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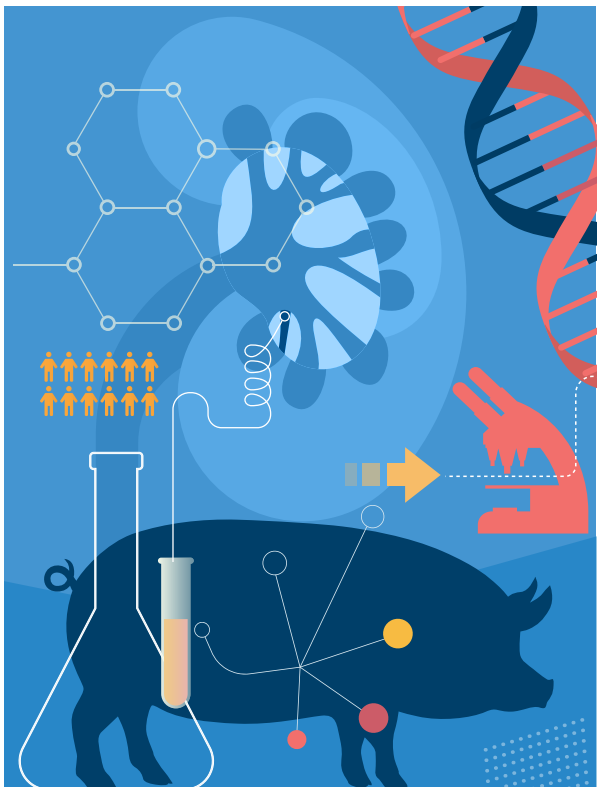
Pig-to-Human Xenotransplants Take Another Step Forward

By Bridget M. Kuehn



The longest-ever transplant of a genetically modified pig kidney into a human recipient, declared dead based on neurological function, wrapped up after 2 months on September 13, 2023. At the time of removal, the kidney had functioned well for 61 days.

"We have seen with good immunosuppression using drugs that are approved for humans by the U.S. Food and Drug Administration (FDA) [that] we seem to be able to hold off rejection, and we seem to be able to demonstrate that the pig kidney can do most of the tasks that the human kidney can," said Robert Montgomery, MD, DPhil, chair of the Department of Surgery and director of the Transplant Institute at NYU Langone Health in New York City, in an interview in late August with *Kidney News*. "We are still waiting for some data to come back. But so far, it looks very promising."

The experiment (1), which has yet to be published in a peer-reviewed journal, is the latest in a string of experiments testing the potential of pig-to-human xenotransplants. The transplant is the fourth pig kidney transplant into a decedent recipient by Montgomery and his colleagues. Another group, led by Jayme Locke, MD, MPH, director of the Division of Transplantation at The University of Alabama at Birmingham, recently published a study demonstrating a successful, 7-day experiment showing that genetically modified pig kidneys not only produced urine but also cleared creatine and maintained hemodynamic stability—a vital role of the kidney—in a deceased individual maintained on mechanical ventilation (2). It was Locke's team's second and longest-running decedent pig kidney transplant.

The Parsons Model

In early 2022 (3), Locke and her team published the results of their first feasibility study of transplanting a genetically engineered pig kidney in a human patient who was declared dead based on neurologic criteria but maintained mechanical life support with consent from his family. The team coined the model The Parsons Model after the decedent recipient whose family generously agreed to let his body be used for the experiment. Montgomery published the results of two similar, short-term, experimental pig transplants using the model in May 2022 (4). Montgomery has since performed two more short-term pig kidney transplants, and his colleagues at NYU Langone Health have also published the results of two short-term pig heart xenotransplants using this experimental model (5).

Continued on page 7 >

Kidney Week Scientific Sessions

THURSDAY

Tiny Conspiracies: Cell-to-Cell Communication in Bacteria and New Approaches to Antimicrobials
State-of-the-Art Lecture: Bonnie L. Bassler, PhD

Thrice Weekly Hemodialysis and Kt/V_{urea}: Carved in Stone?
Garabed Eknoyan, MD, Endowed Lectureship: Laura M. Dember, MD, FASN

Novel Therapies: On the Mechanisms of Action
Robert W. Schrier, MD, Endowed Lectureship: Thomas M. Coffman, MD, FASN

FRIDAY

How Do You Feel? The Molecules That Sense Touch
State-of-the-Art Lecture: Ardem Patapoutian, PhD

Toward Solutions! Pro-Resolving Lipid Mediators of Metabolism and Inflammation
Barry M. Brenner, MD, Endowed Lectureship: Catherine Godson, PhD

Stone Prevention in Patients with Bowel Disease
Jack W. Coburn, MD, Endowed Lectureship: Elaine M. Worcester, MD, FASN

Hypobaric Hypoxia and Its Cardiorenal Benefit for Weight Loss
Burton D. Rose, MD, Endowed Lectureship: Biff F. Palmer, MD, FASN

Podocyte Lipid Handling as a Therapeutic Target for Collagenopathy
Michelle P. Winn, MD, Endowed Lectureship: Alessia Fornoni, MD, PhD, FASN

Human Kidney Organoids for Disease Modeling and Regeneration
ASN-AHA Donald W. Seldin Young Investigator Award: Benjamin S. Freedman, PhD

SATURDAY

Antibodies Against Emerging Infectious Diseases: Global Collaborations
State-of-the-Art Lecture: Erica Ollmann Saphire, PhD, MBA

Nephrology Practice and Therapeutics Through a Genomic Lens
Homer W. Smith Award Lecture: Ali G. Gharavi, MD

Metrics and the Challenge of Improving Access to Kidney Transplantation
Christopher R. Blagg, MD, Endowed Lectureship in Kidney Diseases and Public Policy: Sumit Mohan, MD, MPH, FASN

PROs and PROMs Are What Matter Most to Patients
Celeste Castillo Lee Endowed Lectureship: Amanda Grandinetti, MPH

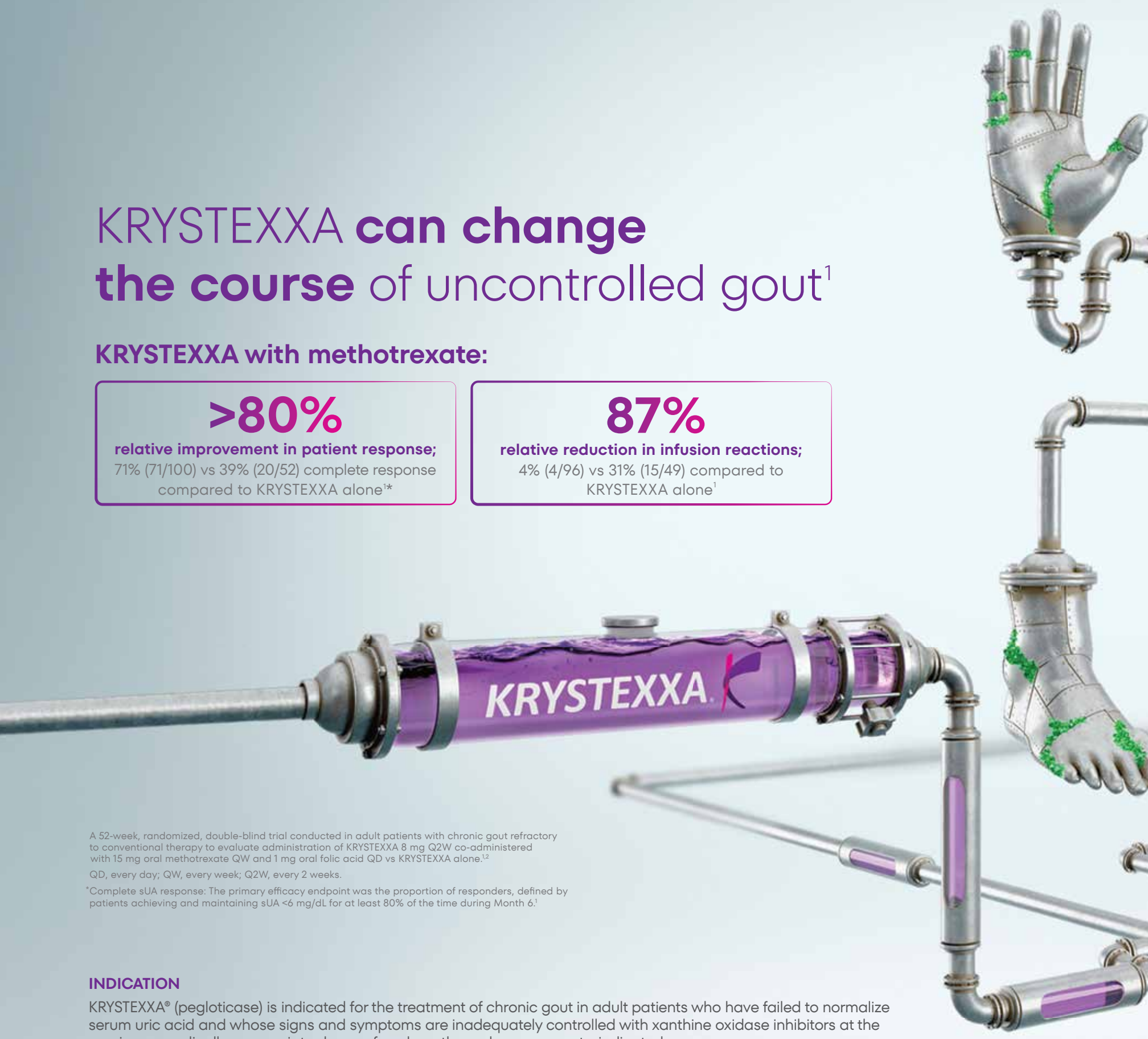
Novel Therapeutic Targets to Control Humoral Responses in Desensitization and ABMR
Barbara T. Murphy, MB BAO BCh, Endowed Lectureship: Flavio Vincenti, MD

SUNDAY

Too Hot: Human Bodies and Inhuman Temperatures
State-of-the-Art Lecture: Bill McKibben

Inside

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.

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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.

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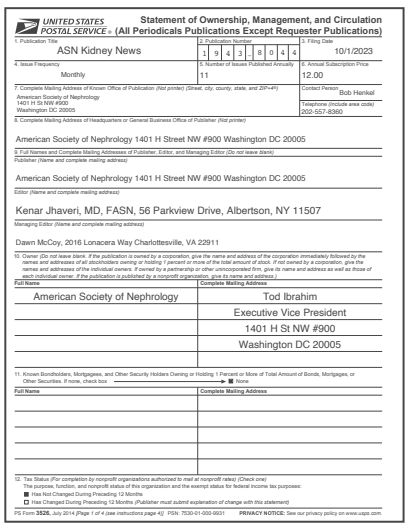

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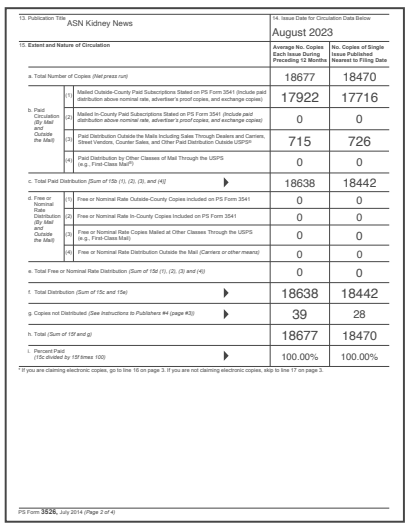

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Correction

The article "Hemodialysis Prescription in Pregnant Women" by Nishanta Tangirala and Michelle A. Hladunewich published in August 2023 *Kidney News* contained an incorrect statement due to a production error. The recommended dialysis intensification in Table 1 "Dialysis prescription recommendations during pregnancy" read:

"Increase dialysis duration to approximately 6 hours/week (5–7 sessions/week)."

This recommendation should read:
"Increase dialysis duration to approximately 36 hours/week (5–7 sessions/week)."

Pig-to-Human Xenotransplants Take Another Step Forward

Continued from cover

Before these experiments, decades of research on primates suggested that xenotransplants may be feasible. However, The Parsons Model provided a path to preliminary human studies. Those initial human experiments demonstrated that the transplanted organs did not trigger hyperacute rejection and that the transplanted organs produced urine. Locke said the model can provide the public and the FDA with critical safety information about xenotransplantation. "I am confident we are all going to learn a ton," Locke said.

So far, that is proving to be true. A detailed molecular and genetic analysis of tissue from the first two pig-to-human kidney transplants, co-led by author Valentin Goutaudier, MD, MSc, a transplant nephrologist and researcher at the Paris Institute for Transplantation and Organ Regeneration in France, found early signs of antibody-mediated rejection, including capillary inflammation and activation of innate immune cells (6). The changes occurred primarily in the glomeruli—tiny blood vessels or capillaries that help filter urine. In an interview with *Kidney News* in late August, Goutaudier said that the immune changes and their location in the glomeruli differ from that typically seen in human-to-human transplants. Alexandre Loupy, MD, professor at Necker Hospital and head of the Paris Institute for Transplantation and Organ Regeneration, and Alessia Giarraputo, MS, PhD, a post-doctoral researcher at the Paris Institute for Transplantation and Organ Regeneration, were co-lead authors of the study.

Based on the results from the first two kidneys, Goutaudier recommended adding a few genetic modifications to the pig kidneys used for transplant and modifying the immunosuppressive treatment given to the recipient. Montgomery said his team has not yet implemented the recommendations because they want to see if the changes persist in longer-term experiments. He noted that the changes reflect the innate immune system's response, which provides an immediate, non-specific immune response. He is also interested in learning from longer-term experiments whether the organs trigger an adaptive immune response, which can take 10 to 14 days to develop.

"We do not know the significance of [the changes]," Montgomery explained. Goutaudier and his colleagues are now analyzing samples from Montgomery's longer-term pig-to-human kidney transplant experiments to see if similar changes occurred in those organs, which may provide additional information. Locke and her colleagues are conducting similar analyses on samples from their pig kidney xenotransplants.

Both groups are monitoring their recipients carefully for signs of infections transmitted from the donor organ, but they have not yet detected any.

Organ choice

Locke and Montgomery currently use pig kidneys with two different sets of genetic modifications for these preliminary human experiments. Having multiple teams working and testing different approaches may help the field identify best practices, Goutaudier said.

"Each team uses different protocols, so everybody is not doing the same thing," he said. "It will allow us to learn the best protocols for xenotransplants."

