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National Academy of Medicine Launches Effort to Strengthen Health Care Worker Well-Being

By Karen Blum

Recognizing the ongoing challenges affecting health care workers nationwide, leading to burnout and moral distress, the National Academy of Medicine (NAM) Action Collaborative on Clinician Well-Being and Resilience has devised the National Plan for health workforce well-being.

"It is critical for us to have a coordinated plan at the national level to help shift US health care from the current reality of a workforce shortage and burnout crisis to a future where every health worker is able to experience joy in their workplace and knows that they are valued," said NAM President Victor Dzau, MD, in a prepared statement. The plan, released June 24, 2022, has seven priority areas, including creating a positive work and learning environment, supporting mental health, and engaging effective technology tools (Table 1). The plan builds on nearly 6 years of work among NAM's network of 200 organizations committed to reversing trends in health care worker burnout.

Helen Burstin, MD, MPH, MACP, CEO of the Council of Medical Specialty Societies (CMSS), was part of the collaborative, which is co-chaired by NAM, the Association of American Medical Colleges, the American Council for Graduate Medical Education, and the US Surgeon General's office. Some issues under study by the group include ensuring access to mental health care, reducing stigma, how to work best with electronic health records (EHRs) and new tools to decrease documentation burden, and system drivers of well-being, Burstin said. Nephrologists can look at the plans to see what fits their health system settings and patient focus, where the sources of burnout exist, and report back to the group on areas where intervention can help, she said. CMSS is also looking at what specialty societies are doing to alleviate burnout and will continue to share best practices, Burstin said. "The classic, 'Come to this meeting and let's do yoga and let's have a pizza party' is not going to get at the core of this," she said. "This is really a systemic issue, and it requires a systemic approach. We will continue to identify issues in technology, mental health service availability, or regulatory issues that we can really challenge that would actually make the lives of practicing clinicians better every day so they can take better care of patients."

Continued on page 7

Kidney Community Voices Concern over Supreme Court Ruling for Health Insurer That Limited Dialysis Benefits

By Eric Seaborg

The recent rulings from the conservative majority on the Supreme Court are being felt in every corner of American life—including the kidney space.

A June 21 ruling "…laid out a roadmap for insurers to shift the costs of end-stage renal disease to Medicare," according to judicial analyst Ronald Mann writing for the Supreme Court-tracking website SCOTUSblog (1).

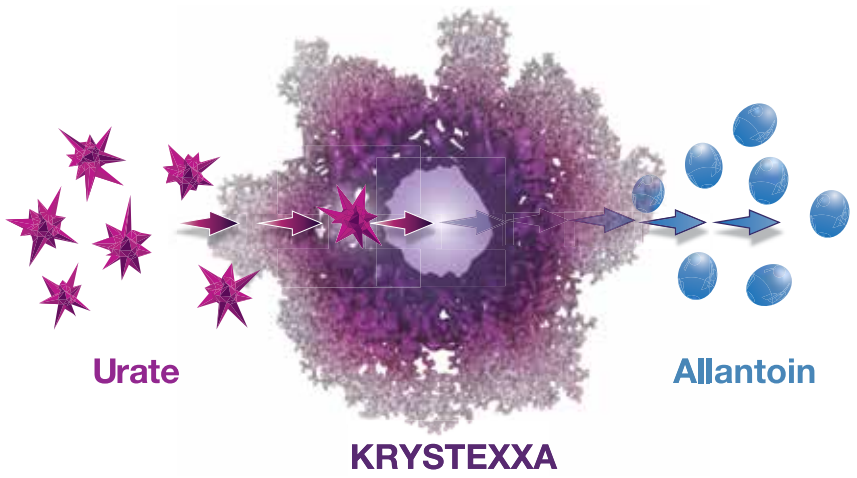
A statement from the National Kidney Foundation (NKF) stated the organization was "deeply disturbed" by the ruling (2) as was Kidney Care Partners, which was "deeply disappointed" and vowed to have Congress overturn the ruling (3).

The case pitted the Marietta Memorial Hospital employee health insurance plan against national dialysis provider DaVita. The issue began in 2018 when Marietta's plan did not include any in-network dialysis providers, meaning that all patients requiring dialysis would face increased out-of-pocket costs from out-of-network providers. The Marietta insurance plan also drastically cut the rates it paid providers to amounts based on Medicare rates. In contrast to the way the plan generally reimbursed out-of-network providers at a "reasonable" fee determined by health care industry stand-

Continued on page 8

Inside

KRYSTEXXA (PEGLOTICASE) IS A RECOMBINANT INTO ALLANTOIN[1]



Artist's renditions.

RENAL EXCRETION OF ALLANTOIN IS UP TO 10 TIMES MORE EFFICIENT THAN EXCRETION OF URIC ACID[2]

INDICATION AND IMPORTANT SAFETY INFORMATION

INDICATIONS AND USAGE

KRYSTEXXA® (pegloticase) is indicated for the treatment of chronic gout in adult patients who have failed to normalize serum uric acid and whose signs and symptoms are inadequately controlled with xanthine oxidase inhibitors at the maximum medically appropriate dose or for whom these drugs are contraindicated.

Important Limitations of Use: KRYSTEXXA is not recommended for the treatment of asymptomatic hyperuricemia.

IMPORTANT SAFETY INFORMATION

WARNING: ANAPHYLAXIS AND INFUSION REACTIONS

Anaphylaxis and infusion reactions have been reported to occur during and after administration of KRYSTEXXA. Anaphylaxis may occur with any infusion, including a first infusion, and generally manifests within 2 hours of the infusion. However, delayed-type hypersensitivity reactions have also been reported. KRYSTEXXA should be administered in healthcare settings and by healthcare providers prepared to manage anaphylaxis and infusion reactions. Patients should be premedicated with antihistamines and corticosteroids. Patients should be closely monitored for an appropriate period of time for anaphylaxis after administration of KRYSTEXXA. Monitor serum uric acid levels prior to infusions and consider discontinuing treatment if levels increase to above 6 mg/dL, particularly when 2 consecutive levels above 6 mg/dL are observed.

The risk of anaphylaxis and infusion reactions is higher in patients who have lost therapeutic response.

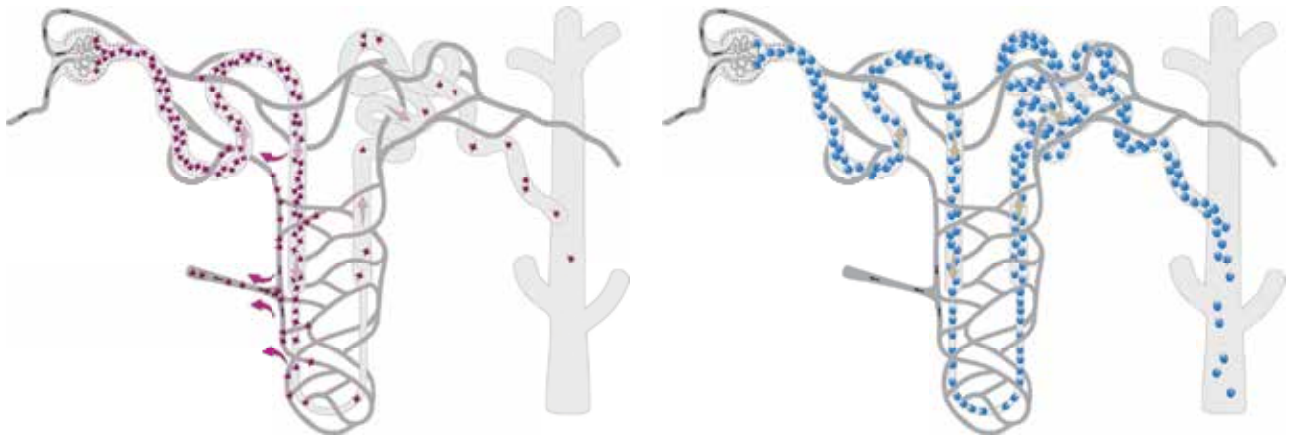
Concomitant use of KRYSTEXXA and oral urate-lowering agents may blunt the rise of sUA levels. Patients should discontinue oral urate-lowering agents and not institute therapy with oral urate-lowering agents while taking KRYSTEXXA.

In the event of anaphylaxis or infusion reaction, the infusion should be slowed, or stopped and restarted at a slower rate.

References: 1. KRYSTEXXA (pegloticase) [prescribing information] Horizon. **2.** McDonagh EM, et al. *Pharmacogenet Genomics*. 2014;24:464-476. **3.** Terkeltaub R, et al. *Arthritis Res Ther*. 2006;8(suppl 1):S4.

HORIZON

URICASE ENZYME THAT CONVERTS URATE



Only 10% of uric acid filtered through the kidney is excreted[3]

vs

Nearly all of allantoin filtered through the kidney is excreted[2,3]

TO LEARN MORE, VISIT KRYSTEXXAHCP.COM

Inform patients of the symptoms and signs of anaphylaxis, and instruct them to seek immediate medical care should anaphylaxis occur after discharge from the healthcare setting.

CONTRAINDICATIONS: G6PD DEFICIENCY ASSOCIATED HEMOLYSIS AND METHEMOGLOBINEMIA

Screen patients for G6PD deficiency prior to starting KRYSTEXXA. Hemolysis and methemoglobinemia have been reported with KRYSTEXXA in patients with G6PD deficiency. Do not administer KRYSTEXXA to these patients.

GOUT FLARES

An increase in gout flares is frequently observed upon initiation of anti-hyperuricemic therapy, including treatment with KRYSTEXXA. If a gout flare occurs during treatment, KRYSTEXXA need not be discontinued. Gout flare prophylaxis with a non-steroidal anti-inflammatory drug (NSAID) or colchicine is recommended starting at least 1 week before initiation of KRYSTEXXA therapy and lasting at least 6 months, unless medically contraindicated or not tolerated.

CONGESTIVE HEART FAILURE

KRYSTEXXA has not been studied in patients with congestive heart failure, but some patients in the clinical trials experienced exacerbation. Exercise caution when using KRYSTEXXA in patients who have congestive heart failure and monitor patients closely following infusion.

ADVERSE REACTIONS

The most commonly reported adverse reactions in clinical trials with KRYSTEXXA are gout flares, infusion reactions, nausea, contusion or ecchymosis, nasopharyngitis, constipation, chest pain, anaphylaxis and vomiting.

Please see Brief Summary of Prescribing Information, including Boxed Warning, for KRYSTEXXA on the following page.

KRYSTEXXA®
pegloticase

KRYSTEXXA® pegloticase

(pegloticase injection), for intravenous infusion

Brief Summary - Please see the KRYSTEXXA package insert for Full Prescribing Information.

WARNING: ANAPHYLAXIS and INFUSION REACTIONS; G6PD DEFICIENCY ASSOCIATED HEMOLYSIS and METHEMOGLOBINEMIA

- **Anaphylaxis and infusion reactions have been reported to occur during and after administration of KRYSTEXXA.**
- **Anaphylaxis may occur with any infusion, including a first infusion, and generally manifests within 2 hours of the infusion. However, delayed-type hypersensitivity reactions have also been reported.**
- **KRYSTEXXA should be administered in healthcare settings and by healthcare providers prepared to manage anaphylaxis and infusion reactions.**
- **Patients should be pre-medicated with antihistamines and corticosteroids.**
- **Patients should be closely monitored for an appropriate period of time for anaphylaxis after administration of KRYSTEXXA.**
- **Monitor serum uric acid levels prior to infusions and consider discontinuing treatment if levels increase to above 6 mg/dL, particularly when 2 consecutive levels above 6 mg/dL are observed.**
- **Screen patients at risk for G6PD deficiency prior to starting KRYSTEXXA. Hemolysis and methemoglobinemia have been reported with KRYSTEXXA in patients with G6PD deficiency. Do not administer KRYSTEXXA to patients with G6PD deficiency.**

INDICATIONS AND USAGE

KRYSTEXXA® (pegloticase) is a PEGylated uric acid specific enzyme indicated for the treatment of chronic gout in adult patients refractory to conventional therapy.

Gout refractory to conventional therapy occurs in patients who have failed to normalize serum uric acid and whose signs and symptoms are inadequately controlled with xanthine oxidase inhibitors at the maximum medically appropriate dose or for whom these drugs are contraindicated.

Important Limitations of Use:
KRYSTEXXA is not recommended for the treatment of asymptomatic hyperuricemia.

CONTRAINDICATIONS

Glucose-6-phosphate dehydrogenase (G6PD) deficiency

WARNINGS AND PRECAUTIONS

Anaphylaxis

During pre-marketing clinical trials, anaphylaxis was reported with a frequency of 6.5% (8/123) of patients treated with KRYSTEXXA every 2 weeks and 4.8% (6/126) for the every 4-week dosing regimen. There were no cases of anaphylaxis in patients receiving placebo. Anaphylaxis generally occurred within 2 hours after treatment. Diagnostic criteria of anaphylaxis were skin or mucosal tissue involvement, and, either airway compromise, and/or reduced blood pressure with or without associated symptoms, and a temporal relationship to KRYSTEXXA or placebo injection with no other identifiable cause. Manifestations included wheezing, peri-oral or lingual edema, or hemodynamic instability, with or without rash or urticaria. Cases occurred in patients being pre-treated with one or more doses of an oral antihistamine, an intravenous corticosteroid and/or acetaminophen. This pre-treatment may have blunted or obscured symptoms or signs of anaphylaxis and therefore the reported frequency may be an underestimate.

KRYSTEXXA should be administered in a healthcare setting by healthcare providers prepared to manage anaphylaxis. Patients should be pre-treated with antihistamines and corticosteroids. Anaphylaxis may occur with any infusion, including a first infusion, and generally manifests within 2 hours of the infusion. However, delayed type hypersensitivity reactions have also been reported. Patients should be closely monitored for an appropriate period of time for anaphylaxis after administration of KRYSTEXXA. Patients should be informed of the symptoms and signs of anaphylaxis and instructed to seek immediate medical care should anaphylaxis occur after discharge from the healthcare setting.

The risk of anaphylaxis is higher in patients whose uric acid level increases to above 6 mg/dL, particularly when 2 consecutive levels above 6 mg/dL are observed. Monitor serum uric acid levels prior to infusions and consider discontinuing treatment if levels increase to above 6 mg/dL. Because of the possibility that concomitant use of oral urate-lowering therapy and KRYSTEXXA may potentially blunt the rise of serum uric acid levels, it is recommended that before starting KRYSTEXXA patients discontinue oral urate-lowering medications and not institute therapy with oral urate-lowering agents while taking KRYSTEXXA.

Infusion Reactions

During pre-marketing controlled clinical trials, infusion reactions were reported in 26% of patients treated with KRYSTEXXA 8 mg every 2 weeks, and 41% of patients treated with KRYSTEXXA 8 mg every 4 weeks, compared to 5% of patients treated with placebo. These infusion reactions occurred in patients being pre-treated with an oral antihistamine, intravenous corticosteroid and/or acetaminophen. This pre-treatment may have blunted or obscured symptoms or signs of infusion reactions and therefore the reported frequency may be an underestimate.

Manifestations of these reactions included urticaria (frequency of 10.6%), dyspnea (frequency of 7.1%), chest discomfort (frequency of 9.5%), chest pain (frequency of 9.5%), erythema (frequency of 9.5%), and pruritus (frequency of 9.5%). These manifestations overlap with the symptoms of anaphylaxis, but in a given patient did not occur together to satisfy the clinical criteria for diagnosing anaphylaxis. Infusion reactions are thought to result from release of various mediators, such as cytokines. Infusion reactions occurred at any time during a course of treatment with approximately 3% occurring with the first infusion, and approximately 91% occurred during the time of infusion.

KRYSTEXXA should be administered in a healthcare setting by healthcare providers prepared to manage infusion reactions. Patients should be pre-treated with antihistamines and corticosteroids. KRYSTEXXA should be infused slowly over no less than 120 minutes. In the event of an infusion reaction, the infusion should be slowed, or stopped and restarted at a slower rate.

The risk of infusion reaction is higher in patients whose uric acid level increases to above 6 mg/dL, particularly when 2 consecutive levels above 6 mg/dL are observed. Monitor serum uric acid levels prior to infusions and consider discontinuing treatment if levels increase to above 6 mg/dL. Because of the possibility that concomitant use of oral urate-lowering therapy and KRYSTEXXA may potentially blunt the rise of serum uric acid levels, it is recommended that before starting KRYSTEXXA patients discontinue oral urate-lowering medications and not institute therapy with oral urate-lowering agents while taking KRYSTEXXA.

G6PD Deficiency Associated Hemolysis and Methemoglobinemia

Life threatening hemolytic reactions and methemoglobinemia have been reported with KRYSTEXXA in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Because of the risk of hemolysis and methemoglobinemia, do not administer KRYSTEXXA to patients with G6PD deficiency [see Contraindications]. Screen patients at risk for G6PD deficiency prior to starting KRYSTEXXA. For example, patients of African, Mediterranean (including Southern European and Middle Eastern), and Southern Asian ancestry are at increased risk for G6PD deficiency.

Gout Flares

During the controlled treatment period with KRYSTEXXA or placebo, the frequencies of gout flares were high in all treatment groups, but more so with KRYSTEXXA treatment during the first 3 months of treatment, and decreased in the subsequent 3 months of treatment. The percentages of patients with any flare for the first 3 months were 74%, 81%, and 51%, for KRYSTEXXA 8 mg every 2 weeks, KRYSTEXXA 8 mg every 4 weeks, and placebo, respectively. The percentages of patients with any flare for the subsequent 3 months were 41%, 57%, and 67%, for KRYSTEXXA 8 mg every 2 weeks, KRYSTEXXA 8 mg every 4 weeks, and placebo, respectively. Patients received gout flare prophylaxis with colchicine and/or nonsteroidal anti-inflammatory drugs (NSAIDs) starting at least one week before receiving KRYSTEXXA.

Gout flares may occur after initiation of KRYSTEXXA. An increase in gout flares is frequently observed upon initiation of anti-hyperuricemic therapy, due to changing serum uric acid levels resulting in mobilization of urate from tissue deposits. Gout flare prophylaxis with a non-steroidal anti-inflammatory drug (NSAID) or colchicine is recommended starting at least 1 week before initiation of KRYSTEXXA therapy and lasting at least 6 months, unless medically contraindicated or not tolerated. KRYSTEXXA does not need to be discontinued because of a gout flare. The gout flare should be managed concurrently as appropriate for the individual patient.

Congestive Heart Failure

KRYSTEXXA has not been formally studied in patients with congestive heart failure, but some patients in the clinical trials experienced exacerbation. Two cases of congestive heart failure exacerbation occurred during the trials in patients receiving treatment with KRYSTEXXA 8 mg every 2 weeks. No cases were reported in placebo-treated patients. Four subjects had exacerbations of pre-existing congestive heart failure while receiving KRYSTEXXA 8 mg every 2 weeks during the open-label extension study. Exercise caution when using KRYSTEXXA in patients who have congestive heart failure and monitor patients closely following infusion.

Re-treatment with KRYSTEXXA

No controlled trial data are available on the safety and efficacy of re-treatment with KRYSTEXXA after stopping treatment for longer than 4 weeks. Due to the immunogenicity of KRYSTEXXA, patients receiving re-treatment may be at increased risk of anaphylaxis and infusion reactions. Therefore, patients receiving re-treatment after a drug-free interval should be monitored carefully.

ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the label:

- Anaphylaxis [see Warnings and Precautions]
- Infusion Reactions [see Warnings and Precautions]
- G6PD Deficiency Associated Hemolysis and Methemoglobinemia [see Warnings and Precautions]
- Gout Flares [see Warnings and Precautions]
- Congestive Heart Failure [see Warnings and Precautions]

Clinical Trials Experience

The data described below reflect exposure to KRYSTEXXA in patients with chronic gout refractory to conventional therapy in two replicate randomized, placebo-controlled, double-blind 6-month clinical trials: 85 patients were treated with KRYSTEXXA 8 mg every 2 weeks; 84 patients were treated with KRYSTEXXA 8 mg every 4 weeks; and 43 patients were treated with placebo.

Because clinical studies are conducted under widely varying and controlled conditions, adverse reaction rates observed in clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug, and may not predict the rates observed in a broader patient population in clinical practice.

The most common adverse reactions that occurred in ≥5% of patients treated with KRYSTEXXA 8 mg every 2 weeks are provided in Table 1.

