ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

KidneyNews

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Donor-Recipient Weight and Sex Mismatch May Contribute to Kidney Transplant Failure

By Tracy Hampton

New research indicates that the success of a kidney transplant may rely in part on how the recipient and donor compare in terms of weight and sex. The findings, which are published in the *Clinical Journal of the American Society of Nephrology*, suggest that changes may be needed to current immunology-based protocols that match donors and recipients.

Several kidney transplantation studies have demonstrated that a smaller donor size relative to recipient is associated with a higher risk of graft loss, perhaps due to increased strain on the relatively smaller transplanted kidney. Very few studies have investigated the outcomes associated with donor-recipient weight mismatching as determined by body mass in isolation, however.

Research has also shown that male recipients of female kidneys are at increased risk of graft loss, presumably due to size mismatch and nephron number. (Studies indicate that female kidneys have an average of 12% to 17% fewer total nephrons than male kidneys.) Female recipients of male kidneys also experience reduced graft survival, but to a lesser extent. The mechanisms involved are likely immunologic in nature, owing to mismatch between H-Y minor histocompatibility antigens (on the Y chromosome in male donors).

To explore the potentially additive effect of size mismatch and sex mismatch, a team led by Amanda Miller, MD, and Karthik Tennankore, MD, of Dalhousie University and the Nova Scotia Health Authority, in Canada, examined whether receiving a kidney transplant from a smaller donor of the opposite sex would impact a recipient's transplant outcomes.

The researchers analyzed information on a cohort of US deceased donor transplant recipients between 2000 and 2014 who were listed in the Scientific Registry

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Variability in Parathyroid Hormone Assays: Better Standardization on the Way?

By Eric Seaborg

Clinicians worried about bone disease developing in patients with chronic kidney disease (CKD) lean on parathyroid hormone (PTH) measurements as a marker for skeletal and mineral disorders. But the utility of PTH assays is controversial—mainly because the variability among analytical techniques makes the interpretation of results difficult.

A working group from the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) is working to standardize the assays and establish protocols for issues such as preanalytical variables. The group has the support of many stakeholders, including testing manufacturers, and expects to show progress within the next couple of years. In the meantime, nephrologists can consult the literature to aid in the interpretation of the assays used by their laboratories.

"There can be differences up to fourfold in the results reported with different methods from the same samples," said the chair of the IFCC group, Catherine M. Sturgeon, PhD, who is consultant clinical scientist at the Royal Infirmary of Edinburgh and director of one of the

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Inside

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  - Have not received prior systemic therapy for advanced disease

427 Keynote 427:
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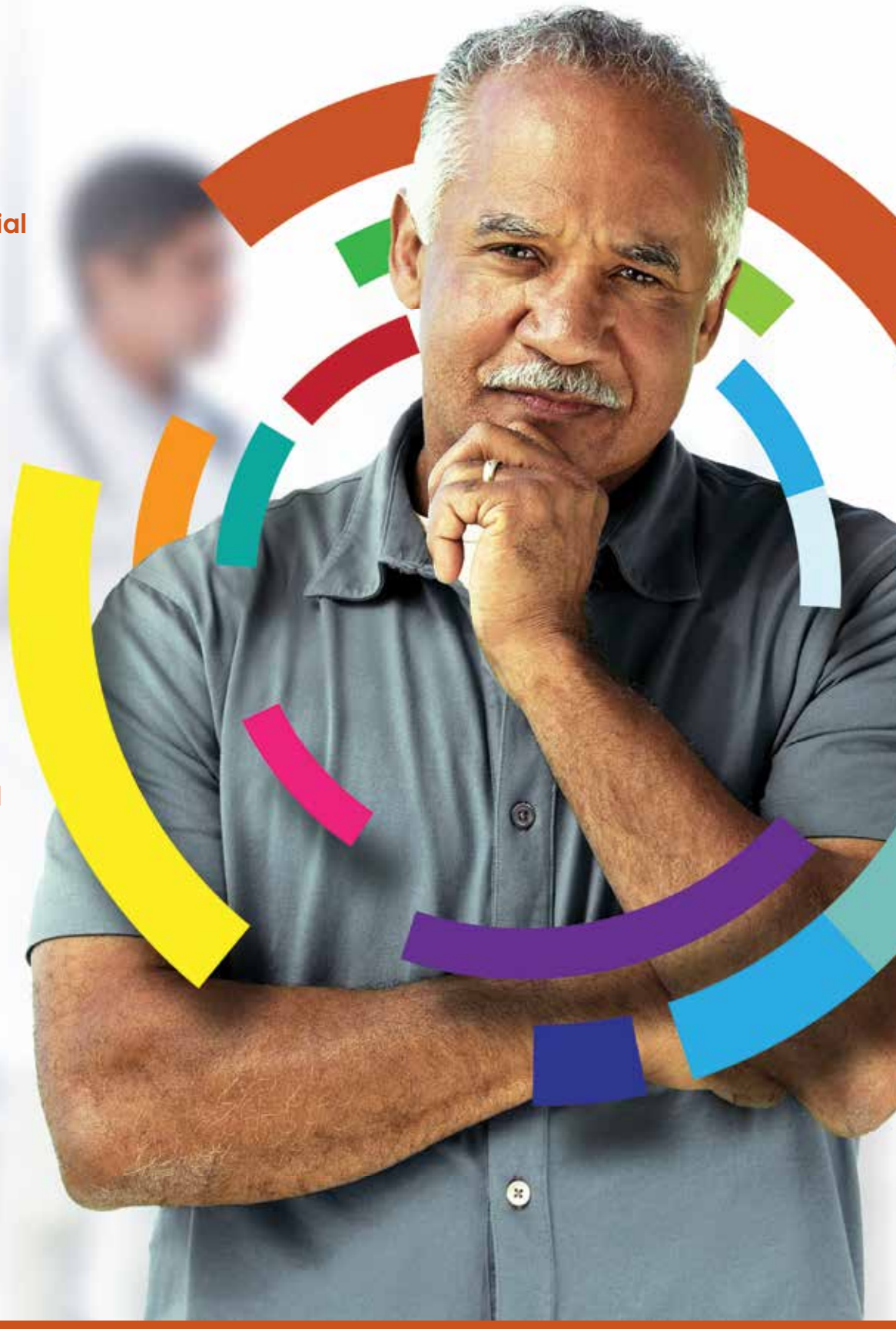
- Patients must*:
  - Have histologically confirmed diagnosis of RCC (clear cell or non-clear cell)
  - Have not received prior systemic therapy for advanced disease



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Kidney Transplant Failure

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of Transplants Recipients. The team excluded living donors, patients <18 years of age, those receiving multiple organs, en bloc or sequential transplants, and patients without a documented donor or recipient weight.

The analysis included 115,124 kidney transplant recipients, and 59.4% and 61.6% of donors and recipients were male, respectively. Over a median follow-up of 3.8 years, 21,261 of the recipients (18.5%) developed transplant failure.

After accounting for other transplant variables, the investigators found that if a kidney transplant recipient was >30 kg (66 pounds) heavier than the donor, there was a 28% higher risk of transplant failure compared with equally weighted donors and recipients. If the kidney was from a smaller donor of the opposite sex, the relative risk of transplant failure was further elevated to 35% for a male receiving a kidney from a female donor and 50% for a female receiving a kidney from a male donor. This risk is similar to that observed when a recipient receives a kidney transplant from a donor who has diabetes, a known risk factor for kidney failure. It is also comparable to other risk factors for graft loss that historically influence organ allocation, including dialysis vintage >4 years and expanded vs. standard criteria donors.

The study is the first large scale analysis to demonstrate that worse kidney transplant outcomes associated with donor and recipient weight mismatch—as determined by absolute differences in body weight, and donor and recipient sex mismatch—are additive.

"This study is extremely important because we have shown that when all else is considered, something as simple as the combination of a kidney donor's weight and sex is associated with a marked increase in kidney transplant failure," Miller said. "While more research is required before including these variables in a recipient matching strategy, this study highlights the importance of donor and recipient matching above and beyond current immunology-based protocols." It will be important to determine the extent to which any benefit derived from weight and sex matching would offset the potential risk of longer times on the transplant wait list for individual candidates.

Jane Tan, MD, PhD, a transplant nephrologist at Stanford University Medical Center who was not involved with the study, noted that the results lend support to previous research as well as provide insights that will be useful when looking toward the future.

"These findings build upon prior studies that demonstrate the long-term risks of low nephron dose for metabolic demand in kidney transplantation, as well as the potential impact of non–human leukocyte antigen immune responses to allograft survival," she said. "With a continued increase in obesity among kidney transplant candidates, donor-recipient weight mismatch may factor into clinical decision-making, especially among recipients with increased metabolic demand."

In an accompanying editorial, Bethany Foster, MD, MSCE. and Indra Gupta, MD, of McGill University, stressed that while matching for sex and body size in organ allocation algorithms deserves consideration, this idea must be approached with a great deal of caution. It would require complex matching, and special care would have to be taken to avoid disadvantaging larger recipients. "Restricting transplant options by prioritizing sex matching may also lead to longer waiting times," they wrote. "Females with a large body size would be particularly disadvantaged by an approach that favoured allocation of sex- and body-size matched kidneys."

Article: "Donor-Recipient Absolute Weight and Sex Mismatch and the Risk of Graft Loss in Renal Transplantation."

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Kidney News

EDITORIAL STAFF

Editor-in-Chief: Richard Lafayette, MD
Executive Editor: Dawn McCoy
Design: Lisa Cain Design
Communications Assistant: Sara Leeds

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

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Parathyroid Hormone Assays

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National External Quality Assessment Service proficiency testing centers in the U.K. "The bigger and more complicated a molecule is, the more difficult it can be to measure consistently."

PTH is one of those complicated molecules. It is an 84-amino-acid peptide protein that breaks down in the body into a large variety of peptide fragments. The fragments are generally considered not biologically active, although there is some controversy about how active some might be.

"Intact" PTH and molecular fragments

Most laboratories use what are called second-generation immunoassays that were originally billed as detecting "intact" PTH, but that in fact detect and include in their quantitation fragments as well. For most patients, the fragments are not an issue because a normally functioning kidney clears them. However, the fragments may accumulate in patients with impaired kidney function and especially in those on dialysis.

The assays measure the fragments to varying degrees, which makes them problematic for monitoring patients with chronic kidney disease–mineral bone disorder (CKD–MBD) and difficult to standardize. Although the assay may have originated more as a tool for the diagnosis of patients with primary hyperparathyroidism or hypoparathyroidism, "in many laboratories the majority of PTH measurements are now performed in patients with CKD," according to an article e-published by the IFCC working group in *Clinica Chimica Acta* in October 2016 (Sturgeon CM, Sprague S, Almond A, et al. Perspective and priorities for improvement of parathyroid hormone (PTH) measurement–a view from the IFCC Working Group for PTH. *Clin Chim Acta* 2016 doi: 10.1016/j.cca.2016.10.016. [Epub ahead of print])

"The average clinician takes the results as gospel. They don't understand the nuances behind the tests," said Stuart M. Sprague, DO, clinical professor of medicine at the University of Chicago Pritzker School of Medicine and chair of the division of nephrology and hypertension at NorthShore University HealthSystem in Evanston, IL.

