (Irving, TX) has received a \$30 million milestone payment from its licensee, Kyowa Hakko Kirin as part of a corporate agreement.

In 2017, Kyowa Hakko Kirin reported positive results from the phase 2 TSUBAKI trial of bardoxolone methyl (bardoxolone) in patients with type 2 diabetes and chronic kidney disease. Initiation of the AYAME phase 3 clinical trial to assess the efficacy and safety of bardoxolone for the treatment of diabetic kidney disease in Japan was the trigger for the payment.

In July 2017, the FDA granted orphan drug designation to bardoxolone for the treatment of Alport syndrome and pulmonary arterial hypertension. Orphan drug designation is given to treatments for diseases that affect fewer than 200,000 people in the United States. About 12,000 people in the United States have Alport syndrome and most develop end stage kidney disease. The disease also affects the ear and eye.

The orphan designation will provide Reata with development incentives, including tax credits for clinical testing, exemption from a prescription drug user fee, and seven years of market exclusivity. The European Commission likewise granted orphan drug designation in Europe to bardoxolone for treatment of Alport syndrome.

Bardoxolone is an investigational medication taken orally, once a day. It is an activator of Nrf2, a transcription factor that induces molecular pathways that decrease inflammation. The pathways help to restore mitochondrial function, reduce oxidative stress, and block signals that cause an inflammatory response.

Recycling Used Dialysis Products

s more consumers eschew plastic straws and water bottles, the dialysis manufacturing sector is taking a closer look at the possibilities of reusing resources used in dialysis, including water and plastic. Water is also being analyzed as a commodity that could be used more sparingly throughout dialysis.

John Agar, a nephrologist at University Hospital, Barwon Health, in Geelong, Victoria (Australia), noted that the "total feed water draw per treatment [approaches] about 500 liters (or about 132 gallons) in typical hemodialysis," and that about 60% of the water is flushed away to drains (1).

Agar suggested that for hospital-based dialysis units, a reuse system for reverse-

osmosis rejected water is feasible, with discarded water moving from the system in the dialysis unit to an elevated water storage tank that could provide water suitable for use in gardens, hospital sterilization department needs, janitorial stations, and window cleaning, for example.

Arguing for such reuse ideas hinges on clear communication, Agar said. For example, it's important to emphasize that the recycled water has not had exposure to patients. Instead, the reject water is generated by a filtration process before patient exposure, as opposed to water from the effluent dialysate that contains the products of the dialysis process after a patient has been dialyzed.

In other work, researchers in Bogota,

Colombia, reported on using less water in dialysis, particularly for patients with lower body weights. Nephrologist Alejandra Molano-Triviño of Fundacion Cardioinfantil and colleagues found in a systematic review of literature that use of lower dialysate flow rates would "lead to significant water conservation without much compromise on dialysis efficacy and efficiency in small patients," those weighing less than 70 kg (154 pounds) (2). She and her team conducted a clinical trial that explored using different dialysate flow rates for lighter-weight patients (3).

Converting plastic dialysis waste into other products is another avenue of reuse for dialysis products. Working with a structural engineer at Deakin University, Melbourne, Australia, Dr. Agar says shredded plastic dialysis waste could be used to formulate an agent that lends strength to concrete by reducing the corrosion of steel bars used in its construction.

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JYNARQUE[™] (tolvaptan)

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.

Use in Patients with Hepatic Impairment: Because of the risk of serious liver injury, use is contraindicated in patients with a history, signs or symptoms of significant liver impairment or injury. This contraindication does not apply to uncomplicated polycystic liver disease which was present in 60% and 66% of patients in TEMPO 3:4 and REPRISE, respectively. No specific exclusion for hepatic impairment was implemented in TEMPO 3:4. However, REPRISE excluded patients with ADPKD who had hepatic impairment or liver function abnormalities other than that expected for ADPKD with typical cystic liver disease.

Use in Patients with Renal Impairment: Efficacy studies included patients with normal and reduced renal function. TEMPO 3:4 required patients to have an estimated creatinine clearance $\geq 60 \text{ mL/min}$, while REPRISE included patients with eGFR_{CKD-Epi} 25 to 65 mL/min/1.73m².