The pig kidneys transplanted by Locke's group have 10 genetic modifications. The pigs were genetically engineered to knock out three genes encoding carbohydrate antigens found to cause hyperacute rejection in non-human primate studies. "Knocking out those three gives you the best cross-match with a human," Locke explained.

Locke said that the scientists who developed the pig knocked out a fourth gene encoding a growth hormone receptor to prevent the pig organ from continuing to grow after transplant. Six other human genes were also inserted into the pig's genomes to modulate the human immune system. "Those edits have allowed us to do xenotransplants with immunosuppression regimens we routinely use in human-to-human transplants," she explained. "All medications are FDA-approved, and we have been using them for decades."

Montgomery and his colleagues used a pig kidney with just one genetic alteration. The gene encoding an enzyme that produces a

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Pig-to-Human Xenotransplants Take Another Step Forward

Continued from page 7

sugar, called alpha-gal, which causes hyperacute rejection in humans and other primates, has been knocked out. He said he chose a simplified version because there are FDA-approved medications available to treat many of the problems targeted by the additional genetic modifications of the other pig kidney. He explained that many of the genetic modifications used in the 10-gene edited version were designed to tackle problems that could not be treated with medication in primates.

"Let us take a stripped-down version that we know will prevent hyperacute rejection, and then by using drugs that work well in humans, let us see if we get a good outcome," Montgomery explained. The plan, he said, is to start over in this new human model to determine which of the genetic alterations are necessary and add them back in as needed.

Montgomery said one advantage of this approach is that the alpha-gal pigs are already FDA-approved as a food source for individuals allergic to alpha-gal. This condition has recently become more prevalent because of the spread in the United States of Lone Star ticks whose bites trigger the condition. The pig producers must meet strict standards for monitoring diseases that could be transmitted to humans, a key concern for xenotransplantation. Montgomery said that single, gene-edited animals are bred and can produce large numbers of offspring, which could help meet the demand for organs more quickly.

The 10-gene altered pigs, by contrast, must be cloned and produce smaller litters, Montgomery said. They also receive close monitoring for disease. Locke noted that some of the immune changes detected by Goutaudier and colleagues are consistent with what would be predicted without knocking out the three carbohydrate antigens. "When we first move into living people, going across a negative cross-match is going to be important," Locke said. However, she also stated that having multiple organ options may be helpful. She noted that about one-third to one-half of patients would have a negative cross-match with the 10-gene edited pig. For those patients, the alpha-gal knockout pig may be an alternative. "Having pig organs with different genetic knockout backgrounds is going to be critical to solve the organ shortage for everyone," she said.

The following steps for Locke's team are to learn more about how genetically engineered pig kidneys function differently than human kidneys and to develop ways to manage those differences clinically. They are also continuing to work toward getting FDA authorization to conduct clinical trials of pig xenotransplant.

Montgomery's team plans to continue studying pig heart and kidney transplants in decedent patients. The heart transplants have used pigs with the 10 genetic alterations, and Montgomery plans to test adding some additional genetic edits to the pigs used for donor kidneys. "We want to develop both heart and kidney transplants simultaneously," he said.

Locke said that using multiple organs from the same donor animal would honor the animals used for these transplants. "How remarkable would it be to have one genetically edited pig that could provide a heart, a pair of lungs, a liver, and two kidneys?" she asked. "I think it speaks to the commitment to trying to do this in an ethically responsible way where we really are trying to study and understand how we can optimize that gift even of the pig itself."

If the work by Montgomery, Locke, Goutaudier, and others in the field is successful, it could have a tremendous impact on the shortage of organs for transplant that leads to patients dying while still on the wait list. It may also create a sustainable supply to extend transplants as an option to patients with end stage kidney disease who are not currently on the transplant wait list. "It would be transformative," Montgomery said. "If we had another sustainable source of organs, we could prevent those deaths." ■

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ASN Executive Vice President's Update

ASN's Next Era: Reimagining Legacy Activities, Advocating for the Specialty, and Confronting Existential Risks

By Tod Ibrahim

ASN will celebrate its 60th anniversary in 2026. The society's history is summarized by three eras: defining nephrology as a discipline (1966–1985), advancing the field (1986–2005), and repositioning the specialty (2006–2025). The throughline across these periods—as well as the need to prepare for existential risks—will help determine ASN's focus for its fourth era beginning in 2026.

ASN was established in June 1966 (1). The founders' vision has since produced the premier nephrology meeting in the world, the most successful programs to help nephrologists promote clinical excellence, the largest publishing enterprise for kidney-related content (including high-impact science), myriad policy wins (most notably the Executive Order on Advancing American Kidney Health, the only such federal policy in U.S. history), and the community's strongest global society of dedicated members who span generations and represent every type of kidney health professional.

These legacy activities are threatened and may not survive this decade let alone the fourth era.

ASN Kidney Week works best as an in-person experience; as an international meeting (approximately 45% of participants come from outside the United States); and with an educational and scientific focus on every aspect of kidney diseases, practice types, and research disciplines. The COVID-19 pandemic accelerated forces against these three goals: online learning is more accepted, resulting in attendees missing the personal interaction among those with whom they have the most in common, and global travel is trickier.

For Kidney Week to survive as the premier nephrology meeting in the world, ASN must consider radical changes. These include, but are not limited to, shortening the presentations to align with how modern content is consumed, expanding Kidney Week material throughout the year (both in-person and online) and across the world, reorganizing the meeting experience to emphasize the many constituencies and micro-communities within nephrology, accentuating the social aspects of the meeting, and considering the need to shorten the entire in-person experience.

ASN's commitment to helping nephrologists certify and recertify must also change. Traditionally, an in-person experience for U.S. participants that occurred in July, the ASN Board Review Course & Update (BRCU) is now a shorter, in-person meeting, valued for its on-demand content and popularity among international participants. Through BRCU, the ASN In-Training Examination for nephrology fellows, the Nephrology Self-Assessment Program (nephSAP), and the Kidney Self-Assessment Program (KSAP), ASN offers a suite of programs to help nephrologists promote clinical excellence.

With the advent of the Longitudinal Knowledge Assessment (LKA) for recertification, however, the American Board of Internal Medicine (ABIM) has broken a longstanding firewall between assessment and education (2). LKA allows nephrologists to maintain their certification by answering regular questions during a 5-year cycle (instead of sitting for a secure examination every 10 years). In fairness, nephrologists and other diplomates requested that ABIM take this step, but it forces ASN to reconsider the role of BRCU, nephSAP, and KSAP in helping nephrologists recertify as well as question whether the society should continue to maintain the firewall.

The future of the publishing industry is also very much uncertain, and it is impossible today to say what *JASN*, *CJASN*, *Kidney360*, and *Kidney News* will look like in the future. People still value information, but they want it instantly, as easily accessible and usefully brief as possible, highly relevant to their specific interests, and (in scientific publishing at least) peer reviewed. Print media (especially daily newspapers), linear television (like ESPN), and streaming entertainment (like Netflix) are evolving at an even faster pace, and it is hard to imagine ASN's publishing enterprise not following suit.

Until the COVID-19 pandemic escalated in 2020, ASN membership had grown every year. While the society has regained most of the members it lost during the pandemic and will soon surpass 2019's total, generational differences signify imminent struggles. These challenges will affect what future generations want from medical specialty societies like ASN. Beyond Kidney Week, other educational offerings, and publishing, the society is already trying to navigate very different preferences related to policy priorities. For example, nephrology fellows and early career nephrologists are much more interested in existential risks—like climate change—than their predecessors were.

In 2000's *Bowling Alone: The Collapse and Revival of American Community*, Robert D. Putnam, PhD, explained why medical societies will struggle to attract members in the future: "Much of the decline in civic engagement in America during the last third of the twentieth century is attributable to the replacement of an unusually civic generation by several generations (their children and grandchildren) that are less embedded in community life" (3). Millennials (born 1981–1996), Generation Z (born 1997–2012), and Generation Alpha (born approximately 2013–2025) only accelerated this disengagement for reasons that Dr. Putnam could not have predicted, such as social media, handheld devices (like smartphones), and a global pandemic.

For the past 20 years, ASN championed kidney care, research, and education as well as promoted the nephrology workforce.

In a previous editorial, I used a table as a metaphor for ASN's efforts in these arenas (4). Patient care is the tabletop, "with education (undergraduate/graduate and continuing), research, and advocacy as the supporting legs. Diversity, equity, and inclusion are the joints that lock aprons (health care justice) to the legs, strengthening the table."

In 2024, ASN will initiate new activities to further advance kidney care, research, education, and advocacy, as well as promote diversity, equity, inclusion, and justice. Besides supporting the society's membership, improving the lives of people with kidney diseases, and benefiting the rest of the kidney community, these efforts will take advantage of opportunities and overcome threats—both seen and unseen today.

Directly or indirectly, these ventures will also help continue the society's efforts to implement the final recommendations from the ASN Task Force on the Future of Nephrology (5):

- Publish kidney health guidance to encourage high-quality, patient-centered care across the spectrum of kidney diseases, covering the patient-care journey from screening and early detection through palliative care.
- Finalize plans for individualized, competency-based education in nephrology training to clarify, expand, and systematize the educational continuum for all types of nephrologists, including subspecialists.
- Pursue accreditation for transplant nephrology fellowship training programs by the Accreditation Council for Graduate Medical Education (ACGME), ideally by working with the American Society of Transplantation.
- Address increasing concerns about the nephrology workforce by trying to partner with other members of the kidney community, such as the American Nephrology Nurses Association and American Nephrologists of Indian Origin.
- Increase nephrology's presence within the American Medical Association (AMA)—including the AMA Specialty Society Relative Value Scale Update Committee (that provides recommendations on physician reimbursement)—by seeking collaboration with the Renal Physicians Association.
- Concentrate on other difficulties in providing high-quality care to people with kidney diseases, such as the U.S. Preventive Services Task Force's need to recognize the value of screening for kidney diseases, structural challenges within the Medicare Advantage program, the Centers for Medicare & Medicaid Services' goal of enrolling all Medicare beneficiaries in accountable care organizations by 2030, and lower compensation for nephrologists when compared with other medical specialties.
- Formalize interactions with integrated kidney care companies to improve kidney health by intervening earlier to prevent, diagnose, coordinate care, and increase awareness of kidney diseases, while working to pursue true value-based care.
- Reevaluate priorities for funding of federal research agencies due to concerns about the government's budget deficit, the politicization of health-related research, the advent of the Advanced Research Projects Agency for Health, and attenuated support for the next generation of "renal researchers."
- Enhance ASN's commitment to diversity, equity, inclusion, and justice considering the U.S. Supreme Court's recent decision on Affirmative Action as well as improve enrollment in clinical trials focused on kidney diseases of people who identify as racial or ethnic minorities.
- Advocate for establishing the U.S. Department of Health and Human Services Office of Kidney Health and Transplantation to ensure the federal government shifts the emphasis from treating kidney failure to promoting kidney health (6).

In addition to these activities, ASN will continue to support efforts to implement the task force's recommendations. On Monday, July 1, 2024, for example, ACGME is expected to implement new requirements for accredited nephrology fellowship training programs. These new requirements will likely compel more training in home-based therapies, such as home hemodialysis, as recommended by the task force.

At least seven existential risks have important connections to kidney health.

The first four of these forces (see list, 1–4) could lead to human extinction, while the remaining three (5–7) could accelerate the demise of humanity:

1. *Climate change and sustainability.* A recent article by Aryn Baker in *Time* declares, "Chronic kidney disease is poised to become the black lung of climate change" (7). Ms. Baker describes chronic kidney disease of non-traditional origin, which "tends to manifest among outdoor laborers who work grueling hours in high heat conditions." The changing climate also increases the likelihood of natural disasters, causing crush injuries from earthquakes, swamped dialysis facilities from hurricanes, and other emergencies for people, regardless of whether their kidneys are healthy or not.
2. *Nuclear war and nuclear winter.* Beyond the casualties, a nuclear war would present many of the same challenges to the kidney community as natural disasters (8). A nuclear winter would result in horrific conditions for the survivors, including people who require dialysis (particularly adequate power and nonradioactive water) or are trying to keep a transplanted kidney healthy (9).
3. *Public health and pandemics.* COVID-19 "disproportionately affected patients with kidney disease, causing significant challenges in disease management, kidney research and trainee education," according to Geetha et al. in 2022 (10). Optimistically, the experience with COVID-19 will result in governments agreeing to work together, support public health, and prepare for future pandemics. Bill Gates (author of *How to Prevent the Next Pandemic*) is not so hopeful: "When the World Health Organization first described Covid-19 as a pandemic just over three years ago, it marked the culmination of a collective failure to prepare for pandemics, despite many warnings. And I worry that we're making the same mistakes again. The world hasn't done as much to get ready for the next pandemic as I'd hoped" (11).
4. *Augmented and artificial intelligence (AI).* In May 2023, the Center for AI Safety issued the following statement signed by more than 350 AI experts, including the top executives from OpenAI, Google DeepMind, and Anthropic: "Mitigating the risk of extinction from AI should be a global priority alongside other societal-scale risks such as pandemics and nuclear war" (12). AI can quickly accelerate and exacerbate human-caused error and bias—especially in health care—threatening our well-being. If harnessed, however, AI has the potential to help address other existential threats and improve health care throughout the world. Unfortunately, as the ASN Augmented Intelligence and Digital Health Task Force noted last year, "[N]ephrology trails other fields—such as cardiology, critical care, and radiology—in bringing these tools to clinical care" (13).
5. *Autocratic and authoritarian governments.* Anne Applebaum (a staff writer at *The Atlantic* and a senior fellow at the Agora Institute at Johns Hopkins University) explains that "autocracies are run not by one bad guy, but by sophisticated networks composed of kleptocratic financial structures, security services (military, police, paramilitary groups, surveillance), and professional propagandists" (14). According to Ms. Applebaum, "the members of these networks are connected not only within a given country, but among many countries." For example, "The Chinese Communist Party is teaching African leaders its authoritarian alternative to democracy at its first overseas training school" (15). This approach to government relies on misinformation/disinformation, is anti-science, and devalues education, placing it at odds with the basic tenants of the medical profession. Life expectancy declines in democracies that become autocracies (and kidney diseases test public health throughout the world), so nephrologists and other kidney health professionals need to care about this risk (16).
6. *Inequities and disparities.* The International Monetary Fund estimates that "Some 10 percent of the world's population owns 76 percent of the wealth, takes in 52 percent of income, and accounts for 48 percent of global carbon emissions" (17). An estimated "252 men have more wealth than all 1 billion women and girls in Africa, Latin America, and the Caribbean, combined" (18). According to the U.S. Department of the Treasury, "Racial inequality in the United States today is rooted in longstanding behaviors, beliefs, and public and private policies that resulted in the appropriation of the physical, financial, labor, and other resources of non-[W]hite people" (19). Of the more than 37 million Americans with kidney diseases, a disproportionate number are Asian American, Black or African American, Hispanic or Latin/o/a/x, Indigenous or Native American, and Native Hawaiian or Other Pacific Islanders. Disproportionately, people with kidney diseases also have lower socioeconomic status.
7. *Migration and workforce.* The United Nations International Organization for Migration's *World Migration Report 2022* estimates that 3.6% of the world's population (or 281 million people) are defined as migrants, moving from one country to another "for reasons related to work, family and study" (20). The United States "remains the primary destination for migrants, at over 51 million international migrants," and "India has the largest emigrant population" with an estimated "18 million people living abroad." Of the 11,554 nephrologists practicing in the United States, 51% graduated from international medical schools (21). At this time, 29% of all U.S. physicians were born abroad, but "Competition for healthcare talent is intensifying at the global level, leaving some countries with an edge and others at a disadvantage, including the U.S." (22).

