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Study Uncovers New Driver, Possible Therapeutic Target for Kidney Cancer

By Laura Williamson

The discovery of a second protein that builds up in cells with a common genetic change has opened the door to investigation of an additional therapeutic target for the most common type of kidney cancer.

A study published in *Science* by researchers at the University of North Carolina Lineberger Comprehensive Cancer Center implicates the protein ZHX2 as a driver in clear cell renal cell carcinoma (ccRCC), which accounts for roughly 70% of all kidney cancers. This is the first time ZHX2, previously reported to be a tumor suppressor in liver cancer and lymphoma, has been implicated as a driver in ccRCC, said lead author Qing Zhang, PhD, an assistant professor at the UNC School of Medicine Department of Pathology & Laboratory Medicine and Pharmacology.

"This protein could be a potential therapeutic target used to treat kidney cancer on its own or in combination with other therapies," he said. "The next step is to try to figure out how we can target it therapeutically."

An important predictor of kidney cancer: loss of VHL

Scientists have long known that an important predictor for this type of kidney cancer is the loss of VHL, a gene that suppresses tumors by degrading proteins that are no longer needed, helping to maintain normal cell function. More than 90% of ccRCC patients experience genetic mutations that cause them to lose VHL function.

Previous studies have shown that VHL loss causes a buildup of the protein HIF2α, which turns on the gene VEGF, leading to cancer growth. Most current therapies for ccRCC focus on inhibiting HIF2α or blocking VEGF activity. But these therapies are only partially effective.

The need for alternative treatment pathways

"We have made significant therapeutic advances over the last 10–15 years in kidney cancer," said UNC Lineberger's William Kim, MD, an associate professor of medicine and genetics in the UNC School of Medicine. "No credit should be taken away from that work. There are studies that show that using these VEGF inhibitors prolongs patients' lives. But in the end, a decent number of patients still don't respond to the drugs and rare patients have long-term survival."

Many kidney cancer therapies "have shown great

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Project Aims to Clear Path for Hemodiafiltration in the United States

By Bridget M. Kuehn

A growing number of patients in Europe and Asia are receiving a new form of renal replacement therapy called hemodiafiltration instead of hemodialysis. In fact, about one-third of patients in Europe currently receive hemodiafiltration, and that number is growing by about 6% a year, according to Bernard Canaud, MD, chief medical scientist at Fresenius Medical Care in Germany.

Hemodiafiltration's growing popularity abroad is being driven in part by European studies suggesting that the newer technique leaves patients feeling better with less fatigue and fewer cramps and because of emerging data suggesting that it may also offer cardiovascular benefits, Canaud explained.

Until recently, the U.S. Food and Drug Administration (FDA) had not approved any hemodiafiltration devices, so it hasn't been an option for patients in the United States. But the Kidney Health Initiative (KHI), a public–private partnership that includes the American Society of Nephrology, the FDA, makers of hemodiafiltration

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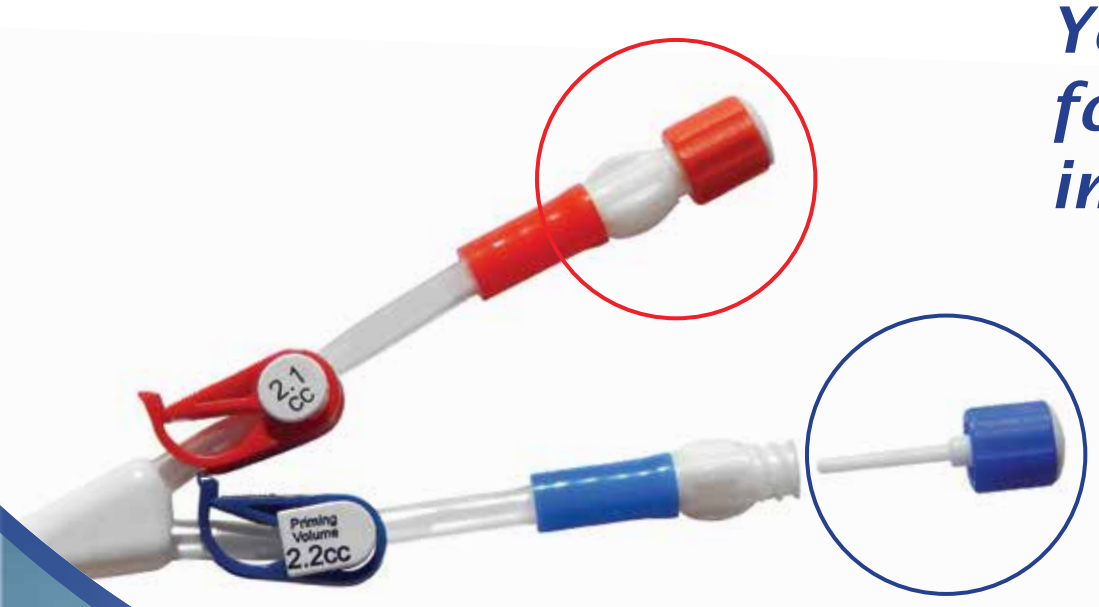

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[1] Brunelli, SM et al. *J Am Soc Nephrol*. 2018; 29:1336-43.
[2] Hymes, JL et al. *Am J Kidney Dis.* 2017; 69:220-7.

Study Uncovers New Driver

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promise, but 100% response is very uncommon," agreed Armine Smith, MD, director of the Johns Hopkins Urologic Oncology Center at Sibley Memorial Hospital. "They keep the disease stable or shrink the tumor down, but usually the cancer does not go away. The cancer cells overcome the medications in multiple ways. They may shunt the medication out from the cell, or find ways of sequestering the medication inside the cell so it becomes less effective. Or, the cells produce a lot more of the target proteins and that just overcomes the effect of the treatment."

Kidney cancer cells may already be resistant or develop resistance to the pathways currently being targeted, added Pavlos Msaouel, MD, PhD, an assistant professor of genitourinary medical oncology at the University of Texas, MD Anderson Cancer Center.

"If there are other pathways of importance to the cancer cell, separate from the HIF pathway, then those may be keeping those cancer cells alive, despite us targeting HIF," he said. That is, "the cells are using the other pathways instead, so they survive. Or, they learn to rely more on the other pathways. This is a major clinical importance for this paper, in that it identifies emerging new pathways of importance to cancer cells that VHL regulates that are separate from the HIF pathway."

Zhang said he asked himself if "maybe something else played an important role in driving kidney cancer? What else is out there besides HIF2α contributing to this process?"

A comprehensive screening technique narrows focus to ZHX2

To find out, Zhang and his team obtained a genomewide, human cDNA library of 17,000 encoded proteins and, using a comprehensive screening technique, looked "to see if we could find something in there that behaves like HIF2α," he said.

"We wanted to see what other proteins bind to VHL. We found another substrate of VHL," said Kim, explaining that their screening process revealed that "not only is HIF upregulated when VHL is lost, but so is ZHX2."

By examining samples of tumors from seven ccRCC patients with VHL loss, they confirmed that tumors from those patients experienced a buildup of ZHX2. "We showed clinical relevance, because we found it in the patients, as well," said Zhang.

To see whether reducing ZHX2 would shrink or stop tumor growth, the team then introduced tumor cells to the renal capsules of immunodeficient mice. After the tumors began to grow, the mice were fed with a special diet to induce ZHX2 depletion. "The tumors stopped growing and even shrank," said Zhang. "That's what we wanted to see."

The novelty here is that we've found a pathway that's turned on by the most commonly inactivated gene in clear cell kidney cancer.

The authors concluded that "ZHX2 accumulates as a result of VHL loss," said Zhang. "We think this accumulation turns on oncogenic pathways."

New questions to answer

The next step, said Kim, is to look for a drug that can either directly inhibit ZHX2 or a key downstream effector of ZHX2. It will take a lot more investigating to determine what that could be.

"We don't have a known agent or drug that can do this yet," said Zhang. "If we can develop a drug that inhibits ZHX2, we can slow the tumor growth. We have data showing that getting rid of ZHX2 will slow the tumor cell's invasion."

Such a drug could potentially be used in combination with HIF2α inhibitors or other therapies to provide a more effective treatment for ccRCC, the authors said, by targeting multiple pathways at once.