OVERDOSAGE: Single oral doses up to 480 mg (4 times the maximum recommended daily dose) and multiple doses up to 300 mg once daily for 5 days have been well tolerated in trials in healthy subjects. There is no specific antidote for tolvaptan intoxication. The signs and symptoms of an acute overdose can be anticipated to be those of excessive pharmacologic effect: a rise in serum sodium concentration, polyuria, thirst, and dehydration/hypovolemia.

No mortality was observed in rats or dogs following single oral doses of 2000 mg/kg (maximum feasible dose). A single oral dose of 2000 mg/kg was lethal in mice, and symptoms of toxicity in affected mice included decreased locomotor activity, staggering gait, tremor and hypothermia.

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*The European Clinical Practice Guideline on the management of hyponatremia recommend the use of oral urea as a treatment option in SIADH for moderate to profound hyponatremia. UpToDate also reviews the use of urea as a management option for hyponatremia.

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Industry Spotlight

continued from page 41

Outset Medical Raises Financing, Looks to Expand Settings for Tablo Use

Utset Medical (San Jose, CA) recently completed another round of financing, raising \$132 million in Series D equity financing to help accelerate production and commercial expansion of the Tablo Hemodialysis System.

The lead investor in this round of financing was Mubadala Investment Company of Abu Dhabi. Other participating investors in Outset Medical, which launched in 2010, include Baxter Ventures, Fidelity Research and Management, and Warburg Pincus, an early investor.

Featuring real-time water purification and dialysis fluid production in a compact system on wheels, the Tablo dialysis technology can meet patients' needs at home, in hospitals, and in dialysis centers, Outset Medical CEO Leslie Trigg told *Kidney News* in an interview.

"The response from patients, dialysis nurses, and healthcare decision-makers in those centers that use Tablo has been extremely positive, as they've seen the benefits of expanding the when, where, and how dialysis is delivered," Trigg said. "This financing will now allow us to rapidly scale up production and commercialization, bringing Tablo to more clinics and hospitals across the country."

The U.S. Food and Drug Administration has cleared Tablo for use in acute and chronic care settings. Outset Medical also hopes to expand Tablo's labeled indication to include home use.

Training and using the equipment is simple for both healthcare workers and for people with kidney disease who use the equipment at home, Trigg noted. "Simplicity is not something people turn down in favor of something more complicated," she said.

In the near future, "we are focused on expanding the commercialization of Tablo into hospitals (for ICU and non-ICU dialysis) and dialysis clinics," Trigg said.

"Tablo is a new tool for the ICU to use for delivering dialysis," Trigg said, noting that its smaller size is easier for nurses to manage for both set-up and usage, compared with some hospital-based machines.

In hospital settings, Tablo is quieter than other dialysis systems, Trigg said. "Alarms can be frequent with conventional machines, and the way we designed Tablo software was part of an effort to minimize noise and alarms."

Tablo can be deployed in dialysis clinics in a couple of different ways, Trigg explained.

First, the product can be set up in dialysis facilities that are still being constructed. "There's an opportunity for dialysis providers to think differently about abilities because Tablo doesn't require a water treatment room," Trigg said. "It offers more flexibility and convenience. Patients will have an opportunity to go to clinics that are smaller. Providers can build out clinics that are smaller and with less expensive equipment because the equipment can fit in the smaller footprint."

In another scenario, Tablo may be used in self-care centers that are starting to appear within existing dialysis clinics. Some patients want a smaller and more personal experience, and the independence they get from running their own dialysis, with technology like the Tablo, suits many patients, Trigg said.

"It is very difficult to solve 2018 problems with 1980s technology. We see a role and value for new technology."

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Growing Medical Identity Theft Puts Patients in Financial Jeopardy

By Bridget M. Kuehn

edical identity theft is a growing threat to patients in the United States, particularly those living in hotspots like the southeastern United States, according to a report released by the World Privacy Forum (1).

Nearly 2 million people in the United States were victims of medical identity theft during a single year, according to estimates in a recent report by the nonprofit Ponemon Institute (2). That number is likely growing, according to the World Privacy Forum. It found higher rates of growth of this crime per capita in certain areas including the Southeast, upper Midwest, Texas, and California.

During a breach of medical records, about one-third of victims' medical and personal information is compromised, while the rest may never find out how their data was stolen, said Pam Dixon, executive director of the World Privacy Forum. Many records are compromised when a staff member at a medical facility accesses and sells patient records to an identity theft ring; others may fall victim to Medicaid or Medicare fraud scams that use free clinics to collect patient credentials, she said.