Table 1. Adverse Reactions Occurring in 5% or More of Patients Treated with KRYSTEXXA Compared to Placebo

Adverse Reaction (Preferred Term)	KRYSTEXXA 8 mg every 2 weeks (N=85) N[a] (%)	Placebo (N=43) N (%)
Gout flare	65 (77%)	35 (81%)
Infusion reaction	22 (26%)	2 (5%)
Nausea	10 (12%)	1 (2%)
Contusion[b] or Ecchymosis[b]	9 (11%)	2 (5%)
Nasopharyngitis	6 (7%)	1 (2%)
Constipation	5 (6%)	2 (5%)
Chest Pain	5 (6%)	1 (2%)
Anaphylaxis	4 (5%)	0 (0%)
Vomiting	4 (5%)	1 (2%)

[a] If the same subject in a given group had more than one occurrence in the same preferred term event category, the subject was counted only once.

[b] Most did not occur on the day of infusion and could be related to other factors (e.g., concomitant medications relevant to contusion or ecchymosis, insulin dependent diabetes mellitus).

Immunogenicity

Anti-pegloticase antibodies developed in 92% of patients treated with KRYSTEXXA every 2 weeks, and 28% for placebo. Anti-PEG antibodies were also detected in 42% of patients treated with KRYSTEXXA. High anti-pegloticase antibody titer was associated with a failure to maintain pegloticase-induced normalization of uric acid. The impact of anti-PEG antibodies on patients' responses to other PEG-containing therapeutics is unknown.

There was a higher incidence of infusion reactions in patients with high anti-pegloticase antibody titer: 53% (16 of 30) in the KRYSTEXXA every 2 weeks group compared to 6% in patients who had undetectable or low antibody titers.

As with all therapeutic proteins, there is a potential for immunogenicity. The observed incidence of antibody positivity in an assay is highly dependent on several factors including assay sensitivity and specificity and assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, the comparison of the incidence of antibodies to pegloticase with the incidence of antibodies to other products may be misleading.

Postmarketing Experience

General disorders and administration site conditions: asthenia, malaise, peripheral swelling have been identified during postapproval use of KRYSTEXXA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no adequate and well-controlled studies of KRYSTEXXA in pregnant women. Based on animal reproduction studies, no structural abnormalities were observed when pegloticase was administered by subcutaneous injection to pregnant rats and rabbits during the period of organogenesis at doses up to 50 and 75 times, respectively, the maximum recommended human dose (MRHD). Decreases in mean fetal and pup body weights were observed at approximately 50 and 75 times the MRHD, respectively.

All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinical recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In 2 separate embryo-fetal developmental studies, pregnant rats and rabbits received pegloticase during the period of organogenesis at doses up to approximately 50 and 75 times the maximum recommended human dose (MRHD), respectively (on a mg/m2 basis at maternal doses up to 40 and 30 mg/kg twice weekly, in rats and rabbits, respectively). No evidence of structural abnormalities was observed in rats or rabbits. However, decreases in mean fetal and pup body weights were observed at approximately 50 and 75 times the MRHD in rats and rabbits, respectively (on a mg/m2 basis at maternal doses up to 40 and 30 mg/kg every other day, in rats and rabbits, respectively). No effects on mean fetal body weights were observed at approximately 10 and 25 times the MRHD in rats and rabbits, respectively (on a mg/m2 basis at maternal doses up to 10 mg/kg twice weekly in both species).

Lactation

Risk Summary

It is not known whether this drug is excreted in human milk. Therefore, KRYSTEXXA should not be used when breastfeeding unless the clear benefit to the mother can overcome the unknown risk to the newborn/infant.

Pediatric Use

The safety and effectiveness of KRYSTEXXA in pediatric patients less than 18 years of age have not been established.

Geriatric Use

Of the total number of patients treated with KRYSTEXXA 8 mg every 2 weeks in the controlled studies, 34% (29 of 85) were 65 years of age and older and 12% (10 of 85) were 75 years of age and older. No overall differences in safety or effectiveness were observed between older and younger patients, but greater sensitivity of some older individuals cannot be ruled out. No dose adjustment is needed for patients 65 years of age and older.

Renal Impairment

No dose adjustment is required for patients with renal impairment. A total of 32% (27 of 85) of patients treated with KRYSTEXXA 8 mg every 2 weeks had a creatinine clearance of ≤62.5 mL/min. No overall differences in efficacy were observed.

OVERDOSAGE

No reports of overdosage with KRYSTEXXA have been reported. The maximum dose that has been administered as a single intravenous dose is 12 mg as uricase protein. Patients suspected of receiving an overdose should be monitored, and general supportive measures should be initiated as no specific antidote has been identified.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

General Information

Provide and instruct patients to read the accompanying Medication Guide before starting treatment and before each subsequent treatment.

Anaphylaxis and Infusion Reactions

- Anaphylaxis and infusion reactions can occur at any infusion while on therapy. Counsel patients on the importance of adhering to any prescribed medications to help prevent or lessen the severity of these reactions.
- Educate patients on the signs and symptoms of anaphylaxis, including wheezing, peri-oral or lingual edema, hemodynamic instability, and rash or urticaria.
- Educate patients on the most common signs and symptoms of an infusion reaction, including urticaria (skin rash), erythema (redness of the skin), dyspnea (difficulty breathing), flushing, chest discomfort, chest pain, and rash.
- Advise patients to seek medical care immediately if they experience any symptoms of an allergic reaction during or at any time after the infusion of KRYSTEXXA.
- Advise patients to discontinue any oral urate-lowering agents before starting on KRYSTEXXA and not to take any oral urate-lowering agents while on KRYSTEXXA.

Glucose-6-phosphate dehydrogenase (G6PD) Deficiency

Inform patients not to take KRYSTEXXA if they have a condition known as G6PD deficiency. Explain to patients that G6PD deficiency is more frequently found in individuals of African, Mediterranean, or Southern Asian ancestry and that they may be tested to determine if they have G6PD deficiency, unless already known.

Gout Flares

Explain to patients that gout flares may initially increase when starting treatment with KRYSTEXXA, and that medications to help reduce flares may need to be taken regularly for the first few months after KRYSTEXXA is started. Advise patients that they should not stop KRYSTEXXA therapy if they have a flare.

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Health Care Worker Well-Being

Continued from cover

The effort is timely and "absolutely a step in the right direction," said nephrologist Karen Warburton, MD, an associate professor at the University of Virginia in Charlottesville. "We're essentially in a burnout epidemic right now," Warburton said, noting that surveys among nephrologists estimate the burnout rate to be between 25% and 50%. A complex patient load, a high administrative burden, work that is protocol driven, and a recruitment crisis are just some of the factors impacting nephrologists in particular, she said. "All of this was brought to the surface before COVID-19, and these same physicians have now been practicing in a pandemic for more than 2 years, which for many of us has meant more work intensity and increased burden because the patients are even more complex," Warburton added.

This initiative could potentially be more effective than previous strategies tried because it has a clear focus on the health care system and the need to look more proactively at system drivers of burnout and mental health issues among physicians rather than blaming clinicians or asking them to become more resilient, Warburton said. EHR reforms, ensuring that physician values and priorities align with those of the people making the rules, establishing a positive work and learning environment for physicians, and reducing stigma around seeking help for mental health concerns are imperative, she said.

It is positive that well-being is being recognized, added nephrologist Matthew Sinclair, MD, MHS, FASN, a medical instructor at Duke University School of Medicine and a staff physician with the Durham Veterans Administration Medical Center in North Carolina. "The first step to change is always recognition of the problem," Sinclair said. "People on the front lines have known about this for a very long time, but COVID-19 kind of brought it to the forefront for people not directly involved in medicine or people who typically were able to ignore it," added Sinclair, who coauthored a mental wellness module offered through ASN's website for dialysis facility staff overwhelmed by compassion fatigue and work throughout the pandemic. He and others are working on additional content for the module.

However, he said, to truly benefit clinicians, changes would have to be built into the daily structure, such as giving physicians a paid half-day a week away from patient care to catch up on documentation or whatever else they need. Changes cannot require anything extra on top of an already busy schedule, he said. "Part of the reason that we're so burned out is that there's not enough hours in the day to do all the things we need to do for our patients and also document and do all the things needed for billing and still take care of ourselves and our families," he said.

Having the issue made visible by such large organizations should help encourage universities and hospitals to jump on the bandwagon, said nephrologist Charuhas Thakar, MD, FASN, Robert G. Luke, MD, Endowed Chair in Nephrology and director of the Division of Nephrology and Hypertension at the University of Cincinnati College of Medicine in Ohio. It has been disheartening to see early-career faculty wanting to cut their time to balance work and family life or facing burnout early, Thakar said. "We need some structural changes if we are going to maintain and sustain a physically and mentally healthy workforce for the next decade and beyond," he added.

Work for most university physicians has expanded from 40 hours a week to 55 to 60, Thakar said. Physicians have about 30 minutes for new patient appointments and 15 minutes for established patient appointments, which means that they are either forced to be on the computer documenting during appointments, potentially losing face time, or making up the documentation time after hours at home—one of the biggest contributors to burnout.

EHRs also mean that the doctor is now always available, Thakar added. For example, if a clinic patient calls an after-hours line at 10 p.m., the on-call triage line sends an EHR message to the patient's nephrologist. Many physicians are anxious when they see their inboxes full of alerts before going to bed, he said. "If we sleep on it, literally, then we worry and risk that something can get missed. The real answer is that to meet current and future work expectations, we need a much larger workforce," he said. "We will have to invest in more doctors if we are going to structurally change people's efforts and allow them the time they need to complete the work that the health system expects us to complete in a timely manner."

Yet, there are several reasons to believe this and other efforts can lead to meaningful change, said L. Casey Chosewood, MD, MPH, director of the Office for Total Worker Health at the Centers for Disease Control and Prevention (CDC). As part of the American Rescue Plan of 2021, the CDC's National Institute for Occupational Safety and Health received $20 million in congressional funding to deliver a national awareness and education campaign, aimed at employers, to safeguard and improve the mental health of health care workers. The nation recognizes the challenge that health care workers have faced, which is encouraging, Casey Chosewood said. People also realize that there is no quick fix, and experts are turning to training programs at medical and nursing schools to empower students to ask for better health conditions. "The other thing that's on our side is there's a shortage of workers in this country, and in general, that is an important lever to move [toward] better working conditions," he said. The shortage of workers after World War II, he explained, led to workplace health care benefits, and many health care workers are unionized, especially in large metropolitan areas. "That gives us hope that we really can make a difference."

For more information about the National Plan for health workforce well-being, see https://nam.edu/initiatives/clinician-resilience-and-well-being/national-plan-for-health-workforce-well-being/. ■

Table 1. NAM Action Collaborative on Clinician Well-Being and Resilience national plan priorities

1. **Create and sustain positive work and learning environments and culture.** Transform health systems and health education and training by prioritizing and investing in efforts to optimize environments that prevent and reduce burnout, foster professional well-being, and support quality care.
   Sample actions: Instill approaches to decrease workplace stress and burnout. Invest in adequate, flexible staffing plans that allow for safe patient care and needed backup. Review leadership pathways to ensure they promote diversity and are equitable and inclusive.
2. **Invest in measurement, assessment, strategies, and research.** Expand the uptake of existing tools at the health system level, and advance national research on decreasing health worker burnout and improving well-being.
   Sample actions: Measure the prevalence and drivers of health worker and learner burnout and distress. Create and manage a national registry of evidence-based interventions to facilitate research and innovation aimed at eliminating health worker burnout. Convene conferences to share strategies for improving well-being.
3. **Support mental health, and reduce stigma.** Provide support to health workers by eliminating barriers and reducing stigma associated with seeking services needed to address mental health challenges.
   Sample actions: Provide supportive mental health services for health workers involved in medical errors and safety events. Train and recruit additional mental health professionals to provide care for the health workforce. Increase reimbursement, and re-evaluate prior authorization for mental health services so health workers receive the care they need.
4. **Address compliance, regulatory, and policy barriers for daily work.** Prevent and reduce the unnecessary burdens that stem from laws, regulations, policies, and standards placed on health workers.
   Sample actions: Remove low-value tasks from processes. Involve direct care workers in the development of hybrid workplace policies. Increase automation and deploy health information technology (IT) to ensure timely care for patients.
5. **Engage effective technology tools.** Optimize and expand the use of health ITs that support health workers in providing high-quality patient care and serving population health, and minimize technologies that inhibit clinical decision-making or add to administrative burden.
   Sample actions: Use technology tools to maintain personal safety when treating communicable diseases. Automate processes to streamline the health care team's workflow. Create market advantages for producing technologies that are highly user friendly.
6. **Institutionalize well-being as a long-term value.** Ensure COVID-19 recovery efforts address the toll on health worker well-being, and bolster the public health and health care systems for future emergencies.
   Sample actions: Provide coverage and compensation for direct care workers to engage in meetings and decision-making forums. Facilitate adequate time off without stigma or punishment. Arrange meetings that focus on best practices to improve workforce well-being.
7. **Recruit and retain a diverse and inclusive health workforce.** Promote careers in the health professions, and increase pathways and systems for a diverse, inclusive, and thriving workforce.
   Sample actions: Train and retain people from underrepresented communities in health care and public health. Provide debt-relief opportunities for students and workers. Limit the use of mandatory overtime to emergent situations.

Letter to the Editor

Physician Burnout or Patient Abandonment?

Colleagues:

Dr. Charuhas V. Thakar hits the target squarely in his June 2022 article, Essential versus Necessary: The Ongoing Story of Physician Burnout (1): "This paradigm of care delivery is simply not sustainable."

His critique of the current relative value unit (RVU) treadmill that is the "traditional business plan" is couched in terms of physician burnout. Let me change the perspective: It amounts to patient abandonment. Despite billions of federal and insurer dollars poured into kidney care, more than 134,000 Americans entered end stage kidney disease (ESKD) in 2019. Is that success? Is that good return on investment? Can any rational human being represent the traditional business plan as anything more than a beautiful demonstration of Einstein's comment on doing the same thing over and over and expecting different results? It's insanity. The traditional business plan for nephrology generates large incomes to the practices, burning out the physicians and failing the patients miserably.

Dr. Thakar's analysis, relaying that "one full-time equivalent (FTE) [equates] to 8 out of 10 half-day sessions…which expects the physician to complete an average of 12 patient visits in a 4-hour clinic session…," indicts the current model. Excuse me, but how can a patient who is "sheep dipped" the rest of the day in advertisements for poor-quality food, whose primary and secondary education neglected basic elements of personal health, and whose social milieu encourages the normalization of deviance regarding weight and health habits be expected to change in a 15- to 20-minute encounter when at least half of that time is spent reviewing and renewing medications? Where is the time for mentorship, for diet counseling, and for repairing the medical illiteracy? Answer: There is none. The traditional business plan encourages one thing: more pills.

Why does this "insanity" continue? Where is the vision needed to direct investment to the root causes of the epidemic of kidney diseases? It certainly is not built into the traditional business plan.

To truly affect the abysmal upward trend of kidney diseases and failure in this country, we must abandon the traditional business plan. First, practices must incorporate nurse educators, renal dieticians, pharmacists, and clinical social workers into every nephrology practice, paying them in a way that supplants the RVU treadmill income and instead encourages a longer-term viewpoint. That won't be easy, because the current fragmented reimbursement system is fiscally incapable of treating the immense ESKD cost as a consequence of systemic failure and incentivizing re-direction of money into prevention. Only Congress can make the systemwide reimbursement changes needed to shift the business model from short-term cash flow to long-term prevention investment. Second, the success metric must be shifted from rewarding a higher volume of "wham-bam" encounters to one lowering the number of patients reaching ESKD. That would amount to requiring practices—both primary care and nephrology—to demonstrate a lowering of the dGFR/dt and a progressive reduction in the annual percentage of patients reaching ESKD.

I completely agree with Dr. Thakar: Unless we abandon the traditional business model for one that is data driven, prevention centered, and outcomes sensitive, "We will be ignoring this physician burnout at our own peril and to the detriment of serving our valuable and vulnerable patients."

No truer words were ever spoken.

Respectfully,

Terrence Jay O'Neil, MD, FACP, FASN, Clinical Professor of Medicine, East Tennessee State University, Johnson City, and volunteer (without compensation) affiliate nephrologist, James H. Quillen Department of Veterans Affairs Medical Center, Mountain Home, TN.

Dr. O'Neil is a member of the ASN Quality Committee; president, HD Clean LLC (dialysis), a disabled veteran-owned small business service devoted to developing dialysis safety devices; and a consultant to Lifeblood Foundation (Gaia Software sponsored) for pre-ESKD patient education material development.

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Supreme Court Ruling

Continued from cover

ards, the plan singled out kidney dialysis providers for reimbursement at an "alternative" rate, pegged at 70% to 125% of the Medicare rate.

DaVita sued, saying that Marietta's action violated the Medicare Secondary Payer act, which lays out rules for coverage of dialysis to prevent cost-shifting, according to Daniel Weiner, MD, MS, a nephrologist at Tufts Medical Center and a member of the ASN Policy and Advocacy Committee. The law provides that private insurers are the primary insurers for 30 months after a diagnosis of end stage renal disease (ESRD), after which Medicare kicks in as the primary insurer.

Organizations in the kidney community submitted amicus briefs in support of DaVita, seeing Marietta's approach as a transparent attempt to push dialysis patients from private insurance to Medicare to exploit kidney care's almost unique Medicare coverage.

The arguments

The statute declares that an insurer "may not differentiate in the benefits it provides between individuals having end stage renal disease and other individuals covered by such plan on the basis of the existence of end stage renal disease, the need for renal dialysis, or in any other manner."

A 7 to 2 majority of the court sided with Marietta. The ruling, written by Associate Justice Brett Kavanaugh, said that because Marietta offered the same benefits to all its enrollees, it did not "differentiate" between those with and without ESRD. Kavanaugh said Marietta "provides the same benefits, including the same outpatient dialysis benefits, to individuals with and without end-stage renal disease."

Associate Justices Elena Kagan and Sonia Sotomayor dissented, with Kagan writing the dissent, which asserted that the majority opinion—that the plan does not differentiate between those with ESRD and those without it—"flies in the face of both common sense and the statutory text. One fact is key to understanding this case: Outpatient dialysis is an almost perfect proxy for end stage renal disease. That a proxy is only 99.5% (not 100%) accurate should make no difference. A tax on yarmulkes remains a tax on Jews, even if friends of other faiths might occasionally don one at a Bar Mitzvah.

"As the majority recognizes, the [Medicare Secondary Payer act's] renal disease provisions were designed to prevent plans from foisting the cost of dialysis onto Medicare. Yet the court now tells plans they can do just that, so long as they target dialysis, rather than the patients who rely on it, for disfavored coverage. Congress would not—and did not—craft a statute permitting such a maneuver," Kagan wrote.

"I think that Kagan and Sotomayor got it right when they said that this decision flew against common sense," David White, ASN regulatory and quality officer, said in a July 6 ASN podcast.

Kidney community reaction

The kidney community was swift in its condemnation of the ruling and its potential consequences if other insurers follow suit with Marietta's practice of excluding dialysis from their networks.

"Unfortunately, the Supreme Court's ruling makes it easier for plans to provide insufficient coverage for kidney failure and in doing so, puts patients in the middle of a long-standing feud over the price of dialysis and its availability," said Kevin Longino, chief executive officer of NKF. "For patients, the impact of the court ruling cannot be understated," Longino said. "Some individuals with kidney failure will have to pay for both Medicare benefits (which cover their dialysis needs) AND their [employer-sponsored] benefits…. Other patients may have to transition to Medicare completely and potentially lose supplemental benefits. Others still might choose to leave the workforce rather than have their wages subsidize benefits that are not fully valuable to them. In each of these scenarios, patients lose their agency to select the health plan that maximizes affordability and access, as well as the ability to fully engage in meaningful work" (2).

"The insurer practice at issue—shifting patients prematurely to Medicare—will exacerbate inequalities in access and quality care for an already vulnerable population," said John P. Butler, chair of Kidney Care Partners. "This ruling is a blow to promoting affordable patient choice and instead unfairly shifts costs to the American taxpayer. We feel this decision leaves patients with ESRD vulnerable to discriminatory and inequitable insurer practices…" (3).

A shift to Congress?

Tufts' Weiner said that "providers are not blameless" in the push by insurers to get out from under the high cost of dialysis, given the wildly different amounts charged, with providers who have dominant market shares sometimes charging 10 times what Medicare pays. He noted that if Marietta's practice becomes widespread, the US Congress is bound to take note because shifting tens of thousands of dialysis patients onto Medicare could cost the government hundreds of millions to billions of dollars a year.