"Studies like this are important, because they delineate the underlying biology of kidney cancer and identify novel, distinct pathways to develop drugs against it," Kim said.

"The novelty here is that we've found a pathway that's turned on by the most commonly inactivated gene in clear cell kidney cancer, a pathway that appears to be completely independent of the HIF pathway. Hopefully in the future, this will allow us to develop a whole new class of inhibitors that can be used independently or combined with current inhibitors."

But that's still a long way off.

"This is basic work," said Kim, "and while exciting, any extrapolation to patient therapy is still a bit away."

One question that needs to be answered in determining whether ZHX2 is an appropriate target, said Msaouel, is whether doing so would cause unintended consequences.

"If ZHX2 functions as a tumor suppressor in different contexts, could inhibiting it promote the development of cancer in other tissues?" he asked. "We don't know. These are clinically relevant questions that we need to elucidate as this pathway is being translationally investigated."

"For example, we may find that it is not as fruitful to target ZHX2, as opposed to other downstream pathways. Finding out will allow us to be a little more precise in targeting this novel pathway," Msaouel said. "In being more precise, we can potentially reduce toxicities and unwanted side effects."

Zhang noted that "there is still some controversy" over whether ZHX2 actually functions as a tumor suppressor in liver cancer and lymphoma because its presence is amplified, or overexpressed, in most other cancers. "So in my mind, there should be more extensive research examining the role of ZHX2 in other cancers."

Researchers may also find that they need to target ZHX2 only in cases of kidney cancer, he said. "It may be important to develop a drug specifically to target ZHX2 in kidney tissue to achieve this selectivity."

"It's promising," said Smith. "I don't think monotherapy for kidney cancer is the answer. This opens up a new avenue. It's definitely exciting."

Hemodiafiltration

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equipment, and other stakeholders have been working to change that.

KHI aims to stimulate innovation and research on kidney diseases, and the treatment of kidney diseases has been one area that has lagged behind in terms of research and new treatment options, said Stephen Ash, MD, a member of the KHI hemodiafiltration work group and medical director at Hemocleanse, Inc. Dialysis.

KHI has brought together nephrologists, regulators, patients, and companies to try to identify and overcome challenges that stand in the way. One of the biggest hurdles to bringing hemodiafiltration to the United States has been that there wasn't a clear pathway for companies to gain clearance from the FDA for marketing hemodiafiltration devices.

"That was the biggest impediment to the improvements in that area," Ash said.

Removing big particles

Hemodialysis was invented in the early part of the 20th century. It is very effective at removing small molecules like urea, creatinine, and potassium from the blood, explained Ash.

In layman's terms, hemodialysis works basically the same way as a tea bag, said Richard Ward, MD, a retired professor of medicine from the University of Louisville, in Kentucky. The small molecules from the blood naturally diffuse through the dialysis membrane to the water on the other side of the membrane. But larger molecules, especially those that are attached to proteins, may not make it through the dialysis membrane.

"There are quite a few larger molecules that accumulate in people without kidney function that are probably contributing to the toxicity of the disease," Ward said. Ash noted that these larger molecules have been linked to hypertension, cardiovascular disease, and ill effects on the immune system.

Hemodiafiltration, developed in the 1980s, was designed to overcome this limitation of dialysis by combining diffusion of molecules across a membrane with convection to help remove some of the larger molecules.

Again, in layman's terms, Ward said, hemodiafiltration works in much the same way a press coffee pot works: by forcing fluid and molecules through a membrane under pressure. The pressure greatly increases the amount of fluid being removed during treatment, Ash said. So instead of removing 2 to 3 liters over 3 to 4 hours as dialysis does, hemodiafiltration removes 20 to 30 liters in the same period. To counteract that large amount of fluid loss, patients are simultaneously infused with an equal amount of sterile fluid. Ash said the intent of hemodiafiltration is to keep patients healthier by creating a renal replacement therapy that more closely resembles the way the kidney works.

"It's really replicating the kind of hemofiltration system that is present in the human body," he said.

Data from four clinical trials have had mixed results, according to a review by the KHI work group.

A Spanish study found that patients treated with hemodiafiltration had a 30% lower risk of cardiovascular disease and of death resulting from all causes. Two other studies failed to show a statistically significant reduction in deaths among individuals receiving hemodiafiltration. A fourth study showed no difference in mortality rates or quality of life in patients over 65 years old, but it did find lower rates of low blood pressure during renal replacement therapy, and fewer muscle cramps. Ash noted that there was a trend toward benefit in all the studies, but some studies may have been too small to enable a statistically significant difference to be found.

"There's no doubt that there's something there that's

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Kidney News

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benefiting patients," Ash said.

A meta-analysis of data from all the trials suggests that the benefits of hemodiafiltration hinge on how much fluid is filtered, Ward noted. The Spanish study also filtered a higher volume than did the other studies.

"It does look like there's a relationship between survival benefit and volume," said Ward.

To provide more definitive evidence, Canaud is launching an 1800-patient randomized trial comparing hemodialysis and high-volume hemodiafiltration in Europe. So far, nephrologists in the United States haven't been able to conduct clinical trials to test the potential value of hemodiafiltration because of the dearth of devices cleared for use in the U.S.

"Right now, the United States is locked out of it," Ward said.

Clarifying the pathway

One of the challenges to gaining FDA clearance for hemodiafiltration devices has been the need to demonstrate that large volumes of safe sterile fluid can be reliably produced to balance out fluid removal.

Ash explained that the FDA's stated standard is less than one bacterium per 1000 liters of fluid. Production facilities that produce large amounts of sterile fluids can meet this standard by taking small samples over time until they add up to 1000 liters. But proving that hemodiafiltration machines, which produce at most 20 or 30 units of sterile fluid per treatment, meet the standard by that method is not practical, he said.

"The requirements, quite frankly, for sterile fluid needed for that therapy as written [are] impossible to meet," Ash said. He noted that European regulators instead used a statistical process to prove that the machines and their reusable filters would produce sufficiently sterile fluids.

As the KHI hemodiafiltration project was getting started, a company called Nephros became the first to win FDA clearance for its hemodiafiltration device, as documented in KHI's review of regulation of these devices. Douglas Silverstein, MD, a medical officer at the FDA and co-chair of the KHI project, said the 510k clearance pathway used by Nephros "required and benefited from a strong collaboration between the FDA and the firm."

Now, the company is participating in the KHI project to establish a clear pathway for other hemodiafiltration devices through the FDA's regulatory process. Silverstein helped coordinate the FDA's contributions to this KHI project.

"Together, FDA personnel provided and clarified the regulatory framework for review of these devices," Silverstein said. He noted that the FDA has partnered with KHI on many projects, "helping KHI and the renal community better understand medical device performance characteristics, develop position papers, discuss clinical trial design, and consider study endpoints. We are poised to continue to work with all stakeholders in the renal community."

The approval pathway recommended by the KHI project relies on testing protocols to prove that the devices can reliably produce fluids that meet the FDA requirements for sterility.

"It turns out to be a very logical pathway, probably the only scientifically sound pathway," Ash said.

Now, the ball is in the manufacturers' court to submit their devices for approval and for the FDA to consider them.

"The FDA is always open to stakeholder input," Silverstein said. "The information we have already and will continue to gain from stakeholders in the renal community has and will undoubtedly strengthen our knowledge and enhance future collaborative efforts."

Ash cautioned that even if more devices are approved, there remain other hurdles to the widespread availability of hemodiafiltration. He noted that hemodiafiltration was easier to adopt in Europe, where dialysis units had already adopted water purification systems that produce ultrapure dialysate.

"It's not easy to implement this therapy in a dialysis unit; that's a caveat," Ash said. "You really have to improve the space and water quality beyond what we usually have in the United States, but toward what is required in Europe."

Still, the proposed approval pathway makes it possible for this new renal replacement option to begin tests and potentially to be offered in the United States.

"The pathway is a step forward," Ward said. ■

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Practice Pointers

Hypertension and Clinical Practice

Kidney News Editorial Board member Edgar Lerma, MD, FASN, interviewed George Bakris, MD, FASN, about clinicians' experience with the 2017 American College of Cardiology/American Heart Association (ACC/AHA) Hypertension Guidelines (1).

