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Microvascular Complications of Diabetic Kidney Disease Addressed in Report

By Eric Seaborg

Innovative therapies and a better understanding of the underlying mechanisms of diabetic kidney disease (DKD) are slowing its progression, according to a new Endocrine Society scientific statement on diabetic microvascular complications. The statement also describes the slow progress in finding genetic markers for diabetic kidney disease and says that the cause of disease is misdiagnosed for many patients.

"Vascular complications are the major cause of morbidity and mortality in diabetic patients," according to "Diabetic Microvascular Disease: An Endocrine Society Scientific Statement." The kidney, eye, and peripheral nervous system form the triad of "classical diabetes microvascular target tissues. Microvascular renal disease is … a major contributor to the development of end-stage kidney disease (ESKD) in the developed world."

The best practices in therapy are not a surprise. "The latest research shows that maintaining tight control over blood sugar levels and blood pressure can help to reduce the risk of complications such as diabetic nephropathy," said Eugene J. Barrett, MD, PhD, of the University of Virginia, who chaired the task force that developed the statement.

"Therapies to prevent or slow the development of DKD are multifactorial and include lowering blood sugar levels with medications, diet, and exercise, as well as treating hypertension and hyperlipidemia," the statement says.

There are several medications that slow the progression of DKD, but they do not halt it, said Barry I. Freedman, MD, professor of internal medicine and chief of nephrology at Wake Forest School of Medicine, the lead author on the renal section of the statement.

Agents that block the renin-angiotensin aldosterone system (RAAS), such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), are effective at slowing the progression of DKD in patients with high levels of proteinuria. New glucose-lowering agents, including sodium-glucose cotransporter-2 (SGLT-2) inhibitors and glucagon-peptide 1 (GLP-1) agonists, provide hope for slowing progression of established DKD or preventing its development.

The statement reviews the various pathways to microvascular damage (see sidebar) and notes that some of the effectiveness of medications may stem from disrupting these pathways. For example, ACE inhibitors may contribute not only by lowering systemic blood pressure, but could also decrease glomerular capillary pressure by inhibiting the kidney's production of angiotensin II. Angiotensin II may lead to kidney damage through the induction of local factors, including extracellular matrix protein synthesis via transforming growth factor-β and inflammatory cytokines.

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Method Could Help Monitor Transplant Referrals from Dialysis Clinics

By Tracy Hampton

For patients with end stage renal disease (ESRD), barriers to kidney transplantation can come from a range of sources. Referral to a transplant center is an essential first step for patients who may be transplant candidates, and it's one that relies on actions taken by the leadership and staff at dialysis centers.

The Centers for Medicare & Medicaid Services, as well as the kidney community, have called for the development of quality measures for dialysis facilities to improve performance and equity in access to kidney transplantation, but little progress has been made. As described in a recent *Clinical Journal of the American Society of Nephrology* article, a new method may be effective for assessing dialysis centers' performance in this area.

"In the past several years, the Centers for Medicare & Medicaid Services has focused on increasing referrals among dialysis facilities as part of the Statement of Work for the 18 End Stage Renal Disease Networks. However, these data are not routinely collected and are not available to the public to determine whether some dialysis facilities are appropriately referring patients for kidney transplanta-

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Inside

Microvascular Complications

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More biopsies needed?

Freedman said an important point in the statement is that "a significant number of people whose kidney disease is attributed to diabetes may be misdiagnosed." In several studies, renal biopsies demonstrated that 30% or more of proteinuric patients with type 2 diabetes had non-diabetic forms of kidney disease.

"Most patients who have diabetes and progressive kidney disease do not get kidney biopsies," Freedman said. "Doctors assume that because the patient has diabetes and kidney failure, it is most likely diabetic kidney disease. But many biopsy studies, particularly in those with shorter diabetes durations and without diabetic retinopathy, have shown a large percentage had other kidney disease. Misclassification is not infrequent."

This misdiagnosis issue is serious not only for patients, who may not receive the most appropriate treatment, but it also interferes with research. If a large percentage of the patients in a diabetic kidney disease treatment trial do not actually have DKD, researchers may miss the effect of a treatment that is actually effective, Freedman said. The inclusion of misdiagnosed patients could also contribute to the difficulties in the search for DKD genes.

The statement notes that its findings apply to both type 1 and type 2 diabetes—along with secondary forms of diabetes resulting from genetic mutations, pharmaceuticals, or surgical interventions—because despite the disparate pathogenesis of these conditions, they all share microvascular dysfunction as a chronic outcome. And it covers much more than the renal aspects of the disease.

Mixed success in genetics for diabetic kidney disease

A bright spot in research in recent years has been the identification of genes related to non-diabetic forms of kidney disease.

"We have had great success in identifying the genetic basis of non-diabetic kidney disease. Results have changed the field," Freedman said.

For example, a single gene—the apolipoprotein L1 (*APOL1*) gene—contributes to 30–40% of ESRD in the African American population, but it is not related to diabetic kidney disease. The *APOL1* discovery may soon change clinical practice, for example in kidney transplantation, Freedman said, and researchers had expected similar success in finding genes causing diabetic kidney disease.

"Family history is an important risk factor for diabetic kidney disease. We know the disease runs in families," Freedman said, so researchers expected that new technologies like genomewide association studies would make finding the genes relatively straightforward.

But that hasn't been the case. "The Family Investigation in Nephropathy and Diabetes—the FIND study—looked at nearly 10,000 people from four different ethnic groups. Evidence of genetic associations was found, but the findings were weaker and less consistent. Other researchers looked for DKD genes in the same regions of the genome and didn't find them," Freedman said. "We will likely need to look at 'genetic risk scores' encompassing results of changes in multiple genes, perhaps 30 or 40 different genes, to see a signal in DKD. Narrowing down those 30 or 40 genes to put into the risk score model has proven to be challenging."

Current therapies

The statement summarizes some of the best practices in therapies and contingencies that clinicians should take into consideration:

- Efforts to improve glycemic control should also consider the risks of hypoglycemia. To this end, the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines recommend a target HbA1c of ~7%. A target HbA1c >7% is recommended in those with comorbidities or limited life expectancy and at risk for hypoglycemia. Glycemic control helps maintain the glomerular filtration rate (GFR), a primary focus for preventing the advance of DKD.
- Kidney function itself can affect the metabolism and safety of blood sugar–lowering medications, and should be adjusted according to a patient's estimated GFR (eGFR). To reduce the risk of prolonged hypoglycemia, KDOQI guidelines suggest using second-generation glipizide rather than first-generation sulfonylureas when eGFR is <60 mL/min/1.73 m^2. The guidelines urge caution when initiating meglitinides when eGFR is <30. According to US Food and Drug Administration guidelines, patients should not start metformin when their eGFR is <45 and avoid it altogether when it is <30. When a patient's eGFR is between these levels, clinicians should follow them closely. Patients with advanced nephropathy may need their doses adjusted if they are taking β-glucosidase inhibitors, dipeptidyl peptidase 4 (DPP4) inhibitors, SGLT-2 inhibitors, incretin mimetics, and islet amyloid polypeptide (IAPP) analogs.
- As kidney function declines to an eGFR of <30, it can affect the accuracy of tests used to assess glycemic control, especially the HbA1c. In the late stages of DKD and ESRD, red blood cell survival drops, and clinicians often prescribe medications to treat anemia. This can lead to inaccurately low HbA1c values and provide a false sense of security. Interpretation of HbA1c in patients with ESRD requires complex statistical adjustment. Frequent measurements of serum glucose or novel assays such as glycated albumin or fructosamine may more accurately reflect glycemia in these patients.
- Lowering systemic blood pressure with antihypertensive medications and dietary modification slows the development and progression of DKD, and the Joint National Commission 8 recommends using RAAS-blocking agents. Although RAAS blockers often slow DKD progression, they do not reliably stop it. Patients who progress to stage 4 CKD or beyond may need to stop taking RAAS blockers because of dangers from hemodynamic effects and hyperkalemia. Combining two RAAS-blocking agents such as ACE inhibitors and ARBs increases risks for adverse events and should be avoided.
- Although RAAS-blocking agents are first-line therapies for hypertension in patients with diabetes, KDOQI guidelines do not recommend their routine use in normotensive, normoalbuminuric diabetes patients. The guidelines recommend ACE inhibitors and ARBs in normotensive diabetic patients with a urine albumin:creatinine ratio 0.30 mg/g, who are at risk for future DKD.

"The statement is an in-depth, detailed report on some of the major microvascular complications of diabetes. It's a go-to site if you don't have time to read a hundred papers on each of the complications. Reading even selected parts of it will give you a very good, up-to-date understanding of each complication," according to George L. King, MD, chief scientific officer at Harvard's Joslin Diabetes Center, who served on the task force that wrote it.

"Diabetic Microvascular Disease: An Endocrine Society Scientific Statement" was published in the December issue of the *Journal of Clinical Endocrinology & Metabolism* and can be found online at https://academic.oup.com/jcem/article-abstract/102/12/4343/4604942?redirectedFrom=fulltext.

Cellular and Biochemical Pathways in Diabetic Kidney Disease

"Multiple levels of breakthroughs have happened in the last 10 years in our understanding of what could be causing cells to be dysfunctional when exposed to high glucose," said George L. King, MD, chief scientific officer at Harvard's Joslin Diabetes Center, who served on the task force that developed that Endocrine Society scientific statement.

The statement lays out many cellular mechanisms linked to vascular complications: nonenzymatic glycation and the formation of advanced glycation end products; enhanced reactive oxygen production and actions; and endoplasmic reticulum stress. Biochemical pathways implicated include the activation of the polyol pathway, excessive oxidants, chronic inflammation, the diacylglycerol–protein kinase C pathway, Src homology-2 domain-containing phosphatase-1, the renin-angiotensin system, and the kallikrein-bradykinin system.

A better understanding of these pathways could help in slowing the development and progression of diabetic kidney disease. Some efforts have not succeeded, such as with protein kinase C. Clinical trials have shown that angiotensin-converting enzyme (ACE) inhibitors and angiotensin type-1 receptor blockers delay the progression of diabetic kidney disease. Other efforts have had ambiguous results.

For example, within the renin-angiotensin system, transforming growth factor-β (TGF-β) has confusing effects. Diabetes increases its expression and it is a major inducer of profibrotic responses in diabetic kidneys. However, many studies have reported that TGF-β has potent anti-inflammatory effects on macrophages and is a negative regulator of T cell and B cell activation. Therefore, TGF-β may have protective actions due to an anti-inflammatory effect, and its elevation may be a reaction to the inflammatory stress of diabetes. Thus, its overexpression in many tissues could be an endogenous response to the inflammatory actions of hyperglycemia in vascular cells. "These paradoxical roles of TGF-β make it a challenging drug target," the statement notes.

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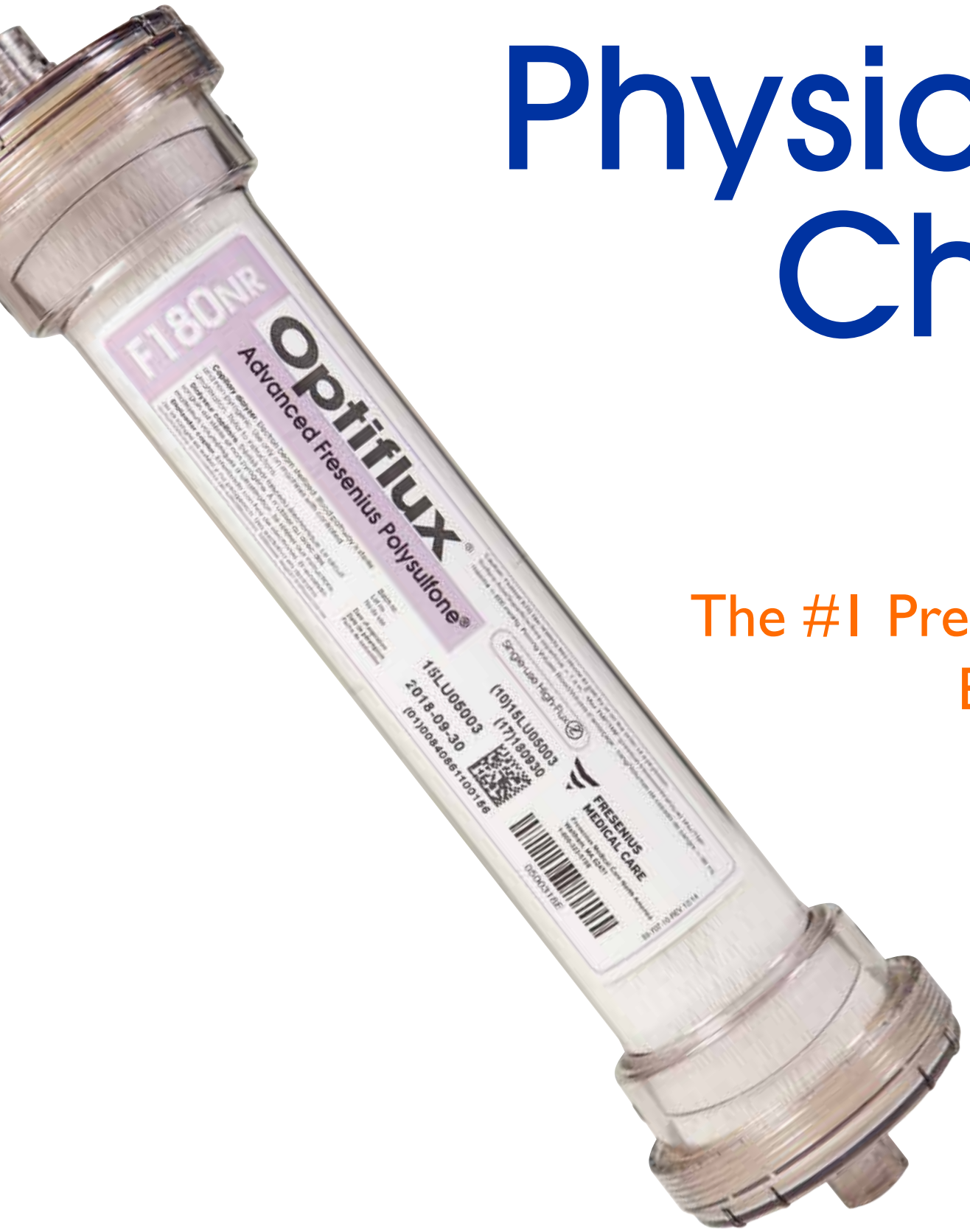

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Transplantation

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tion," said senior author Rachel Patzer, PhD, of the Emory University School of Medicine. "Monitoring transplant referrals among dialysis facilities could help drive quality improvement and increase access to kidney transplantation."