Assay calibration

A major effort of the IFCC working group is to overcome the variability among test platforms through assay calibration. The World Health Organization has established an international standard of recombinant PTH, but none of the commercially available assays is calibrated to it, Sturgeon said. The IFCC group is working to get the assay manufacturers to recalibrate their tests using this standard.

"Manufacturers are absolutely critical, so we are very lucky that they are very enthusiastic and supportive of this effort," Sturgeon said. "For the manufacturers, it is quite a lot of trouble and expense to change the calibration of an assay. For one thing, they have to change all their documentation." It will take at least two years for manufacturers to standardize their methods and change their kit inserts. Sturgeon said that a standard introduced for prostate specific antigen tests cut those tests' variation in half.

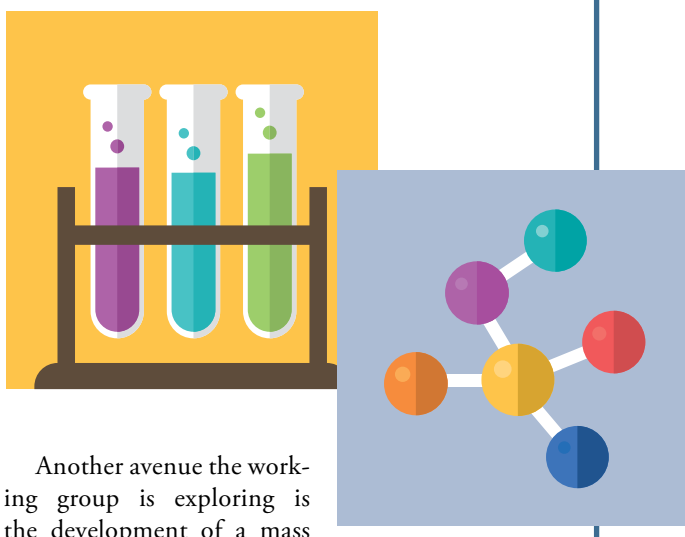
While they wait for that to happen, nephrologists can improve their test interpretation by finding out which manufacturer's assay their laboratory is using, according to Kevin J. Martin, MD, director of the division of nephrology at Saint Louis University in Missouri.

Particular assays are consistent in their results, so by knowing which assay a laboratory is using, a clinician can get a better idea of the meaning of the results. Information on the performance of specific assays can be found in the literature, including the IFCC working group's *Clinica Chimica Acta* article and in a National Kidney Foundation publication that can be found online (https://www.kidney.org/sites/default/files/12-10-0202_LBA_PTH_CKD-MBD_Tool_feb4.pdf).

But clinicians need to stay aware because laboratories can change suppliers without telling physicians. Martin said: "You might notice that follow-up PTH measurements appear higher than prior values and upon checking with the lab learn that they have changed the supplier of the PTH assay reagents. This has happened in our own hospital."

Handling of samples

The working group is also developing evidence-based recommendations for the handling of PTH samples prior to analysis. For example, for blood samples taken in tubes containing EDTA, the group recommends the plasma be separated within 24 hours, the samples should be stored at 4 °C, and the samples should be analyzed within 72 hours. For samples taken in dry tubes, the serum must be separated as soon as possible and analyzed within 4 hours or stored at -20 °C for later analysis. For consistency within and between individuals, samples should be collected from the same sample site—central or peripheral—and clinical guidelines should state whether targets refer to peripheral or central venous concentrations.



Particular assays are consistent in their results, so by knowing which assay a laboratory is using, a clinician can get a better idea of the meaning of the results.

The experts who write clinical treatment guidelines for CKD are aware of the lack of standardization and variation in assays and have tried to take them into account.

"KDIGO [Kidney Disease: Improving Global Outcomes] guidelines have widened the limits for the target levels for renal patients with advanced disease, because they were aware the assays couldn't cope with the tighter limits," Sturgeon said.

The KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease suggests that for patients with CKD stage 5D, PTH levels should be maintained "in the range of approximately two to nine times the upper normal limit for the assay. We suggest that marked changes in PTH levels in either direction within this range prompt an initiation or change in therapy to avoid progression to levels outside of this range."

Because of the lack of faith in a single test or number, the guidelines also recommend that in patients with CKD stages 3–5D, therapeutic decisions should "be based on trends rather than on a single laboratory value, taking into account all available CKD–MBD assessments."

Another avenue the working group is exploring is the development of a mass spectrometry-based reference method. Several mass spectrometry methods have been published that can provide accurate PTH measurements as well as identify and quantify PTH fragments—which could increase the understanding of the clinical relevance of these fragments. But these methods can involve difficult sample preparation steps and are much less sensitive—by a factor of 10—than the immunoassays.

Optimal PTH values for patients on dialysis less certain

Even the overall usefulness of PTH measurements is somewhat controversial and unclear.

"There is considerable uncertainty as to what range of PTH values would be desirable for patients on dialysis," Martin said. "PTH is one marker of bone turnover and bone metabolism, but it is not the only one. And the correlation between these various PTH values and what's happening in the bone is rather weak."

The KDIGO guidelines note the lack of solid research in the area of CKD and bone metabolism: "The evidence on which existing recommended guideline treatment targets for serum concentrations of calcium, phosphate, and parathyroid hormone, and the strategies to achieve those targets, is exclusively observational and thus problematic for that reason."

Just the same, the IFCC working group notes: "Most nephrologists consider there is already sufficient evidence linking high or very low PTH levels with adverse outcomes in patients with CKD–MBD. However, better understanding of the complex disease processes and biological interactions involved would be expected to help improve clinical outcomes for CKD–MBD patients and further research is highly desirable."

But some things are known. "Hyperparathyroidism is common in CKD and results in significant morbidity and mortality if left untreated," Sprague said. Better assays for detecting it would be a big step forward in both research and treatment, and the IFCC group posits that its goal of "improving the standardization of PTH methods is clearly feasible."

Summit Brings Together Experts to Discuss Innovations in Kidney Care

The Department of Veterans Affairs (VA) and ASN co-sponsored the Kidney Innovation Summit on February 9–10, 2017, to advance innovation in kidney disease care through intense knowledge sharing, discussion, and networking. ASN Policy and Communications Specialist David White caught up with ASN President Eleanor D. Lederer, MD, FASN, and Crystal Gadegbeku, MD, Chair of the Policy and Advocacy Committee of ASN, to discuss their thoughts on advancing innovation in kidney disease care.

Eleanor D. Lederer, MD, FASN

Crystal Gadegbeku, MD

DAVID WHITE

What can you tell us about the summit?

DR. GADEGBEKU

The summit provided a sort of meeting of lots of minds about innovating at the various stages of kidney health and disease. What I really enjoyed about the meeting was the diversity of thought, as participants came from many different perspectives—from clinicians and those taking care of patients to those interested in biotechnologies and the science end of things, as well as those involved in research.

DAVID WHITE

I think everyone knows that there is a large connection between ASN and the VA, and particularly a large number of VA patients who suffer with kidney diseases. What do you see regarding the partnership between the VA and ASN?

DR. LEDERER

The VA and ASN are natural partners. Seventy percent of trainees come through the VA as part of their training, and a large number of practicing nephrologists have had some contact with the VA at one time or another. Many of us, such as myself, continue to work at the VA full time or part time.

We can see the toll taken by kidney diseases in our veteran population, and we're trying to grapple with the realities of the increasing number of individuals who have kidney diseases. This is emblematic of what is happening all over the country. We're seeing costs rise, we're looking for ways to prevent kidney diseases, to cure kidney diseases, and to make life better for those who have kidney diseases right now. This type of partnership between the VA and ASN is only natural.

DAVID WHITE

The summit showed just how significant the burden of kidney diseases is within the veteran population. About $18 billion a year is spent on kidney care just for veterans, and this figure does not even include those on dialysis.

Dr. Gadegbeku, you chair the ASN Policy and Advocacy Committee, which recently released a report from the Government Accountability Office (GAO) about the overall cost of kidney diseases and research spent on kidney diseases. What did the report find?

DR. GADEGBEKU

You are correct that this cost figure does not include the many patients who are suffering with earlier stages of kidney diseases. We know that there is a lot of morbidity among this population, so costs for treating these patients are quite high as well. The GAO report confirmed and reaffirmed for us that we need to put more effort and resources into research to prevent the suffering of patients and to stem the rising cost of kidney diseases.

DAVID WHITE

Is it correct that basically for the amount of investment the government puts into the Medicare ESRD treatment program for people on dialysis, that less than 1% of that entire amount is invested in research?

DR. GADEGBEKU

That is correct, and it reinforces that much more investment needs to be put into the research end, so that we can save costs on the other side.

DAVID WHITE

What is the role of the nephrologist in this dynamic of rising disease rates, costs, and the general burden on patients?

DR. LEDERER

I think nephrologists, to some extent, have taken a back seat in trying to address the actual rising costs. We all know that there are treatable risk factors, and we have certainly been proponents of actively addressing those risk factors both for the development and the progression of kidney diseases going on to ESRD. However, there's no question that nephrologists have been generally brought into the picture—for the most part—near the end of the kidney disease process. That is to say, most of us are not brought in at the early stages of kidney diseases at a point where we might be able to intervene to prevent the development of ESRD. Most of us are brought in at the later stages and are preparing people for ESRD and taking care of people who are on dialysis and who have kidney transplants. In that regard, it's actually pretty hard to effect any substantial changes in costs because the damage is done. These people already have a severe disease that is very costly.

DAVID WHITE

Are you saying that to really make a difference in the dynamic that is challenging so many healthcare systems, nephrologists are going to have to be brought in earlier and perhaps maybe even have a larger role?

DR. LEDERER

I would say absolutely, and whether that role ends up being fulfilled by nephrologists per se, or by other non-nephrology providers who are members of the healthcare team, such as dieticians, social workers, or community workers, all of these individuals can play an important role in getting to patients early, helping people to understand what their risks are, and what they can do to either prevent the development or progression of kidney diseases.

DAVID WHITE

In your years of practice at the VA, what would you classify as one of the biggest challenges of dealing with kidney diseases? What do you think are the biggest opportunities as well?

DR. LEDERER

Probably the biggest challenge of dealing with kidney diseases in the VA system is that there are so many individuals who have so many risk factors for its development. The prevalence of hypertension, diabetes, hepatitis C, HIV, family history, smoking … these are all very prevalent risk factors. Just trying to get your arms around the huge number of people who all have multiple risk factors is very challenging and difficult. How do you choose where to start? The individuals who get referred to my clinic are those whose creatinine has already gone up. I want to get them to the clinic before they reach a stage where it's difficult for me to do anything for them.

