ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

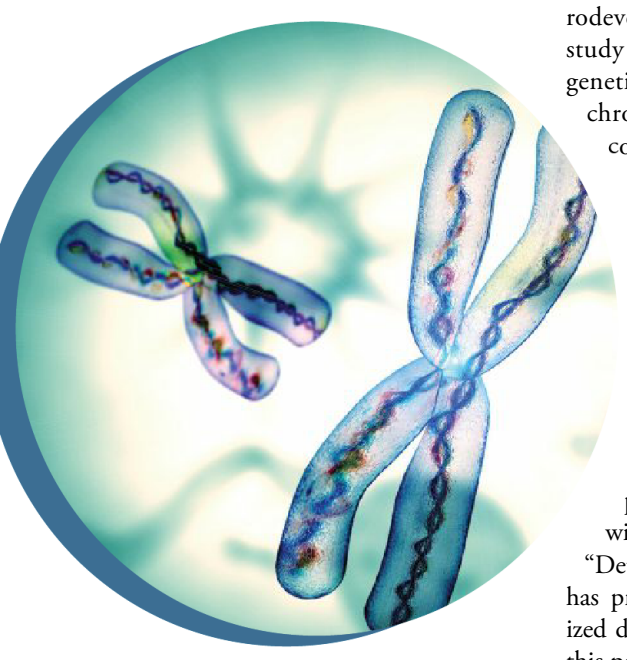
Kidney News

June 2015 | Vol. 7, Number 6

Microarrays Extend Promise of Precision Medicine to Pediatric Nephrology

Testing for CNVs Refines Diagnosis of CKD in Children

By Timothy O'Brien



Many children with kidney disease have rare "genomic imbalances" as the cause of their kidney dysfunction, often as part of neurodevelopmental syndromes. A new study finds that many unsuspected genetic diagnoses can be made using chromosomal microarrays to identify copy number variants (CNVs)—a "precision medicine" approach with major ramifications for treatment selection, family counseling, and long-term patient management.

The prospective study by a team of pediatric nephrologists and other specialists from seven centers found diagnostic copy number disorders in more than 7 percent of a large cohort of children with chronic kidney disease (CKD). "Detection of pathogenic imbalances has practical implications for personalized diagnosis and health monitoring in this population," according to the report in the May issue of *The Journal of Clinical Investigation* (Verbitsky M, et al: *J Clin Invest* 2015; 125:2171–2178). The senior author was Ali G. Gharavi, MD, of Columbia University).

Chromosomal microarrays in pediatric nephrology

The researchers analyzed the genetic findings of patients enrolled in the Chronic Kidney Disease in Children (CKiD) study—an ongoing, long-term follow-up study of risk factors and outcomes in children with kidney disease. Using patient DNA derived from stored samples, the investigators assessed CNVs using high-density microarrays.

"Chromosomal DNA microarray is a relatively new technology, which essentially looks at the entire genome of an individual and tries to identify gain or loss of DNA material that may cause a genetic disease," Gharavi said. Microarrays represent a major advance over the microscopic technique of karyotyping—classicially used to diagnose major chromosomal abnormalities such as Down syndrome.

"With karyotyping, we could only

Continued on page 3

Dialysis Patients' Increased Risk of Cardiac Arrest May Owe in Part to Genetics

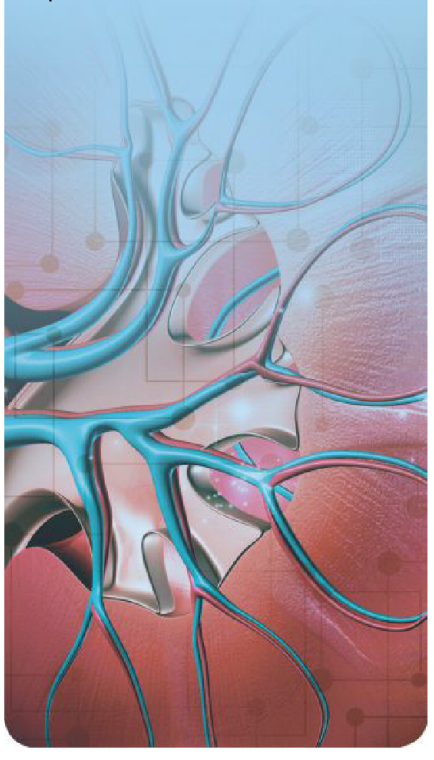
Patients on dialysis have a higher risk of dying from cardiac arrest compared with individuals in the general population, but the factors involved are unknown. Coronary artery disease is often at play in the general population, but investigators found no significant difference in the prevalence of coronary artery disease, decreased left ventricular ejection fraction, valvular heart disease, or left ventricular hypertrophy between dialysis patients who died of cardiac death vs. those who died of other causes.

New research published in the *Journal of the American Society of Nephrology* now shows that the increased risk of cardiac arrest experienced by patients with kidney failure may, in part, be inherited. Uncovering the genes that are involved may point to the mechanisms underlying this risk and suggest new prevention and treatment strategies.

"It is important to stratify sudden death risk in end stage renal disease patients. The study offers a new and

Continued on page 5

Inside



ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

KIDNEYWEEK 2015

San Diego, CA • Nov 3-8

Early Programs: November 3–4

Annual Meeting: November 5–8

Registration and Housing Open Soon

www.asn-online.org/KidneyWeek

Early registration deadline:
Wednesday, September 16

Microarrays

Continued from page 1

look at deletions or duplications larger than 1 to 2 million base pairs. Whereas with [chromosomal microarrays], we are able to detect much smaller gain or loss of DNA material—as small as 100,000 base pairs," Gharavi said. "As a result of this, we are able to make diagnoses that we weren't able to make by karyotyping."

That's important, because small variations in copy number make up a large part of genomic variation. Even in healthy individuals, up to 10 percent of the genome may be subject to this type of variation. Previous studies using microarray techniques have identified CNV disorders associated with a broad range of congenital and neurodevelopmental defects. Genomic imbalances can affect neurologic, cardiac, and skeletal development (an effect called "pleiotropy"), suggesting that common developmental pathways are involved.

The new study applied chromosomal microarrays to understanding the role of CNVs in a well-characterized group of children with clinically diagnosed kidney disease. A previous report found "pathogenic genomic imbalances" in about 10.5 percent of children and young adults with kidney malformations (Sanna-Cherchi S, et al: *Am J Hum Genet* 2012; 91:987–997).

These imbalances were clinically unsuspected and "overlapped significantly with CNV disorders implicated in neurodevelopmental disorders." In the previous study, most known CNV disorders in patients with renal hypodysplasia (RHD) had previously been linked to developmental delay or neuropsychiatric diagnoses.

Matthew Sampson, MD, a pediatric nephrologist and genetic epidemiologist at the University of Michigan, was one of the investigators in the previous study. "Understanding the underlying mechanism always helps in terms of explaining to parents why their child is ill," he said. "From a clinical perspective it often can help in terms of providing more precise prognoses or suggesting to us the optimal therapeutic regimen or further diagnostic tests. And, particularly important in children, it can help in terms of family counseling."

While "personalized medicine" doesn't always mean genetic testing, Sampson pointed out, "Genomic inquiry reveals more molecularly based, fundamental information about the pathogenesis of a child's condition." In regard to the new work by Verbitsky et al., he added, "This study is taking an approach that has really only recently been actualized on a clinical basis, or a research basis—to uncover some potentially causative genetic changes that could be responsible for a small but substantial percentage of the cases we see."

Higher rate of CNV abnormalities in children with CKD

The analysis included 419 unrelated children from CKiD. The patients were being followed up for a wide range of clinical diagnoses, including RHD, obstructive uropathy, reflux nephropathy, and focal segmental glomerulosclerosis (FSGS), among others.

Even though CNVs account for a large part of overall variation in the genome, the population frequency of genomic disorders is very low. To be able to tell apart those low frequency genomic disorders from likely benign common variants, the researchers assembled a multiethnic database of 21,575 children and adults undergoing microarray genotyping for research—either healthy controls or individuals without kidney-related conditions. "By comparing the DNA of children who had chronic kidney disease to the results from these other individuals, we were able to detect rare events that could be disease-causing," Gharavi said.

Overall, chromosomal microarrays found diagnostic copy number disorders in 31 of the children—representing 7.4 percent of the study cohort. The CKiD cases also had a high prevalence of large, gene-disrupting autosomal CNVs: 37.7 percent, compared to 23.4 percent of the reference cohort. "These data suggest that potentially up to 14.3 percent of the pediatric CKD cases might be attributable to a CNV of 100 kb or larger," the researchers wrote.

