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Single Cell Gene Expression Studies Reveal Kidney Clues

By Bridget M. Kuehn

A new genetic technique called single cell genetic sequencing is helping to reveal new insights about the cells that make up the kidney—insights that are essential to understanding what goes wrong in kidney disease and how it might be reversed.

Many types of cells make up the kidney, each with a distinct role in kidney health, making it a challenge for scientists to study. Traditionally, scientists have tried to distinguish these various cell types by their location in the kidney and appearance under a microscope, according to Katalin Susztak, MD, PhD, a professor of medicine at the Perelman School of Medicine at the University of Pennsylvania. But rapid advances in genetic techniques are giving scientists new tools for studying these cells.

Whole genome sequencing studies have allowed scientists to document an individual's entire genetic blueprint. Now the technology has advanced to allow scientists to look at which genes are turned on or off in individual cells.

"Every cell in your body has a full complement of DNA coding for approximately 21,000 proteins," said Mark Knepper, MD, PhD, a senior investigator at the National Heart, Lung and Blood Institute. "However, each cell expresses only around 6000 to 8000 of these genes."

Single cell RNA sequencing allows scientists to determine which 6000 to 8000 genes are turned on in each cell, which "provides a road map" for studying specific cell types, Knepper said.

"The single cell RNA sequencing approach and other next generation sequencing methods will provide essential information at a basic science level that will ultimately result in a better understanding of many renal diseases," Knepper said.

Emerging insights

A groundbreaking study by Susztak and colleagues using single cell sequencing identified several new types of cells in the kidney, and showed that some cells in the kidney can transition back and forth between two cell types to help the kidney adapt to changing conditions.

In their study, published in *Science*, Susztak and her colleagues took one kidney from seven different male mice and used droplet-based single cell RNA sequencing to analyze the gene expression in the more than 43,745 cells in each kidney. They used a special machine to connect each cell with a bead that is able to capture all the genes that are active in that cell. Then, they sorted the cells based on these genes. This method is far cheaper than previous RNA sequencing methods, costing just 10 to 20 cents per sample, Susztak said, compared with older tech-

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Has Momentum for Changes in MOC Shifted to Exam Boards?

By Eric Seaborg

As physicians and state medical societies continue to revolt against high-stakes maintenance of certification (MOC) tests and increased MOC requirements, more state legislatures have considered legislation to limit the use of MOC in professional requirements. This year, Tennessee and South Carolina became the fourth and fifth states to pass legislation restricting the use of MOC in areas such as licensure, reimbursement, employment, malpractice insurance, and insurance panel participation.

Legislation in more than a dozen other states died or languished in committee as the nexus for change may have shifted to the American Board of Medical Specialties (ABMS) and individual specialty boards, which are promising significant change.

"The leadership of the American Board of Internal Medicine has heard clearly that it must change," according to Jeffrey S. Berns, MD, chair of ABIM's nephrology board. ABIM will begin offering nephrologists and internists the option of replacing the 10-year test with an open-book every-two-year test in 2018.

And ABMS has announced a collaborative re-evaluation

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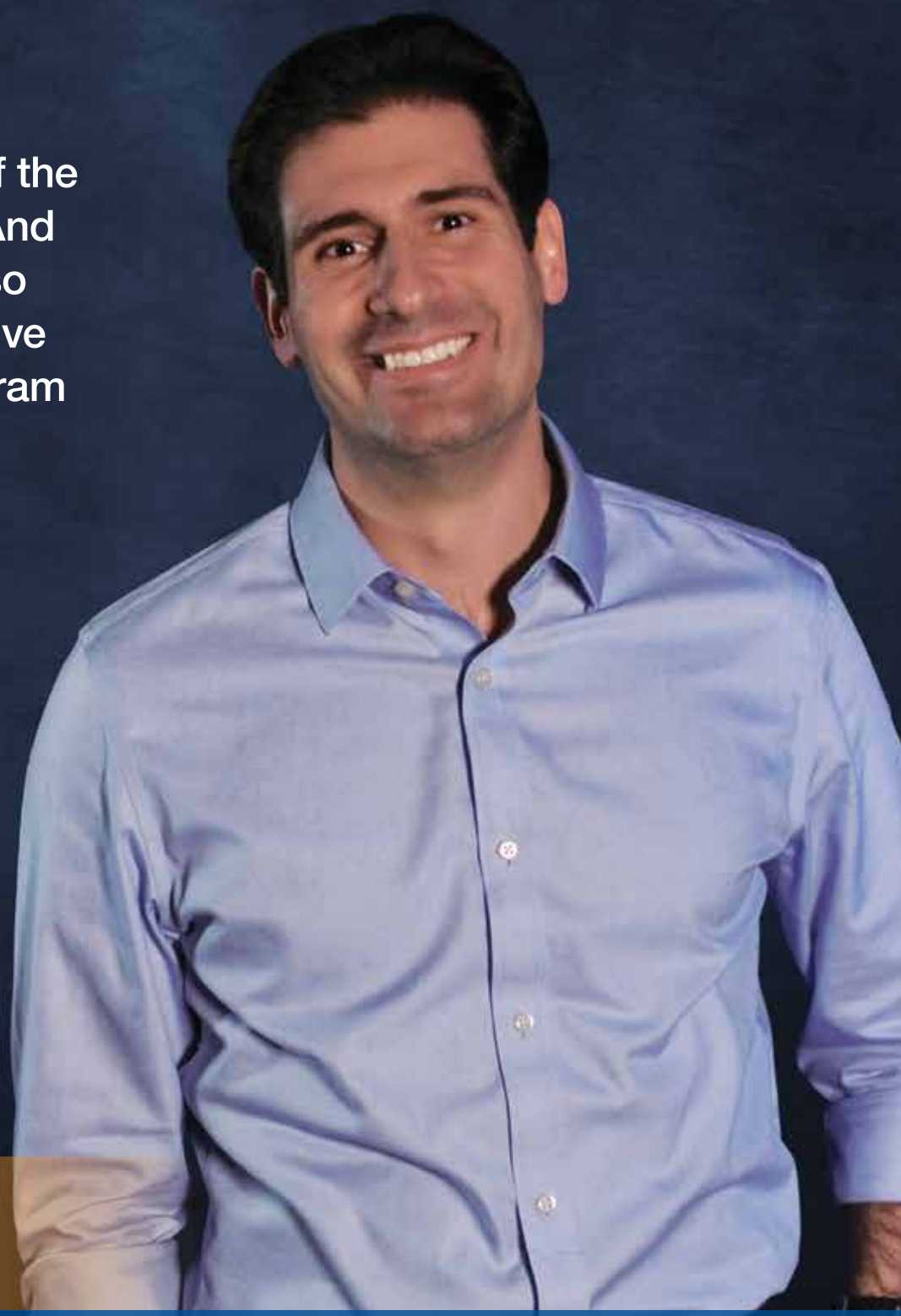
Juan Carlos Aycinena, MD



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Single Cell Gene Expression

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niques that could cost $300 for a single sample.

"Because the cost is much lower, we can actually sequence a large number of cells," she explained.

Another advantage of this approach is that it provides an "unbiased" way of grouping cells, she said. The approach classifies cells only on the genetic information being used in each cell instead of more superficial physical cell characteristics that might be shared by multiple types of cells. This allowed the researchers to discover that 1 of the 3 types of cells previously identified in the collecting duct of the kidney are actually just cells in transition from one type to another. These results reinforce findings from a previous study by Knepper and colleagues that had suggested a transitional cell type in the collecting duct.

"Both of us found hybrid cells that express markers of both principal cells and intercalated cells," Knepper said. "This finding adds to additional evidence from 'fate mapping' studies that principal cells may convert into intercalated cells. This is currently a hot area of research."

Scientists know that the collecting duct and its cells help balance salt, water, and acid–base levels in the body, according to Knepper. To keep up with changing demands, it appears the cells may be able to transition from being principal cells that transport water, sodium, and potassium to intercalated cells that regulate acid–base balance by transporting hydrogen ions.

"We think in healthy adult kidneys this type of interconversion happens on a regular basis to kind of balance the water and acid, but this interconversion also happens more profoundly in [kidney disease] where the kidneys might need to focus on water balance," said Rojesh Shrestha, BS, a research specialist in Susztak's laboratory.

Both Susztak and Knepper's studies also found that most principal cells in the collecting duct expressed the Notch2 gene, and that the gene for its receptor is expressed mostly by intercalated cells. This may help "explain how principal cells and intercalated cells are able to 'talk' with one another," said Knepper. It may also have clinical implications, noted Susztak, who explained that it might be possible to use treatments that manipulate these messages to intervene in diseases where the acid–base balance has gone awry.

The insights were just part of a huge amount of data generated in the study. Susztak and colleagues also showed that the genes for specific kidney diseases were expressed by just one type of cell. For example, genes linked with high and low blood pressure were traced to one type of cell. This insight may help scientists trying to pinpoint the cause of certain diseases. Susztak suggested this likely means that there is a very clear division of labor among kidney cells, and if one type of cell is not working properly, for example because of a gene mutation, the others do not pick up the slack.

The next step for Susztak's research will be to start cataloguing single gene expression in kidneys affected by disease to understand how gene expression changes. In the meantime, she hopes the data from her current study will help fuel other researchers' work.

"We generated the periodic table for the kidney, so now we know where all the elements in the kidney are," she said. "All the researchers who study kidney physiology or kidney homeostasis will be able to put the elements together and understand disease development, and how the kidney works under [healthy] conditions."

Clinical implications

Already some groups have begun to apply single cell sequencing techniques to samples taken from patients with kidney disease. For example, a network of researchers from the Accelerating Medicines Partnership studying rheumatoid arthritis and systemic lupus erythematosus recently used single cell gene sequencing to analyze 16 kidney and 12 skin tissue samples taken from patients with lupus nephritis during routine care. The National Institutes of Health, nonprofit groups, and industry are jointly funding the network with the aim of accelerating the development of new treatments.