"The crime is terrible for providers and it's terrible for patients," Dixon said. "There are no winners here. The only people who do okay are the perpetrators."

Red flags

This increasingly common crime often goes undetected for months or years, while identity thieves rack up medical debts, pollute patients' medical records with incorrect information, and sometimes trigger legal action against their victims.

Most victims of medical identity theft discover the crime when debt collectors come calling. That's what happened to one man who after living overseas for 10 years returned to the United States to find more than \$100,000 in medical bills waiting for him, Dixon said. A woman he'd never met claimed he was the father of her child and used his stolen insurance information, according to a report he made to the Consumer Financial Protection Bureau. Despite his attempts to clear his name, debt collectors put liens on his property and cars. He ultimately had to hire a lawyer to resolve the dispute, Dixon said.

On average, victims of medical identity theft spend more than \$13,000 and 200 hours to resolve the problem, according to the Ponemon report. Still only 10% report a complete resolution.

"It's wildly inconsistent, depending on the persistence of your thief, how long it's been going on, and what silos they're operating in," said Eva Velasquez, president and chief executive officer at the Identity Theft Resource Center (ITRC), a nonprofit organization that offers free help to identity theft victims. "It can be very confusing and it can take a long time, or can be just a couple of hours [to resolve]."

Putting lives in danger

Identity thieves may also put patients' lives in danger by polluting their medical records with inaccuracies. For example, an incorrect blood type or diagnosis in a medical record could lead to patient harm. Illicit behavior by an identity thief, like obtaining excessive narcotic prescriptions, can make it hard for patients with chronic conditions to receive necessary care.

"We talk to folks who are unable to get a legitimate prescription to treat or manage a health condition," Velasquez said.

In some cases, incorrect information can lead to legal or career snags. For example, Dixon said she'd found cases of police officers being denied a job because incorrect information in their records indicated they had a substance abuse problem.

"If it's used to obtain narcotic prescriptions, then that

person also has to potentially deal with law enforcement who is investigating them because their identity was used," Velasquez said.

One woman who called ITRC for help was the target of a large-scale investigation.

"Law enforcement was looking at her as a drug dealer," Velasquez explained. "She was able to get it unwound, but it had a severe impact on her life."

Defending patient data

Patients and their clinicians can take steps to thwart identity thieves (Table 1).

Individuals who receive a notification that their medical records may have been breached should request a complete copy of their medical records, said Dixon. This can help them identify inaccuracies and establish baseline medical information. All patients should create online accounts with the Social Security Administration, Medicare, or their insurance companies to monitor their accounts.

"Having the online account is a lot like having an online banking account," Dixon said. "It gives you instant access to that information. It's just terrific for all of us as patients because we can then track it in real time."

Patients or their caregivers should closely review the explanation of benefits statements they receive from their health insurer, Velasquez suggested. If they see unfamiliar physicians or services they didn't use, that's a red flag, she said. If someone has changed your billing address at a physician's office, that may also be a red flag, Dixon noted.

Patients also should avoid posting information about their medical conditions and care on social media, Velasquez said.

"If you're talking about medical conditions or things that you're doing to manage them or whatever, don't be fooled into thinking that that information is not being scraped, and culled, and managed, and crunched, and reviewed because it is," she said.

If a person thinks they may be a victim of medical identity theft, they should contact their clinicians and insurance company, Velasquez said. They may also want to seek free help from ITRC. She noted that some employers and homeowners' insurance policies offer identity theft resolution services.

"Don't think that you have to figure this out on your own, even if you're not in a position to pay for it," Velasquez said.

Patients should ask all their caregivers how they are protecting their medical and financial information, and avoid giving out sensitive information like Social Security numbers if possible, Velasquez said. Healthcare providers should develop layered systems for data security, including restricting access to sensitive patient data, Dixon said.

"Physicians and healthcare providers should recognize that the data they collect on patients is valuable to thieves and make sure they take precautions to protect it," said Velasquez. "This includes only collecting information they absolutely need."