These existential risks are individually daunting and collectively overwhelming. No one organization can confront any of these threats alone, making it vital that ASN work with other members of the kidney community and beyond to focus on improving the lives of the more than 850 million people with kidney diseases worldwide.

During her ASN President's Address in 2021, Susan E. Quaggin, MD, FASN, charged the audience to:

- Amplify your passion for kidney health.
- Elevate the patient voice and choice.
- Unite. We can solve the most complex problems when we work together.
- Be political and demand change.
- Adopt innovation.
- Don't settle.
- This is our time, our moment, let us stand up to the challenges… (23).

Dr. Quaggin's call to action is the perfect inspiration for each member of the kidney community, including ASN. In 2024 and 2025, the society must determine how best to reimagine legacy activities, advocate for the specialty, and confront existential risks. The decisions made during the next 2 years will determine future success for the specialty, ASN, and—most important—people with kidney diseases. ■

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Systematically Evaluating SGLT2 Inhibitors in Children: An Interview with Howard Trachtman

By Karen Blum

In July, NephCure and the Kidney Health Initiative (KHI) convened a workshop of more than 75 nephrologists and Food and Drug Administration (FDA) and industry representatives from the United States and Europe to discuss the best potential use of sodium-glucose cotransporter-2 (SGLT2) inhibitors in pediatric patients with chronic kidney disease (CKD). *Kidney News* spoke with pediatric nephrologist and workshop Steering Committee member Howard Trachtman, MD, FASN, adjunct professor of pediatrics at the University of Michigan, to learn more about the outcomes of the workshop and next steps. Dr. Trachtman thanks co-members of the workshop Steering Committee William E. Smoyer, MD, FASN, and Debbie Gipson, MD, MS. (Responses have been lightly edited for brevity.)

Kidney News: **What was the impetus for holding this workshop?**

Trachtman: SGLT2 inhibitors have proven to be landmark drugs that have a clear-cut, beneficial effect on cardiovascular and renal outcomes in patients with kidney diseases due to type 2 diabetes. Now, clinical trials such as DAPA-CKD and EMPA-KIDNEY are demonstrating that this class of drugs is beneficial for nearly all causes of underlying CKD. As a result, SGLT2 inhibitors are being used as the standard of care for patients with CKD. However, there has been no organized, systematic effort to evaluate these drugs in the pediatric population. The workshop was convened with all of the relevant stakeholders to ask questions such as: Is there a need for clinical trials of SGLT2 inhibitors in pediatric CKD? Can we extrapolate data from adults to pediatric patients with CKD? If not, what specific populations, endpoints, and safety concerns should guide future trials to ensure that the drugs are used in a thoughtful way in pediatric patients with CKD?

If successful in our goals, we will [...] execute meaningful clinical trials that clarify the best way to treat the full range of pediatric patients with CKD.

Kidney News: **How commonly are the drugs being used off-label in pediatric populations?**

Trachtman: We were apprised of data from PEDSnet, a database from a consortium of eight nationally recognized pediatric centers across the United States that monitors over 8 million children. When reviewing off-label use of SGLT2 inhibitors in 2022, 10% occurred in patients treated by nephrologists and was more common in endocrinology and cardiology clinics. We think that off-label prescription is not the optimal way to treat children because it is not guided by high-quality evidence. It is best to know the efficacy and to define the optimal dose of SGLT2 inhibitors so that children and adolescents are given therapy that matches their clinical needs and their biological reality.

Kidney News: **You helped lead a discussion about trajectories of kidney diseases in children versus adults. What were some of the takeaways from that discussion?**

Trachtman: During a session that I moderated with Mona Khurana, MD, a pediatric nephrologist from the FDA, presentations by Carla Nester, MD, from the University of Iowa and Robert Nelson, MD, PhD, from the National Institute of Diabetes and Digestive and Kidney Diseases highlighted considerable similarity in the disease trajectories in pediatric and adult patients, both with diabetic and non-diabetic CKD. There were also differences and similarities in risk factors such as hypertension and levels of proteinuria and glomerular filtration rate at the time of diagnosis. Overall, the data documented some overlap between the diseases in children and adults but need to be explored in greater detail. The impact of diabetic nephropathy is profound in the pediatric population because those with type 2 diabetes in the pediatric age range are more likely to develop proteinuria compared with those with later-onset diabetes. There also were factors, such as exposure to maternal diabetes during pregnancy, that accelerated the development of diabetes in children, but the effect on the occurrence of kidney diseases was unclear.

Kidney News: **The workshop also addressed potential clinical trial designs for the pediatric population. Can you share more about that?**

Trachtman: The overarching theme of the workshop was the use of extrapolation by the FDA. We framed the discussion in an attempt to promote collaboration among all stakeholders and leverage what we know in the adult population. One of the key issues in extrapolation is determining which pediatric populations are distinct from adult counterparts and which need to be studied. While some diseases have considerable similarity to the adult population, such as focal segmental glomerulosclerosis and immunoglobulin A nephropathy, others are more distinctly pediatric in nature. For example, there is a large group of pediatric patients born with congenital anomalies of the kidney and the urinary tract who do not have a precise adult analog. We may be limited in what we can learn from adults in these cases.

Thus, for clinical trial designs, we must assess which pediatric populations need to be studied and for which populations we can leverage data that are available in adults to shed light on the applicability of drugs in children. Endpoints are important. Although the trajectory of disease may be similar, it does not mean that children will reach the endpoints classically used in clinical trial designs for adults with the same frequency that would allow trials to be conducted with comparable sample sizes and follow-up time. Regarding safety, we have the off-label experience with these drugs in pediatric patients with various conditions and clinical trial data for type 2 diabetes. Notably, before the meeting was convened, the FDA approved empagliflozin for adults with diabetes and for children with type 2 diabetes. The data were reassuring.

Kidney News: **Workshop attendees discussed several questions regarding CKD and the pharmacology of SGLT2 inhibitor drugs. What should our readers know?**

Trachtman: These drugs clearly are enormously beneficial in the adult population. There was a genuine sense of urgency to get these trials done in pediatrics before the therapeutic "cat is out of the bag," and we lose the opportunity as a community to systematically study them in pediatric patients. A key strength of the meeting was the sense of collegiality and shared enterprise among the stakeholders. There were patient advocacy groups, patient representatives, leaders from the FDA, representatives from industry, and, of course, nephrologists. It created a genuine sense of purpose and the need to keep the foot to the pedal. Hopefully, we can channel the momentum from the meeting to move forward and try to develop a clinical trial plan for SGLT2 inhibitors in pediatric CKD that is feasible and that would provide meaningful answers to nephrologists.

Kidney News: **What are the next steps for your group?**

Trachtman: The workshop was the first of a three-pronged effort. Following up from the workshop, we plan to create proceedings of the meeting that are publicly accessible and identify a mechanism to reconvene the group. Once reconvened, we need to identify steps to draft, design, and implement clinical trials that can be done in a timely, cost-effective manner and that answer the critical question: Is this class of drugs safe and effective in targeting the rate of progression of CKD in pediatric patients comparable with what has been observed in adults?

The second prong was the Annual KHI Stakeholders Meeting, held September 6–7, at which nephrologists discussed how they would make trials palatable to patients and care practitioners. The third prong will take place at Kidney Week in Philadelphia, PA, featuring a session (on Thursday, November 2, from 2 to 4 PM) coordinated with assistance from the KHI on "Clinical Trials in Pediatric CKD: Trial with SGLT2 Inhibitors?" William E. Smoyer, MD, vice president for clinical and translational research at Nationwide Children's Hospital, will present on "Designing Trials in Pediatric CKD: Hurdles and Solutions" during the session.

If successful in our goals, we will demonstrate that the pediatric nephrology community can work effectively to execute meaningful clinical trials that clarify the best way to treat the full range of pediatric patients with CKD. Long term, this multipronged approach could provide a model for tackling other urgent problems within pediatric nephrology. ■

Congressional Visits to Dialysis Facilities

By Killian Gause, Zachary Kribs, and Lauren Ahearn

On Wednesday, August 23, and Thursday, August 24, ASN engaged in educational outreach with key Congressional policymakers in Seattle, WA, and Clinton, MD. From opposite sides of the country, ASN members and staff informed congressional members and their staff on recent policy advances and further opportunities to improve kidney care. These events were planned through discussions with congressional staff during the ASN Kidney Health Advocacy Day in March.

Roundtable with Representative Suzan DelBene, Kidney Caucus co-chair

Innovation in kidney health and transplantation were twin foci of interest to Representative DelBene during the visit on Wednesday, August 23. Convened in partnership with Northwest Kidney Centers and the University of Washington (UW), Representative DelBene made a point to connect with patients, researchers, and health professionals in her home district to better understand the needs of the 37 million Americans with kidney diseases and ultimately guide her work as co-chair of the Congressional Kidney Caucus.

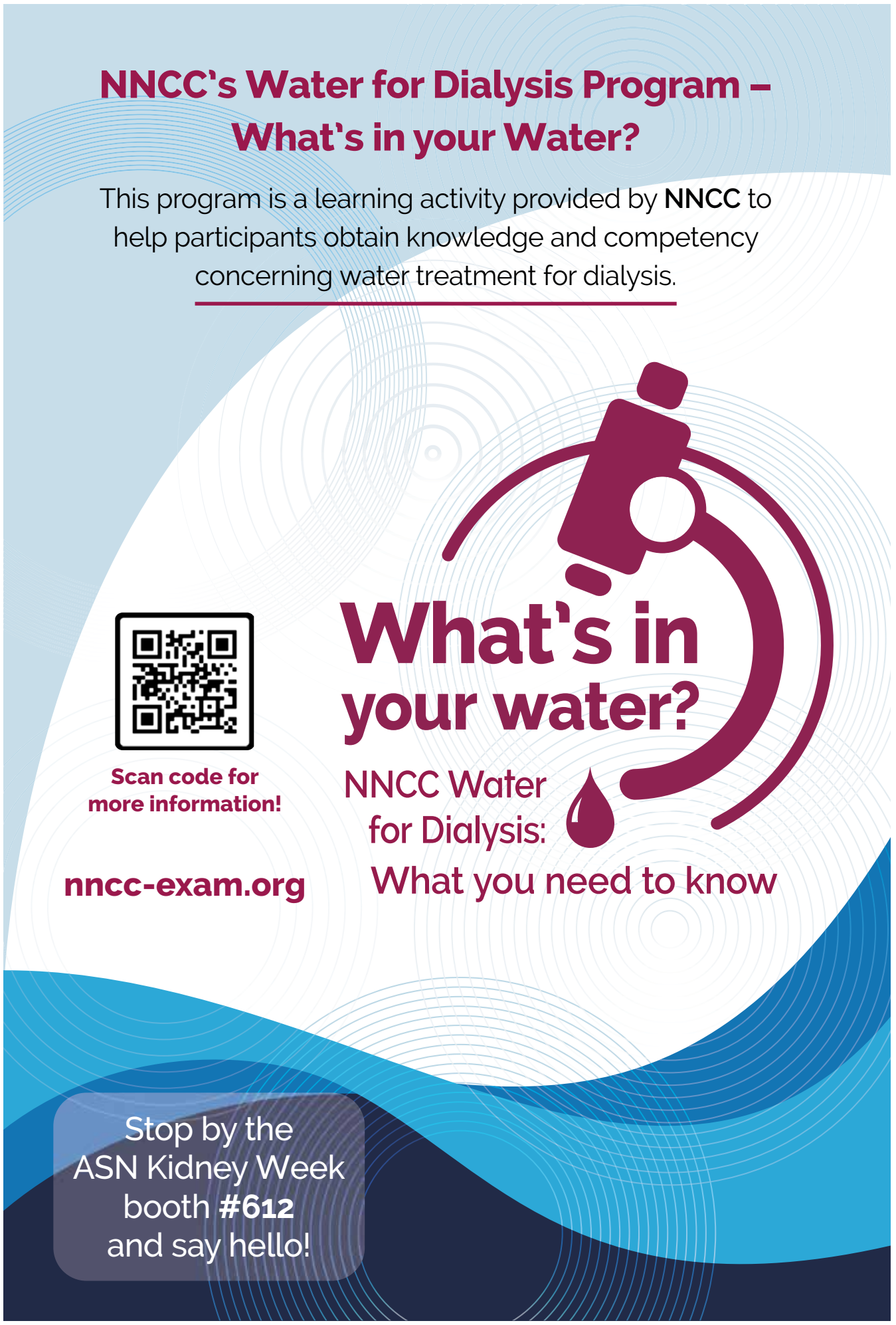
Representative DelBene first reaffirmed her commitment to accelerating innovation in kidney health, visibly through her longstanding championing of the Kidney Innovation Accelerator (KidneyX), while making it clear that what matters most is that patients have choices in their care. Jonathan Himmelfarb, MD, FASN, past president of ASN and co-director of the Center for Dialysis Innovation at UW, thanked the congresswoman for her leadership on behalf of KidneyX and shared several advances his laboratory has made. Encouragingly, he noted that the pace of innovation in kidney health has been steadily increasing, but more work is needed to foster innovation.