Waitlisting of patients is often used as a measure of how well dialysis facilities perform, yet it may not be an ideal quality *performance metric* for facilities. Patzer noted that the use of waitlisting as a performance metric may be problematic owing to geographic variability in waitlisting practices across the United States that are beyond the control of dialysis facilities.

So Patzer and her team developed a risk-adjusted quality metric—the Standardized Transplantation Referral Ratio (STReR)—to evaluate dialysis facility performance in transplantation referrals relative to a regional average with similar patient case-mix.

The researchers applied the measure to transplant referral data from 8308 ESRD patients within 249 dialysis facilities in the state of Georgia that were linked with United States Renal Data System data during the period 2008–2011, with follow-up through 2012. Facility STReRs in Georgia ranged from zero to 4.87. Seventy-seven percent of facilities had observed transplant referrals as expected. Similar numbers of facilities had referrals either greater or less then would be expected: 11% had referrals significantly greater than expected, and 12% had STReRs less than expected.

Conditions significantly associated with the likelihood of referral included age, race, sex, and comorbidity; however, most of the observed variation in dialysis facility referral performance was due to characteristics *within* a dialysis facility rather than patient factors. On average, 67% of the variability in STReRs was attributed to within-facility variation. Between-facility variation accounted for 33% of the variability in dialysis facility performance.

The study demonstrates a method for computing a standardized measure for transplant referral that could be used to monitor the transplant referral performance of dialysis facilities. The investigators expect the metric could be adapted in a larger, national population if national data on transplant referral are collected in the future. For this to happen, collection of national surveillance data on transplant referrals from the more than 5000 US dialysis facilities is essential. A Centers for Medicare & Medicaid expert review panel recommended collection of national data a decade ago.

In an accompanying editorial, Kevin Fowler of The Voice of the Patient, Inc., who is a kidney disease patient and a transplant recipient himself, stated that he was stunned that the data on kidney transplant referrals are not collected nationally.

"I am recommending immediate action," he wrote. "I am requesting that the Centers for Medicare & Medicaid Services mandate that all dialysis facilities collect and record their kidney transplant referrals. This requirement is long overdue."

Fowler noted that after additional studies are complete, it will be very interesting to learn about referral rates besides Georgia.

Obtaining meaningful information on transplant referrals from individual dialysis facilities across the country may help policymakers and clinicians identify gaps in quality and access of care, incentivize dialysis providers to increase referrals of appropriate candidates for transplantation, and lead to new evidence-based guidelines and interventions to increase access to kidney transplantation.

Study co-authors include Sudeshna Paul, PhD, Laura C. Plantinga, PhD, Stephen O. Pastan, MD, Jennifer C. Gander, PhD, and Sumit Mohan.

The article, entitled "Standardized Transplantation Referral Ratio to Assess Clinical Performance of Transplant Referral among Dialysis Facilities," appeared online at http://cjasn.asnjournals.org/ on January 25, 2018, doi: 10.2215/CJN.04690417

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ASN's Quality Committee Faces Packed Year for Dealing with Medicare Regulators

By David White

The American Society of Nephrology's (ASN) Quality Committee has its hands full in 2018. First, the Quality Payment Program (QPP) created by the Medicare Access and CHIP Reauthorization Act (MACRA) enters its second year after a very limited implementation as a transition year in 2017. Foremost, the QPP is beginning to calculate a "cost" section in physician scores and will need to be monitored closely by ASN and other medical societies for unintended consequences. Equally important are efforts to include acute kidney injury (AKI) in the End-Stage Renal Disease Prospective Payment System and Quality Incentive Program (PPS/QIP) and increase access to the use of telehealth in the Physician Fee Schedule. Working with regulators on these three major rules will comprise a significant portion of the ASN Policy team's work in 2018.

In general, three major Medicare rules that largely affect clinician reimbursement and nephrology practice are updated annually and primarily cover the QPP, PPS/QIP, and the Physician Fee Schedule. The ASN Quality Committee, chaired by Daniel E. Weiner, MD, FASN, reviews these rules every year. Medicare rules are issued as proposed first with a 60-day comment period followed by a later issuance of the final rule. The ASN Quality Committee annually provides comment on all three rules and meets with the Centers for Medicare & Medicaid Services (CMS) to provide input on various issues throughout the year.

Here are some of the highlights of these three rules for 2018.

The Quality Payment Program

Complex patient bonus. ASN has advocated for a recognition within the QPP of the challenges of dealing with complex patients. CMS adopted a complex patient bonus of 5 points. While ASN expressed support for the complex patient bonus, it will likely continue to lobby for a more robust bonus.

Costs. Costs in 2017, the first year of the QPP—declared a transition year by Medicare—had a weight of 0% to allow clinicians to adjust to the new system. For 2018, CMS decided to score costs at 10% believing the statutory 30% for 2019 was too big of an adjustment and did not allow enough time for clinicians to adjust to the calculations. CMS will not use episodes it has been designing for this calculation. Instead it will use Medicare Spending per Beneficiary (MSPB) and total per capita costs. This is a separate issue than the ESRD bundle.

Performance threshold. The 2017 transition year for the QPP performance threshold was three points, allowing clinicians to basically report one item and avoid any penalties for that year. CMS has raised the performance threshold to 15 for 2018. ASN advocated for 15 or less for this year and has cautioned CMS to move cautiously while implementing this major new program.

Other issues ASN supported that were adopted for the QPP in 2018 include:

- Allowing the use of 2014 Edition and/or 2015 Certified Electronic Health Record Technology (CEHRT) in 2018 for the Advancing Care Information performance category, and giving a bonus for using only 2015 CEHRT.
- Automatically weighting the Quality, Advancing Care Information, and Improvement Activities performance categories at 0% of the MIPS final score for clinicians impacted by Hurricanes Irma, Harvey, and Maria and other natural disasters.
- Adding 5 bonus points to the MIPS final scores of small practices.
- Adding Virtual Groups as a participation option for MIPS.
- Decreasing the number of doctors and clinicians required to participate to provide further flexibility by excluding individual MIPS eligible clinicians or groups with ≤ $90,000 in Part B allowed charges or ≤ 200 Medicare Part B beneficiaries.

Table 1. Three primary rules influencing nephrologists' reimbursement by Medicare issued for 2018 and updated annually

Medicare Program; Calendar year (CY) 2018 Updates to the Quality Payment Program
Medicare Program; End-Stage Renal Disease Prospective Payment System, Payment for Renal Dialysis Services Furnished to Individuals with Acute Kidney Injury, and End-Stage Renal Disease Quality Incentive Program
Medicare Program; Revisions to Payment Policies under the Physician Fee Schedule and Other Revisions to Part B for CY 2018; Medicare Shared Savings Program Requirements; and Medicare Diabetes Prevention Program

The End-Stage Renal Disease Prospective Payment System and Quality Incentive Program (PPS/QIP)

The Prospective Payment System. The ESRD PPS provides additional payment for high cost outliers when there are unusual variations in the type or amount of medically necessary care. ASN has been encouraging CMS to revise the outlier payment structure such that only the exact necessary amount is withheld to meet payouts or reinvest the difference between actual outlier costs incurred and the funds withheld to support research and other patient-focused initiatives within CMS' scope. CMS has been withholding more than it pays out for its outlier policy. CMS has not acted upon this, and ASN will continue to advocate for changes to this policy.

Patients with Acute Kidney Injury (AKI). ASN has repeatedly cautioned regulators to move very cautiously when considering including patients with AKI in the ESRD PPS/QIP. In the final rule for 2018, CMS acknowledged "that care for AKI patients is different from the care provided to individuals with ESRD." CMS stressed the distinction in its policies stating, "To address the higher costs associated with AKI patients as compared to ESRD patients, we finalized a policy of paying for all AKI dialysis treatments provided to a patient, without applying the monthly treatment limits applicable under the ESRD PPS. We also finalized a policy to pay separately for all items and services that are not part of the ESRD PPS base rate." CMS also will not apply the ESRD Network fee to the AKI dialysis payment rate.

ASN continues to advocate for permitting patients with AKI who do not recover kidney function and go on to receive a diagnosis of ESRD to have their first date of dialysis for AKI count as their first date of dialysis for purposes of transplant waitlisting.

ASN and other members of the kidney community are conducting further outreach to CMS to urge caution when including patients with AKI in the QIP and to only do so in close consultation with nephrologists.

Social Risk Factors in the QIP. CMS continues efforts to develop appropriate adjustors for social risk factors in the QIP to ensure equitable access to care for disadvantaged populations. It is continuing to consider the analyses and recommendations from the December 2016 report prepared by the Office of the Assistant Secretary for Planning and Evaluation, the January 2017 report released by the National Academies of Sciences, Engineering, and Medicine, and the ongoing evaluation work by the National Quality Forum (NQF).

The Physician Fee Schedule

Telehealth. Perhaps one of the most important new areas of coverage for nephrology, after new AKI coverage policies, is in the area of telehealth. In comments to CMS, ASN has affirmed the clinical safety and feasibility of assessing vascular access sites via telehealth technologies. While CMS said it did not believe it had sufficient evidence to make this change for the 2018 rule, it did declare "[W]e are interested in more information about current clinically accepted care practices and to what extent telecommunications technology can be used to examine the access site." ASN is working with CMS to identify the evidence CMS feels it needs to make this change.

ASN is also advocating for adding living donor evaluation, transplant recipient evaluation, and transplant-related follow-up care to the list of telehealth-eligible services.

Evaluation and Management Codes and Chronic Care Management Codes. ASN is urging CMS to reform existing Evaluation and Management coding and documentation guidelines to better align them with the current practice of medicine, reduce the associated burden on healthcare professionals, and refocus efforts on patient care. The society also urges CMS to strengthen access to the chronic care management codes by permitting people with ESRD to access this benefit.

Table 2. ASN Quality Committee

Charge

Assert the value of the nephrology care team, articulating the role of nephrology health professionals in new care delivery models; lead ASN's efforts related to quality measurement; and advise the ASN Council in defining the scope of nephrology practice.

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*Mild renal impairment (CKD stage 2) is defined as estimated glomerular filtration rate (eGFR) 60-89 mL/min/1.73 m^2; moderate renal impairment (CKD stage 3) is defined as eGFR 30-59 mL/min/1.73 m^2; severe renal impairment (CKD stage 4) is defined as eGFR 15-29 mL/min/1.73 m^2.[2]

INDICATION

ULORIC (febuxostat) is a xanthine oxidase (XO) inhibitor indicated for the chronic management of hyperuricemia in patients with gout. ULORIC is not recommended for the treatment of asymptomatic hyperuricemia.