In an analysis focusing on a list of 131 known genomic disorders, 4.5 percent of the CKiD population had a deletion or duplication that was "clearly diagnostic." These patients had a deletion or duplication with a known association with a specific syndrome. The rate of known genomic disorders rose to 10.5 percent in children clinically diagnosed with RHD.

Further annotation identified another 12 patients with a "likely pathogenic imbalance," representing 2.9 percent of the CKiD group. These children had very large, very rare chromosomal abnormalities that were predicted to be pathogenic. "These lesions fulfilled very strict criteria for pathogenicity and would be considered reportable in a clinical setting," the researchers wrote.

Many of the detected CNVs involved genes thought to be involved in kidney development and thus may be "novel candidate genes" for human kidney disease. Although previously unknown, these abnormalities are considered likely to be disease-causing because of their large size and low frequency in the population and because they involve genes important for normal development.

On adjusted analysis, the odds of known genomic disorders were more than 10 times higher in the CKiD cohort overall, and 30 times higher in those with RHD, as compared to controls. Even after exclusion of known disorders (19 cases), a number of "large, rare gene-disrupting CNVs" were found in the CKiD cohort—including 35 cases with CNVs larger than 500 kb.

Close to one-fourth of patients with known or likely pathogenic copy number disorders also had rare, gene-disrupting second-site CNVs. That was consistent with reported series of patients with developmental delay.

Most baseline clinical and demographic characteristics were similar for children with and without pathogenic CNVs. There were "nominal" differences in estimated glomerular filtration rate and proteinuria, consistent with an impact of the genetic changes on kidney function. These differences will need to be validated in longitudinal studies or independent cohorts.

Major effects on diagnosis and clinical management

"If you can diagnose a patient with a known genomic disorder, that might help the treatment of their kidney disease," Sampson said. "But it also may allow us to provide additional medical care—whether it's screening for neurodevelopmental problems, diabetes, or other congenital anomalies. It really provides the opportunity at an early stage, presymptomatically, to provide a genetic diagnosis—which may help to reduce the risk of long-term complications or optimize the care of a patient across their lifespan."

In the CKiD sample, of eight children clinically diagnosed with cystinosis, three were homozygous for a known deletion of the cystinosin lysosomal cystine transporter gene *(CTNS)*. For this group, CNV testing pinpointed the cause of cystinosis and provided information on the exact mutation for family counseling.

In the remaining 28 patients with a diagnostic copy number disorder, the final genomic diagnosis was clinically unsuspected. In these cases, the CNV findings "either resulted in reclassification of the disease or provided additional information that would have warranted genetic counseling, targeted workup, or surveillance."

Identical genetic abnormalities were found across different clinical categories. Diagnoses of 1q211.1 recurrent microduplication were made in children with a clinical diagnosis of FSGS, hemolytic uremic syndrome, and chronic glomerulonephritis, while XXX syndrome was diagnosed in patients classified as having recessive polycystic kidney disease, reflux nephropathy, and RHD.

"Our ability to clinically differentiate some causes of kidney disease is probably more limited than we'd like to think," Gharavi said. "Different kidney disorders can present in the same way or in many different ways that overlap with our classical classification."

He cited the example of a patient with clinically diagnosed glomerular disorder to discuss the deeper insights offered by genetic diagnosis. "We think of glomerular diseases as something that affects just the kidney, and they're usually due to an inflammatory or an immune-mediated disease. These types of classifications are important, because if we think somebody has an immune-mediated disease, they may be treated for it by immunosuppressive medication.

"Whereas if they have a developmental disorder, then we know those medications are not going to help and will only result in side effects. So by making a precise diagnosis, we can at least try to come up with the right therapy and the right course of action."

Making the correct genetic diagnosis is also essential for understanding the long-term clinical course and management. "For example, we found patients who have deletions of a gene called HNF-1 beta, which is diagnostic of a disorder called renal cysts and diabetes syndrome," Gharavi said. "As the name [implies], the kidneys develop cysts, and there are problems with kidney function. In addition, these individuals are prone to developing diabetes later on in life."

Children with renal cysts and diabetes syndrome may also have other metabolic disorders, such as low magnesium or high uric acid levels, with a risk of developing gout. "The issue is that many of these complications won't happen all at once," Gharavi said. "The kidney cysts are evident earlier on in life, sometimes at birth, [while] the diabetes often occurs around the age of 25. Because these individuals are at risk for diabetes, they should receive targeted health monitoring to make sure that their serum glucose levels are monitored regularly."

Patients need ongoing lifestyle advice to reduce their risk of diabetes, and should avoid medications that can potentially increase blood glucose, including immunosuppressive therapy with steroids. Other issues may arise later in life—for example, female patients should be advised that they are at risk of uterine abnormalities and problems with conception.

Precision medicine in pediatric CKD

By providing this type of information, CNV testing in children with kidney disease may be a prime example of the NIH's Precision Medicine Initiative. As President Obama stated when announcing the initiative, precision medicine carries the promise of "delivering the right treatments, at the right time, every time to the right person."

In the case of pediatric CKD, chromosomal microarrays allow nephrologists to define the exact genetic diagnosis, make a profile for specific complica-

Continued on page 5

ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

KidneyNews

ASN Kidney News is published by the American Society of Nephrology
1510 H Street NW, Suite 800, Washington, DC 20005. Phone: 202-640-4660

www.asn-online.org

Postmaster: Please send address changes to *ASN Kidney News*, c/o Customer Service, American Society of Nephrology 1510 H Street NW, Suite 800, Washington, DC 20005.

Publications mail agreement No. 40624074. Return undeliverable Canadian addresses to PO Box 503, RPO West Beaver Creek, Richmond Hill ON L4B 4R6

ASN Kidney News (ISSN print 1943-8044 and online 1943-8052) is an official publication of the American Society of Nephrology, 1510 H Street NW #800, Washington DC 20005, and is published monthly. Periodicals postage paid at Washington, DC and at additional mailing offices. Subscription rates: $12 per year. To order, please email bhenkel@asn-online.org. Subscription prices subject to change. Annual ASN membership dues include $12 for *ASN Kidney News* subscription.

ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

Corporate Supporters

The ASN Corporate Support Program recognizes supporters year round for their generous contributions to the Society. Through this program, supporters help ASN lead the fight against kidney disease. ASN gratefully acknowledges the following companies for their contributions in 2014.

Diamond Level

ALEXION

AMGEN

FRESENIUS MEDICAL CARE

KERYX BIOPHARMACEUTICALS, INC

Mallinckrodt Pharmaceuticals

Platinum Level

SANOFI RENAL

Microarrays

Continued from page 3

tions—in some cases, unrelated to the patient's kidney dysfunction—and plan clinical care accordingly.

Many of the children in the CKiD cohort had pathogenic genomic imbalances associated with neuropsychiatric disorders, such as autism, schizophrenia, intellectual disability, and seizure disorders, Gharavi noted. "That's important to be aware of, because we know that children with CKD in general have impaired neurocognitive function and behavioral issues." Children may have problems at school and at home, or may not meet developmental landmarks.

"And many times that's been attributed to the sequelae of kidney dysfunction and being chronically ill, being on medications, [and] being in the hospital," he added. "We attribute this to kidney disease."

Instead, this group of children has a "fundamental neurodevelopmental disorder," requiring a different approach. In addition to treatment for kidney disease, the clinical plan needs to consider treatment for neurocognitive issues, educational interventions, and appropriate behavioral therapy.

Behavioral issues can also affect compliance and adherence to treatment for renal dysfunction. "You can choose also your therapy for kidney disease better knowing that maybe some medications will affect neurocognitive function," Gharavi said. "You can get a much better appreciation of the spectrum of problems that may be going on with that individual and tailor the therapy directly to their problem."

Of course, much work remains to realize the full impact of precision or personalized medicine for children with CKD. But Gharavi emphasized that DNA microarray studies are clinically available now and are recommended as the first-line diagnostic test for children with intellectual disability, neurocognitive disorders, or major congenital abnormalities.

As these tests come into use for diagnosis of children with kidney abnormalities, Gharavi said the main challenges will be related to test indications and interpretation. While many children will have a clear-cut genetic diagnosis, the situation will be less clear for the significant number of patients with other abnormal findings, including "likely" pathogenic variants. "It's really difficult to interpret what's causal, and what's not, and so you need a lot more studies," he said. Building a national research cohort of a million or more volunteers is a key component of the Precision Medicine Initiative.

Sampson emphasized the importance of saving patient specimens, linked to clinical data, for future research and analysis. "For all us clinicians who are sending patients with kidney anomalies or CKD for chromosomal microarays, I think there needs to be a way to store that information or store that DNA at the same time," he said. "[Verbitsky et al] showed that there's an excess burden of large genomic imbalances in cases versus controls, and we don't know what those mean."