"We stand ready and willing to work with Congress and other policymakers to address the gap created by today's ruling and clarify the intent of the Medicare Secondary Payer Act to better protect patients from exclusionary measures like this," said Kidney Care Partners' Butler. "More must be done to ensure that no one is denied or discriminated against because of the treatment they need because of their disease" (3).

"The American Kidney Fund is profoundly concerned about the ramifications of the Supreme Court opinion," said the organization's President and Chief Executive Officer LaVarne A. Burton. "With this decision…patients may lose vital benefits, and they may not have the ability to select the health plan that they need to survive and that best works for

their personal circumstances. People who live in underserved communities, including Black and rural Americans, are hit hardest by kidney failure. AKF is concerned that this ruling will exacerbate the disproportionate impact that kidney failure has on these communities and jeopardize access to life-saving care. The American Kidney Fund…will strongly advocate for policy solutions to address the challenges created by this Supreme Court ruling" (4).

A statement from Dialysis Patient Citizens said, "A U.S. Supreme Court ruling has nullified the law that protects dialysis patients from discrimination by insurers, threatening the system of financing kidney care that has stood for 40 years…. We and other ESRD patient advocates will go back to Congress immediately to clarify the rules once and for all" (5).

Furthermore, Longino said that "NKF is committed to working with the kidney care community to ensure that health plans are required to cover medically necessary maintenance dialysis services…. Especially in the face of the High Court's ruling, we will accelerate our advocacy to ensure that patients have access to [high-quality], affordable treatment options for their kidney failure" (2).

The kidney care community appears to be rallying around Justice Kagan's comment in her dissent: "Congress will have to fix a statute this court has broken." ■

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Policy Update

Fiscal Year 2023 Draft Funding Bill Supports ASN Policy and Kidney Health Priorities

The House Appropriations Committee on Labor, Health and Human Services, Education, and Related Agencies released its draft funding bill for fiscal year (FY) 2023 on June 22. The report language in the bill bolsters the nation's public health infrastructure and strengthens biomedical research and innovation. The bill allocates funding for and directions to agencies and programs on policy priorities for which ASN and the broader kidney health community have advocated. Key policies are highlighted here.

Centers for Disease Control and Prevention (CDC)

The committee includes a total of $10.5 billion for the CDC, which is $2 billion more than the FY 2022-enacted level. The bill includes an increase of $5 million for activities to increase awareness, diagnosis, and treatment of kidney diseases as part of the CDC Chronic Disease Prevention and Health Promotion program.

Health Resources and Services Administration

The draft language released by the committee supports efforts to improve transparency, accountability, and accessibility in organ donation. Specifically, the committee includes $31 million for the Organ Transplantation program and $8 million for the Living Organ Donation Reimbursement Program, each $1 million above their respective FY 2022-enacted levels. The bill supports the expansion of income eligibility for the Living Organ Donation Program to allow as many donors as possible to qualify.

The committee also declares its support in the bill for Medicare's efforts to minimize excessive and frivolous expenses reimbursed to organ procurement organizations (OPOs) and the Organ Procurement and Transplantation Network (OPTN) and encourages the Department of Health and Human Services (HHS) to make all efforts to promote competition for the OPTN contract.

The bill also attempts to reduce organ discards to help alleviate the organ shortage that the nation is facing and supports the procurement and transplantation of kidneys with a moderate-to-high Kidney Donor Profile Index. The bill requests a report within 180 days of enactment on the OPTN proposal to remove donor service areas from allocation and the impact of this policy on organ discards.

Finally, the bill includes a $10 million increase for the Pediatric Subspecialty Loan Repayment Program for a total $15 million. ASN, the American Society of Pediatric Nephrology, and the broader kidney and pediatric subspecialty communities have advocated for this program to help address the significant shortages of pediatricians in underserved areas by helping reduce the barrier of high levels of graduate debt among providers who seek to complete additional training.

National Institutes of Health (NIH)

The bill includes a $2.5 billion increase for NIH above FY 2022-enacted levels, for a total of $47.5 billion. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) receives a $79.5 million increase over FY 2022-enacted levels, for a total of $2.28 billion.

The committee positively impacts the kidney community beyond just funding. Built on the work of the National Kidney Foundation-ASN Task Force on Reassessing the Inclusion of Race in Diagnosing Kidney Diseases, the draft bill includes report language that requests NIDDK to prioritize research of new ways to diagnose kidney diseases that do not include race and for an update on its efforts during the FY 2024 Congressional Justification. The committee also directs the NIH Office of the Director to release a report on kidney disease research, specifically related to health equity concerns.

Centers for Medicare and Medicaid Services (CMS)

The bill acknowledges the committee's support of efforts by CMS to implement the final rule for OPO Conditions for Coverage, including efforts to decertify underperforming OPOs in advance of 2026. Noting that OPO reform is a health equity issue, the committee also encourages CMS to require OPO process data to be publicly available.

The committee indicates its support for CMS efforts to address the unique care needs and services of children with kidney failure in its December 2020 technical expert panel and in the request for information included in the calendar year 2022 End Stage Renal Disease (ESRD) Prospective Payment System proposed rule. The committee requests an update in the FY 2024 Congressional Budget Justification on progress toward establishing adequate bundled payments for pediatric ESRD services.

Office of the Secretary, HHS

The committee continues to include a total of $5 million for Kidney Innovation Accelerator (KidneyX) to enable the program to continue to accelerate innovation in kidney care. KidneyX has been a significant policy priority for ASN and the kidney community since its creation and is frequently highlighted during ASN's advocacy efforts in Congress

Advanced Research Projects Agency for Health (ARPA-H)

Modeled after the Defense Advanced Research Projects Agency, ARPA-H aims to accelerate transformative breakthroughs for many diseases. The committee includes $2.75 billion in funding for ARPA-H and recommends that the agency be established as a separate entity within HHS to ensure its success in driving innovation.

The report language in the bill is non-binding, and the full House and Senate Appropriations Committees may amend this funding legislation moving forward. Although not legally enforceable, report language helps to show the intent of Congress and provides instruction to executive agencies about how to spend their allocated funding. It is particularly useful in advocacy to highlight specific priorities on which executive agencies should take action; agencies typically take the language seriously. As of publication, the Senate has yet to release its report, but typically all of the language in this House report will be carried over to the final enacted conference report and adopted by Congress. ASN will continue to provide updates on the status of the FY 2023 appropriations package. Follow @ASNAdvocacy on Twitter for updates on policy priorities in real time. ■

ASN President's Update

Nephrology: A Commitment to Courage

By Susan E. Quaggin

As we move into the second half of 2022, almost 29 months since a pandemic changed the world, the time to reflect on how nephrology and our field have evolved seems fitting. My pledge to run 850 miles each year to raise awareness for the 850 million people living with kidney diseases provides me ample time for reflection. This weekend, as I hit mile 3, a single word formed in my mind—courage. This word defines our approach to one of the most complex—and rewarding—areas in medicine.

Courage has many definitions. The one I like the best is "mental and moral strength to venture, persevere, and withstand danger, fear, or difficulty" (1). In our specialty's infancy, courage impelled nephrologists to advocate for care where none existed. Today, it enables us to transform our field even as we struggle with unimaginable external stresses.

Trainees who choose nephrology opt to overcome and to manage understandable fears. Recalling my first month as an intern rotating on the nephrology service, I am reminded of some experiences: using emergent dialysis for pulmonary-renal syndrome and a methanol poisoning, calling in patients in the middle of the night to receive a cadaveric transplant and managing them from recovery room to discharge, managing a potassium of 8.5 and a sine wave rhythm, and managing a sodium as low as 109 or as high as 165. These examples define baptism by fire!

Like countless other trainees, I fell in love with the specialty, inspired by the patients. Each year during fellowship interviews, trainees describe their passion for acute management of complex, life-threatening problems *and* emphasize the privilege to develop long-term patient relationships in the ambulatory setting. The ability to handle—and to embrace—the diversity and complexity of conditions that span emergent and long-term care, to step in where others may not, requires fortitude and fearlessness.

Before the end of training, kidney professionals learn to excel in emergency management of diverse conditions, line placements, immunology, and acid-base disorders. As recently told to me by Jane O. Schell, MD, an Associate Professor of Medicine at the University of Pittsburgh School of Medicine, we must recognize our ability and responsibility to walk beside a patient during his or her journey. Truly remarkable advice that clearly demonstrates how much we gain from stepping up to the challenges and joys of our profession.

Of course, it is not hard to call on inner strength and courage when we partner with patients who continually inspire us with their personal story, individual strength, and unique bravery, guiding the profession and using their powerful voices so that the urgent issues surrounding kidney health and kidney diseases are heard by the public, by policymakers, by media, and by other health professionals.

Then there's physical courage and bravery, clearly not unique to nephrology. Physicians are often called on to put their own lives at risk—most recently with the SARS-CoV-2 pandemic. However, during the Ebola outbreak in several countries and SARs outbreak in Toronto, Canada, nephrologists were called on and answered without question. When personal protective equipment was not available, members of the kidney care team—dealing with the incredible burden of acute kidney failure—did not hesitate to provide lifesaving treatments, often requiring prolonged exposure to patients who were not intubated, placing nurses and physicians in harm's way.

We all know colleagues and team members who contracted SARS or SARS-CoV-2 before the vaccinations or treatments, including many who we tragically lost. As a division chief, I am always struck that there is never a shortage of faculty members who immediately volunteer to provide coverage, place lines, or sleep at the hospital—colleagues who are always stepping up during times of crisis. When protests erupted in Chicago, IL, following the murder of George Floyd, nephrologists transported patients when hospital staff could not access the hospital. No job was left unfilled.

In recent events in Ukraine—and over the years in other war-torn countries or during natural disasters, such as hurricanes and earthquakes—nephrologists have again chosen responsibility over fear. Serhan Tuglular, MD, a European Renal Association (ERA) councillor and ERA Renal Disaster Relief Task Force General Coordinator and a nephrologist at the Marmara University School of Medicine in Istanbul, Turkey, led ERA's recent response in Ukraine with support from ASN, the International Society of Nephrology (ISN), and other societies (2), ensuring medications for transplant patients and dialysis options were available.

In 2017, during the devastating hurricanes in the Caribbean, Zaheeb Choudhry, MD, a nephrologist from Aruba and member of the ASN Emergency Partnership Initiative, received a distress call from the medical director of a dialysis unit in St Maarten, which was directly in the path of Hurricane Maria. Unwilling to put patients' lives at risk, Dr. Choudhry coordinated with a friend in the Aruba military to bring him to the island to transport patients to safety. Just minutes before winds would have prohibited their takeoff, they departed and accompanied patients to life-saving treatments in Aruba.

And we are not afraid to disrupt the status quo, to lead where others are reluctant. The call to remove race—a social and not a biologic construct—from clinical algorithms created sometimes heated opposition and online pressure. The members of the National Kidney Foundation-ASN Task Force on Reassessing the Inclusion of Race in Diagnosing Kidney Diseases maintained their focus on ensuring that patients were managed equitably and in September 2020, released and started to implement a new recommendation for a race-free assessment of kidney function (3). ASN, ERA, and ISN are now working together to tackle the issue of kidney function estimates globally where diet and location may impact measurements.

Perhaps the greatest example of courage in our discipline is the tenacity and stamina we have always shown when the patient-physician relationship is threatened. Nephrologists speak up even in the face of opposition and even in times when we are warned to step back. This is not new in our field. Members of the kidney community have always been social and health care justice activists. We have always been courageous. The fight and commitment to advance care for patients, when no care existed, have been exemplified by the pioneers in our field who innovated and created methods to replace kidney function, refining and improving systems, undaunted by monumental obstacles, and resolute to ensure that care reached the greatest number of those in need.

There are many notable giants in our field, whose names we recognize throughout the world. In addition, there are countless unsung heroes who we all know locally, who have made tremendous contributions to our field. When I arrived in Chicago, Peter Ivanovich, MD, an incredibly kind and gentle nephrologist, adored by nurses and still seeing his patients at the Jesse Brown Department of Veterans Affairs Medical Center at the age of 86 years, had been recruited by Belding Scribner, MD, when he was a research trainee. Dr. Ivanovich, who helped solve issues of calcium homeostasis seen in patients on dialysis, would later travel back and forth behind the Iron Curtain, bridging the gap between European and American advances in renal replacement care that catalyzed innovations in treatment.

In the United States, advocacy from giants and unsung heroes, like Dr. Ivanovich, resulted in a law providing access to dialysis for all people with kidney failure through the Medicare program. Medicare itself became law in 1965, just 7 years before the program was expanded to include every American with kidney failure.

In India, home to 17% of the world's population with kidney diseases, the community advocated successfully to launch the Pradhan Mantri National Dialysis Programme (4), providing needed resources for patients in India requiring dialysis. Still, costs of providing kidney replacement therapy are astronomical. As a global community, we are now seizing the moment to be "United 4 Kidney Health" (5) and to advocate for policies, initiatives, and therapies that:

1. INTERVENE EARLIER to prevent, diagnose, coordinate care, and educate.
2. TRANSFORM TRANSPLANT and increase access to donor kidneys.
3. ACCELERATE INNOVATION and expand patient choice.
4. ACHIEVE EQUITY and eliminate disparities.

Nephrologists' activism is aligned with our approach to care: We have always been precision and data driven. When we see evidence of a negative impact on our patients, we act with courage. This is why we have always led as health care justice activists, providing and fighting for optimal care for all patients (6). Since 1983, ASN has bestowed the John P. Peters Award, which celebrates Dr. Peters' "urging that public funds support medical care for the indigent, medical research, and the improvement of medical education, and that federal health and medical activities be consolidated into a separate department" (7).

In the same week that the U.S. Supreme Court ruled to overturn Roe v. Wade, it also ruled in favor of the Marietta Memorial Hospital Employee Health Benefit Plan in its lawsuit with DaVita (8, 9). The court decided that a health plan can refuse to pay for lifesaving dialysis for its insured patients with kidney failure. In so ruling, the court has likely forced patients prematurely off their health plan onto Medicare, potentially leaving other family members, who do not qualify for Medicare, uninsured and resulting in additional financial burden for kidney patients (10). In her dissent, Justice Elena Kagan asserted, "Now Congress will have to fix a statute this Court has broken" (8).

The entire kidney community is banding together to ensure Congress fixes what the court has broken. "The insurer practice at issue—shifting patients prematurely to Medicare—will exacerbate inequalities in access and quality care for an already vulnerable population," said John P. Butler, chair of Kidney Care Partners (KCP), a coalition of which ASN is a member. "Despite this ruling, KCP remains steadfast in our commitment to ensuring equitable, affordable access to quality care for the millions of individuals living with or at risk for kidney disease," Mr. Butler added (11).

As I wrote to the kidney community earlier this year (12), we will bring our values with us to the first in-person Kidney Week since 2019. ASN Kidney Week 2022 is taking place in Orlando, FL, and we will stand up to legislative actions that threaten our colleagues and patients (13).

Few other specialties require such skill and knowledge, art and creativity, and bravery and resolve in making rapid, "on your feet" decisions and displaying such iron-willed determination to improve and transform a global chronic disease. We

are always on the frontlines—leading during times of turbulence and peace. We stand up and lead when it is convenient and when it is not. We do not stand silently by when actions might harm our patients or our field. We commit to excellence in care and accept all the burden that promise requires.

Courage—by any definition—is nephrology. ■

Susan E. Quaggin, MD, FASN, is with the Division of Nephrology and Hypertension, Northwestern University Feinberg School of Medicine, Chicago, IL, and is ASN President.

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Perspectives from the ASN Task Force on the Future of Nephrology: Development of Its Upcoming Recommendation

The ASN Task Force on the Future of Nephrology was established in April 2022 to evaluate the specialty and develop a recommendation to ensure nephrologists are best prepared to provide care to people with kidney diseases. The ASN task force (see box) has been meeting weekly to discuss core and evolving elements of nephrology that must be considered in future training requirements. Additionally, the task force has hosted a series of listening sessions with various constituencies or partner organizations to understand the changing needs of the community as well as the evolution of medical education.

As medicine and health care continue to evolve and as nephrology continues to face a workforce shortage, it is imperative to pause and reflect on the past, present, and future. "Every profession evolves and changes over time," reflects Benjamin D. Humphreys, MD, PhD, FASN. "I was drawn to serve on the task force because I wanted to contribute to planning for where our field is headed." For these experienced task force members, there is an innate passion for the field of nephrology that exudes in the weekly questioning, discussion, and debate.

"Nephrology needs to reclaim our role as the 'smartest doctors in the room,'" said Sharon Anderson, MD, FASN. "In addition to losing procedures to other specialties, some [specialties] are taking over some of the cognitive areas where nephrology traditionally led, such as treatment of hypertension (cardiology), acid-base and electrolyte disorders (critical care), and others."

While reflecting on what may be lost or changing, there is excitement for current trends and future opportunities in the field. Samira S. Farouk, MD, MS, FASN, stated, "What excites me most about the future of nephrology is simultaneous growth and innovation in several spheres—including therapeutic advances, research, education, clinical care, and personalization of treatment options for our patients with kidney disease." Her fellow task force member, Suneel M. Udani, MD, FASN, couldn't agree more. "The shift in focus of therapeutic interventions from dialysis to earlier in the course of renal disease and with more disease-specific therapies is exciting. The last few years have brought the identification of specific auto-antibodies in diseases such as membranous nephropathy and minimal change disease and the incorporation of genetic testing in diagnostic evaluation as well as the first ever FDA-approved therapy for rare renal diseases such as IgAN [immunoglobulin A nephropathy]. The momentum is clearly there for more progress," Udani said.

With all the opportunity, the task force is listening hard for solutions to several challenges. "Ensuring diversity, equity, and racial justice is probably the most important task before us and will be the most difficult to accomplish. Initiatives to help us diversify our ranks, ensure that we provide culturally competent care, and empower future nephrologists to advocate on behalf of our patients will be needed to help improve the care of patients with kidney disease," reflected Joshua S. Waitzman, MD, PhD.

"In general, training has been trending toward more specialization. I think we need to embrace that trend in nephrology, while making sure that we maintain general nephrology, especially to meet the demands in rural areas. In order to support both general nephrology needs and opportunities for specialization within nephrology, we will need more trainees. Thus, the selection of nephrology subspecialties to support and grow the trainee pool is critical," shared Robert S. Hoover, Jr., MD, FASN, task force member and chair of the ASN Workforce and Training Committee.

Since April, the task force members have contributed hours to dissect and deliberate this challenge. One thing remains clear to Janis M. Orlowski, MD: "I love being a nephrologist and believe our specialty remains interesting, academically rigorous, exciting, dynamically changing, and professionally fulfilling. We need to carve a clear view of what nephrologists can and should contribute now and in the future. I'm honored to have been asked to serve on this committee."

"On behalf of the ASN Council, I would like to thank and acknowledge the ASN Task Force on the Future of Nephrology on their commitment and thoughtful deliberation. I have enjoyed the presentation of data, diverse opinions, but more specifically, the focus on doing the right thing for the future of nephrology," said Keisha L. Gibson, MD, FASN, MPH. "We are on target to release [the task force's] recommendation this fall and look forward to working with the community on implementation."

For more information on the task force or to provide your thoughts and ideas on the future of nephrology, please email Melissa West, ASN's Senior Director for Strategic Relations and Patient Engagement, at mwest@asn-online.org. ■

ASN Task Force on the Future of Nephrology

Sharon Anderson, MD, FASN
Oregon Health and Science University

Samira S. Farouk, MD, MS, FASN
Icahn School of Medicine at Mt. Sinai

Keisha L. Gibson, MD, FASN, MPH, ASN Council Liaison
University of North Carolina, Chapel Hill

Robert S. Hoover, Jr., MD, FASN
Tulane University School of Medicine

Benjamin D. Humphreys, MD, PhD, FASN
Washington University School of Medicine

Janis M. Orlowski, MD
Association of American Medical Colleges (former)

Mark E. Rosenberg, MD, FASN, Chair
University of Minnesota Medical School

Suneel M. Udani, MD, FASN
Nephrology Associates of Northern Illinois and Indiana

Joshua S. Waitzman, MD, PhD
Beth Israel Deaconess Medical Center

Fighting Infections from COVID-19 Misinformation

The medical community steps up efforts to police itself to stop the spread of misinformation and disinformation

By Eric Seaborg

The medical establishment is finding ways to push back against the minority of physicians and other health care providers who have been disseminating misinformation about COVID-19 vaccines and treatments, but in today's polarized environment, even this effort has encountered a backlash from some state legislators.