Suzanne Watnick, MD, FASN, chief medical officer at Northwest Kidney Centers and member of the ASN Quality Committee, provided an overview of the many exciting advancements in transplant care through the Health Resources and Services Administration Organ Procurement & Transplantation Network (OPTN) Modernization Initiative, made possible through the Securing the U.S. OPTN Act. Particularly, Dr. Watnick noted the emphasis placed by the initiative on transparency and accountability, key improvements needed to expand access to transplant care.

The importance of transparency and accountability, especially to empower patient decision-making, was remarked on by Glenda Roberts, director of External Relations and Patient Engagement for the Kidney Research Institute and of the Center for Dialysis Innovation at UW, and John Mosby, PhD, president of Highline College in Washington. Living with kidney diseases, Dr. Mosby and Ms. Roberts shared that increasing patient leadership in their care can only be possible with increased transparency—often patients are excluded from important decision-making, such as deciding whether to accept a donated kidney.

Ms. Roberts noted that further advancements are needed, including an improved system to allow people seeking a transplant to better understand the transplant programs that match their care. At the same time, existing commitments, such as OPTN's policy to recalculate transplant waiting times after adopting a race-neutral formula for diagnosing kidney function, should be followed through. Yue-Harn Ng, MD, a transplant nephrologist and professor at UW, affirmed that a matching system is key to improving outcomes and reducing disparities, noting that it is an active project that she and her colleagues are taking on. At the same time, metrics to which transplant programs are held accountable must also be aligned with expanding access to transplant care for patients, Dr. Ng noted.

Representative DelBene's roundtable concluded with a tour of the Northwest Kidney Centers clinic, which hosted the meeting. A strong champion of kidney health, she pledged to continue her work to support individuals living with kidney diseases. She highlighted her strong bipartisan relationship with Representative Larry Bucshon, MD, of Indiana, the Republican co-chair of the Congressional Kidney Caucus, and shared her hope that efforts to achieve kidney health would rise above partisan differences embroiling Congress. ASN is excited to continue collaboration with



Representative DelBene on the numerous priorities raised during the roundtable and beyond.

Congressional visit to U.S. Renal Care

On Thursday, August 24, ASN, the National Kidney Foundation, and U.S. Renal Care hosted the Congressional Kidney Caucus at a U.S. Renal Care dialysis clinic in Maryland. The event gave congressional staff an opportunity to view different aspects of the facility and witness firsthand the day-to-day experience of people who are affected by kidney failure and undergo in-center dialysis.

Facility administrators guided participants through the dialysis clinic, including the treatment floor, water room, and home dialysis training room. Congressional staff were also given the opportunity to meet with a patient actively receiving dialysis, a living donor, and a kidney donor recipient.

Participants learned how in-center dialysis is the most common therapy used to clear waste and extra fluid from those who are experiencing kidney failure and how dialyzing is typically performed 3 days a week for 4 hours a day. While touring the treatment floor, participants also learned about how an in-center dialysis facility is staffed with two types of technicians: patient care technicians on the treatment floor and biomedical technicians in the water room. Both work under the supervision of a registered nurse or nephrologist. The patient care technician is responsible for starting and ending dialysis treatment, as well as providing patients with any additional support needed during treatment. There are ideally four patients assigned to each patient care technician—a ratio that is being put at risk due to recent health workforce shortages impacting dialysis centers across the country.

In addition to meeting the staff present on the treatment floor, participants were also given the opportunity to speak with a patient actively receiving dialysis. The patient on the treatment floor spoke to congressional staff about how they have been deliberating with the care team about reducing their time receiving dialysis. Thanks to the help of a renal dietitian, they were able to reduce their time on dialysis by 15 minutes per session.

The second stage of the tour was of the facility's water room, the most integral part of the dialysis unit. Participants learned that a water treatment room is a dedicated, secure, and access-controlled area where water filtration and purification occur. The filtration system itself is complex and includes various components, such as sediment filters, water softeners, carbon tanks, microfilters, disinfection units, storage tanks, and reverse osmosis units. In addition to an overview of the water room equipment, participants met with the biomedical technician responsible for the maintenance of the room, as well as ensuring that the water quality meets the standards set by the Association for the Advancement of Medical Instrumentation. The biomedical technician informed participants that, on average, a dialysis patient is exposed to approximately 40 gallons of water per treatment session. As the global water cycle is disrupted by climate change, ensuring an adequate supply of medically pure water for dialysis will be increasingly important.

The third part of the facility tour was an overview of the home dialysis training room, where staff members educate and assist eligible patients during the process of transitioning from in-center dialysis to home dialysis. Training usually takes 4–8 weeks and is conducted individually by a home training nurse. During the training program, patients learn everything they need to know about performing hemodialysis treatments safely and effectively in their homes. Participants met with the home dialysis training nurse to learn about various types of home dialysis machines and the necessary support equipment and supplies used by patients during home dialysis. The home dialysis training nurse emphasized that they make home visits before patients start the treatment to ensure that the patients are equipped with everything needed to dialyze.

The final part of the facility visit consisted of a roundtable discussion among ASN and congressional staff, dialysis facility staff, a home dialysis patient, a kidney donor, and a kidney transplant recipient. The conversation provided an opportunity to learn about each patient's unique experience with the facility and discuss with the congressional staff policy recommendations and ideas that they have. Particularly, passing the Living Donor Protection Act (H.R. 2923/S. 1384) was of major interest.

ASN is currently engaging members of Congress and their staff to schedule similar events in the future. If you would like to plan an event in your district, please reach out to Killian Gause, Policy and Government Affairs Associate, at kgause@asn-online.org, to discuss ways you can engage your members of Congress. ■

COVID-19 Linked to Increased Risk of New-Onset Hypertension

Patients with an episode of COVID-19, whether hospitalized or not, have an increased incidence of new-onset hypertension compared with patients with influenza, reports a study in *Hypertension*.

The retrospective study included 45,398 patients diagnosed with COVID-19 in a health system in the Bronx, NY, from March 2020 to August 2022. Of these, 28,576 had no history of hypertension, and approximately 20% of patients were hospitalized, and 80% were not. Six-month follow-up data were available for 1455 hospitalized and 5565 non-hospitalized patients.

At follow-up, persistent hypertension had developed in 20.6% of hospitalized and 10.9% of non-hospitalized patients with COVID-19. In a comparison sample of patients with influenza, rates of persistent hypertension were 16.3% for hospitalized and 4.4% for non-hospitalized patients. On adjusted analysis, odds ratios for persistent hypertension were 2.23 in hospitalized and 1.52 in non-hospitalized patients with COVID-19, relative to those with influenza.

In a model, including both hospitalized and non-hospitalized patients with COVID-19, the most significant risk factors for persistent hypertension were age, Black race, chronic kidney disease, chronic obstructive pulmonary disease, and coronary artery disease. A model comprising these factors was 80.20% accurate in predicting new-onset, persistent hypertension, with an area under the curve of 71.96%. Sensitivity analyses showed similar patterns.

New-onset, persistent hypertension may develop after COVID-19 in approximately 21% of hospitalized and 11% of non-hospitalized patients. These rates are substantially higher compared with patients with influenza in the same health system.

"These findings should heighten awareness to screen for hypertension following COVID-19 illness in at-risk patients," the researchers conclude. They discuss possible mechanisms of the association between COVID-19 and hypertension [Zhang V, et al. Incidence of new-onset hypertension post-COVID-19: Comparison with influenza. *Hypertension* 2023; 80:2135–2148. doi: 10.1161/HYPERTENSIONAHA.123.21174]. ■

For your patients at risk for rapidly progressing ADPKD

JYNARQUE® (tolvaptan) could change the course of their disease

JYNARQUE is the first and only FDA-approved treatment indicated to slow kidney function decline in adults at risk of rapidly progressing ADPKD.

ADPKD=autosomal dominant polycystic kidney disease.

Scan the QR code to see how JYNARQUE may help your appropriate patients or visit **JYNARQUEdata.com**

IMPORTANT SAFETY INFORMATION:

WARNING: RISK OF SERIOUS LIVER INJURY

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

CONTRAINDICATIONS:

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

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

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

Inhibitors of CYP3A: Concomitant use of JYNARQUE with drugs that are moderate or strong CYP3A inhibitors

Pruritus Predicts Adverse Outcomes in Patients on Dialysis

Up to half of patients experiencing hemodialysis report moderate to severe pruritus, which is associated with increased rates of adverse outcomes, reports a study in the *American Journal of Kidney Diseases*.

The prospective cohort study included 7976 patients from 21 countries enrolled in the Dialysis Outcomes and Practice Patterns Study between 2009 and 2018. Participants underwent two assessments of chronic kidney disease (CKD)-associated pruritus, based on ratings of how much they were "bothered by itchy skin." Patterns of CKD-associated pruritus were assessed, along with associations with laboratory values and patient-reported outcomes.

Moderate to severe pruritus was reported in at least one assessment by 51% of patients and at both assessments by 22%. Prevalence of depression, restless sleep, and feeling drained increased over time in patients with incident pruritus and decreased in those with resolved pruritus compared with little or no change in those with absent or persistent pruritus. Most patients with bothersome pruritus were not taking medications traditionally prescribed for this indication.

Reported pruritus was unrelated to changes in laboratory values over time. However, persistent CKD-associated pruritus was associated with increases in adverse outcomes compared with no pruritus at either assessment: Hazard ratio was 1.29 for all-cause mortality, 1.17 for all-cause hospitalization, and 1.48 for cardiovascular events.

This large, international cohort study finds that many patients are bothered by moderate to severe CKD-associated pruritus and that pruritus symptoms often persist. Pruritus is linked to increased rates of adverse outcomes, including death, hospitalization, and cardiovascular events. The researchers discuss the need for frequent, standardized assessment of CKD-associated pruritus symptoms and studies to determine whether pruritus treatments can affect adverse outcome rates [Sukul N, et al. Pruritus in hemodialysis patients: Longitudinal associations with clinical and patient-reported outcomes. *Am J Kidney Dis*, published online ahead of print August 16, 2023. https://www.ajkd.org/article/S0272-6386(23)00729-1/fulltext].

JYNARQUE® (tolvaptan) has been proven effective in the 2 largest clinical trials of over 2800 patients with ADPKD across CKD stages 1–4[1-3]

TEMPO 3:4 Trial— A 36-month trial in patients with CKD Stages 1, 2, and 3[2,4]

49% reduction
of total kidney volume vs placebo at the end of 3 years*
(*P*<0.001; month 36 treatment effect: -9.2%)

The difference in TKV between treatment groups was most prominent within the first year, at the earliest assessment; the difference was minimal in years 2 and 3. JYNARQUE had little effect on kidney size beyond what accrued during the first year of treatment.†

Study design: TEMPO 3:4 was a double-blind, placebo-controlled randomized trial of 1445 patients with ADPKD. The inclusion criteria were: 18 to 50 years of age; early, rapidly progressing ADPKD (meeting modified Ravine criteria‡); TKV ≥750 mL; creatinine clearance ≥60 mL/min. Patients were treated for up to 3 years. **The primary endpoint was annual rate of change in the total kidney volume.[4]**

REPRISE Trial— A 12-month trial of patients with CKD late Stage 2 to early Stage 4[3,5]

35% reduction
in decline of kidney function vs placebo
(treatment effect: 1.3 mL/min/1.73 m²/year; 95% CI: 0.86 to 1.68; *P*<0.0001)

Study design: REPRISE was a double-blind, placebo-controlled randomized withdrawal trial of 1370 patients with ADPKD. The inclusion criteria were: CKD with an eGFR between 25 and 65 mL/min/1.73 m² if younger than age 56; or eGFR between 25 and 44 mL/min/1.73 m², plus eGFR decline >2.0 mL/min/1.73 m²/year if between ages 56-65. Subjects were to be treated for 12 months; after completion of treatment, patients entered a 3-week follow-up period to assess renal function. **The primary endpoint was the treatment difference in the change of eGFR from pre-treatment baseline to post-treatment follow-up, annualized by dividing each subject's treatment duration.[3,6]**

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

*Data only included those patients who remained in the study for 3 years; effect in those who discontinued is unknown.[2]
†In years 4 and 5 during the TEMPO 3:4 extension trial, both groups received JYNARQUE and the difference between the groups in TKV was not maintained.
‡Ravine criteria defined as at least 2 unilateral or bilateral kidney cysts in at-risk individuals between 15 and 30 years of age; 2 cysts in each kidney in individuals between 30 and 59 years of age; and at least 4 cysts in each kidney in individuals older than 60 years of age.[7,8]

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

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

Other Drug Interactions:

- **Strong CYP3A Inducers:** Co-administration with strong CYP3A inducers reduces exposure to JYNARQUE. Avoid concomitant use of JYNARQUE with strong CYP3A inducers
- **V_2-Receptor Agonist:** Tolvaptan interferes with the V_2-agonist activity of desmopressin (dDAVP). Avoid concomitant use of JYNARQUE with a V_2-agonist

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

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

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

CKD=chronic kidney disease; CI=confidence interval; eGFR=estimated glomerular filtration rate; REPRISE= Replicating Evidence of Preserved Renal Function: An Investigation of Tolvaptan Safety and Efficacy; TEMPO= Tolvaptan Efficacy and Safety Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes; TKV=total kidney volume.

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

References: 1. Data on file. TOLV-008. Otsuka America Pharmaceutical, Inc.; Rockville, MD. **2.** Torres VE, Chapman AB, Devuyst O, et al; for the TEMPO 3:4 Trial Investigators. *N Engl J Med.* 2012;367(25):2407-2418. **3.** Torres VE, Chapman AB, Devuyst O, et al; for the REPRISE Trial Investigators. *N Engl J Med.* 2017;377(20):1930-1942. **4.** Torres VE, Meijer E, Bae KT, et al. *Am J Kidney Dis*. 2011;57(5):692-699. **5.** Data on file. JYN-012. Otsuka America Pharmaceutical, Inc.; Rockville, MD. **6.** Torres VE, Devuyst O, Chapman AB, et al. *Am J Nephrol*. 2017;45(3):257-266. **7.** Belibi FA, Edelstein CL. *J Am Soc Nephrol*. 2009;20(1):6-8. **8.** Ravine D, Gibson RN, Walker RG, Sheffield LJ, Kincaid-Smith P, Danks DM. *Lancet*. 1994;343(8901):824-827.

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Kidney Venous Flow Data Help to Predict Cardiorenal Events in HF

In patients with heart failure (HF), baseline and follow-up changes in kidney venous flow (KVF) provide information on the risk of cardiorenal events, reports a study in the *Journal of the American Heart Association*.