Building patient databases will document the growing experience with children who do, or do not have contributing genomic imbalances. With a growing body of saved data, Sampson said, "We can go back to the medical record and then say over time, 'OK, this is actually a harmless [finding], because we actually see it in quite a few controls.' Or, 'Now, we've seen 10 patients with this same disorder and we're starting to make inferences on their long-term care."

For now, Gharavi said RHD is the main indication for chromosomal microarrays in pediatric nephrology. "We think that children who have congenital kidney malformations are really the ones at highest risk for having chromosomal disorders. So there is pretty good evidence now that [DNA microarrays] should be applied to this subset of individuals."

"And then for the rest of the children with CKD, I think we need to expand the study and see what is the impact," he added. The question to be answered is, "Does it make a difference to make [a genetic] diagnosis in the care of these patients?"

Sampson agreed with the recommendation to test children with kidney malformations. "With the caveat that [testing] has to be done in conjunction with the appropriate specialist who can interpret the results. Any patient who [is] sent for microarray, there should be a plan in place to also send that patient to a genetic counselor or geneticist for evaluation. Being able to properly counsel patients in terms of their genomic disorder, in terms of their risk for developing future problems or the problems they already have is nuanced and really needs help from experts."

Increased Risk of Cardiac Arrest

Continued from page 1

very interesting idea for addressing this problem: assessing, as already done for patients with heart disease, if some hemodialysis patients possess inherited genetic factors that increase their risk of sudden death," said Simonetta Genovesi, MD, who was not involved in the study and is a clinician and scientist at San Gerardo Hospital, in Monza, Italy. Genovesi has published many research articles related to heart health in patients with kidney disease.

For the study, Kevin Chan, MD, MSc, of Massachusetts General Hospital and Fresenius Medical Care North America, led a team that analyzed information on a population of 647,457 patients on chronic dialysis. They identified 5117 pairs of patients who came from the same family, and they matched each of these patients on 26 characteristics to a control patient from the same population.

The researchers found that in 4.3% of family pairs, both members died of a cardiac arrest compared with 2.6% in the control pairs. Genetically related family members who did not cohabitate had an 88% increased risk of dual cardiac arrest compared with their matched unrelated controls, while genetically related family members who lived together in the same environment had 66% increased risk. Spouses, who were genetically unrelated but lived together in the same environment, did not have an increased risk.

"These findings advance the science because they suggest that genetic factors—or differences in DNA sequence—contribute to the high risk of sudden death among patients on dialysis," said Chan. "It paves the way for more detailed genetic studies in the dialysis population to find specific genes that could explain the high risk of cardiac arrest and potentially new treatments for these patients." Multiple genetic variants have been identified that are linked with an increased risk of cardiac arrest in the general population. It will be important to see if these changes are also involved in cardiac arrest in the dialysis population, or whether novel variants specific to patients with end stage renal disease may explain the excess cardiovascular mortality.

Other significant factors associated with an increased risk of cardiac arrest in this study included age (7% increased risk per 5 years), African American race (37% increased risk compared with Caucasian race), serum potassium level (19% increased risk per mEq/L), erythropoietin dose (3% increased risk per 1000 units), and documented coronary artery disease (44% increased risk). Higher albumin levels were associated with a decreased risk of cardiac arrest.

The investigators noted that patients on dialysis have a similar risk for cardiac arrest as patients who fulfill the criteria for prophylactic implantation of a cardioverter defibrillator (ICD), but studies suggest that ICDs would not provide as great a survival benefit to patients on dialysis compared with the general population. Genetic analyses may help distinguish which patients may sufficiently benefit from ICDs.

"The study is particularly well done, despite limitations related to the retrospective nature and the inability to do an analysis of genetic variants that may be associated with sudden death," Genovesi said. She noted that it is likely that a large proportion of the risk of sudden death in hemodialysis patients is linked to problems related to the dialysis session itself (such as hyper- and hypokalemia and acidosis) as well as comorbid conditions such as diabetes.

"I would not like to see this new attention on genetics reduce the effort made to identify the modifiable risk factors operating in end stage renal disease patients who die of sudden cardiac arrest," she said. "I also find it a bit risky to suggest ICD implantation for primary prevention on the basis of genetic markers in a population for which there still are several doubts on the actual usefulness of such an intervention, as the underlying pathogenic mechanism of fatal arrhythmias in this population has not been clarified yet."

Charles Herzog, MD, an investigator at the Hennepin County Medical Center and the University of Minnesota, in Minneapolis, and was also not involved with the study, noted that the approach might make the most sense only in the prevalent hemodialysis population, which has a much lower risk of sudden cardiac death compared with newly incident patients. "In this group, I think a strong case can already be made for attempting primary prevention of sudden cardiac death, which is the rationale for the WEDHED, or Wearable External Defibrillator in Hemodialysis patients, trial," he said.

The findings come at a time when the annual mortality rate for US patients on dialysis is approximately 18 per 100 patient-years. Cardiac arrest has been reported as the largest cause, at 5 events per 100 patient-years.

Chan noted that his study's findings are associative and only provide a promising hypothesis. Detailed genetic studies are needed to come to a definitive conclusion about the role of genetics and cardiac events among dialysis patients.

Study co-authors include Christopher Newton-Cheh, MD, MPH, James Gusella, MD, MPH, and Franklin Maddux, MD.

Disclosures: KC and FWM receive salary support from Fresenius Medical Care North America.

The article, entitled "Heritability of Risk for Sudden Cardiac Arrest in ESRD," is available at http://jasn.asnjournals.org/content/early/2015/04/16/ASN.2014090881.abstract.

Findings

Diabetes in Early Pregnancy Linked to Increased CAKUT Risk

Pregestational exposure to maternal diabetes—during the first 20 weeks of pregnancy—is associated with congenital anomalies of the kidney and urinary tract (CAKUT) in offspring, reports a study in the *American Journal of Kidney Diseases*.

The population-based study included 945 patients with CAKUT born in Manitoba, Canada, between 1996 and 2010. They were matched for gestational age, sex, and birth year to 4725 control children. The study focused on the association between CAKUT and timing of diabetes exposure: pregestational, including the first 20 weeks' gestation; and gestational, beyond 20 weeks. The analysis was adjusted for a wide range of confounders, including size for gestational age as a surrogate for maternal glycemic control.

Pregestational exposure to maternal diabetes was significantly more common among infants with CAKUT: 4.1 percent, compared to 2.3 percent in the control group. There was no significant difference in gestational diabetes: 4.2 versus 3.3 percent, respectively.

In a multivariable model, the odds ratio for CAKUT in infants with pregestational diabetes exposure was 1.67. The estimated incidence of CAKUT in mothers with pregestational diabetes was 8.3 per 1000 live births, compared to 5 per 1000 in the general population. The presence

of CAKUT was associated with both large and small size for gestational age: odds ratio 1.34 and 1.59, respectively.

Previous studies of the association between maternal diabetes and CAKUT have not examined potential differences by the timing of exposure. The new study finds a significant increase in CAKUT among infants with pregestational, but not gestational, exposure to diabetes.

The link with large size for gestational age suggests that poor glycemic control may increase risk. The authors discuss the need for optimal glycemic control during early pregnancy, with consideration of screening for renal anomalies [Dart AB, et al: Maternal diabetes mellitus and congenital anomalies of the kidney and urinary tract (CAKUT) in the child. *Am J Kidney Dis* 2015; 65:684–691].

Living with Polycystic Kidney Disease: Patients' Perspective

The unpredictable nature of pain and the difficulty of establishing long-term life goals are major burdens for patients affected by autosomal dominant polycystic kidney disease (ADPKD), according to a qualitative analysis in *Nephrology Dialysis Transplantation*.

The researchers performed a thematic analysis of qualitative or mixed-methods studies of ADPKD, focusing on patient perspectives and experiences of living with their disease. The analysis included 21 studies totaling

Continued on page 8

Findings

Polycystic Kidney Disease

Continued from page 7

247 patients.

The analysis identified five major themes, including "unvalidated pain" that was not taken seriously by physicians and for which pain management options were inadequate. The theme of "persisting uncertainties and ambiguities" included difficulty accepting the diagnosis, feeling unable to control and monitor their health, unpredictable daily disruptions due to pain, and an uncertain future with inability to plan ahead.

Patients reported "genetic guilt and resentment," blaming their parents and themselves for their disease, and guilt about transmitting the risk to their children. The theme of "precariousness in pursuing parenthood" included prognostic uncertainty in patients who refused genetic testing, 'owning the decision' to have children or not, or a need or wish for directive counseling. Under the theme of "defining parental responsibility for genetic testing and disclosure," patients talked about trying to preserve normality for their child, respecting the child's autonomy in deciding to be tested, and confidence in future technologies to cure the disease.