IMPORTANT SAFETY INFORMATION

- ULORIC is contraindicated in patients being treated with azathioprine or mercaptopurine.
- An increase in gout flares is frequently observed during initiation of anti-hyperuricemic agents, including ULORIC. If a gout flare occurs during treatment, ULORIC need not be discontinued. Prophylactic therapy (i.e., NSAIDs or colchicine) upon initiation of treatment may be beneficial for up to six months.
- Cardiovascular Events: In randomized controlled studies, there was a higher rate of cardiovascular thromboembolic events (cardiovascular deaths, non-fatal myocardial infarctions, and non-fatal strokes) in patients treated with ULORIC [0.74 per 100 P-Y (95% CI 0.36-1.37)] than allopurinol [0.60 per 100 P-Y (95% CI 0.16-1.53)]. A causal relationship with ULORIC has not been established. Monitor for signs and symptoms of MI and stroke.
- Hepatic Effects: Postmarketing reports of hepatic failure, sometimes fatal, have been received. Causality cannot be excluded. During randomized controlled studies, transaminase elevations greater than three times the upper limit of normal (ULN) were observed (AST: 2%, 2%, and ALT: 3%, 2% in ULORIC and allopurinol-treated patients, respectively). No dose-effect relationship for these transaminase elevations was noted.

  Obtain liver tests before starting treatment with ULORIC. Use caution in patients with liver disease. If liver injury is detected, promptly interrupt ULORIC and assess patient for probable cause, then treat cause if possible, to resolution or stabilization. Do not restart treatment if liver injury is confirmed and no alternate etiology can be found.
- Serious Skin Reactions: Postmarketing reports of serious skin and hypersensitivity reactions, including Stevens-Johnson Syndrome, drug reaction with eosinophilia and systemic symptoms (DRESS) and toxic epidermal necrolysis (TEN) have been reported in patients taking ULORIC. Discontinue ULORIC if serious skin reactions are suspected.
- Adverse reactions occurring in at least 1% of ULORIC-treated patients, and at least 0.5% greater than placebo, are liver function abnormalities, nausea, arthralgia, and rash. Patients should be instructed to inform their healthcare professional if they develop a rash or have any side effect that bothers them or does not go away.

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

References: 1. ULORIC (febuxostat) prescribing information. Takeda Pharmaceuticals. **2.** Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int Suppl.* 2013;3(1):1-150.

Takeda

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION
ULORIC (febuxostat) tablet for oral use

INDICATIONS AND USAGE

ULORIC is a xanthine oxidase (XO) inhibitor indicated for the chronic management of hyperuricemia in patients with gout.

ULORIC is not recommended for the treatment of asymptomatic hyperuricemia.

CONTRAINDICATIONS

ULORIC is contraindicated in patients being treated with azathioprine or mercaptopurine *[see Drug Interactions]*.

WARNINGS AND PRECAUTIONS

Gout Flare

After initiation of ULORIC, an increase in gout flares is frequently observed. This increase is due to reduction in serum uric acid levels, resulting in mobilization of urate from tissue deposits.

In order to prevent gout flares when ULORIC is initiated, concurrent prophylactic treatment with an NSAID or colchicine is recommended.

Cardiovascular Events

In the randomized controlled studies, there was a higher rate of cardiovascular thromboembolic events (cardiovascular deaths, non-fatal myocardial infarctions, and non-fatal strokes) in patients treated with ULORIC (0.74 per 100 P-Y [95% Confidence Interval (CI) 0.36-1.37]) than allopurinol (0.60 per 100 P-Y [95% CI 0.16-1.53]) *[see Adverse Reactions]*. A causal relationship with ULORIC has not been established. Monitor for signs and symptoms of myocardial infarction (MI) and stroke.

Hepatic Effects

There have been postmarketing reports of fatal and non-fatal hepatic failure in patients taking ULORIC, although the reports contain insufficient information necessary to establish the probable cause. During randomized controlled studies, transaminase elevations greater than three times the upper limit of normal (ULN) were observed (AST: 2%, 2%, and ALT: 3%, 2% in ULORIC and allopurinol-treated patients, respectively). No dose-effect relationship for these transaminase elevations was noted.

Obtain a liver test panel (serum alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase, and total bilirubin) as a baseline before initiating ULORIC.

Measure liver tests promptly in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice. In this clinical context, if the patient is found to have abnormal liver tests (ALT greater than three times the upper limit of the reference range), ULORIC treatment should be interrupted and investigation done to establish the probable cause. ULORIC should not be restarted in these patients without another explanation for the liver test abnormalities.

Patients who have serum ALT greater than three times the reference range with serum total bilirubin greater than two times the reference range without alternative etiologies are at risk for severe drug-induced liver injury and should not be restarted on ULORIC. For patients with lesser elevations of serum ALT or bilirubin and with an alternate probable cause, treatment with ULORIC can be used with caution.

Serious Skin Reactions

Postmarketing reports of serious skin and hypersensitivity reactions, including Stevens-Johnson Syndrome, drug reaction with eosinophilia and systemic symptoms (DRESS) and toxic epidermal necrolysis (TEN) have been reported in patients taking ULORIC. Discontinue ULORIC if serious skin reactions are suspected. Many of these patients had reported previous similar skin reactions to allopurinol. ULORIC should be used with caution in these patients.

ADVERSE REACTIONS

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.

A total of 2757 patients with hyperuricemia and gout were treated with ULORIC 40 mg or 80 mg daily in clinical studies. For ULORIC 40 mg, 559 patients were treated for ≥6 months. For ULORIC 80 mg, 1377 patients were treated for ≥6 months, 674 patients were treated for ≥1 year and 515 patients were treated for ≥2 years.

Most Common Adverse Reactions

In three randomized, controlled clinical studies (Studies 1, 2 and 3), which were six to 12 months in duration, the following adverse reactions were reported by the treating physician as related to study drug. Table 1 summarizes adverse reactions reported at a rate of at least 1% in ULORIC treatment groups and at least 0.5% greater than placebo.

Table 1: Adverse Reactions Occurring in ≥1% of Patients Treated with ULORIC and at Least 0.5% Greater than Seen in Patients Receiving Placebo in Controlled Studies

	Placebo	ULORIC		allopurinol*
Adverse Reactions	(N=134)	40 mg daily (N=757)	80 mg daily (N=1279)	(N=1277)
Liver Function Abnormalities	0.7%	6.6%	4.6%	4.2%
Nausea	0.7%	1.1%	1.3%	0.8%
Arthralgia	0%	1.1%	0.7%	0.7%
Rash	0.7%	0.5%	1.6%	1.6%

*Of the patients who received allopurinol, 10 received 100 mg, 145 received 200 mg, and 1122 received 300 mg, based on level of renal impairment.

The most common adverse reaction leading to discontinuation from therapy was liver function abnormalities in 1.8% of ULORIC 40 mg, 1.2% of ULORIC 80 mg, and in 0.9% of patients treated with allopurinol.

In addition to the adverse reactions presented in Table 1, dizziness was reported in more than 1% of patients treated with ULORIC although not at a rate more than 0.5% greater than placebo.

Less Common Adverse Reactions

In Phase 2 and 3 clinical studies the following adverse reactions occurred in less than 1% of patients and in more than one subject treated with doses ranging from 40 mg to 240 mg of ULORIC. This list also includes adverse reactions (less than 1% of patients) associated with organ systems from Warnings and Precautions.

Blood and Lymphatic System Disorders: anemia, idiopathic thrombocytopenic purpura, leukocytosis/leukopenia, neutropenia, pancytopenia, splenomegaly, thrombocytopenia.

Cardiac Disorders: angina pectoris, atrial fibrillation/flutter, cardiac murmur, ECG abnormal, palpitations, sinus bradycardia, tachycardia.

Ear and Labyrinth Disorders: deafness, tinnitus, vertigo.

Eye Disorders: vision blurred.

Gastrointestinal Disorders: abdominal distention, abdominal pain, constipation, dry mouth, dyspepsia, flatulence, frequent stools, gastritis, gastroesophageal reflux disease, gastrointestinal discomfort, gingival pain, haematemesis, hyperchlorhydria, hematochezia, mouth ulceration, pancreatitis, peptic ulcer, vomiting.

General Disorders and Administration Site Conditions: asthenia, chest pain/discomfort, edema, fatigue, feeling abnormal, gait disturbance, influenza-like symptoms, mass, pain, thirst.

Hepatobiliary Disorders: cholelithiasis/cholecystitis, hepatic steatosis, hepatitis, hepatomegaly.

Immune System Disorder: hypersensitivity.

Infections and Infestations: herpes zoster.

Procedural Complications: contusion.

Metabolism and Nutrition Disorders: anorexia, appetite decreased/increased, dehydration, diabetes mellitus, hypercholesterolemia, hyperglycemia, hyperlipidemia, hypertriglyceridemia, hypokalemia, weight decreased/increased.

Musculoskeletal and Connective Tissue Disorders: arthritis, joint stiffness, joint swelling, muscle spasms/twitching/tightness/weakness, musculoskeletal pain/stiffness, myalgia.

Nervous System Disorders: altered taste, balance disorder, cerebrovascular accident, Guillain-Barré syndrome, headache, hemiparesis, hypoesthesia, hyposmia, lacunar infarction, lethargy, mental impairment, migraine, paresthesia, somnolence, transient ischemic attack, tremor.

Psychiatric Disorders: agitation, anxiety, depression, insomnia, irritability, libido decreased, nervousness, panic attack, personality change.

Renal and Urinary Disorders: hematuria, nephrolithiasis, pollakiuria, proteinuria, renal failure, renal insufficiency, urgency, incontinence.

Reproductive System and Breast Changes: breast pain, erectile dysfunction, gynecomastia.

Respiratory, Thoracic and Mediastinal Disorders: bronchitis, cough, dyspnea, epistaxis, nasal dryness, paranasal sinus hypersecretion, pharyngeal edema, respiratory tract congestion, sneezing, throat irritation, upper respiratory tract infection.

Skin and Subcutaneous Tissue Disorders: alopecia, angio-edema, dermatitis, dermographism, ecchymosis, eczema, hair color changes, hair growth abnormal, hyperhidrosis, peeling skin, petechiae, photosensitivity, pruritus, purpura, skin discoloration/altered pigmentation, skin lesion, skin odor abnormal, urticaria.

Vascular Disorders: flushing, hot flush, hypertension, hypotension.

Laboratory Parameters: activated partial thromboplastin time prolonged, creatine increased, bicarbonate decreased, sodium increased, EEG abnormal, glucose increased, cholesterol increased, triglycerides increased, amylase increased, potassium increased, TSH increased, platelet count decreased, hematocrit decreased, hemoglobin decreased, MCV increased, RBC decreased, creatinine increased, blood urea increased, BUN/creatinine ratio increased, creatine phosphokinase (CPK) increased, alkaline phosphatase increased, LDH increased, PSA increased, urine output increased/decreased, lymphocyte count decreased, neutrophil count decreased, WBC increased/decreased, coagulation test abnormal, low density lipoprotein (LDL) increased, prothrombin time prolonged, urinary casts, urine positive for white blood cells and protein.

Cardiovascular Safety

Cardiovascular events and deaths were adjudicated to one of the pre-defined endpoints from the Anti-Platelet Trialists' Collaborations (APTC) (cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke) in the randomized controlled and long-term extension studies. In the Phase 3 randomized controlled studies, the incidences of adjudicated APTC events per 100 patient-years of exposure were: Placebo 0 (95% CI 0.00-6.16), ULORIC 40 mg 0 (95% CI 0.00-1.08), ULORIC 80 mg 1.09 (95% CI 0.44-2.24), and allopurinol 0.60 (95% CI 0.16-1.53).

In the long-term extension studies, the incidences of adjudicated APTC events were: ULORIC 80 mg 0.97 (95% CI 0.57-1.56), and allopurinol 0.58 (95% CI 0.02-3.24).

Overall, a higher rate of APTC events was observed in ULORIC than in patients treated with allopurinol. A causal relationship with ULORIC has not been established. Monitor for signs and symptoms of MI and stroke.

Postmarketing Experience

The following adverse reactions have been identified during post approval use of ULORIC. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and Lymphatic System Disorders: agranulocytosis, eosinophilia.

Hepatobiliary Disorders: hepatic failure (some fatal), jaundice, serious cases of abnormal liver function test results, liver disorder.

Immune System Disorders: anaphylaxis, anaphylactic reaction.

Musculoskeletal and Connective Tissue Disorders: rhabdomyolysis.

Psychiatric Disorders: psychotic behavior including aggressive thoughts.

Renal and Urinary Disorders: tubulointerstitial nephritis.

Skin and Subcutaneous Tissue Disorders: generalized rash, Stevens-Johnson Syndrome, hypersensitivity skin reactions, erythema multiforme, drug reaction with eosinophilia and systemic symptoms, toxic epidermal necrolysis.

DRUG INTERACTIONS

Xanthine Oxidase Substrate Drugs

ULORIC is an XO inhibitor. Based on a drug interaction study in healthy patients, febuxostat altered the metabolism of theophylline (a substrate of XO) in humans. Therefore, use with caution when coadministering ULORIC with theophylline.

