ASN American Society of Nephrology

KidneyNews

May 2023 | Vol. 15, Number 5

Mapping a Path to Improved APOL1 Kidney Disease Awareness, Trial Participation, and Care

By Bridget M. Kuehn

Approximately 13% of African American individuals have two copies of variants of the gene encoding apolipoprotein L1 (APOL1), placing them at risk of developing APOL1 kidney disease (1). Yet, few people know they have these variants or the risks they pose to their health.

These APOL1 risk variants are associated with faster kidney disease progression and are more common among individuals with focal segmental glomerulosclerosis, hypertension-associated kidney disease, HIV-associated kidney disease, and lupus nephritis. Lack of awareness may be contributing to disproportionately high rates of kidney diseases and progression to dialysis among African Americans in the United States, who account for 13% of the population but 16% of those with chronic kidney disease and 35% of those on dialysis, said Susanne B. Nicholas, MD, MPH, PhD, a professor of medicine at the David Geffen School of Medicine at the University of California, Los Angeles. "If we aren't able to get these patients with APOL1 risk variants tested early, which allows them to get treated when treatments are available, the consequences are a more rapid progression of their kidney disease to kidney failure, as well as overall poor clinical outcomes," Nicholas said.

To prevent such poor outcomes, Nicholas is participating in a Kidney Health Initiative steering committee that is creating a roadmap to raise APOL1 kidney disease awareness, increase testing for these disease variants, boost participation of at-risk individuals in clinical trials, and reduce barriers to clinical trial participation for individuals in affected communities (2). To achieve this, the steering committee has brought together patient advocates, clinical researchers, pharmaceutical companies, and the US Food & Drug Administration to share their perspectives. "The roadmap will allow us to see where to begin, where we want to end, and how we can maneuver through [barriers] to get to the finish line," said steering committee member Patrick Gee, Sr., PhD, a patient advocate and chair of the Kidney Health Initiative's Patient and Family Partnership Council.

Continued on page 8 >

Government Plans Overhaul of Organ Transplant Network

"Modernization Initiative" Will Target IT Upgrade and Separate Contract Tasks

By Eric Seaborg

The kidney community welcomed the announcement by the Health Resources and Services Administration (HRSA) of a "modernization initiative" that will overhaul the national system for procuring and allocating organs for transplantation.

The changes include plans to upgrade information technology (IT) systems, open the contracting process to competitive bidding that could allow other organizations to take on some of the functions now performed by the United Network for Organ Sharing (UNOS), and double federal spending on organ procurement and transplantation. The HRSA aims to increase "transparency and accountability in the system to better serve the needs of patients and families."

"ASN strongly supports HRSA's efforts to expedite reforms that will maximize transplant care," said ASN President Michelle A. Josephson, MD, FASN, in a statement responding to the announcement. "The policy

Continued on page 8 >

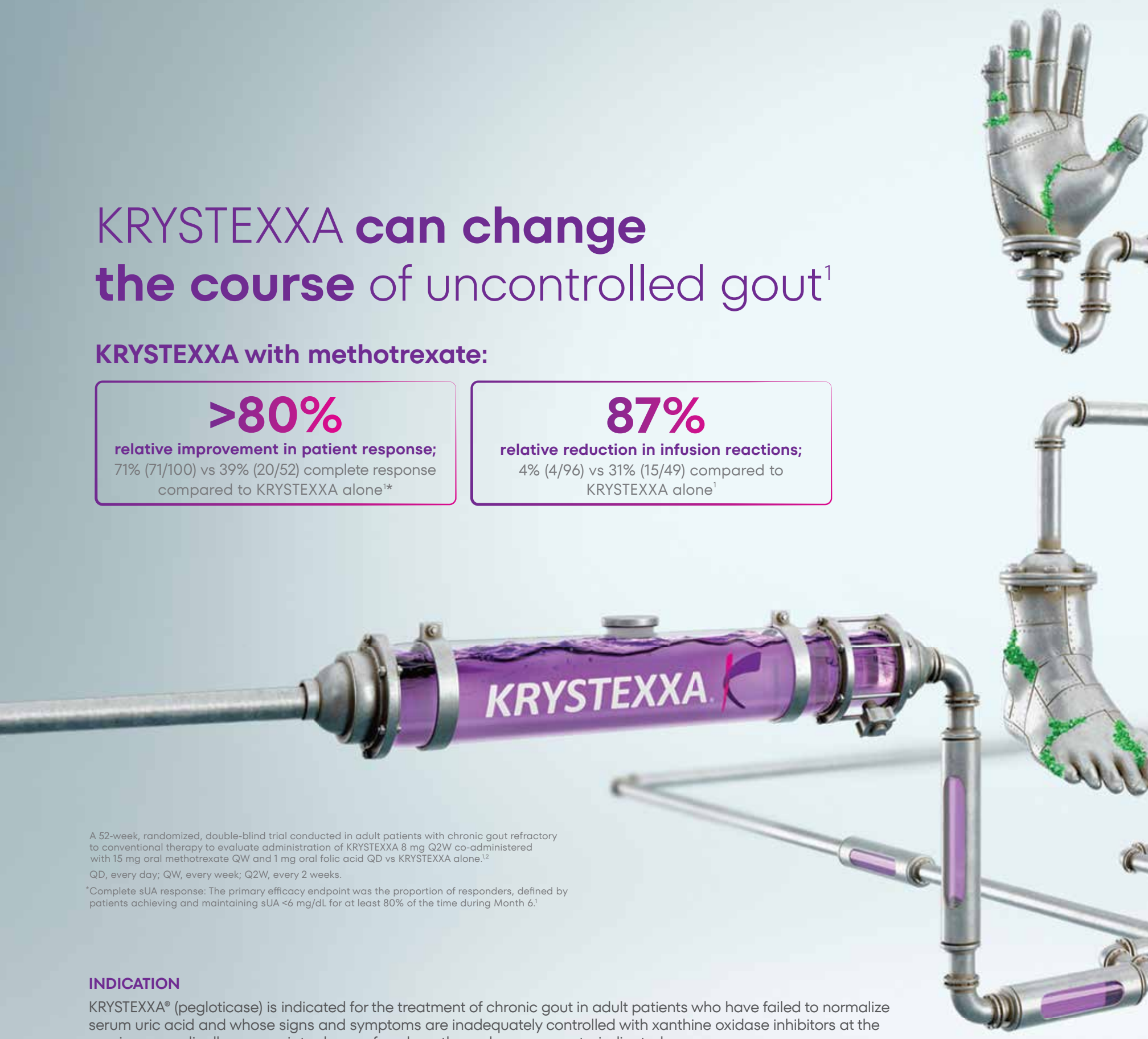
Inside

A moving target
Decision aid helps find what matters most to older people with kidney diseases.

Transplantation
Genetic testing shows value in some donors and recipients.

Overcorrection of hyponatremia
New approach needed? Or not?

KRYSTEXXA **can change the course** of uncontrolled gout[1]



KRYSTEXXA with methotrexate:

>80%
relative improvement in patient response;
71% (71/100) vs 39% (20/52) complete response compared to KRYSTEXXA alone[1]*

87%
relative reduction in infusion reactions;
4% (4/96) vs 31% (15/49) compared to KRYSTEXXA alone[1]

A 52-week, randomized, double-blind trial conducted in adult patients with chronic gout refractory to conventional therapy to evaluate administration of KRYSTEXXA 8 mg Q2W co-administered with 15 mg oral methotrexate QW and 1 mg oral folic acid QD vs KRYSTEXXA alone.[1,2]

QD, every day; QW, every week; Q2W, every 2 weeks.

*Complete sUA response: The primary efficacy endpoint was the proportion of responders, defined by patients achieving and maintaining sUA <6 mg/dL for at least 80% of the time during Month 6.[1]

INDICATION

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.

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

IMPORTANT SAFETY 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. Delayed hypersensitivity reactions have also been reported.**
- **KRYSTEXXA should be administered in healthcare settings and by healthcare providers prepared to manage anaphylaxis and infusion reactions.**
- **Premedicate with antihistamines and corticosteroids and closely monitor for anaphylaxis for an appropriate period after administration of KRYSTEXXA.**
- **Monitor serum uric acid levels prior to each infusion and discontinue 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 glucose-6-phosphate dehydrogenase (G6PD) deficiency prior to starting KRYSTEXXA. Hemolysis and methemoglobinemia have been reported with KRYSTEXXA in patients with G6PD deficiency. KRYSTEXXA is contraindicated in patients with G6PD deficiency.**

CONTRAINDICATIONS:

- In patients with G6PD deficiency.
- In patients with history of serious hypersensitivity reactions, including anaphylaxis, to KRYSTEXXA or any of its components.

Dissolve years of urate deposition[3]
ChangeTheCourse.com

WARNINGS AND PRECAUTIONS

Gout Flares: An increase in gout flares is frequently observed upon initiation of anti-hyperuricemic therapy, including KRYSTEXXA. 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 formally studied in patients with congestive heart failure, but some patients in the pre-marketing placebo-controlled clinical trials experienced exacerbation. Exercise caution in patients who have congestive heart failure and monitor patients closely following infusion.

ADVERSE REACTIONS

The most commonly reported adverse reactions (≥5%) are:

KRYSTEXXA co-administration with methotrexate trial:
KRYSTEXXA with methotrexate: gout flares, arthralgia, COVID-19, nausea, and fatigue; KRYSTEXXA alone: gout flares, arthralgia, COVID-19, nausea, fatigue, infusion reaction, pain in extremity, hypertension, and vomiting.

KRYSTEXXA pre-marketing placebo-controlled trials:
gout flares, infusion reactions, nausea, contusion or ecchymosis, nasopharyngitis, constipation, chest pain, anaphylaxis, and vomiting.

Please see Brief Summary of Prescribing Information for KRYSTEXXA on following page.

References: 1. KRYSTEXXA (pegloticase) [prescribing information] Horizon. **2.** Botson J, et al. *J Clin Rheumatol*. 2022;28:e129-e134. **3.** Data on File. Horizon, March 2022.

HORIZON.

KRYSTEXXA®
pegloticase

KRYSTEXXA® (pegloticase) injection, for intravenous use

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

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

See full prescribing information for complete boxed warning.

- **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 hypersensitivity reactions have also been reported.**
- **KRYSTEXXA should be administered in healthcare settings and by healthcare providers prepared to manage anaphylaxis and infusion reactions.**
- **Pre-medicate with antihistamines and corticosteroids and closely monitor for anaphylaxis for an appropriate period of time after administration of KRYSTEXXA.**
- **Monitor serum uric acid levels prior to each infusion and discontinue 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. KRYSTEXXA is contraindicated in patients with G6PD deficiency.**

INDICATIONS AND USAGE

KRYSTEXXA® (pegloticase) is 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.

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

CONTRAINDICATIONS

KRYSTEXXA is contraindicated in:

- Patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency *[see Warnings and Precautions]*
- Patients with history of serious hypersensitivity reactions, including anaphylaxis, to KRYSTEXXA or any of its components

WARNINGS AND PRECAUTIONS

Anaphylaxis

In a 52-week controlled trial, which evaluated KRYSTEXXA co-administered with methotrexate compared to KRYSTEXXA alone, patients were pre-treated with standardized infusion reaction prophylaxis and were discontinued from treatment with KRYSTEXXA if serum uric acid levels increased to above 6 mg/dL at 2 consecutive visits after the initiation of KRYSTEXXA therapy to reduce the risk of anaphylaxis. One patient randomized to the group treated with KRYSTEXXA co-administered with methotrexate (1%) experienced anaphylaxis during the first infusion and no patients experienced anaphylaxis in the group treated with KRYSTEXXA alone *[see Adverse Reactions]*.

During pre-marketing clinical trials with KRYSTEXXA alone, KRYSTEXXA was not discontinued following 2 consecutive serum uric acid levels above 6 mg/dL. 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, nausea or vomiting. 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 discontinue 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

In a 52-week, controlled trial which evaluated KRYSTEXXA co-administered with methotrexate compared to KRYSTEXXA alone *[see Adverse Reactions]*, patients were pre-treated with standardized infusion reaction prophylaxis and were discontinued from treatment with KRYSTEXXA if serum uric acid levels increased to above 6 mg/dL at 2 consecutive visits after the initiation of KRYSTEXXA therapy to reduce the risk of infusion reactions. Infusion reactions were reported in 4% of patients in the KRYSTEXXA co-administered with methotrexate group compared to 31% of patients treated with KRYSTEXXA alone experienced infusion reactions *[see Adverse Reactions]*. In both treatment groups, the majority of infusion reactions occurred at the first or second KRYSTEXXA infusion and during the time of infusion. Manifestations of these infusion reactions were similar to that observed in the pre-marketing trials.

During pre-marketing 24-week controlled clinical trials with KRYSTEXXA alone, KRYSTEXXA was not discontinued following 2 consecutive serum uric acid levels above 6 mg/dL. 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 discontinue 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

In a 52-week, randomized, double-blind trial which evaluated KRYSTEXXA co-administered with methotrexate compared to KRYSTEXXA alone, patients were administered gout flare prophylaxis similar to that in the pre-marketing, placebo-controlled trials. In this trial, the percentages of patients with any flare for the first 3 months were 66% and 69% for the group treated with KRYSTEXXA co-administered with methotrexate and the group treated with KRYSTEXXA alone, respectively. In the group treated with KRYSTEXXA co-administered with methotrexate, the percentages of patients with any flare for the subsequent 3 month increments of treatment were 27% during Month 6, 8% during Month 9 and 9% during Month 12. In the group treated with KRYSTEXXA alone, the percentages of patients with any flare were 14% during Month 6, 9% during Month 9 and 21% during Month 12.

During pre-marketing, 24-week controlled clinical trials with KRYSTEXXA alone, 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 *[see Dosage and Administration]*.

Congestive Heart Failure

KRYSTEXXA has not been formally studied in patients with congestive heart failure, but some patients in the pre-marketing, 24-week controlled clinical trials experienced exacerbation of congestive heart failure. 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 *[see Adverse Reactions]*.

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

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.

Co-administration with Methotrexate

A 52-week, randomized, double-blind trial was conducted in adult patients with chronic gout refractory to conventional therapy to evaluate administration of KRYSTEXXA 8 mg every 2 weeks co-administered with weekly administration of oral methotrexate 15 mg, compared to KRYSTEXXA alone. In this trial, patients who were able to tolerate two weeks on methotrexate 15 mg were then randomized to receive four additional weeks on either methotrexate 15 mg or matching placebo prior to initiating KRYSTEXXA therapy. A total of 152 subjects were randomized, and of these, 145 subjects completed the 4-week methotrexate run-in period and received KRYSTEXXA (96 subjects received KRYSTEXXA co-administered with methotrexate and 49 received KRYSTEXXA plus placebo) during the treatment period. All patients received pre-treatment with an oral antihistamine, intravenous corticosteroid and acetaminophen. These patients were between the ages of 24 and 83 years (average 55 years); 135 patients were male and 17 and were female; 105 patients were White/Caucasian, 22 were Black/African American,

14 were Asian, 5 were Native Hawaiian/Other Pacific Islander and 5 identified as Other; 28 were Hispanic or Latino. Common co-morbid conditions among the enrolled patients included hypertension (63%), osteoarthritis (25%), hyperlipidemia (24%), gastroesophageal reflux disease (22%), obesity (20%), type 2 diabetes (18%) and depression (16%). Patients with an eGFR <40 mL/min/1.73 m² were excluded from this trial.

The most commonly reported adverse reaction during the methotrexate pre-treatment periods was gout flare. The most commonly reported adverse reactions that occurred in ≥ 5% in either treatment group during the KRYSTEXXA co-administered with methotrexate or KRYSTEXXA alone period are provided in Table 1.

Table 1. Adverse Reactions Occurring in 5% or More of Patients in Either the KRYSTEXXA Co-administered with Methotrexate or KRYSTEXXA Alone Treatment Period

Adverse Reaction	KRYSTEXXA with Methotrexate (N=96) n (%)	KRYSTEXXA Alone (N=49) n (%)
Gout flare	64 (67%)	35 (71%)
Arthralgia	13 (14%)	5 (10%)
COVID-19	9 (9%)	3 (6%)
Nausea	5 (5%)	6 (12%)
Fatigue	5 (5%)	2 (4%)
Infusion reaction	4 (4%)[a]	15 (31%)
Pain in extremity	1 (1%)	3 (6%)
Hypertension	1 (1%)	3 (6%)
Vomiting	0	4 (8%)

[a] Included one case of anaphylaxis

KRYSTEXXA ALONE

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 24-week 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. These patients were between the ages of 23 and 89 years (average 55 years); 173 patients were male and 39 were female; and 143 patients were White/Caucasian, 27 were Black/African American, 24 were Hispanic/Latino and 18 were all other ethnicities. Common co-morbid conditions among the enrolled patients included hypertension (72%), dyslipidemia (49%), chronic kidney disease (28%), diabetes (24%), coronary artery disease (18%), arrhythmia (16%), and cardiac failure/left ventricular dysfunction (12%).