The observational cohort study included 216 consecutive cardiology inpatients with HF who were referred for nephrology evaluation of diuretic resistance and abnormal kidney function. Sixty percent of patients were men; median age was 76 years. Approximately 69.4% of patients had advanced chronic kidney disease, with an estimated glomerular filtration rate (eGFR) of <45 mL/min/1.73 m^2; 66% were receiving combined diuretic therapy.

Patients underwent Doppler spectral kidney assessments at baseline and 25–35 days later to assess patterns of intrarenal KVF (IKVF) and kidney venous stasis index (KVSI). These values were analyzed for association with risk of cardiorenal events.

At up to 18 months' follow-up, 126 patients died or had worsening HF. Risk of these adverse outcomes was associated with baseline KVSI (hazard ratio [HR], 1.49 per 0.1-unit increase) and baseline IKVF pattern (HR, 2.47 per increase in severity from continuous to pulsatile to biphasic to monophasic).

On analysis of 92 patients, increases in both KVSI and IKVF pattern from the first to second Doppler examination were also associated with risk of worsening HF or death: HR, 3.00 and 6.73, respectively. Results were similar on analysis of individual cardiorenal outcomes, initiation of kidney replacement therapy, and decline in eGFR.

Many patients hospitalized for HF have residual congestion at discharge, which may lead to oliguria and worsening HF. Few studies have evaluated the impact of changes in Doppler-derived KVF in patients with HF.

The new findings suggest that initial and subsequent changes in Doppler-derived KVSI and IKVF are predictors of adverse cardiorenal events in hospitalized patients with HF. The researchers write, "Future studies should aim to assess and validate the prognostic ability of serial KVF assessments in HF management" [Husain-Syed F, et al. Changes in Doppler-derived kidney venous flow and adverse cardiorenal outcomes in patients with heart failure. *J Am Heart Assoc* 2023; 12:e030145. doi: 10.1161/JAHA.123.030145]. ■

JYNARQUE® (tolvaptan) tablets for oral use
Brief summary of PRESCRIBING INFORMATION. See full prescribing information for JYNARQUE.

WARNING: RISK OF SERIOUS LIVER INJURY

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

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

CONTRAINDICATIONS: JYNARQUE is contraindicated in patients:

- With a history, signs or symptoms of significant liver impairment or injury. This contraindication does not apply to uncomplicated polycystic liver disease
- Taking strong CYP 3A inhibitors
- With uncorrected abnormal blood sodium concentrations
- Unable to sense or respond to thirst
- Hypovolemia
- Hypersensitivity (e.g., anaphylaxis, rash) to tolvaptan or any component of the product Uncorrected urinary outflow obstruction
- Anuria

WARNINGS AND PRECAUTIONS

Serious Liver Injury: JYNARQUE can cause serious and potentially fatal liver injury. Acute liver failure requiring liver transplantation has been reported in the post-marketing ADPKD experience. Discontinuation in response to laboratory abnormalities or signs or symptoms of liver injury (such as fatigue, anorexia, nausea, right upper abdominal discomfort, vomiting, fever, rash, pruritus, icterus, dark urine or jaundice) can reduce the risk of severe hepatotoxicity.
To reduce the risk of significant or irreversible liver injury, assess ALT, AST and bilirubin prior to initiation of JYNARQUE, at 2 weeks and 4 weeks after initiation, then monthly for 18 months and every 3 months thereafter. At the onset of signs or symptoms consistent with hepatic injury or if ALT, AST, or bilirubin increase to >2 times ULN, immediately discontinue JYNARQUE, obtain repeat tests as soon as possible (within 48-72 hours), and continue testing as appropriate. If laboratory abnormalities stabilize or resolve, JYNARQUE may be reinitiated with increased frequency of monitoring as long as ALT and AST remain below 3 times ULN.
Do not restart JYNARQUE in patients who experience signs or symptoms consistent with hepatic injury or whose ALT or AST ever exceeds 3 times ULN during treatment with tolvaptan, unless there is another explanation for liver injury and the injury has resolved.
In patients with a stable, low baseline AST or ALT, an increase above 2 times baseline, even if less than 2 times upper limit of normal, may indicate early liver injury. Such elevations may warrant treatment suspension and prompt (48-72 hours) re-evaluation of liver test trends prior to reinitiating therapy with more frequent monitoring.
JYNARQUE REMS Program: JYNARQUE is available only through a restricted distribution program under a Risk Evaluation and Mitigation Strategy (REMS) called the JYNARQUE REMS Program, because of the risks of liver injury.
Notable requirements of the JYNARQUE REMS Program include the following:

- Prescribers must be certified by enrolling in the REMS program.
- Prescribers must inform patients receiving JYNARQUE about the risk of hepatotoxicity associated with its use and how to recognize the signs and symptoms of hepatotoxicity and the appropriate actions to take if it occurs.
- Patients must enroll in the REMS program and comply with ongoing monitoring requirements.
- Pharmacies must be certified by enrolling in the REMS program and must only dispense to patients who are authorized to receive JYNARQUE.

Hypernatremia, Dehydration and Hypovolemia: JYNARQUE increases free water clearance and, as a result, may cause dehydration, hypovolemia and hypernatremia. Therefore, ensure abnormalities in sodium concentrations are corrected prior to initiation of therapy.
Instruct patients to drink water when thirsty, and throughout the day and night if awake. Monitor for weight loss, tachycardia and hypotension because they may signal dehydration.
During JYNARQUE therapy, if serum sodium increases above normal range or the patient becomes hypovolemic or dehydrated and fluid intake cannot be increased, then suspend JYNARQUE until serum sodium, hydration status and volume status is within the normal range.
Co-Administration with Inhibitors of CYP 3A: Concomitant use of JYNARQUE with drugs that are moderate or strong CYP 3A inhibitors (e.g., ketoconazole, itraconazole, lopinavir/ritonavir, indinavir/ritonavir, ritonavir, and conivaptan) increases tolvaptan exposure. Use with strong CYP 3A inhibitors is contraindicated; dose reduction of JYNARQUE is recommended for patients while taking moderate CYP 3A inhibitors

ADVERSE REACTIONS

Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. JYNARQUE has been studied in over 3000 patients with ADPKD. Long-term, placebo-controlled safety information of JYNARQUE in ADPKD is principally derived from two trials where 1,413 subjects received tolvaptan and 1,098 received placebo for at least 12 months across both studies.
TEMPO 3:4 -NCT00428948: A Phase 3, Double-Blind, Placebo-Controlled, Randomized Trial in Early, Rapidly-Progressing ADPKD: The TEMPO3:4 trial employed a two-arm, 2:1 randomization to tolvaptan or placebo, titrated to a maximally-tolerated total daily dose of 60-120 mg. A total of 961 subjects with rapidly progressing ADPKD were randomized to JYNARQUE. Of these, 742 (77%) subjects who were treated with JYNARQUE remained on treatment for at least 3 years. The average daily dose in these subjects was 96 g daily.
Adverse events that led to discontinuation were reported for 15.4% (148/961) of subjects in the JYNARQUE group and 5.0% (24/483) of subjects in the placebo group. Aquaretic effects were the most common reasons for discontinuation of JYNARQUE. These included pollakiuria, polyuria, or nocturia in 63 (6.6%) subjects treated with JYNARQUE compared to 1 subject (0.2%) treated with placebo.
Table 1 lists the adverse reactions that occurred in at least 3% of ADPKD subjects treated with JYNARQUE and at least 1.5% more than on placebo.

Table 1: TEMPO 3:4, Treatment Emergent Adverse Reactions in ≥3% of JYNARQUE Treated Subjects with Risk Difference ≥ 1.5%, Randomized Period

Adverse Reaction	Tolvaptan (N=961)			Placebo (N=483)		
	Number of Subjects	Proportion (%)*	Annualized Rate†	Number of Subjects	Proportion (%)*	Annualized Rate†
Increased urination§	668	69.5	28.6	135	28.0	10.3
Thirst‡	612	63.7	26.2	113	23.4	8.7
Dry mouth	154	16.0	6.6	60	12.4	4.6
Fatigue	131	13.6	5.6	47	9.7	3.6
Diarrhea	128	13.3	5.5	53	11.0	4.1
Dizziness	109	11.3	4.7	42	8.7	3.2
Dyspepsia	76	7.9	3.3	16	3.3	1.2
Decreased appetite	69	7.2	3.0	5	1.0	0.4
Abdominal distension	47	4.9	2.0	16	3.3	1.2
Dry skin	47	4.9	2.0	8	1.7	0.6
Rash	40	4.2	1.7	9	1.9	0.7
Hyperuricemia	37	3.9	1.6	9	1.9	0.7
Palpitations	34	3.5	1.5	6	1.2	0.5

*100x (Number of subjects with an adverse event/N)
†100x (Number of subjects with an adverse event/Total subject years of drug exposure)
‡Thirst includes polydipsia and thirst
§Increased urination includes micturition urgency, nocturia, pollakiuria, polyuria

REPRISE-NCT02160145: A Phase 3, Randomized-Withdrawal, Placebo-Controlled, Double-Blind, Trial in Late Stage 2 to Early Stage 4 ADPKD: The REPRISE trial employed a 5-week single-blind titration and run-in period for JYNARQUE prior to the randomized double-blind period. During the JYNARQUE titration and run-in period, 126 (8.4%) of the 1496 subjects discontinued the study, 52 (3.5%) were due to aquaretic effects and 10 (0.7%) were due to liver test findings. Because of this run-in design, the adverse reaction rates observed during the randomized period are not described.
Liver Injury: In the two double-blind, placebo-controlled trials, ALT elevations >3 times ULN were observed at an increased frequency with JYNARQUE compared with placebo (4.9% [80/1637] versus 1.1% [13/1166], respectively) within the first 18 months after initiating treatment and increases usually resolved within 1 to 4 months after discontinuing the drug.
Postmarketing Experience: The following adverse reactions have been identified during post-approval use of tolvaptan. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency reliably or establish a causal relationship to drug exposure.
Hepatobiliary Disorders: Liver failure requiring transplant
Immune System Disorders: Anaphylaxis

DRUG INTERACTIONS

CYP 3A Inhibitors and Inducers: CYP 3A Inhibitors: Tolvaptan's AUC was 5.4 times as large and Cmax was 3.5 times as large after co-administration of tolvaptan and 200 mg ketoconazole. Larger doses of the strong CYP 3A inhibitor would be expected to produce larger increases in tolvaptan exposure. Concomitant use of tolvaptan with strong CYP 3A inhibitors is contraindicated. Dose reduction of JYNARQUE is recommended for patients while taking moderate CYP 3A inhibitors. Patients should avoid grapefruit juice beverages while taking JYNARQUE. Strong CYP 3A Inducers: Co-administration of JYNARQUE with strong CYP 3A inducers reduces exposure to JYNARQUE. Avoid concomitant use of JYNARQUE with strong CYP 3A inducers.
V_2-Receptor Agonist: As a V_2-receptor antagonist, tolvaptan will interfere with the V_2-agonist activity of desmopressin (dDAVP). Avoid concomitant use of JYNARQUE with a V_2-agonist.

USE IN SPECIFIC POPULATIONS

Pregnancy: Risk Summary: Available data with JYNARQUE use in pregnant women are insufficient to determine if there is a drug associated risk of adverse developmental outcomes. In embryo-fetal development studies, pregnant rats and rabbits received oral tolvaptan during organogenesis. At maternally non-toxic doses, tolvaptan did not cause any developmental toxicity in rats or in rabbits at exposures approximately 4- and 1-times, respectively, the human exposure at the maximum recommended human dose (MRHD) of 90/30 mg. However, effects on embryo-fetal development occurred in both species at maternally toxic doses. In rats, reduced fetal weights and delayed fetal ossification occurred at 17-times the human exposure. In rabbits, increased abortions, embryo-fetal death, fetal microphthalmia, open eyelids, cleft palate, brachymelia and skeletal malformations occurred at approximately 3-times the human exposure. Advise pregnant women of the potential risk to the fetus.
The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage in the U.S. general population is 2-4% and 15-20% of clinically recognized pregnancies, respectively.
Lactation: Risk Summary: There are no data on the presence of tolvaptan in human milk, the effects on the breastfed infant, or the effects on milk production. Tolvaptan is present in rat milk. When a drug is present in animal milk, it is possible that the drug will be present in human milk, but relative levels may vary. Because of the potential for serious adverse reactions, including liver toxicity, electrolyte abnormalities (e.g., hypernatremia), hypotension, and volume depletion in breastfed infants, advise women not to breastfeed during treatment with JYNARQUE.
Pediatric Use: Safety and effectiveness of JYNARQUE in pediatric patients have not been established.
Geriatric Use: Clinical studies of tolvaptan did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.
Use in Patients with Hepatic Impairment: Because of the risk of serious liver injury, use is contraindicated in patients with a history, signs or symptoms of significant liver impairment or injury. This contraindication does not apply to uncomplicated polycystic liver disease which was present in 60% and 66% of patients in TEMPO 3:4 and REPRISE, respectively. No specific exclusion for hepatic impairment was implemented in TEMPO 3:4. However, REPRISE excluded patients with ADPKD who had hepatic impairment or liver function abnormalities other than that expected for ADPKD with typical cystic liver disease.
Use in Patients with Renal Impairment: Efficacy studies included patients with normal and reduced renal function. TEMPO 3:4 required patients to have an estimated creatinine clearance ≥60 mL/min, while REPRISE included patients with $eGFR_{CKD\text{-}EPI}$ 25 to 65 mL/min/1.73m^2.
OVERDOSAGE: Single oral doses up to 480 mg (4 times the maximum recommended daily dose) and multiple doses up to 300 mg once daily for 5 days have been well tolerated in trials in healthy subjects. There is no specific antidote for tolvaptan intoxication. The signs and symptoms of an acute overdose can be anticipated to be those of excessive pharmacologic effect: a rise in serum sodium concentration, polyuria, thirst, and dehydration/hypovolemia.
In patients with suspected JYNARQUE overdosage, assessment of vital signs, electrolyte concentrations, ECG and fluid status is recommended. Continue replacement of water and electrolytes until aquaresis abates. Dialysis may not be effective in removing JYNARQUE because of its high binding affinity for human plasma protein (>98%).

PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (Medication Guide).

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

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BEST-Fluids Supports Balanced Crystalloids for Deceased Donor Transplant

Compared with saline solution, intravenous fluid therapy with a balanced crystalloid solution reduces the incidence of delayed graft function (DGF) after deceased donor kidney transplantation, reports a pragmatic randomized trial in *The Lancet*.