Drug interaction studies of ULORIC with other drugs that are metabolized by XO (e.g., mercaptopurine and azathioprine) have not been conducted. Inhibition of XO by ULORIC may cause increased plasma concentrations of these drugs leading to toxicity. ULORIC is contraindicated in patients being treated with azathioprine or mercaptopurine *[see Contraindications]*.

Cytotoxic Chemotherapy Drugs

Drug interaction studies of ULORIC with cytotoxic chemotherapy have not been conducted. No data are available regarding the safety of ULORIC during cytotoxic chemotherapy.

In Vivo Drug Interaction Studies

Based on drug interaction studies in healthy patients, ULORIC does not have clinically significant interactions with colchicine, naproxen, indomethacin, hydrochlorothiazide, warfarin or desipramine. Therefore, ULORIC may be used concomitantly with these medications.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Limited available data with ULORIC use in pregnant women are insufficient to inform a drug associated risk of adverse developmental outcomes. No adverse developmental effects were observed in embryo-fetal development studies with oral administration of febuxostat to pregnant rats and rabbits during organogenesis at doses that produced maternal exposures up to 40 and 51 times, respectively, the exposure at the maximum recommended human dose (MRHD). No adverse developmental effects were observed in a pre- and postnatal development study with administration of febuxostat to pregnant rats from organogenesis through lactation at an exposure approximately 11 times the MRHD *(see Data)*.

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. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

In an embryo-fetal development study in pregnant rats dosed during the period of organogenesis from gestation Days 7 – 17, febuxostat was not teratogenic and did not affect fetal development or survival at exposures up to approximately 40 times the MRHD (on an AUC basis at maternal oral doses up to 48 mg/kg/day). In an embryo-fetal development study in pregnant rabbits dosed during the period of organogenesis from gestation Days 6 – 18, febuxostat was not teratogenic and did not affect fetal development at exposures up to approximately 51 times the MRHD (on an AUC basis at maternal oral doses up to 48 mg/kg/day).

In a pre- and postnatal development study in pregnant female rats dosed orally from gestation Day 7 through lactation Day 20, febuxostat had no effects on delivery or growth and development of offspring at a dose approximately 11 times the MRHD (on an AUC basis at a maternal oral dose of 12 mg/kg/day). However, increased neonatal mortality and a reduction in neonatal body weight gain were observed in the presence of maternal toxicity at a dose approximately 40 times the MRHD (on an AUC basis at a maternal oral dose of 48 mg/kg/day).

Febuxostat crossed the placental barrier following oral administration to pregnant rats and was detected in fetal tissues.

Lactation

Risk Summary

There are no data on the presence of febuxostat in human milk, the effects on the breastfed infant, or the effects on milk production. Febuxostat is present in rat milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ULORIC and any potential adverse effects on the breastfed child from ULORIC or from the underlying maternal condition.

Data

Animal Data

Orally administered febuxostat was detected in the milk of lactating rats at up to approximately 7 times the plasma concentration.

Pediatric Use

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

Geriatric Use

No dose adjustment is necessary in elderly patients. Of the total number of patients in clinical studies of ULORIC, 16% were 65 and over, while 4% were 75 and over. Comparing patients in different age groups, no clinically significant differences in safety or effectiveness were observed but greater sensitivity of some older individuals cannot be ruled out. The C_{max} and AUC_{24} of febuxostat following multiple oral doses of ULORIC in geriatric patients (≥65 years) were similar to those in younger patients (18 to 40 years).

Renal Impairment

No dose adjustment is necessary in patients with mild to moderate renal impairment (Cl_{cr} 30 to 89 mL/min). The recommended starting dose of ULORIC is 40 mg once daily. For patients who do not achieve a sUA less than 6 mg/dL after two weeks with 40 mg, ULORIC 80 mg is recommended. For patients with severe renal impairment (Cl_{cr} 15 to 29 mL/min), the dose of ULORIC is limited to 40 mg once daily.

Hepatic Impairment

No dose adjustment is necessary in patients with mild or moderate hepatic impairment (Child-Pugh Class A or B). No studies have been conducted in patients with severe hepatic impairment (Child-Pugh Class C); therefore, caution should be exercised in these patients.

Secondary Hyperuricemia

No studies have been conducted in patients with secondary hyperuricemia (including organ transplant recipients); ULORIC is not recommended for use in patients whom the rate of urate formation is greatly increased (e.g., malignant disease and its treatment, Lesch-Nyhan syndrome). The concentration of xanthine in urine could, in rare cases, rise sufficiently to allow deposition in the urinary tract.

OVERDOSAGE

ULORIC was studied in healthy patients in doses up to 300 mg daily for seven days without evidence of dose-limiting toxicities. No overdose of ULORIC was reported in clinical studies. Patients should be managed by symptomatic and supportive care should there be an overdose.

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Physician-Focused Payment Models Shaping Up in 2018

2018 is shaping up to be the year for designing and proposing integrated care models for testing by the Centers for Medicare & Medicaid Services (CMS). There are three major factors driving this trend:

1. Physician-Focused Payment Model Technical Advisory Committee (PTAC).
2. Request for Information (RFI) by the Centers for Medicare and Medicaid Services Innovation Center.
3. Perception that the train is leaving the station.

With further examination of these three factors, it becomes clearer how closely tied they are to one another.

PTAC

The Medicare Access and CHIP Reauthorization Act of 2015 (MACRA) created new pathways for the Medicare program to pay physicians for the care they provide. MACRA also created incentives for physicians to participate in Alternative Payment Models (APMs), including the development of physician-focused payment models (PFPMs). To accomplish that goal, MACRA created PTAC to evaluate and recommend to the Secretary of the Department of Health and Human Services (HHS) proposals for PFPMs submitted by individuals and stakeholder groups. The Secretary is required by MACRA to establish criteria for PFPMs and to respond to the recommendations of PTAC.

The PTAC completed its third public meeting and its first year of operations in December 2017. Now, the body seems to have arrived at a fully operational state and is sending out the message to "bring your integrated care models to them for review." At the December 2017 meeting, PTAC voted to recommend a proposal for an Incident ESRD Clinical Episode Payment Model submitted by the Renal Physicians Association (RPA). ASN is currently finalizing a proposal for a comprehensive kidney care model spanning late CKD, ESRD, transplant, and posttransplant that it hopes to submit to the PTAC in 2018.

Information sought by CMS Innovation Center

In late 2017, the CMS Innovation Center issued an RFI seeking feedback on new directions to promote patient-centered care, and test market-driven reforms, as well as PFPMs. ASN answered the call for feedback with a detailed outline of its proposal for a comprehensive kidney care model. This is the same model, described above, under development for the PTAC. This two-tiered approach follows the pathway laid out under MACRA. First, the PTAC will evaluate and recommend models for testing it deems in line with criteria outlined in the MACRA final rule issued in 2016. If the model passes the PTAC and the office of the HHS Secretary, then it is forwarded to the CMS Innovation Center for the actual testing of the model. The RFI by the CMS Innovation Center appears designed to keep this process moving along a forward trajectory.

The train is leaving the station

Under the Quality Payment Program (QPP), which is in and of itself a model that is still evolving, created by MACRA, it is open season for integrated care model development.

With the PTAC having successfully navigated its first year and entering its second and the CMS Innovation Center joining the call for models, the testing grounds appear primed. ASN believes the mechanisms are in place and the conditions are right for nephrology, and other specialties in their own space, to advocate for a nephrology-led integrated care model.

Industry Spotlight

RenalGuard's Premarket Work in US

RenalGuard Solutions (Milford, MA) said in 2017 that it expected a premarket approval filing for its fluid-management device in 2018, based on its contrast-induced nephropathy (CIN) study, CIN-RG, which is currently enrolling subjects.

The company's investigational device, RenalGuard, protects patients from acute kidney injury (AKI), including contrast-induced AKI (CI-AKI). The system was designed to rapidly remove contrast dyes that can be toxic to kidneys.

Investigator-sponsored studies in Europe have demonstrated RenalGuard's effectiveness at preventing CI-AKI in at-risk patients. RenalGuard measures a patient's urine output and automatically infuses hydration fluid based on the level of urine output. The system is designed to induce high urinary excretion rates, which has been shown to protect kidneys.

RenalGuard is Conformite Europeene (CE)-marked and is sold in Europe and some other countries via a network of distributors.

Now the company has reported its first-in-humans feasibility study focused on a different use of the RenalGuard System: management of fluids during diuretic therapy in a group of congestive heart failure patients suffering from fluid overload. A recent study followed the treatment of 10 diuretic-resistant patients with heart failure symptoms receiving diuretic therapy while their fluid management was controlled by the RenalGuard System; results were presented at the annual Devices in Heart Failure (D-HF) congress in Berlin.

"None of the patients we treated experienced a fluid loss rate greater than the settings we established," said Piotr Ponikowski, MD, of the Wroclaw Medical University, Poland, who also serves as chair of the European Society of Cardiology 2016 Heart Failure Guidelines Committee.

Other studies have demonstrated RenalGuard's ability to protect patients from AKI following catheterization procedures when compared to the standard of care, including MYTHOS, which found RenalGuard to be superior to overnight hydration, and REMEDIAL II, which found RenalGuard superior to sodium bicarbonate hydration in preventing CI-AKI in high-risk patients. Meta-analyses of the study results have found RenalGuard reduced kidney injury, dialysis initiation, adverse events, and premature mortality compared to standard therapy, the company states.

New Kidney Stone Products

Flying Brands, based in Jersey, United Kingdom, announced that it has received a CE (Conformité Européene) mark approving its Stone Checker software for use in the European Union and some affiliated nations in Europe. The CE seal confirms that a product meets the essential requirements of relevant European health, safety, and environmental protection legislation.

Flying Brands is an investment company that focuses on opportunities in the technology and logistics sectors, and Stone Checker Software Ltd, is part of Flying Brands.

Stone Checker software provides details about kidney stones to aid in clinical decision-making. The semi-automated kidney stone assessment tool generates metrics for physicians that use a patient's non-contrast CT scans.

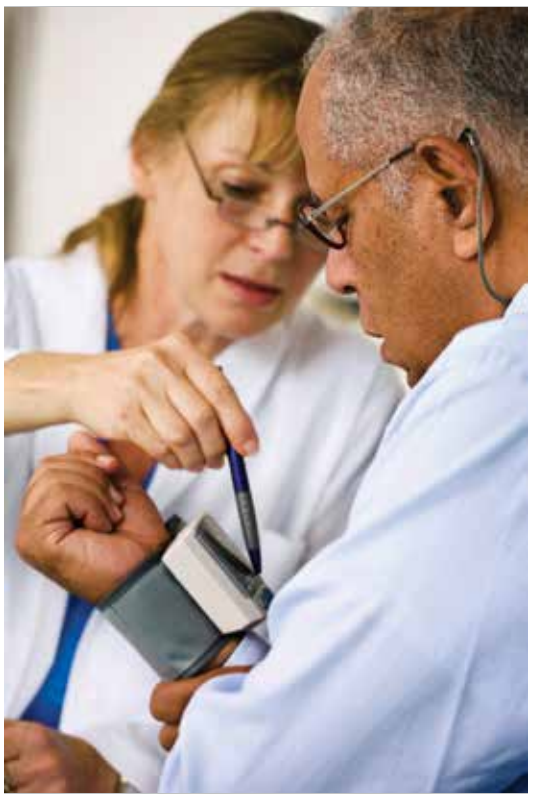
CT Texture Analysis (CTTA) metrics of Stone Checker showed that it reflected stone characteristics and composition, and predicted ease of shock-wave lithotripsy fragmentation in studies.

The strongest correlation with number of shocks required to fragment the stone was mean Hounsfield unit and a CTTA metric that measured the entropy of the pixel distribution of the stone image. Image entropy is a quantity used to describe how "busy" an image is, i.e., the amount of information that must be coded for by a compression algorithm.

Using multiple linear regression analysis, the best model showed that CTTA metrics of entropy and the sharpness of the peak of the frequency distribution curve could predict 92% of the outcome of number of shocks needed to fragment the stone. This method was superior to using stone volume or density as a predictive measure, according to the company.

The company's next goal is for Stone Checker to earn FDA approval in 2018.

What Are the Most Effective Implementation Strategies for BP Control?



Multilevel, multicomponent strategies provide the greatest reductions in blood pressure (BP) for patients with hypertension, concludes a meta-analysis in *Annals of Internal Medicine*.

The researchers performed a systematic review and meta-analysis of randomized trials comparing the effectiveness of eight implementation strategies for BP control in adults with hypertension, compared to regular care. There were two patient-level strategies (home coaching and home BP monitoring), three provider-level strategies (provider training, audit and feedback, and electronic decision-support systems), and three multilevel strategies (multilevel strategy without team-based care and team-based care with medication titration by physicians or nonphysicians). The meta-analysis included 121 comparisons from 100 articles including 55,920 patients.