The study provided a proof of concept that single cell RNA sequencing might reveal useful information from clinical samples. From just several millimeters of kidney tissue the investigators were able to glean important information that added on to earlier work with standard light and electron microscopy studies of biopsies. In addition to providing information that might help classify patients, the study suggested that the sequencing data might also hint at a patient's prognosis 6 months later.

"We're getting a remarkable amount of information which has direct clinical relevance," said Chaim Putterman, MD, chief of the division of rheumatology at Albert Einstein College of Medicine and Montefiore Medical Center, who was the co-principal investigator, along with Jill P. Buyon, MD, director of the division of rheumatology at New York University School of Medicine, and Thomas Tuschl, PhD, head of the Laboratory for RNA Molecular Biology at Rockefeller University in New York.

Putterman said that if other larger studies confirm the potential prognostic value of single cell RNA sequencing, it might encourage physicians to intensify initial treatments for patients exhibiting molecular predictors of a more aggressive disease.

The researchers also did single cell sequencing on skin cells collected from patients with lupus to see if it might provide useful information about the progression of the disease. Putterman explained that kidney biopsies are critical to assessing patients with lupus nephritis, but its invasive nature together with the potential risks associated with the procedure limit how many times it can be repeated. Skin cells could be more easily and safely collected over time. The study showed that some of the same lupus-linked genetic changes occurring in kidney cells may also be seen in skin cells.

"If we can use the skin to reflect what's happening in the kidney, that would be a major advance forward," Putterman said.

While single cell sequencing is an enormously promising technique and will likely lead to many new insights in nephrology research, Knepper was cautious in his assessment of the clinical potential of the technique. He noted there are still many practical issues that would have to be resolved before such technology could be used in the clinic. For example, it's difficult to apply to glomerular cells, although some groups are working to solve this problem, he said. It's also not clear whether the process itself might alter gene expression in the cells or if the genes expressed by cells in isolation are the same ones expressed by cells in the kidney that may be interacting with neighboring cell types.

"That kind of thing limits the potential direct clinical use," Knepper said. "This is predominantly a research method. With present technology, I don't see this being applied directly to a patient admitted to the hospital. But the information the technique provides is marvelous and unique."

Jihwan Park, et al. Single-cell transcriptomics of the mouse kidney reveals potential cellular targets of kidney disease. *Science* 2018. DOI: 10.1126/science.aar2131

Changes in MOC

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called the Vision Initiative commission, with the task "to provide a set of recommendations about the future of continuing board certification for consideration by ABMS."

Rebellion brews at AMA

The movement for change has been building for years, according to Donald J. Palmisano Jr., JD, executive director and CEO of the Medical Society of Georgia, which successfully pushed for MOC-limiting legislation last year.

"The physicians had reached their limits with the high-stakes exam, and they felt frustrated by the fact that nobody was really listening to them. They had complained to their boards and their boards were not responding," Palmisano said. "The physicians themselves got active and got their message across, and the boards are responding now. They understand that there are some challenges and they are trying to fix them."

Palmisano said that one turning point came at last year's American Medical Association (AMA) meeting when the CEOs of the American College of Obstetricians and Gynecologists and the American Academy of Neurology suggested that state medical societies and national specialty societies should work together toward reform to avoid creation of a patchwork of state laws regulating MOC. Their organizing led 41 state medical societies and 33 national medical specialty societies to send a letter on August 18, 2017, to ABMS stating that "concerns regarding the usefulness of the high-stakes exam, the exorbitant costs of the MOC process, and the lack of transparent communication from the certifying boards have led to damaging the MOC brand" and a "crisis" that needed to be addressed.

The letter proposed a meeting of the leadership of ABMS certifying boards, national medical specialty societies, and state medical societies on Dec. 4, 2017, the day before the ABMS and Council of Medical Specialty Societies dyad meeting in Illinois. A summary of that meeting noted that representatives from state medical societies "articulated the anger and distrust of physicians about the boards and a shared perception that the boards are dominated by academics and executives who have lost touch with the needs of the community physician."

ABMS envisions changes

During the meeting, Lois Margaret Nora, MD, JD, MBA, then the president and CEO of ABMS, called upon the state medical societies "to hold back on further legislative action to professional self-regulation, allow the boards to work within the profession to make positive and appropriate change, and to eliminate unintended consequences including public confusion and loss of faith in the profession." She announced the recently launched "Continuing Board Certification: Vision for the Future" initiative as an opportunity to involve state medical societies and other stakeholders in envisioning a revamped MOC process.

The initiative will be led by a 34-member commission that includes physicians and representatives of "professional medical organizations, national specialty and state medical societies, hospitals and health systems, the general public and patients, and the 24 member boards of ABMS," according to the initiative's website. At its first gathering, a two-day meeting in March 2018, "Commission members heard testimony on continuing certification from a wide range of stakeholders from the medical profession, including practicing physicians, ABMS member boards, medical associations and professional societies, as well as those representing the public perspective."

The commission will hold four such meetings around the country before releasing a draft report for comment in November 2018, with final recommendations due to ABMS in

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February 2019.

Some specialty society leaders at the December meeting expressed suspicion that the commission could be a delaying tactic. But the Medical Society of Georgia's Palmisano—who was selected to be a member of the commission and attended its first meeting—said he is "cautiously optimistic that the concerns of the physicians are going to be addressed."

Checking in with nephrology

ABMS has said that all its boards are already implementing changes to "make their programs more convenient, supportive, relevant, and cost-effective," and this includes ABIM, which is introducing an option to replace the 10-year exam. Internal medicine and nephrology will be the first specialty and subspecialty to be offered this shorter test option, called the Knowledge Check-In, beginning in 2018.

The Knowledge Check-In can be taken every two years; can be taken at home, work, or a test center; is an open book test, using UpToDate® as the permitted reference; and is offered four to six times a year. It is much shorter than the 10-year test, lasting three hours at most. A failed exam will not lead to loss of certification. Physicians will be able to take the test again two years later.

"The two-year Knowledge Check-In should be lower stress and certainly lower stakes, because you cannot lose your board certification by not doing well on one of these," Berns said. He said that the nephrology board has been working on adjusting its exam blueprint and honing the relevance of its questions for years. "Nephrology is actually fortunate … to be the first subspecialty to be included in the Knowledge Check-In. It is because we had such a good exam pool, both in terms of quality and numbers of questions that could be rolled into this new format."

But the approach is still a summative, pass-or-fail test rather than a formative process more aimed at learning, according to Charles Cutler, MD, an internist and former president of the Pennsylvania Medical Society, who has been a critic of ABMS' MOC system. Cutler has also been appointed to the Vision Initiative commission.

Anesthesiologists lead the way

Cutler and other reformers often cite the American Board of Anesthesiology for successfully introducing a formative process by dropping its every-10-years recertification test and replacing it with regular online tests and learning modules called the MOCA (Maintenance of Certification in Anesthesiology) Minute. "MOCA Minute allows you to continuously assess your knowledge, fill knowledge gaps and demonstrate your proficiency," according to the board's website. The process is ongoing, with participants required to answer 30 questions each quarter of the year.

"The American Board of Anesthesiology polled their diplomates and asked whether they like this system or the test. Some 80 or 85% of the doctors said, 'We like this new system. You are making us better with this,'" Cutler said.

Jin Soo Kim, ASN senior director of education, agrees that the Knowledge Check-In in its current form is a high-stakes, summative approach that does not fully address ASN's concerns. ABIM is working with three of the larger specialty societies to develop alternatives to the summative exam, but has not yet offered the same opportunity to smaller societies.

Cutler said he has been told by the leadership of other boards that they are "moving away from a summative process and going to a sequential formative process of identifying gaps in physicians' knowledge and filling in those gaps."

Kim also noted that many nephrologists have a specific focus, such as interventional nephrology, but the nephrology MOC exams cover the entire field, which will contain many questions not relevant to their practices. In contrast, cardiologists, for example, can choose among exams focusing on five subspecialties. "We've been told that ABIM is open to exploring modularity in the future," she said.

Kim said that although the test will be open-book, UpToDate® will be the only resource currently, despite the fact that specialty societies offer resources such as ASN's Kidney Self-Assessment Program (KSAP). ABIM has indicated that this limitation has to do with technical issues and costs, but is open to adding more resources in the future.

Legislative efforts continue

Many state medical societies and legislators remain dissatisfied with the pace of change. According to a compilation from ABMS, 17 bills introduced or pending in state legislatures prohibit the state licensing board from requiring MOC for licensure, 16 prohibit use of MOC by health plans for reimbursement, and 15 prohibit requiring physicians to participate in MOC for hospital privileges, credentialing, reimbursement, and employment. The great majority of this legislation died or is languishing in committee.

ABMS has put resources into fighting the legislation on the grounds that it undermines the traditional professional commitment to self-regulation, the standards for specialty certification, and public confidence in ABMS board certification.

Even proponents of the legislation acknowledge their hesitation about involving the government in physician self-regulation. Frank McDonald Jr., MD, MBA, a neurologist who is president of the Medical Association of Georgia, said that it is a "slippery slope" to get the state government involved in physicians' affairs, but his association turned to the legislature because the membership was "very frustrated" by the specialty boards adding requirements to MOC without listening to physicians' concerns.

"Everywhere I go, I talk about what the Medical Association of Georgia is doing," CEO Palmisano said. "This is one issue that unites physicians across the board. Everybody in the country is feeling the same way, that physicians weren't being listened to. Even the ones that have had a good experience with their board and their MOC still get concerned that it could maybe go in a bad direction at one point. They want to make sure that doesn't happen." ■

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ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

Patients at the Center

Kidney Health Initiative Holds Sixth Annual Stakeholders Meeting

By Zach Cahill

Urgency and innovation are frequent themes in the kidney community. The Kidney Health Initiative (KHI) holds an annual meeting to translate these themes into reality. A public-private partnership with the U.S. Food and Drug Administration (FDA) and over 90 companies and organizations from various stakeholder groups in the kidney community, KHI was established to spur innovation and enhance patient safety.