The double-blind Better Evidence for Selecting Transplant Fluids (BEST-Fluids) trial enrolled 808 patients undergoing deceased donor kidney transplantation at 16 hospitals in Australia and New Zealand between 2018 and 2020. The patients were 512 males and 296 females; mean age, 55 years; and four patients younger than 16 years old. Patients were randomly assigned to receive intravenous balanced crystalloid solution (Plasma-Lyte 148) or saline solution during surgery and up to 48 hours afterward. DGF, defined as need for dialysis within 7 days, was the main outcome of interest.

Incidence of DGF was 30% in the group assigned to balanced crystalloid solution compared with 40% in the saline group: adjusted relative risk, 0.74. The advantage of balance crystalloid solution persisted in sensitivity and subgroup analyses. The benefit appeared larger in patients receiving kidneys from donors after circulatory death compared with donors after brain death.

Secondary outcomes were similar between groups, including a ranked composite outcome of duration of DGF and creatinine reduction ratio on day 2. Serious adverse events occurred in three patients in the balanced crystalloid group and five in the saline group.

The choice of intravenous fluid therapy might affect the risk of DGF after deceased donor kidney transplant. Saline solution is the most common type of fluid therapy but may increase DGF risk due to its high sodium content. Previous data comparing balanced crystalloids with saline have shown low certainty of evidence.

The BEST-Fluids results show a reduced risk of DGF in deceased donor kidney recipients assigned to balanced crystalloid solution. Balanced crystalloids prevent approximately one case of DGF for every 10 patients treated, with no increase in serious adverse events or hyperkalemia. The investigators conclude: "Balanced crystalloid solution should be the standard-of-care intravenous fluid used in deceased donor kidney transplantation" [Collins MG, et al. Balanced crystalloid solution versus saline in deceased donor kidney transplantation (BEST-Fluids): A pragmatic, double-blind, randomised, controlled trial. *Lancet* 2023; 402:105–117. doi: 10.1016/S0140-6736(23)00642-6]. ■

KIDNEY WEEK 2023

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Join ASN and approximately 12,000 other kidney professionals from across the globe at ASN Kidney Week 2023 in Philadelphia, PA. The world's premier nephrology meeting, Kidney Week, provides participants with exciting and challenging opportunities to exchange knowledge, learn the latest scientific and medical advances, and listen to engaging and provocative discussions with leading experts in the field.

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ASN
American Society of Nephrology

Thursday, November 2 –
Saturday, November 4
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KIDNEY WEEK 2023

Educational Symposia Schedule

Breakfast or lunch will be served at each symposium.
Seating is limited and available on a first-come, first-served basis to fully paid Annual Meeting participants.

Doors open approximately 15 minutes prior to each symposium.

Continuing Education Credit
These live activities are eligible for continuing education credit. Please visit www.asn-online.org/KidneyWeek for more information.

Thursday, November 2 12:45 p.m. – 1:45 p.m.

Anemia in CKD and ESKD: From Epidemiology and Pathophysiology to Current Treatments
Grand Ballroom Salon I
*Support is provided by an educational grant from **GSK**.*

Real-World Management of Hyperkalemia in Cardiorenal Patients
Grand Ballroom Salon D
*Support is provided by an educational grant from **CSL Vifor**.*

What's New with SGLT2 Inhibitors in 2023
Grand Ballroom Salon A
*Support is provided by an educational grant from **AstraZeneca**.*

Friday, November 3 6:45 a.m. – 7:45 a.m.

Radiofrequency Renal Denervation: The Next Frontier for Difficult-to-Control Hypertension
Grand Ballroom Salon I
*Support is provided by an educational grant from **Medtronic**.*

Regulating the Regulator: Exploring the Therapeutic Landscape for Complement-Mediated Kidney Diseases
Grand Ballroom Salon D
*Support is provided by an educational grant from **Novartis Pharmaceuticals Corporation**.*

Friday, November 3 12:45 p.m. – 1:45 p.m.

Caring for the Patient with AKI in Cirrhosis: New Tools and Opportunities
Grand Ballroom Salon L
*Support is provided by an educational grant from **Mallinckrodt Pharmaceuticals**.*

Hyperkalemia in Diabetes and Heart Failure: Optimizing Management to Mitigate Risk
Grand Ballroom Salon I
*Support is provided by an educational grant from **AstraZeneca**.*

IgA Nephropathy: Proteinuria, Vasoactive Peptides, and the Evolving Treatment Landscape
Grand Ballroom Salon A
*Support is provided by an educational grant from **Travere Therapeutics, Inc**.*

What's Complement Got to Do with It? ANCA Vasculitis and the Complement System
Grand Ballroom Salon D
*This activity is supported by educational funding provided by **Amgen**.**

Saturday, November 4 12:45 p.m. – 1:45 p.m.

Cytokines and IgA Nephropathy: Pathogenesis and Novel Therapies
Grand Ballroom Salon A
*Support is provided by an educational grant from **Otsuka America Pharmaceutical, Inc**.*

Glucagon-Like Peptide-1 Receptor Agonists Are Becoming Important Players in Diabetic Kidney Disease
Grand Ballroom Salon I
*Support is provided by an educational grant from **Novo Nordisk**.*

Principles of Gout Management in Patients with Kidney Diseases
Grand Ballroom Salon L
*Support is provided by an educational grant from **Horizon Therapeutics USA, Inc**.*

**The symposium, "What's Complement Got to Do with It? ANCA Vasculitis and the Complement System," will not be recorded. All other symposia will be recorded and available in the ASN eLearning Center for up to three years starting in late November; continuing education credits will not be awarded for the online content.*

PLENARY SESSION

STATE-OF-THE-ART LECTURE

Opening Plenary to Focus on Bacterial Conversations

Bonnie L. Bassler, PhD

Bonnie L. Bassler, PhD, will deliver a state-of-the-art lecture on how bacteria talk, titled "Tiny Conspiracies: Cell-to-Cell Communication in Bacteria and New Approaches to Antimicrobials," on Thursday, November 2, at the opening plenary.

Dr. Bassler chairs the Department of Molecular Biology at Princeton University and is a Howard Hughes Medical Institute investigator.

Her laboratory's research focuses on the molecular mechanisms that bacteria use for intercellular communication. The researchers aim to understand how bacteria detect and communicate environmental cues and then process this information to respond to it, with the goal of developing new therapies for combating bacteria.

The laboratory studies a phenomenon, called quorum sensing, which is a process that allows bacteria to communicate using secreted chemical signaling molecules known as autoinducers. Quorum sensing enables a population of bacteria to collectively regulate gene expression and, therefore, behavior.

In quorum sensing, bacteria assess their population density by detecting the concentration of a particular autoinducer, which is correlated with cell density. This "census-taking" enables the group to express specific genes only at particular population densities. Quorum sensing is widespread; it occurs in numerous gram-negative and gram-positive bacteria. Quorum sensing can be used to control processes that are unproductive when undertaken by an individual bacterium but effective when undertaken by a group, thus allowing bacteria to function as multicellular organisms. Therapies that disrupt quorum sensing could be used to counter bacterial growth.

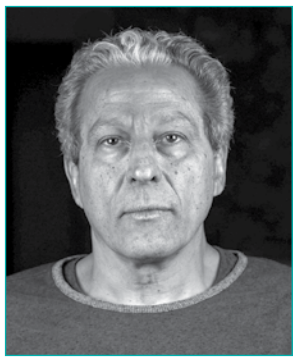
Dr. Bassler teaches both undergraduate and graduate courses at Princeton. She has directed the molecular biology graduate program and chaired the university's Council on Science and Technology. She describes herself as a passionate advocate for diversity in the sciences and is committed to educating the public about science.

Her remarkable contribution of national and international service includes serving as president of the American Society for Microbiology (ASM), chairing the American Academy of Microbiology Board of Governors, and serving as a member of the board that oversees the National Science Foundation.

Among her many awards and honors, Dr. Bassler received a MacArthur Foundation Fellowship, the ASM Eli Lilly Investigator Award for fundamental contributions to microbiological research, the Princeton University President's Award for Distinguished Teaching, the Wiley Prize in Biomedical Science, the National Academy of Sciences Richard Lounsbery Award, the Max Planck-Humboldt Research Award of the Alexander von Humboldt Foundation, and the Dickson Prize in Medicine.

Dr. Bassler received a PhD in biochemistry from the Johns Hopkins University and performed postdoctoral work in genetics at the Agouron Institute. She joined the Princeton faculty in 1994.

Photojournalist and CKD Advocate to Receive President's Medal



Ed Kashi

Renowned photojournalist and filmmaker Ed Kashi will receive the ASN President's Medal during the opening plenary on Thursday, November 2, in recognition of his work that raises awareness about chronic kidney disease from undetermined causes (CKDu).

ASN presents this medal to individuals who have advanced the society's mission to fight against kidney diseases by educating health professionals, sharing new knowledge, advancing research, and advocating for patients.

Kashi became interested in CKDu when he learned that in recent years, young people—primarily agricultural workers from hot, rural, resource-limited parts of the world—have been arriving at clinics with advanced stages of kidney failure. Thousands of people in locations, such as Sri Lanka, Nicaragua, Peru, and India, are dying from CKDu—and its incidence is increasing faster than any disease other than HIV.

He has spent the past 5 years documenting the effects of CKDu around the world. Research implicates climate change as an important contributor to its rise because repeated dehydration, severe heat, and environmental toxins are the likely factors in the rising death toll among sugarcane workers.

"Given the lack of medical attention, CKDnT [CKD of non-traditional origin] is devastating communities, families, and individuals who are caught between precarious work, inactive governments, abusive employers, and inhuman labor practices," Kashi says.

In the short film, *With Every Breath*, Kashi and his colleague Tom Laffay highlight the experience of a young woman living with the disease in Peru who faces pain, fear, and the reality of being dependent on dialysis for the rest of her life.

Another short film, *Hidden Under the Indian Sun*, follows a young student in southeastern India whose dreams of becoming an engineer are threatened by her duty to care for her father who is on dialysis and is unable to work digging wells since being diagnosed with CKDu. Furthermore, *Under Cane* takes viewers to a town in Nicaragua where one-third of the men, mostly those who harvest sugarcane, have end stage kidney disease.

Kashi has covered topics as diverse as the impact of oil in Nigeria, the Protestant community in Northern Ireland, Jewish settlers in the West Bank, an aging society, climate change, and the plight of Syrian refugees. His work has been published and exhibited worldwide and received numerous awards.

A sensitive eye and an intimate and compassionate relationship with his subjects are signatures of his intense and unsparing work. "I take on issues that stir my passions about the state of humanity and our world, and I deeply believe in the power of images to change people's minds," he says.

PLENARY SESSION

Parekh to Be Presented Barbara T. Murphy Trailblazer Award

Rulan S. Parekh, MD, MS, FASN

ASN will present the Barbara T. Murphy Trailblazer Award to Rulan S. Parekh, MD, MS, FASN, on Thursday, November 2. This is just the third presentation of this award, which honors leaders who strengthen the foundation of nephrology while advancing the field through innovation, creativity, inspiration, and tenacity.

Dr. Parekh is vice president of academics at Women's College Hospital, responsible for research, innovation and education; a staff nephrologist at Women's College Hospital and The Hospital for Sick Children; and professor of medicine and pediatrics at the University of Toronto. She is a trailblazer who has often been the first woman—and the first woman of color—in the many leadership roles she has held, and she continues to break barriers in nephrology and beyond.

Dr. Parekh is a clinician-scientist, nephrologist, and international leader in clinical epidemiology and translational research in kidney diseases. She is known for a genetic discovery that accounts for a higher risk of chronic kidney disease among those of African ancestry. Her discoveries revolutionized the understanding of genetic risk factors for kidney diseases when she identified the genetic locus that accounts for 70% of the prevalence of end stage kidney disease among African Americans. Her research is now focused on determining the utility of genetic screening for kidney diseases in sub-Saharan Africa in children and adults.

Dr. Parekh has been an active member of ASN since 1995, serving on the Scientific Organizing Committee and as associate editor of *CJASN*. Additional editorial positions include serving on the boards of the *American Journal of Kidney Diseases*, *Advances in Chronic Kidney Disease*, and *BMC Nephrology*. In addition to supporting ASN's mentoring resource development, she has mentored hundreds of students and post-doctoral trainees and is a steadfast advocate for equity in science and medicine.

She chairs the International Society of Nephrology North America and the Caribbean Regional Board and is a member of the Standing Committee on Science of the Canadian Institutes of Health Research and the medical review panel for the Gairdner Foundation.

Dr. Parekh has received many awards, including the National Kidney Foundation Serving Maryland & Delaware Research Award, the C. Phillips Rance Nephrology Award of Merit, the American Nephrologists of Indian Origin Award for Clinical Excellence, and the ASN Carl W. Gottschalk Research Scholar Grant.

She received her MD from Albany Medical College and her MS in clinical research design and biostatistics from the University of Michigan. She completed an internship and residency in internal medicine and pediatrics, a nephrology fellowship, and a postdoctoral research fellowship at the University of Michigan, as well as a research fellowship at Johns Hopkins University.

CKD Researcher's Eknoyan Lecture to Focus on Correct Hemodialysis Dosing

Laura M. Dember, MD, FASN

The Garabed Eknoyan, MD, Endowed Lectureship will be delivered by a leading chronic kidney disease (CKD) researcher on Thursday, November 2.

Laura M. Dember, MD, FASN, will speak on "Thrice Weekly Hemodialysis and Kt/V_{urea}: Carved in Stone?" The lecture will be presented during a session on "Dosing Hemodialysis: One Size Does Not Fit All."

Dr. Dember is professor of medicine and epidemiology in the Renal Electrolyte and Hypertension Division, a senior scholar at the Center for Clinical Epidemiology & Biostatistics, and director of the Certificate Programs in Clinical Research at the University of Pennsylvania Perelman School of Medicine.

She conducts patient-oriented research in CKD with a particular focus on interventions to improve clinical outcomes for patients treated with maintenance hemodialysis. She has held leadership roles in several multi-center clinical trials and observational studies, including the Dialysis Access Consortium, the Hemodialysis Fistula Maturation Study, the Hemodialysis Novel Therapies Consortium, the Hemodialysis Opioid Prescription Effort (HOPE) Consortium trial, and the Chronic Renal Insufficiency Cohort (CRIC) study, all funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).