"Multilevel, multicomponent strategies were most effective for systolic BP reduction," the researchers write.

Mean reductions achieved were 7.1 mm Hg with team-based care with medications titrated by nonphysician providers, 6.6 mm Hg with medications titrated by physicians, and 5.0 mm Hg with multilevel strategies without team-based care.

Analysis of patient-level strategies showed systolic BP reductions of 3.9 mm Hg with health coaching and 2.7 mm Hg with home BP monitoring. On analysis of provider-level strategies, there was a 3.7 mm Hg reduction with electronic decision-support systems, but no significant effect of provider training or audit and feedback. Analysis of diastolic BP noted similar effects.

Various implementation strategies have been shown to improve BP control in patients with hypertension, but there are few data on the comparative effectiveness of these approaches. The new analysis finds that multilevel, multicomponent strategies achieve the largest reductions in BP, followed by patient-level strategies. The authors call for wider dissemination and scale-up of these types of strategies in clinical practice and public health programs [Mills KT, et al. Comparative effectiveness of implementation strategies for blood pressure control in hypertensive patients: a systematic review and meta-analysis. *Ann Intern Med* 2017; DOI: 10.7326/M17-1805]. ■

High Mortality with Emergency-Only Dialysis in Undocumented Immigrants

For undocumented immigrants with end stage renal disease (ESRD), standard dialysis three times weekly reduces mortality and hospital days, compared to emergency-only dialysis, reports a study in *The Journal of the American Medical Association*.

The retrospective cohort included 211 undocumented immigrants with ESRD treated at three US centers between 2007 and 2014. Patients at centers in Denver and Houston received emergency-only dialysis based on signs of critical illness. Patients treated at a San Francisco hospital received standard dialysis, scheduled three times weekly. The main outcome of interest was mortality at 3 years, adjusted for propensity to undergo emergency versus standard dialysis.

The patients were 125 men and 86 women, mean age 46.5 years: 169 received emergency-only dialysis and 42 received standard hemodialysis. The standard dialysis patients were more likely to have an arteriovenous fistula or graft in place when starting dialysis and had higher albumin and hemoglobin levels.

On adjusted analysis, the hazard ratio for death among patients receiving emergency dialysis was 4.96 at 3 years,

increasing to 14.13 at 5 years, compared to those receiving standard dialysis. Similar results were found when the analysis was limited to Hispanic patients.

At 5 years, the rate ratio for acute care days in the emergency-only group was 9.81. The rate ratio for ambulatory care visits was 0.31, compared to standard dialysis, and there was no significant difference in the rate of bacteremia episodes. Compared with the entire US dialysis population, 5-year age-standardized mortality ratios were 2.26 for undocumented patients receiving emergency-only dialysis and 0.86 for those receiving standard dialysis.

In many states, undocumented immigrants with ESRD do not receive dialysis until they develop severe complications of kidney disease. This study finds that emergency-only dialysis is associated with increased mortality and more acute hospital days, compared to standard hemodialysis. The investigators conclude, "States across the country providing emergency-only hemodialysis to undocumented immigrants should reconsider the substantial human and economic effect of providing less-than-standard hemodialysis care" [Cervantes L, et al. Association of emergency-only vs standard hemodialysis with mortality and health care use among undocumented immigrants with end-stage renal disease. *JAMA Intern Med* 201; doi: 10.1001/jamainternmed.2017.7039].

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Risk Equation Predicts Outcomes in Pediatric CKD

In children with chronic kidney disease (CKD), the kidney failure risk equation (KFRE) performs well in predicting the risk of progression to end stage renal disease (ESRD), concludes a study in *JAMA Pediatrics*.

The retrospective analysis included 603 children from a multicenter pediatric CKD cohort study. About 63% of the patients were boys. Their median age at study entry was 12 years and they had a median estimated glomerular filtration rate (eGFR) of 44 mL/min/1.73 m^2. Two versions of the KFRE were analyzed for their ability to predict progression to ESRD: a four-variable version (age, sex, bedside Schwartz eGFR, and ratio of albumin to creatinine) and an eight-variable version (the same four variables plus serum calcium, phosphate, bicarbonate, and albumin).

The median follow-up time was 3.8 years. By 5 years, 23.9% of the children had progressed to ESRD. Both versions of the KFRE provided excellent discrimination of ESRD risk. With the four-variable equation, C statistics were 0.90 at 1 year, 0.86 at 2 years, and 0.81 at 5 years.

The C statistics were higher for Hispanic versus non-Hispanic patients and for children less than 12 years versus older patients. Progression to ESRD occurred in 27.9% of children in the top tertile of 2-year KFRE score versus 1.7% in the bottom tertile.

The KFRE has proven a useful guide to clinical decision-making in adults with CKD. The new results show that the KFRE is also a good predictor of risk of progression to ESRD in a large group of children with mainly nonglomerular kidney disease. This simple tool "may provide opportunities to improve the care of children with CKD," the researchers write [Winnicki E, et al. Use of the kidney failure risk equation to determine the risk of progression to end-stage renal disease in children with chronic kidney disease. *JAMA Pediatr* 2017; doi:10.1001/jamapediatrics.2017.4083].

Dipstick Test Shows Promise for Diagnosing Obstetric AKI

A salivary urea nitrogen (SUN) dipstick test is specific—but not sensitive—for diagnosis of obstetric-related acute kidney injury (AKI) in high-risk Malawian women, reports a study in the open-access journal *Kidney International Reports*.

The study included 301 pregnant or postpartum women at high risk of AKI. The women were admitted to the obstetric unit of a district hospital in Blantyre, Malawi, over a 12-week period. The patients' mean age was 26 years, and 11% were HIV positive. On admission, patients underwent the SUN dipstick test as well as serum creatinine measurement, with additional testing as indicated.

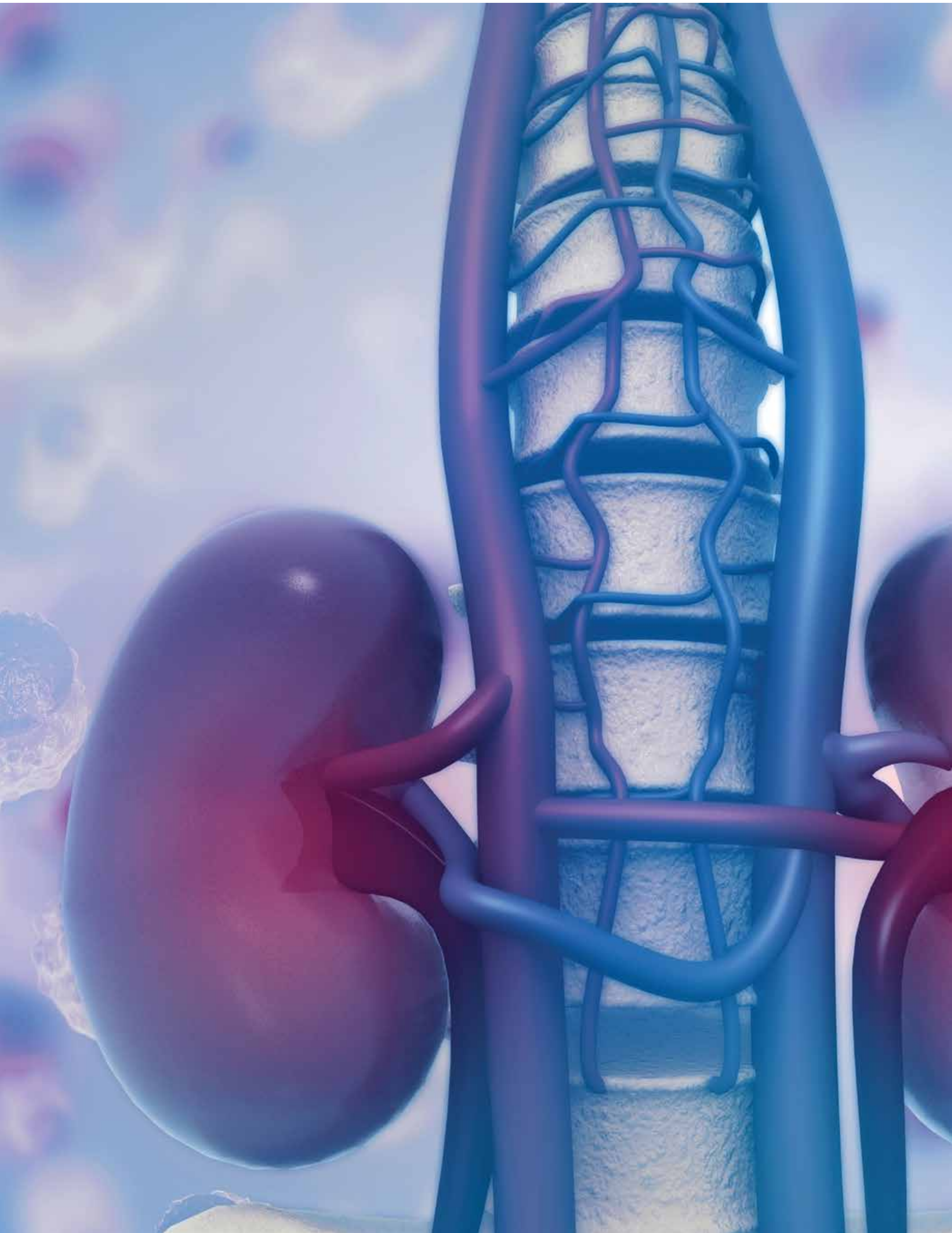
Acute kidney injury was diagnosed in 23 women. Of these, nearly half had stage 1 AKI, mainly due to preeclampsia or eclampsia. Mean admission serum creatinine was 108.8 mg/dL in women with stage 1 AKI, 1.33 mg/dL in stage 2, and 1.36 mg/dL in stage 3. A SUN dipstick value of greater than 14 mg/dL was 97.33% specific for the diagnosis of AKI, with sensitivity of just 12.82%.

Area under the receiver operating characteristic curve with the SUN dipstick test was 0.551. Perinatal mortality was 25.0% for women with an SUN dipstick value greater than 14 mg/dL, compared to 11.8% for those with normal admission SUN.

Laboratory-independent tools for diagnosis of obstetric-related AKI in low-income countries are needed. The SUN dipstick test has shown good performance in diagnosis of kidney injury in adult patients with acute and chronic kidney disease.

This study finds that the SUN dipstick is a specific but insensitive test for obstetric-related AKI among high-risk women in Malawi. A modified dipstick test with better sensitivity at lower ranges of SUN is under development and will be tested in pregnant and nonpregnant patients [Evans RDR, et al. A salivary urea nitrogen dipstick to detect obstetric-related acute kidney disease in Malawi. *Kidney Int Rep* 2018; 3:178– 184]. ■

TRANSPLANT Innovations and Policy



Has the New Kidney Allocation System Benefited Patients?

By Alejandro Diez

It is well established that kidney transplantation is the treatment of choice for patients with end stage renal disease (ESRD), as this treatment modality has been shown to provide improved patient survival and quality of life compared with dialysis (1). In an ideal system, patients in need of a kidney transplant would receive one as soon as the need arises. Unfortunately, the well-described mismatch between a limited number of available organs and the larger number of patients in need of a transplant makes this impossible, necessitating policies for the allocation of this limited resource. Available organs had been, until recently, allocated to potential recipients based on an algorithm that primarily weighed "time on the waitlist from the moment of listing."

Under this system there were several limitations: The system did not take into account matching organs and recipients for graft longevity post-transplant, leading to a significant re-transplant rate. There was variability in access to transplantation depending on level of anti-HLA antibody sensitization, blood type, and geographical location. And there was a higher than desired organ discard rate leading to underutilization of kidneys that could have been potentially transplanted.

To address these limitations and to increase the efficiency of kidney allocation, the United Network for Organ Sharing (UNOS) and the Organ Procurement and Transplantation Network (OPTN) implemented a new kidney allocation system (KAS) in December 2014.

The KAS incorporated new parameters to allocation algorithms, previously described in *Kidney News* (2). Major changes included:

- The adoption of new donor and recipient quality metrics: Kidney Donor Profile Index (KDPI) and Estimated Post Transplant Survival (EPTS). These metrics are the basis for longevity matching between recipients and donors: Donors with EPTS scores of 0–20% are prioritized for kidneys with a KDPI of less than or equal to 20%.
- Increasing the priority assigned to highly sensitized recipients (as defined by calculated panel reactive antibody [cPRA] score). The KAS assigns points on the basis of a sliding scale points system for cPRA. Whereas previously candidates received an absolute 4 additional points for a cPRA at or above 80% KAS, candidates now receive approximately 4 points at a cPRA of 85 to 89 and rapidly increase afterward. Candidates with cPRA scores of 99% and 100% receive 50 and 202 points, respectively.
- Modifying the blood type eligibility of candidates with blood types associated with longer wait times by allowing ABO type non-A1 and non-A1B kidneys to be allocated to type B candidates.
- Modification of the waiting time calculation by adding the pre-registration dialysis time into a candidate's waiting time.