Dr. Lerma What are the highlights of the new ACC/AHA 2017 Hypertension Guidelines? How are they different from the previous guidelines?

Dr. Bakris Highlights and novel features of the new hypertension guidelines are as follows, compared with previous reports:

1. They are the first to focus on overall 10-year cardiovascular (CV) risk and attempt to provide a goal blood pressure (BP) to minimize CV risk.
2. They strongly endorse home BP measurement for all patients with hypertension to provide them with more feedback and improve adherence. Note that home BP has been validated against daytime ambulatory BP monitoring.
3. They emphasize proper measurement of BP in the office.
4. They expand the previous Joint National Committee 7 guidance on lifestyle modification as the cornerstone of BP therapy.
5. They put more emphasis on sleep disorders than did previous guidelines.
6. They change the threshold to diagnose hypertension and make it the goal as well: <130 mm Hg.

Dr. Lerma Under the new hypertension classification, there is an increase in the incidence and prevalence of hypertension. There is some perception that this benefits the pharmaceutical industry tremendously. What is your take on this?

Dr. Bakris This assertion couldn't be further from the truth. First, no new BP-lowering medication has been developed in over 15 years. Second, no one on the committee had any ties to industry. Last, the guidelines clearly emphasize lifestyle management as initial treatment and specifically state no drug therapy in the 130 mm Hg to 139 mm Hg goal unless the risk of CV disease is very high and lifestyle approaches have failed to reduce BP.

Dr. Lerma What have we now learned about white coat hypertension that we didn't know before? How is this going to affect clinical practice?

Dr. Bakris We know that white coat hypertension is not benign, and with the recent publication of Banegas and colleagues from Spain we know that white-coat and masked hypertension have higher all-cause mortality rates in comparison with sustained primary hypertension (2). Anxiety or inability to handle stress effectively is a major component of white coat hypertension, but it is not the only factor. Hence, identifying anxiety or stress and providing the patient with a psychologist or approaches to handle such situations could minimize these BP increases, which can be as high as 50 mm Hg systolic.

Dr. Lerma One of the issues that has received a lot of attention (and criticism) with the Systolic Blood Pressure Intervention Trial (SPRINT) is the method of taking blood pressure. What is your opinion on this, and how do you think it will affect clinical practice?

Dr. Bakris The reason SPRINT's method of taking blood pressure received criticism was that it is time consuming and requires trained, qualified personnel. This is fine for a trial, but not for routine practice. Unfortunately, there is a difference of as much as 13 to 15 mm Hg in systolic pressure between the SPRINT approach and routine practice. Hence, you may be overtreating a subset of people. This would lead to more side effects being ascribed to drugs rather than BP being too low. It is worth the effort to make the change.

Dr. Lerma What about 24-hour urine sodium?

Dr. Bakris This is a great test to check on whether patients are following a low-sodium diet. Check sodium and total creatinine. I have used this sometimes in people who swear they are following a low-sodium diet and always find that they are taking in two to five times more sodium than they should be. In many cases, correction by the patient results not only in better BP control but also in a reduction of medication doses or in termination of some drugs.

Dr. Lerma What is your prediction about the future of hypertension management? Do you think we'll keep these present guidelines before another revision?

Dr. Bakris I think these recent guidelines are an excellent public health document and have a lot of useful information. As for the goal and the staging and the risk, those will change over time.

The European Society of Hypertension guidelines were just announced, and they have <140/90 mm Hg as the goal. The American Diabetes Association has <140/90 mm Hg for everyone, and those at higher risk (>10% over 10 years) should be at <130/80 mm Hg. Moreover, numerous well-done studies have just been published or are in press from populations in Europe and Asia, all uniformly showing no significant advantage to going below 130/80 mm Hg in the general population or even among those with diabetes and low CV risk. Moreover, separate and recent studies demonstrate that one needs at least 18% 10-year CV risk to benefit from <130/80 mm Hg, with greater likelihood of harm than benefit at lower risk (3). Also, the Heart Outcomes Prevention Evaluation 3 trial showed no benefit among those with low CV risk unless BP was above 140 mm Hg (4). ■

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DIALYSIS AND PREGNANCY

By Manisha Singh

Manisha Singh

When pregnancy is complicated by ESRD, symptoms and complications like anemia add to hypogonadism, lower libido, and poor self-image. As expected, the data show that about 84% of women with ESRD report sexual dysfunction, and only 35% of women report being sexually active. Hormonal imbalances result in anovulatory cycles. In addition, maintaining a pregnancy to near term has been a challenge for these women. Higher incidences of lost pregnancies, intrauterine growth restriction, small-for-date babies, and premature labor continue to be challenges faced by most pregnant women receiving dialysis.

However, in recent years, outcomes in pregnant women receiving dialysis have improved. With intensified hemodialysis (HD) and the increasing number of renal transplantation patients, the incidence of pregnancy continues to rise in women with ESRD, with a median gestational age of 33.8 weeks and a median birth weight of 1750 g. More than 40% of pregnancies extend over 34 weeks, and the 28-day neonatal survival rate is 98%.

Better outcomes are noted in patients with residual renal function, which re-emphasizes the need to preserve this function. Dialysis vintage reduces the chances of conception. The best opportunity for conception has been within 2 years of starting dialysis.

Pregnancy is considered harder to achieve during peritoneal dialysis (PD) because of concerns regarding a possible barrier of PD fluid to the normal migration of ova. About 1.1% of reproductive-age women receiving PD conceive, versus 2.4% receiving HD. Regardless, the outcomes are not very different because PD provides an opportunity for high-efficiency dialysis.

Table 1 presents an overview of pregnancy hormones and the effect of dialysis on their function.

Diagnosis and maintenance of pregnancy

Given that most women with ESRD have hormonal imbalances, the diagnosis and maintenance of pregnancy is complex. Women with ESRD commonly have amenorrhea, nausea, vomiting, and increased levels of human chorionic gonadotropin, even without pregnancy. Pregnancy-associated plasma protein-A levels are higher in patients receiving hemodialysis, and levels are increased by the administration of heparin. These laboratory results raise concerns about false positive screening results for Down syndrome. Thus, to diagnose pregnancy and to assess fetal well-being, ultrasonography is considered the modality of choice.

Hemodialysis

A more intensive dialysis schedule is recommended, with BUN levels targeted to <16 to 18 mmol/L. This is usually achieved by increasing the frequency of HD sessions to five to seven per week, or switching to long nightly HD sessions, targeting a weekly Kt/V of 6 to 8. The target prescription for potassium is 3.5 to 4 meq/L; for sodium, 130 to 135 meq/L; for bicarbonate, 25; and calcium, 2.5.

Anticoagulation

We recommend the minimum required dose of heparin. Aspirin can be used for pre-eclampsia prophylaxis but needs to be stopped in the last few weeks of pregnancy during plans for surgery.

Peritoneal dialysis

Intensifying PD as pregnancy progresses, by decreasing volumes and increasing the number of cycles, is sufficient for most patients. Supplemental HD can be used. Icodextrin can be used when the benefits outweigh the risks (pregnancy category C).

Anemia

Anemia, which is common in both pregnancy and ESRD, is compounded in pregnant women receiving HD, whereas PD offers some advantage. The use of erythropoiesis-stimulating agents (ESA) to treat anemia (pregnancy category C) is required. There are case reports of darbepoetin being successfully used in pregnancy, with no obvious side effects. ESA dosing may need to be (twofold to threefold) higher in these patients. Vitamin B12 and folate replenishments are recommended. If the woman is iron deficient, intravenous iron sucrose (pregnancy category B) can be used. A target hemoglobin of 10 to 11 g/dL is ideal.

Bone mineral disease management

Sevelamer, lanthanum, aluminum, cinacalcet, and paricalcitol have not been well tested or established for use during pregnancy, but it is not anticipated that the woman will need these because of increased dialysis. There are case reports of successful outcomes with cinacalcet; however, more data are needed before recommendations can be made.

Phosphorus may need to be replenished, as may dialyzable multivitamins (vitamin C, thiamine, riboflavin, niacin, vitamin B6). Although it is quite unlikely, if the patient has elevated phosphorus, she can be safely treated with calcium-based binders throughout the pregnancy. Limited data are available regarding the use of other binders.