As the principal investigator for the National Institutes of Health Time to Reduce Mortality in End-Stage Renal Disease (TiME) trial, Dr. Dember played an important role in introducing large, pragmatic trials embedded in clinical care delivery to the nephrology community, an effort that she is continuing as a co-investigator for the NIDDK, including HiLo: Pragmatic Trial of Higher vs Lower Serum Phosphate Targets in Patients Undergoing Hemodialysis and as an investigator for the Patient-Centered Outcomes Research Institute Comparative Effectiveness of Two Approaches to Symptom Monitoring in Hemodialysis study.

Dr. Dember has mentored numerous nephrology fellows and faculty members during the early stages of their independent research careers. She has served as a deputy editor of the *American Journal of Kidney Diseases* and received the National Kidney Foundation's J. Michael Lazarus Distinguished Award.

She is a graduate of the Yale University School of Medicine. She completed her internal medicine residency training at the University of Pennsylvania and her nephrology fellowship training at the University of Pennsylvania and at Brigham and Women's Hospital in Boston.

Schrier Lectureship Looks at Changes in Treating Diabetic Kidney Disease

Thomas M. Coffman, MD, FASN

Researcher Thomas M. Coffman, MD, FASN, will provide a clinical update on "Novel Therapies: On the Mechanisms of Action" in the Robert W. Schrier, MD, Endowed Lectureship on Thursday, November 2. The lecture will be presented during a session titled "Changing the Landscape of Diabetic Kidney Disease Treatment."

Dr. Coffman is the dean of Duke-National University of Singapore (NUS) Medical School and the James R. Clapp Professor of Medicine at Duke University School of Medicine. Before moving to Singapore, Dr. Coffman held several leadership positions at Duke, including chief of the Division of Nephrology, vice chair of the Department of Medicine, and founding director of the Duke Cardiovascular Research Center. He was also the founding director of the Duke-NUS Cardiovascular and Metabolic Disorders signature research program.

Dr. Coffman's laboratory made seminal contributions to understanding diabetic nephropathy, hypertension, and the renin-angiotensin system. He has been a productive researcher, publishing more than 200 scientific papers. He is currently the lead investigator for DYNAMO (Diabetes Study in Nephropathy and Other Microvascular Complications), a large, collaborative study funded by the National Medical Research Council of Singapore.

Dr. Coffman also serves on the boards of directors of Singapore Health Services (the largest public hospital cluster in Singapore), the Singapore Eye Research Institute, the Singapore National Medical Research Council, and the King Faisal Specialist Hospital & Research Centre in Saudi Arabia.

An international leader in the field of nephrology, Dr. Coffman served ASN in many capacities—including as president—as well as treasurer of the International Society of Nephrology and a member of the nephrology subspecialty board of the American Board of Internal Medicine.

He has held a number of editorial positions, including associate editor of *The Journal of Clinical Investigation*. He currently serves on the editorial board of *Cell Metabolism*.

Among many honors, he received an award for excellence in hypertension research from the American Heart Association and a distinguished faculty award from the Duke Medical Alumni Association.

Dr. Coffman obtained his MD from The Ohio State University College of Medicine. He moved to Duke for his medicine residency and nephrology fellowship, joining the faculty in 1985 to pursue his career as a clinician and researcher.

PLENARY SESSION

STATE-OF-THE-ART LECTURE

Nobel Prize Winner to Describe Mechanisms Underlying Sense of Touch

Ardem Patapoutian, PhD

A winner of the Nobel Prize in Physiology or Medicine will discuss his work in a state-of-the-art lecture, titled "How Do You Feel? The Molecules That Sense Touch," on Friday, November 3.

A molecular biologist and physiologist, Ardem Patapoutian, PhD, is the presidential endowed chair in neurobiology at Scripps Research and an investigator at the Howard Hughes Medical Institute.

Dr. Patapoutian considers the sense of touch unique because it perceives both physical stimuli (temperature and mechanical) and chemical stimuli (compounds that cause pain and itch). In each modality, touch neurons distinguish noxious from innocuous stimuli. The sensitization of touch neurons in response to injury and inflammation is the basis for many clinically relevant chronic pain states. The molecules that mediate detection of touch stimuli had been a long-standing mystery.

In the early 2000s, his laboratory began investigating how pressure is translated into nerve impulses. He noted that some cells gave off a measurable electric signal when they were poked and assumed that the cause was a receptor—an ion channel—on the cell membrane. His laboratory then identified the molecules that sense temperature and pressure involved in touch, pain, and regulating blood pressure.

Dr. Patapoutian's laboratory first identified and characterized ion channels activated by changes in thermal energy, thus functioning as the molecular thermometers of the body. A subset of these same ion channels also acts as polymodal chemosensors, playing an essential role in pain and inflammation.

His laboratory is also investigating ion channels that sense mechanical force, which are postulated to play critical roles in sensing touch and pain, sound, and more. The researchers recently identified mechanically activated cation channels that are expressed in many mechanosensitive cell types.

In addition to the Nobel Prize, Dr. Patapoutian is also a co-recipient of the Kavli Prize in Neuroscience and the BBVA Foundation Frontiers of Knowledge Award (all shared with David Julius, PhD).

A native of Lebanon, Dr. Patapoutian immigrated to the United States in 1986. He received his doctorate in biology from the California Institute of Technology in 1996 and joined the faculty of Scripps Research in 2000.

Brenner Lectureship to Feature Diabetic Kidney Researcher

Catherine Godson, PhD

A researcher whose experience spans the Atlantic Ocean will present the Barry M. Brenner, MD, Endowed Lectureship on the topic, "Toward Solutions! Pro-Resolving Lipid Mediators of Metabolism and Inflammation," on Friday, November 3. The lecture will be presented during a session titled "Bioenergetics of Diabetic Kidneys."

The speaker will be Catherine Godson, PhD, who is full professor of molecular medicine at University College Dublin (UCD) in Ireland, director of the UCD Diabetes Complications Research Centre, and dean for research in the UCD School of Medicine. She previously served the university as vice president for innovation. She is also a visiting professor at the Diabetes Centre of Monash University in Melbourne, Australia.

She leads a group of investigators whose research focuses on innate immunity and chronic complications of diabetes. Their investigations into the molecular mechanisms underlying the initiation, progression, and potential regression of diabetic kidney disease have identified several novel therapeutic targets, susceptibility genes, and potential modulators of disease. The investigators have also made noteworthy progress recently toward understanding inflammatory processes in these contexts.

Among her research contributions is the discovery that lipoxins—a class of endogenously generated lipid mediators—promote the resolution of inflammation. Synthetic mimetics of these molecules are now being developed toward clinical application.

Dr. Godson has served on the Health Research Board of Ireland, the European Medical Research Council, and the Wellcome Trust's Physiological Sciences Committee. She serves as Secretary for Science of the Royal Irish Academy. She is a trustee of Barts Charity, London, and was recently appointed to the board of the Irish Research Council and the Medical Council, Ireland.

She co-chaired the ASN Kidney Week Education Committee in 2022 and served on the European diabetic nephropathy subgroup of the European Association for the Study of Diabetes. She has served on numerous editorial boards, including the *Journal of Biological Chemistry* and *Molecular Pharmacology*.

Dr. Godson has received numerous honors, including the Women in Science award of the International Association of Inflammation Societies, the Robert Graves Lecture and Medal 2021 of the Royal Academy of Medicine in Ireland, and the outstanding achievement award of the International Eicosanoid Research Foundation 2022.

She received her doctorate in pharmacology from UCD, followed by postdoctoral fellowships at the University of Geneva and the University of California San Diego. She joined the faculty of Harvard University before returning to Dublin.

Kidney Stone Researcher to Provide Update in Coburn Lectureship

Elaine M. Worcester, MD, FASN

Elaine M. Worcester, MD, FASN, a longtime researcher into the processes that contribute to kidney stone formation in humans, will deliver the Jack W. Coburn, MD, Endowed Lectureship on Friday, November 3. The topic will be "Stone Prevention in Patients with Bowel Disease." The lecture will be presented during a session titled "Clinical Stone Disease: Tools and Risk Factors."

Dr. Worcester is professor of medicine at The University of Chicago Medicine, where she has worked since 2000. She also serves the university as director of the Chronic Hemodialysis Program, the Kidney Stone Evaluation Laboratory, and the Clinical Research Center Laboratory.

Dr. Worcester is a physician scientist whose research focuses on the causes of idiopathic hypercalciuria, which is a common cause of kidney stones and bone disease, as well as acid-base abnormalities that contribute to stone formation. Her work has also touched on the link between kidney stones and chronic kidney disease and the role of urinary crystallization inhibitors in stone disease. This research has improved the understanding of the role of mineral deposition in the renal papilla in stone formation.

Her exhaustive studies of the renal absorption and excretion of minerals along with descriptions of the clinical characteristics of patients with differing types of kidney stones have helped improve treatment of patients with kidney stones. Her most recent interests have delved into the effects of age and gender on the kidney as it relates to renal acidification and mineral excretion.

Dr. Worcester has been the principal investigator of a National Institutes of Health program that funds multi-disciplinary studies of stone formers at The University of Chicago and at Indiana University.

Her service contributions include serving the National Kidney Foundation of Wisconsin in many capacities, including as president; on the Nephrology Test-Writing Committee of the American Board of Internal Medicine; as president of the Research on Calculus Kinetics Society; and as a member of the enteric hyperoxaluria work group of the Kidney Health Initiative.

She has served as associate editor of *CJASN* and on the editorial board of the *Journal of Nephrology*.

Dr. Worcester received her medical degree from the University of Illinois Chicago and completed her internal medicine residency at Loyola University Medical Center in Maywood, IL, followed by clinical and research fellowships in nephrology at The University of Chicago.

Rose Lecture Will Examine Weight Loss and CKD

Biff F. Palmer, MD, FASN

"Hypobaric Hypoxia and Its Cardiorenal Benefit for Weight Loss" is the title of the Burton D. Rose, MD, Endowed Lectureship, which Biff F. Palmer, MD, FASN, will deliver on Friday, November 3. The lecture will be presented during a session titled "New Insights into Achieving Meaningful Weight Loss in CKD."

A tenured professor of internal medicine at The University of Texas (UT) Southwestern Medical Center, Dr. Palmer has authored more than 300 articles and chapters and served on the nephrology subspecialty board for the American Board of Internal Medicine.

He served as editor for the Southwestern Internal Medicine Conference in *The American Journal of the Medical Sciences*. He is an associate editor of the *American Journal of Nephrology* and is on the editorial boards of *CJASN*, *Clinical Nephrology*, and the *American Journal of Kidney Diseases*.

Dr. Palmer has served ASN in many capacities, including as a member of the Education Committee, Corporate Relations Committee, Pre-Course Program Committee, as well as an abstract reviewer. He has also served on ASN's and the National Kidney Foundation's Program Committees.

Among his numerous honors, he is designated as a distinguished teaching professor by The UT System and has received many teaching awards, including the Regents' Outstanding Teaching Award, the Piper Professorship, and the Parkland Memorial Hospital Internal Medicine Housestaff Outstanding Teacher Award, and he has been elected into The UT Kenneth I. Shine, MD, Academy of Health Science Education.

Dr. Palmer received his MD from The UT Southwestern Medical School, followed by an internship and residency in internal medicine and a research fellowship in nephrology at Walter Reed National Military Medical Center, Bethesda, MD. He returned for a clinical fellowship in nephrology at The UT Southwestern Medical Center and Parkland Memorial Hospital, where he has also served as director of clinical nephrology and program director of the nephrology fellowship program.

Researcher in Pathogenesis of Kidney Diseases to Speak on Genetic Discoveries

Alessia Fornoni, MD, PhD, FASN

A researcher known internationally for her work in chronic kidney disease will speak on "Podocyte Lipid Handling as a Therapeutic Target for Collagenopathy" in the Michelle P. Winn, MD, Endowed Lectureship on Friday, November 3. The lecture will be presented during a session titled "Translation of Genetic Discoveries in Nephrotic Syndrome."

Alessia Fornoni, MD, PhD, FASN, is a tenured professor of medicine as well as molecular and cellular pharmacology at the University of Miami Miller School of Medicine. She is also the chief of the Katz Family Division of Nephrology and Hypertension and director of The Peggy and Harold Katz Family Drug Discovery Center.

Dr. Fornoni gained experience in drug development as global head of discovery in cardiovascular and metabolism at F. Hoffmann-La Roche in Basel, Switzerland. She founded several start-up companies focused on finding a cure for patients affected by chronic kidney disease.

As a physician-scientist whose research program has provided novel and seminal contributions to our understanding of the pathogenesis of kidney diseases, her research is supported by grants from the National Institutes of Health, industry, and private foundations.

Dr. Fornoni's pioneering work on insulin signaling, cholesterol metabolism, and sphingolipid-related pathways uncovered novel pathogenetic mechanisms and therapeutic approaches for glomerular disorders that have been successfully translated into ongoing clinical trials. Her internationally recognized research findings have challenged existing paradigms and have dramatically altered the research direction in these areas. She envisions bringing together industry, investors, and not-for-profit organizations to the table to match science with innovation and patients' motivation to find a cure for kidney diseases.

Dr. Fornoni has served on the editorial boards of *The Journal of Clinical Investigation*, *Diabetes*, *Kidney International*, and *Kidney360* and is associate editor of *Glomerular Diseases*. She has served as guest editor of *Current Diabetes Reviews* and *Frontiers in Endocrinology*.

She has been a visiting professor at more than 50 academic institutions and international meetings worldwide. She serves as a grant reviewer for the National Institutes of Health, the American Diabetes Association, and several other leading organizations. Dr. Fornoni has received many teaching and mentorship awards. She received her MD and PhD in medical pharmacology from the University of Pavia in Italy.

Young Investigator Benjamin S. Freedman Recognized for Work on Regenerative Medicine

Benjamin S. Freedman, PhD

The ASN-American Heart Association Donald W. Seldin Young Investigator Award will be presented to Benjamin S. Freedman, PhD, who will speak on "Human Kidney Organoids for Disease Modeling and Regeneration" on Friday, November 3.

Dr. Freedman is associate professor of medicine at the University of Washington (UW), where he works with the Division of Nephrology, Kidney Research Institute, and Institute for Stem Cell & Regenerative Medicine.

Dr. Freedman's research focuses on how microscopic events in human cells produce macroscopic organs and tissues. As a postdoctoral fellow, Dr. Freedman showed that human pluripotent stem cells from patients with polycystic kidney disease express molecular defects. He developed innovative protocols to change human pluripotent stem cells into kidney organoids, which are microscopic structures that resemble nephrons. Combining this with clustered regularly interspaced short palindromic repeats (CRISPR) gene editing, he established the first kidney organoid models of polycystic kidney disease and glomerulosclerosis.