The Federation of State Medical Boards (FSMB) took a major step on July 29, 2021 (1), when it posted a statement on its website "in response to a dramatic increase in the dissemination of COVID-19 vaccine misinformation and disinformation by physicians and other health care professionals on social media platforms, online[,] and in the media. Physicians who generate and spread COVID-19 vaccine misinformation or disinformation are risking disciplinary action by state medical boards, including the suspension and revocation of their medical license." Many certification boards quoted FSMB or posted similar statements, including the American Board of Internal Medicine (ABIM) (2), American Board of Medical Specialties, and the boards of emergency medicine, pathology, family medicine, and pediatrics.

Board officials might have thought that standing against disinformation was just a part of their jobs, but after one state board of medical examiners posted its statement, a powerful state legislator threatened to dissolve the board for overstepping its bounds. "A plethora of bills" have been introduced in state legislatures seeking to rein in the powers of state boards of medicine when it comes to physician actions and statements on COVID-19 vaccines and treatment, according to Lisa Robin, MLA, chief advocacy officer at FSMB.

In December 2021, FSMB released findings from an annual survey, which found that two-thirds of state boards experienced an increase in complaints related to licensee dissemination of false or misleading information. FSMB noted that at least 15 state boards had published statements against misinformation, and at least 12 boards had "taken disciplinary action against a licensee for spreading false or misleading information."

Ethics Committee report

FSMB followed up in April 2022 (3) when its House of Delegates adopted a report from its Ethics Committee, entitled "Professional expectations regarding medical misinformation and disinformation." The report noted that "Honesty, truthfulness[,] and transparency are virtues that society expects of all health professionals." It defined medical misinformation as "Health-related information or claims that are false, inaccurate[,] or misleading, according to the best available scientific evidence at the time." It defined disinformation as "Misinformation that is spread intentionally to serve a malicious purpose, such as financial gain or political advantage."

Cautions from ABIM

On the heels of the FSMB action, *The New England Journal of Medicine* published a "perspective" article on May 18, 2022, on "Physicians spreading misinformation on social media…" by Richard J. Baron, MD, CEO of ABIM, and Yul D. Ejnes, MD, chair of the ABIM Board of Directors (4). "ABIM has long had a policy that unprofessional or unethical behavior can lead to revocation of an ABIM certificate," Baron and Ejnes wrote. They said ABIM issued a policy statement in October "making clear that 'providing false or inaccurate information to patients or the public is unprofessional and unethical and … constitutes grounds for disciplinary sanctions.'"

The authors wrote that many areas of medicine are not settled and are subject to disagreement, but when "Someone certified by the ABIM says something like … 'children can't spread COVID' or 'vaccines don't prevent COVID deaths or hospitalizations,' we are not dealing with professional disagreement; we are dealing with wrong answers. We physicians need to use the institutions we've created for professional self-regulation to maintain public trust by establishing some recognizable boundaries."

Legislative pushback

However, even what FSMB and ABIM consider an obvious principle—to not disseminate misinformation—has received pushback from those claiming that patients should have the

"freedom" to access treatments, such as ivermectin and hydroxychloroquine, even though the vast majority of physicians accept the evidence that they are ineffective treatments for COVID-19.

At a meeting in September 2021, the Tennessee Board of Medical Examiners endorsed the FSMB statement and posted a version on its website. When a powerful Republican member of the Tennessee Senate learned of the action, he notified the board that it had exceeded its legal authority and threatened to introduce legislation to dissolve the board. The board had a special meeting at which it voted to remove the statement from the website but did not necessarily abandon its efforts against misinformation.

The FSMB's Robin said that "The board chair pushed back. She publicly stated that the board would continue to investigate instances of physicians spreading disinformation."

But this pattern of state legislatures challenging boards' independence has become common, with more than 83 bills introduced in 31 states in 2021 to restrict boards' disciplinary authority or to explicitly protect off-label uses of drugs to treat COVID-19 (5). A few of the bills have passed. North Dakota enacted a law that prohibits its Board of Medicine from disciplining a licensee solely because the licensee dispensed ivermectin for off-label treatments, such as for COVID-19. Tennessee and Missouri enacted similar legislation prohibiting disciplinary action against physicians for their approach to treating COVID-19.

FSMB opposes such legislation to limit a board's work because "It sets a dangerous precedent and puts the public at risk." Robin said, "It is something that we have not seen before.... It is concerning…" to see a legislature override the authority of the professionals and public members who are appointed for their expertise.

Most of these bills are being considered in red states, and in contrast, California is the only state with a bill moving through its legislature that defines misinformation and specifically empowers the state medical board to act against physicians who spread it. On June 13, 2022, the American Medical Association adopted a policy aimed at combating public health disinformation, with one of its priorities to ensure that "…licensing boards have the authority to take disciplinary action against health professionals for spreading health-related disinformation…" (6).

Nephrology angle

Despite the increase in complaints about misinformation to

Continued on page 14 >

COVID-19 Misinformation

Continued from page 13

medical boards, several prominent nephrologists interviewed by *Kidney News* agreed that the problem is less visible in nephrology.

"Fortunately, it seems that spreading misinformation is not a widespread problem in the nephrology physician community," said Rudolph A. Rodriguez, MD, director of hospital and specialty medicine at the Veterans Affairs (VA) Puget Sound Medical Center in Seattle, WA, and chair of the ABIM Nephrology Board. "Health systems and professional societies need to step up and find ways to ensure patients know how to find good information."

"The ABIM Nephrology Board will not be taking any action independent of the general ABIM actions," Rodriguez said, but a top-level administrator at the VA sent a link to *The New England Journal of Medicine* article to a list that included all the VA chief medical officers "reminding our staff that sharing and condoning medical misinformation is an issue that we continue to address nationally."

As part of its campaign, ABIM emailed medical society leaders and others a "communications toolkit" encouraging them to become active in its campaign against misinformation. The toolkit includes sample emails to send colleagues with a link to *The New England Journal of Medicine* article, a draft copy to use in a newsletter, a sample Letter to the Editor to send to mainstream media, and sample social media posts.

Deidra Crews, MD, a former ABIM Nephrology Board member and professor of medicine at Johns Hopkins University in Baltimore, MD, said that she has encountered some disinformation in the kidney community, but it is "rare." She said that some "safeguards" in place to prevent the spread of misinformation at forums, such as conferences, are the presence of gatekeepers to "guard against those who may be known for spreading misinformation" and to request slides ahead of time to review what a person plans to say. "There can be times when what is said during a conference could be something that many may find to be offensive or to be misinformation, and then you [may have to] make a counter statement," Crews said.

Matthew Sparks, a current ABIM Nephrology Board member and assistant professor of medicine at Duke University in Durham, NC, said that "It is becoming increasingly important to have a presence online to whatever capacity you feel comfortable. That can be just a website," or

it could involve finding ways for greater advocacy to combat misinformation. Sparks is the program director for the Nephrology Social Media Collective Internship, a yearlong curriculum that teaches how to use social media effectively "to be part of the solution." Information on the program, which began in 2015, is available at www.nsmc.blog (7). "There is no way to eliminate misinformation, so it is imperative that all of us take it upon ourselves to call it out and also put out information that is not only accurate but [is also] backed up by data," Sparks said. ■

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Findings

Azithromycin Linked to Sudden Cardiac Death in Dialysis Patients

In patients with hemodialysis-dependent kidney failure, treatment with the macrolide antibiotic azithromycin is associated with an increased risk of sudden cardiac death (SCD), reports a preproof paper in *Kidney International*.

Using data from the US Renal Data System, the researchers performed a cohort study to assess the cardiac safety of azithromycin compared with amoxicillin-based antibiotics in patients on hemodialysis from 2007 through 2017. A separate cohort study compared azithromycin with levofloxacin, a fluoroquinolone antibiotic that, like azithromycin, is known to prolong the QT interval.

The two studies included 381,306 treatment episodes with azithromycin versus 344,125 with amoxicillin-based antibiotics and 387,382 treatment episodes with azithromycin versus 167,175 with levofloxacin. The main outcome of interest was the 5-day risk of SCD.

Compared with amoxicillin or amoxicillin/clavulanic acid, azithromycin was associated with a significantly increased risk of SCD (weighted hazard ratio [HR], 1.70). Absolute risk was also higher with azithromycin (weighted incidence, 36.5 vs. 15.5 per 100 treatment episodes). For the first 5 days, azithromycin would result in one additional case of SCD for every 4000 treatment episodes compared with amoxicillin.

In the second cohort study, azithromycin was associated with a lower risk of SCD compared with levofloxacin. The weighted HR for azithromycin was 0.79, with an absolute

Table 2: Incidence of Overall[a] and Severe[b] Hypoglycemic Events in Placebo-Controlled Clinical Studies[c]

Monotherapy (24 weeks)	**Placebo (n=229)**	**JARDIANCE 10 mg (n=224)**	**JARDIANCE 25 mg (n=223)**
Overall (%)	0.4	0.4	0.4
Severe (%)	0	0	0
In Combination with Metformin (24 weeks)	**Placebo + Metformin (n=206)**	**JARDIANCE 10 mg + Metformin (n=217)**	**JARDIANCE 25 mg + Metformin (n=214)**
Overall (%)	0.5	1.8	1.4
Severe (%)	0	0	0
In Combination with Metformin + Sulfonylurea (24 weeks)	**Placebo (n=225)**	**JARDIANCE 10 mg + Metformin + Sulfonylurea (n=224)**	**JARDIANCE 25 mg + Metformin + Sulfonylurea (n=217)**
Overall (%)	8.4	16.1	11.5
Severe (%)	0	0	0
In Combination with Pioglitazone +/- Metformin (24 weeks)	**Placebo (n=165)**	**JARDIANCE 10 mg + Pioglitazone +/- Metformin (n=165)**	**JARDIANCE 25 mg + Pioglitazone +/- Metformin (n=168)**
Overall (%)	1.8	1.2	2.4
Severe (%)	0	0	0
In Combination with Basal Insulin +/- Metformin (18 weeks[d])	**Placebo (n=170)**	**JARDIANCE 10 mg (n=169)**	**JARDIANCE 25 mg (n=155)**
Overall (%)	20.6	19.5	28.4
Severe (%)	0	0	1.3
In Combination with MDI Insulin +/- Metformin (18 weeks[d])	**Placebo (n=188)**	**JARDIANCE 10 mg (n=186)**	**JARDIANCE 25 mg (n=189)**
Overall (%)	37.2	39.8	41.3
Severe (%)	0.5	0.5	0.5

[a]Overall hypoglycemic events: plasma or capillary glucose of less than or equal to 70 mg/dL
[b]Severe hypoglycemic events: requiring assistance regardless of blood glucose
[c]Treated set (patients who had received at least one dose of study drug)
[d]Insulin dose could not be adjusted during the initial 18 week treatment period

Genital Mycotic Infections: In the pool of five placebo-controlled clinical trials, the incidence of genital mycotic infections (e.g., vaginal mycotic infection, vaginal infection, genital infection fungal, vulvovaginal candidiasis, and vulvitis) was increased in patients treated with JARDIANCE compared to placebo, occurring in 0.9%, 4.1%, and 3.7% of patients randomized to placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg, respectively. Discontinuation from study due to genital infection occurred in 0% of placebo-treated patients and 0.2% of patients treated with either JARDIANCE 10 or 25 mg. Genital mycotic infections occurred more frequently in female than male patients (see Table 1). Phimosis occurred more frequently in male patients treated with JARDIANCE 10 mg (less than 0.1%) and JARDIANCE 25 mg (0.1%) than placebo (0%). *Urinary Tract Infections:* In the pool of five placebo-controlled clinical trials, the incidence of urinary tract infections (e.g., urinary tract infection, asymptomatic bacteriuria, and cystitis) was increased in patients treated with JARDIANCE compared to placebo (see Table 1). Patients with a history of chronic or recurrent urinary tract infections were more likely to experience a urinary tract infection. The rate of treatment discontinuation due to urinary tract infections was 0.1%, 0.2%, and 0.1% for placebo,JARDIANCE 10 mg, and JARDIANCE 25 mg, respectively. Urinary tract infections occurred more frequently in female patients. The incidence of urinary tract infections in female patients randomized to placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg was 16.6%, 18.4%, and 17.0%, respectively. The incidence of urinary tract infections in male patients randomized to placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg was 3.2%, 3.6%, and 4.1%, respectively *[see Use in Specific Populations]*. Clinical Trials in Patients with Heart Failure: The EMPEROR-Reduced study included 3730 patients with heart failure and left ventricular ejection fraction (LVEF) ≤40% followed for a median of 16 months, and EMPEROR-Preserved included 5988 patients with heart failure and LVEF >40% followed for a median of 26 months. In both studies, patients were randomized to JARDIANCE 10 mg or placebo. The safety profile in patients with heart failure was generally consistent with that observed in patients with type 2 diabetes mellitus. *Laboratory Tests:* Increases in Serum Creatinine and Decreases in eGFR: Initiation of JARDIANCE causes an increase in serum creatinine and decrease in eGFR within weeks of starting therapy and then these changes stabilize. In a study of patients with moderate renal impairment, larger mean changes were observed. In a long-term cardiovascular outcomes trial, the increase in serum creatinine and decrease in eGFR generally did not exceed 0.1 mg/dL and -9.0 mL/min/1.73 m^2, respectively, at Week 4, and reversed after treatment discontinuation, suggesting acute hemodynamic changes may play a role in the renal function changes observed with JARDIANCE. Increase in Low-Density Lipoprotein Cholesterol (LDL-C): Dose-related increases in low-density lipoprotein cholesterol (LDL-C) were observed in patients treated with JARDIANCE. LDL-C increased by 2.3%, 4.6%, and 6.5% in patients treated with placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg, respectively. The range of mean baseline LDL-C levels was 90.3 to 90.6 mg/dL across treatment groups. Increase in Hematocrit: In a pool of four placebo-controlled studies, median hematocrit decreased by 1.3% in placebo and increased by 2.8% in JARDIANCE 10 mg and 2.8% in JARDIANCE 25 mg treated patients. At the end of treatment, 0.6%, 2.7%, and 3.5% of patients with hematocrits initially within the reference range had values above the upper limit of the reference range with placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg, respectively. **Postmarketing Experience:** Additional adverse reactions have been identified during postapproval use of JARDIANCE. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure. *Gastrointestinal Disorders:* Constipation; *Infections:* Necrotizing fasciitis of the perineum (Fournier's gangrene), urosepsis and pyelonephritis; *Metabolism and Nutrition Disorders:* Ketoacidosis; *Renal and Urinary Disorders:* Acute kidney injury; *Skin and Subcutaneous Tissue Disorders:* Angioedema, skin reactions (e.g., rash, urticaria).

DRUG INTERACTIONS:

Table 3: Clinically Relevant Interactions with JARDIANCE

Diuretics	
Clinical Impact	Coadministration of empagliflozin with diuretics resulted in increased urine volume and frequency of voids, which might enhance the potential for volume depletion.
Intervention	Before initiating JARDIANCE, assess volume status and renal function. In patients with volume depletion, correct this condition before initiating JARDIANCE. Monitor for signs and symptoms of volume depletion, and renal function after initiating therapy.
Insulin or Insulin Secretagogues	
Clinical Impact	The risk of hypoglycemia is increased when JARDIANCE is used in combination with insulin secretagogues (e.g., sulfonylurea) or insulin.
Intervention	Coadministration of JARDIANCE with an insulin secretagogue (e.g., sulfonylurea) or insulin may require lower doses of the insulin secretagogue or insulin to reduce the risk of hypoglycemia.
Positive Urine Glucose Test	
Clinical Impact	SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests.
Intervention	Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.
Interference with 1,5-anhydroglucitol (1,5-AG) Assay	
Clinical Impact	Measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors.
Intervention	Monitoring glycemic control with 1,5-AG assay is not recommended. Use alternative methods to monitor glycemic control.

USE IN SPECIFIC POPULATIONS: Pregnancy: *Risk Summary:* Based on animal data showing adverse renal effects, JARDIANCE is not recommended during the second and third trimesters of pregnancy. The limited available data with JARDIANCE in pregnant women are not sufficient to determine a drug-associated risk for major birth defects and miscarriage. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy *[see Clinical Considerations]*. In animal studies, adverse renal changes were observed in rats when empagliflozin was administered during a period of renal development corresponding to the late second and third trimesters of human pregnancy. Doses approximately 13-times the maximum clinical dose caused renal pelvic and tubule dilatations that were reversible *[see Data]*. The estimated background risk of major birth defects is 6% to 10% in women with pre-gestational diabetes with a HbA1c >7 and has been reported to be as high as 20% to 25% in women with HbA1c >10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. Clinical Considerations: *Disease-associated maternal and/or embryo/fetal risk:* Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity. *Data:* Animal Data: Empagliflozin dosed directly to juvenile rats from postnatal day (PND) 21 until PND 90 at doses of 1, 10, 30 and 100 mg/kg/day caused increased kidney weights and renal tubular and pelvic dilatation at 100 mg/kg/day, which approximates 13-times the maximum clinical dose of 25 mg, based on AUC. These findings were not observed after a 13-week, drug-free recovery period. These outcomes occurred with drug exposure during periods of renal development in rats that correspond to the late second and third trimester of human renal development. In embryo-fetal development studies in rats and rabbits, empagliflozin was administered for intervals coinciding with the first trimester period of organogenesis in humans. Doses up to 300 mg/kg/day, which approximates 48-times (rats) and 128-times (rabbits) the maximum clinical dose of 25 mg (based on AUC), did not result in adverse developmental effects. In rats, at higher doses of empagliflozin

risk difference of –18.9 per 100,000 treatment episodes. Compared with levofloxacin, azithromycin would avoid one case of SCD during the first 5 days per 5921 treatment episodes.

Azithromycin is a broad-spectrum macrolide antibiotic, widely used for respiratory infections, and has a known QT-prolonging potential. Hemodialysis patients may be especially susceptible to this QT-prolonging effect and its potential consequences, including SCD.

This large analysis of US hemodialysis patients shows a higher risk of SCD after starting treatment with azithromycin compared with amoxicillin-based antibiotics. Azithromycin is associated with a lower SCD risk than levofloxacin in the same patient population. The investigators conclude: "When selecting among azithromycin, levofloxacin, and amoxicillin-based antibiotics, clinicians should weigh the relative antimicrobial benefits of these drugs against their potential cardiac risks" [Assimon MM, et al. Azithromycin use increases the risk of sudden cardiac death in patients with hemodialysis-dependent kidney failure. *Kidney Int*, published online ahead of print June 22, 2022; doi: 10.1016/j.kint.2022.05.024; https://www.kidney-international.org/article/S0085-2538(22)00461-6/fulltext]. ■

Stem Cell Protocol May Enable Kidney Transplant without Immunosuppression in Pediatric Patients

A dual immune/solid organ transplant procedure has been successfully used to perform kidney transplantation without the need for long-term immunosuppressive therapy in three children with a rare genetic disorder, according to a brief report in *The New England Journal of Medicine* (1). The study was led by Alice Bertaina, MD, PhD, of the Division of Stem Cell Transplantation and Regenerative Medicine and associate professor of pediatrics at Stanford University.

The patients were three children (two siblings) with Schimke immuno-osseous dysplasia (SIOD), an autosomal recessive disease associated with short stature due to bone dysplasia, glucocorticoid-resistant nephrotic syndrome, and T cell immunodeficiency. All underwent αβ T cell-depleted and CD19 B cell-depleted hematopoietic stem cell transplantation from haploidentical parents. This regimen has been successfully used in patients with nonmalignant diseases with low rates of acute and chronic graft-versus-host disease and transplant-related death.

After the children had received confirmation of immune reconstitution, they received living-donor kidney transplants from the same parental donors. Peri-transplant immunosuppressive drugs were given to reduce reperfusion-related inflammation, but the drugs were tapered off within 30 days, after which, the children received no further immunosuppression.

Follow-up studies confirmed successful engraftment, with full donor and myeloid chimerism. At up to 34 months after transplantation, the transplant recipients had normal kidney function with no evidence of rejection. In vitro studies showed that circulating donor-derived T cells had functional tolerance to the transplanted kidney alloantigens and thus were potentially unable to mediate graft rejection.