During the pre-marketing placebo-controlled clinical trials, the most commonly reported adverse reactions that occurred in greater than or equal to 5% of patients treated with KRYSTEXXA 8 mg every 2 weeks are provided in Table 2.

Table 2. Adverse Reactions Occurring in 5% or More of Patients Treated with KRYSTEXXA Compared to Placebo

Adverse Reaction	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

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.

In a 52-week, randomized, double-blind trial which evaluated KRYSTEXXA co-administered with methotrexate compared to KRYSTEXXA alone, approximately 26% of patients had pre-existing antibodies to pegloticase. Patients with an increase in titer from baseline or who were negative at baseline and developed an anti-pegloticase response at one or more post dose time points was 30% and 51%, for the KRYSTEXXA co-administered with methotrexate and KRYSTEXXA alone treatment groups, respectively. Patients with higher antibody titers were more likely to have faster clearance and lower efficacy.

During pre-marketing 24-week controlled clinical trials with KRYSTEXXA alone, 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.

Postmarketing Experience

The following adverse reactions 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.

General disorders and administration site conditions: asthenia, malaise, peripheral swelling

DRUG INTERACTIONS

Methotrexate

KRYSTEXXA 8 mg every 2 weeks has been studied in patients with chronic gout refractory to conventional therapy taking concomitant oral methotrexate 15 mg weekly. Co-administration of methotrexate with KRYSTEXXA may increase pegloticase concentration compared to KRYSTEXXA alone.

PEGylated products

Because anti-pegloticase antibodies appear to bind to the PEG portion of the drug, there may be potential for binding with other PEGylated products. The impact of anti-PEG antibodies on patients' responses to other PEG-containing therapeutics is unknown.

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 *[see Data]*.

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. In a 52-week, randomized, double-blind trial which evaluated KRYSTEXXA co-administered with methotrexate compared to KRYSTEXXA alone, 85% of patients had chronic kidney disease based on estimated glomerular filtration rate (eGFR) of ≥ 40 to < 90 mL/min/1.73 m² at baseline. In the pre-marketing 24-week controlled clinical trials with KRYSTEXXA alone, 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).

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, nausea or vomiting.
- 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 *[see Warnings and Precautions, Adverse Reactions]*
- 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 *[see Warnings and Precautions, Contraindications]*.

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 *[see Warnings and Precautions, Adverse Reactions]*. Advise patients that they should not stop KRYSTEXXA therapy if they have a flare.

Manufactured by:
Horizon Therapeutics Ireland DAC
Dublin, Ireland

US License Number 2022
Distributed by:
Horizon Therapeutics USA, Inc.
Deerfield, IL 60015

ASN American Society of Nephrology

KidneyNews

ASN Kidney News is published by the American Society of Nephrology
1401 H Street, NW, Suite 900, Washington, DC 20005. Phone: 202-640-4660

www.asn-online.org

Postmaster: Please send address changes to *ASN Kidney News*, c/o Customer Service, American Society of Nephrology 1401 H Street, NW, Suite 900, Washington, DC 20005.

Publications mail agreement No. 40624074. Return undeliverable Canadian addresses to PO Box 503, RPO West Beaver Creek, Richmond Hill ON L4B 4R6

ASN Kidney News (ISSN print 1943-8044 and online 1943-8052) is an official publication of the American Society of Nephrology, 1401 H Street, NW, Suite 900, Washington DC 20005, and is published monthly 11 times a year except November. Periodicals postage paid at Washington, DC and at additional mailing offices. Subscription rates: $12 per year. To order, please email bhenkel@asn-online.org. Subscription prices subject to change. Annual ASN membership dues include $20 for *ASN Kidney News* subscription.

★ WINNER OF 3 DESIGN AWARDS ★

GD USA 2018 WINNER

WINNER 2019 APEX AWARDS FOR PUBLICATION EXCELLENCE

GD USA 2020 WINNER

AMERICAN SOCIETY OF NEPHROLOGY · ASN ·

CORPORATE SUPPORTERS 2022

ASN gratefully acknowledges the society's Diamond and Platinum Corporate Supporters for their contributions in 2022.

DIAMOND LEVEL

CSL Vifor

FRESENIUS MEDICAL CARE

GSK

Otsuka | Visterra
Otsuka Group of Companies

TRAVERE THERAPEUTICS

PLATINUM LEVEL

AstraZeneca

calliditas THERAPEUTICS

ChemoCentryx

CHINOOK THERAPEUTICS

A Moving Target: Trial of a Decision Aid for Renal Therapy (DART) for Older Adults with CKD

By Megan E. Rau and Jennifer S. Scherer

By 2050, 83.7 million adults in the United States will be 65 or older (1). The Age-Friendly Health Systems initiative was launched to meet the needs of older adults by providing evidence-based quality care focusing on key health care domains (Figure 1) (2). A specific element, "What Matters," aligns an individual's values and goals with his or her medical prognosis when formulating treatment plans, also known as shared decision-making (SDM) (3). Dialysis is an example of an intervention where SDM is imperative. For older adults, dialysis may prolong life but often at the cost of treatment burden, morbidity, cognitive decline, and loss of physical function. Unfortunately, most relevant decision aids are not designed for older adults and lack education on conservative kidney management (4).

A multicenter randomized controlled trial by Ladin et al. (5) shows that the Decision Aid for Renal Therapy (DART)—an online interactive decision aid specifically designed for older adults—has the potential to address this gap. In this trial, individuals aged 70 or older with chronic kidney disease (CKD) stage 4 or 5 were randomized to DART plus standard education or standard education alone. Standard education included in-person information from a nephrologist plus an educational booklet, called *Choosing a Treatment for Kidney Failure* (6), published by the National Kidney Foundation. The study showed statistically significant decreases in decisional conflict (mean difference on the decisional conflict scale score, −8.5; 95% confidence interval [CI], −12.0 to −5.0; $p < 0.001$), such as uncertainty about treatment choices and feeling unsupported in one's decision-making, whereas statistically significant increases were seen in "knowledge" at 3 months (mean difference, 7.2; 95% CI, 3.7–10.7; $p < 0.001$), with similar findings at 6 months in the DART group.

The study gives providers tools to meaningfully focus on what matters for older adults with CKD. One caveat is that although patient enrollment was geographically diverse, racial and ethnic diversity was limited. Furthermore, 79% of the participants completed high school or more and had the cognitive reserve to engage in the intervention, limiting the applicability of the tool. We are encouraged that Ladin et al. (5) have provided a key resource to empower older adults with CKD to consider what matters most, and we look forward to further diversification of the tool to expand applicability. ■

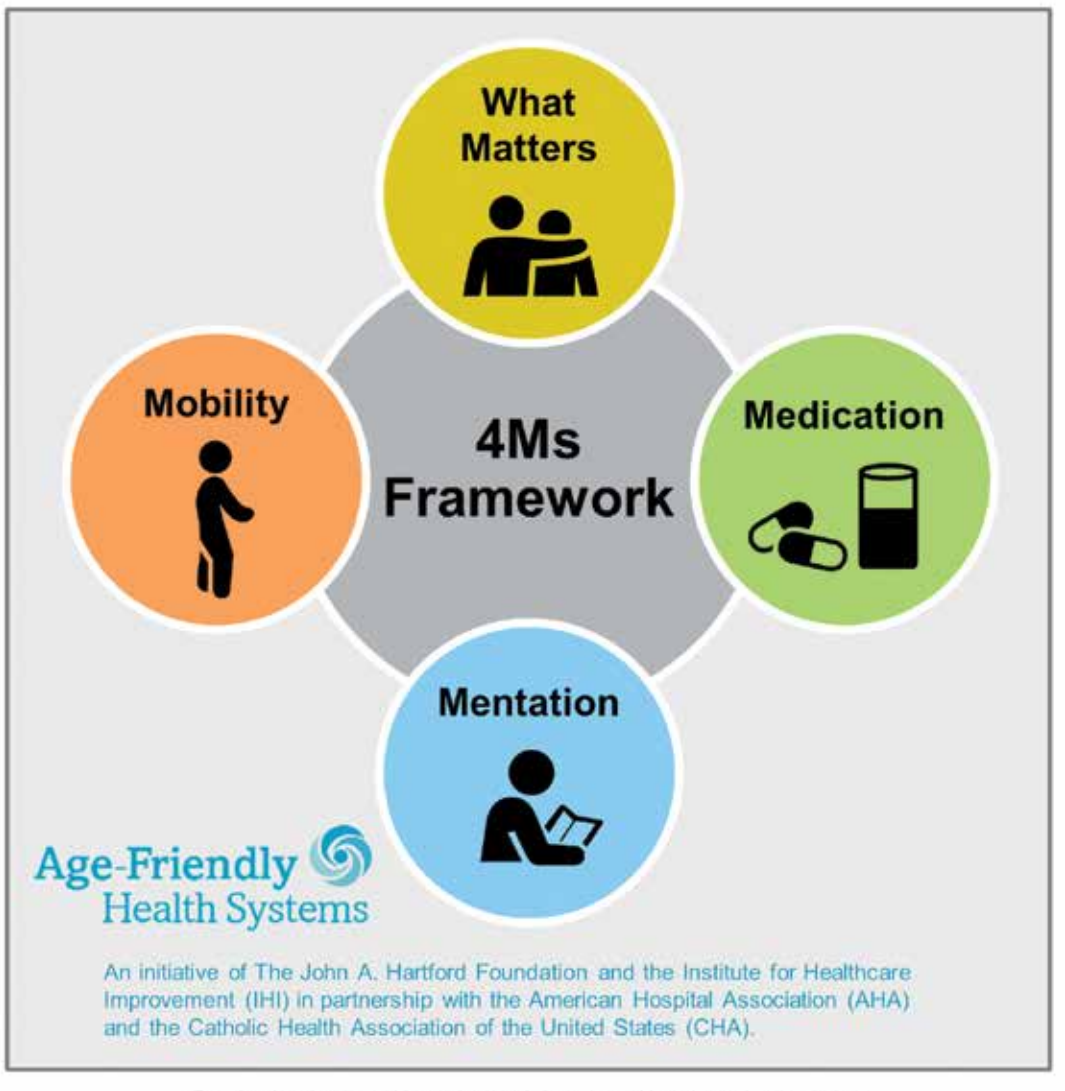
Megan E. Rau, MD, MPH, FACP, and Jennifer S. Scherer, MD, MSCI, are with the Department of Internal Medicine, New York University Grossman School of Medicine, New York, NY.

Dr. Rau reports stock ownership in Doximity Inc. Dr. Scherer reports one-time consulting/speaking fees for Vifor Pharma and Cara Therapeutics, as well as an appointment on the Clinical Advisory Board for Monogram Health.

References

1. Ortman JM, et al. An aging nation: The older population in the United States: Population estimates and projections. US Census Bureau. May 2014; 1–28. https://www.census.gov/content/dam/Census/library/publications/2014/demo/p25-1140.pdf
2. Tinetti M; Institute for Healthcare Improvement. Age-Friendly Health Systems. What is an age-friendly health system? 2023. Accessed February 28, 2023. https://www.ihi.org/Engage/Initiatives/Age-Friendly-Health-Systems/Pages/default.aspx
3. Stevens LA, et al. Chronic kidney disease and end-stage renal disease in the elderly population: Current prevalence, future projections, and clinical significance. *Adv Chronic Kidney Dis* 2010; 17:293–301. doi: 10.1053/j.ackd.2010.03.010
4. Song MK, et al. Patient perspectives on informed decision-making surrounding dialysis initiation. *Nephrol Dial Transplant* 2013; 28:2815–2823. doi: 10.1093/ndt/gft238
5. Ladin K, et al. Effectiveness of an intervention to improve decision making for older patients with advanced chronic kidney disease: A randomized controlled trial. *Ann Intern Med* 2023; 176:29–38. doi: 10.7326/M22-1543
6. National Kidney Foundation. *Choosing a Treatment for Kidney Failure*. https://www.kidney.org/atoz/content/choosingtreat#:~:text=There%20are%20two%20treatment%20options%20for%20kidney%20failure%3A,a%20different%20type%20of%20treatment%20in%20the%20future

Figure 1. Age-Friendly Health Systems initiative



Reprinted from the Institute for Healthcare Improvement (2).

Mapping a Path to Improved APOL1 Kidney Disease Awareness, Trial Participation, and Care

Continued from cover

Raising awareness

Many people in African American communities, particularly with low income or in rural communities, may be unaware of the threat of kidney risks associated with specific APOL1 variants. In fact, 8 of 10 people with kidney diseases do not know they have kidney diseases until they are diagnosed with kidney failure, said Opeyemi Olabisi, MD, PhD, assistant professor of medicine at Duke University School of Medicine (Durham, NC), who is advising the steering committee on the roadmap. "Kidney disease[s do] not announce [themselves] early," Olabisi said. Instead, patients do not discover the disease until they may have lost 80% of their kidney function and begin experiencing symptoms like leg swelling.

Gee said people with kidney diseases also want to know why they have them, and many African American individuals may not find out they have an APOL1 kidney disease variant until a late stage of the disease. "They find out somewhere down the road, [the disease] was caused by APOL1, and they feel like they have been deceived," Gee said.

That can further fuel mistrust in the medical community among African American individuals who are aware of historical mistreatment of the population in clinical research, such as the US Public Health Service's Syphilis Study at Tuskegee (3) or the use of Henrietta Lack's cervical cancer cells for research without consent (4), noted Olabisi. Lack of trust and structural barriers, such as the unavailability of transportation to clinical trial sites or less time to participate because of employment obligations, have led to low participation in clinical trials among African American individuals, he said. African American participants comprise <10% of clinical trial participants despite being disproportionately affected by kidney diseases, according to a publication co-authored by Nicholas on behalf of the Clinical Care & Innovation Workgroup of the ASN Health Care Justice Committee (5). The committee, of which Nicholas is a member, recommends that kidney disease clinical trials increase the number of African American participants to 35% to reflect the burden of kidney diseases. Committee members have created a scorecard to help clinical trials meet that goal.

Raising awareness of APOL1 kidney disease and its impact on African American communities can help empower individuals at risk and encourage more people to participate in clinical research. "People will be more willing to come forward because they understand that this does not just impact them, but it impacts family members, friends, and everybody in their community," Gee said. "This roadmap has the potential to break down institutional biases and systemic roadblocks that have been in place for decades."

Community engagement

The initiative is already helping to support community engagement and stakeholder partnerships. For example, through the initiative, Olabisi connected with representatives from Labcorp, who allow him to use a mobile clinic for his community engagement and clinical trial enrollment efforts. Olabisi and his team took the mobile clinic to the General Baptist State Convention of North Carolina in Wilmington. They used it to screen 60 participating church elders and leaders for APOL1 risk variants and protein in their urine. "We returned the results to them for free," Olabisi said. "We were able to identify some people with high-risk APOL1 and some people who did not know they had protein in their urine."

The participants are also given the information that they can share with their physicians and are alerted about ongoing clinical trials enrolling patients, including Olabisi's Janus Kinase-STAT Inhibition to Reduce APOL1 Associated Kidney Disease (JUSTICE) trial (6). "We can engage the community productively," he said. "It helps to bridge some of those historical, structural barriers that prevent African Americans from participating in research."

Olabisi and his team have also collaborated with The River Church in Durham, NC. Bishop Ronald L. Godbee invited the group to a Sunday service to share information about APOL1 kidney disease and later held a screening event at the church during a Tuesday Bible study. Bishop Godbee and his wife volunteered to be the first people screened, and 80 individuals participated in that screening event, including some who have registered to participate in the JUSTICE trial. "When we meet people where they are, and we provide information that is accessible, African Americans are just as willing to participate in clinical trials as any other group," Olabisi said.