The analysis lends insights into the complex factors affecting the lives of patients with ADPKD. The authors discuss the implications for improving patient-centered care outcomes, including increased engagement in pain management, self-care strategies, counseling to address "genetic guilt," and disease-specific decision support tools for family planning [Tong A, et al: A painful inheritance—patient perspectives on living with polycystic kidney disease: thematic synthesis of qualitative research. *Nephrol Dial Transpl* 2015; 30:790–800].

Many Kids with Type 1 Diabetes Have Ketoacidosis at Diagnosis

In recent years, close to half of young patients with type 1 diabetes in Colorado have had diabetic ketoacidosis (DKA) when their diabetes was diagnosed, according to a research letter in *The Journal of the American Medical Association*.

The researchers analyzed 3439 patients diagnosed with type 1 diabetes before age 18 between 1998 and 2012. All were followed up at a Denver center that serves more than 80 percent of diabetic youth in Colorado. Rates, trends, and risk factors for DKA at diagnosis were assessed.

Overall, 38.9 percent of patients had DKA at the time of diabetes diagnosis. Incidence of DKA at diagnosis increased from 29.9 percent in 1998, to 35.0 percent in 2007, to 46.2 percent in 2012. The percentage of patients on public insurance increased from 17.1 percent in 2007 to 37.5 percent in 2012.

Incidence of DKA at diagnosis was higher for younger and African American patients, and lower for those with private insurance or with a first-degree relative affected by type 1 diabetes. In recent years, incidence increased to a larger extent among children with private insurance.

The study suggests rising rates of DKA at diagnosis of type 1 diabetes, consistent with diagnosis and treatment. The authors note the incidence is similar to that reported in countries with poor health care access, and much higher than in Canada or the United Kingdom. The recent trends may be related to a rising prevalence of child poverty [Rewers A, et al: Incidence of diabetic ketoacidosis at diagnosis of type 1 diabetes in Colorado youth, 1998–2012. *JAMA* 2015; 313:1570–1572].

No Difference in Response to Nitrofurantoin with Reduced Kidney Function

Mild to moderate reductions in kidney function don't alter the treatment failure rate of nitrofurantoin in older women with urinary tract infections, concludes a report in the *Canadian Medical Association Journal*.

Using Ontario health databases, the researchers identified a cohort of 9223 older women with reduced kidney function receiving one of four oral antibiotics commonly used for reduced urinary tract infections: nitrofurantoin, ciprofloxacin, norfloxacin, or trimethoprim/sulfamethoxazole (TMP-SMX). The women's median age was 79 years and median estimated glomerular filtration rate (eGFR) 38 mL/min/1.73 m^2.

Fourteen-day treatment failure rates were examined in terms of need for a second antibiotic or hospital encounter for urinary tract infection. The same outcomes were assessed in a cohort of 182,634 women with relatively high eGFR: median 69 mL/min/1.73 m^2.

Women receiving the four antibiotics had similar baseline characteristics. Among those with low eGFR, failure rates were significantly higher with nitrofurantoin compared to ciprofloxacin and norfloxacin (but not TMP-SMX).

However, analysis of the cohort with relatively high eGFR revealed a similar pattern of higher treatment failure rates with nitrofurantoin. Compared to nitrofurantoin, adjusted odds ratios for a second prescription with ciprofloxacin were 0.43 for women with lower kidney function and 0.50 for those with higher kidney function.

Previous reports have suggested subtherapeutic concentrations of nitrofurantoin in patients with reduced kidney function, leading to the suggestion that this antibiotic be avoided when the eGFR is less than 40 mL/min/1.73 m^2. The new analysis finds no increase in the nitrofurantoin failure rate in older women with mild to moderate reductions in kidney function. Regardless of eGFR, treatment failure is more likely with nitrofurantoin than with other antibiotic choices [Singh N, et al: Kidney function and the use of nitrofurantoin to treat urinary tract infections in older women. *CMAJ* 2015. DOI:10.1503/cmaj.150067].

High CPR Rates, Poor Survival in Dialysis Patients

Hemodialysis patients have a high rate of in-hospital cardiopulmonary resuscitation (CPR), with low rates of long-term survival after CPR, according to a study in *JAMA Internal Medicine*.

Rates and outcomes of in-hospital CPR were assessed in 663,734 Medicare beneficiaries who started maintenance dialysis from 2000 through 2010, identified from the US Renal Data System registry. All hospital admissions and in-hospital CPR events occurring more than 90 days after dialysis initiation were assessed, along with survival to hospital discharge after the first CPR event.

In this national cohort, the annual incidence of CPR was 1.4 events per 1000 hospital days. Survival to discharge after CPR was 21.9 percent; median survival after discharge was 5.0 months. About 15 percent of patients who died in the hospital underwent CPR during that admission.

The incidence of in-hospital CPR events per 1000 in-hospital days increased from 1.0 in 2000 to 1.6 in 2011, while the percentage of patients surviving to discharge increased from 15.2 percent to 28.0 percent. The percentage of in-hospital deaths with CPR during the terminal hospitalization increased from 9.5 percent to 19.8 percent. There was no change in postdischarge survival after CPR.

These national data suggest a rising incidence of in-hospital CPR among hemodialysis patients, despite poor survival after CPR. The researchers conclude, "These findings support the relevance of advance care planning and setting realistic expectations regarding resuscitation treatment in this population [Wong SPY, et al: Trends in in-hospital cardiopulmonary resuscitation and survival in adults receiving maintenance dialysis. *JAMA Intern Med* 2015; doi: 10.1001/jamainternmed.2015.0406].

Minority Patients Have Lower Rates of Fistula Access

African American and Hispanic patients are less likely to have an arteriovenous fistula (AVF) in place when starting hemodialysis, compared to white patients with similar characteristics, reports a study in *JAMA Surgery*.

The analysis included US Renal Data System data on 396,075 patients initiating hemodialysis from 2006 through 2010. Multivariable analysis and propensity-score matching were used to compare hemodialysis access rates—including AVF, arteriovenous graft, and intravascular hemodialysis catheter—for patients of different racial/ethnic groups but otherwise similar characteristics.

An AVF was in place at the start of hemodialysis for 18.3 percent of white patients, compared to 15.5 percent of African American and 14.6 percent of Hispanic patients. This was so even though the minority patients were younger and had lower rates of comorbid conditions: coronary artery disease, chronic obstructive pulmonary disease, and cancer.

Odds ratios for AVF access were 0.90 for uninsured and 0.85 for insured African American patients, and 0.72 for uninsured and 0.81 for insured Hispanic patients. The difference was significant even among the subgroup of patients who had been under a nephrologist's care for more than one year: odds ratio 0.81 for African American and 0.86 for Hispanic patients.

The results show persistent racial/ethnic disparities in the presence of an AVF for initial hemodialysis access in the United States. The lower rates of AVF access among African American and Hispanic patients are independent of insurance status, nephrology care, and other factors driving fistula placement. "The sociocultural underpinnings of these disparities deserve investigation and redress to maximize the benefits of initiating hemodialysis via fistula in patients with end-stage renal disease irrespective of race/ethnicity," the investigators conclude [Zarkowsky DS, et al: Racial/ethnic disparities associated with initial hemodialysis access. *JAMA Surg* 2015; doi:10.1001/jamasurg.2015.0287].

ASN Board Review Course & Update

July 25–31, 2015 | Chicago, IL

Fairmont Chicago, Millennium Park

Registration now open

Face the boards with *confidence*

Maximize your readiness for the ABIM nephrology examination.

ASN's Board Review Course & Update is designed for fellows and practicing physicians preparing for certification or recertification in nephrology. Each topic and its time allocation are patterned after the ABIM nephrology examination, giving you the most efficient preparation. Lectures, interactive case discussions, and panel Q&A sessions contribute to ASN's unparalleled review course.

Earn CME credits.

ASN designates this live activity for a maximum of 69 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

The best choice for your board preparation.

- Free post-course access to BRCU Online
- 250 practice exam questions
- Exam-focused curricula
- Renowned expert faculty
- Comprehensive syllabus with lecture outlines, explanatory text, and key slides

Learn more and register at www.asn-online.org/brcu.

Education | The ASN Advantage
www.asn-online.org/brcu

ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

Clinical Trials in Diabetic Kidney Disease: Opportunities and Obstacles

By Jula Inrig, Peter Linde, and Matthew Breyer

Worldwide, diabetic kidney disease (DKD) is the leading cause of end stage kidney disease (ESKD), and its global incidence and prevalence are both increasing. More than 10 years ago, the Irbesartan Diabetic Nephropathy Trial, the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan, and similar trials demonstrated that blockade of the renin-angiotensin-aldosterone system delays DKD progression. Yet patients continue to experience progression to ESKD and to die of it.