December 2017 marked the three-year anniversary of the new KAS. Reports have been published describing six- and 12-month outcomes analyzing incident transplant changes pre- and post-KAS implementation. The two-year KAS implementation data were reported during the summer of 2017. This report included new data points not available in earlier reports, including stratified delayed graft function (DGF) rates, one-year survival outcomes, and re-listing rates. The two-year data also revealed the development of interesting trends and patterns (3).

- Among the encouraging trends, data show that pre-KAS differences in the rates at which African American, Hispanic, and Caucasian transplant candidates received kidneys from deceased donors have attenuated post-KAS; hence the percentage of kidney transplants performed by recipient ethnicity now reflects the ethnic composition of candidates on the waitlist. Longevity matching continues to function as designed; over half (56%) of EPTS 0–20% adult recipients received a KDPI 0–20% kidney, while only 1% received a KDPI 86–100% kidney. There is a continued increase in the number of blood type A2/A2B subtype to blood type B recipients (0.2% pre-KAS vs. 1.4% post-KAS). Finally, although not statistically significant, re-listing rates within one year of transplant decreased from 1.64% to 1.38%.
- There appears to be an attenuation of the "bolus effects" initially observed in candidates who received increased transplant priority under KAS (highly sensitized candidates and long dialysis times prior to listing). Prior to KAS, the percentage of transplants to candidates with greater than 10 years of dialysis was 4.5%, sharply increasing to 18.6% immediately after implementation. Newer data show that these rates have decreased substantially and appear to have leveled off at approximately 6%. Likewise, the increased rates of DGF initially observed immediately after KAS have improved. Prior to KAS the rate of DGF was 24.4%, rising to 29.6% 1-year post-KAS, and subsequently decreasing to 27.7% 2 years post-KAS.
- Unfortunately, the kidney discard rate post-KAS remains higher than prior to implementation. As expected, there is an association between higher KDPI scores and discard rates: 3% of kidneys with a KDPI of 0 to 20 are discarded vs. 60% of kidneys with a KDPI between 86 and 100. Although overall one-year patient and graft survival remain very high post-KAS, two-year data show a slight decrease compared with pre-KAS. The underlying etiology for these observations is equivocal, but may be a sequel to the earlier observed bolus effect. Longer outcomes data may aid in elucidating this observation.

. . . the new KAS is far from perfect. Persistent disparities in access to deceased donor organs still exist. However, KAS has, as a whole, benefited our patients.

Based on limited data this new report is certainly compelling, but it begs the question, "Has the new KAS benefited patients?" This question is particularly contentious because when the allocation criteria to a limited resource are modified, the waiting time might become shorter for some patients and longer for others. The Equity in Access Report released in August 2017 may provide some insight to help answer this question (4). This report relies on a recently developed metric, Access-to-Transplant Score (ATS), a numerical measure developed to quantify the variability in expected waiting times for receiving a deceased donor kidney transplant among waitlisted patients. After implementation of KAS, the overall ATS among waitlisted candidates has not just decreased, but also remained relatively stable suggesting that KAS has improved equity in access to deceased donor kidney transplants. Long-term data will provide further clarification to this question.

Looking ahead

As we look back at the past and now at the present, we must ponder the future implications of KAS. Currently, the data generated after KAS implementation remain in a state of flux. If current trends persist in upcoming reports, we would expect an abrogation of the bolus effect, which should

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Kidney Allocation

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help provide much more reliable data for analysis. At that juncture one would predict an improvement in patient and graft survival, as there would a decrease in the proportion of transplants performed on patients with disproportionally high dialysis time and cPRA, approximating or surpassing outcomes prior to KAS. Projected outcomes of longevity matching, one of the goals of KAS, should become clearer. If the outcomes are as expected one could see an increase in graft survival in groups receiving lower KDPI grafts with a concomitant decrease in re-transplant rates. One point of re-examination may include adjustment of priority points assigned to highly sensitized candidates. Other areas of modification may focus on addressing the discard rate of higher KDPI kidneys as a means to increase utilization.

Finally, the new KAS is far from perfect. Persistent disparities in access to deceased donor organs still exist. However KAS has, as a whole, benefited our patients. Overall the data show that many difficult-to-match patients, those who were once thought of as "un-transplantable," are now being transplanted. In a sense, KAS implementation has provided these patients with a "new lease on life," which ultimately is our mission and goal as clinicians.

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Kidney Allocation and Transplant: Disparities and Regulatory Burden

By David White

The numbers speak for themselves. There are currently 121,678 people waiting for life-saving organ transplants in the US. Of these, 100,791 await kidney transplants. A patient is added to the kidney waitlist every 14 minutes and 13 people die every day waiting for a kidney transplant (1). These numbers and their implications led to the Kidney Week 2017 session, *Political Correctness? Public Policy Influences on Transplantation*, moderated by Roy D. Bloom, MD, and Michelle A. Josephson, MD.

In the segment Kidney Allocation Changes: Past, Present, and Future, Richard N. Formica, MD, of the Yale School of Medicine, outlined where the Organ Procurement and Transplantation Network (OPTN) Kidney Allocation System (KAS) changes of December 2014 have led. Formica is professor of medicine and surgery and director of transplant medicine at Yale.

He laid out several precepts for consideration:

- An organ allocation system without disparities is probably not possible.
- Equity may not always be desirable if other goals are adversely affected.
- Allocation policy only addresses disparities in allocation for waitlisted patients—it does not address disparities in access to the kidney waitlist itself.

Simply put, getting on the waitlist is an access issue, and receiving a kidney is an allocation issue.

Prior to revisions to the KAS, disparities existed in several areas. Revisions to the KAS were designed to address four of these areas (Table 1).

One of the key revisions now shaping allocation policy is the introduction of longevity matching, which basically pairs those patients with the longest life expectancy with kidneys expected to last the longest. This is the first of four pillars of the current KAS. The remaining three pillars are:

- Matching the allocation score to the biological need of the highly sensitized recipient.
- Recalculating waiting time to start at the date of dialysis initiation instead of the date of listing.
- Improving access for minority candidates by allocating donor organs with blood type A2 to B blood type recipients.

Issues of insurance and geography still persist. Those with the resources can be waitlisted in multiple locations, increasing their chances of moving up the waitlist. Those without those resources may be affected by living in a donor service area with much lower rates of transplantation. Formica pointed out that under section 121.8 of the OPTN Final Rule, organ allocation, "shall not be based on the candidate's place of residence or place of listing, except to the extent required by paragraphs (a)(1)-(5) of this section." The presence of geographic disparities seems to be, on its face, in violation of stated policy. The next big challenge according to Formica was access to the transplant list itself.

Transplant regulation: benefits and challenges

Transplant is arguably one of the most regulated parts of medicine, noted Jesse D. Schold, PhD, Director of the Center for Population Health Research at the Cleveland Clinic.

Use of quality oversight report cards yields potential benefits but also potential ill effects. Objectively, Schold said that report cards:

- Inform patients and caregivers—healthcare transparency.
- Ensure regulatory oversight—quality assurance.
- Provide incentives and feedback for quality monitoring—a lot more people paying attention.
- Identify best processes.
- Invoke competition in quality.

Concerns about using report cards in healthcare include the creation of artificial objectives at the expense of patient care efforts, variability in assessments by statistical methods used, the selected or limited use of information by consumers, the deleterious impact on access to care for vulnerable populations, and the lack of input of patient practices.

The Scientific Registry of Transplant Recipients (SRTR) has the data to evaluate the challenges currently facing patients. In 2017, 35,000 organ transplants were performed in the US (2). To be eligible to participate as a transplant center in the US the center must have its outcomes measured on a semi-annual basis and assessed based on observed and expected survival. These measured outcomes are equated to public funding dollars. Approximately 10% of US transplant programs have lower than expected graft or patient survival in a given year.

CMS flags a transplant program for review based on the assessment of a center's risk-adjusted expected (E)* and observed (O) events for 1-year patient survival and 1-year graft survival. However, different statistical analysis approaches are used by CMS and UNOS.

Schold pointed out that in 2014, a Bayesian statistical model was incorporated into the SRTR outcomes assessment for transplant centers. Bayesian analysis is a statistical method that answers research questions about unknown parameters of statistical models by using probability statements. Bayesian analysis rests on the assumption that all model parameters are random quantities and thus can incorporate prior knowledge. This assumption is in sharp contrast with the more traditional, also called frequentist, statistical inference where all parameters are considered unknown but fixed quantities. This second approach, frequentist, is used by CMS.

Table 1. Disparities in Kidney Transplant

- Geographic location (donor service area)
- Excessive time delays for highly sensitized individuals
- Different waiting time based on blood type
- Age
- Gender
- Race/ethnicity
- Insurance rates

The Kidney Allocation System was designed to address disparities shown in highlighted areas.

Has kidney transplant regulation gone too far?

With these factors in mind, Schold laid out the four areas that help answer the overall question: Has kidney transplant regulation gone too far?

Too much flagging?

Using data on flagging of facilities and observed and expected outcomes at small and large centers (3), the level of regulation does not appear proportional—the ramifications and layers of regulation exceed the level of existing outliers.

Influence of confounding factors

The adjustment for co-morbid information obtained from Medicare claims would change the qualitative performance of 8–9% of centers. This lack of comorbidity adjustment may disadvantage centers willing to accept higher risk patients (4). Community risk is strongly associated with pre-transplant processes and outcomes—where you live matters significantly (5).

Significant unintended consequences

There are many smaller consequences tied to the new rating system, but the most significant change is the culling of the waitlist by a transplant center following a low performance rating. The removal of people classified as removed for being "too sick" or "other" reasons leaves some concerned that relatively healthy transplant candidates may get caught up in the zeal to avoid any additional low performance scores with overly stringent list culling (6).

Wrong Endpoints

A one-year survival rate may have made sense 25 to 30 years ago, but is that the appropriate timeframe today? In an era of comprehensive care and payment models, perhaps patients would be better served by a more comprehensive quality assessment that also captures pre-transplant and factors impacting access to waitlist.

Patient survival rates should have real life relevancy, which means factoring in dialysis and survival rates for patients who remain on a waitlist when evaluating performance.

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Novel Normothermic Perfusion Technique for Preserving Donor Organs

By Uday Nori

Is it possible to turn unusable organs into transplantable organs? Ex vivo pulsatile machine perfusion of donor organs is a proven technique for superior organ preservation, reduced delayed graft function, and reduced ischemia-reperfusion injury. This has been the standard of care for over four decades in high-volume transplant centers.

The perfusate solutions used for kidneys are typically crystalloids with several additives, such as antioxidants, electrolytes, antibiotics, nutrients, vasodilators, and corticosteroids. The perfusion temperatures are typically kept at 4°C to 8°C to help minimize cell metabolism and hence, have a better preserved organ. However, the significant drawback of this hypothermic perfusion technique is its inherent inability to allow any cellular repair.

Marginal kidneys, designated as "high kidney donor profile index," make up a substantial proportion of transplanted kidneys currently. The quality of deceased donor organs has declined significantly over the past three decades because of the cause of death: improved traffic safety led to fewer donors who died accidentally, and more organ donors died from natural causes or substance abuse. Therefore, in the current paradigm of organ shortage and high organ discard rates, perfusion techniques that allow organ repair in addition to the preservation are highly desired.

The notion of organ perfusion at the usual body temperature has several advantages:

1. Aerobic metabolism allows the kidney to regain function and minimize or avoid the cold ischemic insult.
2. The kidney can be maintained in a stable state, allowing close observation and assessment of viability.
3. Organ perfusion provides the opportunity to add therapies to a functioning organ to directly manipulate and improve its condition.

Although the concept of normothermic machine perfusion (NMP) has existed for more than two decades, it was only in the past few years that significant progress has been made in terms of optimal perfusion solutions, equipment, and favorable outcomes in animal models (Figure1). At present, most normothermic perfusate solutions include packed red blood cells for oxygen carriage and use highly specialized equipment. Many acellular solutions are being investigated to replace hemoglobin as the oxygen carrier. Although most of the studies using NMP involve the lung and liver transplantation fields, owing to their high organ discard rates and underused marginal donors, the adaptation of NMP in kidney transplantation is seen as naturally feasible and practical.