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Table 1Protecting your medical identity

Patients can help protect their health data from identity thieves by following the Identity Theft Resource Center's (ITRC) tips:

- Strengthen passwords by using at least 8 characters and a mix of numbers and symbols.
- Update privacy settings on social media.
- Handle personal identifying information with care and don't give out sensitive information like health insurance or Social Security numbers unless necessary.
- Empty your purse or wallet. Never carry more than you need and leave your Social Security card at home.
- Review statements from health insurers for unfamiliar physicians or claims you didn't make.
- Check credit reports for collections or fraudulent activity.
- File a police report or Federal Trade Commission (www. identitytheft.gov) report if you suspect you've been a victim of identity theft.
- Contact the ITRC or identity theft resolution services available through your work or homeowners insurance for assistance resolving the problem.

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IS CKD a Risk Factor for Diabetes?



A new analysis of data from the Chronic Renal Insufficiency Cohort (CRIC) study finds an increased incidence of type 2 diabetes at long-term follow-up in CKD patients who were initially free of diabetes. The findings support the need for greater vigilance for type 2 diabetes in the CKD population, the authors reported in the *American Journal of Kidney Diseases*.

The analysis included 1713 participants from the prospective CRIC study. All had reduced kidney function at baseline, with a median eGFR of 47.3 mL/min/1.73 m². About 51% were white, 36% black, and 8% Hispanic. The participants' median age was 59 years. Based on blood glucose levels, HbA1c, and/or use of oral hypoglycemic medications, 81.8% of patients had diabetes at baseline.

The incidence of type 2 diabetes was assessed over a median follow-up of 7.69 years. A wide range of potential risk factors for developing diabetes were analyzed, including baseline measures of renal function and damage; HbA1c; homeostatic model assessment of insulin resistance (HO-MA-IR); demographic factors; family history of diabetes, smoking, blood pressure- and lipid-lowering medications; systolic blood pressure; lipid profile; body mass index; and physical activity.

In this sample of participants who

had reduced eGFR but were initially free of diabetes, 11.85% developed type 2 diabetes during follow-up. The diabetes incidence rate was 17.81 cases per 1000 person-years overall. Broken down, the diabetes incidence rate was 12.17 per 1000 for patients with a baseline fasting blood glucose of less than 100 mg/dL, and 46.55 per 1000 for those with a fasting blood glucose greater than 100 mg/dL. There was low concordance between fasting blood glucose and HbA1c.

On multivariable analysis, fasting blood glucose level and family history of diabetes were independent risk factors for incident type 2 diabetes. Measures of renal function and kidney damage were not significantly associated with type 2 diabetes incidence, nor did the investigators find that these measures improved the ability of models to predict diabetes risk. On adjusted analysis, the association of HOMA-IR with type 2 diabetes was similar to that of fasting blood glucose, while HbA1c was not a significant factor.

Measures of glycemic control and family history of diabetes are independently associated with incident diabetes, while measures of kidney function and damage are not, the authors noted. Yet previous models of type 2 diabetes risk incorporating measures of kidney function and damage have not included individuals with CKD before the occurrence of end stage renal disease. The study's findings demonstrated that because of their common risk factors, CKD may increase the risk of developing type 2 diabetes.

Jepson C, et al. Incident type 2 diabetes among individuals with CKD: findings from the Chronic Renal Insufficiency Cohort (CRIC) Study. *Am J Kidney Dis* 2018; DOI: 10.1053/j. ajkd.2018.06.017].

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TO MY NEPHROLOGIST, FROM A PATIENT: Help me connect to new treatments that I need.

For too long, I have suffered through the grief of constant steroid and other immunosuppresant use. I know you are just as frustrated as I when I show up at your office, relapsing again, and you have to put me back on another round of the same treatments. It was demoralizing when I found out that there are no FDA-approved drugs for my condition, but even worse when it seemed like no new breakthroughs were made over the past few years—just the same old steroid regimen.