In terms of opportunities, the VA has excellent electronic medical records creating mechanisms to identify people at risk and then reach out to primary care providers to let them know. Several different projects have been piloted and are in use in some VA systems to help identify individuals with chronic kidney disease and to help manage their disease. The ability of the VA to develop such an integrated healthcare system and to have available its massive amount of patient information in electronic medical records represents a tremendous opportunity to help veterans who have kidney diseases or who are at risk for kidney diseases.

DAVID WHITE

There was some lively conversation at the summit about whether or not some of the ways we measure and treat kidney diseases have advanced in the past few decades. Would you care to weigh in on that?

DR. GADEGBEKU

Even as a researcher, I would say that we have not seen the advances in the last couple of decades that other fields have seen. Part of the reason is that we need

more investment in research—we need to have researchers able to do the experiments and testing they need to make the next developments happen.

DAVID WHITE

What do you want readers to take away from this conversation?

DR. LEDERER

From a patient standpoint, society needs to decide that there must be a bigger push to lead people toward healthier lifestyles. I think that the challenge comes in educating people that eating unhealthy foods all the time is detrimental. To never exercise more than your thumbs on a videogame is detrimental to your health in general, and the consequences can be dire and life-changing.

From my standpoint as a physician, I need people to help me in this educational process. I can sit down with a patient in my "20-minute allocation" for that clinic visit, but that's not time enough to really educate people on what they need to do.

DAVID WHITE

The future. Do you think it's on the move?

DR. GADEGBEKU

I think it is. There is a lot of ripe research right now, and our technological advances are basically in key with what we want to do, such as informatics and science translational research. We have a lot of tools now, and if we are able to get the investment that we need, it's all about putting them together in a way that we can develop into new norms, new science, that will lead to better care.

ASN News

PhD Summit Sets Aims, Recommendations

In September of 2016, ASN hosted its Second PhD Summit in Washington, DC, to discuss how the society can better serve PhD members. Participants outlined seven recommendations for the ASN Council to consider to achieve that goal. This February, ASN Council approved a plan to implement the Summit's recommendations. Table 1 shows the final recommendations and the relevant ASN committee assigned to implement them.

Over the next year, look for updates on these items in the Basic Science Research community in ASN Communities and in communications from the Committees.

These are exciting first steps to make ASN a more welcoming and enticing society for PhDs working in the kidney space. Following through on these goals is critical to expose young researchers to the field, offer exceptional content at our scientific meetings, and provide meaningful leadership roles for PhD members. If you have any questions about the implementation process, please contact ASN Communities Associate Zach Cahill at zcahill@asn-online.org or 202-640-4674.

Table 1.

	COUNCIL RECOMMENDATION	COMMITTEE
1.	Consider offering five to ten partial stipends of $10,000 to $20,000 each to PhD students on a competitive basis.	Career Advancement Committee
2.	Provide information about career paths for various PhD tracks.	Workforce and Training Committee
3.	Raise awareness of kidney diseases in schools or departments of public health to increase interest among students who are typically aware of other diseases (such as cardiovascular disease, cancer, and diabetes).	Workforce and Training Committee
4.	Address the "perception" issue that basic science is underrepresented or diluted at ASN Kidney Week during the annual meeting.	Continuous Professional Development
5.	Conduct a market analysis to determine the possibility of expanding the "Scientific Exposition" at ASN Kidney Week by soliciting exhibitors, vendors, and other entities that appeal to basic scientists; consider creating a Basic Science Marketplace within the exhibit floor.	Meetings Team
6.	Explore the possibility of partnering to support a spring scientific meeting focused on a rotating topic of interest to segments of the membership.	Continuous Professional Development
7.	Disseminate the recommendations of the Second PhD Summit to increase awareness of its accomplishments.	Media and Communications Committee

Have a tip or idea you'd like to share with your fellow peers and the broader kidney community?

Send your idea to the *Kidney News* Fellows Corner column at kidneynews@asn-online.org

Findings

Are Anticoagulants Useful for CKD Patients with Atrial Fibrillation?

Anticoagulants don't reduce the risk of stroke in older adults with atrial fibrillation and chronic kidney disease, suggests a study in *Kidney International*.

The researchers analyzed data on 6544 Ontario residents aged 66 years or older with advanced CKD—estimated glomerular filtration rate less than 45 mL/min/1.73 m^2—and atrial fibrillation. Of these, 1475 filled an anticoagulant prescription, mainly for vitamin K antagonists. Propensity matching was used to identify 1417 matched pairs with or without anticoagulation; median follow-up was 269 and 254 days, respectively. Risks of ischemic stroke, hemorrhagic events, or death were compared between groups.

The rate of ischemic stroke was not significantly different for patients with and without an anticoagulant prescription: 41.3 and 34.4 per 1000 person-years, respectively. But hemorrhagic events were significantly more frequent in the anticoagulation group: 61.3 versus 34.3 per 1000 person-years, hazard ratio (HR) 1.42. In contrast, all-cause mortality was significantly lower in patients receiving anticoagulants: 122.6 versus 136.3 per 1000 person-years, HR 0.74.

In competing risk models, there was still no significant difference in ischemic stroke risk. For hemorrhagic events, the HR increased to 1.60 in the anticoagulation group. Sensitivity analysis accounting for variations in time of anticoagulant exposure yielded similar patterns.

It has been unclear whether anticoagulant therapy reduces the risk of stroke related to atrial fibrillation in patients with CKD. No studies have addressed this issue specifically in elderly CKD patients, who have a high incidence of atrial fibrillation.

This matched case-control study finds no reduction in ischemic stroke risk with anticoagulants among patients with atrial fibrillation and advanced CKD. Anticoagulation is also associated with increased bleeding risk, but lower all-cause mortality. Decisions about anticoagulation in elderly patients with atrial fibrillation and stage 3b to 5 CKD should be based on individual assessment of risks and benefits [Keskar V, et al. The association of anticoagulation, ischemic stroke, and hemorrhage in elderly adults with chronic kidney disease and atrial fibrillation. *Kidney Int* 2017; 91:928–936].

What's Behind the Jump in Kidney Discard Rate?

A broadening donor pool, increased risk aversion, and inefficient organ allocation may all contribute to the long-term increase in the percentage of deceased donor kidneys discarded, concludes a study in *Transplantation*.

The researchers analyzed Organ Procurement and Transplantation Network data to explore possible reasons for the well-documented, two-decade-long increase in the US deceased donor kidney discard rate (DKR). Beginning at 5.1% in 1988, the KDR rose more or less steadily to a high of 19.1% in 2009. This trend occurred at a time when the number of kidneys nearly doubled, from 7705 to 14,394. The KDR subsequently stabilized at 18% to 19% between 2010 and 2015. Multivariable regression and propensity analysis were performed to evaluate changes in donor characteristics and other potential explanatory factors.

The findings suggested that at least 80% of the increase in KDR was related to changes in the donor pool and in biopsy and pumping practices. Median donor age increased from 26 years in 1987 to 43 years in 2009, while the median Kidney Donor Risk Index increased from 1.1 in 1994 to 1.3 in 2009. There were also significant increases in black and Hispanic donors, diabetic donors, and donation after circulatory death.

Increased biopsy rates also contributed to the increase in KDR, as did an increase in kidneys pumped. During the 2000s, the percentage of kidneys placed on a pulsatile perfusion pump increased from 10% to 30%. Without this change in pumping practice, the increase in KDR would have been even greater.

The results suggest that the increase in deceased donor KDR from the late 1980s to the late 2000s largely reflected increased age and other changes related to the broadening of the donor pool. The unexplained residual increase may be partly related to behavioral factors including increased risk aversion, with transplant programs lowering their acceptance rates for less-than-ideal kidneys.

Inefficiencies in the organ allocation system may also be a contributing factor. In light of this and previous findings, the researchers conclude that "routine pumping . . . may be a potent and cost-effective way to increase the organ supply by reducing discards" [Stewart DE, et al. Diagnosing the decades-long rise in the deceased donor kidney discard rate in the United States. *Transplantation* 2017; 101:575–587].

Urine Potassium Linked to Mortality, but Not Kidney Failure Risk

In patients with chronic kidney disease (CKD), higher urine potassium excretion—as a surrogate for dietary potassium intake—is associated with a lower risk of death but no difference in the risk of kidney failure, reports a study in *American Journal of Kidney Diseases*.

The study was a post hoc analysis of 812 participants from the Modification of Diet in Renal Disease study. That trial, performed between 1989 and 1993, analyzed the effects of blood pressure control and dietary protein restriction on progression of stage 2 to 4 CKD. The current study analyzed the association of 24-hour urine potassium excretion, measured at baseline and at various times during the study, with the occurrence of kidney failure, defined as dialysis initiation or transplantation. All-cause mortality was also assessed.

At a median follow-up of 6.1 years, kidney failure occurred at a rate of 9 events per 100 patient-years. At a median of 19.2 years, all-cause mortality was 3 deaths per 100 patient-years. The patients' baseline mean 24-hour urinary potassium excretion was 2.39 g/d.

Urine potassium excretion was unrelated to the risk of kidney failure, but was associated with mortality. For each one-standard deviation increase in baseline urine potassium excretion, there was a 17% decrease in all-cause mortality (hazard ratio 0.83).

In the general population, low urine potassium excretion is associated with increased risks of hypertension and cardiovascular disease. The new study is one of the few to evaluate the association of potassium intake with CKD outcomes.

The results suggest lower all-cause mortality in CKD patients with higher urine potassium excretion, but no significant association with kidney failure risk. "[H]igher potassium intake may provide some benefit even in a population with nondiabetic CKD," the researchers write. They call for further studies to examine these associations in other groups of kidney disease patients and to explore the underlying mechanisms [Leonberg-Yoo AK, et al. Urine potassium excretion, kidney failure, and mortality in CKD. *Am J Kidney Dis* 2017; 69:341–349].

In Nondiabetic CKD, No Overall Benefit of Intensive BP Control

Intensive blood pressure control does not further reduce the risk of kidney disease progression among nondiabetic patients with kidney disease, concludes a meta-analysis in *JAMA Internal Medicine*.

A systematic review identified nine randomized controlled trials comparing intensive BP control—targeting levels less than 130/80 mm Hg—with standard BP control in CKD patients without diabetes. The studies included a total of 8127 patients with a median follow-up time of 3.3 years, including more than 800 kidney disease progression events. Meta-analysis was performed for the outcomes of annual rate of change in glomerular filtration rate (GFR), doubling of serum creatinine or 50% reduction in GFR, end-stage renal disease, a composite renal outcome, and all-cause mortality.

In the overall patient population, there was no significant difference in progression of renal disease or mortality with intensive versus standard BP control. However, there was a trend toward lower kidney disease progression with intensive BP control among nonblack patients and those with higher levels of proteinuria. Adverse events were similar between groups, except for a higher rate of dizziness with intensive BP control.