There are several animal model studies that have shown the success of NMP, but some human trials were also recently reported. A study by Watson et al. (1) subjected 12 discarded livers to the NMP, with six of them under high perfusate oxygen tension and the other six under near-physiologic oxygen tension. All six in the latter category reperfused uneventfully, and 11 patients were alive at a median of 12 months. Vogel et al. reported a study of 13 discarded livers that were preserved with NMP for 24 hours, and they showed both biochemical and histologic evidence for suitability for organ transplantation (2). Similarly, Hosgood et al. reported that two kidneys from the same donor that were declined by all transplant centers and preserved with NMP for 60 minutes cleared up significant areas of ischemia (3). In the largest series so far, Nicholson and Hosgood compared 18 marginal kidneys that received 1 hour of preimplantation NMP with 47 matched hypothermic perfusion controls (4). Remarkably, low delayed graft function rates were seen with preimplantation NMP (5.6% versus 36.2%). The benefits of NMP are significant, because hypothetically, organ quality improves with time as opposed to a gradual decline with conventional hypothermic perfusion. Therefore, NMP offers improved organ utilization rate, minimized ischemia-reperfusion injury, reduced delayed graft function, and stabilized endothelial cells. However, the costs and labor of this modality are also exceedingly high at present, not to mention the logistic complexities.

NMP, which allows organs to undergo perfusion for extended periods of time, has also allowed for other novel therapies, such as targeted immunosuppression therapies using sirolimus-infused nanoparticles to "silence" endothelial cell signaling—an important mechanism for acute rejection.

Success in the NMP field is believed to be imminent by many investigators and can potentially change the practice of transplantation in many ways. The idea of a centralized organ preservation laboratory, where all of the marginal, unusable organs undergo NMP to improve their quality and then are distributed to the individual transplant centers, seems to be possible in the near future.

A query of clinical trials.gov returned 11 human clinical trials currently underway, with one in kidney transplantation. This is indeed a highly promising field to watch out for in organ transplantation.

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Figure 1. Schematic diagram of normothermic perfusion

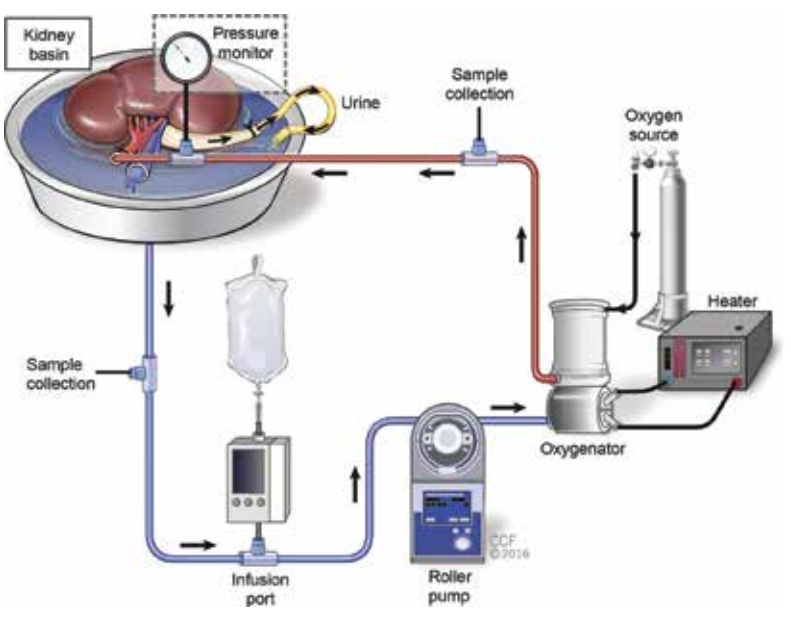

Illustration courtesy of Elsevier ScienceDirect

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Transplantation
Increasing Living Donation

By Kevin Fowler, Marian Charlton, and Mendy Reiner

Photo courtesy of Sharon Waggoner

Past *Kidney News* articles have addressed ways to increase the rate of kidney transplantation in the United States. One of these ways is to increase the rate of living donation. This article presents three viewpoints on the challenges to living donation and ways to meet these challenges. The authors include a patient advocate who received a transplanted kidney from a living donor (Kevin Fowler), a transplant coordinator (Marian Charlton), and the founder of a living donor support service (Mendy Reiner). The article is based on deliberations at a recent roundtable on increasing the rate of kidney transplantation.

Kevin's story

Fowler: In December 2000, I began to notice lower back pain. Initially, I attributed the pain to carrying large amounts of wood to our fireplace, but in the back of my mind, I knew the source of my pain could be something else. My deceased mother had polycystic kidney disease (PKD). I saw her suffer from constant back pain due to the enlarged size of her kidneys caused after PKD. Up until this time, I never had the courage to determine if I too had PKD. I was too scared after seeing how my mother suffered with both the disease and with her dialysis treatment.

Now I needed to determine if I too had PKD. I was 39 years old and had been married to my wife, Kathy, for 5 years. We had two children: Kelley, 3 years old, and Jack, 8 months old. Right after Christmas, I asked my primary care physician (PCP) to schedule an ultrasound test for January 2001. Once and for all, I would learn whether I had PKD.

On a bright, sunny January morning, our lives were changed forever. The ultrasound test revealed that my kidneys were consumed with PKD cysts, and my PCP informed me that I would be on dialysis or need to have a transplant within the next 3 to 5 years. When I shared the news with Kathy, we both broke down crying. As a family, we faced a very uncertain future.

My PCP offered to make a nephrology referral to a community-based nephrologist. At that time, I was working in the pharmaceutical industry as a District Manager in St. Louis and had developed a friendship with a gastroenterologist at Barnes–Jewish Hospital. I called my physician friend and explained my situation to him. He referred me to a Barnes–Jewish Hospital nephrologist.

I had my first appointment with the nephrologist on March 6, 2001, which was, coincidentally, my mother's birthday. Before the appointment, Kathy and I were very nervous. Frankly, I was convinced I would be facing the same fate as my mother.

What happened at that first appointment exceeded my wildest expectations. My doctor said it would be approximately 5 to 7 years before my kidneys failed. When my kidneys did fail, he recommended that I have a preemptive kidney transplant and avoid dialysis completely. He explained that a preemptive kidney transplant was the best treatment option for the following reasons:

1. By avoiding dialysis, I would be relatively healthy compared with dialysis patients who were waiting for transplants.
2. I would avoid development of antibodies that patients develop on dialysis. The antibodies make it more difficult for the body to accept a transplanted kidney.
3. Because I had several years before I needed a transplant, I had time to find a living donor before the need for dialysis.

When I left the doctor's appointment, I thought I had won the lottery. *You mean you don't have to be on dialysis first before you have a kidney transplant? Are you kidding me?* Now I was facing a future with a little more certainty. My kidneys were going to fail, but I did not have to go on dialysis. Although my fear remained, I knew what treatment option we would choose.

Unfortunately, my kidney function declined much faster than anticipated. In January 2004, my nephrologist notified us that I would need to be transplanted within the next 12 months and needed to find a donor. The problem was we had no idea how to find a donor. Until this time, I had not shared my medical condition with anyone other than my family and a handful of very close friends. Now my wife reminded me that I would have a difficult time finding a donor if I was unwilling to share my medical condition. She had a point.

Thanks to Kathy's leadership, we developed a communication strategy to find a living donor. Kathy wrote letters to many of our friends and family notifying them of my medical condition. I chose to call friends and coworkers to update them on my situation. I was motivated to relieve myself of this emotional burden I had kept secret for over 3 years. Although the intent of our commu-

nication was to alert our friends to my medical condition, it resulted in 14 people offering to be a living donor. Every time I think of their generosity of spirit, I am humbled.

What initially started out as a very scary and overwhelming situation became one of the most beautiful chapters in our life: August 5, 2017, will be the 13th anniversary of my kidney transplant.

What are some barriers to increasing living donation?

Charlton: Barriers to living donation for any one donor may be multifactorial: financial, psychosocial, medical, and/or cultural. For many patients, these barriers may seem insurmountable. However, living donor professionals can often provide insight and assist with solutions to overcome many of the perceived barriers.

Financial barriers

The medical evaluation, surgery, and hospital stay for the donor are covered by the recipient's insurance. However, donors may experience out of pocket expenses that create an obstacle to donation. Financial resources to assist with travel and lodging expenses are available through the National Living Donor Assistance Center (1) and the American Kidney Fund (2). These resources are limited, and therefore, donors and recipients must meet eligibility criteria through means testing. Expansion of the National Living Donor Assistance Center to include nondirected donors and to eliminate or broaden means testing for recipients would reduce financial burden by allowing more people to access these resources (3). At this time, there is no mechanism for most donors to receive reimbursement of lost wages. This alone may be the most significant obstacle to living donation. Recommendations from the 2014 Live Donor Consensus Conference suggest that financial neutrality for living donors must be achieved for the number of living donations in the United States to increase (4).

Psychosocial barriers

Psychosocial barriers may present in several different ways. Lack of support from immediate family; significant history of drug or alcohol abuse; and fear of pain, surgery, and the long-term unknown are but a few of the emotional barriers to living donation. Access to living donor professionals early in the process who provide education and recommendations may allow a potential donor to overcome these barriers and proceed with living donation.

Medical barriers

All living donors undergo a comprehensive medical evaluation to ensure they are both medically and psychosocially suitable to donate. The safety and well-being of the living donor are of primary importance, and living donor professionals are risk averse when providing final clearance to proceed with living donation. During the evaluation process, obstacles (i.e., high body mass index or a mildly elevated hemoglobin A1c) may surface, and with appropriate treatment and guidance, these may be resolvable and allow the donor to move forward. Education at a community level that dispels misconceptions regarding medical exclusion criteria for living donors may encourage donors to come forward who otherwise may not consider themselves acceptable candidates.

Cultural barriers

There are many barriers to organ donation among minorities. These include decreased awareness of transplantation, cultural mistrust of the medical community, financial concerns, and fear of the transplant operation (5). Culturally sensitive education on both national and community levels geared toward these barriers may ameliorate disparities and improve access to living donor transplantation (6). Community-based organizations can also play a part in providing education and support to potential donors. One of the main benefits of such organizations is their understanding of the unique barriers within their community.

What recommendations can you share to increase the likelihood of a living donor transplant?

Fowler: Here are some suggestions:

1. ***Early nephrology referral*** I referred myself to a nephrologist when I had stage 3 chronic kidney disease (CKD). This early referral allowed time to arrange a preemptive transplant.
2. ***Knowledge of kidney function*** Less than 10% of patients with stage 3 CKD are aware of their impaired kidney function. This means that 40% of patients initiate treatment in crisis mode and underscores the need for policies that reward early detection of CKD.
3. ***Dialysis versus transplantation*** I do not believe that patients are fully informed of their life expectancy when they initiate dialysis. This lack of transparency inhibits patients from seeking information on all available treatment options.
4. ***Medicare Part B ESRD benefit reform*** The original intent of the Medicare part B ESRD benefit was to ensure access to dialysis, which could then serve as a bridge to kidney transplantation. Because of unforeseen demographic changes and financial incentives for dialysis treatment, dialysis is no longer just a bridge to transplantation but a final destination. Reform should include rewards for risk-benefit conversations, shared decision-making, and placing the patient at the center of care.

How does one find a living donor?

Reiner: Early engagement in the quest for a donor is critical. It is important for a recipient's support team to come together and strategize about how best to communicate the need for a donated organ. Creating an advertisement explaining the need for a donor that can be sent out via an email chain and using social media to spread the message can be very effective tools in this campaign.

Fowler: I cannot overestimate the important role my wife Kathy had in finding my donor. Like many kidney disease patients, I was afraid of sharing my situation with others. She taught me to be open to others and accept the help and love they offered.

How can the transplant community increase living donation?

Reiner: Many people are not aware of what kidney donation entails. They do not realize this is something that ordinary people are doing. It is important to be knowledgeable about all of the steps in the process to answer any basic questions. Understanding the process helps potential donors be more comfortable in taking the next step: calling the transplant center.

Charlton: The key component in overcoming real and perceived barriers to living donation is early access to the evidence-based education of transplant professionals who can provide guidance, recommendations, and support to allow the potential donor to proceed.

Kevin Fowler is president of The Voice of the Patient. Marian Charlton, RN, is chief transplant coordinator at Weill Cornell Kidney and Pancreas, The New York–Presbyterian Hospital/Weill Cornell Medicine Center. Mendy Reiner is founder and chairman of Renewal in Brooklyn.

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Improved Transplant Outcomes for Children with FSGS

Children with focal segmental glomerulosclerosis (FSGS) who undergo kidney transplantation are at high risk of recurrent disease and allograft failure. A new study provides insights into long-term posttransplant survival for this group of patients.

The retrospective study in *American Journal of Kidney Diseases* included 12,303 pediatric patients receiving a first kidney transplant from 1990 through 2009, identified from the US Renal Data System database. In 11% of patients, FSGS was the primary cause of end stage renal disease. All-cause mortality and allograft loss were compared for patients with FSGS versus other causes.