The 5-year survival of a dialysis patient with DKD is less than 25 percent—worse than most cancers—yet the number of active clinical trials testing therapeutic agents to slow the progression of DKD to dialysis is less than one-tenth of the number of active trials for breast cancer, prostate cancer, or colon cancer (1). Unfortunately, the results of recent large clinical trials testing novel therapies for DKD have been negative or have been complicated by cardiorenal safety concerns. New treatments are desperately needed to spare this high-risk patient population. In order for DKD trials to enter the mainstream of drug development, key hurdles to facilitating trial feasibility, patient identification, and recruitment must first be overcome.

Endpoints

Historically, global regulatory and payer stakeholders have mandated demonstration of efficacy against "hard" clinical endpoints, such as delaying time to dialysis or death. This approach requires that enrolled study participants be late in the course of disease and have already experienced loss of renal function. Trial sample sizes must also be in the thousands, and have a long follow-up period to account for the fact that such endpoints have event rates that are relatively low.

Highly predictive dynamic biomarkers of efficacy and safety are lacking. With regard to efficacy, proteinuria (specifically albuminuria) is typically used in phase 2 clinical trials as an early marker for hard outcomes such as doubling of serum creatinine, ESKD, or both. Albuminuria does have some prognostic significance in assessing risk (e.g., for ESKD) but has significant liabilities. Key limitations include its substantial intrapatient variability, its nonlinearity in predicting risk, and the fact that substantial cohorts of patients exist who have advanced DKD but are normoalbuminuric. Highly predictive safety biomarkers are also sorely needed to provide early clues to the salutary or harmful effects of novel therapeutic agents. The nephrology community needs to continue developing the evidence to identify precise safety and efficacy biomarkers that are acceptable to the regulatory agency, payers, nephrologists, and ultimately our patients.

Feasibility

Most nephrologists consider patients with DKD to be a "dime a dozen" and are surprised that enrollment in trials is a challenge. But for patients to be suitable for an endpoint trial, a very select subset of patients with DKD with rapid progression must be identified. If a sufficient number of patients do not experience progression over the duration of the trial, the trial will fail. Typically, some loss of renal function reflected by an above-normal serum creatinine level, coupled with proteinuria, is used to select these patients. Identifying an "enriched" patient population at highest risk of progression using a criterion such as urine albumin-to-creatinine ratio (UACR) above 300 significantly narrows the eligible patient pool and thus has an impact on the feasibility of a clinical trial. According to the Kidney Early Evaluation Program (KEEP), fewer than 2 percent of diabetes patients with estimated GFR 60 to 90 mL/min/1.73 m^2 have macroalbuminuria (UACR >300), and fewer than 10 percent of those with estimated GFR 30 to 60 mL/min/1.73 m^2 have macroalbuminuria (2). As noted earlier, substantial intrapatient variability is a limiting factor here, too, because study participants on some occasions will qualify by this standard but at other times will not.

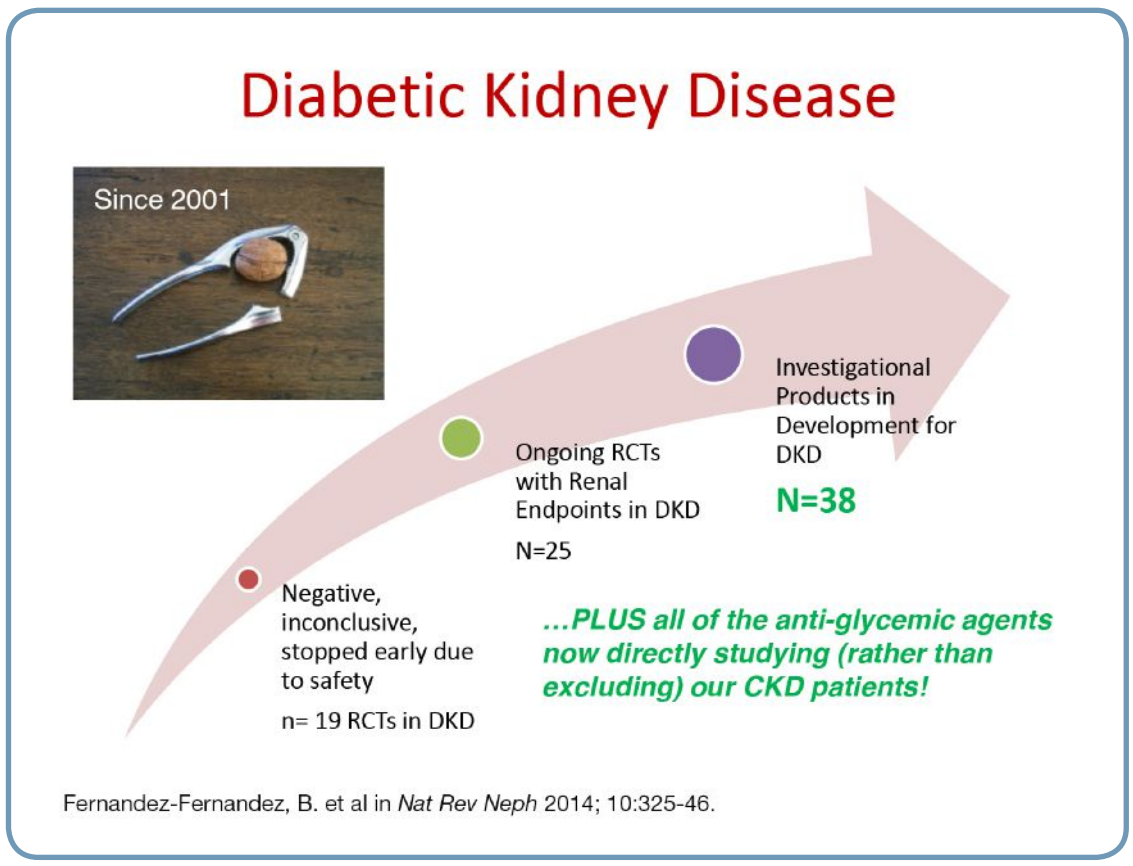
Slow patient enrollment makes a trial with a large sample size impractical because of prolonged time and cost. The overall recruitment rates for a DKD trial are approximately 0.25 patients per site per month (p/s/m) which is one-fourth the number of patients enrolled per month for a diabetes trial (at 1 p/s/m) (clinicaltrials.gov). Although the size of clinical trials may be similar for studies of cardiovascular conditions and diabetes, the rate at which patients enroll into DKD trials significantly delays the timelines and increases cost. This reality often stifles drug development in DKD by pharmaceutical companies. In addition, factors such as high screen failure rates (resulting from lack of prescreening or narrow inclusion/exclusion criteria) and high dropout rates have a significant impact on trial feasibility. Aside from the need for pragmatic study designs to avoid patient burden and minimize dropout, investigators need to fully educate patients about trial requirements and study commitments.

The last two issues would be favorably affected by a long-term substantial investment in an international clinical trial "infrastructure," built initially on a country-by-country basis where significant numbers of clinical trials are and would be performed. In each country this could take many forms, three of which include the following: 1) establishment of a free-standing, independent DKD national clinical trial network (where developers could simply pay fees into the network and benefit from pre-established infrastructure at member "go-to" DKD sites within the network); 2) establishment of a national DKD public database, where clinical outcomes data from all studies could be shared, particularly the standard-of-care comparator arm data; and 3) establishment of a virtual registry of DKD patients. All DKD (not only those seeing research physicians) would be encouraged to go online to register their information, find out about their disease, and obtain information about ongoing trials. This registry could also have an opt in/opt out choice for being contacted about future trials. Although we are aware that some regional centers are creating such infrastructures, a global outreach is needed to facilitate execution of the number of ongoing and upcoming trials in DKD (Figure 1).

Lack of patient awareness

According to 2011 KEEP data, only 23 percent of participants with CKD were aware that they had kidney disease (3) . Given the lack of awareness and thus the lack of knowledge about the high morbidity and mortality caused by DKD, motivating patients to participate in trials can be challenging. In other diseases wherein patients' awareness

Figure 1. Development in diabetic kidney disease



and engagement is high (such as polycystic kidney disease), recruitment into trials can occur quickly. Education needs to come ultimately from nurses, physicians, primary care providers, and nephrologists, but as has been observed in the oncology and cardiology fields, national disease societies, such as the American Heart Association and the American Cancer Society, can play a pivotal role in educating the public about important issues connected with a particular disease. New approaches to engage and educate patients and families affected with DKD, such as trial networks and social media, need to be promoted within the nephrology community in order to enhance enrollment into research trials.