Patients took center stage at the 2018 KHI Stakeholders Meeting, held in Silver Spring, MD, May 14–15. Each session at the meeting included a patient or care partner who provided the patient perspective on the session topic. Their personal stories and experiences highlighted the collective sense of urgency and communicated the need for advances in therapies for people living with kidney diseases.

KHI values the input of patients by integrating them into every aspect of the initiative. They serve on the KHI Board of Directors and in project workgroups. In 2015, KHI formed the Patient and Family Partnership Council (KHI PFPC), which is made up of 10 patient and care partner advocates representing different therapies and kidney diseases.

"Has there been enough progress? No."
—Pamela Duquette, KHI PFPC member

Pamela Duquette, a member of the KHI PFPC, described her daughter's 14-year journey with focal segmental glomerulosclerosis (FSGS) during the opening session. Duquette expressed the fear that comes from being a parent of a child who has a disease without a cure. She described the exhausting hospitalizations, debilitating side effects, and fear of infection that come with treating the disease. Her daughter received a living donor transplant that dramatically improved her life and opened the door to school and a social life. Duquette knows the transplant will not last forever and is hopeful for new innovations in the future.

"We are grateful for the progress that has been made, but [my daughter] asks for more, not just for her but for others," Duquette said.

KidneyX, a new public-private partnership between the U.S. Department of Health and Human Services (HHS) and the American Society of Nephrology, could provide the progress Duquette and other patients and caregivers seek. KidneyX will launch a pilot prize competition around next generation dialysis to provide seed funding to companies that are creating innovations to improve patients' lives and disrupt the market for potential new therapies for kidney diseases.

KidneyX seeks to accelerate innovation by providing non-dilutive funds to innovators, and by coordinating the various agencies within HHS to accelerate new products, said Bruce Greenstein, HHS Chief Technology Officer. The hope is that innovators and entrepreneurs will receive the funding and approval support from HHS to accelerate new therapies into the hands of clinicians and people living with kidney diseases.

It sometimes takes a long time for an idea to make it through the regulatory process and ultimately start benefiting patients. From the perspective of the FDA, it not only takes time to get new drugs, devices, and therapies approved, but many more years to develop best practices for a new treatment.

The wait time is too long for people living with any disease, according to Janet Woodcock, MD, Director of the FDA Center for Drug Evaluation and Research and keynote speaker at the KHI Stakeholders meeting. Woodcock said consortia like KHI can be effective in moving the needle on innovation and shortening the translation time for new discoveries. She noted that each stage in the approval process can be improved when consortia bridge the gaps and bring together all the important players in the field. KHI can help the translation process in many ways by developing frameworks to track the natural history of a disease, acceptable trial designs and endpoints, and patient-reported outcomes.

"When I first heard of the artificial kidney, my first thought was my wait for a kidney is over."
—Caleb Davy, 16-year-old kidney patient on dialysis for seven years

Caleb Davy has battled kidney diseases his entire life and has been waitlisted for a kidney for seven years. He spoke of the realities of life on dialysis: his four vascular access surgeries, the fluid limitations of only being able to drink a liter a day, and the emotional toll of waiting for a kidney for the past seven years.

Yet he also described the hope he felt when he first heard of the artificial kidney. He called on the researchers and innovators present at the meeting to develop and obtain approval for an artificial kidney. Patients understand that innovations take time, Davy noted, but "if patients must wait, researchers and innovators must persevere to overcome barriers and create results."

Work is ongoing across fields and around the world to develop alternatives to renal replacement therapy. The KHI Renal Replacement Therapy (RRT) Roadmap project seeks to capture the scientific, technical, and regulatory milestones required to develop a viable replacement for dialysis. The RRT Roadmap will help to identify the challenges, design requirements, and scientific priorities to link with fundable projects through programs such as KidneyX.

"What we don't take seriously enough is the timeframe for patients."
—Murray Sheldon, MD, Associate Director of Technology, FDA

Karin Hehenberger, MD, PhD, type 1 diabetic and pancreas and kidney transplant recipient, spoke to KHI members about the sense of isolation she has felt as a patient. After being diagnosed with type 1 diabetes at age 14, Hehenberger tried to live a normal life, but ultimately realized that she was hiding her diabetes because she didn't think others would understand. After earning her medical degree and working in industry, Hehenberger realized there was another way to live with her disease and provide purpose to many others. She founded Lyfebulb to foster patient entrepreneurs—individuals living with a disease who influence product design or develop innovative products—by connecting them with industry or sources of capital. Hehenberger encouraged KHI members to engage with people living with kidney diseases so that products are truly patient-centered and patients can become empowered to live fully and avoid the isolation she experienced.

"I didn't know my options for treatment and I have never been asked to participate in a research trial."
—Vanessa Evans, home hemodialysis patient and Patient Manager with NxStage

The KHI meeting concluded with a strong call to action from Vanessa Evans. As an individual who has worked in industry and lived with kidney failure, she called on KHI members to help stop the progression to kidney failure. She shared her personal story and interest in seeing more therapies developed to help patients earlier.

"By intervening earlier, patients can be more prepared for dialysis or request preemptive transplants," Evans said. "Patients need to know the options for RRT, including peritoneal dialysis and home hemodialysis." When asked if she had the opportunity to participate in a clinical trial, she stated, "I have never been asked, but would gladly enroll. Patients want to help. We just need to ask them to be involved and support their partnership."

With more than 150 attendees, the Sixth Annual KHI Stakeholders Meeting was the largest in KHI history, providing an opportunity for representatives from industry, government agencies, researchers, patients and care partners, and clinicians to network and build relationships that will create collaboration and innovation. The meeting provided hope for new and innovative solutions to improve lives for people with kidney diseases.

Video and audio recordings of the KHI Sixth Annual Stakeholders Meeting are available on the KHI website at www.kidneyhealthinitiative.org

Zach Cahill is Marketing and Communications Specialist, Kidney Health Initiative.

ASN-FDA Collaboration Takes on Rare Kidney Disease

Patients, Industry, and Clinicians Work to Find Surrogate Endpoints for Hyperoxaluria Clinical Trials

By Bridget M. Kuehn

Kristi Ouimet is hopeful her 15-year-old daughter will be admitted into a clinical trial of an experimental treatment for hyperoxaluria, a rare kidney condition that causes formation of painful and even life-threatening kidney stones. If she is enrolled in the trial, it will require a monthly commute from California to Minnesota for 2 years. But she's not deterred. She's already managed 2 years of a 6-day-per-week commute for 4 hours of daily dialysis plus 7 days a week of peritoneal dialysis for her younger son, who is also affected by hyperoxaluria and required a kidney and liver transplant.

"[If] driving all through snowstorms in Minnesota is going to prevent her from having to experience what my son did, I'm there," Ouimet said in an interview with *Kidney News*.

Ouimet and other patient advocates shared their perspectives about the disease and the need for treatment options at a February 2018 workshop convened by ASN's Kidney Health Initiative (KHI). KHI is partnering with the US Food and Drug Administration (FDA) and other stakeholders to pave the way for development of new treatments or the repurposing of existing medications to treat kidney diseases. Hyperoxaluria is one of the first rare diseases that KHI has set its sights on. The goal is to help identify clinical trial endpoints and designs that pharmaceutical companies or researchers can use to test potential new therapies.

"We like to work on projects where there's a clear need and then there's also kind of a clear opportunity," said Melissa West, project director for KHI. Companies are interested in producing medications for hyperoxaluria, but one of the hurdles is finding ways to measure if their treatments are working in clinical trials, she said.

"A ticking time bomb"

Due to a missing liver enzyme, patients with primary hyperoxaluria have too much of the chemical compound oxalate in their urine, according to the Oxalosis & Hyperoxaluria Foundation. Oxalate is found in certain foods of plant origin, and most people are able to efficiently eliminate it through urine. But in people with hyperoxaluria, too much oxalate builds up and causes the formation of kidney stones and kidney damage.

"This is not your common kidney stone," explained the Oxalosis & Hyperoxaluria Foundation's Executive Director Kim Hollander. The stones form very frequently and they can be so large they must be surgically removed. Patients often require urgent medical attention with little warning.

"Although patients look fine from the outside, inside they're like a ticking time bomb, and we just don't know when it's going to go off," Hollander said.

Patients often face numerous surgeries to remove kidney stones, and the procedures and the stones themselves can damage their kidneys, Hollander said. Eventually, many patients with severe forms of hyperoxaluria face kidney failure. But the course of the disease is unpredictable. For example, Ouimet's daughter had her first kidney stone at 3 years old and wasn't diagnosed with primary hyperoxaluria until she was 5. She has had frequent surgeries since then to remove kidney stones. Ouimet's youngest son was diagnosed via genetic testing while she was still pregnant with him. Despite her and her doctor's awareness and monitoring of the condition, he went into kidney failure at just 5 months old.

"My children presented so completely opposite of each other, same environment, same parents, same everything," Ouimet said.

There are also different types of hyperoxaluria. Primary hyperoxaluria, which affects 1 to 3 individuals out of a million people, is caused by genetic variations in one of 3 enzymes that are important in the production of oxalate by the liver, said Dawn Milliner, MD, a nephrologist at the Mayo Clinic's Hyperoxaluria Center and principle investigator for the Rare Kidney Stone Consortium. The severity of the disease may vary based on which of the three enzymes is affected. Some people develop enteric hyperoxaluria as a complication of another condition. For example, Crohn's disease or gastric bypass surgery may cause individuals to absorb too much oxalate from their food.

Limited treatment options

Despite how serious the disease is, treatment options are limited. Physicians have found ways to better manage patients' symptoms, Milliner said. For example, patients can substantially increase their water intake to help prevent the formation of stones, and some can benefit from limiting oxalate in their diet, she said, but both are hard to maintain long term. About one-third of patients with primary hyperoxaluria type 1 (PH1) benefit from prescription strength doses of pyridoxine or vitamin B6, Hollander said.