Most CKD patients do not have diabetes, and BP control can reduce decline in renal function and cardiovascular risk. Previous studies of intensive BP control in this large group of patients have yielded conflicting results.

The new meta-analysis of more than 8000 nondiabetic CKD patients with 3 years' follow-up shows no reduction in kidney disease progression with intensive versus standard BP control. However, the data show a trend toward reduced kidney disease progression in nonblack patients and those with heavy proteinuria. Adverse events appear similar at both BP targets [Tasi W-C, et al. Association of intensive blood pressure control and kidney disease progression in nondiabetic patients with chronic kidney disease: a systematic review and meta-analysis. *JAMA Intern Med.* Published online March 13, 2017. doi:10.1001/jamainternmed.2017.0197].

"Language-Concordant" Care Improves Diabetes Control in Latino Patients

For Latino patients with limited English proficiency (LEP), switching to a primary care provider who speaks Spanish is associated with improved control of type 2 diabetes, reports a study in *JAMA Internal Medicine*.

Using data from the Kaiser Permanente Northern California healthcare system from 2007 through 2013, the researchers analyzed the effects of language-concordant (LC) versus language discordant (LD) care on risk factor control among LEP Latino patients with type 2 diabetes. Of 1605 patients (mean age 60.5 years), about 26% switched from LD to LC care—i.e., from a primary care provider who spoke English only to one who spoke Spanish. Measures of diabetes control for this group were compared to those of patients who remained in LC care (26%), remained in LD care (28%), or switched from an LC to an LD provider (19%).

Patients who switched from LD to LC care had greater improvement in glycemic control and low-density lipoprotein (LDL) cholesterol, compared to those who remained in LD care. On adjusted analysis accounting for secular trends, the rate of glycemic control (defined as HbA1c less than 8%) increased by 10% among the LD to LC group, while the rate of poor glycemic control (HbA1c greater than 9%) decreased by 4%. Switching from an English-only to a Spanish-speaking primary care provider was also associated with a 9% increase in the rate of LDL control (less than 100 mg/dL). Language concordance had no effect on BP control. There was also a 15% increase in LDL control among patients who switched from LC to LD care. None of the four groups had a reduction in risk factor control after switching from one primary care provider to another.

There are more than 50 million Latinos in the US, 30% to 40% of whom may have LEP. Language discordance between these patients and their healthcare practitioners may pose challenges in providing culturally competent care.

This pre-post study of LEP Latino patients in a large California healthcare system suggests improvements in diabetes risk factor control after switching from a PCP who speaks English only to one who speaks Spanish. Findings include a 10% increase in the prevalence of glycemic control among patients who switch from LD to LC care. Facilitating LC care may be an effective strategy for improving disease control for LEP Latino patients with diabetes [Parker MM, et al. Association of patient-physician language concordance and glycemic control for limited-English proficiency Latinos with type 2 diabetes. *JAMA Intern Med* 2017; 177:380–387].

Increased Creatinine after Starting ACEIs/ARBs May Increase Cardiorenal Risk

Patients who have even relatively small increases in creatinine after starting angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEI/ARB) treatment are at increased risk of adverse cardiorenal events, suggests a study in the *British Medical Journal*.

Using linked UK primary care and hospital databases, the researchers identified 122,363 patients who initiated treatment with ACEIs or ARBs between 1997 and 2014. Of these, 1.7% had creatinine increases of 30% or more after starting renin-angiotensin system blockade. Rates of end stage renal disease, myocardial infarction, heart failure, and death were compared for patients with and without a 30% increase in creatinine, with adjustment for patient characteristics and clinical factors. Differences in risk per 10% increase in creatinine after starting ACEI/ARB therapy were evaluated as well.

Patients with creatinine increases of 30% or greater were older, median age 68 versus 63 years; more likely to be female, 56.1% versus 46.1%; and more likely to have stage 3b or 4 chronic kidney disease, 8.9% versus 4.3%. This group also had higher rates of myocardial infarction, heart failure, arrhythmias, and peripheral artery disease and were more likely to be taking loop or potassium-sparing diuretics and nonsteroidal anti-inflammatory drugs.

Rates of all adverse cardiorenal outcomes were significantly higher for the patients with a 30% or greater increase in creatinine, compared to those with increases of less than 30%. Adjusted incidence rate ratios were 3.43 for ESRD, 1.46 for myocardial infarction, 1.37 for heart failure, and 1.87 for death. These increases were greatest in the year after starting ACEI/ARB treatment.

Among those with lesser increases in creatinine, all risks increased in graduated fashion. In patients with creatinine increases of 10% to 19% up to 40% or higher, IRRs increased steadily: from 1.73 to 4.04 for ESRD, 1.12 to 1.59 for myocardial infarction, 1.14 to 1.42 for heart failure, and 1.15 to 2.11 for mortality (compared to creatinine increases of less than 10%).

Some patients experience a sudden drop in kidney function after starting ACEI/ARB therapy. Creatinine increases of up to 30% are generally regarded as safe, and even as an indicator of preserved renal function. The authors sought to determine the long-term implications of increased creatinine, including increases of less than 30%.

The results suggest significant increases in cardiorenal events and mortality for patients with increases in creatinine after starting ACEI/ARB treatment. The increased risks are apparent even under the 30% threshold, in "dose-response" fashion. The investigators conclude, "Increases in creatinine after starting ACEI/ARB treatment identify a high risk group needing close monitoring and in whom the risks and benefits of ACEI/ARB prescribing should be considered" [Schmidt M, et al. Serum creatinine elevation after renin-angiotensin system blockade and long term cardiorenal risks: cohort study. *BMJ* 2017; 356: j791].

Liraglutide Reduces Diabetes Risk in Prediabetic Patients

Added to diet and exercise, once-daily treatment with subcutaneous liraglutide reduces the risk of developing diabetes among obese adults with prediabetes, concludes a trial in *The Lancet*.

The multicenter trial included 2254 obese adults (body mass index 30 kg/m^2 or higher, or 27 kg/m^2 or higher with comorbid conditions) meeting criteria for prediabetes. In a 2:1 ratio, patients were randomly assigned to receive once-daily liraglutide, 3.0 mg sc, or matching placebo. Both groups received a diet and exercise intervention. The main outcome of interest was time to onset of type 2 diabetes over 3 years' follow-up.

Fifty percent of patients completed the study; withdrawal rates were 47% in the liraglutide group versus 55% in the placebo group. During double-blind follow-up, type 2 diabetes was diagnosed in 2% of patients in the liraglutide group versus 6% in the placebo group. Mean time to diabetes diagnosis was 99 versus 87 weeks, respectively.

After accounting for differences in diabetes frequency, time to diabetes onset in all randomized patients was 2.7 times longer with liraglutide versus placebo. The associated hazard ratio for type 2 diabetes was 0.21. After 3 years, mean weight loss was 6.1% of body weight in the liraglutide group versus 1.9% with placebo. Liraglutide was also associated with a higher rate of regression from prediabetes to normoglycemia: odds ratio 3.6, with a number needed to treat of 3. Adverse events, including serious events, were similar between groups.

In obese adults with prediabetes, daily treatment with liraglutide appears to reduce the risk of developing type 2 diabetes over 3 years' follow-up, as an adjunct to lifestyle changes. Liraglutide is also associated with greater weight loss, improved glycemic control, and reduced cardiometabolic risk factors. The authors note that their study did not include follow-up data on the large proportion of patients who did not complete the study [le Roux CW, at el. 3 years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes: a randomised, double-blind trial. *Lancet* 2017; DOI. http://dx.doi.org/10.1016/S0140-6736(17)30069-7.

Continued on page 10

Policy Update

Repeal and Replace? What Happened and What Lies Ahead

By David White

The legislative effort to repeal the Affordable Care Act (ACA) suffered a stunning setback when the bill designed to replace the ACA, the American Health Care Act (AHCA), was withdrawn from consideration on the floor of the House of Representatives on March 24. After seven years of Republicans in Congress promising to strike the signature health care law of former President Barack Obama, this strategic legislative undoing so rapidly and publicly left many in Washington scratching their heads. How did it happen and what comes next? How it happened is becoming clearer. What comes next is still difficult to see.

In September 2016, then Republican nominee Donald J. Trump told "60 Minutes" that when it comes to repealing Obamacare, he was "going to take care of everybody. I don't care if it costs me votes or not. Everybody's going to be taken care of much better than they're taken care of now." This mantra became a rallying cry for his campaign and for many Republicans in, or running for, Congress. When the dust settled from the November 2016 elections, the Republicans had maintained control of the Senate, not expected just 10 months before, and the House and had won the White House—a surprise to nearly all including, many said, the Trump campaign itself.

With that aligning of control in the legislative and executive branches, repeal of the ACA was considered by most to be a foregone conclusion. Republican leadership in Congress decided to use a little known legislative device called budget reconciliation to accomplish ACA repeal. The reconciliation process can be temperamental. The rules in the Senate require it to be used directly with a budget resolution and allow it to only have one set of instructions for three distinct categories: revenues or taxes, expenditures, and the national debt. Why use such a constraining legislative device? Because in the Senate, a reconciliation vote cannot be filibustered, meaning it only needs 51 votes to pass—not the 60 needed to end a filibuster. Republican leaders in the Senate knew they could not make it to 60 votes.

On the same day as his inauguration, President Trump optimistically signed an executive order directing agencies to begin preparing for the repeal of Obamacare. The AHCA repeal bill was introduced by House Speaker Paul Ryan and fellow Republicans the first week of March 2017, and Health and Human Services (HHS) Secretary Tom Price joined in attempting to sell the plan. However, many conservatives were not pleased and felt the bill did not go far enough.

In the days that followed its introduction, the bill appeared to be on track and was approved by the House Energy and Commerce Committee and House Ways and Means Committee. But that appearance was not the complete picture.

As Speaker Ryan and HHS Secretary Tom Price were promoting the plan, the conservative Freedom Caucus of the House Republican Caucus were planning something different. On the evening of March 7, the Freedom Caucus met in a conference room in the Rayburn House Office Building and made a secret pact.

The pact was an agreement that no caucus member would commit their vote before consulting with the entire group—not even if President Trump himself called to ask for an on-the-spot commitment. The idea, hatched by Freedom Caucus Vice Chair Rep. Jim Jordan (R-Ohio), was to bind them together in negotiations and ensure the White House or House leaders could not peel them off one by one. Twenty-eight of the group's roughly three dozen members made the pledge. Three weeks later, Republican leaders, as many as 25 votes short of passage, were forced to pull their bill from the House floor.

During a last-minute Friday, March 24, afternoon plea from Vice President Mike Pence, Freedom Caucus members including Reps. Andy Harris (R-Md.), Scott DesJarlais (R-Tenn.) and even Mark Meadows (R-N.C.) were visibly upset, *Politico* reported. But no one cracked before Speaker Ryan pulled the bill.

Since then, recriminations have been made and fingers have been pointed among Republicans.