As noted in a press release from Stanford Medicine (2), the dual immune/solid organ transplant procedure has received US Food and Drug Administration approval for use in SIOD and several other diseases causing kidney damage. The researchers plan further studies evaluating the protocol for other patients in need of kidney transplantation and for other types of solid organ transplants. ■

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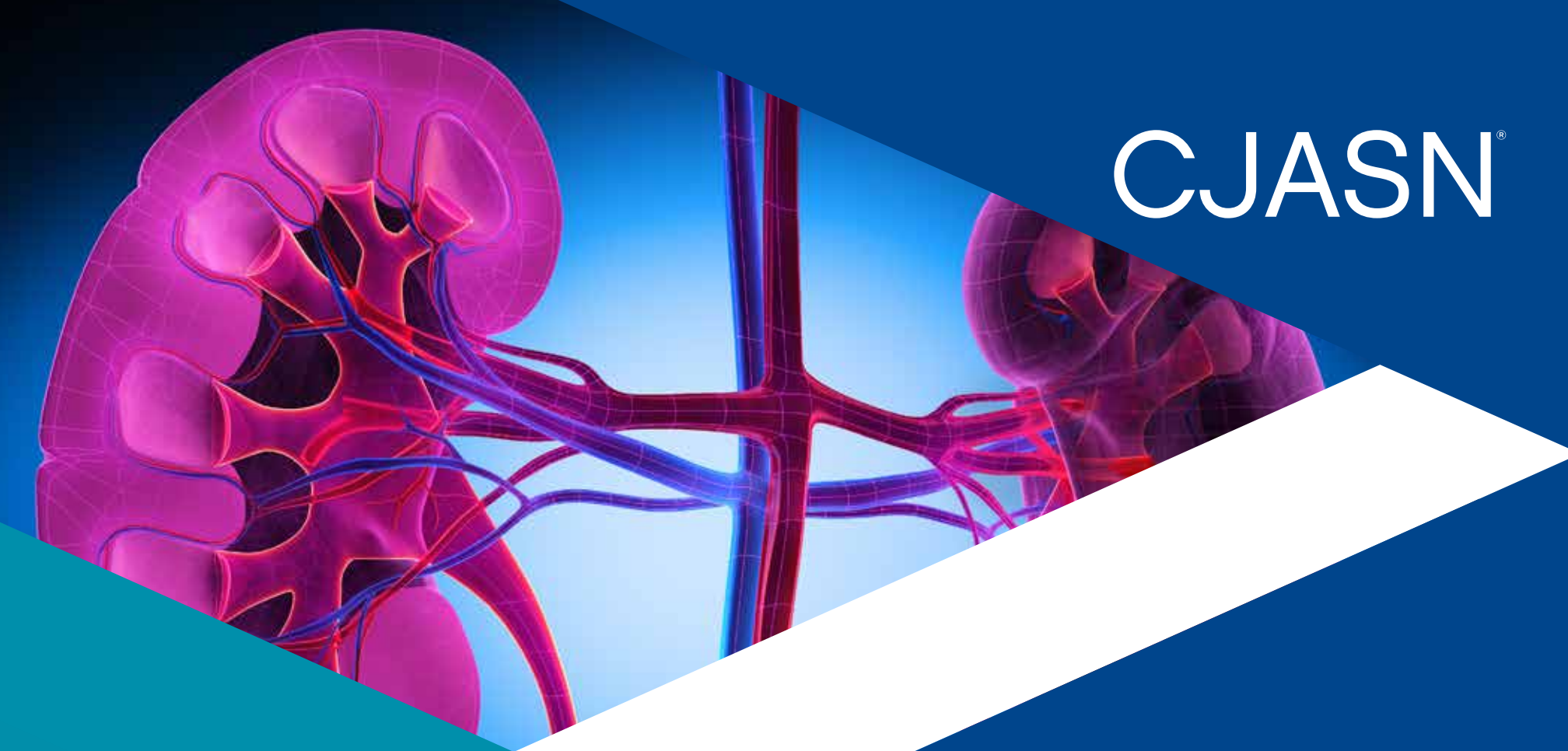

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KIDNEY TRANSPLANTATION
Arrival of the Next Frontier
PART II

By Sam Kant, Daniel C. Brennan, and Samira Farouk

As featured in the July edition of *Kidney News*, this issue again highlights advances in kidney transplantation. The July issue included articles on the new kidney transplant allocation system, updates from the *apolipoprotein L1* (*APOL1*) Long-term Kidney Transplantation Outcomes (APOLLO) study, recent groundbreaking advances in xenotransplantation, racial inequities and measures to address them, and a review of the increasingly encountered challenge of oxalosis in kidney transplantation. We now turn our attention to genomics, biomarkers, new insights into thrombotic microangiopathy (TMA), focal segmental glomerulosclerosis recurrence in transplantation, and finally, updates on the use of belatacept.

Since the first successful kidney transplant in 1954, genetic mismatch has been recognized as an important factor in determining graft outcomes. In this issue, Dr. Elhassan and colleagues track the arc of genomics in kidney transplantation over the last six decades. We now recognize that genomics in kidney transplantation goes beyond the human leukocyte antigen system. Genome-wide association studies have identified genetic signals that can be associated with 5-year graft outcomes and development of skin cancer (1). In addition to discussing genetic determinants affecting the metabolism of immunosuppression, the authors delve into the novel concept of "genomic collision," defined as a phenomenon in which kidney donor cells express proteins on their surface that are not present in the recipient and elicit an immunologic response, which ultimately results in measurable donor-specific antibodies and poorer graft outcomes (2).

Kidney transplantation has progressed on multiple fronts.

Reliable biomarkers continue to elude the field of kidney transplantation, and a large number of kidneys may be discarded because of unfavorable "donor characteristics," despite the lack of association between severe donor kidney injury and adverse recipient outcomes (3). Drs. Wen and Parikh discuss emerging kidney repair biomarkers that could be used to predict the likelihood of delayed graft function and therefore, reduce organ discards.

Dr. Java provides new insights into the pathogenesis of TMA in transplantation, which can be a diagnostic conundrum. She describes different presentations of TMA, an algorithmic approach in the setting of suspected disease, and guidelines for the duration of eculizumab treatment.

Focal segmental glomerulosclerosis (FSGS) continues to be a therapeutic quandary for both general and transplant nephrologists. Drs. Hullekes and Verhoeff and co-authors provide a background to this disease in kidney transplantation, along with updates to our understanding of the pathogenesis. Anti-nephrin antibodies have been increasingly implicated in FSGS, with the authors proposing their use as a potential biomarker before transplantation in a subset of patients (4, 5). In addition, they discuss the importance of genetic testing in FSGS to further clarify risk of recurrence post-transplantation.

Belatacept is increasingly being used as part of the immunosuppression regimen in the United States. Dr. Kott and colleagues discuss recent studies involving belatacept and various settings in which it may be considered an alternative to calcineurin inhibitors.

The content covered in these editions of *Kidney News* has shown that kidney transplantation has progressed on multiple fronts. There continue to be multiple challenges and uncertainties that will require a concerted, patient-centered effort to solve. ■

Sam Kant, MD, and Daniel C. Brennan, MD, are with the Comprehensive Transplant Center, Johns Hopkins University School of Medicine, Baltimore, MD. Samira Farouk, MD, MS, FASN, is with the Barbara T. Murphy Division of Nephrology, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY.

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Genomics in Kidney Transplantation

By Elhussein A. E. Elhassan, Kane Collins, Edmund Gilbert, and Peter J. Conlon

The importance of genomic mismatch between donor and recipient in organ transplantation has been appreciated since Dr. Joseph E. Murray undertook the first successful kidney transplantation in 1954 (1). This seminal event confirmed the critical role that genetics plays in transplant outcome. Subsequent studies demonstrated the importance of genetically inherited human leukocyte antigen (HLA) mismatch between donor and recipient. To guide decision-making in living donors, genomics functions as an additional toolkit to determine susceptibility of a specific inherited disease aggregating among families or specific ancestries, such as apolipoprotein L1 (APOL1) nephropathy.

In the 1990s and early 2000s, several groups studied the impact of individual single nucleotide polymorphisms (SNPs) on graft outcome and kidney transplantation complications. Many studies were undertaken in which an investigator's specific SNP of interest was chosen and examined for transplant-related outcomes, such as acute rejection or graft function. However, these studies were substantially underpowered statistically, and their findings were rarely replicated.

In 2007, the genome-wide association study (GWAS) was introduced. With this approach, hundreds of thousands of SNPs were investigated for association with transplant-related outcomes. These studies brought several methodological improvements; they involved many patients to achieve statistical power, they adjusted for multiple comparisons, and they typically required a p value of 10^8 to be considered significant. Furthermore, and critically, these studies often replicated results in a separate independent sample.

Several GWASs were used to assess candidate genes or loci with transplant outcomes (Table 1). Our group undertook some of the earliest transplant GWASs, initially in a cohort based in Dublin, Ireland (2), and subsequently in a larger group of approximately 2500 kidney donor recipient pairs across the United Kingdom and Ireland (United Kingdom and Ireland Renal Transplant Consortium) (3). In the first large transplant GWAS, we confirmed the critical role that HLA plays in graft outcome but also failed to replicate any of the previously published SNPs in a data set that was approximately 10 times larger than previously published studies (4).

Subsequently, we undertook GWASs, incorporating a trans-national consortium, called the International Genetics & Translational Research in Transplantation Network (*i*GeneTRA*i*N), to identify genetic signals associated with kidney function at 5 years post-transplantation (3) and the development of skin cancer post-transplantation. We were able to identify a strong genetic predisposition to skin cancer between patients at the highest and lowest polygenic risk score. Other investigators have used the GWAS approach to identify genetic signals for the development of other complications post-transplantation, such as allograft rejection and diabetes.

Advancement in immunosuppressant medications is one of various factors that has contributed to the enormous improvement of long-term allograft survival to its current state. The genetic determinants influencing immunosuppressant metabolism have been apparent for many years, initially with involvement of the thiopurine methyltransferase enzyme on azathioprine metabolism and more recently, the cytochrome P450 genetic variation having a considerable impact on the pharmacokinetics of calcineurin inhibitors (5). As a result,

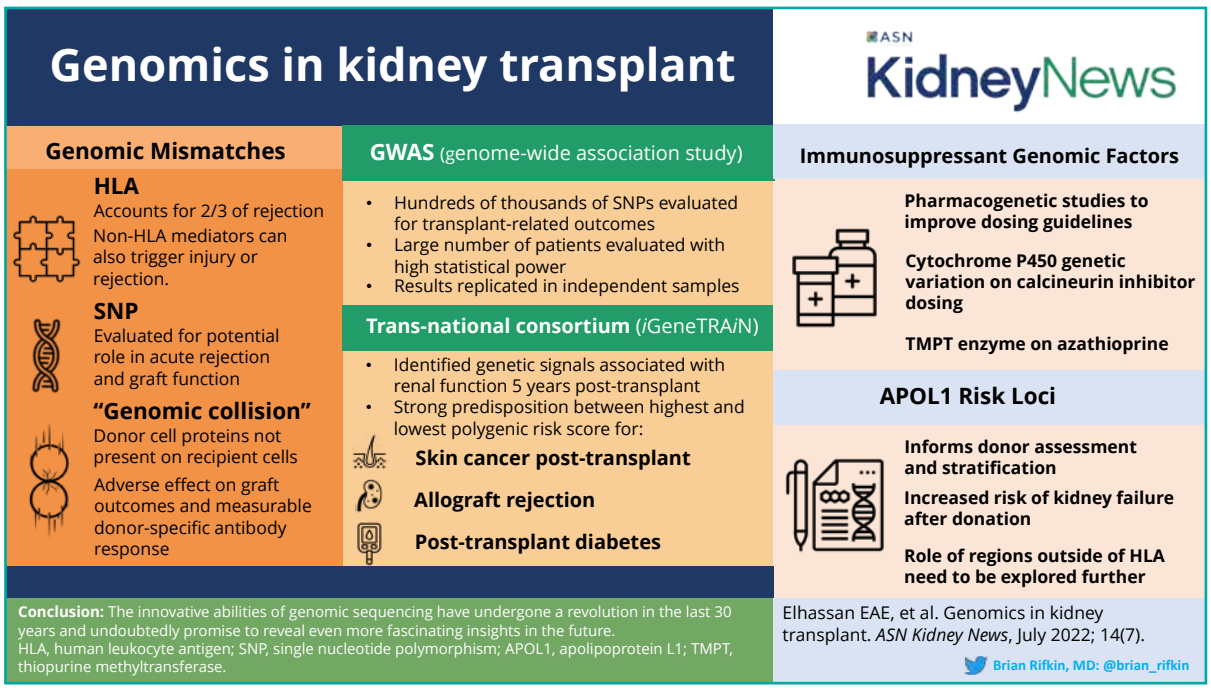

Table 1. Genome-wide association studies in kidney transplantation

Authors	Year	Subjects	Outcome studied	Main result	Replication/results/ PMID number	Ref.
O'Brien et al.	2013	326	Allograft function at 5 years	2 Loci	Yes/no association was detected/27483393	(2)
McCaughan et al.	2014	707	NODAT	26 SNPs	Yes/1 SNP associated with NODAT/26802601	(10)
Oetting et al.	2018	197	Tacrolimus trough blood concentrations	2 SNPs	Yes/2 SNPs associated with tacrolimus trough concentrations/29318894	(5)
Ghisdal et al.	2017	4127Di 2765Re	Acute allograft rejection	2 Loci	Yes/no association was detected/27272414	(11)
Israni et al.	2018	5291	Acute allograft rejection	30 Recipient SNPs, 39 donor SNPs	No/NA/NA	(12)
Hernandez-Fuentes et al.	2018	2094Di 5866Re	Short- and long-term allograft survival	0 SNP	No/NA/NA	(3)
Stapleton et al.	2019	10844	eGFR at 1 year posttransplant	0 SNP	No/NA/NA	(13)
Steers et al.	2019	705Di 2004Re	Acute allograft rejection	1 Loc	Yes/confirms association with acute allograft rejection/33909908	(8)
Reindl-Schwaighofer et al.	2019	477 Pairs	Graft loss	Genetic non-HLA mismatch in immune-accessible transmembrane and secreted proteins is significant.	Partially/NA/30773281	(9)
Markkinen et al.	2022 (pre-print)	1025 Pairs	Acute allograft rejection	Replication of some signals of non-HLA mismatch with acute rejection	No/NA/NA	(14)

Di, discovery cohort; eGFR, estimated glomerular filtration rate; HLA, human leukocyte antigen; NA, not applicable; NODAT, new-onset diabetes after transplantation; PMID, PubMed reference number of replication studies, when available; Re, replication cohort; SNP, single nucleotide polymorphism.

although not widely adopted, guidelines have been proposed to integrate the knowledge of pharmacogenetic studies to improve immunosuppressant-dosing optimization (6).

Following the discovery of the HLA, knowledge about other genetic factors of donors and recipients, such as incompatibilities and APOL1 risk loci, has pushed the boundaries of precision medicine. Accumulating evidence indicates that mismatches and antibodies against non-HLA mediators can trigger transplant injury and rejection and elicit underlying etiology of graft failure, as one-third of all transplants that fail for immunological reasons cannot be explained by HLA mismatch. Some of this failure is proposed to be due to so-called minor histocompatibility antigens. Also, in live kidney donors, the APOL1 genotype informs the donor-assessment and stratification process, as reports suggest that donors with greater than typical risk (i.e., high-risk genotype) are associated with an increased rate of kidney failure after donation (7). It is critical that the role of regions outside of the HLA is further explored.

Kiryluk and co-workers (8) have recently proposed the idea of "genomic collision" in which kidney donor cells expressing proteins on their surface that were not present in the recipient demonstrate a robust adverse response on graft outcome and can have measurable donor-specific antibodies. A team in Austria has demonstrated the impact of a summation cell surface-expressed protein-coding variation between donors and recipients on long-term graft outcome (9).

The innovative abilities of genomic sequencing have undergone a revolution in the last 30 years and undoubtedly promise to reveal even more fascinating insights in the future. ■

Elhussein A. E. Elhassan, MBBS, and Peter J. Conlon, MB, Bch, BAO, are with the Department of Nephrology and Transplantation, Beaumont Hospital and Royal College of Surgeons, Dublin, Ireland. Kane Collins, PhD, and Edmund Gilbert, PhD, are with the School of Pharmacy and Biomolecular Sciences, Royal College of Surgeons, Dublin, Ireland.

The authors report no conflicts of interest.

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Clinical Utility of Repair Markers in Deceased Donor Kidney Transplantation

By Yumeng Wen and Chirag R. Parikh

In the United States, approximately 40,000 new patients are added to the waitlist for kidney transplantation each year, yet in 2021, only 19,000 on the waitlist received deceased donor kidney transplants (1). Because of the burdens of dialysis and the kidney shortage, nearly 8000 waitlisted patients died or became too sick to receive a transplant in 2021 (1). From 2010 through 2020, 18%–21% of procured kidneys were not transplanted, and kidney discards are on the rise (2). In 2021 alone, a total of 5080 kidneys were procured and then discarded. A minority of donor kidneys (<5%) are not transplanted due to medically justifiable reasons, but evidence, such as unilateral discards, weekend discards, and the high rate of organ turndown, all support the contention that the majority of discarded kidneys are potentially transplantable (3–5). This phenomenon is more pronounced in the United States than in other countries, with recent data suggesting that nearly two-thirds of discarded kidneys in the United States would have been transplanted in France (6).

Although a subset of these kidneys may be unsuitable for transplant, many kidneys—especially those from donors with acute kidney injury (AKI) or a high kidney donor risk index (KDRI)—may be unnecessarily discarded. Such kidneys are often biopsied to assess organ quality and undergo machine perfusion for organ preservation; however, >30% of these kidneys are still being discarded, despite growing evidence demonstrating comparable recipient graft outcomes as transplantation with kidneys from non-AKI donors (7). This high rate of organ discard likely results from the inability to accurately assess organ quality and predict recipient graft function by the KDRI and histological examination (8). Thus, better prognostic tools, especially non-invasive biomarker assessment that can be easily implemented, are needed to reduce organ discard and improve the availability of transplantation for patients with end stage kidney disease.

Biomarkers of tubular injury may have limited value in providing insights into the quality of deceased donor kidneys. Urinary neutrophil gelatinase-associated lipocalin (NGAL) was found to be associated with a lower glomerular filtration rate (GFR) at 6 months, only in those without delayed graft function (DGF), and the difference between the

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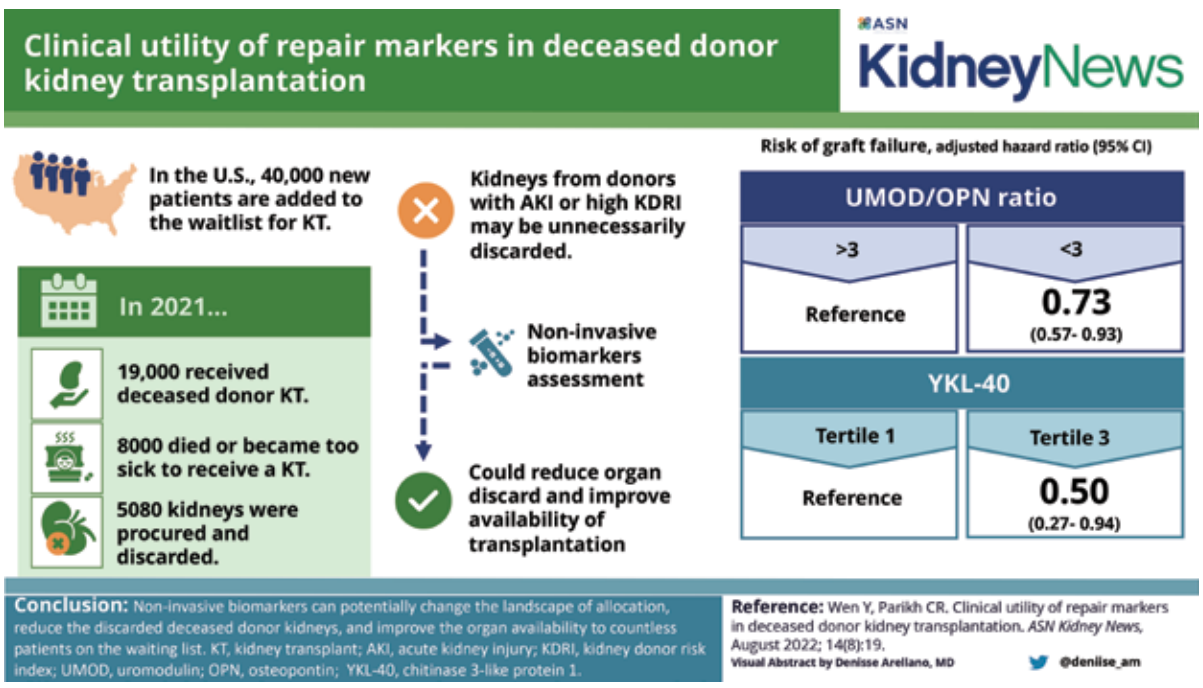

Clinical Utility of Repair Markers

Continued from page 21

highest and lowest tertiles was only 3.15 mL/min/1.73 m^2 (9). At 3 years after transplant, neither urinary NGAL nor kidney injury molecule 1 was associated with adverse graft outcomes (10). This is possible because ischemia-reperfusion injury is ubiquitous in the process of deceased donor kidney transplant; thus, donor kidney injury occurring before organ procurement may have a small contribution in determining recipients' long-term graft function.