"We're trying to blunt the effects of the hyperoxaluria," Milliner said. "We can slow it down, we can modify it, but nothing we have in our current armamentarium aside from the pyridoxine or transplantation really gets at the root of the problem and reduces the oxalate burden."

A liver and kidney transplant can correct metabolic defects that cause a buildup of oxalate, but it comes with its own set of complications, including the need for lifelong use of immune suppressive drugs, said Milliner.

"Transplant is highly valuable where it's needed, but none of us feel that's the best long-term option," she said. Recently, promising new treatments have been identified that are now ready to be tested for both effectiveness and safety in hyperoxaluria patients, Milliner said.

Finding consensus

The KHI workshop brought together patients, clinicians, FDA staff, and pharmaceutical companies to reach a consensus on how to best test new therapies. That starts with understanding patients' needs, according to Hollander.

"The patients are looking to make sure their kidneys stay healthy for as long as possible," Hollander said.

Given the high burden of existing treatments, and the anxiety of worrying about kidney failure, patients and caregivers at the workshop expressed a willingness to accept potential risks associated with clinical trials, said Jennifer Lawrence, a physician who has a son with hyperoxaluria. The Oxalosis & Hyperoxaluria Foundation is hoping to reach out to other patients and caregivers to find out their level of risk tolerance for trials.

Another goal is to design clinical trials that rigorously assess the safety and efficacy of potential kidney-preserving therapies. One challenge is deciding how to measure a treatment's success. Kidney failure, the need for dialysis, or death are accepted ways to measure a drug's effects. But trials using these endpoints would not be feasible because they would have to test very large numbers of patients and last for years because of hyperoxaluria's variability among patients, Milliner noted. Assessing the development of kidney stones might be another endpoint, but the only reliable way to know if stones are forming would be to subject patients to multiple radiographic examinations, Milliner said. So, the KHI project is hoping to identify surrogate endpoints that can tell whether a treatment is providing a benefit to patients in a much shorter timeframe.

"Identifying a surrogate endpoint will allow us to look for a substitute for the progression of the disease since it takes so long for kidney failure to potentially show up," West said.

To do this, the KHI project will tap data collected in US and international registries of patients with hyperoxaluria to try to identify factors that predict disease progression, West said. One promising surrogate endpoint might be to measure whether a treatment lowers urinary or plasma oxalate levels.

"What we all are struggling with is how much you have to reduce those [levels] so the patients feel better and survive better," said Elisabeth Lindner, MS, MBA, chief operating officer of OxtheraAB, which is developing a drug for primary hyperoxaluria that would dissolve crystals in the kidneys and hopefully stop the formation of kidney stones. She noted that there are at least 3 other companies working to develop drugs that would decrease the production of oxalate.

One of the strengths of KHI in tackling these challenges is that the project brings the FDA into the conversation early in the process to ensure that surrogate endpoints would be accepted for drug marketing applications, West said. The project will also look to developing post-marketing safety studies that would be used to verify the safety and efficacy of new drugs over the longer term, West noted.

"The regulators at FDA on the medical side are very interested in joining these conversations and being helpful," West said. "They still do require the evidence has to be there to support the decision to use a surrogate endpoint, but they're very collaborative."

Working together and developing a consensus around surrogate endpoints will also help advance the scientific understanding of hyperoxaluria, said Tracy McGregor, MD, MSCI, director of clinical research at Alnylam Pharmaceuticals in Cambridge, Massachusetts. Alnylam is developing a drug for primary hyperoxaluria that uses RNA interference to reduce the production of oxalate.

"Everyone brings a different perspective and we can all learn from each other," McGregor said.

Differences in Pre-ESRD Care for VA versus Medicare Patients

Older veterans receiving pre-ESRD nephrology care in the Department of Veterans Affairs (VA) healthcare system have a lower rate of dialysis initiation—and lower mortality—than those receiving pre-ESRD care via Medicare, reports a study in *JAMA Internal Medicine*.

Using data from the VA, Medicare claims, and the US Renal Data System, the researchers identified 11,215 veterans aged 67 years or older who developed kidney failure from 2008 through 2011. Nearly 99% of patients were men; mean age was 79 years. Within 2 years after diagnosis of kidney failure, 63.0% of patients initiated dialysis and 47.1% died.

Dialysis initiation was more likely for patients receiving pre-ESRD care via Medicare: 82% versus 53%, with an adjusted risk difference of 28 percentage points. The differences persisted on analysis of patients with at least two pre-ESRD visits and those with sustained estimated glomerular filtration rate of 15 mL/min/1.73 m^2 or less. The difference in dialysis use was greater among patients aged 80 or older and those with dementia or metastatic cancer and less in those with paralysis.

Veterans receiving pre-ESRD care in Medicare had a higher 2-year mortality rate: 53% versus 44%, adjusted risk difference 5 percentage points. The outcome differences were similar on analysis of propensity score-matched groups of 2966 veterans who received pre-ESRD care in the VA system versus Medicare.

Differences in nephrology care before the development of ESRD may affect decisions about initiating dialysis. Most older veterans eligible for care in the VA healthcare system are also eligible for Medicare.

The new analysis shows differences in 2-year outcomes for older veterans treated in the VA system versus Medicare. "Default" treatment with dialysis under Medicare does not appear to lead to better overall survival. The investigators conclude, "The VA's integrated health care system and financing appear to favor lower-intensity treatment for kidney failure in older patients without a concomitant increase in mortality" [Tamura MK, et al. Dialysis initiation and mortality among older veterans with kidney failure treated in Medicare vs the Department of Veterans Affairs. *JAMA Intern Med* 2018; 178: 657–664].

Higher Rate of AKI with Restrictive Fluid Policy for Abdominal Surgery

In patients undergoing major abdominal surgery, a restrictive fluid policy leads to an increased rate of acute kidney injury compared to liberal fluid therapy, while other outcomes are similar between groups, reports a study in *The New England Journal of Medicine*.

The "Restrictive versus Liberal Fluid Therapy in Major Abdominal Surgery" (RELIEF) trial included 3000 patients considered at increased risk of complications while undergoing major abdominal surgery. High-risk criteria included age 70 or older, heart disease, diabetes, renal impairment, and morbid obesity. The patients, enrolled at 47 centers in 7 countries, were randomly assigned to restrictive or liberal intravenous fluid regimens. One-year disability-free survival was compared between groups, along with a range of secondary outcomes.

Modified intention-to-treat analysis included 1490 patients assigned to the restrictive fluid strategy and 1493 to the liberal strategy. During surgery and up to 24 hours afterward, median IV fluid totals were 3.7 versus 6.1 L, respectively. There was no significant difference in disability-free survival at 1 year: 81.9% with the restrictive strategy and 82.3% with the liberal strategy.

Acute kidney injury, defined according to KDIGO criteria, was significantly more frequent in the restrictive fluid group: 8.6%, compared to 5.0% with the liberal fluid strategy. Rates of some other secondary outcomes were higher with the restrictive strategy: 2.18% versus 19.8% for septic complications or death, 16.5% versus 13.6% for surgical-site infection, and 0.9% versus 0.3% for renal replacement therapy. However, these differences were not significant after adjustment for multiple comparisons.

A restrictive intravenous fluid strategy has been recommended for enhanced recovery after abdominal surgery. However, there are questions about the evidence behind this recommendation, and concern that it could lead to impaired organ perfusion.

The pragmatic RELIEF trial shows similar disability-free survival with restrictive versus liberal fluid therapy for high-risk patients undergoing major abdominal surgery. However, the restrictive strategy is associated with a significant increase in acute kidney injury.

"[W]e found that restricting intravenous-fluid administration with the aim of zero balance increased the risk of acute kidney injury," the researchers write. They believe their findings show that "a regimen that includes a modestly liberal administration of fluid is safer than a restrictive regimen" [Myles PS, et al. Restrictive versus liberal fluid therapy for major abdominal surgery. *N Engl J Med* 2018; DOI: 10.1056/NEJMoa1801601].

Higher FGF23 Predicts Greater Increases in BP with Aging

In young to middle-aged adults, higher fibroblast growth factor-23 (FGF23) levels are independently associated with rising blood pressure levels over time, according to a report in *Hypertension*.

The analysis included data on a multiethnic cohort of 1758 adults participating in the Coronary Artery Risk Development in Young Adults (CARDIA) study. All were free of hypertension or cardiovascular disease when participating in year 20 follow-up examination. At that time, the subjects' mean age was 45 years—about 58% were women, and 40% were black.

Levels of C-terminal FGF23 at year 20 were analyzed for association with longitudinal BP levels and hypertension at years 25 and 30. Hypertension was defined as being on antihypertensive drugs and/or BP levels of 130/80 mm Hg or higher.

Incident hypertension occurred in 35.2% of subjects. In multivariable models, subjects with higher FGF23 levels had greater increases in BP. For the highest compared to lowest FGF23 quartile, increases in systolic BP were +2.1 mm Hg from year 20 to 25 and +2.2 mm Hg from year 25 to 30. Being in the highest quartile of FGF23 was also associated

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Higher FGF23

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with a greater increase in diastolic BP from year 20 to 25: +1.6 mm Hg.

Relative risk of developing hypertension during follow-up was 1.45 in the highest quartile of FGF23, compared to the lowest quartile. Overall incidence of hypertension was higher in black than white participants: 47.7% versus 27.8%. Although black participants and women were more likely to be in the highest quartile of FGF23, the association with incident hypertension did not vary by race or sex. There was also no difference based on underlying kidney disease, which was present in only a small percentage of subjects.

Higher FGF23 levels have been linked to worse cardiovascular outcomes. The association of FGF23 with longitudinal increases in blood pressure, or with the increased prevalence of hypertension in black Americans, has been unclear.

These CARDIA study results suggest that higher FGF23 levels are associated with rising blood pressure over time, as well as with an increased incidence of hypertension. Higher FGF23 does not appear to explain the higher rate of incident hypertension among black compared to white participants. The researchers conclude, "FGF23 could have a clinical role as a novel marker in helping to identify individuals at higher risk of developing hypertension, beyond known risk factors" [Akhabue E, et al. FGF23 (fibroblast growth factor-23) and incident hypertension in young and middle-aged adults: the CARDIA study (Coronary Artery Risk Development in Young Adults). *Hypertension* 2018; https://doi.org/10.1161/HYPERTENSIONAHA.118.11060].