Resource mapping

In addition to connecting stakeholders, the steering committee is building an online, interactive roadmap and a print version that should be available in August 2023. The roadmap will bring together existing resources for physicians, patients, researchers, drug makers, and other stakeholders. "We are not going to reinvent the wheel because there is a lot of information already out there," Nicholas said. "The steering committee wants to engage more physicians in sharing information about APOL1 kidney disease with their colleagues and patients," Nicholas continued. "Physicians can spread the word and recommend genetic testing for at-risk patients," she said. "They can also become more knowledgeable about interpreting the testing and know which patients they should refer for genetic counseling."

There will also be resources to help encourage more community engagement efforts like those of Olabisi's and information crafted by patient advocates like Gee for individuals with APOL1 kidney disease and those at risk.

"We would like patients to understand their risk factors for developing APOL1 kidney disease and to become empowered to incorporate disease-prevention strategies within their lifestyle, to seek out genetic testing, and to get actively involved in clinical trials, which is very, very important," Nicholas said.

Participation and collaboration among all stakeholders are essential to developing new prevention and treatment strategies for patients with APOL1. "Our ultimate goal, through our trial and trials like it, will be to come up with treatments that prevent [kidney function] from being drained down to zero," Gee said. "Can we stop the disease that APOL1 causes in the kidney?" ■

References

1. Yusuf AA, et al. Kidney disease and APOL1. *Hum Mol Genet* 2021; 30:R129–R137. doi: 10.1093/hmg/ddab024
2. ASN Steering Committee Workgroup Members. Kidney Health Initiative. Current project. Roadmap to increase disease awareness and clinical trial participation of people carrying high-risk genetic variants of APOL1-associated nephropathy. Accessed March 7, 2023. https://khi.asn-online.org/projects/project.aspx?ID=91
3. US Centers for Disease Control and Prevention. The U.S. Public Health Service Syphilis Study at Tuskegee. https://www.cdc.gov/tuskegee/timeline.htm
4. Henrietta Lacks: Science must right a historical wrong. *Nature* 2020; 585:7. doi: 10.1038/d41586-020-02494-z
5. Nicholas SB, Cervantes L; Clinical Care & Innovation Workgroup of the American Society of Nephrology Health Care Justice Committee. Health care equity and justice scorecard to increase diversity in clinical trial recruitment and retention. *J Am Soc Nephrol* 2022; 33:1652–1655. doi: 10.1681/ASN.2022040427
6. Clinicaltrials.gov. Janus Kinase-STAT Inhibition to Reduce APOL1 Associated Kidney Disease (JUSTICE). ClinicalTrials.gov Identifier: NCT05237388

Government Plans Overhaul of Organ Transplant Network

Continued from cover

changes announced today are a positive step in the right direction."

ASN has been advocating for these changes for many years, according to ASN Strategic Policy Advisor Rachel Nell Meyer.

Kevin Longino, chief executive officer of the National Kidney Foundation (NKF), also welcomed the "long overdue" HRSA announcement and said that the NKF has long advocated the "common-sense changes" vital to creating "a patient-centric organ donation and transplantation system."

Nephrologists and patients alike have long voiced dissatisfaction with a system that many consider opaque and inefficient. Approximately 20% of kidneys procured for transplant in the United States go unused, which is roughly double the discard rate in France, the United Kingdom, and other European countries. The waste of organs occurs even though approximately 6000 Americans die each year while waiting for organ transplants, with people of color and people in rural communities being disproportionately affected, according to the HRSA.

The HRSA announced that its Organ Procurement and Transplantation Network (OPTN) modernization initiative will "strengthen accountability, equity, and performance in the organ donation and transplantation system through a focus on five key areas: technology, data transparency, governance, operations, and quality improvement and innovation." The OPTN was established by the National Organ Transplant Act of 1984 and coordinates a network that has grown to include 56 organ procurement organizations and approximately 250 transplant centers.

The OPTN has contracted out the work of managing the network to UNOS, which is so closely identified with OPTN that many nephrologists think they are the same organization, according to Sumit Mohan, MD, MPH, FASN, a member of the ASN Quality Committee and a nephrologist at Columbia University Irving Medical Center (NY): "The vast majority of people don't realize that UNOS is not the OPTN. It is just the contractor for the OPTN."

That confusion is easy to understand—the boards of directors of the two organizations are the same, including the same president and other officers—but the arrangement sets up a system in which the OPTN is essentially granting itself a multi-million-dollar contract to manage the system.

Several years ago, the HRSA began an effort to separate the two organizations, but UNOS objected and filed a complaint with the U.S. Government Accountability Office (GAO) claiming that the attempt violated the National Organ Transplant Act. The GAO ruled in favor of the HRSA, and now the HRSA intends to continue its work to separate the two organizations with independent governance boards, by splitting contracts for managing the

system—now managed by UNOS on a single contract—into multiple contracts covering different tasks within the system, and by offering competitive bids.

Restructuring an archaic system

The IT portion is the function mentioned most that could be separated between UNOS and the OPTN. Separating IT would be in agreement with a recommendation from a National Academies of Sciences, Engineering, and Medicine study, "Realizing the Promise of Equity in the Organ Transplantation System" (1), published last year, as well as a recommendation from the U.S. Digital Service, a government agency dedicated to improving government services through technology modernization and data science. In July 2022, *The Washington Post* reported that a confidential assessment by the U.S. Digital Service designated the UNOS technological system archaic and recommended it be "vastly restructured" (2).

Kidney community leaders have been making this point for years, with the ASN statement noting that separating the OPTN contract into distinct pieces that can be bid on by multiple entities would align the contract with federal contracting protocols, increase competition, and drive innovation. "There is a sense in the community that the existing information technology is outdated, and it could better serve patients if it were operated by a contracting entity with a more specific focus on technology and IT expertise," Meyer said.

"UNOS has not invested adequately in the resources," said Mohan, who also chairs the UNOS Data Advisory Committee. "If you don't invest in the resources, you end up with an archaic system that has not moved much in the last 20 years." He said the UNOS systems are based on a programming language that is "years and years old and hasn't really progressed."

Mohan explained that one example of the difficulty in improving UNOS's system was the long, drawn-out process of introducing new codes to transplant centers to specify why they declined to use a kidney for transplant. That process—which involved creating a single, pull-down menu—took nearly 5 years.

Another oft-cited source of frustration is the difficulty in tracking kidneys procured for transplant. "You have the ability to track any package that you have ordered on Amazon and know approximately where it is at any given point in time," Mohan said. "The fact that UNOS has never looked at creating a GPS [global positioning system] tracking system for organs underscores the lack of desire to make progress."

UNOS' management of transplant waiting lists is another common target of complaint. "The waitlists are often poorly curated and maintained due to insufficient communication among transplant centers, dialysis facilities, and patients or their care partners. As a result, nearly one in five kidneys is now offered to a deceased person still on the waitlist because the transplant center is unaware that the patient is deceased," ASN's Past President Susan E. Quaggin, MD, FASN, wrote in a letter to the HRSA in response to a request for information on improving the OPTN (3).

ASN Quality Committee Chair Scott Bieber, DO, told ASN *Kidney News* that as a general nephrologist practicing in rural, northern Idaho, he and his patients "struggle with the lack of transparency in the transplant program. It has been opaque to us as to what the transplant programs expect from patients. They are not consistent or clear about what it takes for a patient to get onto the transplant list. Certain patients are able to navigate the system fairly easily, and others really struggle or don't have the resources to make it happen."

Even for patients who make it onto the list, "as a referring nephrologist and as a patient, you are kept in the dark. You don't have any clue where you are on the list and you are never told if an organ is offered or if the transplant system has bypassed you," Bieber said. Mohan noted that in most health systems, patients can access current information through a program like MyChart, but nothing like that exists for transplant patients.

The HRSA announcement promised to increase transparency through the introduction of "data dashboards detailing individual transplant center and organ procurement organization data on organ retrieval, waitlist outcomes, and transplants, and demographic data on organ donation and transplant." Representatives of the agency said that it started the process of upgrading OPTN IT last year by engaging the U.S. Digital Service to leverage its expertise and advice in implementing the modernization initiative.

As part of its announcement, HRSA unveiled "a new data dashboard to share de-identified information on organ donors, organ procurement, transplant waitlists, and transplant recipients. Patients, families, clinicians, researchers, and others can use [these] data to inform decision-making. Today's launch is an initial data set, which HRSA intends to refine over time and update regularly." The dashboard can be found at https://data.hrsa.gov/topics/health-systems/organ-donation.

Increased funding

Upgrading IT will cost money, and the HRSA announcement also noted that the Biden administration's fiscal year 2024 budget request would more than double federal investment in organ procurement and transplantation. The $36 million increase over the previous year would bring the total to $67 million. The administration is also requesting Congress to update the National Organ Transplant Act of 1984 to remove the appropriations cap on OPTN contracts and to expand the pool of eligible contractors to increase competition. The National Organ Transplant Act currently places constraints on HRSA, but in an interview with *The Washington Post*, HRSA Administrator Carole Johnson said that HRSA has the legal authority to move forward even without congressional action. She said that bid solicitations could go out as soon as this fall (4).

Congress has already begun to move to support HRSA's efforts. On April 10, Rep. Larry Bucshon, MD (R-Ind.), and Rep. Robin Kelly (D-Ill.) said they had introduced legislation that would allow HRSA to "run a competitive process to choose the best contractors for different national OPTN functions (e.g., health IT and logistics)."

Whether Congress will agree to such an increase in spending is anyone's guess at a time when the Republican leaders in the House of Representatives say they will not increase the debt ceiling without as-yet unspecified budget cuts. "We know that this is going to be a very challenging year for appropriations," said ASN's Meyer. "It remains to be seen how much of the $67 million request will be granted by Congress and the extent to which the funding will allow HRSA to fully realize the promise of the reforms it announced. ASN will be working with Congress on a bipartisan basis to ensure that [lawmakers] understand how important these changes are, and kidney transplantation has enjoyed a lot of bipartisan support in recent years."

Bipartisan support

That bipartisan support was evident in statements praising the HRSA announcement from Sen. Ron Wyden (D-Ore.) and Sen. Chuck Grassley (R-Iowa), the chair and past chair, respectively, of the Senate Finance Committee, who have collaborated on hearings on and investigations into the OPTN.

"[HRSA's] announcement is a big victory for families across the country who have been fighting for a more effective organ procurement and transplantation system," Wyden said. "For too long it's been clear that UNOS has fallen short of the requirements for this contract and the expectations of Americans waiting for a transplant." Wyden's statement said HRSA's "intent to issue multiple contracts for the OPTN contract" is "an important step towards breaking up a longstanding monopoly contract held by UNOS." Grassley added that "The U.S. transplant network has failed at all levels, putting lives at risk, wasting valuable life-saving organs, and [disproportionately] affecting people of color and those living in rural America. Today's announcement is welcome news after years of uncovering troubling trends in our nation's organ procurement programs."

The drive for more funding could receive a boost from a 2020 report from the Senate Finance Committee that said: "Experts also project that improvements to the OPTN could save the federal government and taxpayers up to $40 billion over the next decade, particularly through reductions in dialysis and treatment of End Stage Renal Disease, which accounts for $36 billion in Medicare spending each year."

UNOS response

For its part, UNOS responded that it "supports HRSA's plan to introduce additional reforms into the nation's organ donation and transplantation system. We also stand united with HRSA in our shared goal to get as many donor organs as possible to patients in need while increasing accountability, transparency, and oversight. We welcome a competitive and open bidding process for the next OPTN contract…. We believe we have the experience and expertise required to best serve the nation's patients and to help implement HRSA's proposed initiatives."

As previously noted, the NKF joined ASN in welcoming the initiative. "Our current transplant system still relies on antiquated technology and inefficient systems that create life-threatening bureaucracy and delays," Longino said. "HRSA's move to redesign the OPTN contract will allow leaders in technology, artificial intelligence, supply chain management, and other critical business operations to bring their ideas and talent to a system that is in desperate need of reform." He noted that the NKF has advocated for several years on the need to modernize the IT infrastructure, install an OPTN board of directors independent of UNOS, and develop a public dashboard of key measures.

ASN President Josephson said: "Ensuring OPTN's technology systems are fully modernized and leveraging their capabilities is a foundational step to improving the transparency and efficiency of the kidney health ecosystem and is a prerequisite to achieving ASN's goal of maximizing access to kidney transplantation. I applaud HRSA's public commitment to building that capacity and ensuring future systems better serve the needs of patients and their families." ■

References

1. National Academies of Sciences, Engineering, and Medicine. Realizing the promise of equity in the organ transplantation system. 2022. https://doi.org/10.17226/26364
2. Menn J, Bernstein L. Thousands of lives depend on a transplant network in need of "vast restructuring." *The Washington Post*, July 31, 2022. https://www.washingtonpost.com/health/2022/07/31/unos-transplants-kindeys-hearts-technology/
3. Quaggin SE. Letter to The Honorable Carole Johnson, Administrator, Health Resources and Services Administration. American Society of Nephrology. May 23, 2022. https://www.asn-online.org/policy/webdocs/ASNfinalMay23RFIOPTNContract_(002).pdf#:~:text=The%20waitlists%20are%20often%20poorly%20curated%20and%20maintained,failure%20to%20understand%20the%20import%20of%20the%20problem
4. Bernstein L. Troubled U.S. organ transplant system targeted for overhaul. *The Washington Post*, March 22, 2023. https://www.washingtonpost.com/health/2023/03/22/transplant-system-overhaul-unos/#:~:text=Carole%20Johnson%2C%20administrator%20of%20the%20federal%20Health%20Resources,entity%20ever%20to%20operate%20the%20U.S.%20transplant%20system

ASN President's Update

From Mother to Daughter: Four Decades of Evolution in Medicine

By Michelle A. Josephson

This month, I'm attending my 40th medical school reunion. Besides looking forward to catching up with old friends and accepting the reality that so much time has passed, I've used this milestone to think about how much medicine has changed since I graduated. This reflection has also been intensified by the many emotions and memories that have accompanied the happy news of my daughter Maya's recent acceptance to medical school. The profession she has chosen to pursue is not the same one I entered. Please don't misunderstand me: I am not saying that is a bad thing, just that it is very different.

Of course, health care, medicine, and science have evolved since I started medical school. HIV and AIDS were yet to be, cyclosporine had not even been introduced, PCR did not exist, donor nephrectomies were all open, bacterium *Helicobacter pylori* was not recognized, CAPD was mostly used because CCPD was in its infancy, RVUs were not a thing, scalpels were still flying in ORs and barely missing medical students, and duty hour limits for residents and fellows resulting from the Libby Zion case did not exist. But the greatest difference since my time in medical school has been the fundamental change in the culture of medicine. It is easy to be nostalgic (as I will be at my reunion) and think upon the "good old days." Truth be told, much was not so good.

In the 5th Edition of *On the Origin of Species*, Charles Darwin wrote: "This preservation of favourable variations and the destruction of injurious variations, I call Natural Selection" (1), or the survival of the fittest. This concept has been paraphrased as: "In the struggle for survival, the fittest win out at the expense of their rivals because they succeed in adapting themselves best to their environment" (2). With these concepts of adaptability and resilience in the face of change in mind, let's consider how things have changed, what my Generation Z daughter will encounter that her Baby Boomer mom did not, and how we "more-seasoned" physicians might consider our roles as we adapt to new realities.

The year that I started medical school, 27.9% of first-year medical students were women (Table 1) (3, 4). By contrast, for 2022–2023, women made up 56% of matriculants (5). To put the year I started medical school in context, Jimmy Carter was the U.S. president, Margaret Thatcher was elected Prime Minister of the United Kingdom, China instituted the "one child per family" rule, the Three Mile Island nuclear accident occurred in Pennsylvania, Sony introduced the Walkman, and "60 Minutes" was the most-watched television show (followed closely by "Three's Company").

I entered medical school in the early phases of a major demographic shift. My female classmates and I recognized that more of us were in medical school than ever before, and we were happy about it. At the same time, however, we also felt that we were not the dominant culture. It is not that much was particularly overt; it was more below the surface. For example, after an exam, the men would get together and play video games and drink beers. Whether any of the women wanted to join them is not the point. I don't think we were actively excluded, but we were not actively included.

After I graduated, my intern class had more women in it than ever before. This new reality was accompanied by some surprising reactions. Our residency program director, for example, was concerned that having so many women in the class would inevitably result in several of us needing maternity leave. He could not fathom how this could be managed. We laughed when we learned that, but we should have been very angry. We were young adults whose biological clocks were not based on the prevailing medical training paradigm. Why shouldn't there have been a plan in place for pregnancies during training, as there is now? It was too early in the demographic shift, and the idea of adapting training to the needs of the trainees (be they reproduction or sleep) was not in vogue, and that was just not the way it had been done in the past.