Call to action

Whereas there are many practical aspects and challenges to getting therapies to market for patients with DKD, we believe that there needs to be a call to action within the nephrology community to support the rapid advancement of novel therapies through the approval process and into the hands of doctors who treat patients with DKD. Presently, there is a vicious cycle of slow-performing trials, combined with unengaged or poorly informed patients, combined with the large sample sizes demanded because of a lack of precise endpoints, which negatively feeds back upon itself, which in turn makes DKD trials unattractive, unfeasible, or both for innovative therapeutic developers in the diabetic nephropathy space.

We, the nephrology community, need to break this cycle! Practical aspects with regard to improving clinical trial infrastructure, trial endpoints, patient identification, education of patients, and encouraging patient participation in DKD trials as outlined here are some of the first steps we can take toward answering this call so that new and desperately needed therapies for diabetic nephropathy can be expeditiously delivered to our patients.

Jula Inrig, MD, MHS, FASN, is medical director and therapeutic strategy lead in nephrology at Therapeutic Strategy and Medical Delivery, Quintiles, Yorba Linda, CA. Peter Linde, MD, FASN, is project director of renal development, Global Pharmaceutical R&D, AbbVie. Matthew Breyer, MD, FASN, is chief scientific officer at Lead Generation Biology, Biotechnology Discovery Research, Lilly Research Laboratories.

1. Strippoli G, Craig JC, Schena FP. The number, quality and coverage of randomized controlled trials in nephrology. *J Am Soc Nephrol* 2004; 15:411–419.
2. Amin A, et al. The synergistic relationship between estimated GFR and microalbuminuria in predicting long-term progression to ESRD or death in patients with diabetes: results from the Kidney Early Evaluation Program (KEEP). *Am J Kidney Dis* 2013; 61 (4) (suppl 2):S12–S23.
3. Whaley-Connell AT, et al. National Kidney Foundation's Kidney Early Evaluation Program (KEEP) Annual Data Report 2011: Executive Summary. *Am J Kidney Dis* 2012; 59(3) (suppl 2):S1–S4.

KIDNEYWEEK 2015

San Diego, CA • Nov 3-8

Kick off ASN Kidney Week 2015 with Early Programs

The following 1- or 2-day courses (November 3–4) require separate registration from the ASN Annual Meeting (November 5–8).

- Advances in Research Conference: Engineering Genomes to Model Disease, Target Mutations, and Personalize Therapy
- Business of Nephrology: Impact of the Evolving US Health Care System on Nephrology Practice
- Critical Care Nephrology: 2015 Update
- Curing Kidney Disease: At the Crossroads of Biology, Infrastructure, Patients, and Government **new!**
- Diagnosis and Management of Disorders of Acid-Base, Fluid, and Electrolyte Balance: Challenging Issues for the Clinician
- Fundamentals of Renal Pathology
- Geriatric Nephrology: Caring for Older Adults with Kidney Disease
- Glomerular Disease Update: Diagnosis and Therapy 2015
- Kidney Transplantation
- Maintenance Dialysis
- Maintenance of Certification: NephSAP Review and ABIM Modules
- Polycystic Kidney Disease: Translating Mechanisms into Therapy
- Women's Renal Health across the Decades **new!**

Early registration deadline: Wednesday, September 16

Register online at www.asn-online.org/KidneyWeek

ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

Policy Update

ASN and AAKP: Forging Relationships on Capitol Hill

By Grant Olan

ASN President Jonathan Himmelfarb, MD, FASN (second from left), and ASN Dialysis Advisory Group chair, Rajnish Mehrotra, MD, FASN (third from left), discuss the CKD Improvement in Research and Treatment Act of 2015 in the office of their congressional representative Jim McDermott, MD (D-WA), together with ASN Executive Director Tod Ibrahim.

For the third consecutive year, the ASN Public Policy Board and Board of Advisors partnered with patient advocates from the American Association of Kidney Patients (AAKP) in Washington, DC, in April for Kidney Health Advocacy Day 2015. ASN and AAKP met with nearly 70 congressional offices to raise awareness about kidney disease and urge support for legislative measures that would improve care for patients with kidney disease.

Participants met with members of Congress from their home states, as well as members on the House Energy and Commerce Committee, which has jurisdiction over the 21st Century Cures initiative. The goal of 21st Century Cures is to spur medical research and innovation. Participants advocated in support of three provisions in the bill related to patient-focused drug development, expansion of telehealth, and research funding for young investigators.

Participants also advocated in support for the Chronic Kidney Disease Improvement in Research and Treatment Act of 2015 (H.R.1130/S.598). The bill includes provisions that call for three federal reports to address key needs for patients with kidney disease. The reports would assess the adequacy of federal investments in kidney research compared to the cost of kidney care, outline legislative and regulatory steps to reduce kidney health disparities, and identify disincentives in the Medicare payment systems that create barriers to kidney transplantation and posttransplant care for beneficiaries with kidney failure.

Three Kidney Health Advocacy Day 2015 participants offered reflections on their experience.

Deidra C. Crews, MD, FASN, MPH
Chair, ASN Chronic Kidney Disease Advisory Group
Member, ASN Diversity and Inclusion Work Group

My first time as a Kidney Health Advocacy Day participant was simply terrific. The day began with ASN staff members prepping all of us on the legislation we would be discussing, and preparing us for potential "traps" that we might find ourselves in when speaking with legislative staffers.

These pearls of wisdom stuck with me throughout the day, reminding me to stay on message. We had a terrific team for the day—nicknamed 'Huskie-Terrapins' which garnered some interest on Twitter. Our group included Nancy Day Adams, MD (Chair of the ASN Training Program Directors Executive Committee, veteran advocate, and nephrology faculty at University of Connecticut) and Richard Knight (Vice President of AAKP and a Maryland native).

We took turns presenting key points during the day, based upon our complementary expertise. Our presentations were quite seamless, thanks to our preparation over breakfast that morning. We met with five different congressional offices: Sen. Richard Blumenthal (D-CT), Rep. Elijah Cummings (D-MD), Rep. Donna Edwards (D-MD), Rep. John Larson (D-CT), and Sen. Barbara Mikulski (D-MD). A special treat was when Rep. Edwards emerged from her office to share with us her personal connection to kidney disease. It was a fun day of advocacy.

Brian Hess
Member, AAKP Board of Directors

Kidney Health Advocacy Day 2015 was by far the best congressional advocacy day I have attended. The day started as ASN staffers prepared everyone during breakfast for what we were lobbying for that day. I appreciated this so I would better understand what I was to speak about.

Additionally, I think my team was very well balanced this year. My team consisted of two doctors, one a younger, newer doctor (Kevin F. Erickson, MD, an ASN Public Policy Board intern) and the other an older experienced doctor (Raymond M. Hakim, MD, PhD, a member of the AAKP Board of Directors and ASN Public Policy Board). I was the third team member and the patient advocate, with 27 years of experience as a patient.

In every meeting we had, I felt as if the three of us played off of each other discussing the information we wanted to present. My group met with four different congressional offices, three of which were from my home state of Oklahoma: Sen. Dianne Feinstein (D-CA), Sen. Jim Inhofe (R-OK), Sen. James Lankford (R-OK), Rep. Steve Russell (R-OK).

Thanks to how well my team worked together, I felt we successfully illustrated all we intended. Everyone we spoke with indicated they would support the legislation we presented that day. When we were done for the day, I felt like it had been a big rush! This experience was one of the best I have ever had on Capitol Hill.

Daniel W. Ross, MD, MPH
Intern, ASN Public Policy Board

This year was my first time participating in Kidney Health Advocacy Day. We started with a morning briefing during which we discussed the importance of both the 21st Century Cures initiative and the CKD Improvement in Research and Treatment Act. Then we broke into teams for congressional office meetings to raise awareness about the legislation and how it would benefit patients with kidney disease.

I was joined by ASN Public Policy Board member Uptal D. Patel, MD, an adult and pediatric nephrologist, and AAKP advocate Edward Scott, a patient with Polycystic Kidney Disease. We met with a total of six congressional offices: Sen. Richard Burr (R-NC), Rep. G.K. Butterfield (D-NC), Sen. Kirsten Gillibrand (D-NY), Rep. Steve Israel (D-NY), Sen. Chuck Schumer (D-NY), and Rep. Lee Zeldin (R-NY).

I was surprised by the genuine interest in kidney disease by each of the offices. All of them recognized the value of investing in kidney research for reducing the significant societal burden of kidney disease. After the excitement of the day died down, I was left with a feeling that our efforts were not in vain and that there is real hope for big change.