Ambulatory BP Beats Clinic BP for Mortality Prediction

Ambulatory blood pressure measurements are a consistently better predictor of mortality than clinic BP measurements, concludes a study in *The New England Journal of Medicine*.

The study included 63,910 adult primary care patients enrolled in the national Spanish Ambulatory Blood Pressure Registry from 2004 through 2014. Clinic and 24-hour blood pressure measurements were compared for associations with all-cause and cardiovascular mortality. The researchers also analyzed mortality associations for specific hypertension phenotypes: sustained hypertension (both clinic and ambulatory BP elevated), "white-coat" hypertension (elevated clinic but normal ambulatory BP), masked hypertension (normal clinic but elevated ambulatory BP), and normal BP by both measures.

Fifty-eight percent of cohort members were men; the mean age was 58 years. With a median follow-up of 4.7 years, the analysis included 3808 deaths from any cause and 1295 from cardiovascular causes. In a model including both sets of measurements, 24-hour systolic BP was more strongly associated with all-cause mortality compared to clinic BP: adjusted hazard ratio (HR) 1.58 versus 1.02 per 1-standard deviation increase, respectively. For nighttime and daytime ambulatory systolic BP, adjusted HRs were 1.55 and 1.54, respectively.

Associations with ambulatory BP remained stronger in subgroup analyses by age and sex, obesity, cardiovascular disease, and antihypertensive therapy. By phenotype, the association with all-cause mortality was stronger for masked hypertension (HR 2.83) compared to sustained or white-coat hypertension (HR 1.80 and 1.79, respectively). Cardiovascular mortality showed similar patterns of associations with BP measures.

Based on limited data, ambulatory BP measurements are thought to better predict health outcomes compared to clinic and home measurements. These data from a Spanish national registry show that ambulatory BP measures are more strongly associated with all-cause and cardiovascular mortality compared to clinic-measured BP.

The study also lends insight into the outcomes associated with various BP phenotypes defined by ambulatory and clinic BP. The authors conclude, "White-coat hypertension was not benign, and masked hypertension was associated with a greater risk of death than sustained hypertension" [Banegas JR, et al. Relationship between clinic and ambulatory blood-pressure measurements and mortality. *N Engl J Med* 2018; 378:1509–1520].

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FOR YOUR CKD PATIENTS

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

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Why So Many Kidneys Are Discarded: An Analysis of 36,700 Discards

Discarded and transplanted deceased-donor kidneys overlap considerably in quality, with many potentially transplantable organs being discarded, suggests a study in *Kidney International*.

Using the Scientific Registry of Transplant Recipients, the researchers identified 212,305 deceased-donor kidneys recovered for transplantation between 2000 and 2015. Of these, 36,700 kidneys were discarded: a rate of 36.7%. Reasons for organ discard were analyzed, along with associated donor- and organ-related factors. The quality of transplanted and discarded organs was compared using the Kidney Donor Risk Index and the Kidney Donor Profile Index.

Three-fourths of discarded kidneys were bilateral discards. The most common reason for discard was "biopsy findings" (38.2%); others included inability to locate a recipient (14.6%), "poor organ function," (9.6%), and "other" (16.3%). Discarded kidneys had a higher median Kidney Donor Risk Index, 1.78 versus 1.12, but there was large overlap in scores between discarded and transplanted kidneys.

Discard was more likely for kidneys from donors who were black, obese, diabetic, or positive for hepatitis, and from donors with multiple unfavorable characteristics. Unilaterally discarded kidneys—which accounted for 21.5% of all discards—were from donors with the most desirable characteristics. The transplanted partner kidneys from these donors had good outcomes, with 1-year death-censored survival of over 90%.

The likelihood of discard showed considerable geographic variation, with increased odds of discard for organs recovered in the Southeast, Southwest, and part of the Midwest region.

The number of deceased-donor kidneys that are recovered but subsequently discarded has been rising steadily in the United States. The factors associated with this trend are unclear.

The new analysis confirms the significant overlap between kidneys that are transplanted versus discarded. Although some discards are inevitable, the researchers write, "this overlap suggests that there are opportunities for improving allocation to facilitate increased utilization." They discuss the issues raised by organs with "no recipient" located and the rising rate of unilateral kidney discards [Mohan S, et al. Factors leading to the discard of deceased donor kidneys in the United States. *Kidney Int* 2018; DOI: https://doi.org/10.1016/j.kint.2018.02.016].

NIH Launches National Enrollment for Historic *All of Us* Research Program

The National Institutes of Health (NIH) has launched national enrollment for its All of Us Research Program. This historic project aims to collect data from more than 1 million volunteers to accelerate research and enable the delivery of precision medicine by considering factors such as individual lifestyles, environment, and biology.

Participants who volunteer for the program will be asked to contribute information about their medical history and lifestyle over time by completing health surveys, sharing electronic health records, and potentially submitting physical measurements and biosamples. Researchers will conduct studies using the data collected to identify patterns that may lead to medical breakthroughs. Enrollees will be asked to provide input throughout their participation and will be provided their individual study results and summarized data from across the program.

Enrollment is open to anyone over the age of 18 who is living in the United States, regardless of health status. In the future, the program hopes to enroll those younger than 18.

The All of Us Research Program's goal of collecting data from more than 1 million volunteers has great potential to spur scientific and medical breakthroughs. The American Society of Nephrology applauds NIH for undertaking this bold initiative and encourages the entire kidney community to participate in the program. It is essential that individuals affected by kidney diseases volunteer to enroll to ensure the nephrology community makes advances in precision medicine to prevent, treat, and cure kidney diseases.

To learn more about enrollment, please visit JoinAllofUs.org.

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ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

Detective Nephron

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

Henle A case for you, sir!

The detective sits facing the window, awaiting the arrival of his new students.

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

Henle It's a case of hyperkalemia.

Nephron (*smiling*): Ah, yes. Electrolyte disorders. The best part of nephrology! Nevertheless, no patient will thank you for fixing their acidosis.

Aldo This is an 81-year-old man with a serum potassium level of 7.5 mmol/L.

Nephron (*interrupting*): I don't need any of that information…. Oh, new fella! Dr. Aldo, welcome to nephrology. And you have a potassium case? Great!

Aldo Yes! Fits well with my name.

Henle Yes, Dr. Nephron, we did repeat the serum potassium level, and it's actually 8 mmol/L; and yes, you are right—the creatinine is normal at 0.6 mg/dL, with an estimated GFR of 85 mL/min.

Nephron Hyperkalemia with acute kidney injury is boring. But hyperkalemia with normal renal function is a treat for the nephrologist!

Henle (*whispering to Aldo*): I told you he is a bit strange.

Nephron How do we categorize the causes of hyperkalemia?

Aldo Too much intake?

Nephron Increasing potassium intake alone is not a common cause of hyperkalemia unless it is paired with decreased renal potassium excretion. In patients with low GFR or hypoaldosteronism, moderate increases in potassium intake can be an important contributor to the development of hyperkalemia, but otherwise it's rare.

Henle Shifting?

Nephron (*laughing*): Shifting where?

Pause.

Henle (*happy*): Out of the cells?

Nephron Are you going to stop after each answer and not complete your thoughts?

Aldo Insulin deficiency and hypertonicity can do it. Insulin promotes potassium entry into the cells. So, insulin deficiency and associated hyperglycemia can lead to hyperkalemia. The increase in plasma tonicity results in osmotic water movement from the cells into the extracellular fluid. This is accompanied by potassium movement out of the cells. Increased β-2-adrenergic activity drives potassium into the cells and lowers the serum potassium. So, β-blockers can actually lead to hyperkalemia. This patient has neither elevated blood glucose nor insulin deficiency, nor is he taking any β-blockers.

Henle (*showing off*): Acidosis can also lead to hyperkalemia. In patients with metabolic acidosis, such as lactic acidosis or ketoacidosis, excess hydrogen ions move inside the cells, which leads to potassium movement into the extracellular fluid, a transcellular shift that is obligated in part by the need to maintain electroneutrality. But this patient's laboratory results show no signs of acidosis.

Nephron (*angry*): That is not accurate. Organic acidosis such as lactic acidosis or ketoacidosis does not cause as much hyperkalemia as inorganic acidosis…

Henle (*interrupting Nephron*): … but I have seen a lot of patients with diabetic ketoacidosis that then had hyperkalemia …

Nephron (*interrupting Henle*): Aldo just said it! Diabetic ketoacidosis causes hyperkalemia because of the associated insulin deficiency and hypertonicity, not because of the acidemia.

Henle (*embarrassed*): Oh! My bad.

Henle But I think the most common cause of hyperkalemia is decreased renal excretion.

Nephron Please continue.

Aldo (*jumping in*): Renal potassium excretion primarily occurs in the principal cells in the segments that follow the early distal convoluted tubule: the late distal convoluted tubule, the connecting tubule, and the collecting duct.

Nephron Three major factors are required for adequate potassium secretion at these sites: adequate aldosterone secretion, appropriate response to aldosterone, and adequate distal sodium and water delivery.

Henle (*shocked*): So basically, what I was trying to say is that the main causes of reduced loss of potassium in the urine are reduced ALDO secretion, reduced response to ALDO, reduced distal sodium delivery in hypotension, and acute kidney injury.

Aldo (*interrupting*): Thanks for the shout-out!

Nephron Good work, team.

Henle Basically, our patient has normal renal function, good blood pressure control, and good urine output, and I doubt he has a hypo-ALDO state. He is taking no medications. He has a normal serum bicarbonate level, suggesting no signs of any form of distal renal tubular acidosis. He also is not taking any heparin or potassium-sparing diuretics.