Vitamin D deficiency should be addressed. Calcitriol has been used in pregnancy, with additional calcium supplementation of 1.5 to 2 grams daily. The developing fetus requires approximately 30 grams of calcium for development. Although hypocalcemia is a concern, the patient should also be monitored for hypercalcemia, which can cause restricted development of the fetal parathyroid gland.

Nutrition

The pregnant woman with ESRD needs proper nutrition to support fetal development and maintain weight gain. Most dietary restrictions are relaxed because of intensified dialysis. A target protein intake of 1.5 to 1.8 g/kg of her prepregnancy weight per day + 20 g/day is recommended, with calories increased to 25 to 35 kcal/kg of pregnant weight per day.

Dry weight management

Dry weight management is complicated in most HD patients. The complexity increases when pregnancy weight gain must be factored into this equation. Ultrafiltration goals are usually relaxed to accommodate for weight gain. However, a close watch on BP and physical signs and symptoms must be kept because these patients are at risk of overloading rapidly. About 1 kilogram gain in weight is expected in the first trimester, followed by about 0.5 kilograms per week in the second and third trimesters. Avoiding large fluid removal is of paramount importance to prevent compromised uterine blood flow.

Hypertension

Hypertension is commonly associated with both pregnancy and ESRD. Severe hypertension is a significant concern for the health of the mother and the fetus. Medications should be reviewed if pregnancy is suspected. Many common medications used in ESRD, like angiotensin-converting enzyme and angiotensin receptor blockers, can be harmful if taken during pregnancy, although recent data show less risk in the first trimester. Antihypertensive agents found to be safe and effective for use during pregnancy include calcium channel blockers, labetalol, and methyldopa. Care should be taken to control BP yet prevent hypotension.

For patients with significantly elevated BP, complete blood count should be monitored for hemolytic anemia, thrombocytopenia, and elevated liver enzymes. The target for BP control is <140/90 mm Hg.

Diabetes management

A pregnant woman with chronic kidney disease is anticipated to have an increase in proteinuria. In addition, insulin use is recommended. The target for best glycemic control is hemoglobin A1c 7%. Close collaborative ties with an endocrinologist are highly recommended.

Immunosuppression in pregnancy and dialysis

Cyclosporine, tacrolimus, azathioprine, and prednisone are considered relatively safe during pregnancy, but immunosuppressants do cross the placental barrier. Their clinical significance in this setting is not well studied. Cyclosporine has been associated with prematurity and growth retardation, and tacrolimus has been associated with hyperkalemia and renal insufficiency in the fetus. Adrenal insufficiency and thymic hypoplasia have occasionally been described in the infants of transplant recipients, but these problems are unlikely if the dose of prednisone has been decreased to 15 mg. Mycophenolate mofetil and sirolimus are contraindicated in pregnancy. Cotreatment of such a high-risk patient by the obstetrician and the transplantation nephrologist is of paramount importance.

Obstetric care

These high-risk pregnancies with precious babies in health-compromised mothers need multispecialty dedicated care.

Diagnosing pre-eclampsia in anuric patients is challenging because neither proteinuria nor impaired renal function can be used as a means of diagnosis. Placental ultrasonography at about 22 weeks with uterine and umbilical Dopplers to assess placental size and morphology, and to quantify pulsatility indices, can be used. Abnormal pulsatility indices combined with fetal growth restriction indicate a diagnosis of pre-eclampsia. Although not widely available, antiangiogenic and angiogenic factor measurements, including soluble FMS-like tyrosine kinase and placental growth factor, may be used to aid in the diagnosis of pre-eclampsia. The use of magnesium for treatment will require caution because of its possible toxicity.

Cervical cerclage may be required to treat early cervical incompetence and prevent preterm birth. The reasons for this are unclear. Planned delivery (preferably vaginal if possible) at about 37 weeks is best. Postdelivery monitoring of the neonate for at least 48 hours is usual care.

Breastfeeding

The benefit of breastfeeding supersedes the associated risks. Significantly higher levels of creatinine, urea, and uric acid were found in pre-HD breast milk than in post-HD milk. Sodium and chloride were significantly increased in post-HD samples. Phosphate was significantly lower in pre-HD and post-HD breast milk than in milk from control women (low-risk mothers matched for postpartum age), whereas calcium showed no significant differences. In terms of nutrient components, glucose levels were decreased, whereas protein, triglycerides, cholesterol, and immunoglobulins were similar to control milk and were not affected by dialysis. Similarly, no significant differences were found in iron, potassium, and magnesium content. Thus overall, there was a high similarity of breast milk samples from HD patients to samples from low-risk control mothers. The significant variations in breast

milk composition between pre-HD and post-HD samples suggest that breastfeeding after a dialysis session is preferable to breastfeeding beforehand. The authors of that study suggested that the mother discard milk pumped immediately before dialysis.

We could not find any data on women receiving PD; however, we assume that similar changes can be expected but without major variations because of the continuous nature of PD. Lactation-safe medications for hypertension and comorbid conditions will be needed; they include methyldopa, labetalol, and nifedipine. Methyldopa, though the best recommended for this period, does have the potential of causing further depression in the mothers, who are already in a high-stress situation. Angiotensin-converting enzyme inhibitors, including captopril and enalapril, are secreted in low amounts in breast milk and may be used if needed, with close assessment of neonates for hypotension. Aggressive ultrafiltration may reduce the milk supply. Avoiding heparin that contains the preservative benzyl alcohol is prudent because it is potentially toxic to at-risk infants.

Emotional support

Through all this, it is evident that mothers with ESRD face multiple extremely stressful challenges. Difficulty in conception, difficulty in maintaining pregnancy, and the need to care for a child by a patient who is already struggling for her own survival on dialysis require major coping skills. Postpartum depression should be expected. The role of follow-up emotional supportive care and mental health counseling cannot be emphasized enough. However, data are strikingly lacking in this area.

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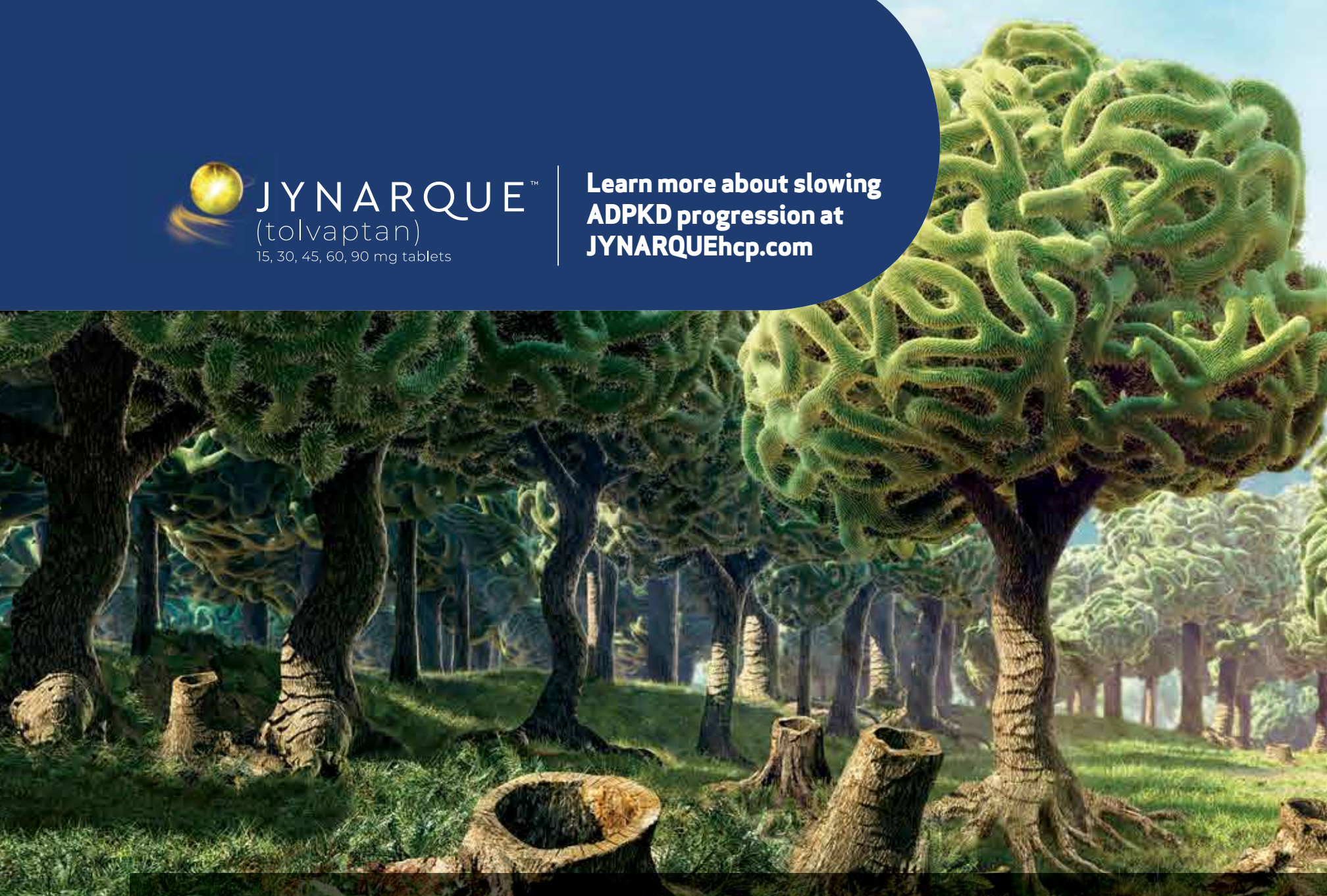
Table 1. An overview of pregnancy-related hormones