On the other hand, the lack of association between severe donor kidney injury and adverse recipient outcomes indicates significant recovery potential in these kidneys. Indeed, our previous work showed that deceased donor urinary chitinase 3-like protein 1 (YKL-40), a protein involved in the adaptive repair process after kidney injury, was strongly associated with a lower risk of DGF (11). More importantly, in recipients who developed DGF, those who received donor kidneys with the highest tertile of urinary YKL-40 had a 50% lower risk of graft failure compared with those receiving kidneys from donors with low urinary YKL-40 (Table 1) (11). In the same cohort of patients, urinary osteopontin (OPN), a protein with renoprotective effects via reducing tubular cell apoptosis and promoting repair of the injured tubule, was inversely associated with graft failure (12). Additionally, donor uromodulin (UMOD) may induce the expression of major histocompatibility complex II in bone marrow-derived mouse macrophages, and its urine level is associated with a higher risk of graft failure and lower recipients' estimated GFR at 6 months. A lower donor urine UMOD/OPN ratio (e.g., <3 in our study), which may reflect a greater potential for adaptive repair and a lower risk of chronic rejection, is associated with a 27% risk reduction in graft failure than kidneys from a donor with a UMOD/OPN ratio >3. This evidence suggests that non-invasive biomarkers reflecting the kidney repair potential may provide more granular information for the organ quality beyond traditional donor characteristics and are valuable tools in facilitating decisions on organ procurement and allocation.

A gap between the knowledge derived from the above prospective cohort studies and clinical implementation is the availability of biomarker measurement results at the bedside to guide clinical decision-making. These biomarkers were measured using the gold standard immunoassay, which requires extensive laboratory expertise and may be infeasible to provide immediate results to the clinicians on-site. A potential solution is to develop lateral flow point-of-care devices for rapid testing for these biomarkers, similar to point-of-care antibody testing devices for assessing SARS-CoV-2 immunity. By providing rapid and more accurate assessments of the organ quality at the bedside, these non-invasive biomarkers can potentially change the landscape of allocation, reduce the number of discarded deceased donor kidneys, and improve organ availability to countless patients on the waiting list. ■

Table 1. Deceased donor urinary repair biomarkers are associated with lower risk of graft failure

Urinary biomarkers (reference)		Adjusted hazard ratio (95% CI) of graft failure	
UMOD/OPN ratio* (11)	Category	All recipients	
	>3	Reference	
	<3	0.73 (0.57–0.93)	
	Tertile	Recipients without DGF	Recipients with DGF
YKL-40# (12)	1	Reference	Reference
	2	1.01 (0.63–1.61)	1.07 (0.67–1.70)
	3	1.15 (0.60–2.19)	0.5 (0.27–0.94)

95% CI, 95% confidence interval.
*Hazard ratio adjusted for donor KDRI, urine creatinine, cold ischemia time, and the following recipient characteristics: age, Black race, sex, previous kidney transplant, diabetes as the cause of end stage kidney disease, number of human leukocyte antigen mismatches, panel-reactive antibody, body mass index, and preemptive transplant status.
#Hazard ratios adjusted for donor age, height (cm), weight (kg), Black race, terminal serum creatinine, history of hypertension, history of diabetes, stroke as cause of death and donation after circulatory death status, and cold ischemia time and for recipient factors (e.g., age, sex, Black race, history of previous transplant, human leukocyte antigen mismatch, panel-reactive antibody, and diabetes as cause of end stage renal disease).

Yumeng Wen, MD, and Chirag R. Parikh, MD, PhD, are with the Division of Nephrology, Johns Hopkins University School of Medicine, Baltimore, MD.

Dr. Wen reports no conflicts of interest. Dr. Parikh is a member of the advisory board of and owns equity in RenalytixAI. He also serves as a consultant for Genfit and Novartis.

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New Insights into TMA in Kidney Transplantation

By Anuja Java

Thrombotic microangiopathy (TMA) is a clinicopathological entity characterized by microangiopathic hemolytic anemia, thrombocytopenia, and organ injury, occurring due to endothelial damage and microthrombi formation in small vessels (1, 2). It can affect up to 15% of transplanted patients and is associated with significant morbidity and mortality (3).

TMA is primary when a genetic or acquired defect is identified (as in atypical hemolytic uremic syndrome [aHUS] and thrombotic thrombocytopenic purpura) or secondary when occurring in the context of another disease process, such as infection, autoimmune disease, malignancy, or drugs (4) (Table 1). This classification is not absolute because genetic defects have been identified in secondary TMA (6). Kidney transplantation poses a challenging setting due to multiple potential triggers for TMA development (Table 1). Posttransplant TMA can be recurrent or de novo. Recurrent TMA is almost always complement mediated, whereas de novo TMA may be complement mediated or secondary to triggers. De novo TMA is reported in 1%–15% of patients, although the true frequency is unknown, and the implication of a dysregulated complement system may be underestimated (7). We have identified patients carrying a complement genetic variant who did not manifest TMA in the native kidneys but developed posttransplant disease in the setting of multiple triggers (unpublished results). Therefore, all patients presenting with "de novo TMA" should undergo genetic testing for complement disorders. Differentiating between a primary complement-mediated process and one triggered by secondary factors is critical to minimize allograft damage since the former is non-responsive to supportive therapy and has a high risk of recurrence.

Clinical features of TMA range from a renal-limited form, diagnosed only on a kidney biopsy, to full-blown systemic manifestations (8). TMA commonly occurs in the first 3 months but can appear at any time in the posttransplant course. An update on the most common TMAs associated with kidney transplantation is presented below.

Complement-mediated TMA (aHUS) stems from a dysregulated complement system due to genetic variants in complement proteins or due to acquired defects (such as factor H autoantibodies), which predispose patients to endothelial damage. However, less than 50% of the identified variants have a known functional consequence and are therefore classified as variants of uncertain significance (VUSs). The presence of VUSs is vexing for clinical management. Laboratories that specialize in functional analysis of genetic variants can assist in defining the significance of the variant. Eculizumab should be initiated early to offer the best chance of renal recovery, and duration depends on the underlying genetic abnormality (Figure 1).

Drug-induced TMA can occur after calcineurin inhibitor (CNI) or mammalian target of rapamycin inhibitor use and is commonly direct toxicity mediated due to arteriolar vasoconstriction and endothelial injury (10). The endothelial injury results in release of von Willebrand factor multimers overwhelming the capacity of a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13), thereby causing platelet aggregation and complement activation (due to the complement-coagulation crosstalk). Management involves supportive care and withholding the causative medication. Case reports have shown resolution of TMA when the CNI was switched (for example, from tacrolimus to cyclosporine) (11, 12). It is my speculation that patients who responded to the drug change developed TMA from a combination of triggers in the early posttransplant phase but did not manifest disease when a CNI was introduced later in the course (in the absence of triggers). Some centers would consider switching to belatacept if CNI-induced TMA is suspected. ADAMTS13 assay and genetic testing should be undertaken in cases that do not respond to conventional treatment. As a gentle reminder, all clinicians should ask for other agents in the medications list that can also cause TMA, such as quinine.

Antibody-mediated rejection (AMR)-associated TMA has the highest risk for premature graft loss compared with other TMAs (13, 14). Concomitant rejection is believed to be the main driver for kidney failure with an aberrant humoral alloimmune response being the most important risk factor (because donor-specific antibodies can bind to human leukocyte antigens on the endothelium and activate complement). C4d staining and presence of donor-specific antibodies help to distinguish AMR-associated TMA from other causes. Transplant glomerulopathy may represent a chronic smoldering form of TMA (the pathology pattern of injury is membranoproliferative glomerulonephritis).

Infection-associated TMA can occur due to direct endothelial injury (because of virus tropism), platelet activation and generation of thrombin, development of ADAMTS13 inhibitors, and complement activation. Cytomegalovirus (CMV) is most frequently associated with TMA after transplantation and typically responds to anti-viral treatment. TMA can also occur after COVID-19 due to the combined effects of complement activation, dysregulated neutrophilia, endothelial injury, and hypercoagulability induced by coronaviruses (15). Supportive management and treatment of the underlying infection should be the initial focus. Testing for complement genetic variants should be conducted when the clinical picture is unusually severe.

A high degree of suspicion is needed for prompt recognition and treatment of TMAs. A thorough systematic approach can help make the correct diagnosis and facilitate individualized treatment decisions for patients (Figure 2). ■

Anuja Java, MD, is with the Division of Nephrology, Department of Medicine, Washington University School of Medicine in St. Louis, MO.

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Continued on page 24 >

Table 1. Causes of thrombotic microangiopathy (TMA)

ADAMTS13 deficiency-associated TMA (Thrombotic thrombocytopenic purpura)
Complement-mediated TMA (Atypical hemolytic uremic syndrome)
Pregnancy-associated TMA (Preeclampsia/HELLP)
Drug-induced TMA
- Calcineurin inhibitors/sirolimus/everolimus
- Quinine
- Estrogen/progesterone
- Gemcitabine/mitomycin C
- Interferon
- VEGF inhibitors/tyrosine kinase inhibitors
- Cocaine
- Oxymorphone

Autoimmune diseases-associated TMA
- Systemic lupus erythematosus
- Antiphospholipid antibody syndrome
- Scleroderma
- Monoclonal Gammopathy
- Membranous nephropathy
- IgA nephropathy
- Cryoglobulinemia

Malignancy-associated TMA

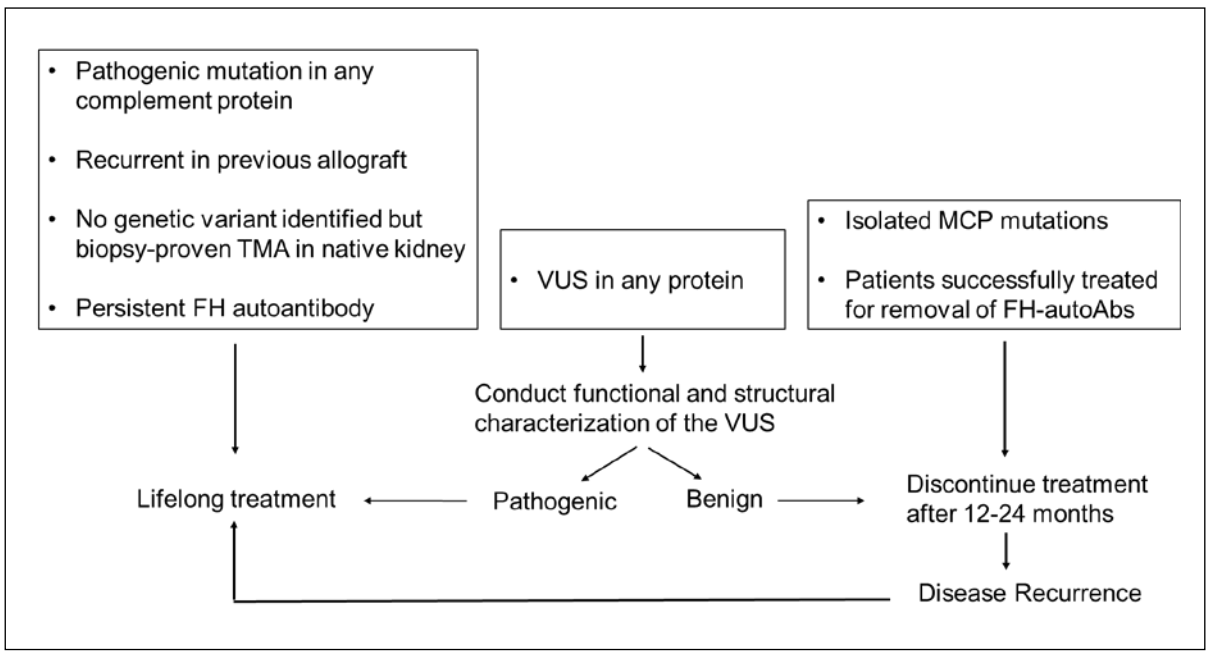
Infection-associated TMA
- STEC-HUS and others (*Shigella dysenteriae*, *Campylobacter jejuni*, and *Moraxella osloensis)*
- Viral infections: CMV, BK virus, Epstein-Barr virus, Varicella zoster, Parvovirus B19, HIV, Influenza, SARS-CoV2
- Respiratory tract infection agents: *Bordetella pertussis*, *Streptococcus pneumoniae*, *Mycoplasma pneumoniae*
- Protozoa: *Toxoplasma gondii*
- Others: Ehrlichiosis, *Capnocytophaga canimorsus*, *Plasmodium vivax,* snake bites, dengue fever, West Nile virus, Chikungunya fever

Metabolic/Coagulation defects-associated TMA
- Cobalamin C defect/Methylmalonic aciduria and homocystinuria (*MMACHC)*
- Diacylglycerolkinase ε (DGKE) mutations
- B12 deficiency
- G6PD Deficiency

Transplantation-associated TMA (can be associated with any of the above) - Common triggers include infections, drugs, ischemia-reperfusion injury, antibody-mediated rejection, prolonged cold-ischemia time

HELLP, hemolysis-elevated liver enzymes and low platelets; VEGF, vascular endothelial growth factor; IgA, immunoglobulin A; STEC-HUS, Shiga toxin producing *Escherichia coli*-associated hemolytic uremic syndrome; CMV, cytomegalovirus; G6PD, glucose-6-phosphate dehydrogenase. Reprinted from Visweswaran and Ponticelli (5).

Figure 1. Guidelines for duration of eculizumab in kidney transplantation



FH, factor H; VUS, variant of uncertain significance; MCP, membrane cofactor protein; Pts, patients; autoAbs, autoantibodies. Reprinted from Java (9).

New Insights into TMA

Continued from page 23

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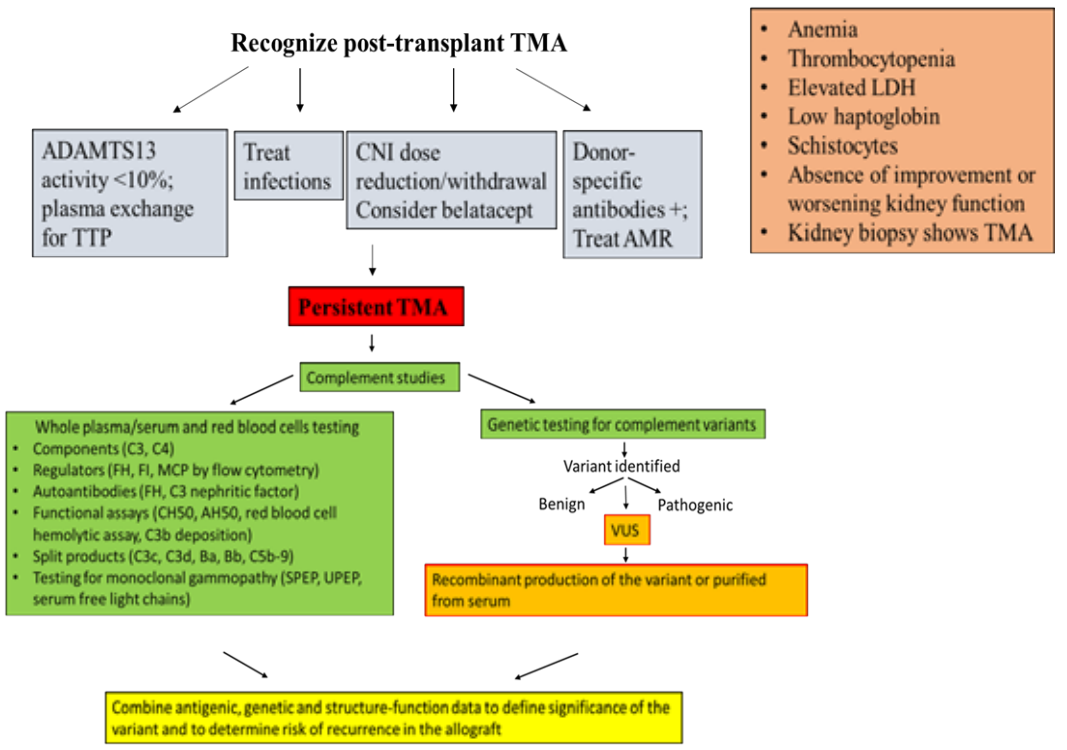
Figure 2. Approach to diagnosis of posttransplant TMA



ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; TTP, thrombotic thrombocytopenic purpura; CNI, calcineurin inhibitor; AMR, antibody-mediated rejection; LDH, lactate dehydrogenase; FH, factor H; FI, factor I; MCP, membrane cofactor protein; CH50, total complement hemolytic assay; AH50, alternative pathway hemolytic activity; SPEP, serum protein electrophoresis; UPEP, urine protein electrophoresis; VUS, variant of uncertain significance. Reprinted from Ren et al. (16).

Focal Segmental Glomerulosclerosis Recurrence Posttransplant: It Takes Two to TANGO

By Frank Hullekes, Ruchâma Verhoeff, Paolo Cravedi, and Leonardo V. Riella

Focal segmental glomerulosclerosis (FSGS) recurrence post-transplantation represents one of the most challenging conditions causing kidney allograft failure. Despite intensive research over the past decades, many gaps remain in understanding its pathophysiology. Herein, we review several questions highlighting recent advancements and their potential use in clinical practice.

Are there any reliable predictors of FSGS recurrence?

FSGS is not a specific disease entity but a histopathological "pattern of injury" seen on light microscopy that primarily targets podocytes. Multiple underlying etiologies that lead to podocyte loss have been identified, including systemic, genetic, and medication induced and those mediated by adaptive kidney responses (Figure 1).

Systemic FSGS is thought to be mediated by a still-elusive circulating factor, inducing podocyte injury and cytoskeleton disorganization, which ultimately leads to proteinuria. The existence of permeability factor(s) is supported by multiple observations: early-onset recurrence after kidney transplantation; resolution of podocyte injury if a kidney transplant is retransplanted in another recipient (1), and remission after plasmapheresis (2). The estimated FSGS recurrence rate is 30% to 60% and represents a major risk for graft loss (3). FSGS recurrence can manifest within hours to days after transplant, in contrast to other glomerular diseases such as immunoglobulin (Ig)A nephropathy, which may recur years posttransplant (3, 4) (Figure 2). Several risk factors are associated with recurrent FSGS: older age at native kidney disease onset, White race, native kidney nephrectomy, and short duration of native kidney disease (<3 years) (3, 5). It has been estimated that recurrent FSGS patients have a hazard ratio for graft failure of 4.8 (95% confidence interval, 2.9–12.2) compared with patients without recurrence (3). Available treatment options for recurrence often fail to achieve remission (2, 3, 6).

Although the potential circulating factor(s) driving systemic FSGS have not been clearly identified, reports indicate a role of anti-nephrin autoantibodies in damaging podocytes (8). Investigators found anti-nephrin autoantibodies in 18 of 62 (29%) patients with minimal change disease (MCD), a condition thought to represent an early stage of FSGS. In a subset of MCD patients, anti-nephrin autoantibody levels correlated with disease activity. Anti-nephrin autoantibodies were also elevated in a case of FSGS recurrence at the time of disease onset. After successful treatment with plasmapheresis and rituximab, the patient achieved remission of proteinuria, associated with the disappearance of anti-nephrin autoantibodies. A recent report from Japan identified a patient with early FSGS recurrence with circulating anti-nephrin autoantibodies at time of recurrence and evidence of punctuate IgG deposits at the 1-hour post-perfusion graft biopsy that co-localized with nephrin (9). Although more research is needed, anti-nephrin autoantibodies may represent a useful biomarker of FSGS disease activity. Quantification of anti-nephrin autoantibodies could allow for risk stratification of FSGS recurrence before transplantation in a subset of patients.

Does genetic testing help predict the risk of FSGS recurrence?