Aldo (*confident*): You know that his white blood cell count is 796,000 per cubic millimeter, and he carries a diagnosis of chronic lymphocytic leukemia (CLL). Subsequently, he was given intravenous calcium chloride, dextrose, insulin, and resins. A 12-lead electrocardiogram (ECG) did not reveal any changes.

Nephron I love it! Love it! I love it when you guys hide important information from me!

Henle A repeated serum potassium level after the initial treatments revealed an increase to 9.8 mmol/L. A repeated ECG did not show any new

changes, and the patient continued to be asymptomatic.

Nephron So, you are telling me that this patient might have pseudohyperkalemia?

Aldo (*puzzled*): Great! But how do we prove it is pseudohyperkalemia?

Nephron Let's end this confusion once and for all. He is not diabetic, nor does he have renal failure, and he has other normal laboratory results except for a crazy high white blood cell count and an alarming fatal potassium level, but he is laughing and talking in the examination room. Clearly, it is not real, and ECG repeated twice was normal. If this were real, he would have sine waves by now!

Henle Hmmm. Does CLL cause this degree of hyperkalemia?

Nephron The most common electrolyte disorder encountered in CLL patients is pseudohyperkalemia. An artifactually elevated serum potassium level or spurious hyperkalemia was first described with extreme leukocytosis (>600 × 109/L) in the 1970s and thereafter in several case reports.

Aldo (*jumping in*): I've heard about a large study. In over 300 patients with CLL listed in the Minnesota Tumor Registry between 1997 and 2014, the researchers found that the adjusted odds of hyperkalemia increased by 1.4 for every 10 × 109/L increase in white blood cell count. Below white blood cell counts of 50 × 109/L, the median estimated percentage of a patient's serum potassium being elevated was 1.7%, but it was considerably higher at 8.1% when the white blood cell count was ≥100 × 109/L. This is the first and only study to systematically look at serum and plasma potassium values in CLL patients, demonstrating that the results are related to pseudohyperkalemia.

Nephron (*shocked*): Usually, I don't like discussing random studies at this forum, but good for you. How do you remember that stuff? However, to our knowledge, there is no specific way to predict or correct the serum potassium value based on the white blood cell count.

Aldo The elevation in white blood cells causing pseudohyperkalemia is actually a rare cause. The three most common causes are mechanical trauma during venipuncture, hemolysis, and exercise-induced potassium movement out of muscle cells. When the platelet counts are very high (500,000/μL), as in thrombocytosis, measured serum potassium is elevated as potassium is released from the fragile platelets during clotting. However, in these cases, if the plasma potassium is checked (in a heparinized unclotted sample), the measured potassium will be normal because no clot formation occurred and no potassium was released. Elevation of blood platelet count by 1000 × 109/L can lead to an increase in 0.2 mmol/L in plasma potassium and 0.7 mmol/L in serum potassium. As a result, the potassium concentration is generally higher in serum than in plasma. Similarly, elevated potassium levels have been described in leukocytosis as well.

Nephron Dr. Aldo, you are on a roll!

Henle (*getting anxious and jealous*): How then does one get an accurate potassium result?

Aldo I would get a plasma potassium level. The definition of pseudohyperkalemia is a difference between serum and plasma potassium of more than 0.3 mmol/L.

Nephron keeps smiling.

A few hours later:

Aldo The plasma potassium is also elevated at 7 mmol/L. Now what? This must be real!

Nephron Are you sure?

Henle Routine serum analysis leads to high measured potassium levels resulting from release of potassium from the fragile leukemic cells during the clotting process. But in CLL, even the plasma levels of potassium are elevated. Severe leukocytosis leads to consumption of metabolic fuels that can impair Na-K ATPase activity, leading to release of potassium from a large number of white blood cells. Whereas in elevated platelet levels, serum and plasma levels can differentiate pseudohyperkalemia, elevated white blood cell–related pseudohyperkalemia might be not as straightforward to distinguish. Another interesting electrolyte disorder in CLL patients, though extremely rare, is reverse pseudohyperkalemia, where plasma potassium is higher than serum potassium. The mechanism is not well understood but can be due to increased sensitivity to heparin-mediated cell membrane damage during transport in pneumatic tubes, processing, or centrifugation in a hematologic malignancy.

Nephron Brilliant, Henle!

Aldo So, if plasma and serum potassium are both elevated, and we still think this is pseudohyperkalemia, should we get a whole blood potassium level from venous blood gas?

Nephron Let's try that.

A few hours later:

Aldo The venous blood gas potassium is also 7 mmol/L.

Henle (*with a smirk*): The time to collection and analysis of the blood sample can help eliminate some of these findings. Hence, blood gas levels are a good idea. Venous and arterial blood gas samples for potassium measurement can decrease the transit time to allow for more accurate potassium measurement. But we have to keep in mind that venous samples have more mechanical stressors compared with arterial blood draw techniques, making arterial draws more accurate.

Aldo (*angry*): Oh, well! Should we get an arterial blood gas, then?

Nephron Please get an arterial blood gas.

A few hours later:

Henle (*relieved*): The arterial blood gas potassium was 4.5 mmol/L.

The detective's eyes brighten.

Nephron Fascinating. Very well, then. And so, yet again, the nephrologists did it! Ask them to stop measuring the serum potassium and use the arterial blood gas potassium to check levels. Perhaps, do no harm—send the patient home! The exact mechanism of pseudohyperkalemia in extreme leukocytosis is not clear. However, the presence of pseudohyperkalemia should be strongly suspected with elevated potassium, the absence of clinical signs of hyperkalemia, absence of acid–base abnormalities, preserved kidney function, a normal ECG, and, in this case, the presence of extreme leukocytosis. Unlike thrombocytosis, plasma and serum potassium can both be misleading in elevated white blood cell counts. Arterial blood gas potassium might be the only accurate way to diagnose pseudohyperkalemia in such cases. Once again, great work, team, and let's get some New York–style coffee. I feel like having a banana today as well.

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

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FDA Approves Tolvaptan for ADPKD

Otsuka Pharmaceutical's drug Jynarque (tolvaptan) received US Food and Drug Administration (FDA) approval as the first drug treatment in the United States to slow kidney function decline in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD). The drug is a selective vasopressin V2-receptor antagonist.

Tolvaptan showed a greater reduction in estimated glomerular filtration rate compared to placebo, meeting the primary endpoint of the REPRISE trial (Replicating Evidence of Preserved Renal Function: an Investigation of Tolvaptan Safety and Efficacy in ADPKD).

The data appeared in a late-breaking abstract at ASN Kidney Week 2017 and were simultaneously published online in the *New England Journal of Medicine* (1).

Tolvaptan caused "more elevations in aminotransferase and bilirubin levels," according to the *NEJM*. "The efficacy and safety of tolvaptan in patients with later-stage ADPKD are unknown." After tolvaptan therapy ended, the results were reversible for aminotransferase, and bilirubin levels did not exceed twice the upper limit of the normal bilirubin range, the *NEJM* noted.

"We are thrilled to be a part of this first milestone in treatment for ADPKD," said PKD Foundation CEO Andy Betts. "For the past 35 years, our goal has been to walk with PKD patients every step of the way. It is gratifying to play a part in the inception of the discovery of this treatment, and to see it come to fruition. We hope that this is just the beginning of a new chapter for adults at risk of rapidly progressing ADPKD who suffer from the disease."

Jynarque is available only through a restricted distribution program, according to FirstWord Pharma. Patients must have testing for blood alanine and aspartate aminotransferases levels, as well as bilirubin, before initiating treatment with tolvaptan. Patients also must be tested at two weeks and four weeks after treatment begins, as well as monthly for 18 months and every three months afterward.

The company noted that the drug will be sold in a 28-day treatment pack at a wholesale cost of $13,041.10.

Reference

1. Torres V, et al. Tolvaptan in later-stage autosomal dominant polycystic kidney disease. *N Engl J Med* 2017; 377:1930–1942.

CVS Enters Kidney Care Market

Pharmacy giant CVS (Woonsocket, RI) recently announced that it will enter the kidney care market. The company will take a stepwise approach in a new initiative that will focus on chronic kidney disease and home-based dialysis.

The company's first focus will be on patient education and early detection of kidney disease. It also plans to introduce a new home hemodialysis technology designed to make home hemodialysis simple and safe for patients, and to facilitate longer and more frequent treatments.

"While in-center dialysis clinics are currently the most common choice for hemodialysis treatment, published clinical research has shown improved cardiac health, metabolic control, and survival for patients who are treated with longer, more frequent dialysis treatments," said Bruce Culleton, MD, vice president and chief medical officer, CVS Specialty. "This treatment paradigm is best delivered in the convenience of a patient's home. CVS Health is uniquely positioned to build a solution that will enable us to identify and intervene earlier with patients to optimize the management of chronic kidney disease, while at the same time making home dialysis therapies a real option for more patients."

CVS runs walk-in "Minute Clinics" in some CVS and Target stores. These clinics offer treatment for minor illnesses and injuries, vaccinations, and other services.

CVS decided to enter the kidney care field partly owing to its ". . . deep payer relationships at CVS Caremark," said Alan Lotvin, MD, executive vice president and head of CVS Specialty. "When we get ready to launch this, presumably there's going to be a payer angle," Lotvin told MarketWatch, adding that CVS is "looking to work within existing systems."

In 2017, CVS signed a deal to acquire major health insurer Aetna for $69 billion.

Fresenius Launches Foundation to Raise CKD Awareness

Fresenius Medical Care North America (FMCNA, Waltham, MA), has launched a foundation to create awareness and a national dialog about chronic kidney disease (CKD) and transplantation.

The funding will come from FMCNA employees and medical staff and other individuals, with FMCNA pledging to match up to $1 million of contributions during the first year.

The nonprofit Fresenius Medical Care Foundation will address the social and economic conditions that increase the risk for developing CKD, with a focus on population health, childhood obesity, and transplant and donor awareness. The foundation will aim to engage with nonprofit organizations and with communities that include individuals at risk for developing type 2 diabetes and high blood pressure.