Senate Minority Leader Charles Schumer (D-N.Y.) signaled that Democrats will not let the issue go, saying his party would be willing to work with Republicans if the GOP stops "undermining" ObamaCare. "We Democrats, provided our Republican colleagues drop replace and stop undermining the ACA, are willing to work with our Republican friends—as long as they say, 'no more repeal,'" Schumer said March 27 during an interview on ABC's "This Week," referring to the Affordable Care Act.

What's next?

Secretary Price indicated in early March that ACA repeal would be done in three phases.

- Phase One: Repeal ACA through legislation.
- Phase Two: Review all regulations pertaining to ACA.
- Phase Three: Pass insurance legislation to allow selling across state lines and grant the government authority to negotiate lower drug prices.

The details of these three phases remain unclear. There is nothing preventing Congress and the Trump Administration from continuing to try to repeal or water down the ACA.

White House Budget Would Severely Cut Kidney Research

By Zachary Kribs

On March 16, 2017, President Trump released the annual White House Budget Request. Dubbed the "Skinny Budget," the budget—while light on details—is heavy-handed in the cuts it proposes to non-defense discretionary (NDD) funding. Chief among the $54 billion worth of cuts to NDD funding is a $15.1 billion cut to the Department of Health and Human Services (HHS), roughly 18% less than the department received last year.

The National Institutes of Health (NIH), which resides within HHS, would receive an even larger cut proportionally. If enacted, President Trump's budget would result in the loss of $5.8 billion, over 18% of the NIH's funding from the previous year. If distributed equally among all of the research centers that comprise the NIH, cuts to the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) would total nearly $332.8 million.

Additional provisions including the elimination of the Fogarty International Center, which researches the effect of global climate change on international health outcomes, and the "consolidation" of the Agency for Healthcare Research and Quality (AHRQ) into the NIH could result in an additional $10 million cut from NIDDK's budget.

The cuts proposed by President Trump would be devastating to medical research. Facing nearly 20% cuts to their budget, the NIH would be forced to reduce funding for many existing grants, and to decrease the number of available grants, making already competitive funding even harder to come by. These cuts would filter directly to universities and labs across the country, and would result in a shortage of opportunities for scientists and a decrease in participation by this highly skilled workforce.

The kidney research community would be especially at risk. According to a recently released report by the Government Accountability Office (GAO), kidney research is vastly underfunded in comparison to the cost effects that kidney diseases and kidney failure have on Medicare. Spending more than the 2017 budget of the entire NIH on treating kidney failure alone through Medicare's End Stage Renal Disease (ESRD) program, the federal government invests less than 1% of the amount spent on kidney disease in kidney research.

Additionally, the GAO report found that NIDDK spends what scant allocations it does receive judiciously, sending the majority of its allocation directly to researchers in the community. The GAO report found that NIDDK was in need of increased funding, and should not be made vulnerable to arbitrary cuts that will slow the development of life-saving, and cost-saving, treatments for kidney diseases.

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Kidney Transplantation 2017
Breaking Down Barriers and Building Bridges

By David Serur, Adam Bingaman, and Barry Smith

Kidney transplantation, whether using organs from deceased or living donors, has been well established as the optimal management for patients with end stage renal disease (ESRD). Unfortunately, it is not nearly as widely available as it should be.

On December 9, 2016, the Rogosin Institute, a full-spectrum kidney care and research organization offering both dialysis and transplantation in New York City, convened a transplant roundtable of 24 experts drawn from multiple sectors from medicine and surgery to media across the United States. Discussants included three individuals who have experienced the benefits of such transplants, one individual waiting for a transplant, and two living kidney donors. The assembled group was charged with determining new ways to overcome the obstacles to the improvement of the rate of kidney donation.

A passion to increase kidney donation clearly emerged from the discussion. Here we provide a brief overview of the facts and challenges to increasing kidney donation, and we present five potential solutions. More details for each proposed solution will be included in future issues of *Kidney News*.

Although 2016 was a good year for deceased-donor kidney transplants (over 13,000 for the first time), up 11% over 2015, the rate for living donation has not improved at all since it achieved its highest level over a decade ago. Here are some numbers to think about: Only 20% of the half million dialysis patients make it to the transplant wait list, and of those, 5000 die each year waiting. Chronic kidney disease (CKD) is growing, with more than an estimated 26 million Americans affected by it, and it occurs three times more often in the African American community. Dialysis costs Medicare $31 billion annually, and commercial insurers, another $9 billion. It is known that transplant patients live longer and better at a fraction of the cost of dialysis care, and yet the wait list for a kidney is growing each year. Optimally, dialysis should be considered as a bridge to transplant, with the emphasis on finding a living donor for as many ESRD patients as possible

Proposed solutions

How can we make a difference and increase the volume of transplants? Here are 5 ways that were emphasized at the roundtable:

1. **Decreasing the need for a transplant through health promotion and disease prevention**
   Early education, detection, and intervention regarding obesity, hypertension, and diabetes, the major drivers of ESRD, are needed.

2. **Increasing the supply of kidneys**
   Only 52% of American adults are registered for deceased organ donation. Some areas, such as New York state, are much lower at 24%. Concerted efforts to increase registration to 80% to 90% would certainly increase transplantation. Educational efforts regarding donor registration at the school level and community level would go far.

3. **Decreasing the kidney discard rate**
   Twenty percent of kidneys procured are never used and are thrown out. Some of these organs may be salvageable. We need to consider what factors contribute to this discard rate. Are centers fearful of retribution if they take a chance on a marginal organ? Centers may currently be risk adverse to avoid increased oversight.

4. **Increasing living donation**
   The option of living donation should be part of CKD education and not just at transplant centers. Transplant centers should have a dedicated donor team with experience and focus on live donors. A new slogan for patients to consider is, "Family and friends before fistula." Education that transplantation may be a way to avoid dialysis is needed. The processes for donor screening and work-up should be quick and efficient, and policies should be in place to help decision-making for medically complex donors. Donor loss of wages and out-of-pocket expenses should be reimbursed. Because only 20% of the dialysis population is listed for transplant, a greater effort by dialysis units and nephrology clinics is needed to boost referrals. Although these efforts may not increase the number of deceased donors available, they have the potential to result in more live-donor opportunities.

5. **Increasing kidney paired donation (KPD)**
   About 600 donations (10% of all living kidney donations) occur in swaps, a procedure that allows best-matched donors and recipients to be paired. This option needs to increase. More than half of all the kidney programs in the US had no KPD transplants in 2015, while the more experienced centers had 10% to 28% of their live donor volumes attributable to KPD. A major effort to encourage more centers to participate in the KPD process is needed. This includes making it easier for centers to be part of this process. Peer mentoring in the actual process would support such an increase.

It was the consensus of the participants in the roundtable that an urgent and concerted effort among all the stakeholders representing the various sectors involved is needed if a meaningful increase in the rate of transplantation is to be achieved. There is no excuse for not meeting this challenge. Hemodialysis units, nephrologists, transplant centers, the CKD community, and both CKD and ESRD patients and potential living donors and donor families need to come together to help overcome the barriers and build bridges in order to significantly reduce the enormous transplant wait list and the needless loss of life and suffering of individuals on this list. Finally, this roundtable was seen as a new call to action and only the first of an ongoing effort to increase kidney transplantation.

David Serur, MD, is Medical Director of the Kidney & Pancreas Transplant Program of New York-Presbyterian Hospital/Weill Cornell Medical Center, The Rogosin Institute, NY, NY. Adam Bingaman MD, PhD, is Director of Abdominal Organ Transplantation; Director, Live Donor Kidney Transplant Program; and Director, Renal Transplant Research Program; and also Kidney & Pancreas Transplant Surgeon at Methodist Specialty and Transplant Hospital, San Antonio, TX. Barry Smith, MD, PhD, is President/CEO, The Rogosin Institute, and Professor of Clinical Surgery, Attending Physician, New York-Presbyterian Hospital/ Weill Cornell Medical Center.

The Rogosin, an independent 501c3 organization, pioneered dialysis in New York in the late 1950s and kidney transplantation in 1963 with a living-related donor transplant program and has been a pioneer participant in the Center for Medicare and Medicaid Innovation's integrative care model, the End-Stage Renal Disease Seamless Care Organization (ESCO). The institute has held roundtables and symposia on health literacy, quality measures in CKD and ESRD, mental health, nutrition, and the achievement of truly integrated care since 2015.

Roundtable participants included: L. Baxter, recipient/advocate; N.R. Benavides, MS, LiveOnNY; A.W. Bingaman, MD, PhD, Methodist Specialty and Transplant Hospital; Councilwoman J. Bonner (donor); M.B. Charlton, RN, SRN, CCTC, NYP-Weill Cornell Transplant Program; D. Clapper, APRN-BC, MSN, CCRN, CPTC, CTBS, DCI Donor Services; D. Dadhania, MD, MS, FAST, NYP-Weill Cornell Transplant Program; T. D'Antonio, recipient/advocate; T.H. Feeley, PhD, College of Arts and Sciences, University of Buffalo, State University of New York; K.J. Fowler, recipient/advocate; M.L. Ganikos, PhD, Division of Transplantation, Healthcare Systems Bureau, HRSA; P. Hoyt-Hudson, BSN, RN, Center for Health Action and Policy, The Rogosin Institute; S. Kapur, MD, FACS, Transplant Surgery, Weill Cornell Medicine; G.J. Kassar, Office of NY State Senator M. J. Golden; C. Lawson, RN, BSN Reach Kidney Care (TN); T. Loranger, Consultant, The Rogosin Institute; C. O'Leary, PhD, LMSW, Health Literacy Missouri; R.E. Patzer, PhD, MPH, Emory Transplant Center; G. Payne, MS, RN, CNN, Nephrology Clinical Solutions; M. Phillips, MPH, MSW, Center for Health Action and Policy, The Rogosin Institute; D.L. Rudow, DNP, Recanati/Miller Transplant Institute, The Mount Sinai Medical Center; M. Reiner, Renewal in Brooklyn; E. Scheele, ORGANIZE; D. Serur, MD, Kidney and Transplant Program, The Rogosin Institute and NYP-Weill Cornell Transplant Program; J. Sinacore, National Kidney Registry; B.H. Smith, MD, PhD, The Rogosin Institute; A. D. Waterman, PhD, Transplant Research and Education, David Geffen School of Medicine, UCLA.