Fortunately, many things have changed for the better, such as duty hours and greater respect for work-life balance. And yet, some things have not changed for the better. Women are still woefully underrepresented in leadership positions. On average, only 19% of department chairs at the most research-intensive institutions are female (6). Other leadership positions in academic medicine have been slow to change too. Based on the trends in positions of permanent, acting, or interim department chairs and medical school deans since 1992, it will take another 50 years to reach gender parity (7). A study that assessed the gender pay gap for female academic physicians found that when comparing male and female physicians in their own racial or ethnic group, Black women earned 79 cents on the dollar, White women earned 77 cents on the dollar, and Asian women earned 75 cents on the dollar (8).

At last year's Kidney Week, I was honored to give the Annual Nancy E. Gary Memorial Lecture, which Women in Nephrology (WIN) has hosted at the ASN Annual Meeting since 2005. Having joined WIN in the 1990s, I've seen firsthand how Kidney Week and other international meetings have intentionally attempted to include as speakers more women and other faculty who identify as underrepresented in medicine. Former National Institutes of Health Director Francis S. Collins, MD, PhD—another former Gary lecturer whose daughter is a nephrologist—used his unparalleled platform to publicly call out all-male panels, or "manels," at medical meetings.

From 1966 through 2009, ASN had 43 successive presidents who were male. Sharon Anderson, MD, FASN, started her tenure as the first female ASN president at Renal Week (now Kidney Week) 2009. Since Sharon's historic tenure, 4 of the 12 ASN presidents have been female (five if you add Barbara T. Murphy, MD, MB, BAO, BCh, FRCPI, who was elected to serve as president but died before her term), including ASN Past President Susan E. Quaggin, MD, FASN, and me. Next year, Deidra C. Crews, MD, MS, FASN, will become the first Black,

Table 1. A tale of two eras: Demographic shifts among medical school matriculants over 40 years

Characteristic	My Era	Maya's Era
Female	27.9%	56.0%
Persons of Color	9.0%	23.0%
Lesbian Gay	UK	4.3%
Bisexual	UK	5.0%
Transexual	UK	0.7%

Source: AAMC. Medical School Graduation Questionnaire: 2021 All Schools Summary Report.
Figure: Kurtis A. Pivert, MS.
Abbreviation: UK = unknown.

female ASN president. She is also our first Generation X president, bringing us one step closer to Maya and her Generation Z classmates.

In the class of 2022–2023, the race and ethnicity of a combined 23% of the total matriculating students are Black or African American; Hispanic, Latino, or of Spanish descent; American Indian or Alaska Native; Native Hawaiian or Other Pacific Islander; and "other" than Asian or White (5). By contrast, during my first year of medical school, 9% of the class nationally was comprised of matriculants who were Black, Mexican American, mainland Puerto Rican, and American Indian (3). This change is not accidental. It is a consequence of policy goals of the Association of American Medical Colleges (AAMC) and medical school efforts to increase the number of applicants and matriculants with individuals who identify as underrepresented in medicine.

During his tenure as AAMC president from 1994 to 2006, Jordan J. Cohen, MD—a nephrologist and former teacher of mine—recognized that greater physician diversity will lead to improved patient-doctor relationships, stronger physician teams (across the tripartite mission), and ultimately to improved public health. The impact of increased diversity in medical schools is already having a positive impact. After all, it was medical students who led the charge to remove race from clinical algorithms, compelling us to remove race from the eGFR.

One of my closest friends from medical school is a gay man, who was closeted for much of medical school. At the time, there were medical students who were open about their sexual orientation and identity, but my friend was far from being alone in his concerns about encountering homophobia. We matriculated only 6 years after the American Psychiatric Association removed the diagnosis of homosexuality from the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*), which had equated homosexuality with a pathologic state. By including homosexuality in the *DSM*, medicine played a significant role in the social stigmatization of LGBTQ+ communities (9). Not surprisingly, LGBTQ+-related medical topics were not routinely taught. By the time my friend was training as a resident, he was living openly. He was also the person in his residency to educate others about caring for LGBTQ+ individuals, because there was no such curriculum in medical school.

Although considerable room for improvement still exists, the situation is better. Medical schools are encouraging applications from LGBTQ+ individuals (10). In 2014, the AAMC released the first guidelines (11) to support medical schools in training students to care for LGBTQ+ and gender-nonconforming patients, as well as for those born with differences in sexual development (12). For the past decade, the ASN Diversity, Equity, and Inclusion Committee has supported LGBTQ+ communities within ASN and the broader kidney community. For example, ASN hosts an annual reception at Kidney Week for LGBTQ+ participants and their allies. Last year in Orlando, FL, ASN supported the onePULSE Foundation—which was established in response to the 2016 massacre at the Pulse nightclub—and the foundation's executive director spoke at the reception.

During the past four decades, I have welcomed the changes described above. I would be disingenuous, however, if I give the impression that I welcome all change. I don't. Change is often hard and sometimes not good. Holding onto the past can feel comfortable and safe, and many good reasons exist for precedent. That is part of the draw of events like reunions. So, yes, I am guilty of nostalgia. But change is inevitable, and to be fair, it is often a good thing. I, for one, am not trading my computer for an electric typewriter. As we age, we all must figure out how to adapt to novel technology, approaches, and perspectives.

Social scientist Arthur Brooks observed that as we age, our strengths evolve, and we shift from fluid intelligence (that which allows us to solve problems or innovate faster) to crystallized intelligence (that which is built on wisdom or enables us to form teams better) (13). Our gained wisdom can help those with less experience. Even if there is not a term limit on a position, transitioning after a period makes sense, not only because our strengths may no longer be as good a fit for the job but also because we must allow the next generation to have its turn.

Nevertheless, giving up a position can feel difficult for many reasons, including that we may fear losing our value or relevance and becoming invisible. And, in the current medical culture, which is based on a business model that values productivity, teaching or sharing one's experience is not billable and does not generate RVUs. Career opportunities are not as abundant for maturing physicians. In other words, leaving a position is not often followed by a new opportunity. Career development workshops are usually directed at those in the early career stages and sometimes those who are midcareer. Providing resources for career and life decisions to those who are past these phases is rare. Although some physicians may be ready to retire or back off, others may continue to want to contribute.

Taken together, these forces lead to marginalization or ageism across society, from those of us who've dedicated our careers to medicine to those in the entertainment business to everyone, everywhere in between. As we embrace diversity, equity, and inclusion in medicine, we must continue to harness the irreplaceable wisdom of those who entered the profession before us.

Last month, I stepped down as Medical Director of Kidney Transplantation at The University of Chicago, giving a talented Generation X nephrologist an opportunity. This transition has not come easily for me, especially since I founded and developed the transplant nephrology program. However, it is time, and I am taking on a new, ded-icated, educational position in the transplant program. After all, someday, in the not-too-distant future, Maya deserves to have opportunities to advance in her career. That won't be possible unless we all adapt, evolve, and support the next generations. ■

Michelle A. Josephson, MD, FASN, is Professor of Medicine and Surgery, University of Chicago, IL, and is ASN President.

References

1. Darwin *C. On the Origin of Species by Means of Natural Selection, or the Preservation of Favoured Races in the Struggle for Life*, 5th Edition. London: John Murray, 1869.
2. Today in Science History. Charles Darwin quote on survival of the fittest. https://todayinsci.com/D/Darwin_Charles/DarwinCharles-SurvivalOfTheFittest-Quotations.htm
3. Institute of Medicine (US) Division of Health Sciences Policy. Medical Education and Societal Needs: A Planning Report for the Health Professions. Washington, DC: National Academies Press, 1983. doi: 10.17226/729; https://www.ncbi.nlm.nih.gov/books/NBK217680/
4. Association of American Medical Colleges. Medical School Graduation Questionnaire. 2021 All Schools Summary Report. July 2021. https://www.aamc.org/media/55736/download
5. Association of American Medical Colleges. Diversity increases at medical schools in 2022. December 13, 2022. https://www.aamc.org/news-insights/press-releases/diversity-increases-medical-schools-2022
6. Valantine HA. Where are we in bridging the gender leadership gap in academic medicine? *Acad Med* 2020; 95:1475–1478. doi: 10.1097/ACM.0000000000003574
7. Beeler WH, et al. Unplugging the pipeline—a call for term limits in academic medicine. *N Engl J Med* 2019; 381:1508–1511. doi: 10.1056/NEJMp1906832
8. Gottlieb AS, Jagsi R. Closing the gender pay gap in medicine. *N Engl J Med* 2021; 385:2501–2504. doi: 10.1056/NEJMp2114955
9. Drescher J. Out of DSM: Depathologizing homosexuality. *Behav Sci (Basel)* 2015; 5:565–575. doi: 10.3390/bs5040565
10. U.S. medical schools push to recruit more LGBTQ students. *ASH Clinical News*. February 20, 2020. https://ashpublications.org/ashclinicalnews/news/5000/U-S-Medical
11. Association of American Medical Colleges. *Implementing Curricular and Institutional Climate Changes to Improve Health Care for Individuals Who Are LGBT, Gender Nonconforming, or Born with DSD: A Resource for Medical Educators*, 2014. https://store.aamc.org/implementing-curricular-and-institutional-climate-changes-to-improve-health-care-for-individuals-who-are-lgbt-gender-nonconforming-or-born-with-dsd-a-resource-for-medical-educators.html
12. Krisberg K. New curricula help students understand health needs of LGBT patients. Association of American Medical Colleges. September 29, 2016. https://www.aamc.org/news-insights/new-curricula-help-students-understand-health-needs-lgbt-patients
13. Brooks, AC. *From Strength to Strength: Finding Meaning, Success, and Deep Purpose in the Second Half of Life*. New York: Portfolio/Penguin, 2022.

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

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

Fine Particulate Matter Air Pollution Is a Risk Factor for Kidney Failure in Patients with IgA Nephropathy

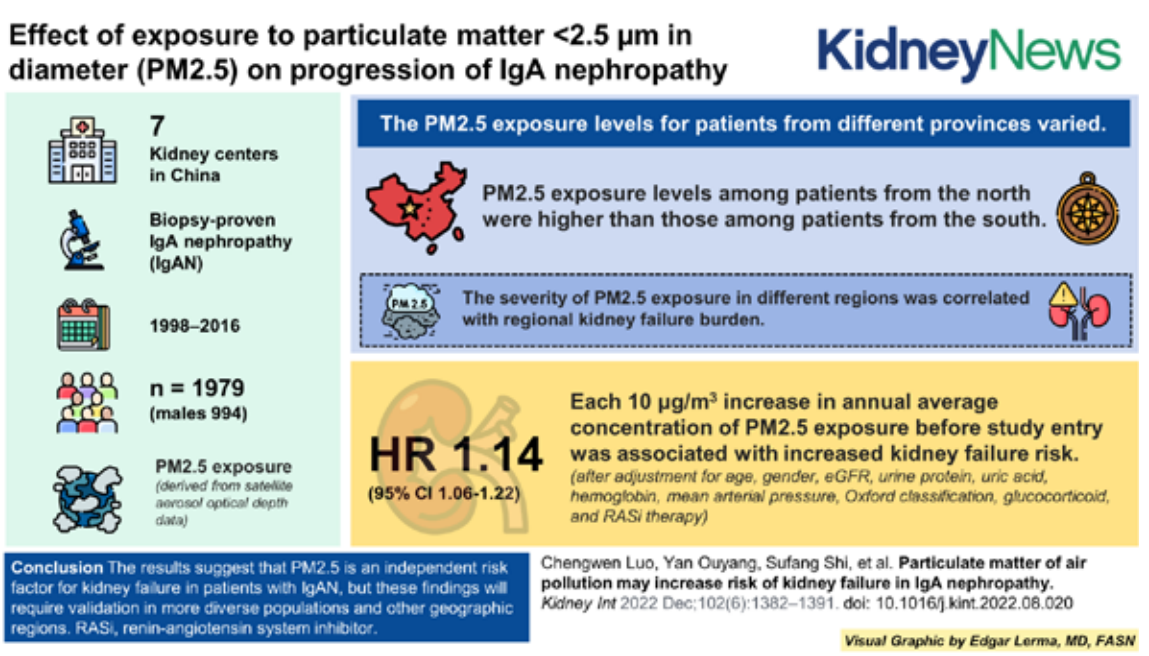
By Rose Mary Attieh

Despite decades of research, our understanding of the pathophysiology of immunoglobulin A (IgA) nephropathy and the risk factors predicting progression to kidney failure remains incomplete. A multi-hit mechanism has been proposed, necessitating a trigger by certain bacterial or viral infections in a genetically predisposed individual (1).

Since galactose-deficient (Gd)-IgA production is believed to be related to mucosal immune dysfunction of the respiratory tract (2), an innovative clinical investigation recently published in *Kidney International* by Luo et al. examined the effect of air pollution, as measured by exposure to fine particulate matter <2.5 µm in diameter (PM2.5), on the risk of kidney failure in patients with IgA nephropathy (3).

This study enrolled 1979 patients with biopsy-proven IgA nephropathy in China. The investigators used satellite data to evaluate PM2.5 exposure in different Chinese regions from 1998 until 2016. The trends in PM2.5 exposure, incidence of end stage kidney disease (ESKD) at 5 years after study enrollment, and estimated glomerular filtration rate (eGFR) decline were compared between provinces. Patients residing in north provinces had a higher burden of exposure to PM2.5 compared with south residents. The provinces with the highest PM2.5 exposures clearly had faster rates of eGFR decline and higher incidence of ESKD. Each 10 µg/m^3 increase in annual average concentration of PM2.5 exposure before study entry led to a 14% increase in risk of ESKD, and each 10 µg/m^3 increase in time-varying PM2.5 exposure after study entry increased the risk of ESKD by 10%. Above-median PM2.5 pollution exposure both before and after study entry increased the risk of ESKD by 54%. The associations held after the authors adjusted the models for lab/clinicopathologic covariates known to affect outcomes in IgA nephropathy, as well as time period, city size, and cardiovascular risk factors. City size was used as a proxy for socioeconomic status, given their known correlation in China. The authors concluded that PM2.5 is an independent risk factor for kidney failure in patients with IgA nephropathy.

This study moves the field further by proposing that an incremental dose-response relationship exists between pollution and the progression of kidney diseases in IgA nephropathy, thus reinforcing similar findings in the general chronic kidney disease population (4) and in patients with membranous nephropathy (5).



This study has many limitations. First, there was a lack of ethnic diversity within the studied cohort. Socioeconomic status and access to health care were inferred by city size. Moreover, there are significant limitations that made it impossible to objectively measure an individual's actual particulate exposure, which depends on multiple factors such as the residence's proximity to air pollution sources, indoor air pollution, time spent outside, or potential change in address after enrollment, for example. Furthermore, the low number of participants with available serum Gd-IgA levels could explain the lack of effect of serum Gd-IgA1 levels on ESKD progression in either PM2.5 exposure group.

Although they would need to be confirmed in subsequent studies with multi-ethnic cohorts, the results of this clinical investigation are most certainly thought provoking. Future work should be directed to provide insight into the exact pathophysiology by which air pollution can alter mucosal IgA galactosylation and how this is influenced by an individual's genetic background. Other polluting toxins, such as heavy metals, industrial agricultural chemicals and pesticides, and secondhand smoke, also need to be examined. Such information may help guide regulatory strategies to reinforce pollution control and prevent exposure to populations at risk. ■

Rose Mary Attieh, MD, is a renal transplant fellow at the Mayo Clinic, Jacksonville, FL.

The author reports no conflicts of interest.

References

1. Knoppova B, et al. The origin and activities of IgA1-containing immune complexes in IgA nephropathy. *Front Immunol* 2016; 7:117. doi: 10.3389/fimmu.2016.00117
2. Emancipator SN. Immunoregulatory factors in the pathogenesis of IgA nephropathy. *Kidney Int* 1990; 38:1216–1229. doi: 10.1038/ki.1990.337
3. Luo C, et al. Particulate matter of air pollution may increase risk of kidney failure in IgA nephropathy. *Kidney Int* 2022; 102:1382–1391. doi: 10.1016/j.kint.2022.08.020
4. Bowe B, et al. Associations of ambient coarse particulate matter, nitrogen dioxide, and carbon monoxide with the risk of kidney disease: A cohort study. *Lancet Planet Health* 2017; 1:e267–e276. doi: 10.1016/S2542-5196(17)30117-1
5. Xu X, et al. Long-term exposure to air pollution and increased risk of membranous nephropathy in China. *J Am Soc Nephrol* 2016; 27:3739–3746. doi: 10.1681/ASN.2016010093

Four Studies Show Nova POC Creatinine/eGFR as Accurate or More Accurate Than Laboratory Methods

These peer reviewed studies evaluated the accuracy of both Nova StatSensor and laboratory creatinine/eGFR methods versus the **gold standard measured GFR**, not estimated eGFR.