More than 50 different pathogenic mutations affecting the podocyte or glomerular basement membrane (GBM) have been described in FSGS patients. Mutations in podocyte-related genes include *NPHS1*, *NPHS2*, *TRPC6*, and *INF2*, whereas GBM-related genes include *COL4A3/A4/A5* (10). Genetic FSGS is frequently overlooked because there are no distinctive clinical or histopathological features. When 662 adult patients with familial or sporadic FSGS were analyzed, 30% carried mutations associated with genetic FSGS (11).

The risk of recurrence is low in patients with genetic FSGS (12). A unique genetic form of FSGS is related to the *apolipoprotein L1* (*APOL1*) gene that disproportionally affects patients of Black race. A high-risk *APOL1* genotype is present in approximately 75% of patients with FSGS of Black race (13). Patients with *APOL1*-related FSGS have a low risk of recurrence, likely related to the intrinsic pathogenic role of *APOL1* variants in kidney tissue. Transplant recipients who received a kidney from a donor carrying two *APOL1* high-risk alleles have an increased risk of allograft failure (14). One important exception is a specific mutation in *NPHS1* (nephrin gene), mostly found in Finland. This condition recurs in 25% to 34% of the grafts of patients, driven primarily by the emergence of antibodies against the non-mutated donor nephrin (15).

As a result of widespread availability of genetic panels, it has become easier to diagnose genetic FSGS. The importance of identifying genetic mutations cannot be underestimated for guiding treatment and family counseling. It is important even in cases with advanced kidney failure, as this allows for stratification of a potential recurrence risk post-transplantation.

How can we further advance our understanding of glomerular disease recurrence post-transplantation?

Although posttransplant FSGS recurrence is a major cause of allograft failure, its relative low incidence and heterogeneity pose major challenges to research. Large registries are needed to achieve insight into disease patterns to identify genetic risk factors. In 2017, we established the TANGO (Post-Transplant Glomerular Diseases) Consortium, a multi-phase collaborative project involving retrospective and prospective study initiatives using patient data and biological samples to better characterize glomerular disease recurrence post-transplant. So far, two major studies have been published on FSGS and IgA recurrence post-transplantation with over 1500 patients recruited (3, 4). The multi-phase approach will set the foundation for a shared international biorepository of samples from glomerular disease patients. All patients diagnosed with FSGS and other glomerular diseases across the United States are invited to participate in the TANGO Consortium's currently ongoing prospective observational studies, aiming to gain better insight into glomerular disease recurrence and its associated risk factors, including anti-nephrin autoantibody levels.

Overall, there is an urgent need to investigate predictors, disease activity biomarkers, pathogenic mechanisms, and response to novel treatments. This necessitates large-scale collaborations among physicians, scientists, funding agencies, industry partners, and patients to redefine and optimize transplant care for glomerular disease patients: It takes two to TANGO! ■

Frank Hullekes, MD, and Leonardo V. Riella, MD, PhD, are with the Center for Transplantation Sciences, Department of Nephrology, Massachusetts General Hospital, Harvard Medical School, Boston, MA. Dr. Hullekes and Ruchâma Verhoeff, BS, are with the Groningen Transplant Center, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands. Paolo Cravedi, MD, PhD, is with the Translational Transplant Research Center, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY.

Dr. Hullekes and Ms. Verhoeff are co-first authors.

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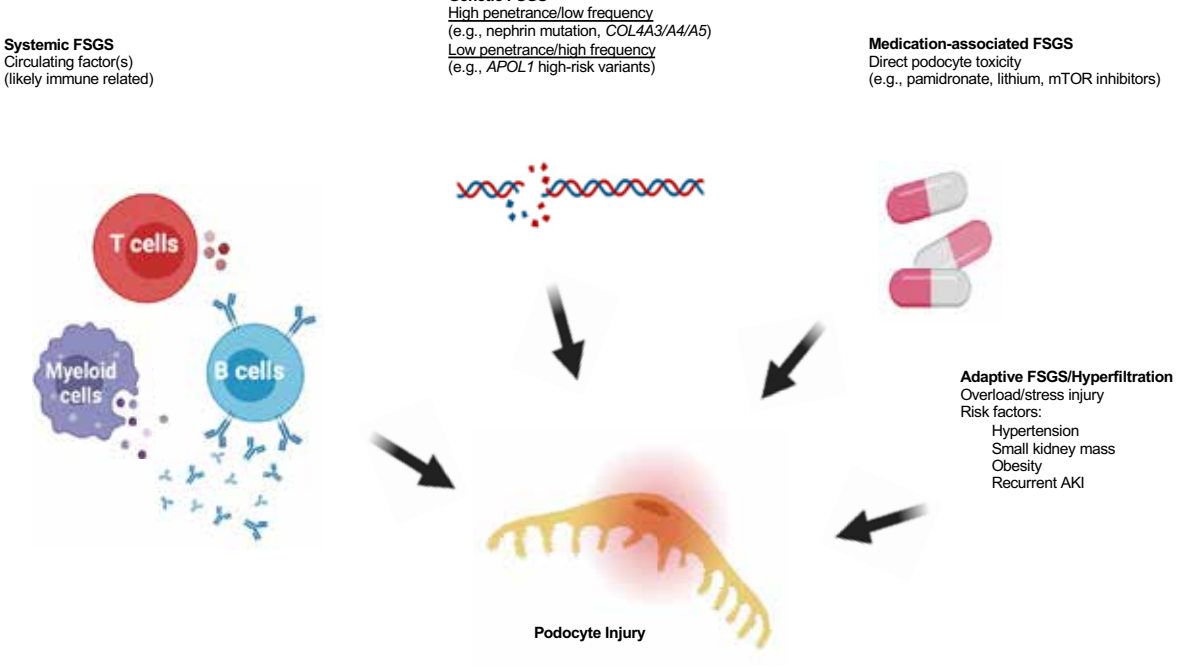
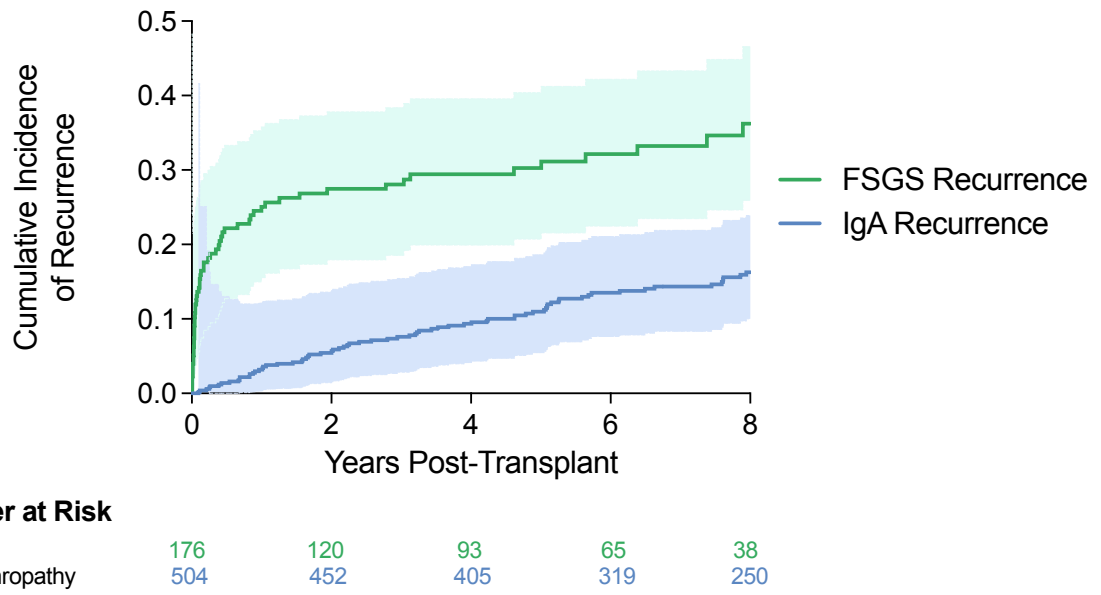
Figure 1. Underlying etiologies for the podocytopathy in FSGS patients



AKI, acute kidney injury; mTOR, mammalian target of rapamycin. Created with BioRender.com.

Figure 2. Cumulative incidence of recurrent FSGS and IgA nephropathy post-transplantation



Reprinted from the TANGO Consortium (7).

Updates on Belatacept in Kidney Transplantation

By Jeffrey Kott, Jorge Chancay, and Fasika M. Tedla

Belatacept is a soluble recombinant fusion protein composed of the constant fragment of human immunoglobulin G1 and modified extracellular domain of cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). It inhibits T-lymphocyte activation by blocking costimulation, the requisite signal that T-lymphocytes must receive through interactions between proteins expressed on antigen-presenting cells and T-lymphocytes in addition to signal from engagement of the antigen receptor (Figure 1).

In 2011, the US Food and Drug Administration (FDA) approved belatacept for prophylaxis against acute rejection in de novo adult kidney transplant recipients based on randomized trials that showed better graft function and less incidence of hypertension, posttransplant diabetes, and hyperlipidemia as compared with cyclosporine, although with a higher rate of acute rejection (1). The incidence of posttransplant lymphoproliferative disorder (PTLD), although generally low, was also higher in belatacept-treated patients, leading the FDA to mandate a post-marketing risk evaluation and mitigation strategy and limit use of belatacept to Epstein-Barr virus-seropositive individuals. Long-term follow-up of the original clinical trials documented that belatacept-treated patients had better graft and patient survival and low incidence of PTLD, which was largely confined to the first 2 years of treatment (1). Despite a favorable side effect profile and acceptable efficacy of belatacept, the overwhelming majority of kidney transplant recipients are treated with tacrolimus-based maintenance immunosuppression (2).

There are many potential barriers to widespread use of belatacept. First, belatacept was studied in comparison with cyclosporine, as required by the FDA at the time. In clinical practice, thymoglobulin and tacrolimus have largely supplanted basiliximab and cyclosporine as the mainstays of induction and maintenance immunosuppression, respectively, with historically low rates of acute rejection and modest improvement in long-term graft survival (3). The questions of efficacy and safety of belatacept in comparison with the commonly used immunosuppression regimen, therefore, have not been answered. Second, some reports have associated belatacept with increased incidence and severity of opportunistic infections (4). Third, there is no assay for therapeutic drug monitoring for, or clinical experience in, adjusting the dose of belatacept in the presence of infection or cancer.

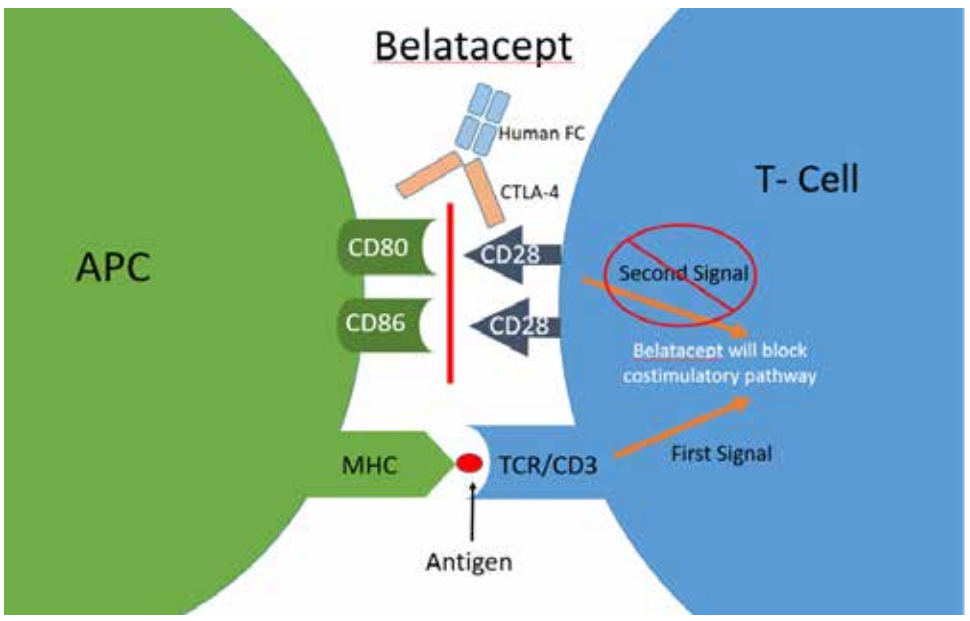
Studies of strategies for reducing the risk of rejection associated with belatacept generally fall into two categories: 1) conversion from calcineurin inhibitors (CNIs) to belatacept after the high-risk period for acute rejection and 2) use of belatacept with lymphodepleting induction or inhibitors of mechanistic target of rapamycin (mTORis) or both. In randomized trials of conversion from CNIs to belatacept after 6 months posttransplant, acute rejection rate and overall rates of infection or malignancy were similar between the two groups, whereas graft function was better in the belatacept group (5). Observational studies have reported improvement in graft function after belatacept conversion and use of belatacept in the first 6 months posttransplant or with higher-risk patient groups, although efficacy and safety relative to CNIs are difficult to assess in the absence of controls (6). Some centers have reported less rejection with transient addition of tacrolimus to belatacept-based immunosuppression (7). Rejection rate was higher in belatacept- than in tacrolimus-treated patients in a randomized trial, despite lymphodepleting induction (8). Small studies have reported acceptable graft and patient outcomes using lymphodepleting induction and mTORis with belatacept (9, 10).

In summary, long-term graft and patient outcomes using belatacept appear to be equivalent to those using CNIs in low immunologic-risk patients, albeit with higher risk of acute rejection, whereas belatacept achieves better graft function and a better cardiovascular risk profile than CNIs. Registry data indicate that there is a modest increase in the proportion of kidney transplant recipients in the United States treated with belatacept, largely driven by a few centers that use belatacept in a significant proportion of their patients (11). Patients who are at high risk of nephrotoxicity from or are intolerant to CNIs, such as those with delayed graft dysfunction, evidence of fibrosis on allograft biopsy, or thrombotic microangiopathy, are potential candidates for belatacept-based immunosuppression. Late conversion, transient addition of tacrolimus, combination with mTORis instead of mycophenolate mofetil, and use of depleting antibody induction have been evaluated as strategies for reducing acute rejection when using belatacept, with variable results. Future studies should investigate the appropriate patient group suited for belatacept-based immunosuppression, the optimal induction agent, and ideal ways of monitoring for immunologic injury or infection complications (12). ■

Jeffrey Kott, MD; Jorge Chancay, MD; and Fasika M. Tedla, MD, are with the Division of Nephrology, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY. Dr. Tedla is also with the Recanati/Miller Transplant Institute, Mount Sinai Hospital, New York, NY.

The authors report no conflicts of interest.

Figure 1. Belatacept mechanism of action



APC, antigen-presenting cell; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; FC, fragment crystallizable (region); MHC, major histocompatibility complex; TCR, T-cell receptor.

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Weaning of Immunosuppression after Kidney Transplant Failure

By Abhijit S. Naik

Optimal management of immunosuppression in patients returning to dialysis after kidney transplant failure is an area of active investigation. It is common practice to start weaning immunosuppression over the first year after graft failure. To date, most literature on the effects of immunosuppression on those with transplant failure comes from single-center studies and expert opinion based on these studies. Maintaining immunosuppression after transplant failure is driven by the desire to reduce sensitization and prevent acute rejection of the failed transplant while preserving residual kidney function (1–3). However, this has to be balanced by the higher risk of infections, malignancy, and increased cardiovascular disease (4, 5). Recommendations based on poor quality data have led to a considerable variation in clinical practice, as shown in a recent publication that surveyed US academic nephrologists (6), a group that subsequently presented their recommendations (7).

In the June 2022 edition of *JASN* (8), a group of Canadian investigators prospectively enrolled patients with failed primary kidney transplants across 16 Canadian transplant centers and chose to focus on four outcomes that are relevant for patients. Immunosuppression exposure was divided into three main groups: those who discontinued all immunosuppression, discontinued all immunosuppression except prednisone, and continued immunosuppression with an immunosuppressant other than prednisone alone. The outcomes included death, infection needing hospitalization, rejection of the failed allograft, and anti-human leukocyte antigen (HLA) antibody sensitization. Patients underwent prospective evaluation of their immunosuppressant medication use. Death, hospitalized infection, rejection of the failed allograft, and anti-HLA panel reactive antibodies (a measure of the sensitization) were determined at 1, 3, 6, and 12 months and then twice yearly until death, repeat transplantation, or loss to follow-up.

The median study follow-up was 558 days (interquartile range, 298–875), and only 14% of patients underwent repeat transplantation. The probability of first-year patient survival was 94%, with leading causes of death including cardiac (18%), sepsis (18%), and other (33%). Most of the infections occurred within the first year of transplant failure. Nine of 18 patients with rejection needed allograft nephrectomy. Interestingly, 60% of the patients were still taking prednisone after 2 years, 40% were on a calcineurin inhibitor, and 25% were taking an antiproliferative, such as mycophenolate or azathioprine. The authors observed that the continued use of immunosuppressant medication other than prednisone was associated with a 60% lower hazard of death without any increase in the risk of infections needing hospitalization or rejection of the failed allograft. Although sensitization levels were higher in those who were off immunosuppression versus those on immunosuppression, this difference was not statistically significant (Figure 1). Data regarding the benefit of allograft nephrectomy were not conclusive. Given their findings, the authors express concerns that perhaps current immunosuppression use after transplant failure might be of insufficient intensity to prevent sensitization and graft rejection—a logical conclusion.

So, what does all this mean for the nephrologist in practice? In this observational study, where eventually only 14% of the patients enrolled in the study were transplanted, the continued use of immunosuppression was associated with a 60% lower mortality without significantly increasing the risk of infections needing hospitalization or sensitization. The study also demonstrates that despite a large proportion of this cohort not being retransplanted, the continuation of immunosuppressive therapy was protective. These data, despite their flaws, provide a much higher level of evidence than previous retrospective studies and raise the question of whether persistent allograft inflammation after transplant failure is associated with higher mortality. However, there is still a lack of granularity regarding the intensity, duration, and type of immunosuppressive therapy, and these questions need to be addressed with well thought-out prospective clinical trials. ■

Abhijit S. Naik, MD, MPH, FASN, is an Associate Professor of Internal Medicine with the University of Michigan, Ann Arbor.

The author reports no conflicts of interest.

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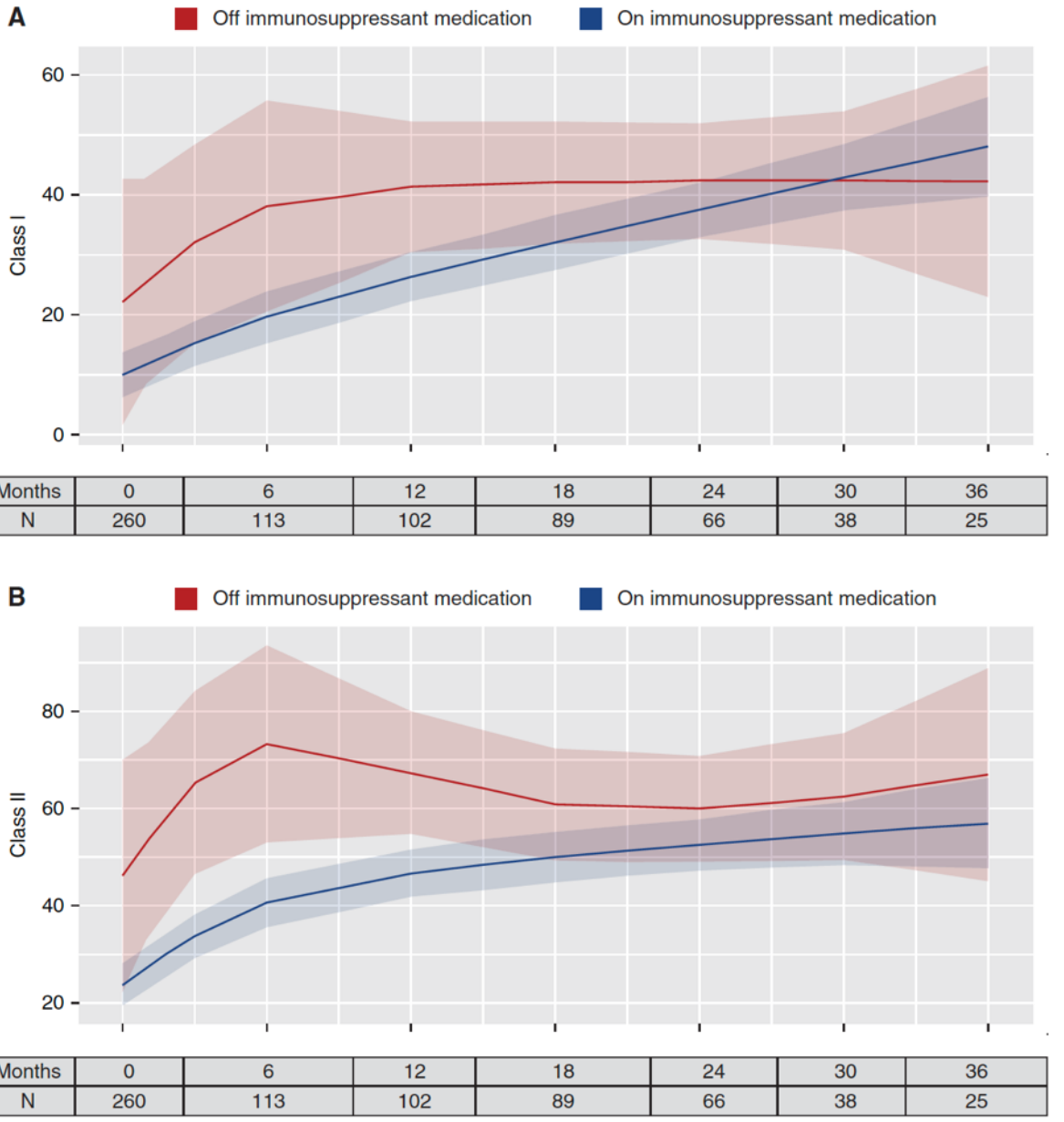
Figure 1. Sensitization levels off and on immunosuppressant medication



Sensitization for class I (A) and class II (B) antibodies for patients who were on some immunosuppression versus off all immunosuppression was similar. Reprinted from Knoll et al. (8).