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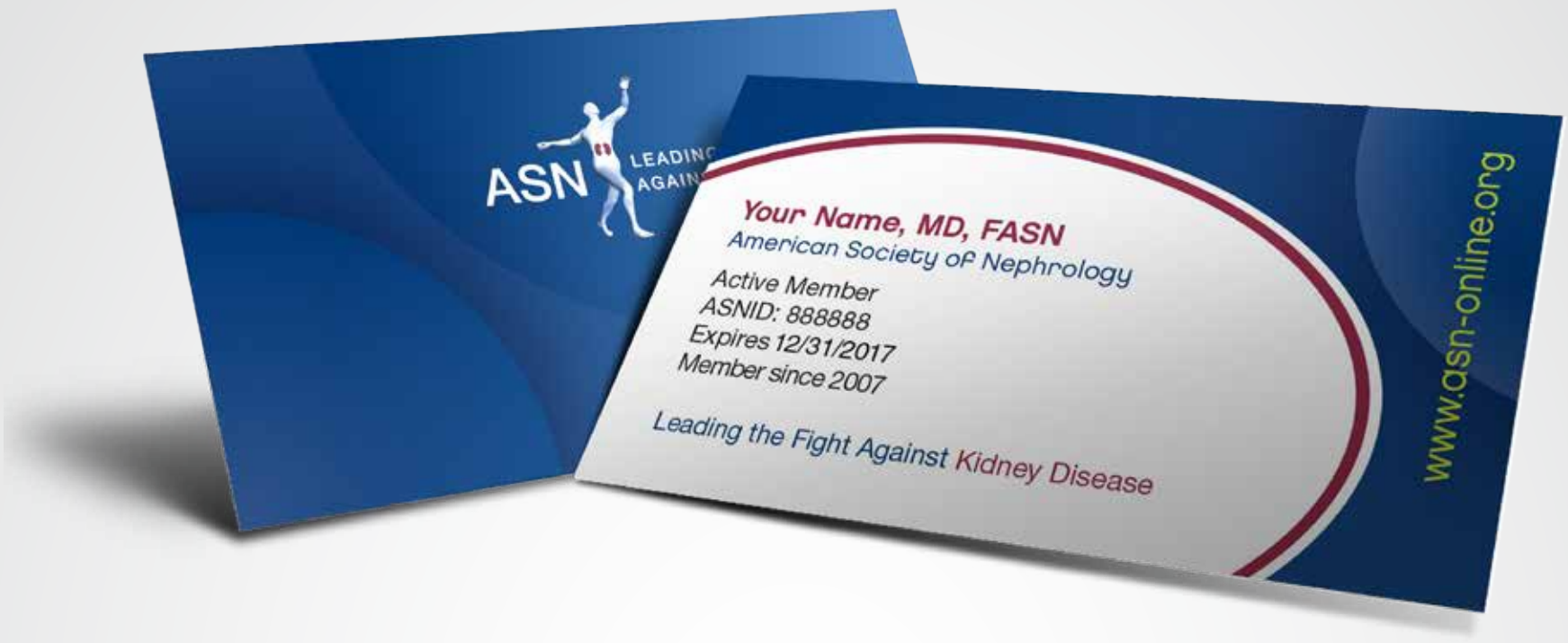

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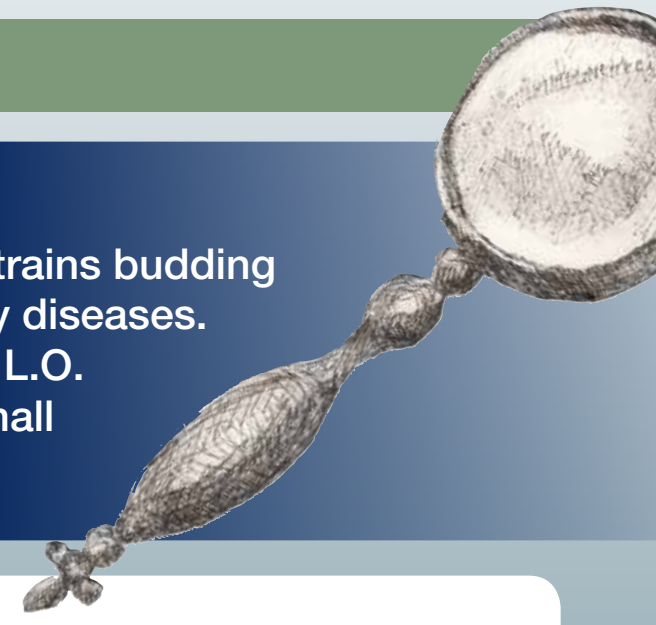
ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

Detective Nephron

By Kenar D. Jhaveri

Detective Nephron, world renowned for expert analytic skills, trains budding physician-detectives on the diagnosis and treatment of kidney diseases. Wildly waving a stack of paper records, budding nephrologist L.O. Henle and medical student Ms. Curious Tubule run down the hall toward Detective Nephron's office.



Henle (*with a smile*): A case for you sir!

The detective sits facing the window. He is observing a mob outside his office with his coffee mug in hand.

Nephron (*curious*): Finally, something that might put an end to this utter boredom.

Henle It's a case of metabolic acidosis.

Nephron (*smiling*): Ah yes. Similar to last time! Don't you want to give me some variety in nephrology *(with a smirk)*.

Tubule So this is a 50-year-old female with a history of type 2 diabetes mellitus who was admitted yesterday with left thigh abscess and eventually….

Nephron (*interrupting*): I don't need any of that information. What is the bicarbonate level?

Tubule She was found to have a serum bicarbonate of 8 mmol/L. Her sodium was 140 mmol/L, chloride was 103 mmol/L. That gives her a serum anion gap of….

Nephron (*surprised look*)

Tubule . . . An anion gap of 29. So this is a high-anion gap metabolic acidosis.

Henle Her serum pH was 7.1, and she had a PCO_2 of 22 mm Hg.

Nephron Interesting. So we have a high-anion gap metabolic acidosis and…?

Tubule Given that she has a high-anion gap metabolic acidosis…and using Winter's Formula would give me an expected PCO_2 of 20 mm Hg. So pure high-anion gap metabolic acidosis.

Nephron Remember there are only two body systems in my nephrocentric mind … renal and extrarenal; are we missing anything in the gap?

Tubule Hmm, with normal anion gap being 12, her anion gap is 29. Her bicarbonate is 8 for a normal of 24. So the difference in her anion gap is close to the difference in her bicarbonate level. Hence, no other disorder exists (no additional nongap metabolic acidosis or metabolic alkalosis).

Henle (*stepping in*): You just told me the △△!

Nephron △△! Who comes up with these names? Airline industry? Let's march and rule out all causes via GOLDMARK.

Tubule (*not chuckling*): That was not even funny.

Nephron (*laughing loudly*): Nicely done. So at this point, there is just a pure high-anion gap metabolic acidosis.

Pause.

Nephron Hold your horses, Tubule. Can we get a urinalysis to get a sense of the urine pH?

Tubule (*happy*): Urine pH was 5.5.

Nephron Good, so the kidney is dumping acid and doing its job. I assume this is a case of normal renal function?

Tubule Yes, of course! It would be too easy for you otherwise!

Nephron So what's with the new GOLDMARK mnemonic?

Henle Two popular mnemonics were used to remember the major causes of the high-gap metabolic acidoses. The first was KUSMALE, which represents ketoacidosis, uremia, salicylate poisoning, methanol, aldehyde (paraldehyde), lactate, and ethylene glycol. The second was MUD PILES, representing methanol, uremia, diabetes, paraldehyde, iron (and isoniazid), lactate, ethylene glycol, and salicylate. Metabolic acidosis due to excessive paraldehyde use has become exceedingly rare. Iron and isoniazid are just two of many drugs and toxins that cause hypotension and lactic acidosis.

Three new organic anion gap–generating acids and acid precursors have been recognized in recent years. They are D-lactic acid, which can occur in some patients with short bowel syndromes; 5-oxoproline (or pyroglutamic acid) associated with chronic acetaminophen use; and the anion gap acidosis generated by high-dose propylene glycol infusions used in lorazepam and phenobarbital drips. Therefore, recently, a newer proposal has been used to teach causes of anion gap for the 21st century: GOLDMARK. This acronym represents glycols (ethylene and propylene), oxoproline, L-lactate, D-lactate, methanol, aspirin (salicylate), renal failure, and ketoacidosis (starvation, alcohol, or diabetic).

Nephron (*jumping in*): Thank you for a short historical update on this! Nice job, my apprentice! Now I assume you have checked all of the above.

Tubule Yes.

Henle (*confident*): She has no ingestion history and no signs of overdose of any glycols; her urine microscopy had no visualization of oxalate crystals, and she did not have toxic optic neuropathy or any neurologic findings, ruling out ethylene glycol and methanol toxicity. The psychiatry team didn't feel she had any form of overdose. Her blood sugar is 125 mg/dL, and blood alcohol levels are negative. She has no history of any chronic use of acetaminophen, which was confirmed by a level. Her salicylate levels were negative. She was never given any medications that were prepared in propylene glycol…

Nephron So no G, no O, no M, no A, no R, and no K? You didn't mention anything regarding her lactic acid levels?

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Detective Nephron

Continued from page 15

Henle Yes, given no hypotension, lactic acid was normal. A D-lactate was not checked.

Tubule I am confused. What is drug-induced lactic acid then? She must be on metformin?

Nephron So let's end this confusion once and for all. Not unusual to get confused. There are two types of L-lactic acidosis: type A and type B. Type A is the usual variety that you encounter in the intensive care unit with marked tissue hypoperfusion and shock state. Type B is a form of L-lactic acidosis with no apparent hypoperfusion. This is classically seen with diabetic patients on metformin and sometimes, in patients with lymphoma or other solid malignancies.

Anaerobic metabolism due to dense clusters of tumor cells and/or metastatic replacement of the hepatic parenchyma has been proposed, but lactic acidosis can develop in patients with relatively small tumor burdens. Other possible mechanisms include increased rates of lactate production by the neoplastic cells that shift to primarily aerobic glycolysis (the Warburg effect) and thiamine and/or riboflavin deficiency. It is likely that lactate metabolic clearance is also impaired. D-lactic acidosis is a rare form of lactic acidosis that can occur in patients with short bowel syndrome or other forms of gastrointestinal malabsorption. In these patients, abnormally large amounts of glucose and starch are metabolized by intestinal bacteria to multiple organic acids, including D-lactic acid. Because humans metabolize D-lactic acid very slowly, systemic absorption of the D-optical isomer of lactic acid from the bowel can lead to high plasma D-lactate levels and metabolic acidosis. She didn't have any of those findings, I assume?

Henle She was not on metformin.

Nephron (*with a smirk*): What is she taking for her diabetes? What is her A1c?

Tubule (*relieved*): I am not sure, but her A1c was 8.6.

Nephron What is her urine glucose?

Henle (*jumping in*): Funny you ask that; it was 1000 mg/dL at multiple occasions?

Nephron What do we think?

Tubule With normal glucose in the serum, that is strange that she has a high urine glucose level…

Nephron Is she on a glucoretic?

Tubule I have heard of diuretics, aquaretics; what are glucoretics?

Henle (*jumping in*): He is talking about the new class of agents used to treat diabetes called sodium glucose cotransporter (SGLT-2) inhibitors. They cause increased glucose excretion via blocking this pathway in the proximal tubule.

Tubule So what about them? What does that have to do with this acidosis?

Nephron (*excitement in his eyes*): In GOLDMARK, the K is ketoacidosis. It comes in three types: alcoholic, diabetic, and starvation. You told me that she has a normal alcohol level. Does she have ketoacidosis?