KIDNEY HEALTH INITIATIVE

Kidney Health Initiative Seeks Patient Input into Medical Device Development

The Kidney Health Initiative (KHI) continues to make advances toward addressing the needs of the kidney community and fulfilling its mission through member-driven, multidisciplinary projects. This public-private partnership between the American Society of Nephrology (ASN), the US Food and Drug Administration (FDA), and over 70 member organizations and companies is coordinating 10 different projects focused on enhancing patient safety and fostering innovation in kidney disease.

One project focuses on the importance of incorporating patient preferences into product development programs and into regulatory decision-making. The KHI workgroup, "Workshop to Elucidate Role of Patient Preferences in Support of CDRH Regulatory Actions in Kidney Disease," has been charged with addressing this issue by seeking input from patients and their families on new treatment options to reduce the burden of kidney disease, which affects more than 20 million Americans.

The workgroup recently developed and launched a short animated video to engage patients and encourage them to attend one of three webinars held in April 2015. The video has since been viewed over 1200 times, resulting in more than 160 patients expressing interest in attending one of the workgroup's webinars (245 total registrants).

The webinars served to educate patients on device product lifecycle, the role of the FDA/Center for Devices and Radiological Health (CDRH) in device development, and how the agency is seeking patients' ideas to help guide new treatments and products that meet their needs through the CDRH Patient Preferences Initiative. The webinars also sought to collaboratively increase patient interest and knowledge of this area, before their invitation to participate in the workgroup's upcoming workshop.

The workgroup's animated video and webinar slides can be viewed in the Patient Info section of the KHI website: www.kidneyhealthinitiative.org

In phase II of this project, the KHI workshop will build on the lessons learned at the FDA Public Workshop held September 18-19, 2013, on patient preferences, and will provide a forum for interactive discussions between FDA regulators and other stakeholders to find practical solutions to address patient preference issues relevant to kidney health. Patients will be able to share their ideas directly with the FDA, scientists, doctors, nurses. and technicians. The workshop will be held August 12-13, 2015, at the Hilton Baltimore, BWI Airport. More information about the program, how to register, and the application process for travel support for patients, family members, and care partners is available at the Patient Info section of the KHI website: www.kidneyhealthinitiative.org.

Following the workshop, the workgroup will generate a white paper that will concisely define the major barriers and solutions to developing patient preference tools for medical devices within therapeutic areas relevant to individuals with kidney disease.

KHI hopes that this workgroup will be an important step forward in its efforts to develop a more patient-centric approach to drug and device development and looks forward to continued success of this project, "Workshop to Elucidate Role of Patient Preferences in Support of CDRH Regulatory Actions in Kidney Disease." For additional information or to discuss KHI and its projects, please contact the KHI staff at KHI@asn-online.org.

Introducing KSAP

The Kidney Self-Assessment Program (KSAP) is a new CME and Part 2 MOC product designed to help you review the essentials of nephrology. The program is composed of challenging, clinically-oriented questions that will refresh your understanding of the core elements of nephrology.

Based on the American Board of Internal Medicine (ABIM) nephrology examination blueprint, KSAP provides excellent preparation for fellows preparing for initial certification or practicing nephrologists preparing for recertification.

Refresh your nephrology knowledge and earn 25 Maintenance of Certification (MOC) points and 15 *AMA PRA Category 1 Credits*™.

Learn more and get started at www.asn-online.org/ksap

Education | The ASN Advantage
www.asn-online.org/ksap

ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

Industry Spotlight

Higher Revenues in First Quarter 2015

The two largest dialysis firms in the US reported higher revenues recently. Fresenius had a first quarter revenue of $3.96 billion, which was an increase of 11 percent, but its dialysis product revenue of $778 million remained unchanged compared with the first quarter of 2014, the company reported. Zack's online investment research experts had predicted total revenue of $3.92 billion, or about $40 million less for the enterprise. Fresenius reported that "organic growth" through good performances from all of its regions worldwide was positive during the quarter, outpacing analysts' expectations.

Fresenius saw North America "net dialysis care revenue" increase by 4 percent to $2.14 billion. Dialysis product revenue increased by 4 percent to $200 million compared with the first quarter of 2014. Fresenius North America overall revenues rose 16% year over year to $2.77 billion.

The company reaffirmed its guidance for 2015: it expects revenues to grow at 5 percent to 7 percent. Zacks reported that a strong performance in North America and particularly in the Asia Pacific, "coupled with an encouraging pharma business in North America is expected to help the company, going forward." However, declining margins remain a potential problem, Zacks said.

With business in more than 50 countries around the world, Fresenius has approximately 60,000 employees in North America, according to its US web site. Fresenius "will lie in wait for an overheated healthcare deal market to cool down" before making additional larger acquisitions, CEO Ulf Schneider said.

DaVita Kidney Care, based in Denver, announced on May 4, 2015, net revenue of $3.3 billion for the first quarter of 2015, an increase of 10 percent compared with $3 billion the same three months in 2014.

While revenues were higher, net income was not. DaVita HealthCare Partners' first-quarter income performance was a net loss of $111 million compared with a year ago, when the kidney care and medical group operator posted net income of $183.3 million.

As of March 31, 2015, the company had provided dialysis services to approximately 181,000 patients at 2290 outpatient dialysis centers, of which 2197 centers are located in the United States; 93 centers are located in 10 countries outside of the United States. During the first quarter of 2015, DaVita opened a total of 18 new dialysis centers, acquired one dialysis center, and closed two dialysis centers in the United States. The company also opened two new dialysis centers outside of the United States.

DaVita's first quarter results included a tentative $495 million settlement for a civil suit brought by private attorneys in 2009, Modern Healthcare reported. The suit alleged DaVita wasted medication and billed Medicare for it. DaVita has invested heavily in compliance programs to avoid any potential problems.

Nephrogenex Raising Research Funds

NephroGenex, a drug development firm based in Raleigh, NC, plans to raise $34.5 million in a secondary public offering, according to the Triangle Business Journal. The goal is to increase the number of clinical trial sites to test the company's drug Pyridorin, a treatment for diabetic nephropathy, commonly stemming from acute kidney injury (AKI) and diabetes.

In its first quarter results, Nephrogenex announced that it aims to expand its Phase 3 clinical trial of Pyridorin to 150 sites worldwide and to file for an Investigational New Drug (IND) Application through the US Food and Drug Administration (FDA). Last February, the company raised $33 million in an initial public offering.

In late December 2014, NephroGenex, announced it had "successfully completed a thorough QT/QTc (TQT) cardiac safety study on Pyridorin." This study assessed a drug's risk of QT prolongation and its proarrhythmic potential, and is a standard component of all clinical development programs for new molecular entities. Pyridorin showed no effect on the QT/QTc interval at the expected therapeutic dose of 300 mg and at a quadrupled dose of 1200 mg.

"These are important study results that support the use of Pyridorin in patients with diabetic nephropathy, many of whom suffer from cardiovascular disease," said Chief Executive Officer Pierre Legault. "They are also important given the concerns over cardiac safety seen with other therapies in development for this disease."

In March 2015, the company presented a poster session on preclinical findings in an ischemia-reperfusion model in mice that were administered doses of Pyridorin before surgically induced AKI. Pyridorin treatment significantly reduced the level of kidney injury, enhanced renal function recovery, and reduced post-injury fibrosis, the company reported. Treatment with a higher dose of Pyridorin was shown to be even more beneficial in the animals.

"We're in discussion with the US FDA regarding design of a clinical program in acute kidney injury and anticipate initiating an AKI Phase 1 study during second half of 2015," Legault said.

In 2014, NephroGenex spent $11.3 million in research and development and $5.3 million on general administrative costs. Cash, cash equivalents, and short-term investments were approximately $28.7 million as of Dec. 31, 2014, compared with approximately $2.1 million as of Dec. 31, 2013.

Greens for CKD

Welcome to the expanding market for factory-produced low-potassium lettuce aimed at people with chronic kidney disease (CKD).

The new lettuce produced by Fujitsu has been selling for about $4.90 (500 yen) for a 90 gram bag, just over 3 ounces in some locations in Japan. The lettuce has only about 20 percent of the potassium found in typical lettuce, manufacturers say, which makes it a good substitute for people craving salad and who have to closely watch potassium intake. Because the lettuce leaves are grown in the repurposed clean rooms of electronics manufacturers, no pesticides are necessary. So far, the products are available in Asia.

In 2013, Japanese electronics manufacturer Fujitsu converted an old semiconductor plant into the 2000 m^2 Akisai Plant Factory in Japan. For the vegetable facility, Fujitsu has combined its own and Microsoft's products.