Hormone	Normal secretion in pregnancy	Status during HD	Status during PD	Function
HCG	Elevated with pregnancy	Elevated with dialysis	Elevated with dialysis	Development of anchoring villi during pregnancy (establishment and maintenance)
TSH	Elevated T3, T4, result in lower TSH values	No significant change; both 10% increase or decrease have been reported	Despite large TBG losses, no major change noted; however, early thyroid failure has been noted in nonpregnant PD patients warranting follow-up	Increased fT3, T4 to maintain increased metabolic demands of pregnancy
Prolactin	Anterior pituitary hormone, increases throughout pregnancy	ND	ND	Increases during pregnancy to lactation
Progesterone	Up to 10 weeks secreted from the corpus luteum, then by placenta	ND Average change reported about 15%, not considered to be clinically significant	ND	Prepares endometrium, required for implantation, suppresses maternal rejection of trophoblast, prevents preterm labor; postpartum fall was not noted in one case report
Human placental lactogen	Produced and secreted by the syncytiotrophoblast of the placenta	ND	Data unavailable; considered ND	Promotes fetal growth
FSH	Together with LH, the gonadotropins stimulate ovarian follicle and help further the pregnancy cascade hormones	Data unavailable; considered ND	Data unavailable; considered ND	Maturation of primordial cells
LH		Data unavailable; considered ND	Data unavailable; considered ND	
Estradiol		Gradual suppression	Gradual suppression	Promotes uterine blood flow, myometrial growth, stimulates breast growth
ACTH		ND, but a significant increase is noted after dialysis likely due to stress of dialysis	Not as high as HD	
Oxytocin	Postpituitary hormone, concentrations rise continuously until parturition			Parturition and the “let down” response during lactation
ADH	Postpituitary, metabolic clearance rate of ADH increases in second trimester due to vasopressinase released by the placenta			

Abbreviations: ACTH = adrenocorticotropic hormone; ADH = antidiuretic hormone; FSH = follicle stimulating hormone; HCG = human chorionic gonadotropin; HD = hemodialysis; LH = luteinizing hormone; PD = peritoneal dialysis; TBG = T4-binding globulin; TSH = thyroid stimulating hormone.

JYNARQUE™
(tolvaptan)
15, 30, 45, 60, 90 mg tablets

Learn more about slowing ADPKD progression at JYNARQUEhcp.com



INDICATION and IMPORTANT SAFETY INFORMATION for JYNARQUE™ (tolvaptan)

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

IMPORTANT SAFETY INFORMATION:

WARNING: RISK OF SERIOUS LIVER INJURY

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

CONTRAINDICATIONS:

- History, signs or symptoms of significant liver impairment or injury. This contraindication does not apply to uncomplicated polycystic liver disease
- Taking strong CYP3A inhibitors
- With uncorrected abnormal blood sodium concentrations
- Unable to sense or respond to thirst
- Hypovolemia
- Hypersensitivity (e.g., anaphylaxis, rash) to JYNARQUE or any component of the product
- Uncorrected urinary outflow obstruction
- Anuria

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

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

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

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

ADPKD=autosomal dominant polycystic kidney disease.

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

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

Other Drug Interactions:

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

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

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

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

Otsuka

Otsuka America Pharmaceutical, Inc.

Manufactured by Otsuka Pharmaceutical Co., Ltd., Tokyo, 101-8535 Japan.
Distributed and marketed by Otsuka America Pharmaceutical, Inc., Rockville, MD 20850.

June 2018 10US18EBP0160

European agency rejects kidney drug combo

The Committee for Medicinal Products for Human Use in the European Union recommended denial of a change to the marketing authorizations already in place for the drugs Opdivo (nivolumab) and Yervoy (ipilimumab), according to the European Medicines Agency.

Bristol-Myers Squibb (New York, NY) asked the committee to consider authorizing marketing for use of both drugs in combination to treat patients with untreated, advanced renal cell carcinoma.

According to the European Medicines Agency, "Although improvements in survival were seen in previously untreated patients given the combination of Opdivo and Yervoy compared with sunitinib, there was no evidence showing whether Yervoy contributed to these results and if so, how much. It is known that Opdivo alone produces benefit in previously treated patients with renal cell carcinoma." Another objection was that the "combination with Yervoy resulted in more side effects than are seen with Opdivo alone." The committee noted that "it is vital that the contribution of each component of the combination, and its appropriate dose, is properly established and justified to avoid giving unnecessary or ineffective treatments."

Bristol-Myers Squibb has requested a re-examination of the opinion, PharmaPhorum.com noted.

The disappointing news for Bristol-Myers Squibb comes at a time when quarterly figures showed that Merck & Co's rival PD-1 class drug Keytruda (pembrolizumab) overtook Opdivo in sales "after playing catch-up for several years," PharmaPhorum.com noted. Merck is based in White House Station, NJ.

Comparing second-quarter sales in 2017 with those in 2018, sales of Keytruda rose 89.2% to $1.67 billion and just passed Opdivo, which saw revenues increase 36% and generated sales of $1.65 billion during the same time frame, PharmaPhorum.com reported.

In April 2018, the FDA approved an Opdivo plus low-dose Yervoy combination as the first treatment to show significantly superior overall survival benefit when compared with sunitinib (brand name Sutent), manufactured by Pfizer (New York, NY).

Otsuka acquires a kidney care partner

Otsuka Pharmaceutical (Tokyo) has signed a merger agreement to acquire the clinical-stage biotechnology company Visterra (Waltham, MA) for about $430 million in cash.

The company is attractive to Otsuka because of its pipeline of programs, including those targeting IgA nephropathy and other kidney diseases, cancer, infectious diseases, and chronic pain. In IgA nephropathy, the antibody IgA builds up in the kidneys, affecting the glomeruli and causing irreversible scarring of nephrons. The National Institute of Diabetes and Digestive and Kidney Diseases notes that researchers have not found a specific cure for the disease.

Visterra offers a platform for the design and engineering of antibody-based drug candidates designed to bind to and modulate disease targets. The Visterra Hierotope platform targets drug candidates that are not adequately addressed by traditional approaches to creating and developing drugs.

The platform also includes fragment crystallizable (Fc) engineering capabilities for half-life extension of a drug, bispecific antibodies, and antibody-drug conjugates.

"I am highly gratified that Visterra's exceptional antibody platform technology, promising pipeline, and talented researchers will join up with Otsuka," said Otsuka Pharmaceutical President Tatsuo Higuchi.

FierceBiotech website reported that VIS410 is Visterra's most advanced pipeline candidate. The compound is in phase 2 development for hospital-based influenza.