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* Kidney Week 2018 oral and/or poster abstract presenter

Detective Nephron

The detective sits facing the window while he awaits the arrival of his

Detective Nephron, world-renowned for his expert analytical skills, trains budding physician-detectives on the diagnosis and treatment of kidney diseases. Budding nephrologist L.O. Henle is now accompanied by another budding nephrologist, Dr. Aldo

trainees.	
Henle	Here's a case that is going to make you smile.
Nephron	(curious): Finally. Anyone for some Coke?
Henle	I shall take some Coke, thanks. By the way, it's a case of hypophosphatemia.
Nephron	(<i>smiling</i>): Ah, yes. Electrolyte disorders. The best part of nephrology, and phosphate stuff is always entertaining.
Aldo	This is a 71-year-old woman with a phosphorus level of 1.4 mg/dL, but ranging from 1.4 to 2.4 mg/dL.
Nephron	(<i>interrupting</i>): That would be good enough.
Henle	Yes, Dr. Nephron, we did want to let you know that she has a GFR >60 mL/min, and there's no mention of any diarrhea.
Nephron	Please stop!
Henle	(whispering to Aldo): He likes to stop at only one electrolyte value.
Nephron	How do we categorize the causes of hypophosphatemia?
Aldo	Renal loss, extrarenal loss, and shifting; works for all electrolytes in nephrology (almost all).
Nephron	(arrogant): Indeed, I always like to start with redistribution or shifting.
Henle	Shifting?
Nephron	(laughing aloud): Shifting where?
Pause.	
Henle	Into the cells?
Aldo	The patient didn't have any signs of respiratory alkalosis or an increase in insulin availability, such as treatment of diabetic ketoacidosis (DKA), or a recent illness leading to refeeding that would cause the shifting. She has been sick for a few days but is able to eat a bit. She did have a 30-pound weight loss.
Nephron	Good work. So, the main causes of redistribution that can lead to hypophosphatemia are respiratory alkalosis, treatment of DKA, refeeding syndrome, and hungry bone syndrome. I suppose she is not a dialysis patient and didn't get a parathyroidectomy? That would be too easy.
Henle	No and no!
Henle	But I feel we need some more information, don't you think? Does she have a parathyroid-related process? What is her urinary phosphorus level?
Nephron	Hold your binders!
Aldo	(<i>chewing a protein bar</i>): I assume you want to move next to extrarenal loss, which in this case is gastrointestinal loss such as taking phosphate

binders, chronic and acute diarrhea (not in her case), and/or vitamin D deficiency.

- Nephron Strong work. I assume she is not taking binders, and she may be vitamin D deficient, given her history of intake as you suggested. Could that explain the severe hypophosphatemia? By the way, what are you eating? Aldo I am on a high-protein diet these days, eating a lot of bars, meats, dried beans, and peas. Henle (annoyed): No, she is not on any medications except tramadol for pain, and her 25-hydroxyvitamin D3 (25[OH]D3) was slightly low at 18 ng/mL (reference range 30-100 ng/mL), and her 1,25-dihydroxyvitamin D3 (1,25[OH]2D3) level was 2.6 pg/mL (reference range 19-79.3 ng/mL). Aldo (interrupting): Hmmm, 1,25 (OH)2D3 is low ... that is interesting. My guess is that this is going to be a renal loss. Nephron (jumping in): Definitely! How does the kidney handle this low phosphorus? Aldo (showing off): The kidney's response to phosphate depletion is to increase phosphate reabsorption, leading to almost zero phosphate excretion in the urine. Most of the filtered phosphate is reabsorbed in the proximal tubule via the sodium-phosphate cotransporters NaPiIIa and NaPiIIc in the proximal tubule. Phosphate depletion leads to increased gene expression and synthesis of new transporters, thereby enhancing the uptake of filtered phosphate into the cell. Henle Basically, our patient has normal kidney function, good blood pressure control, and good urine output. Her calcium is 8.4 mg/dL, albumin is 2.8 mg/dL, and parathyroid hormone level (PTH) is 6 pg/mL. She also was noted to have new 2+ pitting edema and ascites along with new worsening liver biochemistries. While her liver biochemistries were slightly elevated, her alkaline phosphatase was disproportionately elevated. Aldo (confident): Hmmm, that is interesting. Nephron (excited): I love it. This is going to be fun! Henle So now we are likely left with increased urinary excretion as the cause of the hypophosphatemia. This could be part of a Fanconi syndrome and/or sole excretion issue. She is not taking any medications that can cause any specific excretion such as chemotherapy agents or tenofovir or that carry a diagnosis of multiple myeloma. Aldo She has normal immunofixation, and no serum free light chain excess. She has normal magnesium, glucose, uric acid, and potassium levels.
- Fanconi syndrome. Hmmm. Nephron So, let's end this confusion once and for all. The usual causes of excretion of phosphorus are primary or secondary hyperparathyroidism, severe vitamin D deficiency, hypophosphatemic rickets (not the right age group), and tumor-induced osteomalacia (TIO).