Nearly 1,000 patients in under resourced primary care settings in rural South Africa, agricultural settings in Nicaragua, and university hospitals in Belgium and France were studied.

Study One:

Accuracy Better Than the Laboratory Jaffe Creatinine/eGFR

"The performance of POC devices to detect eGFR in the range 60–89 mL/min/1.73 m2 is of particular interest…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 Lab Med (2021).

Study Two:

Accuracy Comparable to the Gold Standard Measured GFR

"The use of a handheld blood creatinine monitoring system provides a good estimation of GFR as compared with a gold standard method for GFR determination. Creatinine measurement and GFR estimation provide good results either with capillary blood or with venous blood and can be thus easily used in clinical practice to screen patients"

Lemoine S et al. Point of care creatinine derived eGFR measurement in capillary blood for identifying patients at risk. Practical Laboratory Medicine 31 (2022).

Study Three:

Accuracy Equal to the Laboratory IDMS Traceable Creatinine/eGFR

"Consequently, the specificity of the venous and capillary blood testing post-calibration alignment was 100% and 98.3% respectively, indicating 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 J et al. Creatinine standardization: a key consideration in evaluating whole blood creatinine monitoring systems for CKD screening. Analytical and Bioanalytical Chemistry 414 (2022)).

Study Four:

Accuracy Equal to the Laboratory Enzymatic Creatinine/eGFR

"When compared to the iohexol determinate GFR, POC performance seems valid for screening of high-risk patients because its performance for GFR CKD classification is comparable to the routine method."

Stojkovic V et al. Estimated glomerular filtration rate using a point of care measure of creatinine in patients with iohexol determinate GFR. Clinica Chimica Acta 499 (2019).

StatSensor®

Point-of-Care Whole Blood
Creatinine and eGFR Testing

nova® biomedical

novabiomedical.com

We Do Not Need to Rethink Our Approach to Overcorrection of Hyponatremia

By Helbert Rondon-Berrios and Richard H. Sterns

Despite significant rates of overcorrection, very low rates of osmotic demyelination syndrome (ODS) were observed in a large cohort of hyponatremic patients, reported a study in *NEJM Evidence* (1).

Using the General Medicine Inpatient Initiative (GEMINI) database, which links electronic patient data with administrative hospital data for all patients admitted under general internal medicine, MacMillan et al. (1) conducted a multicenter cohort study of patients with hyponatremia, defined as an initial plasma sodium (PNa) <130 mmol/L, who were admitted to five academic hospitals in Toronto, Canada, over a period of approximately 10.5 years. Subsequent admissions for the same patient during the study period were included if the admissions met inclusion criteria. The researchers excluded patients who developed hyponatremia during hospitalization, patients with a plasma glucose ≥25 mmol/L (450 mg/dL), and patients with a history of diabetes insipidus because they may have been taking desmopressin.

The researchers identified 22,858 admissions (17,254 unique patients) meeting inclusion and exclusion criteria. The mean PNa in the entire cohort was 125 mmol/L, with 86.9% of patients with a PNa ≥120 mmol/L, a population already known to be at very low risk for ODS. Only 265 patients in the entire cohort had a PNa <110 mmol/L. Patients with acute, self-induced water intoxication, another group known to be at very low risk for ODS, were not excluded.

The primary outcome was the proportion of patients with hyponatremia who developed ODS on the index admission. ODS was identified by electronically searching for key words in radiology reports of magnetic resonance imaging (MRI) of the brain or computed tomography scans of the head. For any given positive screening report, the imaging report was reviewed. The investigators then identified a subset for manual chart review. In addition, using *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (*ICD-10*) codes for the diagnosis of ODS, a manual review was performed of all admissions, as well as readmissions, within 7 days of index admission with hyponatremia. ODS was reported in 12 patients in the entire cohort (0.05%). The rate of ODS in patients with a PNa <120 mmol/L was 0.3%. Patients with ODS had a lower initial PNa compared with patients without ODS (111 ± 10 mmol/L vs. 125 ± 4.6 mmol/L, respectively); 7 of the 12 patients with ODS had a PNa <110 mmol/L. Hypokalemia and alcohol use disorder occurred at a higher frequency in patients with ODS.

Secondary outcomes included overcorrection of hyponatremia, defined as an increase in PNa of >8 mmol/L in any 24-hour period. Since PNa measurements are not commonly obtained exactly at 24-hour time points, the investigators used the closest PNa within 6 hours before or after that time point. PNa values to estimate correction rates were available in 20,572 (90%) admissions in the entire cohort, and of these, 17.7% experienced overcorrection of hyponatremia. Overcorrection occurred in 184 (69.4%) patients with a PNa <110 mmol/L, with 81 patients correcting a PNa by ≥12 mmol/L. Of the 12 patients who developed ODS, 7 patients did not experience overcorrection of hyponatremia per the authors' definition. However, some of these patients became severely hypernatremic after correction of hyponatremia and had at least two other risk factors for ODS. It is now well known that rapid correction of hyponatremia is not the only osmotic challenge that can result in ODS; acute hypernatremia (2) and severe hyperglycemia (3) can also cause the disorder.

Although most of the identified cases of ODS had experienced either correction by >8 mmol/L in 24 hours or overcorrection resulting in hypernatremia, the investigators concluded that in most cases, overcorrection of hyponatremia is not causally related to ODS and infer that other factors that are as-yet unidentified must be implicated in the development of ODS in this setting. We believe this conclusion to be unwarranted.

The authors also concluded that ODS is an extremely rare complication of rapid correction of hyponatremia, citing an incidence of 0.05% in their cohort. We believe this conclusion to be extremely misleading. Most of the studied patients had a PNa >120 mmol/L, and some may have had acute hyponatremia from self-induced water intoxication. The recommended limit of 8 mmol/L in 24 hours does not apply to such patients because it is known that their risk of ODS is vanishingly low. For patients at higher risk, the 8-mmol/L limit was proposed since correction by 9 mmol/L *can* result in ODS (not because it commonly does), and because of the likelihood of "overshooting the mark" (4).

ODS [osmotic demyelination syndrome] is a clinical diagnosis, and its severity varies considerably.

A more valid incidence of ODS can be found in patients with a PNa <110 mmol/L, the only group of participants in the study by MacMillan et al. (1) who were at a reasonably high risk of ODS. Seven of 265 patients with PNa <110 mmol/L (2.6%) developed ODS. Only 81 of the patients with a PNa <110 mmol/L were corrected by ≥12 mmol/L. Because of confidentiality safeguards, we do not know exactly how many of the patients with a PNa <110 mmol/L who developed ODS were corrected by ≥12 mmol/L. If there were five patients, the incidence of ODS was 6% (5 of 81). Inclusion of patients with a blood glucose as high as 450 mg/dL makes even these estimates suspect, as 1) the number of patients with a glucose-corrected PNa <110 mmol/L may have been <265, and 2) treatment of hyperglycemia could have raised PNa by as much as 6 mmol/L, resulting in an overestimate of the number of patients who were overcorrected.

The authors' methodology for defining overcorrection may also have led them to erroneous conclusions. Since most PNa is not measured exactly at a 24- or 48-hour time point, the investigators used the closest PNa within 6 hours of the time points. However, there could be considerable change of PNa in 6 hours affecting the 24-hour change of the PNa estimate. To address this issue, other studies have used an estimated PNa at the 24-hour time point (PNa24h) using a formula developed by Geoghegan et al. (5): PNa24h = PNaA + [(PNaB – PNaA) x (24 – TA)/(TB – TA)], in which PNaA and TA are the nearest PNa and time values before the 24-hour mark, respectively, and PNaB and TB are the nearest PNa and time values after the 24-hour mark, respectively. Although the authors also considered the maximum rate of correction in any 24-hour period, they did not provide their methodology for determining this rate, leaving the reader with unanswered questions: Was the increase in PNa for all 24-hour intervals during the entire hospitalization determined, and if so, how? If the PNa was immediately re-lowered after an increase of >8 mmol/L, was this still defined as overcorrection?

Other studies, in which most of the patients had mild to moderate hyponatremia or acute hyponatremia, have also reported low rates of ODS (6, 7). Studies of patients with chronic severe hyponatremia report very different findings. In a study by Vu et al. (8), 15% of patients with a PNa ≤120 mmol/L were corrected by >12 mmol/L over the first 24 hours; 4 of the 37 overcorrected patients (11%) developed ODS. All of the patients with ODS had a PNa ≤105 mmol/L; although the denominator of overcorrected patients with a PNa ≤105 is not given, their incidence of ODS must have been considerably higher. In two other studies (9, 10), approximately half of the overcorrected patients with a PNa ≤105 mmol/L developed ODS.

ODS is a clinical diagnosis, and its severity varies considerably. Patients with evidence of central pontine and extrapontine myelinolysis on MRI represent the more severe end of the spectrum, and even these cases can be missed when the case finding is based on radiology reports obtained during hospitalization for hyponatremia. Images are typically negative at the onset of clinical symptoms and may not be positive until weeks later. Some patients with a delayed onset of transient, apparently self-limited neurologic symptoms that emerge after discharge may not require readmission and may never have a positive MRI. For these reasons, the number of cases with ODS could easily have been underestimated in the study by MacMillan et al. (1).

Based on the results of this study, do we need to rethink our current approach to overcorrection of hyponatremia? Do we need to relax our PNa correction limits? Is it safe to rapidly correct all patients with hyponatremia? We believe the answer to these questions is no. Detractors of the current approach (e.g., use of desmopressin) point to drawbacks of a slow PNa correction, such as more frequent blood draws for PNa monitoring and increasing the length of hospital stays, but we should ask ourselves what percentage risk of ODS would we be willing to accept for our patients or family members so that they can be discharged from the hospital 1 day or 2 days earlier. The answer is probably none. There is a need for a multicenter study of patients with a PNa ≤105 mmol/L (a population likely to have a relatively high incidence of ODS) with meticulous manual chart review, not data mining using diagnostic codes and radiology results in a population with mild hyponatremia, which can be very misleading. ■

Helbert Rondon-Berrios, MD, MS, is with the Renal-Electrolyte Division, University of Pittsburgh School of Medicine, Pittsburgh, PA. Richard H. Sterns, MD, is with the School of Medicine and Dentistry, University of Rochester, Rochester, NY.

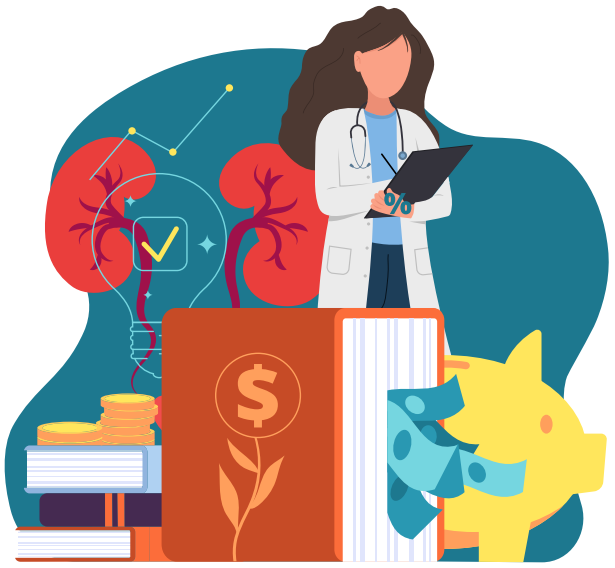
Dr. Rondon-Berrios reports receiving grant R21DK122023 from the National Institute of Diabetes and Digestive and Kidney Diseases for exploratory/developmental research and speaker honorarium from the Memorial Sloan Kettering Cancer Center and serving as an associate editor for *Frontiers in Medicine/Nephrology* and as an editorial board member for the *Clinical Journal of the American Society of Nephrology*. Dr. Sterns reports no conflicts of interest.

References

1. MacMillan TE, et al. Osmotic demyelination syndrome in patients hospitalized with hyponatremia. *NEJM Evid* 2023; 2:1–9. https://evidence.nejm.org/doi/full/10.1056/EVIDoa2200215
2. Shah MK, et al. Osmotic demyelination unrelated to hyponatremia. *Am J Kidney Dis* 2018; 71:436–440. doi: 10.1053/j.ajkd.2017.10.010
3. Burns JD, et al. Central pontine myelinolysis in a patient with hyperosmolar hyperglycemia and consistently normal serum sodium. *Neurocrit Care* 2009; 11:251–254. doi: 10.1007/s12028-009-9241-9
4. Adrogue HJ, Madias NE. Hyponatremia. *N Engl J Med* 2000; 342:1581–1589. doi: 10.1056/NEJM200005253422107
5. Geoghegan P, et al. Sodium correction practice and clinical outcomes in profound hyponatremia. *Mayo Clin Proc* 2015; 90:1348–1355. doi: 10.1016/j.mayocp.2015.07.014
6. Aegisdottir H, et al. Incidence of osmotic demyelination syndrome in Sweden: A nationwide study. *Acta Neurol Scand* 2019; 140:342–349. doi: 10.1111/ane.13150
7. Nzerue CM, et al. Predictors of outcome in hospitalized patients with severe hyponatremia. *J Natl Med Assoc* 2003; 95:335–343. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2594506/
8. Vu T, et al. Grossmann M. Patients presenting with severe hypotonic hyponatremia: Etiological factors, assessment, and outcomes. *Hosp Pract (1995)* 2009; 37:128–136. doi: 10.3810/hp.2009.12.266
9. Sterns RH. Severe symptomatic hyponatremia: Treatment and outcome. A study of 64 cases. *Ann Intern Med* 1987; 107:656–664. doi: 10.7326/0003-4819-107-5-656
10. Sterns RH, et al. Neurologic sequelae after treatment of severe hyponatremia: A multicenter perspective. *J Am Soc Nephrol* 1994; 4:1522–1530. doi: 10.1681/ASN.V48152

ASN Offers Scholarships for Nephrology Fellowships to the Home Dialysis University

By Karen Blum



A new collaboration between ASN and Home Dialysis University (HDU) aims to boost nephrology trainees' knowledge and familiarity with home dialysis therapies. Starting this year, ASN is offering up to 30 scholarships for nephrology fellows to attend a 2-day, in-person HDU training course and participate in a new, 12-month virtual education program.

"ASN has been trying to understand and better assess how we can help the nephrology community in the areas of home dialysis advocacy and education," said Jeffrey Perl, MD, FRCP, a member of ASN's Home Dialysis Steering Committee and a staff nephrologist at St. Michael's Hospital in Toronto. One key driver, he said, has been in meeting the Advancing American Kidney Health initiative, an executive order signed by former President Trump in 2019. The initiative—designed to transform how kidney diseases are managed over the next decade—called for increased utilization of home dialysis treatment and kidney transplants for Medicare beneficiaries.

Home dialysis is now coming full circle, Perl said. Most patients receiving dialysis in the 1960s did so at home, but through a series of policies and health care reimbursement changes, the majority shifted to receiving dialysis in facilities. Changes since 2011 in the Centers for Medicare & Medicaid Services' prospective payment system have equalized the payment structure for home versus in-center dialysis.

"There's quality-of-life and cost-saving benefits to patients receiving dialysis at home," he said. "One area ASN chose to focus on was educating the nephrologists of the future…. Nephrology training and education [are key components] to our goal of universal access to home therapy and our ability to provide high-quality care."

Some nephrology fellowship programs today still do not adequately educate their trainees in home dialysis therapy, either because faculty are not as familiar with home dialysis, or the programs do not have patients receiving the therapy, said Joel Glickman, MD, FACP, activity director of HDU and director of home dialysis programs at Penn Medicine in Philadelphia. "If you educate patients about home therapy, 30% to 40% will want to do it, but in the country, utilization is 15% or less," he said. "There's a disconnect…and lack of education is a big part."