FDA approves smartphone camera–based dipstick product

Healthy.io, based in Tel Aviv, Israel, has obtained U.S. Food and Drug Administration (FDA) marketing clearance for its first digital dipstick kit offering. The Dip.io is advertised on the company's website as having the accuracy of "the standard lab-based urinalysis analyzer."

The dipstick is being marketed in Europe and is certified by CE and International Organization for Standardization (ISO) 13485 for sale in the European Union. The urinalysis dipstick includes 10 determinations, including indicators for possible CKD, on the strip.

With the FDA nod, Healthy.io stated in its news release: "This approval opens the door for improved screening for kidney disease, a condition which affects over 10 percent of the population globally. Dip.io home testing for protein, glucose, and blood in urine can be enormously helpful for patients. It is also a welcome tool helping improve diagnosis and awareness of chronic kidney disease."

According to Josef Coresh, MD, PhD, professor of epidemiology at Johns Hopkins Medicine and chair of Healthy.io's medical advisory board, "It's exciting to see the FDA applying its rigor and enabling the use of the smartphone for better patient care."

The dipstick uses "computer vision algorithms" and a "unique calibration method" to ensure accurate reading and interpretation of results, accounting for the many different smartphone cameras available and "infinite lighting conditions," according to the company's website.

A photo of the dipstick with its color changes as test results will then be automatically sent to a patient's electronic medical record so a clinical professional can follow up.

Findings

CKD Registry Improves Some Outcomes in Safety-Net Clinics

A team-based CKD registry improves some clinical measures and care processes for patients in a safety-net primary care setting, reports a trial in the *American Journal of Kidney Diseases*.

Many patients with CKD do not receive guideline-based care shown to improve clinical outcomes. Disease registries embedded in electronic health records can improve quality of care for some chronic diseases.

The pragmatic trial evaluated in the *AJKD* study looked at an electronic CKD registry designed to identify patients with CKD and provide primary care team members with data relevant to their care. The study included 746 patients at a public safety-net care setting in San Francisco that had a high burden of hypertension and CKD. Patients and providers were assigned to 1 year of the CKD registry or a usual-care registry.

The primary care CKD registry targeted all patients with CKD, those with blood pressure over 140/90 mm Hg, those without an ACEI/ARB prescription, and those without an albuminuria measurement in the past year. In addition to sending alerts to the primary care team, the registry provided quarterly feedback to promote outreach to patients with CKD. Change in systolic BP at 1 year was assessed, along with BP control, ACEI/ARB prescribing, measurement and severity of albuminuria, and eGFR.

The patients' mean age was about 57 years; 53% were women. About 36% were black, 25% Hispanic, and 24% Asian. Based on albuminuria and/or eGFR measurements, 41.6% of patients had stage 1 or 2 CKD, 38.6% had stage 3a and 15% stage 3b CKD, and 4.8% had stage 4 disease. Thirty-eight percent of patients had a baseline albuminuria measurement; in this group, the average albumin–creatinine ratio was 421 mg/g. About 20% of patients had glycated hemoglobin greater than 6.5%, while 36% had uncontrolled BP. Overall, 30 primary care patients and 285 other patients were assigned to the CKD registry. Forty-nine primary care patients and 461 other patients were assigned to the usual care registry.

At 1 year, there was no significant difference in change in systolic BP (the primary outcome) between groups. There was also no difference in the percentage of patients with uncontrolled BP. Patients assigned to the CKD registry were twice as likely to have an ACEI/ARB prescription, adjusted odds ratio (OR) 2.25; and to undergo albuminuria measurement, OR 2.44. There was no significant difference in the degree of albuminuria or eGFR.

The CKD registry evaluated in this trial focused on behavior change throughout the healthcare team, not just for individual physicians.

While it didn't improve blood pressure, the primary care CKD registry increased rates of albuminuria measurement and ACEI/ARB prescribing in a public safety-net care setting. "Adoption of team-based CKD registries may represent an important step in translating evidence into practice for CKD management," the researchers write [Tuot DS, et al. Impact of a primary care CKD registry in a US public safety-net health care delivery system: a pragmatic randomized trial. *Am J Kidney Dis* 2018; 72:168–173].

Falling Amputation Rates in Dialysis Patients

Rates of lower-extremity amputation among ESRD patients on dialysis have decreased by about half in recent years, but mortality remains high among those who do undergo amputation, reports a study in *JAMA Internal Medicine*.

The study included 3.7 million records of *ESRD* patients receiving dialysis from 2000 through 2014, drawn from the US Renal Data System. Yearly cohorts were analyzed to assess trends in nontraumatic lower extremity amputations, classified as major (above- or below-knee) and minor (below-ankle). The effects of age, sex, diabetes, and hospital referral region were examined, along with one-year mortality after amputation.

In each annual cohort, more than half of patients were white; the percentage of women declined over the years. The adjusted rate of lower-extremity amputations declined from 5.42 per 100 person-years in 2000 to 2.66 per 100 person-years in 2014, for a relative decrease of 51%. The trend was driven by a 65.0% decrease in above-knee amputations and a 58.5% decrease in below-knee amputations, but there was also a 25.9% decrease in below-ankle amputations.

Amputation rates were more than five times higher in ESRD patients with diabetes, compared to nondiabetic patients. Adjusted amputation rates were higher for patients under age 65, compared to younger patients, and higher for men versus women. Adjusted 1-year mortality decreased from 52.2% in 2000 to 43.6% in 2013. Amputation rates decreased in all hospital referral regions, but remained higher in the South and Northeast regions. These regional variations persisted after adjustment for demographic variables and comorbidity.

Patients with ESRD receiving dialysis are at high risk of amputation, likely reflecting both traditional risk factors and risks specific to kidney disease. Recent studies have reported declining lower extremity amputation rates in the general Medicare population—possibly due to improved screening and management of peripheral arterial disease, especially in diabetic patients.

This retrospective study finds a 51% relative decrease in lower extremity amputations in dialysis patients since the year 2000. Reasons for this trend may include more aggressive management of cardiovascular risk factors and improved diabetic foot care.

One-year mortality after amputation in dialysis has improved as well, but remains over 40%. "Our results highlight the need for more research on ways to prevent lower extremity amputation in this extremely high-risk population," the investigators conclude [Franz D, et al. Trends in rates of lower extremity amputation among patients with end-stage renal disease who receive dialysis. *JAMA Intern Med* 2018; 178:1025–1032].

Canagliflozin Reduces Risks Even at Lower eGFR Levels

In patients with type 2 diabetes, canagliflozin has cardiovascular and renal benefits even at lower levels of kidney function, according to an analysis of clinical trial data reported in *Circulation*.

The analysis included data on 10,142 patients with type 2 diabetes and high cardiovascular risk enrolled in the industry-sponsored "Canagliflozin Cardiovascular Assessment Study" (CANVAS). Patients were randomly assigned to treatments with canagliflozin, a sodium-glucose co-transporter 2 inhibitor, or placebo. About 20% of patients had CKD, defined as a baseline eGFR of less than 60 mL/min/1.73 m^2. Of this group, about 72% had a history of cardiovascular disease. Estimated glomerular filtration rate was less than 45 mL/min/1.73 m^2 in 5.5% of patients; the trial excluded patients with eGFR less than 30 mL/min/1.73 m^2.

The primary outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction, and nonfatal stroke. This and secondary outcomes were assessed in patients with and without CKD, and at different levels of baseline eGFR.

At all eGFR levels, canagliflozin reduced HbA1c, systolic blood pressure, body weight, and albuminuria, compared to placebo. The HbA1c-lowering effect was attenuated at lower eGFR levels. There was a significant reduction in the composite outcome with canagliflozin: hazard ratio 0.86. This benefit remained significant in patients with versus without CKD and in all kidney function subgroups, including those with eGFR less than 45 mL/min/1.73 m^2. The effect on fatal/nonfatal stroke was "possibly greater" in patients with lower levels of kidney function.

Canagliflozin was also associated with a reduced risk of kidney disease progression (sustained 40% reduction in eGFR, development of ESRD, or death from renal causes). The overall hazard ratio for reduction in kidney disease progression was 0.60, and was consistent across CKD and eGFR groups. Safety outcomes and absolute risk reductions were also similar between groups.