Henle Hmm, her urine did have moderate ketones. Her albumin is 3.4 g/dL, and she was eating well. Doubt she has starvation.

The detective's eyes brighten as he suddenly looks up at Ms. Tubule for a split second, then back down again.

Nephron Fascinating.

Henle and Ms. Tubule appear puzzled.

Nephron Please check a serum ketone level.

Tubule and Henle return a day later.

Tubule It was high!

Henle Why do you ask?

Nephron So you have ruled out all causes of high-gap acidosis in this patient, but the patient has ketoacidosis clearly by urine and blood work. No starvation and no alcohol. She has diabetes and is on this novel class of agents called the SGLT-2 inhibitors. This is euglycemic diabetic ketoacidosis (eDKA); eDKA was mentioned in 1973 in the *British Medical Journal* in patients who were diabetic but didn't have hyperglycemia. Compared with classic diabetic ketoacidosis (DKA), eDKA presents with mild to moderate hyperglycemia, typically <300 mg/dL blood glucose levels, which she had.

Tubule Why is this more important now?

Nephron (*continues on*): In 2013, many SGLT-2 inhibitors got approved for diabetes mellitus management (the glucoretics). The Food and Drug Administration (FDA) performed an FAERS search of adverse effects with these agents, and identified 73 cases of ketoacidosis linked to SGLT-2 inhibitors. All patients required hospitalization, and 60% had DMII. Blood glucose levels ranged from 90 to 1300 mg/dL (median of 211 mg/dL). Timing of onset was around 43 days of starting or dose change of the agent. The majority of the cases also had dehydration, infection, or change in insulin doses. No mortality has been reported with this effect. All patients respond quickly with intravenous hydration and insulin once recognized.

Henle (*curious*): Is it a class effect?

Nephron Yes. The initial FDA reporting was done with canagliflozin (Invokana). A more recent study found an incidence rate of 0.07% with this agent. In a large study with dapagliflozin (Farxiga), 0.1% of patients got eDKA. Empagliflozin (Jardiance) also has been found to cause eDKA.

Nephron (*adds on*): Dehydration, alcohol use, decrease in insulin use, infection, low-carbohydrate diet, reduction in caloric intake, and advanced age have been suggested to be risk factors for development of this entity. Apparently, she had an infection (perhaps her risk).

Henle I don't understand how a normal glucose level can lead to this entity?

Nephron Ketosis results from restriction of carbohydrate usage with increased reliance on fat oxidation for energy production. The pathogenesis of hyperglycemic DKA is well understood. SGLT-2–induced glycosuria can happen over 24 hours, and this artificial low plasma glucose does not stimulate insulin. Remember, she had the high urine glucose of 1000 all along with a near-normal serum glucose. In eDKA, insulin deficiency and insulin resistance are milder; therefore, glucose overproduction and underutilization are quantitatively less than in DKA. More important, renal glucose clearance (i.e., the ratio of glycosuria to prevailing glycemia) is twice as large with eDKA than with DKA. Ketoacidosis follows with the same sequence of events in eDKA as in DKA. Insufficient insulin levels will then decrease glucose utilization and promote lipolysis and ketogenesis. In addition, these drugs can increase glucagon levels, leading to increased ketone production.

Tubule So if I had to summarize, eDKA is pathophysiologically similar to DKA, except for the circumstance—SGLT-2–induced glycosuria—that artificially lowers plasma glucose levels and predisposes to increased ketogenesis.

Nephron Precisely!

Henle I just found out; she was on empagliflozin for over 3 weeks before admission.

Nephron As I suspected.

Henle Let me make sure I understand. To summarize, we have a patient who presented with eDKA symptomatic for 1 week, with bicarbonate initially of 8. So, obviously, she is off the drug. How do I treat?

Nephron Hydration, and treating it similar to DKA with insulin will improve the acidosis. No data exist on a safe time to start the drug again. I wouldn't!

Tubule Fascinating. . .

One week later.

Tubule Do you remember the patient we suspected of having eDKA?

Nephron Of course.

Tubule Right, so on our recommendation, the primary team discontinued the medication. She was given aggressive hydration and insulin treatment; eventually, acidosis resolved, and ketoacidosis disappeared. She was sent home on alternative diabetes medication.

Nephron Very well then. And so, yet again, from a diagnosis of an acid-base disturbance, you have identified an easily reversible cause, and I hope one you will never forget. Let's have some New York–style pizza…I am starving!

Special thanks to Massini Merzkani and Holly Koncicki, both from Hofstra Northwell School of Medicine, for submitting this case. A special thanks to Helbert Rondon (Assistant Professor of Medicine, Renal-Electrolyte Division at the University of Pittsburgh School of Medicine) and Rimda Wanchoo (Professor of Medicine, Nephrology Division, Hofstra Northwell School of Medicine) for content editing.

The concept of Detective Nephron was developed by Kenar D. Jhaveri, MD, Professor of Medicine at Hofstra Northwell School of Medicine and an Attending Nephrologist at Northwell Health System (NY). Send correspondence regarding this section to kjhaveri@northwell.edu or kdj200@gmail.com.

Fellows Corner

Referring the Preventable Before It Becomes the Inevitable

By Daniel Edmonston

Daniel Edmonston, MD

Despite initiatives to improve access and delivery of preventive care, much of medicine is still reactionary. We wait behind brick-and-mortar walls for our patients to come to us with a list of problems in hand.

The field of nephrology is not immune to this limitation. Arguably, we are among the most susceptible. Like the "silent killer" hypertension, most patients with chronic kidney disease (CKD) are asymptomatic until the disease approaches advanced, often irreversible, levels. This lack of symptoms leads to patient under-recognition of even advanced CKD.

Compounding this problem, provider recognition of CKD may also be lacking (1). The adoption of formulas, such as the MDRD and CKD-EPI formulas, to report an estimated glomerular filtration rate may have improved provider recognition of earlier stages of CKD. However, the impact on referral patterns has produced conflicting results (2–4). A large percentage of patients referred to nephrology clinic have mild CKD with low risk of progression, while many high-risk patients go without a referral.

While limited by a lack of randomized-controlled trials, multiple cohort studies and a large Cochrane Review have suggested that timely nephrology referral (defined as referral greater than six months before the initiation of dialysis) leads to an improvement in outcomes including reduced mortality, earlier placement of fistulas, and more patients starting peritoneal dialysis over conventional in-center hemodialysis (5). Furthermore, early referral can potentially decrease the overall cost of care for these patients who may otherwise require a prolonged inpatient admission to initiate hemodialysis.

Although the scope of this problem is vast, as a fellow I did not have to look far for important work addressing these issues. Blake Cameron, MD, pioneered multiple programs to combat this problem while still a nephrology fellow at Duke University. During his fellowship, Blake completed a Masters in Biomedical Informatics and led a team that harnessed electronic health record (EHR) data to identify these at-risk patients. His work is sponsored by the Duke Institute for Health Innovation.

One such program integrates select insurance claims data and information from the EHR to utilize prediction models such as the Kidney Failure Risk Equation to determine which patients in the Duke system are at greatest risk for progression to end stage kidney disease (ESKD) (6–7). Once these patients are identified, a multidisciplinary team including Blake, a primary care provider (PCP), a pharmacist, and nurse care managers meet regularly to determine which of these high-risk patients warrant intervention. The intervention may include home visits, care management, communications to the PCP, arranging for a referral, or re-establishing care if the patient had previously been seen by nephrology.

Another issue regarding provider recognition of CKD is "over-referral" of patients with very low risk of progression to ESKD. To address this issue, a "CKD Help Desk" program was designed to improve communication between PCPs and specialists. A major component of this program is "E-consultations," whereby PCPs can obtain advice from a nephrologist electronically, based on chart review, without the need for a face-to-face referral.

Often, the PCP may have an issue that can be easily resolved with the suggestion of a lab test or imaging study rather than scheduling a traditional consult. This program not only combats over-referral but also helps patients and PCPs have access to the expertise of a specialist without enduring long wait times for appointments and large co-pays. Alternatively, if the patient is appropriate for referral or the question too complex to be addressed in this manner, the nephrologist can recommend full referral and arrange for expedited care.

In addition, the program includes care pathways with algorithms and suggestions for evaluation and management of early CKD that will not only provide early, evidence-based interventions to these patients, but also improve the quality of information available to the nephrologist should the patient ultimately require a referral. Often important labs and imaging may be missing at the time of the initial consult visit leading to multiple visits to address a single problem. Programs such as the E-consultations and CKD Help Desk are part of a larger "Virtual Medical Neighborhood" that will eventually be expanded to include all specialties.

These interventions are intended to not simply increase referrals, but rather to refine the referral of patients with high-risk CKD. Other approaches that rely solely on automatic EHR prompts to providers may contribute more to provider alarm fatigue than improvement in patient care.

Blake's program and other similar ventures across the country are working to make consultative nephrology proactive rather than reactive. By facilitating timely referral and improving communication between nephrologists and PCPs, these programs have the potential to provide earlier access to evidence-based interventions that may slow progression of CKD, limit "crash starts" to hemodialysis, and ultimately improve mortality. This work will hopefully lead to all specialists addressing the preventable before it becomes the inevitable.

Daniel Edmonston, MD, is a first-year nephrology fellow at Duke University.

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Costs of Care Rise Rapidly with CKD Progression

By Bridget M. Kuehn

The costs of care for patients with chronic kidney disease (CKD) rise rapidly—even in the early stages of the disease, according to new research.

About 26 million US adults have CKD (Coresh J, et al. *JAMA* 2007; 298:2038–2047). Patients who progress to end stage renal disease (ERSD) require expensive care, which currently accounts for as much as 6% of Medicare spending despite such patients only making up 1% of the Medicare population. To reduce such spending, efforts to slow progression of the earlier stages of CKD have been proposed. But the costs of CKD at various stages, and the potential cost-effectiveness of slowing progression, haven't been well studied.

A 2014 study by Amanda A. Honeycutt, PhD, and her colleagues found that estimated annual Medicare costs for CKD-associated care increase from about $0 for stage 1 patients to $1700 for stage 2, $3500 for stage 3, and $12,700 for stage 4 (Honeycutt AA, et al. *J Am Soc Nephrol* 2014; 24:1478–1483). Honeycutt is director of the Public Health Economics program of the nonprofit Research Triangle International.

New research shows that the all-cause costs to Medicare and private insurers for treating CKD patients rapidly increase as the disease progresses.

Ladan Golestaneh, MD, an associate professor of clinical medicine at the Albert Einstein College of Medicine in New York, and her colleagues identified patients who were prescribed a renin-angiotensin-aldosterone system inhibitor in the Humedica electronic medical record (EMR) database. Then they compared the costs of care for patients with stage 1 or higher CKD (based on diagnosis or estimated glomular filtration rate) with costs for control patients without the condition for at least 90 days.