In a 2010 ASN survey of recent graduates of nephrology training programs (1), only 15.8% said they felt well trained and competent in the care of home hemodialysis patients. A more recent survey that examined home dialysis training needs for fellows (2) found that only 30% of program directors felt their graduates could provide home hemodialysis management without supervision. A majority of program directors (74%) requested a virtual home dialysis mentorship program.

An initial solution is ensuring that fellowship program directors and fellows know there are available resources, such as HDU, which provide enhanced education on home dialysis, Perl said. Glickman added that the HDU curriculum covers the physiology of home hemodialysis and peritoneal dialysis, prescriptions and dialysis access and how to monitor patients and handle infectious and non-infectious complications, among other topics.

"The way HDU is structured, there's a lot of time for fellows to have contact with our faculty," Glickman said. "We have our meals together and use frequent breaks to continue conversations about taking care of home dialysis patients. The faculty of HDU are passionate about making sure patients have the opportunity to [receive] home dialysis; promoting the use of home dialysis; and educating physicians, fellows, and other advanced practice professionals. I think that is one of the reasons we're going to be successful."

To keep the momentum and education going in the new ASN-HDU program, following the in-person coursework, fellows will enroll in a 1-hour per month, yearlong, virtual component. In these continuing education sessions, nephrologists skilled in home dialysis will use case-based learning to continue trainees' exposure to a wide range of topics in home dialysis, Perl said. "We would like this to be the start of a greater focus on how fellowships can be enhanced to support home dialysis learning," he said. "The ultimate goal is to train nephrologists to go into practice and feel comfortable and skilled in managing patients on home dialysis."

Eligible applicants must be a second- or third-year nephrology fellow in an Accreditation Council for Graduate Medical Education-accredited training program, must never have attended HDU, and must have support from their training program director to attend the course and participate in the 12-month, longitudinal education program. They can have any level of prior experience with home dialysis.

Fellows selected for the program will receive meeting costs of up to $1500 to cover HDU registration, two hotel nights, meals during the meeting, and travel costs up to $300.

The in-person sessions will be held August 27–29 in Costa Mesa, CA, and September 10–12 in Charlotte, NC. For more information or to apply, visit https://epc.asn-online.org/projects/hdp/, and select "Apply for Scholarship Here." ■

References

1. Berns JS. A survey-based evaluation of self-perceived competency after nephrology fellowship training. *Clin J Am Soc Nephrol* 2010; 5:490–496. doi: 10.2215/CJN.08461109
2. Reddy YNV, et al. Home dialysis training needs for fellows: A survey of nephrology program directors and division chiefs in the United States. *Kidney Med* (published ahead of print March 17, 2023). https://doi.org/10.1016/j.xkme.2023.100629

BRCU
Board Review Course & Update

JULY 23–25, 2023
Fairmont Chicago, Millennium Park

Face the Boards with Confidence.

Discover the top three reasons why Board Review Course & Update is the leading live course to help you prepare for the ABIM Nephrology Board exams.

1. **Benefit from Exam-Focused Curricula**
Participate in an immersive learning experience with interactive case discussions mapped directly to the ABIM nephrology board exam blueprint.

2. **Earn CME Credits & MOC Points**
Take advantage of the opportunity to earn up to an estimated 65 CME credits and MOC points for attending the course.

3. **Meet Expert Faculty**
Learn from renowned faculty to cover content from each exam topic. Expert nephrologists are an indispensable resource when preparing for examinations.

Early registration pricing ends June 22.
Register today and save $100.
www.asn-online.org/brcu

SCAN THIS ITEM TO REGISTER

"Dialysis Was Hell to Me"

A Minister's Injustice in His Own Medical Care Creates His Passion for Patient Advocacy

In this article, ASN staff member Abbey Martin interviews Patrick O. Gee, Sr., PhD, about his journey with kidney disease. Dr. Gee received the ASN President's Medal at Kidney Week 2022 in recognition of his work in advocating for the highest quality care for kidney patients. Ms. Martin, program associate, Research, Discovery, and Innovation at ASN, is pursuing a master's degree in Health Communications.

By Abbey Martin

Patrick Gee is physically exhausted. His white T-shirt and sweatpants are the only things he can fit in now. In just 8 months, he has gained over 150 pounds of fluid, to the point where when he lies down, he feels like he is drowning.

He and his wife are making their way to the in-center dialysis clinic near the hospital. In the dimly lit hallway, men and women, many of whom are amputees, are lined up in chairs, with tubes and wires poking out of their arms. Pain and exhaustion paint their faces.

"That was hell to me."

As a man of faith and minister at Mountain Movers Ministry in Richmond, VA, his words weigh heavily. After his diagnosis in April 2013, Gee is "crashing into dialysis," just like many men and women in minority populations, and struggling to keep his faith while facing the harsh reality of his diagnosis.

Diagnosed with kidney failure too late

In April 2013, Gee was headed to a routine appointment with his endocrinologist. He had been receiving treatment for type 2 diabetes for the past 10 years and was meeting with his doctor on a quarterly basis. As Gee reached for the doorknob at the end of an otherwise normal check-in, he heard his doctor call back to him.

"As I was walking out the door, she was like, 'Hey, Patrick. I completely forgot to tell you that looking at your labs, you are at stage 3B of ESRD [end stage renal disease]'" (1).

"I didn't know where my kidneys were or what they did," Gee said. "I didn't know that diabetes was the number one leading cause of kidney disease. It just went over my head to be perfectly honest."

He would soon learn that his kidneys were functioning at 35%. Blame, anger, and sadness were overwhelming. His doctor, who he had been seeing regularly, had not mentioned that his kidney function was declining or that his diabetes put him at a higher risk (2).

Gee was in a waiting game. He was slowly watching his kidney function decline from 13% to 5%. On November 23, 2013, his only option was to start dialysis. Walking in to the in-center dialysis clinic, he recalls cycling through every emotion in the grief process. His decision to opt out of in-center hemodialysis was made after that experience.

The medical system had failed him, and as a Black man, his experience was not unique. Although Black people make up 13% of the population in the United States, they represent 35% of people receiving dialysis (3). Kidney disease progression is dependent on early detection, and in a system that is still rooted in institutional racism, Black people do not have access to the same care and are often diagnosed too late (4).

Navigating a hidden illness

For the next couple of years, Gee hid his illness from his friends and his congregation. The only one in his family aside from his wife who could watch him dialyze was his 3-year-old granddaughter. "My kids could not see my dialyze. They refused to come in the room. They didn't even want to see the catheter. But my granddaughter thought that I was one of the transformers."

Dialysis was defeating and lonely. He would have to lie on his bed and allow the dialysate to flow into his abdomen for 4–6 hours. It was painful and physically draining. "I was so tired of doing dialysis that I would take the first kidney that came my way."

In 2017, while Gee was advocating on Capitol Hill, his declining health would make that his only option to survive.

"Help me in my disbelief"

Gee was on Capitol Hill to support the Living Donor Protection Act of 2021 (5) when he passed out twice while talking to members of Congress. Medics told him he needed to see his doctor immediately. He remembers seeing his nurse on her knees crying. His results showed that he had hypercalcemia and was potentially living with bone cancer.

"Help me in my disbelief," he said, as he called his minister. His health was declining, and dialysis was no longer his best treatment option. However, Gee was aware of the staggering inequities in transplant opportunities. Black Americans make up 33% of the transplant waiting list and in the last three decades, have been less likely than their White counterparts to receive a transplant (6).

In April 2017, Gee finally received a call about a living donor kidney. Unfortunately, after his surgery, he was told that the new kidney was not functioning, and he would have to continue with 24 hours of dialysis every other day. He could not find an answer in his faith that could explain his misfortune.

Bringing his story to action

Gee's story drives his passion for advocacy. He saw the injustices of the medical system firsthand. It brought him through some of his deepest battles with his faith. Today, he champions the Kidney Health Initiative Patient and Family Partnership Council (7). He makes sure that the patient voice is at the center of every discussion relating to new options for the prevention, treatment, and diagnosis of kidney diseases.

"He's a fierce, consistent advocate for people in his community, especially in terms of addressing the racial-ethnic disparities in kidney diseases and the importance of fostering collaborative and shared decision-making between patients and their care team," said Glenda V. Roberts, Director of External Relations and Patient Engagement of the Kidney Research Institute (8) and the Center for Dialysis Innovation (9).

Respecting the process

Gee spent 33 days in the hospital after his kidney transplant waiting for his kidney to start functioning. On the 47th day from his transplant, he screamed so loud that his wife came running up the stairs. He had finally produced urine and realized the full meaning of some of the words he heard during his hospital stay.

"Respect the process."

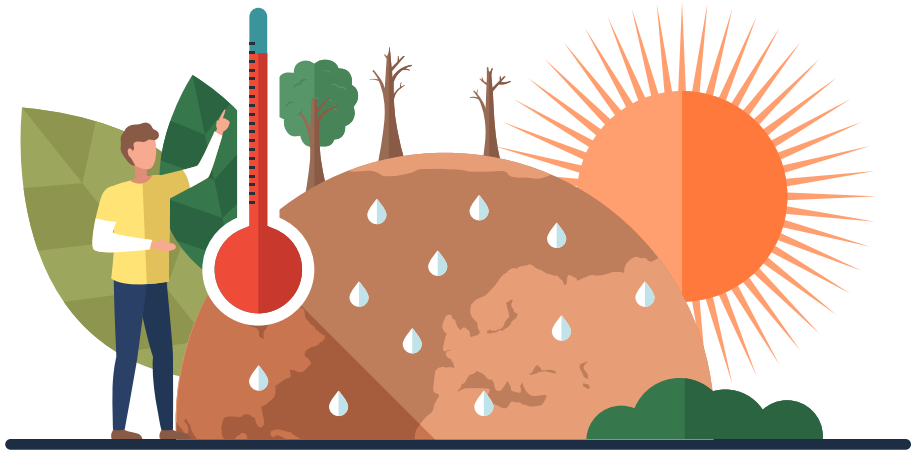
He would carry these words with him to provide support to others living with chronic illnesses. ■

References

1. American Kidney Fund. Stages of kidney disease. October 26, 2022. Accessed February 21, 2023. https://www.kidneyfund.org/all-about-kidneys/stages-kidney-disease
2. Centers for Disease Control and Prevention. Diabetes and chronic kidney disease. Last Reviewed: December 30, 2022. Accessed February 9, 2023. https://www.cdc.gov/diabetes/managing/diabetes-kidney-disease.html#:~:text=Over%20time%2C%20high%20blood%20sugar,which%20can%20damage%20kidneys%20too
3. National Kidney Foundation. Health disparities. Accessed February 9, 2023. https://www.kidney.org/advocacy/legislative-priorities/health-disparities
4. Dembosky A. Kidney failure disproportionately affects people of color. Will Proposition 23 improve care? October 16, 2020. https://www.kqed.org/news/11842376/kidney-failure-disproportionately-affects-people-of-color-will-proposition-23-improve-care
5. Nadler J.; 117th Congress (2021–2022). H.R.1255–Living Donor Protection Act of 2021. https://www.congress.gov/bill/117th-congress/house-bill/1255
6. Harding K, et al. Health disparities in kidney transplantation for African Americans. *Am J Nephrol* 2017; 46:165–175. doi: 10.1159/000479480
7. Kidney Health Initiative. KHI Patient and Family Partnership Council. Accessed February 9, 2023. https://khi.asn-online.org/pages/group.aspx?ID=KHI-PFPC
8. Kidney Research Institute. Welcome to the KRI. Accessed February 21, 2023. https://kri.washington.edu/
9. Center for Dialysis Innovation. News. https://cdi.washington.edu/

Achieving Kidney Health in a Warming World

By Zachary Kribs



In January 2019, Suraj Thapa Magar, a 28-year-old Nepalese migrant worker, collapsed on his Kuwait job site with what would later be diagnosed as kidney failure. Now waiting for a kidney transplant, Magar is among a growing number of young men with heat-related kidney failure, profiled in a January 2023 article in *The Washington Post*, titled "The world's torrid future is etched in the crippled kidneys of Nepali workers" (1).

Photojournalist Ed Kashi has also recently trained his lens on the impact of climate change on kidney health, including a joint *Time* magazine and Pulitzer Center series profiling the climate-related health conditions facing migrant workers in Qatar preparing for the 2022 World Cup (2).

"Both nephrolithiasis and acute kidney injury (AKI) are associated with higher ambient temperatures," wrote Australian kidney health researchers Matthew Borg and Peng Bi in a 2021 article published in *Nature Reviews Nephrology* (3). Borg and Bi described that "AKI can result not only as a consequence of hypovolemia but also as a consequence of extreme heat exposure through the induction of rhabdomyolysis and inflammation" and that "recurrent episodes of AKI can lead to chronic kidney disease (CKD) and eventual kidney failure, and patients with CKD are at increased risk of future episodes of AKI."

Thinking globally, acting locally

Although the consequences of climate change on kidney health are visible and critical issues to address in international contexts, particularly in developing countries facing extreme temperatures with limited infrastructure, it is vital for U.S. health professionals to recognize the domestic impact of climate change on kidney health and the importance of addressing climate change on a local level. According to a new report from the Intergovernmental Panel on Climate Change (IPCC) (4), a body of global experts assessing climate change-related science: "Human-caused climate change is already affecting many weather and climate extremes in every region across the globe. This has led to widespread adverse impacts and related losses and damages to nature and people."

The IPCC noted that these adverse impacts are most easily observed scientifically in the western areas of the United States, although southern and midwestern areas of the United States, where combined temperature and humidity pose a risk of human mortality, are already experiencing 10–50 days per year with levels of heat that risk human mortality. These figures are only expected to increase in geographic size and severity as global temperatures rise. Research conducted in Brazil suggests that for every 1-degree Celsius increase in daily mean temperature, the risk of hospitalization for kidney diseases increases by 0.9% at a national level (5). Furthermore, the IPCC wrote that "[t]here is a rapidly closing window of opportunity to secure a [livable] and sustainable future for all…. Every increment of global warming will intensify multiple and concurrent hazards." However, if within this decade, "[d]eep, rapid and sustained mitigation" efforts to reduce greenhouse gas emissions are implemented with accelerated "adaptation actions," together, they would "reduce projected losses and damages for humans and ecosystems…and deliver many co-benefits, especially for air quality and health."

ASN action

In April 2022, ASN's Statement on Climate Change (6) articulated that "climate health is kidney health" and called on kidney health professionals across the world to: "Support people with kidney diseases to survive climate change," "Diminish the contribution of kidney care to climate change," and "Advocate for public policy to address climate change as a contributor to kidney health." Since the publication of this statement, interest in climate change and kidney health has rapidly grown in the United States, yet more work is needed to sustain and increase climate health actions to meet the needs of people at risk for or living with kidney diseases in a changing climate.

Building toward climate resilience

As U.S.-based kidney health professionals grapple locally with the consequences of climate change, people living with and at risk for kidney diseases must be empowered with tools and skills that enable resilience and adaptability. "Moving forward, the kidney community must rapidly transform practices to build resilience to the effects of climate change on the care of people with kidney disease," reported Struthers et al. in a 2022 *JASN* perspective (7).

Although there is much work to be done to educate and empower people with kidney diseases to face the challenges of climate change, progress is steadily being made. In 2021, the Biden-Harris administration established the Office of Climate Change and Health Equity, focused on addressing the impact of climate change on health, particularly for communities and populations at risk for the most severe impacts of climate change. As part of its scope of work, the office publishes a Climate and Health Outlook, which includes a monthly forecast of climate risks across the United States (8). Such surveillance tools will become increasingly important for disaster preparation and disease mitigation: During 2017's Hurricane Maria, a majority of the 11,652 people receiving dialysis in Puerto Rico were evacuated from the island ahead of the storm. Because of emergency preparedness efforts by public officials, dialysis providers, and Puerto Rican citizens, there was not a noticeable increase in patient mortality (9). As severe weather incidents increase across the United States, more frequent disaster responses will be needed.

Addressing the impact of kidney care on climate health

Kidney health professionals must also be aware of their own impact on climate change and "urgently develop more climate-friendly methods of managing patients with kidney disease," reported Young and colleagues in a 2023 *CJASN* review (10). The authors noted that dialysis, while lifesaving, "can be associated with marked water usage (up to 600 L per dialysis session), energy usage (with one 4-hour session averaging as much as one fifth of the total energy consumed by a household per day), and large clinical wastes (with hemodialysis accounting for one third of total clinical medicine–associated waste)."