"Fujitsu brought together its Eco-Management Dashboard, the IoT/M2M platform, Microsoft cloud services, and Windows tablets in a way that could enable managers, engineers, and scientists to improve product quality, streamline systems, and enhance functionality while reducing costs," Microsoft reported recently.

SG Greenhouse has constructed a facility that can produce 3500 bunches of low-potassium lettuce per day. The facility is on the Saibu Gas facility grounds in Kitakyushu, Japan.

Horiba, another Japanese company that conventionally trades in automotive test systems, semiconductors, and other devices, is also contributing to the production of low-potassium and low-sodium lettuce. Yoshio Miyashita, CEO of Oizumi Yasaikobo Co., Ltd., has opened a lettuce factory in Oizumi-machi, Oura-gun, Gunma Prefecture, to produce and sell lettuce free of insect damage and agricultural chemicals in a completely enclosed factory environment. Oizumi uses the LAQUAtwin compact water quality analyzer from Horiba to manage water quality and nutrient solutions for the new, factory-produced lettuce.

Classified Ads

Kidney News
Classified Advertising Information

Classified space is for advertising positions available, open faculty positions, course announcements, seminars, meetings and educational courses.

Display Advertising Rates

Ad Size	1x	3x
Full Page	**$2,525**	**$2,345**
1/2 Page	$1,665	$1,485
1/3 Page	**$1,435**	**$1,375**
1/4 Page	$1,205	$1,090
1/6 Page	**$1,035**	**$1,025**

Line Advertising Rates

Please contact for rate information

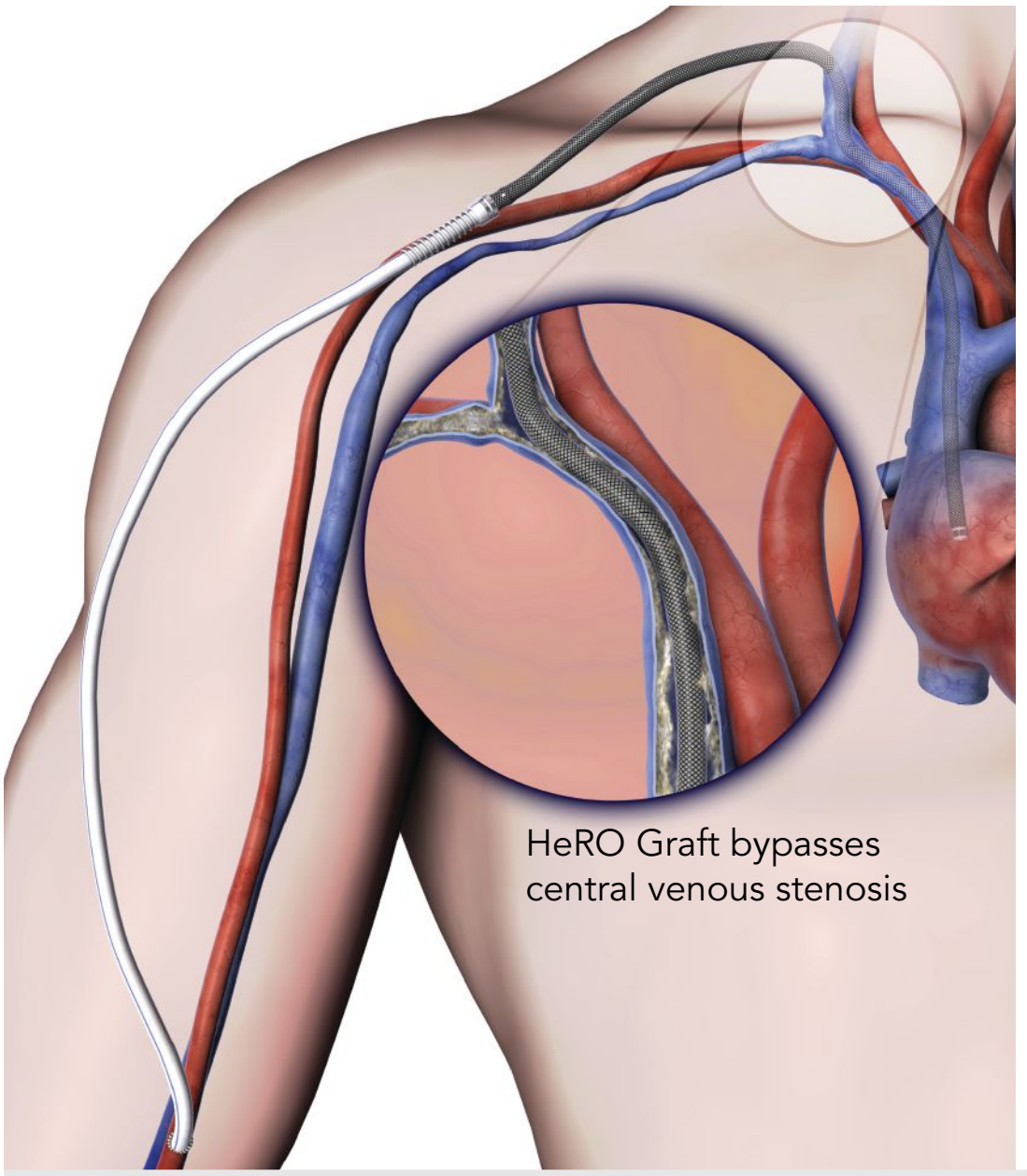
Closing Date & Cancellations:

Copy must be received four weeks in advance of the month in which the ad is to appear. Cancellation requests must be made in written form by fax, e-mail or postal mail and will be honored for the earliest applicable issue.

All Ads Must be Prepaid

Contact:
Rhonda Truitt
rhonda.truitt@wt-group.com
P: 443-512-8899 x. 106 F: 443-512-8909

Index to Advertisers



HeRO (Hemodialysis Reliable OutFlow) Graft is the **ONLY** fully subcutaneous AV access solution clinically proven to maintain long-term access for hemodialysis patients with **central venous stenosis.**

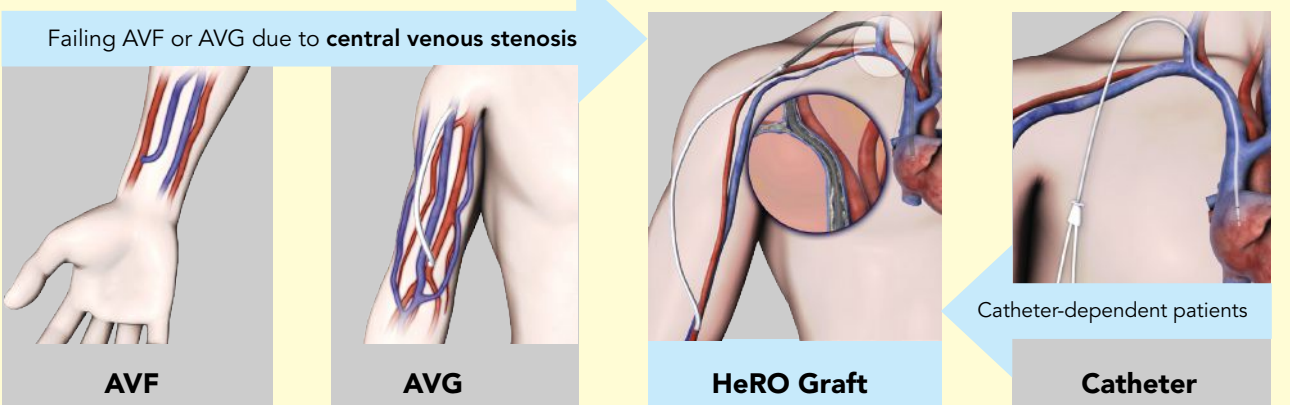
- **Fewer Infections:** 69% reduced infection rate compared with catheters[1]
- **Superior Dialysis Adequacy:** 1.7 Kt/V, a 16% to 32% improvement compared with catheters[1]
- **High Patency Rates:** Up to 87% cumulative patency at 2 years[1, 2]
- **Cost Savings:** A 23% average savings per year compared with catheters[3]

Reducing Catheter Dependency

HeRO Graft Candidates

- Catheter-dependent or approaching catheter-dependency
- Failing AVF or AVG due to central venous stenosis

Treatment Algorithm



Learn more at **www.herograft.com**
Order at: **888.427.9654**

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

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

HeRO Graft is classified by the FDA as a vascular graft prosthesis.

1. Download the App
2. Scan the code with your mobile device to watch video

Get the free mobile app at
http://gettag.mobi

1655 Roberts Boulevard, NW • Kennesaw, Georgia 30144 • Phone (888) 427-9654 • (770) 419-3355

CryoLife®
Life Restoring Technologies®