All-cause mortality for children with FSGS improved significantly from the 1990s to the 2000s: from 12.24 to 6.72 deaths per 1000 patient-years, hazard ratio (HR) 0.55. These children also had a smaller but still significant reduction in allograft loss: 75.91 versus 89.05 events/1000 patient-years, HR 0.85.

With adjustment for baseline characteristics at transplantation, mortality was similar for children with and without FSGS. That was so despite higher rates of allograft loss for those with FSGS: HR 1.27 in the 1990s and 1.17 in the 2000s. But additional analysis of children transplanted in the 2000s, adjusted for allograft failure as a time-varying covariate, found lower mortality in the FSGS group: HR 0.70.

The results showed that survival improved for children and adolescents with FSGS undergoing kidney transplantation from the 1990s to the 2000s. In the more recent period studied, the 2000s, posttransplant survival for children with FSGS was similar to that for children without FSGS, and may be even better after adjustment for allograft failure.

"This suggested that allograft loss is a potential mediator of patient survival in FSGS, and that a focus on interventions to decrease allograft loss due to disease recurrence may improve patient survival," the investigators conclude.

Wang C-s et al. Mortality and allograft loss trends among US pediatric kidney transplant recipients with and without focal segmental glomerulosclerosis. *Am J Kidney Dis* 2017; doi: 10.1053/j.ajkd.2017.09.025

The Future of Kidney Transplantation

By Leif Oxburgh and Barry Smith

The facts are straightforward. A kidney transplant is the optimal therapy for renal replacement therapy in ESRD. It is optimal from the point of view of its ability to restore both the health and quality of life of the individual affected and its long-term cost-effectiveness. Dialysis, whether hemo- or peritoneal and whether in-center or at home, is life preserving and necessary, but in the final analysis, it cannot compete with transplantation.

Today, 104,706 people are on the waiting list for a kidney transplant. In 2016, only 19,061 kidney transplants were accomplished. Roughly one-third of these involved living organ donors, and two-third involved deceased donors. An eligible person waits a median of 3.6 years for a kidney transplant, with some waiting 8 years or more. Sadly, one-fifth of those on the waiting list die every year (13 die each day) or become too sick or frail to undergo the surgical transplant procedure. Clearly, this is not acceptable.

This article is part of a series arising from a roundtable recently held at The Rogosin Institute. Other articles have explored many of the issues related to increasing living and deceased organ donation and transplantation. Among the concerns addressed were how more kidneys can be made available for transplantation, the use of extended criteria donor kidneys, the incentives and disincentives transplant centers face in using not just the healthiest of kidneys with the best immunological matches, reduction of the kidney discard rate, and the optimization of the allocation system.

Here, we will look at not only additional ways to increase both living and deceased donation in the future but also, prospects for the repair and rebuilding of whole kidneys, such that the shortage of kidneys for transplantation can be eliminated. We can now envision the possibilities of using an individual's own stem cells to create a new immunologically matched replacement kidney or editing the genome of banked human stem cells to create a kidney that is a "perfect" immunological match with no requirement for immunosuppression.

Rebuilt or newly built kidneys are an exciting prospect for the treatment of ESRD. Research still has a way to go before such kidneys are available, but the progress is very encouraging. Knowing that, however, are there actions we can take in the meantime to increase the number of available organs to shorten the waiting list time and decrease the mortality and lost opportunities that characterize the situation today? The answer to this question is a definite "yes."

Previous articles in *Kidney News* have focused on a multitude of ideas to increase the rate of kidney transplantation (Table 1).

Discarding old assumptions about willingness to donate

An important point is that one potential solution does not fit every situation. For example, a northeastern urban African American community has not been known to have a high rate of living or deceased kidney donation. One might assume that the residents of that community would not be willing to donate. Yet, a community-implemented survey carried out by leaders and volunteers in the Central Brooklyn Health Movement in collaboration with The Rogosin Institute found that 62% of residents were willing to consider giving a kidney as a living donor and a somewhat smaller percentage (56%) were willing to consider giving a kidney as a deceased kidney donor. Although one must be very cautious in interpreting these data (e.g., many of those willing to be living kidney donors would not prove to be medically suitable or might ultimately decide not to follow through), it is also true, as some residents contacted in the survey stated, that they had never been asked the question. These findings indicate that we need to be very careful about the assumptions we make about the willingness to donate organs in any given community.

It is also important that people in the community who are trusted ask the questions about willingness in the "language" of the community. Put another way, different communities need to be asked in ways that are meaningful to them, and their concerns, cultural norms, and mores must be taken into account. In this way, more reliable information can be obtained, and more importantly, the donation of kidneys and other organs can be increased.

These observations lead to other questions about how to best increase organ donation in a given community in a fashion that is sustainable over the long term. The desired changes will not happen all at once. Education about both living and deceased organ donation needs to begin in schools (middle and high schools), and it needs to be carried out where people live, work, play, and worship. The information needs to be provided repeatedly and pervasively in the community, such that it becomes a part of the fabric of the community. The desired message is, "We are a community whose residents care for each other."

Much of this message can and should be conveyed by community leaders and residents themselves because theirs is the voice that will be listened to in the community. The creation of a culture of organ donation must arise within and be fostered by the community itself. Health professionals have an important role to play in all of this, but it is most often a supportive and reinforcing one that ensures the supply of correct information. The Central Brooklyn Health Movement, mentioned above in relation to the kidney transplantation survey, is a movement of just this sort—a movement for better health of, by, and for the people of eastern New York and Brownsville, Brooklyn, NY—places where the health indices for hypertension, diabetes, and kidney disease, for example, are far higher than they should be and the need for kidneys for transplantation is great.

Advances in newly built kidneys

Even with all these efforts, it is unlikely there will ever be enough living and deceased donor kidneys to meet the need. So how can we address that need? This requires that we consider the prospects for "newly built" kidneys. What are the prospects?

Recent years have seen an explosion of activity in the development of stem cell–based strategies to build new

Table 1. Ideas for increasing the rate of kidney transplantation

1. Increased communication and publicity designed to draw the public's attention to the great gift that one human being can give to another in the form of a needed kidney.
2. Public education about the ease and safety of both living and deceased organ donation and education regarding the value of preemptive kidney transplantation (i.e., done before dialysis must be initiated).
3. Adoption of important programs, such as those involving drivers' licenses, with designation of a presumed willingness to donate an organ after death approaches but with an opt-out provision.
4. Legislative approaches to encouraging living donation, making it both economically and emotionally easier for individuals to donate a living kidney, i.e., the current Federal Living Donor Protection Act [H.R.1270] sponsored by Rep. Jerrold Nadler (D-NY) and three recent New York State Assembly bills providing reimbursement for donor expenses, insurance protection, and paid leave.
5. The nationwide computer-based best matching of donors and recipients through the National Kidney Registry, creating chains of donors and recipients.
6. Encouragement of altruistic kidney donation.
7. The use of social media to connect those in need of a kidney with potential donors.

tissues. Because of its structural complexity, the kidney is a relative latecomer to this aspect of regenerative medicine. However, work in the past 5 years has highlighted the feasibility of this approach as a potential long-term solution to the organ shortage crisis, resulting in a surge of research activity.

Before going into more detail regarding research strategies being pursued to generate new tissue, the tenacious work over the past decades on xenografting should be discussed. Although many obstacles have been encountered along the road to developing the pig xenografting strategy, such as the discovery of unforeseen layers of immune protection against cross-species engraftment and the identification of porcine endogenous retroviruses as a significant risk to human recipients, this field has undergone a revitalization with the discovery of new tools for genome modification. Outcomes of grafting tissues from new generations of multigene knockout pigs into primates show increasing tolerability, and there is good reason to be optimistic about this approach.

The possibility to generate entirely new and patient-specific kidney tissue gained traction when it was shown that pluripotent stem cells derived from adult humans could be directed to form the major cell types required for a fetal kidney: nephron progenitors; collecting duct progenitors; interstitial, mesangial, and pericyte progenitors; and endothelial progenitors. This mix of fetal progenitor cells can be induced to differentiate in vitro, and through their intrinsic self-organizing properties, they form small aggregates of tissue containing rudimentary patterned nephrons, collecting ducts, and structures resembling glomeruli. Although these remarkable in vitro-generated organoids display characteristics of fetal rather than adult tissue, the potential of this approach is clear, and many research groups are pursuing key aspects of its development. Ongoing research is addressing issues such as the maturity of this synthetic tissue, its ability to be vascularized by a host into which it is engrafted, and how it may be assembled on a biological scaffold that would encourage its integration into a recipient. Although many difficult hurdles remain, the potential of this approach to generate patient-specific tissue, minimizing or perhaps eliminating the need for immunosuppression, is very exciting.

Simultaneous pursuit of distinct strategies such as xenografting and the generation of laboratory-grown tissue ensures vigorous and dynamic activity in the area of alternative sources of tissue for renal replacement. With the recent injection of optimism into this research field, we are seeing an increase in resources, for example, the (Re)Building a Kidney Consortium established by the National Institute of Diabetes and Digestive and Kidney Diseases. With resources come new investigators with fresh ideas, and, if the current momentum is maintained, it is realistic to predict both an acceleration of ongoing work and the development of brand new approaches that may complement or supersede current strategies. Now that we can clearly see a way forward for kidney regenerative medicine, it is essential to designate resources for the long term. Strategic thinking and realistic expectations of progress are essential to avoiding the hype and boom/bust economies that have been obstacles to progress in so many fields of biomedicine. Perhaps by being a relative latecomer to this field, kidney regenerative medicine can learn from past mistakes and avoid these traps (1–4). ■

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Kidneys from Very Old Donors Benefit Very Old Recipients

By Bridget M. Kuehn

Older kidney recipients can benefit from organs from older donors. But previous cerebrovascular disease may reduce the survival benefits of these kidney transplants, according to a recent study.

Kidney transplants offer many advantages over dialysis for people with end stage renal disease (ESRD). But a shortage of donors can make it particularly difficult for older patients to secure a donor organ, said Amado Andrés, MD, transplant coordinator at the Hospital Universitario 12 de Octobre in Madrid, Spain. Kidneys from older donors, which may have reduced function owing to age-related conditions, are a poor bet for younger patients. But in older patients with shorter life expectancies these organs may be sufficient.

"The ideal match for renal transplantation in old and very old recipients are old or very old kidney donors," Andrés said.

However, the practice is not very common in Spain or other countries because ESRD patients age 70 and up often have serious cardiovascular comorbidities, said Andrés. The Eurotransplant organization has an "old for old" kidney transplant program (Schlieper G, et al. *Clin Transplant* 2001; 15:100–105). But although the program often uses organs from donors older than 70, it typically transplants them in patients younger than 70, Andres said. And many countries do not have many older organ donors. Spain, with its very successful deceased donor program, however, has a good supply of older organs, he said.

"In other countries, access to transplantation of recipients older than 70 years is more limited because

they require [recipients] to be absent of cardiovascular comorbidity," he said.

Andrés and his colleagues have begun to extend kidney transplant eligibility to older patients with some cardiovascular morbidity using kidneys from older deceased donors. In their retrospective analysis of 155 kidney transplant recipients age 70 and older, the median donor age was 77 and the median recipient was 75. The 3-year survival rate for recipients was 73.1% and the 5-year survival rate was 67.1%. About 16% of patients died in the first year after transplant. Graft survival, censored for death, was 83.4% at 3 years posttransplant and 80.8% 5 years posttransplant.

The only factor associated with worse survival was a history of cerebrovascular disease (HR 5.12, p=0.27). A history of diabetes was the only factor associated with graft loss (HR 4.40, p=0.0001).

"Our experience opens the door for the administrations of Western countries to promote organ donation in the elderly [as Spain does], "Andrés said. "[It] also demonstrates that patients of very advanced age can receive kidney transplant, improving survival and quality of life, without competing with the youngest patients on the waiting list."

Jon Kobashigawa, MD, director of the Heart Transplant Program at Cedars-Sinai Medical Center in Los Angeles, noted that currently many older organs are not being used in the United States. His program does use older organs for older donors.

"It's a precious resource that could be used for a good cause and the benefits greatly outweigh the risks," he said.

He acknowledged that outcomes may not be as good for older transplant patients as for younger ones, but the improvement in quality of life for older recipients is still substantial. One factor that might hold some US programs back from participating in older donor/older recipient transplants is the way the programs are regulated. All US organ transplant programs are overseen by the United Network for Organ Sharing (UNOS) and must meet certain thresholds for recipient and organ survival. Because older organs and older donors may not survive as long it could cause some programs, particular smaller ones, to be flagged by UNOS.

"Regulatory issues do make programs hesitant to take on older donors," he said.

He said it is not surprising that prior cerebrovascular problems or diabetes were associated with worse outcomes in the study. He noted his program typically reserves the limited organs available for those patients with the fewest risk factors.

"We are taking pains to achieve best outcomes," he said.

Andres presented results from his study at Kidney Week 2017. ■

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