A 2022 study by Sehgal and colleagues (11) of greenhouse gas emissions in 15 dialysis facilities in Ohio found that "[a]nnual emissions per facility averaged 769,374 kg CO_2-eq (95% CI, 709,388 to 848,180 kg CO_2-eq)" with "patient and staff transportation (28.3%), electricity (27.4%), and natural gas (15.2%)" comprising the three largest contributors. This rate of emission per facility is equivalent to the "annual energy use of 93 homes, and emissions per treatment are equivalent to driving an average automobile for 238 km (149 miles)."

Perhaps the greatest opportunity to improve the environmental impact of existing therapies for people with kidney failure is to reduce the water usage in dialysis. Globally, dialysis requires enough medically pure water to fill Lake Tahoe annually. Young and colleagues (10) wrote that "[h]emodialysis is an extremely water-hungry treatment.... Reverse osmosis (RO) machines are at the center of water treatment procedures in hemodialysis units and are very inefficient, often rejecting >50% of the water. This water is never in contact with a patient and does not pose a risk, but it is nonetheless discarded down the sewer...most US citizens use about 310 L of water a day but a patient on dialysis requires one to two times this amount for a single treatment."

Methods to reduce water usage in dialysis are already being implemented internationally, particularly in Australia (12), and could be applied to a U.S. context. Additionally, great possibility exists for innovation in dialysis water-reduction technology to be developed through programs such as The Kidney Innovation Accelerator (KidneyX) (13), the public-private partnership between ASN and the U.S. Department of Health and Human Services to accelerate innovation in the prevention, diagnosis, and treatment of kidney diseases. Furthermore, reduced water usage in dialysis will be beneficial to areas in the United States facing droughts and restrictions on water use, freeing up supply of a scarce resource for other critical uses.

Increasing research and awareness

Finally, increased investment in awareness, research, and public policy to address the impact of climate change on kidney health is needed. Struthers and colleagues (7) wrote that "kidney health professionals must step into this advisory role and advocate for the development of greener kidney care."

Encouraging signs exist that U.S. kidney health professionals are doing just this. In 2023, ASN joined the Medical Society Consortium on Climate and Health (MSCCH) (14), a group of medical professional societies focused on raising awareness about the impact of climate change on health, hosted by the George Mason University Center for Climate Change Communication in collaboration with the Sean N. Parker Center at the Stanford School of Medicine. ASN's membership in MSCCH will allow ASN to raise the profile and scope of its advocacy on climate and kidney health.

Research on climate change and kidney health is also increasing and importantly, in the U.S. health system context. In 2022, the National Institutes of Health (NIH) launched the NIH Climate Change and Health Initiative (15), an "all hands on deck" collaborative effort among multiple NIH investigative centers "to advance the science of climate change and health." Through the initiative, the NIH now provides dedicated funding opportunities, educational programs, and scholarships to improve understanding about the connections between climate change and heath. More can be read on the initiative's website: https://www.nih.gov/climateandhealth.

Climate change is already impacting people in the United States and around the world. Overcoming the challenges posed by climate change, particularly in the context of kidney health, will require deep, rapid, and sustained action. U.S. kidney health professionals must join international colleagues in thinking globally, and simultaneously act locally to create a world without kidney diseases. ■

References

1. Shih G. The world's torrid future is etched in the crippled kidneys of Nepali workers. *The Washington Post*, January 6, 2023. https://www.washingtonpost.com/world/2023/01/06/climate-change-heat-kidney-disease/

2. Baker A, Kashi E; Pulitzer Center. Thousands of migrant workers died in Qatar's extreme heat. The World Cup forced a reckoning. *Time,* November 3, 2022. https://pulitzercenter.org/stories/thousands-migrant-workers-died-qatars-extreme-heat-world-cup-forced-reckoning
3. Borg MA, Bi P. The impact of climate change on kidney health. *Nat Rev Nephrol* 2021; 17:294–295. doi: 10.1038/s41581-020-00365-4
4. Intergovernmental Panel on Climate Change (IPCC). Synthesis Report of the IPCC Sixth Assessment Report (AR6). Summary for Policymakers. https://report.ipcc.ch/ar6syr/pdf/IPCC_AR6_SYR_SPM.pdf
5. Wen B, et al. Association between ambient temperature and hospitalization for renal diseases in Brazil during 2000–2015: A nationwide case-crossover study. *Lancet Reg Health Am* 2021; 6:100101. doi: 10.1016/j.lana.2021.100101
6. American Society of Nephrology (ASN). Statement on Climate Change. April 22, 2022. https://www.asn-online.org/policy/webdocs/22.4.22StatementOnClimateChange.pdf
7. Struthers SA, et al. Policy and kidney community engagement advance toward greener kidney care. *J Am Soc Nephrol* 2022; 33:1811–1813. doi: 10.1681/ASN.2022070741
8. Department of Health and Human Services, Office of Climate Change and Health Equity. Climate and Health Outlook. https://www.hhs.gov/climate-change-health-equity-environmental-justice/climate-change-health-equity/climate-health-outlook/index.html
9. Rivera-Hernandez M, et al. Changes in migration and mortality among patients with kidney failure in Puerto Rico after Hurricane Maria. *JAMA Health Forum* 2022; 3:e222534. doi: 10.1001/jamahealthforum.2022.2534
10. Young SE, et al. Climate and the nephrologist: The intersection of climate change, kidney disease, and clinical care. *Clin J Am Soc Nephrol* 2023; 18:411–417. doi: 10.2215/CJN.08530722
11. Sehgal AR, et al. Sources of variation in the carbon footprint of hemodialysis treatment. *J Am Soc Nephrol* 2022; 33:1790–1795. doi: 10.1681/ASN.2022010086
12. Talbot B, et al. A survey of environmental sustainability practices in dialysis facilities in Australia and New Zealand. *Clin J Am Soc Nephrol* 2022; 17:1792–1799. doi: 10.2215/CJN.08090722
13. American Society of Nephrology (ASN). KidneyX: The Kidney Innovation Accelerator. https://www.kidneyx.org/about-kidneyx/
14. Medical Society Consortium on Climate and Health (MSCCH). https://medsocietiesforclimatehealth.org/about/
15. Woychik R; National Institutes of Health. Climate Change and Health Initiative to expand research, build resiliency. *NIH Director's Blog*, July 26, 2022. https://directorsblog.nih.gov/2022/07/26/climate-change-and-health-initiative-to-expand-research-build-resiliency/

Covered Stent Improves PTA Outcomes in Upper Extremity Fistulae

Placement of a covered stent provides better outcomes than percutaneous transluminal angioplasty (PTA) alone in hemodialysis patients with stenosis of upper extremity fistulae, concludes a randomized trial in *Kidney International*.

The multicenter Arteriovenous [AV] Stent Graft in the Treatment of Venous Outflow Stenosis in AV Fistula Access Circuits (AVeNEW) study enrolled 280 patients with stenosis of 50% or greater in an upper extremity AV fistula (AVF). Patients were randomly assigned to PTA alone or PTA followed by placement of the Covera self-expanding covered stent. A 6-month target lesion primary patency (TLPP) rate was compared between groups.

Thirty-day safety outcomes were "significantly non-inferior" between the two procedures. Patients receiving the covered stent had superior patency compared with PTA alone: 78.7% versus 55.8% at 6 months and 47.9% versus 21.2% at 12 months, respectively. Six-month access circuit primary patency was similar between groups.

On secondary outcome analysis at 2 years, TLPP was 40.0% in the covered-stent group versus 11.6% with PTA. Stent placement was associated with fewer target-lesion revascularizations (1.6 versus 2.8) and a longer interval between reinterventions (249.5 versus 217.6 days).

Stenoses of hemodialysis AVFs are commonly treated with PTA, but the restenosis rate is high. The AVeNEW study is the first large, randomized trial, to date, to compare the benefits of covered-stent placement with PTA alone.

The results show improvement in TLPP in the covered stent group at 6 and 12 months, with observational evidence of a continued patency advantage at 24 months. Safety outcomes are similar between groups. The researchers conclude, "Overall, the use of the Covera covered stent...provided a safe alternative to angioplasty with statistically superior TLPP results and modest clinical benefit for patients" [Dolmatch B, et al. Prospective, randomized, multicenter, clinical study comparing a self-expanding covered stent to percutaneous transluminal angioplasty for treatment of upper extremity hemodialysis arteriovenous fistula stenosis. *Kidney Int*, published online ahead of print March 27, 2023. doi: 10.1016/j.kint.2023.03.015; https://www.kidney-international.org/article/S0085-2538(23)00182-5/fulltext].

Hair-Straightening Treatment and Acute Kidney Injury

By Jia H. Ng

Acute kidney injury (AKI) from toxin exposure is seen with systemic medications, including analgesics, certain antibiotics, and anti-neoplastic medications (1). However, the association of AKI with topical toxin exposure is not commonly recognized.

In a recent publication by Bnaya et al. (2) in the *American Journal of Kidney Diseases*, the authors reported a case series of 26 patients who developed AKI following exposure to hair-straightening products in Israel, suggesting an under-recognized cause of AKI.

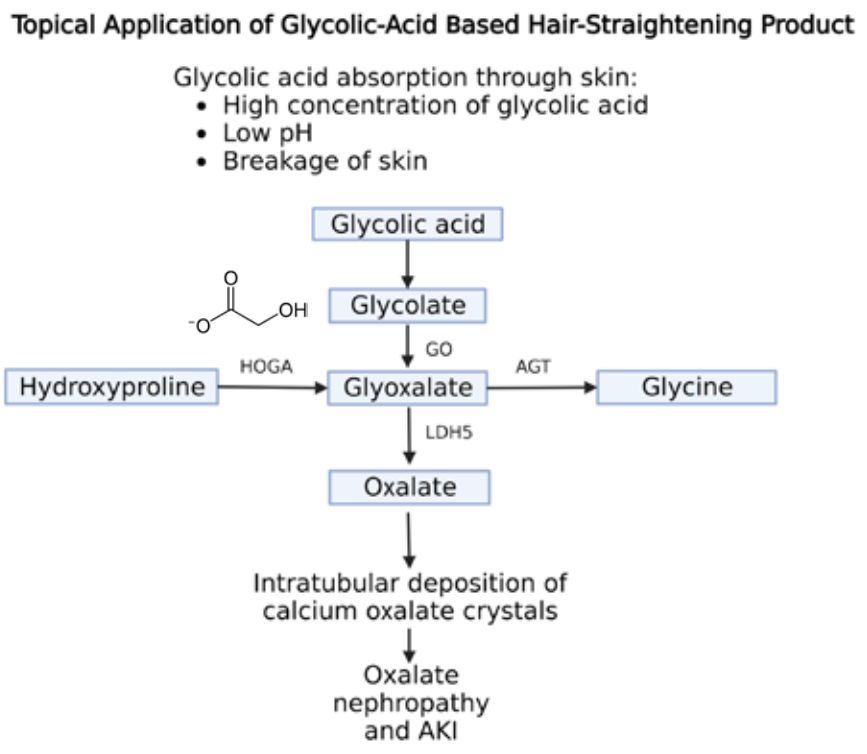
Keratin-based hair straightening is a popular method used to style hair. Previous hair products were formaldehyde-based, but formaldehyde was found to be carcinogenic (3). Thus, straightening products in Israel have largely been replaced by glycolic acid derivatives because they were considered to be safe when used topically. However, as reported in this case series, the use of hair-straightening products that contain glycolic acid derivatives may not be as safe as it appears.

The authors reported that 26 patients developed severe AKI following the hair-straightening procedure, with three of them requiring temporary dialysis. Two of the patients had recurrent AKI episodes each time following hair-straightening procedures. Seven patients underwent a kidney biopsy, in which five of them showed oxalate nephropathy, one showed a few calcium oxalate crystals, and another showed microcalcification in the tubular epithelium. Given that glycolic acid is within the metabolic pathway of oxalate formation (Figure 1), the authors have attributed the AKI to glycolic acid.

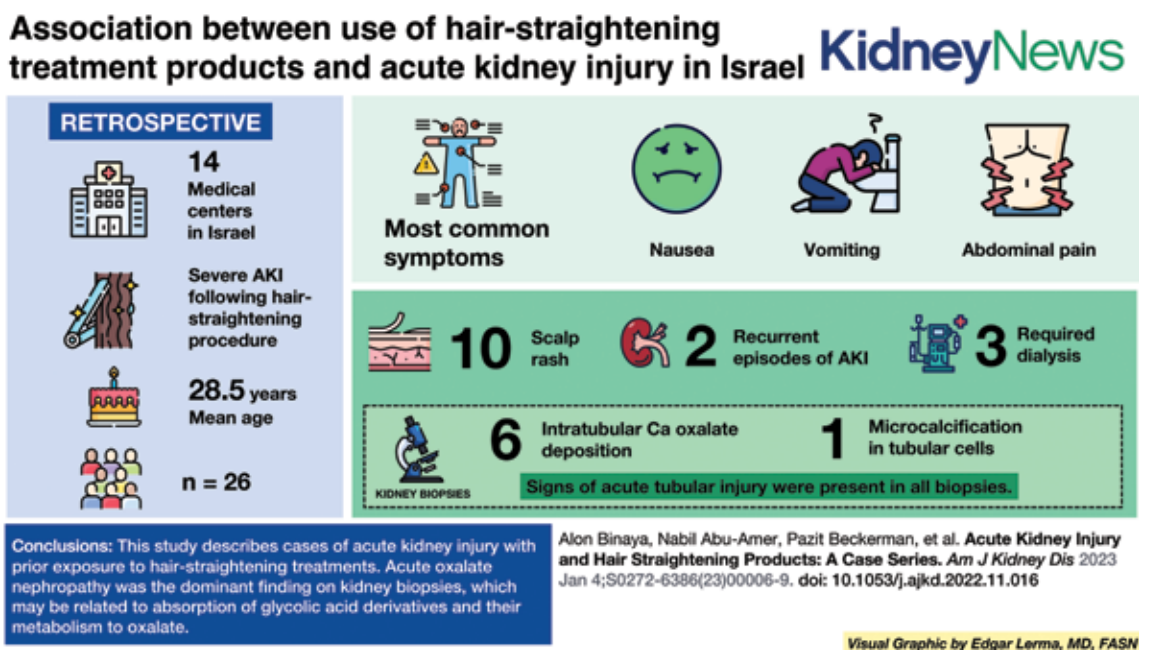
Systemic absorption of glycolic acid through the skin is not well-documented. In this case series, only two people had serum glycolic acid and formic acid levels measured. The levels were negative for both, but one test was only performed 1 week after the hair-straightening procedure. Other studies have suggested that glycolic acid can be absorbed through the skin, particularly when the product has a low pH and high concentration of glycolic acid and the exposure time on the skin is prolonged (4, 5).

This case series suggests that a glycolic acid-based hair-straightening product is associated with the development of AKI. Although glycolic acid-based topical products have been considered safe, it is possible that systemic absorption may occur at high concentrations. Thus, caution must be taken when considering the safety of hair products. Future studies are needed to understand the extent of the problem. ■

Figure 1. AKI following hair-straightening treatment: suggested mechanism



AGT, alanine:glyoxylate aminotransferase; GO, glycolate oxidase; HOGA, 4-hydroxy-2-oxoglutarate aldolase; LDH5, lactate dehydrogenase 5. The figure is adapted from Bnaya et al. (2).