Previous results have suggested that canagliflozin can reduce cardiovascular events and mortality in high-risk patients with type 2 diabetes. Because its blood sugar-lowering effects depend on kidney function, canagliflozin is not currently approved for patients with eGFR 45 under mL/min/1.73 m^2.

Secondary analysis of CANVAS data suggests that the cardiovascular and renal benefits of canagliflozin extend to type 2 diabetics down to an eGFR of 30 mL/min/1.73 m^2. The researchers conclude: "Reassessing current limitations on the use of canagliflozin in CKD may allow additional individuals to benefit from this therapy" [Perkovic V, et al. Cardiovascular and renal outcomes with canagliflozin according to baseline kidney function. *Circulation* 2018; 0:CIRCULATIONAHA.118.035901].

Gene Panel Detects Inherited Cystic and Glomerular Kidney Diseases

A new kidney disease gene panel provides a comprehensive, cost-effective tool for genetic diagnosis of patients with cystic and glomerular inherited kidney diseases, reports a clinical investigation in *Kidney International.*

The researchers developed and evaluated a kidney disease panel consisting of 140 genes having causal or other associations with cystic and glomerular inherited kidney diseases. The study included a validation cohort of 116 patients with known mutations and a diagnostic cohort of 305 patients: 207 with suspected inherited cystic disease and 98 with glomerular disease.

In the validation cohort, 134 of 135 previously known mutations were identified by targeted next-generation sequencing using the kidney disease panel, for a sensitivity of 99%. In the diagnostic cohort, the panel identified causative mutations in 78% of patients with inherited cystic kidney diseases and 62% with glomerular diseases. Rates of familial cases were 44% in patients with cystic diseases and 81% in those with glomerular diseases.

Copy number variants were detected in about 10% of diagnosed cases. Fifteen percent of patients had an unspecified clinical diagnosis at referral, while 2% had an inaccurate diagnosis. The costs of sequencing using the kidney disease gene panel were 50% to 70% lower than with other genetic testing approaches.

Molecular diagnosis of inherited kidney disease poses a difficult challenge. The new study validates the 140-gene kidney disease panel as a noninvasive, cost-effective tool for diagnosis of cystic and glomerular inherited kidney diseases. This approach leads to an etiologic diagnosis in three-fourths of cases; the authors find it particularly valuable in patients with nonspecific or atypical phenotypes [Bullich G, et al. A kidney-disease gene panel allows a comprehensive genetic diagnosis of cystic and glomerular inherited kidney diseases. *Kidney Int* 2018; 94:363–371].

Lower Rates of Microvascular Complications after Bariatric Surgery

In severely obese adults with type 2 diabetes, bariatric surgery reduces the incidence of microvascular complications, including nephropathy, reports a study in *Annals of Internal Medicine*.

The retrospective study included 4024 patients who underwent bariatric surgery at four US health systems from 2005 to 2011. The patients, aged 19 to 79, were followed up to 2015. About three-fourths of patients were women; the same percentage had a body mass index of 40 kg/m^2 or higher.

Bariatric surgery patients were matched for age, sex, body mass index, hemoglobin A1c, insulin use, duration of diabetes, and intensity of healthcare use to 11,059 patients who received usual care. A composite of the first incident retinopathy, neuropathy, or nephropathy was compared between groups.

Five-year risk of incident microvascular disease was 16.9% after bariatric surgery versus 34.7% with usual care: adjusted hazard ratio 0.41. The incidence of all three complications was lower in the bariatric surgery group: 4.9% versus 10.0% for nephropathy, 7.2% versus 21.4% for neuropathy, and 7.2% versus 11.2% for retinopathy. Hazard ratios were 0.41, 0.37, and 0.55, respectively. Nephropathy risk was initially higher in the bariatric surgery group, but declined rapidly and remained lower in years 1 through 7.

Previous studies have shown that bariatric surgery can induce remission of type 2 diabetes. The new study is one of the first to look at how surgical treatment for obesity affects the risk of diabetes-related microvascular complications.

The matched cohort study finds about a one-half reduction in the incidence of microvascular complications in the 5 years after bariatric surgery. Although this trend is driven mainly by a reduction in neuropathy, significant reductions in nephropathy and retinopathy are observed as well. The findings "should help patients and providers to better understand the potential tradeoffs of bariatric surgery as treatment of T2DM and help them to make more informed decisions about care," the investigators conclude [O'Brien R, et al. Microvascular outcomes in patients with diabetes after bariatric surgery versus usual care: A matched cohort study. *Ann Intern Med* 2018; DOI:10.7326/M17-2383].

Are you a fellow and 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

Early Programs

October 23 – 24, 2018

Take advantage of the Early Programs at Kidney Week 2018. These 1- or 2- day courses will be held October 23- 24 and address specific topics in nephrology.

This year's Early Program topics include:

- Acid-Base, Fluid, and Electrolyte Balance Disorders: Challenging Issues for Clinicians
- **NEW!** Advances in Research Conference: -Omics, Organoids, and Organs-on-Chips
- Clinical Nephro-Pharmacology Across the Spectrum of Kidney Diseases
- Critical Care Nephrology: 2018 Update
- Evaluation and Management of Kidney Stones
- Fundamentals of Renal Pathology
- Glomerular Diseases Update 2018
- Kidney Transplantation
- Maintenance Dialysis
- Polycystic Kidney Disease: Translating Mechanisms into Therapy

Visit www.asn-online.org/KidneyWeek for more details.

Proposed E/M Coding Changes Overshadow Other Fee Schedule, Quality Provisions

By David White

On July 12, 2018, the Centers for Medicare & Medicaid Services (CMS) released a combined proposed rule for the Physician Fee Schedule (PFS) and the Quality Payment Program (QPP) for performance year 2019. Led by its Quality Committee, the American Society of Nephrology (ASN) has been reviewing the proposed changes, meeting with peer societies and coalitions, and drafting comments and recommendations. Most readers will have heard about one particular aspect of the proposed changes: recommendations by CMS to simplify Evaluation and Management (E/M) coding documentation requirements with the stated goal of providing relief from regulatory burden for clinicians. CMS has characterized this and other recommended changes as part of the Department of Health and Human Services' high priority *Patients Over Paperwork* program.

The proposed changes to E/M coding and valuation begin with a stated approach of allowing physicians to justify the level of complexity of a visit based on medical decision-making or time involved, but the result is a valuation system that many ASN members have characterized as devoid of nuance for the gradation of care involved.

The proposed changes are hugely impactful—even by CMS' own account. As CMS wrote in the proposed rule, "In total, E/M visits comprise approximately 40% of allowed charges for PFS services, and office/outpatient E/M visits comprise approximately 20% of allowed charges for PFS services." ASN and other stakeholders have long maintained that many of the E/M documentation guidelines are administratively burdensome and outdated with respect to the practice of medicine and recently provided CMS with examples of such outdated requirements, which sap clinicians' time and contribute to burnout. The good news is that CMS has listened to similar concerns from ASN and virtually every medical specialty society and proposes to ease those requirements.

The bad news is that CMS is proposing to make those positive changes as part of a larger, deeply concerning proposal to collapse payments for E/M codes 2–5 into a single payment. CMS would leave reimbursement for E/M level 1 visits as is.

In its comment letter, ASN will oppose the proposed compression of reimbursement rates for E/M coding for levels 2–5 visits into a single reimbursement payment set. Specifically, CMS proposes to set the new, single payment around the current E/M level 3 payment. There will be one reimbursement rate for a new patient visit and one for an existing patient visit. This proposal reduces the reimbursement for the most complex patient encounters by $76 per visit for new patients and by $55 per visit for established patients, while reducing reimbursement for current level 4 visits by $32 and $16, respectively. ASN believes these proposed changes have many potential adverse consequences for patients and clinicians, particularly in nephrology. (Notably, the proposal does not affect the ESRD Monthly Capitated Payment.)

ASN has identified at least five areas of concern regarding the proposed E/M changes that would have negative implications for patients with kidney diseases:

1. Incentivizes non-patient centered care.
2. Reinforces the gap between cognitive and procedural care.
3. Disincentivizes CKD/preventive care.
4. Fails to account for critical patient care documentation needs.
5. Understates the impacts on nephrology practices, with reductions far higher than suggested by CMS.