She has a urinalysis with no glucosuria, making this less likely to be

is a rare paraneoplastic syndrome, causing TIO, also referred to as oncogenic osteomalacia. A majority of the cases reported are caused by benign mesenchymal tumors of soft tissue or bone, but there are several cases in the literature of various malignant neoplasms secreting FGF-23. Malignant neoplasm-induced TIO, however, is quite rare, making up fewer than 5% of cases of oncogenic osteomalacia. Cases

Henle	Hmmm. She has a low PTH level, making this not a PTH-mediated process. However, her 1,25 (OH)2D3 level is very low. What is her urinary phosphorus? It has to be high!			
Nephron	(<i>with a smile</i>): Now you are thinking like a nephrologist.			
Aldo	(<i>still chewing his protein bar</i>): It was 134.4 mg/dL, and a FePhos was 48%.			
Nephron	(<i>shocked</i>): This is a phosphate wasting of the kidney. Two hormones can do this—either PTH or fibroblast growth factor 23 (FGF-23). I suggest you get an FGF-23 level. Come back when it's ready. Let me finish reading my <i>JASN</i> issue for this month.			
A few days later:				
Aldo	(<i>holding a bag of beans</i>): The FGF-23 was 1500 RU/mL (reference range <180 RU/mL).			
Nephron	Dr. Aldo, you are on a roll. So, this is an FGF-23–induced hypophosphatemia. Where is this coming from?			
Henle	(<i>getting anxious</i>): Hmmm. That is interesting, and a good question. Wonder if her edema and the worsening liver function have anything to do with this?			
Nephron	Oncogenic renal phosphate wasting secondary to FGF-23 secretion			

	involved include malignant neoplasms such as small cell lung cancer, squamous cell cancer, colon cancer, prostate cancer, ovarian cancer, lymphoma, osteosarcoma, and multiple myeloma.
Aldo	(<i>showing off again</i>): An ultrasound-guided fine-needle aspiration and two core biopsies of the 2-cm liver mass revealed metastatic pancreatic adenocarcinoma.
Henle	(<i>whispering</i>): Don't give him too much information; he won't like it.
Nephron	(<i>interrupting</i>): Hmmm, that could explain the liver function concerns and ascites. Does that explain the hypophosphatemia?
Henle	(<i>relieved</i>): FGF-23 is a phosphatonin made by osteocytes and plays a major role in the bone-kidney axis by regulating phosphate, 1,25(OH)2D3, and bone mineralization. In response to high serum phosphorus and vitamin 1,25(OH)2D3 levels, FGF-23 is secreted. It then binds to the FGF receptor, Klotho complex, in renal tubular epithelial cells, decreasing proximal tubule expression of sodium- phosphate cotransporters. This results in decreased phosphorus
	Continued on page 52 >



Basic science and clinical research advances patient care. Submit your innovative ideas and research plans to the following programs funded by the ASN Foundation for Kidney Research.



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William and Sandra Bennett Clinical Scholars Program provides support for a clinician-educator to conduct a project to advance all facets of nephrology education and teaching.

Detective Nephron continued from page 51

reabsorption, phosphaturia, and corresponding hypophosphatemia. In addition, FGF-23 inhibits 1\alpha-hydroxylase activity in the proximal tubule by downregulation of CP27B1, thus decreasing 1,25(OH),D3 levels. This, in turn, decreases phosphate absorption in the gut, which potentiates the hypophosphatemia. FGF-23 is also thought to be an inhibitor for PTH secretion. In TIO, FGF-23 is secreted in an unregulated fashion, likely by tumor cells, causing marked hypophosphatemia and osteomalacia.

Aldo (jumping in): TIO can present before a tumor is diagnosed, and this might be what happened in our case, making it an important entity to understand and recognize, especially given the increasing case reports of TIO in malignant neoplasms. Typically, with TIO, serum phosphorus is low and serum 1,25(OH)2D3 levels are low or inappropriately normal. The 25(OH)D3 and calcium levels are usually normal. A markedly elevated FGF-23 level is usually the hallmark finding in TIO and provides strong support for a diagnosis of TIO. I think that given all that, this patient likely has pancreatic cancer causing paraneoplastic FGF-23 production, causing renal phosphate wasting.