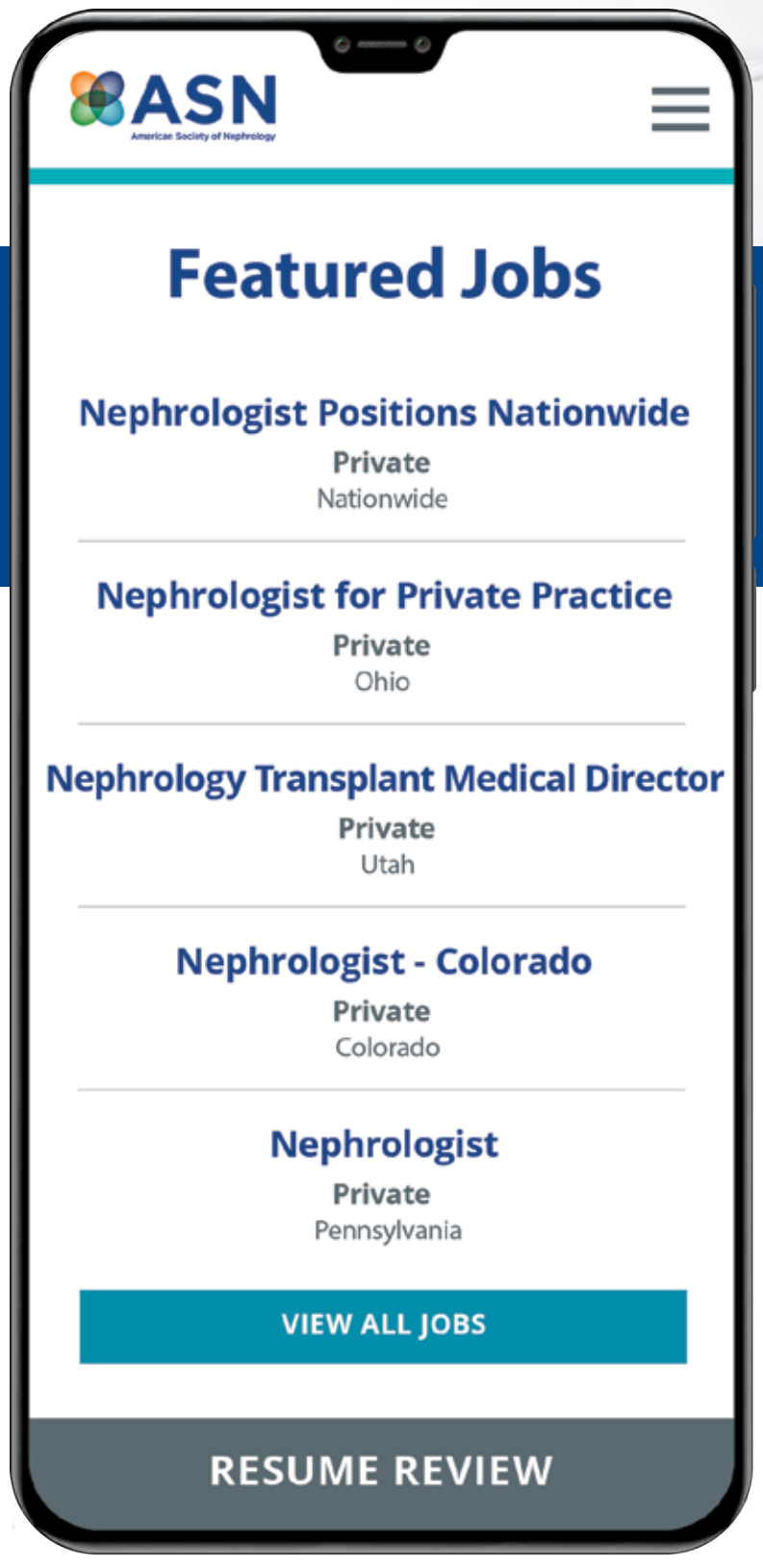
Jia H. Ng, MD, MSCE, is an assistant professor of medicine with the Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY.

The author reports no conflicts of interest.

References

1. Pierson-Marchandise M, et al. The drugs that mostly frequently induce acute kidney injury: A case–noncase study of a pharmacovigilance database. *Br J Clin Pharmacol* 2017; 83:1341–1349. doi: 10.1111/bcp.13216
2. Bnaya A, et al. Acute kidney injury and hair straightening products: A case series. *Am J Kidney Dis* (published online ahead of print January 4, 2023). doi: 10.1053/j.ajkd.2022.11.016; https://www.ajkd.org/article/S0272-6386(23)00006-9/fulltext
3. National Cancer Institute. Formaldehyde and cancer risk. Updated 2011. Accessed February 6, 2023. https://www.cancer.gov/about-cancer/causes-prevention/risk/substances/formaldehyde/formaldehyde-fact-sheet#:~:text=The%20International%20Agency%20for%20Research,Report%20on%20Carcinogens%20(3)
4. Jiang M, Qureshi SA. Assessment of in vitro percutaneous absorption of glycolic acid through human skin sections using a flow-through diffusion cell system. *J Dermatol Sci* 1998; 18:181–188. doi: 10.1016/s0923-1811(98)00039-5
5. Copoví A, et al. Enhancing effect of alpha-hydroxyacids on "in vitro" permeation across the human skin of compounds with different lipophilicity. *Int J Pharm* 2006; 314:31–36. doi: 10.1016/j.ijpharm.2006.01.033

ASN
American Society of Nephrology



Find your next nephrology career opportunity with the ASN Career Center

Search and apply to top nephrology jobs at organizations that value your credentials.

Upload your resume so employers can contact you. You remain anonymous until you choose to release your contact information.

Create job alerts and receive an email each time a job matching your criteria is posted.

Access career resources, job searching tips and tools.

Upload or update your resume today.

Visit **careers.asn-online.org** to get started.

Findings

In Selected Patients, Genetic Testing Shows Value in Transplant Selection

A multidisciplinary approach to genetic testing in the kidney transplant evaluation clinic provides useful input for selection of kidney donors and management of transplant recipients, suggests an evaluation in *Transplantation*.

The authors describe their experience in implementing a multidisciplinary genetic testing approach for potential kidney donors and recipients at the transplant clinic of a major medical center. Between 2018 and 2020, recipients were considered for genomic evaluation, based on previously published criteria. Genetic testing was also considered for potential donors to biologically related recipients with genetic causes of kidney diseases.

Genomic DNA testing was performed using a custom-curated exome slice gene panel, comprising 344 genes linked to various kidney diseases and candidate genes highly expressed in the kidney. Each patient considered for genetic testing was reviewed by a nephrology genomic board consisting of nephrologists with expertise in genetic causes of kidney diseases, renal pathologists, researchers, medical geneticists, and genetic counselors with expertise in kidney diseases.

Of 1100 transplant evaluations performed between 2018 and 2020, 34 recipients were selected for genetic testing. Approximately three-fourths of patients were non-Hispanic White individuals. Testing was canceled in four patients, mainly due to reimbursement issues.

Testing led to genetic diagnosis of a pathogenic or likely pathogenic variant in 13 of 30 patients—a rate of 43.4%. Of 24 tested patients with focal segmental glomerulosclerosis (FSGS), 10 (41.6%) had a genetic diagnosis. Collagen type 4 gene variants were detected in 7 of the 24 patients with FSGS.

Other genetic diagnoses included tubulointerstitial nephritis, nephrolithiasis, and unknown causes of kidney diseases. The only clinical characteristic associated with positive versus negative results was family history of kidney diseases: 76.9% versus 29.4%, respectively. Testing of five potential donors led to exclusion of one individual with a pathogenic or likely pathogenic variant.

With a careful selection approach, diagnosis of a pathogenic or likely pathogenic variant is made in approximately 40% of patients selected for genetic testing at a transplantation clinic. This approach "facilitated the screening of potential living related donors and counseling of recipients about risk of recurrence of their native disease, which are of particular importance in FSGS," the researchers write. They emphasize the importance of a multidisciplinary approach, focused on achieving transplant-specific goals while providing patients with genetic counseling both before and after testing [El Ters M, et al. Incorporation of genetic studies in the kidney transplant evaluation clinic: The value of a multidisciplinary approach. *Transplantation* 2023; 107:952–960; doi: 10.1097/TP.0000000000004363].

Cystatin C-Based eGFR May Affect Staging

Cystatin C- and creatinine-based estimated glomerular filtration rate (eGFR) values are strongly correlated with each other, whereas cystatin C-based estimates can have a substantial impact on chronic kidney disease (CKD) staging, reports a study in *Kidney Medicine*.

The retrospective analysis included 1783 patients who had cystatin C and creatinine levels measured within 24 hours of each other in a large health system for over 4 years. Analysis focused on correlations between eGFR values based on cystatin C versus creatinine and their impact on CKD staging and delivery of kidney care.

The results showed that cystatin C-based eGFR was "very strongly correlated" with creatinine-based eGFR. In multivariable analyses, older age was progressively associated with lower cystatin C-based eGFR at a given creatinine-based eGFR level, at all stages of CKD.

Compared with creatinine eGFR, cystatin C eGFR was associated with a change to a later CKD stage in 27% of patients, an earlier stage in 7%, and no change in 66%. Change to a later stage was less likely for Black compared with White patients (odds ratio [OR], 0.53). Older patients were more likely to have change to a later stage (OR, 1.03/year), as were those with higher comorbidity (OR, 1.22/point on an Elixhauser score). The most common reason for ordering a cystatin C measurement was diagnostic workup (48%), followed by transplant evaluation (21%).

A recent report by the Task Force on Reassessing the Inclusion of Race in Diagnosing Kidney Diseases called for increased use of cystatin C to confirm eGFR in clinical decision-making. The new analysis shows a very strong correlation between cystatin C- and creatinine-based eGFR in a large and diverse patient sample.

Cystatin C led to a CKD change in approximately one-third of patients, mainly to a later stage. These changes are affected by factors such as age, race, and comorbidity. The authors discuss the implications for care delivery as cystatin C measurement comes into routine clinical use [Gottlieb ER, et al. Estimated GFR with cystatin C and creatinine in clinical practice: A retrospective cohort study. *Kidney Med* 2023; 5:100600; doi: 10.1016/j.xkme.2023.100600].

Mycophenolate Mofetil Reduces Progression of IgAN

In patients with high risk of immunoglobulin A nephropathy (IgAN), adding mycophenolate mofetil (MMF) to standard care reduces the risk of disease progression, concludes a randomized trial in *JAMA Network Open*.

The open-label Effect of Mycophenolate Mofetil on Renal Outcomes in Advanced Immunoglobulin A Nephropathy (MAIN) study enrolled 238 adult patients with IgAN at high risk of kidney function loss. Patients underwent a 3-month run-in period of optimized supportive care (SC), including losartan. Those who did not achieve a urinary protein excretion rate of 0.75 g/day or greater were randomly assigned to 3 years of treatment with MMF added to SC or to SC only. The initial MMF dose was 1.5 g/day for 12 months, maintained at 0.75–1.0 g.

Of 170 randomized patients, 55.3% were men; the mean age was 36.6 years. The mean estimated glomerular filtration rate (eGFR) was 50.1 mL/min/1.73 m^2, and the proteinuria level was 1.9 g/day. The analysis focused on two co-primary outcomes: a composite of doubling of serum creatinine, end stage kidney disease, or death due to kidney or cardiovascular disease and progression of chronic kidney disease (CKD).

Of 168 patients who completed the trial, 157 were alive and free of dialysis or transplantation. A primary composite outcome event occurred in 7.1% in the MMF group versus 21.2% with SC only. Rates of CKD progression were 8.2% and 27.1%, respectively; for both outcomes, the adjusted hazard ratio was 0.23.

The benefits of MMF were apparent across subgroups. After the end of the study and withdrawal of MMF in 66 patients, annual loss of eGFR increased from 2.9 to 6.1 mL/min/1.73 m^2. Adverse events were similar between treatment groups.

There are conflicting data on the effectiveness of immunosuppressive therapy for IgAN. MMF is relatively lymphocyte selective compared with other immunosuppressive agents and is a stronger inhibitor of B cell antibody production.

Adding MMF to SC can reduce disease progression in high-risk patients with IgAN, the MAIN results suggest. The researchers conclude that MMF "may be an alternative therapy for patients with IgAN, particularly those with CKD and subnephrotic proteinuria despite receiving SC, as well as those not appropriate for steroid therapy" [Hou FF, et al. Effectiveness of mycophenolate mofetil among patients with progressive IgA nephropathy: A randomized clinical trial. *JAMA Network Open* 2023; 6:e22254054; doi: 10.1001/jamanetworkopen.2022.54054].

Metformin Shows Benefits after Kidney Transplant

Treatment with metformin may reduce the risk of graft failure and death in diabetic kidney transplant recipients (KTRs), reports a study in the *American Journal of Kidney Diseases*.

The retrospective analysis included 1995 patients with type 2 diabetes who underwent kidney transplantation at six centers in the Republic of Korea from 2000 through 2019. Of these, 1193 patients used metformin for longer than 90 days after kidney transplant; 802 patients did not receive metformin. The two groups were compared for all-cause mortality and death-censored graft failure (DCGF), with biopsy-proven acute rejection (BPAR) and lactic acidosis events as secondary outcomes. Analyses accounted for the impact of changes in metformin dose and hemoglobin A1c over time.

There were some differences in patient characteristics: 3 months after transplantation, metformin-treated KTRs had better kidney function but poorer glycemic control. During a mean follow-up of 65 months, 5.1% had graft failure. Patients using metformin had lower DCGF (adjusted hazard ratio, 0.47 on a fully adjusted analysis). Metformin was associated with lower DCGF and all-cause mortality for patients with pre-transplant and post-transplant diabetes.

Among KTRs with post-transplant diabetes, metformin was associated with a lower risk of BPAR, although this difference was not significant in the fully adjusted analysis. There were no confirmed cases of metformin-associated lactic acidosis. Among metformin users, those receiving higher doses had lower rates of DCGF and BPAR.

Metformin is increasingly recommended for patients with advanced chronic kidney disease, based on evidence of a survival benefit and renal protective effect with a low risk of lactic acidosis. Few studies have evaluated the use of metformin in KTRs with pre-transplant or post-transplant diabetes.

This retrospective study shows a reduced risk of DCGF in diabetic KTRs treated with metformin, with no evidence of lactic acidosis. The benefits may be greater in patients receiving higher metformin doses. The researchers call for randomized trials to validate their findings [Kwon S, et al. Metformin use and long-term clinical outcomes in kidney transplant recipients. *Am J Kidney Dis*, published online ahead of print March 23, 2023. doi: 10.1053/j.ajkd.2023.01.446; https://www.ajkd.org/article/S0272-6386(23)00578-4/fulltext].

KidneyNews

Free Subscriber Service Request Card

☐ **I wish to start/renew a FREE* subscription to Kidney News**

7-digit number label (Required for change of name/address only)

Name

Address

City State Zip

Telephone Fax

Email Address

Signature Date

Title/Position
- ☐ Physician
- ☐ Researcher
- ☐ RN, CNN, NM, LPN, APN, PA
- ☐ Dialysis Center Director
- ☐ Administration
- ☐ Clinic Manager/Coordinator
- ☐ Social Work
- ☐ Other

Specialty Area
- ☐ General Nephrology
- ☐ Transplantation
- ☐ Dialysis
- ☐ Laboratory
- ☐ Other

Institution
- ☐ Hospital <100 beds
- ☐ Hospital 100-250 beds
- ☐ Hospital 251-500 beds
- ☐ Hospital > 500 beds
- ☐ Dialysis Center
- ☐ Clinical Lab
- ☐ Other

Please Circle Degree:

MD MD/PhD DO
PhD MBA RN MS
BS Other_____

ASN American Society of Nephrology

Return the completed form to:
Bob Henkel, 1401 H Street NW, #900, Washington, DC 20005
or Fax: 202-403-3615 or Email: bhenkel@asn-online.org

Index to Advertisers

Horizon . . . . . Pages 2–5
Nova Biomedical . . . . . Page 13
Novartis . . . . . Back Cover
Otsuka . . . . . Cover Tip

Despite current management, patients can still struggle with disease burden and psychosocial impacts[1,2]

Learn more about a key component of these diseases—complement system dysregulation.[1-5]

Visit **GlomTalk.com**

C3G, complement 3 glomerulopathy; IgA, immunoglobulin A.

References: 1. Feldman DL, Bomback A, Nester CN. *Voice of the Patient: Report of Externally Led Patient-Focused Drug Development Meeting on Complement 3 Glomerulopathy (C3G)*. National Kidney Foundation; 2018. **2.** Feldman DL, White EM, Julian B, et al. *The Voice of the Patient: Externally Led Patient-Focused Drug Development Meeting on IgA Nephropathy*. National Kidney Foundation; 2020. **3.** C3 glomerulopathy: dense deposit disease and C3 glomerulonephritis. National Organization for Rare Disorders (NORD). Accessed September 24, 2022. https://rarediseases.org/rare-diseases/c3-glomerulopathy-dense-deposit-disease-and-c3-glomerulonephritis/ **4.** Treatment for C3G. National Kidney Foundation. Accessed September 24, 2022. https://www.kidney.org/atoz/content/treatment-c3g **5.** Cheung CK, Rajasekaran A, Barratt J, Rizk DV. An update on the current state of management and clinical trials for IgA nephropathy. *J Clin Med*. Published online June 4, 2021. doi:10.3390/jcm10112493

NOVARTIS

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080

12/22 250794