Key to ASN's objections to the proposed changes is that in order to improve public health, nephrologists need to focus on efforts to slow the progression of kidney diseases, manage the complications of advanced kidney diseases, and optimally prepare patients for kidney failure, including preparations for dialysis, transplant, and conservative non-dialysis care. Kidney diseases affect more than 40 million people in the United States, with Medicare alone spending more than $33 billion (1) annually on its End-Stage Renal Disease (ESRD) program and over $103 billion (2) annually on all kidney diseases. This outlay does not include Medicaid, the Veterans Affairs Department, the Department of Defense, and private insurers.

Adjusting the E/M codes in the proposed manner has led to serious concern in the nephrology community. Many ASN members believe these efforts have historically been undervalued. The proposed PFS further disincentivizes clinicians from focusing on the complex, cognitive care that is required to slow the progression of CKD to dialysis and to optimally care for people who have received a kidney transplant.

Following are some of the other provisions of the proposed rule that were more welcome than the E/M payment reduction proposals:

- Paying physicians for their time when they reach out to beneficiaries via telephone or other telecommunications devices to decide whether an office visit or other service is needed.
- Paying for the time it takes physicians to review a video or image sent by a patient seeking care or diagnosis for an ailment.
- Eliminating the requirement to justify the medical necessity of a home visit in lieu of an office visit.
- Allowing practitioners to simply review and verify certain information in the medical record that is entered by ancillary staff or the beneficiary, rather than re-entering it.
- Starting in Year 3, permitting clinicians or groups to opt-in to MIPS if they meet or exceed one or two, but not all, of the low-volume threshold criteria.
- Liberalizing and expanding the rules for reporting methods and types in the QPP.
- Expanding MIPS-eligible clinicians to include physical therapists, occupational therapists, clinical social workers, and clinical psychologists.
- Weighting costs in MIPS at 15%, per congressional direction, instead of the original 30% weighting called for in the original MACRA legislation.

ASN will inform members of what CMS decides to include in the final rule due out this fall.

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Advocates from Kidney and Transplant Community to Visit Lawmakers in September

By Zach Kribs

On Thursday, September 27, 2018, a broad coalition of advocates representing patients and physicians from across the kidney and transplant community will meet with their lawmakers in Washington, D.C., to raise awareness of critical issues facing the kidney community as part of ASN's fourth Kidney Community Advocacy Day (KCAD).

Recognizing the need to bring to lawmakers greater awareness of kidney diseases and the burden they place on over 40 million Americans, KCAD presents an opportunity for a community diverse in perspectives to speak in a unified voice. This year, participants will attend from 15 organizations representing patients, as well as kidney and transplant physicians, and will bring three key messages to their congressional delegations: increase investment in kidney research at the National Institutes of Health (NIH), support innovation in kidney medicine, including KidneyX, and cosponsor the Living Donor Protection Act.

Advocates plan to build on the success of prior advocacy efforts to increase research funding and build support for innovation in kidney medicine. Last year, extensive work by advocates participating in KCAD and across the entire medical research community helped result in a historic $3 billion increase for NIH.

During KCAD, advocates plan to ask lawmakers for a $2 billion increase for NIH—an amount recently supported by the Senate in its final spending package—and draw attention to the groundbreaking research conducted at the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) like the Kidney Precision Medicine Project, which aims to bring precision medicine to the kidney space.

Advocates will also call on Congress to support innovation in kidney medicine, including KidneyX, a public-private partnership led by the Department of Health and Human Services to seed, incent, and accelerate breakthroughs to promising new therapies for people with kidney diseases. Despite the significant burden of kidney diseases, there has been a dearth of innovation in the kidney space compared to other areas of medicine. During KCAD, advocates hope to create a sense of urgency among lawmakers about the need for innovation in kidney medicine and show that the field is ripe for investment.

Finally, KCAD participants plan to keep pushing Congress to pass the Living Donor Protection Act. Designed to offer job security through the Family and Medical Leave Act and to prevent life, disability, and long-term care insurance plans from limiting or denying coverage to living donors, the legislation is a longstanding priority of the kidney and a transplant community. Advocates see passing the legislation as a key step in removing barriers to transplantation and to increasing access to a life-saving therapy.

Undergirding advocates' push during KCAD for congressional support of research and innovation is the uncertainty around the mid-term elections this fall. As races play out across the United States and Washington, D.C., prepares for a new Congress, maintaining the historic support for medical research and generating new enthusiasm among lawmakers—and new champions—is crucial. By participating in KCAD, advocates will demonstrate to Congress that the kidney community stands together in transforming care for the more than 40 million Americans living with kidney diseases.

Fellows Corner

A Fellow's Perspective
On Mentorship

By Samaya Qureshi

Samaya Qureshi

As my fellowship inches toward completion, a new path is on the horizon. With anticipation, I am ready to embark on a new academic career in nephrology.

I often reflect on the factors that have brought me to this point, including years of education and training. I know one thing for certain: I could not have arrived here without my mentors and their guidance.

I feel fortunate to have had several mentors, including family members, friends, and teachers. These extraordinary people entered my life at various points and shaped me into the person I am today. All my mentors, even with their differences, also share many similarities. They all lead by example. They are always available for questions or talks, whether related to work and education or personal matters. They always give me honest advice and feedback. They exemplify what it means to be a mentor. I hope to emulate them in the future.

The mentor–mentee relationship is invaluable in the field of medicine, where confidence in making decisions is a direct result of the mentee's having an experienced person available for consultation at critical moments.

At a time when interest in nephrology as a specialty is low and some fellowship programs remain vacant, it is up to those who love this field to inspire and motivate trainees and medical students in order to help shape their careers and futures. Personally, if it had not been for my amazing nephrology attendings during residency training, and their enthusiasm for teaching, love for the field, and constant encouragement, I might not have chosen nephrology. I can only hope to have the same impact on someone else in the future.

Recently, I had the privilege of attending the Women in Leadership workshop at the Renal Physicians Association Spring 2018 Meeting in Orlando, Florida. There, a group of mostly women, including fellows and those in established practices, gathered to hear the insights of great women in nephrology, including Eleanor Lederer, MD, Rebecca Schmidt, DO, and Ellie Kelepouris, MD. These leaders spoke about how they achieved success, and they named mentorship as one of the essentials to their success. They also noted the importance of mentorship for women by other women. When audience members were asked, "How many of you have female mentors?" only a few raised their hands compared with those who raised their hands when asked about having male mentors. This should serve as a motivation to women in the field to step up to the challenge of being a mentor but also to those seeking out mentors to reach out to women who can often provide different perspectives and experiences.

A June 2018 twitter chat about Women in Medicine uncovered several common themes participants considered key traits for mentors:

1. **Honesty.** Mentees look to their mentors for the hard truth that they cannot get from others and for advice to make them better physicians and guide them through their decisions.
2. **Availability.** Mentors must be available and open to questions. To this day, I can text, call, or email my mentors knowing I will always get a response no matter how long it has been since we last spoke or saw each other.

   Mentors may not always be available for hours at a time, but even a short text or email can do wonders. For example, after a particularly challenging call weekend at the start of my fellowship, my mentor from residency emailed me: "You are an awesome doc, special person, hang in there, a pleasure to work with you and train, now crush this fellowship thing!" His five short statements were just the calm voice amid the chaos I needed to get back to my goal.
3. **Motivation:** A mentor not only motivates through advice but also inevitably leads by example, and it is this example that mentees can rely on and try to emulate in their own careers.

Going forward, I can only hope to be able to mentor someone else in the same way my mentors have mentored me. To those of us graduating and moving on to our new respective careers, I hope we are encouraged to help those behind us, share our experiences, and hopefully propel the future generation to greatness.

So, if you have not done so already—especially for those just entering the field of medicine and nephrology—I encourage you to find a mentor. Better yet, find a few and hold on to them for life, as they will be the backbone to your future. On a personal note, I would like to thank all my mentors throughout nephrology fellowship. I hope that one day I might have the same impact on someone else that you have had on me.

Samaya Qureshi, MD, is a class of 2018 nephrology fellow at Baylor College of Medicine in Houston, TX.

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