The detective's eyes brighten.

Nephron Fascinating explanation.



Clinical Studies in CKD patients have shown a serum bicarbonate <22-23 meq/L is associated with:

- A 2 fold greater risk of of developing reduced GFR.*
- A greater risk of ESRD and increased mortality.°
- A 2 fold greater risk of reaching ESRD.[#]

*Health ABC Study, Goldenstein L. et al., AJKD 2014 Veterans CKD study, Kovesdy CP. et al. NDT 2009 *Chronic Renal Insufficiency Cohort (CRIC), Dobre M, et al, JAHA 2015

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But this patient had no bone lesions on CT scan and on MRI findings? Nephron An MRI or CT of the head and neck is usually advised, given the fact that most TIO-related tumors are mesenchymal in origin. If

the tumor cannot be located, an octreotide scan can be performed because many of these tumors express somatostatin receptors. In our patient, both the hypophosphatemia and the metastatic hepatic lesions were found at the same time. In addition, the patient was found to have no signs of osteomalacia on either physical examination or on imaging. The lack of observed osteomalacia in this patient is likely due to the short duration of hypophosphatemia because the bone mineralization process was not yet impaired. She did, however, have the typical serologic features of TIO such as markedly elevated FGF-23, elevated alkaline phosphatase, low 1,25(OH)2D3 level, low PTH, and elevated urinary fractional excretion of phosphorus. Aldo Brilliant!

Nephron	Please have her get treatment for her cancer to help with the hypophosphatemia.
Henle	(sadly): She refused treatment and has asked for hospice care.
Nephron	Well, that is a sad ending.

Pause.

Aldo

Nephron Nevertheless, I am glad you brought this case for discussion. Now I am hungry. Let's get some New York style pizza today. I am craving a high phosphorus diet!

Special thanks to Dr. Helbert Rondon, associate professor of medicine, Renal-Electrolyte Division, University of Pittsburgh, PA, and Dr. Rimda Wanchoo, associate professor of medicine, Nephrology Division, Zucker School of Medicine at Hofstra/Northwell for content editing. Special thanks to Dr. Mala Sachdeva and Valerie Barta for providing the details of this case.

The concept of Detective Nephron was developed by Kenar D. Jhaveri, MD. professor of medicine at Zucker School of Medicine at Hofstra/Northwell and an attending nephrologist at Northwell Health System, New York. Send correspondence regarding this section to kjhaveri@ northwell.edu or kdj200@gmail.com.





Educational Symposia

Thursday, October 25 – Saturday, October 27

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Breakfast or lunch will be served at each symposium. Seating is limited and available on a first-come, first-served basis to fully paid Annual Meeting participants. Doors open 15 minutes prior to each symposium.

Thursday, October 25 12:45 p.m. – 1:45 p.m.

Autosomal Dominant Polycystic Kidney Disease: Advances in Pathogenesis and Treatment*

Support for this symposium is provided by an educational grant from Otsuka America Pharmaceutical, Inc.

Challenges and Management of Gout in Patients with Kidney Diseases*

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Rethinking Anemia Management in CKD: A Focus on Patient-Oriented Outcomes, Policy, and Innovation*

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Volume Management in Hemodialysis Patients: From Art to Science*

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Friday, October 26 6:45 a.m. – 7:45 a.m.

Fabry Disease for the Nephrologist: Present and Future*

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Risk and Treatment of Hyperkalemia*

Support for this symposium is provided by an educational grant from **AstraZeneca**.

Friday, October 26 12:45 p.m. – 1:45 p.m.

Basic Science Symposium: Artificial Intelligence—Trends in Machine Learning Applied to Biomedical Research

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Diet and Lifestyle with CKD: Focus on Phosphorus*

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Continued Friday, October 26

Secondary Hyperparathyroidism: What's New?

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SGLT2 Inhibitors and the Kidneys: Cause for Excitement?*

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Saturday, October 27

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Reshaping Our Approach to CKD*

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Nephcentric	Pages 24, 42 and 52
NephCure Kidney	Page 47
Otsuka	Pages 38-41
Pursuit Vascular	Page 2
Relypsa	Pages 17 and 18
Renal Research Institute	Page 8
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