Average claims costs from the commercial and public payers were then applied to the services and prescriptions the patients received. ERSD-related dialysis was excluded. The study, which included 93,912 patients younger than age 65 and 81,829 patients age 65 or older, was funded by Relypsa, Inc., and was presented at Kidney Week 2016 ("Healthcare Cost Rises Exponentially by Stage of Chronic Kidney Disease").

The average estimated annual all-cause cost per patient in 2016 increased from $7500 in patients with no CKD, to $27,200 at Stage 3a, and $77,000 by stage 4–5 in patients covered by commercial insurance in the Golestaneh analysis. Among Medicare beneficiaries, the average estimated annual all-cause costs per patient were lower overall, but also increased rapidly from $8100 in CKD-free patients, to $20,500 at stage 3a, and $46,100 by stages 4–5. (Table 1)

Although these estimates were higher than those found by Honeycutt et al. for patients with Medicare, they were consistent with a 2011 US Renal Data System report on Medicare costs across all people with diagnosed CKD. The Honeycutt study looked only at CKD-related costs of care, and controlled for other disease-related costs. Yet CKD is a marker of medically complex and severely ill patients that partially contributes to increasing costs by worsening cardiovascular outcomes, Golestaneh noted. The presence of CKD also may lead clinicians to provide more aggressive care, she said.

Another difference between the two studies is that use of EMRs in the Golestaneh study allowed for a larger sample size and analysis of costs for patients younger than age 65 as well as those older than 65.

Inpatient care and rising costs

Inpatient care contributed to the bulk of the costs for patients at every stage of kidney disease in the Golestaneh analysis, and it accounted for an increasing share of the costs in the later stages of progression. Future studies are needed to tease out which admissions are avoidable or in which situations care might be safely shifted to an outpatient setting, Golestaneh said.

"Efforts to slow CKD progression and reduce hospital admissions and readmissions are likely to be important for reducing disease morbidity and should translate into substantial cost reductions," she said.

Diagnosis is an important first step. Many patients with CKD have historically gone undiagnosed, she said.

"Because inpatient costs increased considerably for higher CKD stages, earlier diagnosis may result in better control and a reduced likelihood of inpatient stays for CKD," Honeycutt said.

Additional study is needed to understand whether increased awareness of the burden of CKD and ESRD has led to more diagnoses in patients before and after age 65. Policymakers may also need to find ways to boost diagnosis.

"Given historically low CKD diagnosis rates, policies to promote routine testing, especially among older adults, could lead to reduced costs and better quality of life for those with CKD, Honeycutt said.

Nephrologists also can play a central role in improving CKD care and reducing its costs.

"We need to redesign the way we care for these patients," Golestaneh said. "We need to provide them with tools and resources such that they do not have to resort to the emergency room when they can't reach us or when they are having problems that they cannot address without assistance. Above all we need to study them and listen to them to fully understand why [these patients] have high inpatients costs."

Table 1
CKD: Average estimated all-cause cost per patent in 2016

	Commercial insurance	Medicare
No CKD	$ 7,500	$ 8,100
Stage 3a CKD	$27,200	$20,500
Stage 4–5 CKD	$77,000	$46,100

Source: Golestaneh, et al. "Healthcare Cost Rises Exponentially by Stage of Chronic Kidney Disease" (Kidney Week 2016, Abstract 2289)

Cognitive Impairment and Transplantation Policy

How should patients' cognitive function be weighed when allocating organs? A perspective recently published in the *New England Journal of Medicine (NEJM)* (1) shed some light on the issue. State and federal officials are also weighing in, and new laws are under consideration to keep the scarce organ supply open to a wider population and diversity of patients.

To date, four states, California, New Jersey, Maryland, and Massachusetts, have passed laws with provisions to protect citizens who may face discrimination when in need of an organ transplant or anatomical gift. Four other states have introduced bills: Delaware, Kansas, Oregon, and Pennsylvania.

At the federal level, in October 2016, 30 congressional members asked the Department of Health and Human Services (HHS) Office for Civil Rights to issue instructions that discrimination in organ transplantation violates the Americans With Disabilities Act.

An HHS spokesperson said in a statement that the agency is working "to clarify the obligations of covered entities participating in the transplant process and to provide equal access to their programs to individuals with disabilities," the *Washington Post* reported.

The *NEJM* article, by Scott Halpern, MD, PhD, and David Goldberg, MD, both of the Perelman School of Medicine at the University of Pennsylvania, suggested that a workable solution for patient transplant deliberation should prevent preference for the privileged and support accountability for reasonableness.

Review boards could function to adjudicate disputes, the authors noted. The boards might comprise transplant physicians from other regions (via videoconference), ethicists, behavioral psychologists, social workers, and community representatives.

Halpern and Goldberg noted that evaluations of patients with cognitive impairments could include judgments about the severity and permanence of impairments that might render a transplant "imprudent." The review board's decision would not be binding or final, but rather would serve as a set of recommendations for consideration by all transplant centers that might become involved in the case.

Harvard's Center for Bioethics Community Ethics Committee (CEC), reviewed the topic of cognitive impairment and transplantation, and its report suggested that pediatric patients with intellectual development disorders "should not be categorically excluded from listing for an organ transplant." The CEC report noted a patient with cognitive impairment receiving a transplant should be able to survive and likely be better off than before the transplant—which would exclude people in a vegetative state.

In response to the *NEJM* article, the CEC's Carol Powers, JD, wrote that an advisory committee at each transplant center could assess non-medical criteria used in listing decisions and monitor data.

In the age of social media, Halpern and Goldberg said guidance on transplant decision-making can help level the playing field. They referenced the case of a girl three years of age with Wolf-Hirschhorn syndrome, a rare genetic disease, who was denied a kidney transplant in 2012 because of her severe cognitive impairment. She later received a kidney after her family launched a successful media campaign.

A regional review board could serve impartially as a source of information as campaigns to obtain new organs are publicized in traditional and social media, Halpern and Goldberg said.

As the need for organs continues to be a medical, societal, and ethical issue, debate about how best to allocate the scarce resource is sure to yield more governmental and legal inquiry and new institutional programs that aim for fairer deliberation and allocation.

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Industry Spotlight

Fresenius' New Partnerships

Fresenius Medical Care North America (FMCNA), a division of Fresenius Medical Care, has been busy forming partnerships with national insurers. FMCNA announced a partnership in March 2017 with Humana Inc. with plans for a new program to improve care and health outcomes for Humana's members with end stage renal disease (ESRD). In February 2017, FMCNA announced a partnership with Cigna in a national program to lower the cost and improve quality of care for people with ESRD who are undergoing dialysis.

Under the program with Humana, FMCNA will implement its proprietary care coordination model. Each patient will be supported by a collaborative team of local nephrologists and clinicians working in partnership with the Care Navigation Unit (CNU), FMCNA's group of specialized nurses and service coordinators who provide 24/7 care coordination services. By focusing on the physical and emotional needs of each patient, the CNU aims to foresee issues before they arise and to help patients, their families, and their providers respond as conditions change.

"Through this partnership, we will positively impact the overall medical care of Humana's ESRD members who receive treatment within our dialysis centers, and it's our responsibility to ensure they can access the care they need, when they need it," said William McKinney, president of FMCNA's Integrated Care Group.

In the new Cigna partnership, FMCNA will continue to be paid for the kidney dialysis services it provides to its Cigna patients, while its affiliate, Fresenius Health Partners, will assume separate responsibility for providing management of medical costs and improving patient outcomes.

Implementing its proprietary care coordination model for this purpose, FMCNA may be eligible for additional reimbursement if it achieves such goals, the company noted in an announcement. The dialysis clinics must maintain or improve their star ratings within parameters set by the Centers for Medicare & Medicaid Services (CMS) in its Dialysis Facility Compare (DFC) quality rating. Cigna will evaluate outcomes for a number of quality measures that correlate directly to the total cost of care and overall patient experience.

One of the program's goals is to reduce emergency room use and hospital admission for dialysis by keeping patients healthier and providing them with additional access to dialysis at Fresenius Kidney Care outpatient facilities as needed, Fresenius announced.

Kidney Cancer Developments

The National Institute for Health and Care Excellence (NICE), has approved everolimus (brand name Afinitor, manufactured by Novartis) for routine use as a regular National Health Service (NHS) treatment option for patients with advanced renal cell carcinoma (RCC). NICE provides evidence-based guidelines on health care for the NHS and other medical organizations in England.

Previously, the drug was available only to NHS patients if they applied through the Cancer Drugs Fund (CDF). However, NICE reappraised the drug and assessed the cost and clinical effectiveness. As part of the reappraisal, Novartis Pharmaceuticals submitted a further discount to the cost of everolimus.

NICE originally published guidance not recommending everolimus as a standard NHS offering in April 2011, because it was deemed not to have sufficient benefits to justify its cost. It was then made available through the Cancer Drugs Fund.

A different fate met rocapuldencel-T, which was in a Phase 3 trial as a personalized cancer vaccine for metastatic renal cell carcinoma, wrote SeekingAlpha.com, an investment news website. Argos Therapeutics, based in Durham, NC, progressed in its new drug development to the Phase 3 ADAPT Trial, but was unable to show significant benefit in patient survival for its drug. An Independent Data Monitoring Committee reviewed data from earlier trials that showed the drug warranted moving to a Phase 3 trial.

After the trial results emerged, Argos announced it would cut more than a third of its employees, the *Durham Herald-Sun* wrote.

Nephros' New Filter Approved

The US Food and Drug Administration (FDA) has approved a new filter from Nephros (River Edge, NJ).

In early March 2017, Nephros received 510(k) clearance to market its EndoPur™ Endotoxin 10-Inch Filter.

The filter is designed to provide hemodialysis-quality water to dialysis machines. It fits into existing filter cartridge housings of the reverse osmosis (RO) water systems that provide dialysis clinics with high volumes of ultrapure water. The EndoPur™ has an endotoxin barrier with the smallest pore size on the market, the company announced.

"With the FDA clearance of the EndoPur, we have achieved a significant milestone in the expansion of our dialysis water filter portfolio," said Daron Evans, president and CEO of Nephros. "We now can provide our industry-leading 5-nanometer pore-size endotoxin protection to all dialysis clinic RO systems. We expect to begin selling the EndoPur to customers in the second quarter of 2017."

The filter can be used in large clinic-based, and small, portable machine scenarios.

Nephros' primary objectives in the second half of 2016 were to support the commercial launch of the S100 Point-of-Use filters and to complete the regulatory process for the 10-inch filter platform. The company also focused efforts on launching its hemodiafiltration treatment at a dialysis clinic managed by Vanderbilt University, according to a corporate update announcement.

Nephros expected total revenue for fourth quarter 2016 to exceed $740,000 and predicts it will be cash flow positive by the end of the second quarter of 2017, as its 10-inch cartridge product line becomes available. Nephros ultrafilters are used by dialysis centers to assist in the added removal of biological contaminants from water and bicarbonate concentrate in hemodialysis machines.

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