New Tools for an Old Problem: Metagenomic Sequencing of Peritoneal Effluent Cell-Free DNA and Peritoneal Dialysis-Associated Peritonitis

By Nupur Gupta and Brent W. Miller

Infection remains a major cause of morbidity and mortality in dialysis and kidney transplantation. Despite dramatic improvements over the last 3 decades, peritoneal dialysis (PD)-associated peritonitis remains a common complication, occurring at an incidence of approximately 0.25 episodes per patient-year, and is the leading cause of technique failure with catheter removal, the eventual outcome in approximately 20% of infectious episodes (1). The causative agents of peritonitis are generally skin organisms introduced into the system by "touch contamination" or enteric organisms entering the glucose-rich dialysate via translocation.

Early diagnosis and prompt administration of antibiotics improve the clinical outcome and reduce the treatment failure rate. Subsequently, prompt identification of the causative agent allows tailoring of the antibiotic regimen to reduce overuse of broad-spectrum antibiotics or in the case of fungal peritonitis, quick removal of the catheter. Guidelines, endorsed by the International Society for Peritoneal Dialysis, recommend the diagnosis of peritonitis be based on both clinical presentation and laboratory parameters. Cultures of the peritoneal effluent, obtained and processed with appropriate methodology, are the gold standard for the diagnosis of the causative organism (2). However, in approximately 20% of episodes, cultures do not yield a causative organism in patients with high clinical suspicion, so-called "culture-negative peritonitis." Several novel technologies are in development for both early detection and reducing culture-negative rates in PD peritonitis (3).

In a recent article published in *Kidney Medicine*, Burnham et al. (4) studied the utility of metagenomic sequencing of cell-free DNA (cfDNA) in the peritoneal effluent to diagnose and monitor infection. The authors collected 68 peritoneal effluent samples from 33 separate patients on PD with either clinical evidence of peritonitis (peritonitis group) or no peritonitis (no peritonitis group) at a single center from September 2016 to July 2018. The samples were cultured traditionally in blood culture bottles. The prepared cfDNA libraries from peritoneal effluents were quantified and compared with plasma and urine cfDNA. They also compared the concentration of host-derived peritoneal effluent cfDNA and microbial-derived cfDNA in the peritonitis group and the no peritonitis group. The concentration of host cfDNA was significantly higher in specimens within 2 days of presentation in the peritonitis group than specimens from the no peritonitis group ($p = 2.5 \times 10^{-10}$; Wilcoxon rank-sum test). However, microbial cfDNA was non-significant at 2 days ($p = 0.34$; Wilcoxon rank-sum test). Thus, the cfDNA confirmed the presence of bacteria consistent with cultured pathogens in the peritonitis group and the resolution of the infection. Furthermore, cfDNA from human viruses, atypical bacteria, and fungi was detected in samples from patients with and without peritonitis.

cfDNA is now available for the monitoring of kidney transplant allografts for the presence of possible rejection before overt traditional signs (5). For similar logistical, scientific, and economic reasons, it is unlikely that peritoneal cfDNA of bacterial or viral organisms will be a primary diagnostic test for peritonitis but rather, an adjunctive measure. It further has the possibility to refine our pathophysiologic understanding of the etiology and progression of peritonitis.

The current study is the first to use cfDNA in PD fluid to analyze peritonitis in a clinical setting. Earlier studies demonstrated that cfDNA declines in PD fluid with the resolution of clinical symptoms of peritonitis (6). The detection and quantification of microbial cfDNA could be advantageous over traditional culture methods, especially in culture-negative peritonitis and in cases of prior or ongoing antibiotic therapy where a positive culture is unlikely. This could aid in narrowing the antibiotics and preventing antibiotic resistance. Metagenomic sequencing of cfDNA may be useful in deciding ultimate resolution of infection beyond gross clinical measures and may have some prognostic value by predicting the likelihood of relapsing or recurrent peritonitis. As the authors noted, it also aids in diagnosing some slow-growing and atypical pathogens, including viruses and fungi.

The study reports promising results for cfDNA in diagnosing and monitoring peritonitis but lacks the specificity of culture; this is not an unexpected finding at this stage. It was also a single-center cohort study with a small sample size at a major institution in an urban setting. The results need validation on a larger sample size from diverse geographies to develop universal reference libraries like cfDNA isolation for bloodstream infections (7). The authors used a filtering process that eliminates background contamination and may remove potential pathogens that may add to the practical complexity. Multiplex real-time polymerase chain reaction (RT-PCR) assays are widely used to detect pathogenic agents from body fluids that could be used in PD peritonitis. A single-center study demonstrated that RT-PCR was more sensitive and rapid in diagnosing peritonitis than traditional cultures (8).

The cost, infrastructure, and technical expertise required to create libraries, extract data, and implement in a clinical setting will require exploration for both of these techniques. Thus, the broader application of these techniques is yet to be determined. ■

Nupur Gupta, MD, and Brent W. Miller, MD, are with the Division of Nephrology, Department of Medicine, Indiana University School of Medicine, Indianapolis.

Dr. Gupta received honoraria for serving on the Advisory Board of Velphoro and AstraZeneca. Dr. Miller is a consultant for Fresenius Kidney Care and receives royalties from UpToDate in Medicine.

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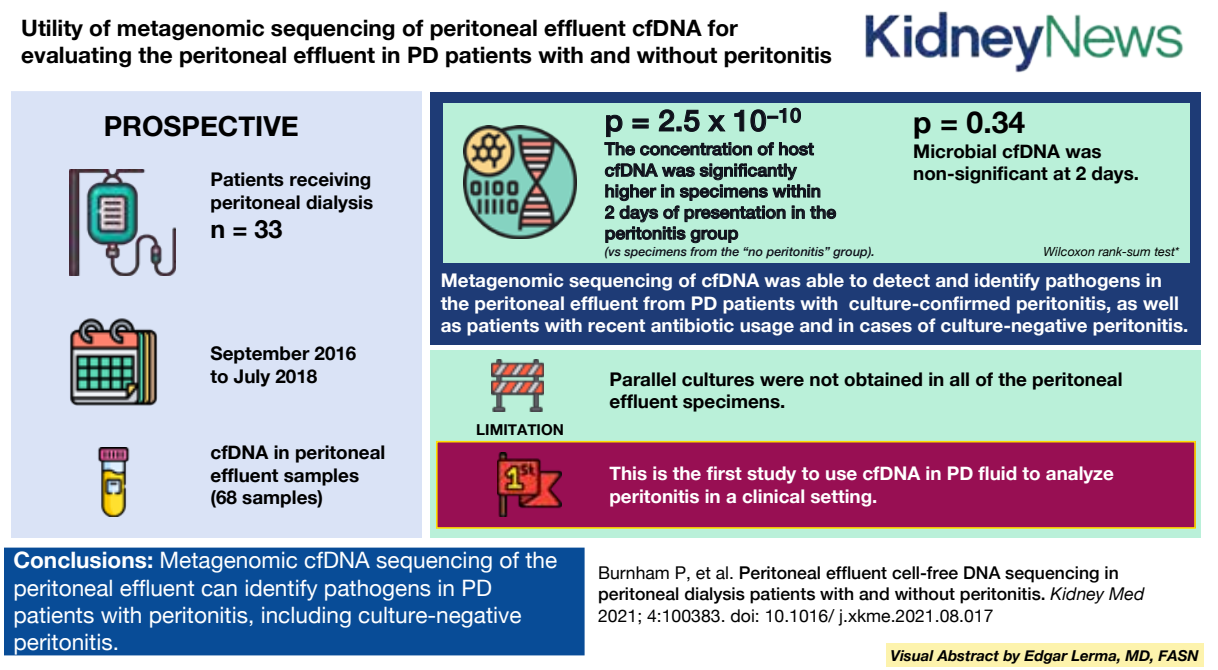


Assessment of Cathepsin C Inhibition as an Effective Treatment for Anti-PR3 Antibody ANCA-Associated Vasculitis

By Suneel M. Udani

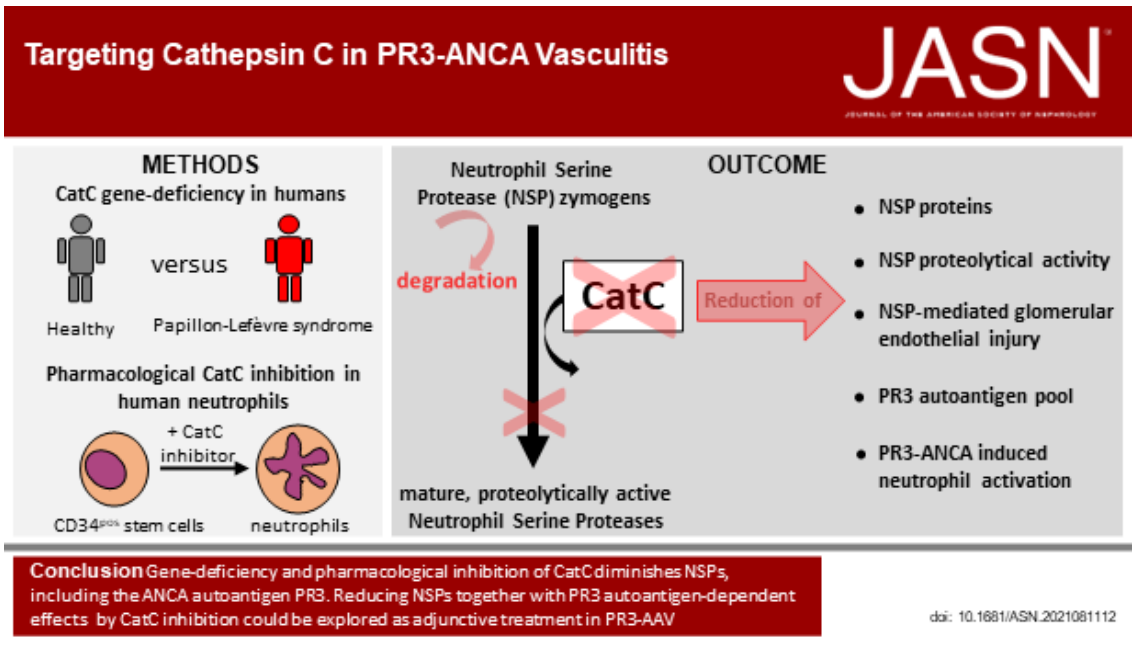
Can targeting the cathepsin C (CatC) in proteinase-3 (PR3)-anti-neutrophil cytoplasmic antibody (ANCA) vasculitis prevent the inflammatory injury associated with ANCA-associated vasculitis (AAV) (1)? Recognizing that neutrophils from individuals with a loss-of-function mutation in a non-serine protease—CatC—maintain bactericidal activity but have limited ANCA reactivity, the authors of a recent study propose pharmacologic inhibition of CatC as a therapeutic target for anti-PR3 antibody (anti-PR3 Ab) AAV (1).

Genetic CatC deficiency is associated with the autosomal recessive condition known as Papillon-Lefèvre syndrome (PLS). After previously noting that mice with CatC deficiency were protected from AAV, the authors designed a study to assess whether human neutrophils from those with PLS would similarly be protected from ANCA-immunoglobulin (Ig) activation and subsequent endothelial injury. Neutrophils from healthy controls (HCs) and individuals with PLS were incubated with endothelial cells and exposed to ANCA-Ig. Antibody deposition, indicators of neutrophil activation (e.g., generation of reactive oxygen species), and degree of endothelial cell injury were assessed. Neutrophils from those with PLS had negative immunofluorescence, less neutrophil activation, and less endothelial cell injury. To assess the impact of pharmacologic CatC inhibition, hematopoietic stem cells that differentiated into neutrophils from HCs were exposed to ANCA-Ig with and without a pharmacologic inhibitor of CatC. Neutrophils treated with CatC inhibition demonstrated similar outcomes as did individuals with PLS—less neutrophil activation and less endothelial injury. Ultimately, the authors concluded that a pharmacologic inhibitor of CatC prevented AAV-associated neutrophil activation and endothelial cell injury (1).

AAV is a life-threatening disease with a mortality of greater than 90% if untreated (2). Accordingly, the need for effective therapy to prevent the severe complications of the disease is self-evident. Although the current therapeutic approach effectively induces remission in greater than 60% of individuals, it remains associated with significant toxicity of prolonged impaired humoral immunity (3). An estimated 25% to 30% of patients with AAV will develop infection—significantly higher than a comparable population without AAV (4, 5). Furthermore, lymphopenia associated with induction treatment is strongly correlated with risk of serious and non-serious infection (6).

Induction therapeutic strategies to prevent organ injury with minimal systemic immunosuppression are needed. Furthermore, anti-PR3 Ab AAV remains a high risk for relapse after remission; therefore, clinical management must include a safe, reliable option for long-term use. The recent experience with the C5a inhibitor avacopan provides insight into the potential benefits of targeted therapy in AAV. When glucocorticoids were minimized in favor of avacopan, the risk of serious and non-serious infections fell without a reduction in therapeutic efficacy (7).

Ultimately, if CatC inhibition proves to be an effective treatment for anti-PR3 Ab AAV, and similar targets can be identified for both anti-PR3 Ab AAV and anti-myeloperoxidase Ab AAV, then the balance between effective therapeutic intervention and complications of treatment can move even more favorably toward optimizing patient outcomes. ■



Suneel M. Udani, MD, FASN, is with Nephrology Associates of Northern Illinois and Indiana, Oak Brook, IL.

Dr. Udani reports receiving consulting fees from ChemoCentryx, Travere, and Boehringer Ingelheim.

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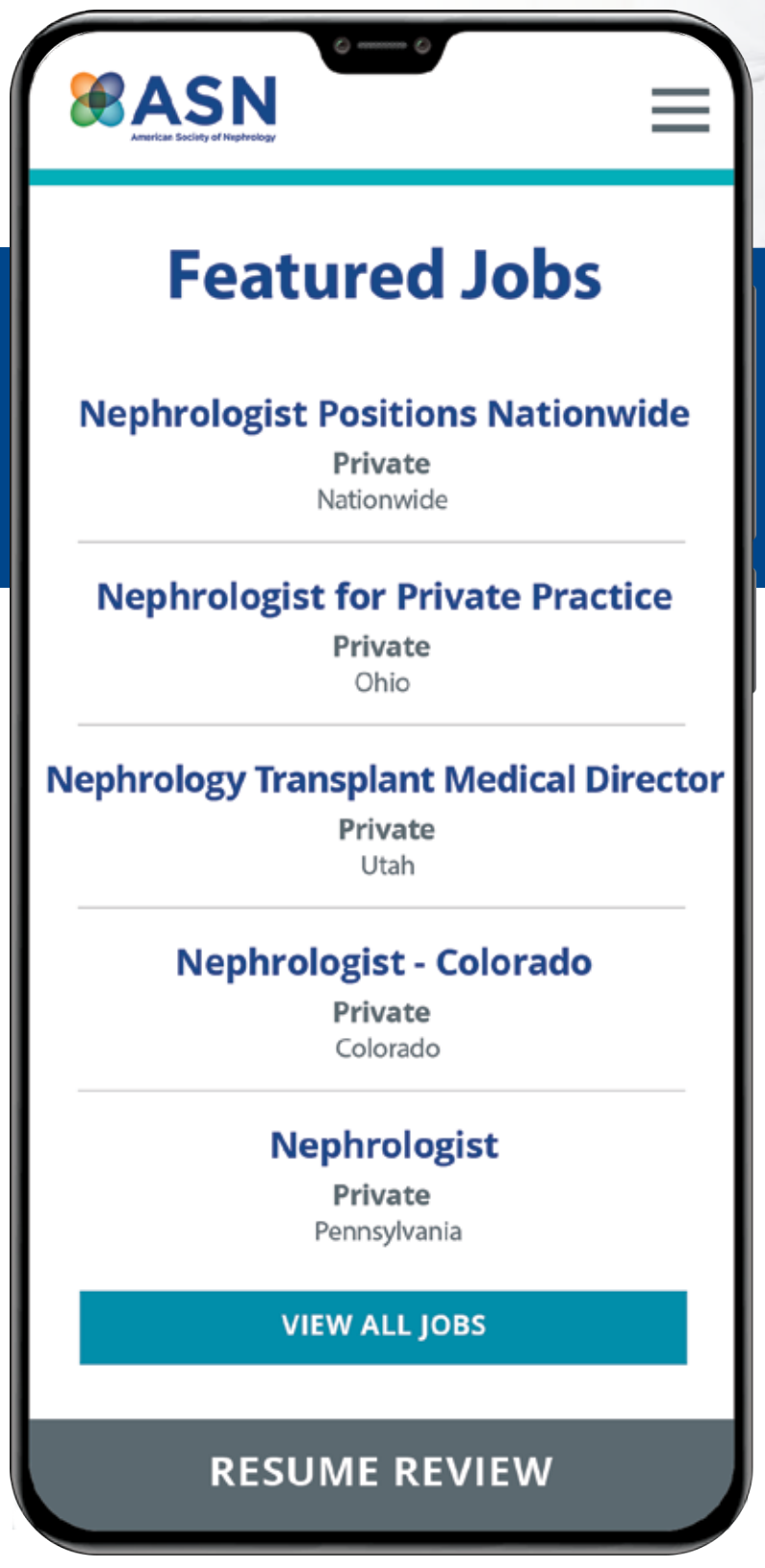

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Two More Studies Show Nova POC Creatinine/eGFR is As Accurate or More Accurate Than Laboratory Methods

Study One:

Accuracy Equal to Traceable Gold Standard Creatinine Method

Nova StatSensor capillary and venous whole blood POC specimens were directly compared to the same patient's venous samples measured by the laboratory gold standard ID-LCMS creatinine method. StatSensor POC concordance with ID-LCMS at a creatinine decision-making level of 1.2 mg/dL performed equally to the laboratory.

"Consequently, the sensitivity and specificity of the capillary blood testing post-calibration alignment was 100% and 98.3% respectively, indicating that the device is suitable to screen for CKD in POC settings and is a reliable method to assess a patient's renal status in the field."

Dubois JA et al. Creatinine standardization: a key consideration in evaluating whole blood creatinine monitoring systems for CKD screening. Analytical and Bioanalytical Chemistry (2022) 414:3279–3289.

Study Two:

Accuracy Better Than the Laboratory Jaffe Creatinine/eGFR Method

StatSensor Creatinine/eGFR showed better accuracy than the Jaffe creatinine/eGFR at identifying patients in the decision-making eGFR range of 60-89 when both methods were compared to the gold standard measured GFR.

"The performance of POC devices [StatSensor] to detect eGFR in the range 60–89 mL/min/1.73 m2 is of particular interest. With limited access to renal replacement therapy for severe kidney disease, it is advantageous to detect individuals with early disease who may benefit from renal protective measures. There was improved accuracy in this area compared to laboratory Jaffe measurements."

Currin S et al. Evaluating chronic kidney disease in rural South Africa: comparing estimated glomerular filtration rate using point-of-care creatinine to iohexol measured GFR. Clin Chem Med Lab 2021

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