Addressing the health of young people in particular, FNMCA kicked off the launch by assembling 4000 Healthy Eating, Active Lifestyle (HEAL) kits that included sports balls and air pumps for Chicago public school students. The foundation will also donate $50,000 to the YMCA of metropolitan Chicago to support its summer camp program for children who have diabetes and kidney disease.

"When we look outside the walls of our dialysis clinics, we know we must help people at risk for developing kidney disease, and our new foundation is a significant step toward that important, long-term goal," said Bill Valle, FMCNA CEO and president of the Fresenius Medical Care Foundation.

Puerto Rican Patients, Saline Industry Still Recovering

In mid-April 2018, Puerto Rico again experienced a total blackout, this time because of an electrical subcontractor's mistake, not an act of nature like Hurricane Maria, which devastated the island in September 2017.

Many patients have to travel far—sometimes up to 12 hours—to find functional dialysis opportunities. In March 2018, Puerto Rico's health secretary said the department was working to bring in mobile units for dialysis. Luis Emanuelli, regional vice president of Fresenius Kidney Care, said he is aware of plans for the mobile units but is unaware of the timeline for bringing them on line.

To assist in getting help to people affected by Hurricane Maria, the National Kidney Foundation (NKF) set up a special fund for those needing dialysis. ASN joined NKF as a sponsor in the effort to raise money. Other organizations, and dialysis manufacturers and providers, joined in the effort:

- Akebia Therapeutics, Inc.
- Alliant Health Solutions
- Amgen Foundation
- American Renal Associates
- American Medical Technologists
- American Society of Nephrology
- American Society of Pediatric Nephrology
- DaVita Healthcare Partners
- Dialysis Clinic, Inc.
- Fresenius Medical Care
- Keryx Biopharmaceuticals
- National Renal Administrators Association
- OPKO Renal
- Relypsa, Inc.
- U.S. Renal Care

The hurricane-induced problems are a two-way street of dependence. The United States is very low on saline bags for dialysis, many of which are manufactured in Puerto Rico. The *Washington Post* reported that supply issues were made worse by the impact of Hurricane Maria on the medical products manufacturing sector in Puerto Rico, which affected small volume IV bags.

A statement from the US Food and Drug Administration (FDA) noted an effort to preserve the current stock of resources provided by Puerto Rican manufacturers. The FDA urged companies to submit data to extend expiration dates on products that could be stored for longer periods without safety issues.

Fellows Corner

A Fresh Set of Guidelines for the Transplantation Rulebook

By Samira Farouk, MD

Samira Farouk, MD

During my rotation as a nephrology fellow at a high-volume liver transplantation center, I vividly remember an afternoon consultation from the medical team's intern: "Our patient needs a simultaneous liver-kidney transplant (SLKT)."

Several questions came to mind. How do they know he needs both a liver and a kidney? Are there guidelines for this seemingly monumental decision? What determines whether and when a patient receives a kidney from the donor pool—an increasingly scarce resource, with wait times approaching a decade? I found no rules to guide me. No criteria existed to aid me in the determination of candidacy for simultaneous liver-kidney allocation in the United States.

At the time, the only guideline I found was the "Final Rule" of the Organ Procurement and Transplantation Network (OPTN), which stated that allocation policies should avoid "futile transplants" and be based on "sound medical judgment" and "standardized criteria" to achieve the "best use of organs " (1). Given the vague terminology and absence of medical eligibility criteria, it was clear to me that this was a gap in patient-centered, evidence-based care (2). The OPTN policy prioritizes multiorgan candidates before kidney-alone candidates if the candidate is in the same donor service area as the donor. Because there are no medical criteria on which allocation is based, it is "geographic proximity between the donor and candidate alone that is the determining factor.

A system using the Model of End-Stage Liver Disease (MELD) score to prioritize candidates for liver transplantation was implemented by the United Network for Organ Sharing in 2002. The MELD score is determined in part by the serum creatinine level and thus leads to an increase in candidates for liver transplantation with kidney injury. Serum creatinine has been shown to be an unreliable marker of renal function in patients with end-stage liver disease (ESLD) by both overestimating the GFR due to sarcopenia and at times underestimating GFR when bilirubin interferes with the Jaffe assay that is commonly used to measure serum creatinine (3).

In 2016, a new SLKT allocation policy and medical eligibility criteria were introduced to guide clinicians (Table 1) (4). These criteria aim to identify patients with chronic kidney disease and potentially unrecoverable acute kidney injury (AKI) to avoid dual organ transplantation in patients who may ultimately recover their native kidney function. It is possible that ESLD patients with renal dysfunction will not recover kidney function after the liver transplantation alone, despite evidence of reversible kidney injury at the time of SLKT evaluation. For these patients whose renal function fails to recover by 60 days after liver transplantation, a "safety net" has been introduced that increases the priority of liver transplant recipients on the kidney waiting list up to 1 year after liver transplantation.

A retrospective cohort study by Locke et al. (5) found that between 1986 and 2006, kidney graft survival after SLKT was inferior to graft survival after kidney transplantation alone, whereas liver graft survival was not different with or without a kidney transplant. It is interesting that, of the 494 and 557 SLKTs in 2014 and 2015, respectively, 19% would not have been performed on the basis of the new medical eligibility criteria (4). With a mean kidney donor profile index (KDPI) below 35% in 2014, the quality of kidneys used for SLKT is usually significantly better than those used for kidney transplantation alone (6).

The KDPI is derived from the kidney donor risk index (KDRI), an estimate of the relative risk of post-transplantation allograft failure, which is calculated with the use of various donor characteristics including age, race, creatinine level, cause of death, and history of hepatitis C, hypertension, and diabetes mellitus. A KDPI of 20% implies that the KDRI exceeds 20% of all donors in the reference population, and a KDPI of 80% implies that the KDRI exceeds 80% of all donors. The new dual liver-kidney allocation system may now allow the transplantation of high-quality kidney allografts into patients who have waited as long as 10 years on the kidney-alone transplantation waiting list.

There are several challenges to consider in the evaluation of candidates for SLKT. One such challenge involves the difficulty in identifying the cause of AKI in patients with ESLD. With the likelihood of renal recovery from hepatorenal syndrome after liver transplantation, the distinction between hepatorenal syndrome, acute tubular necrosis, and other intrinsic kidney diseases is crucial. The fractional excretion of sodium, often used to aid in the diagnosis of AKI, may be similar in cirrhotic patients with prerenal azotemia, hepatorenal syndrome, or acute tubular necrosis (6).

Although kidney biopsies are not routinely performed in patients with coagulopathic cirrhosis (7), an interesting study of 59 liver transplantation candidates with renal dysfunction found that renal biopsies can be safely performed. The use of biomarkers also presents an exciting opportunity to more accurately diagnose AKI in the ESLD patient. Belcher et al. (8) found that urinary biomarkers such as neutrophil gelatinase-associated lipocalin, IL-18, kidney injury molecule-1, liver-type fatty acid binding protein, and albumin were elevated in ESLD patients with acute tubular necrosis compared with those with hepatorenal syndrome.

Furthermore, accurate prediction of renal recovery remains problematic in most clinical settings, including AKI and ESLD. In a cohort of candidates for liver transplantation, the best histologic predictor of glomerular function after liver transplantation was global glomerular sclerosis (9). The risk of ESRD after liver transplantation has also been predicted by the use of an equation that includes the recipient's race, history of diabetes, hepatitis C status, and levels of serum albumin, serum bilirubin, and serum creatinine (10).

Table 1
Medical eligibility criteria for simultaneous liver-kidney transplant

1. **CKD (must be confirmed by a nephrologist)**
   - eGFR 60 for 90 consecutive days AND
   - eGFR or CrCL < 30 at or after registration on kidney waiting list OR
   - Dialysis in the setting of ESRD
2. **AKI (must be confirmed by a nephrologist)**
   - Dialysis for 6 consecutive weeks
   - eGFR or CrCl <25 for 6 consecutive weeks
   - Combination of above two criteria
3. **Metabolic disease (must be confirmed by a nephrologist)**
   - Atypical HUS from mutations factor H and factor I
   - Hyperoxaluria
   - Familial nonneuropathic systemic amyloidosis
   - Methylmalonic aciduria

AKI = acute kidney injury; CKD = chronic kidney disease; CrCl = creatinine clearance; eGFR = estimated GFR; HUS = hemolytic uremic syndrome.

Reprinted with permission from Asch and Bia (4).

My approach to the same consultation I received as a first-year fellow has drastically changed now that I am a third-year fellow. I now use a set of medical criteria to make informed recommendations regarding the patient's appropriateness for SLKT. Although the decision to allocate an organ or organs should never be made based solely on rules, we can now be more consistent with our decisions and optimize our organ use with the new allocation system. As a new member of the transplant nephrology community, I look forward to observing changes in the landscape of SLKT so we may continue to improve the allocation system and provide appropriate, guideline-based care for our kidney patients.

Samira Farouk, MD, is a third-year and chief nephrology/transplant fellow at Icahn School of Medicine at Mount Sinai, New York.

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How Transplanted Livers Help Defend against Rejection in Multiple-Organ Transplantations

By Tracy Hampton

A new study points to factors involved in the reduced likelihood of rejection in liver-kidney transplant recipients compared with solitary kidney transplant recipients.

"For many years, transplant physicians and researchers have known that the liver transplant recipients require less immunosuppression than the recipients of other organs, to prevent rejection," said Timucin Taner, MD, PhD, a transplant surgeon at the Mayo Clinic and lead author of the *Kidney International* study. "This has been attributed to the liver being less immunogenic compared to the other commonly transplanted organs; however, the liver itself is an immunologically active organ, so we hypothesized that this phenomenon is more of an active process, brought about uniquely by the liver."

Over the past several years, Taner and his colleagues have systematically investigated this question by comparing the clinical outcomes of multiple organ transplant recipients, as well as the histologic and genetic changes that occur in the allografts of these patients. An earlier study revealed that, when compared with kidneys from solitary kidney transplant recipients, kidneys of simultaneous liver-kidney transplant recipients had fewer molecular markers of inflammation and T-cell activation and greater expression of genes associated with tissue integrity and metabolism

In this latest study of 28 simultaneous liver-kidney transplant recipients, 61 recipients of a solitary kidney, and 31 recipients of liver allografts, the phenotypic and functional characteristics of the circulating blood cells of the simultaneous liver-kidney transplant recipients resembled those of solitary liver transplant recipients and were associated with donor-specific hypo-alloresponsiveness.

Solitary kidney transplant recipients had more circulating CD8+ cytotoxic T cells, activated CD4+ and effector memory T cells, and interferon gamma–producing alloreactive T cells. Simultaneous liver-kidney transplant recipient T cells had a lower proliferative response to donor cells compared with solitary kidney recipients (11.9% vs. 42.9%), but their response to third party cells from a different donor was unaltered.

The results indicate that the circulating white blood cells of liver transplant recipients are less reactive to the transplanted organ than the same cells of kidney transplant recipients.

"In the current study, we demonstrate for the first time that the overall alloimmune responses in liver transplant recipients are downregulated while the immune responses to other antigens are preserved," Taner said.

He noted that the goal in any organ transplantation is to achieve long-term function of donor organs with minimal immunosuppression so as not to increase patients' risk for infection, cancer, and other issues.

"Given the findings of the current study and our previous publications, it appears that liver allografts have the unique ability to reduce the overall need for immunosuppression," Taner said. "Our goal is to find out the underlying mechanisms, so that novel therapeutic approaches could be used."

Such a strategy may help patients receiving various types of transplants reduce their need for anti-rejection drugs.

"These findings are significant as they provide the first evidence from a direct comparison of simultaneous liver-kidney and solitary graft recipients that the liver graft regulates host alloimmunity," noted Angus Thomson, PhD, DSc, Distinguished Professor of Surgery and Immunology at the University of Pittsburgh, who was not involved with this research. "While the study was not designed to elucidate underlying mechanisms, the findings suggest that identification of mechanisms may lead to design of improved therapeutic strategies in renal transplantation and other immune-mediated kidney disorders."

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ASN

Using a Computer Simulation to Teach Undergraduate Students the Principles Behind GFR Autoregulation

By José J. Reyes-Tomassini

The concept of glomerular filtration rate (GFR) and its regulation is central in renal physiology. Estimates of GFR are often used in the clinical setting to assess kidney health. GFR is an effective measure of kidney function (1). Many pathophysiologic conditions affect GFR by altering the glomerular capillary pressure, including diabetes mellitus and essential hypertension. Afferent and efferent arteriole resistance plays a crucial role in the regulation of GFR. Whereas dilation of the afferent arteriole causes an increase in GFR, dilation of the efferent arteriole decreases GFR (2, 3). The concept is familiar to all nephrologists, but can be challenging to explain to nursing and other students.

Simulations are a great way to introduce students to basic physiologic concepts. Simulations that feature graphics are especially useful to relate these concepts. I have developed a computer simulation that uses animations and graphics to show the basic concepts underlying GFR control. The program also simulates autoregulation by changing the size of the afferent and efferent arterioles. By use of a recursive algorithm, the simulation alters afferent and efferent arteriole resistance to move GFR toward normal while maintaining renal blood flow. The efferent arteriole is thought to be less involved in autoregulation but is thought to be the target of some hypertensive drugs (4).

The role of permeability to proteins on transglomerular pressure is also simulated. By sliding a control on the simulation, users can change the permeability of the glomerulus to proteins and observe what occurs when proteins, such as albumin, pass intact through the glomerular barrier. This can happen in some chronic diseases such as hypertension and diabetes.

Users can increase or decrease blood pressure by moving a slider control. Users can also turn off autoregulation and manually control the diameter of the efferent and afferent arteriole. Changes in renal blood flow are shown visually by changing the color of the blood flowing through the glomerulus and by an indicator bar. The relative difference between the afferent and efferent arterioles is shown both in the animation of the glomerulus and in a separate figure that shows the relative difference between the two arterioles.

Since I began using this in my classroom to teach this section of kidney physiology, I have found that students do well on the concept of GFR and can articulate the relationship between afferent and efferent arteriole resistance and GFR and also the relationship between blood pressure and unregulated GFR. Student feedback on the use of this simulation has been overwhelmingly positive.

The program runs in any Windows 95 or higher system. It was written in Visual Basic 6.0. I plan to make a game version of the program. If you have suggestions or ideas or if you would like to use this simulation in your classroom or for other educational purposes, you may reach me at jose.reyestomassini@wartburg.edu.

The program is free and available upon request.

Figure 1. The simulation shows the students the size of the efferent and afferent arterioles, GFR values, capillary pressure, and the direction of the net pressure within Bowman's capsule.

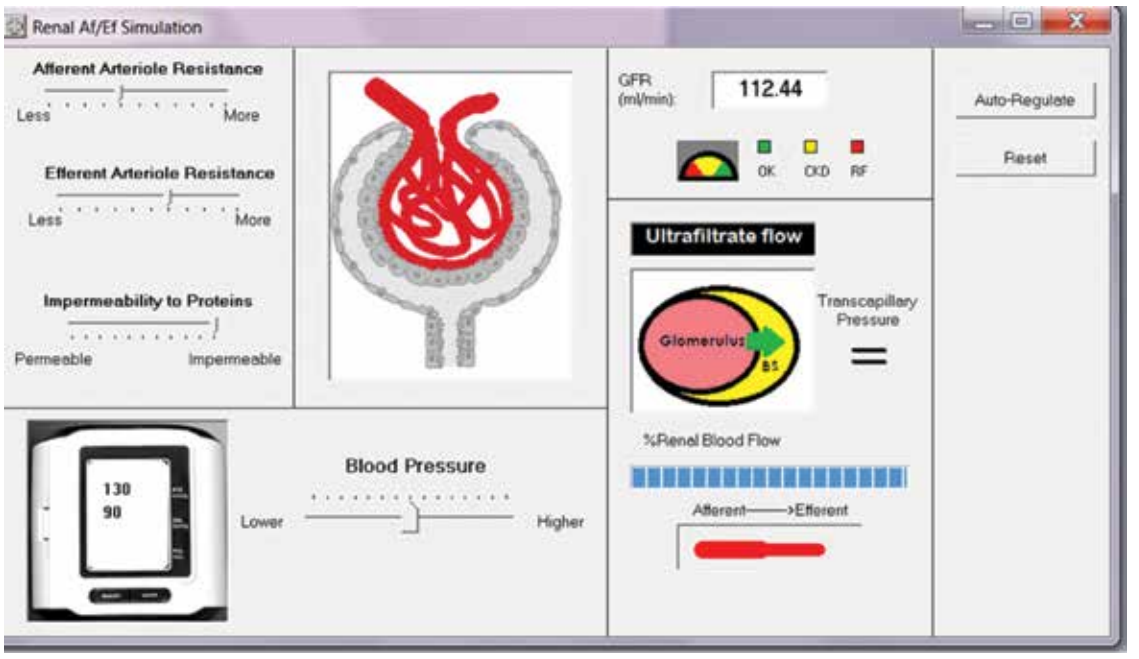
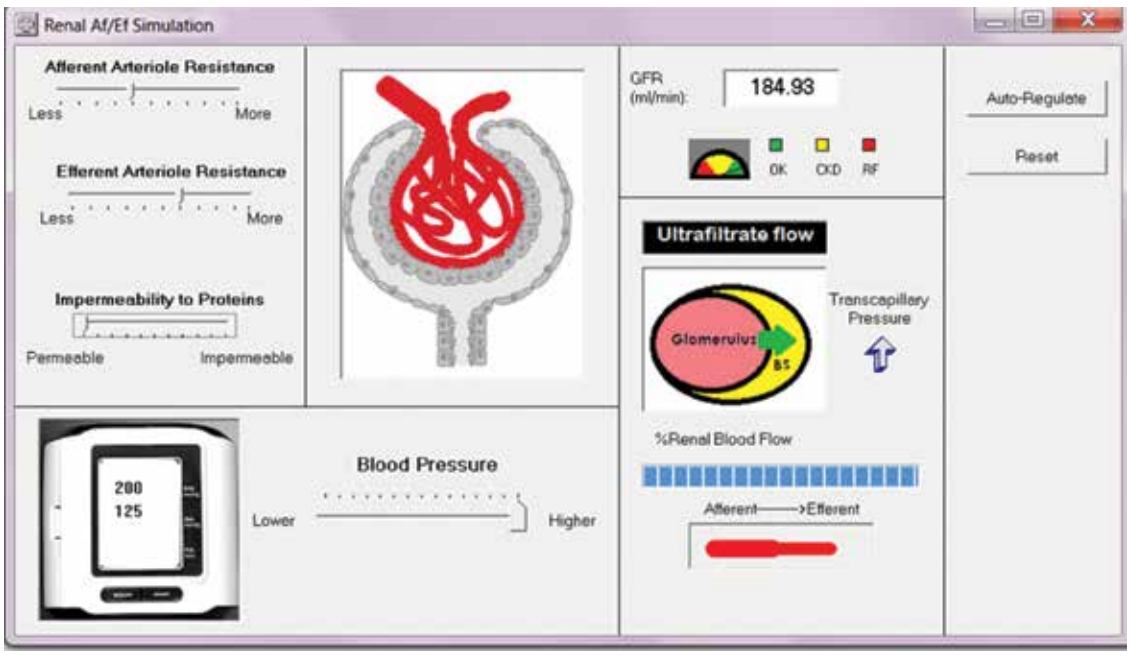


Figure 2. When a student increases the blood pressure and makes the glomerular filtration barrier permeable to proteins, GFR is increased. Proteins can permeate this barrier and enter Bowman's space in conditions such as diabetes and hypertension, which make oncotic and hydrostatic pressure additive forces in the Starling equation.



José J. Reyes-Tomassini is a visiting assistant professor at Wartburg College in Waverly, Iowa.

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