After joining UW, Dr. Freedman applied kidney organoids to produce new, mechanistic insights into the cellular and molecular basis of kidney disease states and established new, human, phenotypic models of ciliopathies, apolipoprotein L1 kidney disease, and SARS-CoV-2 infection. He automated the mass production of organoids from stem cells using liquid-handling robots—the first time such a feat had been achieved for any organ lineage. He recently merged organoid and organ-on-chip technologies, enabling microfluidic flow and bringing these structures even closer to actual nephrons.

Dr. Freedman has published more than 50 peer-reviewed articles in leading journals and a chapter on gene editing, organoids, and kidney regeneration for *Brenner and Rector's The Kidney*. He was a steering committee member of the Kidney Health Initiative.

Dr. Freedman's patented method to generate kidney organoids has been developed into a commercial kit by STEMCELL Technologies.

Dr. Freedman has received numerous awards, including researcher honoree of the Polycystic Kidney Disease (PKD) Foundation, a career development award from the National Institutes of Health, a young investigator grant from the National Kidney Foundation, and a Carl W. Gottschalk Research Scholar Award from ASN.

He received his PhD in molecular and cell biology from the University of California, Berkeley, followed by a postdoctoral fellowship in the Renal Division at Brigham and Women's Hospital and Harvard Medical School.

John P. Peters Award to Honor Katherine R. Tuttle

Katherine R. Tuttle, MD, FASN

ASN will recognize the wide-ranging contributions of Katherine R. Tuttle, MD, FASN, with the presentation of the John P. Peters Award on Friday, November 3. This award is given for outstanding contributions to improving the lives of patients and furthering the understanding of the kidney in health and diseases.

Dr. Tuttle is executive director for research at Providence Health Care in Spokane, WA; co-principal investigator at the Institute of Translational Health Sciences; and professor of medicine at the University of Washington (UW). She oversees a regional network of 17 clinical research centers and chairs the regional executive council for UW.

Dr. Tuttle's major research interests are in diabetes and chronic kidney disease (CKD). As a clinical and translational scientist, she has published more than 300 original, peer-reviewed articles. Early in her career, she produced a landmark study elucidating physiological principles underlying glomerular hyperfiltration in humans with diabetes. This foundational work led to a number of physiological and pre-clinical studies that laid a foundation for new, therapeutic targets in clinical trials. Over more than three decades, that work helped deliver sodium-glucose cotransporter-2 inhibition as the most impactful therapy to reduce risks of kidney failure, cardiovascular events, and death in individuals with and without diabetes.

Dr. Tuttle has also been a leading investigator for other breakthrough therapies, including incretins and anti-inflammatory agents. She led the original clinical trial that elevated glucagon-like peptide-1 receptor agonists as potential therapeutics for CKD.

She leads the Center for Kidney Disease Research, Education and Hope (CURE-CKD) registry of real-world data for CKD, diabetes, pre-diabetes, and hypertension from nearly 4 million patients of the health system. Her work has shaped the "pillars of therapy" approach to CKD across the spectrum of scientific discovery, clinical trials, and population-level implementation.

Dr. Tuttle currently chairs the ASN Diabetic Kidney Disease Collaborative Task Force. She served on the inaugural board of directors of the Kidney Health Initiative and has chaired numerous other working groups and committees for organizations including the National Institute of Diabetes and Digestive and Kidney Diseases, National Kidney Foundation (NKF), International Society of Nephrology, and American Diabetes Association. She served as associate editor of *CJASN* and the *American Journal of Kidney Diseases*.

She has received many honors including the Medal of Excellence from the American Association of Kidney Patients, Garabed Eknoyan Award from the NKF, YWCA Women of Achievement Award in science, and two outstanding clinical faculty awards from UW.

Dr. Tuttle earned her medical degree and completed her residency in internal medicine at Northwestern University. She was a fellow in metabolism and endocrinology at Washington University in St. Louis and then completed her nephrology fellowship at The University of Texas Health Science Center at San Antonio.

Cele's Champions: Cele Fogarty Travel Support Program for Patients

On behalf of the 850,000,000 people worldwide with kidney diseases, the Cele Fogarty Travel Support Program for Patients ("Cele's Champions") honors people living with kidney diseases or caring for an individual with kidney diseases by supporting their voice and advocacy.

Cecilia "Cele" Agnes Fogarty was a leading executive in event management and member services for decades, advancing the work of several major organizations, including ASN, in health care, medicine, science, and other areas. She was renowned for her ability to manage the most complex meeting logistics, anticipate challenges, and meet unexpected crises—large and small—with aplomb and sometimes magic.

Despite being diagnosed with kidney disease herself, Ms. Fogarty continued to work towards "A world without kidney diseases," including the strenuous onsite meeting management, due to the flexibility of peritoneal dialysis, and the support of her care team. Her dedication and persistence parallel the courage and diligence to live well with a chronic disease.

Patient advocates who speak out for the people worldwide with kidney diseases.

ASN is committed to including the patient voice throughout the organization and in its activities. To honor Ms. Fogarty, her commitment to mentorship, and her passion for accommodating all people regardless of the challenges they may face, ASN is pleased to announce the group of **2023 "Cele's Champions" – patient advocates who speak out for the people worldwide with kidney diseases.**

- Joshua Albright
- Thelma Barber
- John Bayton
- Alexis Conell
- Maribel Costel
- Arnold Davis
- Valen Keefe
- Roberta Reed
- Janet Tennyson
- Dominika Woch

ASN American Society of Nephrology

PLENARY SESSION

STATE-OF-THE-ART LECTURE

Expert to Share Current Efforts to Combat Emerging Diseases

Erica Ollmann Saphire, PhD, MBA

With the COVID-19 pandemic raising questions about what might be next, a virology researcher will present a fresh perspective on approaching, new diseases at a state-of-the-art lecture on Saturday, November 4.

Erica Ollmann Saphire, PhD, MBA, president and chief executive officer of the La Jolla Institute for Immunology, will speak on "Antibodies Against Emerging Infectious Diseases: Global Collaborations."

A structural biologist, virologist, and immunologist, Dr. Saphire's research has examined at the molecular level how and why viruses are pathogenic and provided a roadmap for medical defenses against them. Her team has elucidated the structures of glycoproteins from Ebola, Sudan, Marburg, Bundibugyo, and Lassa viruses; how the viruses mediate entry into cells; how their proteins suppress immune function; and where human antibodies can defeat these viruses.

Her laboratory's research has further revealed how viral matrix proteins hijack host lipids to polymerize virus assembly and proved that certain viral proteins rearrange into different structures at different times for different functions. A recent discovery in her laboratory revealed why neutralizing antibodies had been so difficult to elicit against the Lassa virus and provided the template for a vaccine. Other work in the laboratory has shown how viruses replicate and assemble using a variety of biophysical, biochemical, and immunological methods.

Dr. Saphire leads the Viral Hemorrhagic Fever Immunotherapeutic Consortium, which is supported by the National Institute of Allergy and Infectious Diseases. The consortium has united 44 previously competing academic, industrial, and government laboratories across five continents to understand and provide antibody therapeutics against Ebola, Marburg, Lassa, and other viruses.

She is also leading a consortium supported by the Bill & Melinda Gates Foundation to evaluate antibody therapeutics against SARS-CoV-2 to prevent and treat COVID-19.

Dr. Saphire's work has been recognized by the Presidential Early Career Award for Scientists and Engineers, as well as young investigator awards from the International Conference on Antiviral Research, American Society for Microbiology, and Medical Research Council (MRC) Centre for Virus Research in the United Kingdom. She has received a Fulbright Global Scholar fellowship from the U.S. State Department and a Mercator fellowship from the Deutsche Forschungsgemeinschaft to develop international collaborations using cryoelectron microscopy to further global health.

Dr. Saphire received her doctoral degree from Scripps Research. After postdoctoral work at Scripps Research, she joined the faculty there as an assistant professor in 2003 and became a full professor in 2012. She joined the La Jolla Institute for Immunology in 2019.

Pioneering Researcher Ali G. Gharavi to Receive Smith Award

Ali G. Gharavi, MD

Prominent investigator Ali G. Gharavi, MD, will be presented the Homer W. Smith Award on Saturday, November 4. This award recognizes outstanding contributions to understanding how kidneys function in normal and diseased states.

Dr. Ghaveri will speak on "Nephrology Practice and Therapeutics Through a Genomic Lens."

Dr. Gharavi is the Jay Meltzer Professor of Nephrology and Hypertension and chief of the Division of Nephrology at the Columbia University Irving Medical Center in New York City. He is also director of the Center for Precision Medicine and Genomics and interim director of the Institute for Genomic Medicine at Columbia University.

Dr. Gharavi's research is focused on the molecular genetics of kidney diseases. His work has led to the discovery of genes and loci for glomerulonephritis, hypertension, polycystic liver disease, and congenital defects of the kidney and urinary tract. His research has demonstrated the utility of sequencing in the diagnosis and management of patients with nephropathy. His current focus is on the genetics of immunoglobulin A nephropathy (the most common glomerulonephritis) and the genetics of the kidney and the urinary tract (the most common cause of kidney failure in children). His laboratory is also studying the applications of genomic medicine to clinical care for patients with kidney diseases.

Dr. Gharavi has contributed more than 160 publications on the genetics of kidney diseases, and his studies have clarified basic pathophysiology and influenced clinical practice across multiple areas. Dr. Gharavi is the principal investigator of multiple scientific projects funded by the National Institutes of Health.

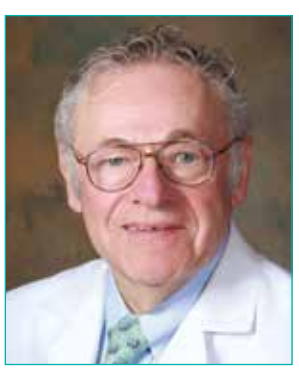
He has served ASN in many capacities, including chairing abstract reviews for genetics, molecular genetics, and basic and experimental immunology; co-chairing several oral communications sessions, a symposium on genetic tools to study renal function, and a conference on genome engineering; and serving on the Program Committee of an annual meeting. He served on the Board of Directors of the Eastern Chapter of the American Society of Hypertension.

Dr. Gharavi has served on the editorial boards of the *American Journal of Physiology—Renal Physiology*, *Kidney International*, and the *Journal of Nephrology*. He is currently associate editor of *JASN*.

Among his many honors, he has received the Judson Daland Prize for Outstanding Achievement in Clinical Investigation from the American Philosophical Society, the National Kidney Foundation Clinical Scientist Award, and the Kidney and Urology Foundation Innovator Award.

After receiving his medical degree from The George Washington University, Dr. Gharavi completed his residency in internal medicine and fellowships in hypertension and nephrology at Mount Sinai Medical Center in New York City. He then completed a postdoctoral fellowship in human genetics at Yale School of Medicine. He joined Columbia University in 2003.

Michael Emmett to Be Given Robert G. Narins Award for Contributions in Education



Michael Emmett, MD

Michael Emmett, MD, will receive the Robert G. Narins Award for his many efforts in the education and training of the next generation of nephrologists on Saturday, November 4.

Dr. Emmett is chair emeritus of the Department of Internal Medicine at Baylor University Medical Center, clinical professor of internal medicine at Texas A&M Health Science Center School of Medicine, adjunct professor at The University of Texas Southwestern Medical School, and attending physician in internal medicine and pathology at Baylor University Medical Center in Dallas. He served as chief of nephrology for 10 years at Baylor.

For more than 40 years, Dr. Emmett's contributions to the teaching of medical students, residents, fellows, and peers in nephrology and internal medicine have been widely recognized. During his tenure at Baylor, he has participated in the training of more than 100 nephrology fellows and received many Best Teacher of the Year awards.

Dr. Emmett has published numerous peer-reviewed articles and textbook chapters. These publications have advanced the knowledge of the pathophysiology of multivalent ion and potassium disorders in renal disease and influenced the clinical approach to the diagnosis and therapy of patients with advanced kidney diseases.

He has served on the editorial boards of *CJASN*, *Clinical Nephrology*, *Kidney International*, and *The American Journal of Cardiology*. He served for many years as a member of the Nephrology Board of the American Board of Internal Medicine.

Since 2010, Dr. Emmett has been an editor of the online textbook UpToDate, focusing on nephrology topics and sections on the pathophysiology, diagnosis, and therapy of fluid, electrolyte, and acid-base disorders.

Dr. Emmett received his medical degree from Temple University (Lewis Katz) School of Medicine, followed by a residency at Yale New Haven Medical Center and a nephrology fellowship at the Hospital of the University of Pennsylvania. He joined the faculty at Baylor in 1976.

ASN to Bestow Belding H. Scribner Award on Philip Li

Philip Kam-Tao Li, MBBS, MD, MRCP

The Belding H. Scribner Award will be tendered on Saturday, November 4, to Philip Kam-Tao Li, MBBS, MD, MRCP, for his career-long contributions to the practice of nephrology. Dr. Li's clinical and basic research efforts have significantly advanced the management of patients with kidney diseases and the science of nephrology.

Dr. Li is a consultant physician in the Department of Medicine and Therapeutics at the Prince of Wales Hospital, Hong Kong, and honorary professor of medicine at The Chinese University of Hong Kong. He is also the director of the university's Carol and Richard Yu Peritoneal Dialysis Research Centre.

Established in 1995, the Belding H. Scribner Award is presented to individuals who have made outstanding contributions to the care of patients with renal disorders or have substantially influenced the clinical practice of nephrology.

A global leader in service to the profession of nephrology, Dr. Li is president of the International Association of Chinese Nephrologists, vice president of the Hong Kong Academy of Medicine, immediate past president of the Hong Kong College of Physicians, president of The Asian Pacific Society of Nephrology (APSN), and president of the International Society for Peritoneal Dialysis.

His past positions include serving as a visiting professor at Harvard Medical School, Brown University, and the University of Virginia in the United States; Nanjing University, Fudan University, and Peking University in China; Nagoya University in Japan; and the Karolinska Institutet in Sweden.

Dr. Li's research interests are in peritoneal dialysis, immunoglobulin A nephropathy, and integrated care of chronic kidney disease. He has published more than 630 original and review journal articles, 5 books, and 22 book chapters. He has given over 260 lectures to international congresses, meetings, and academic institutions.

He has received several international awards, including the International Distinguished Medal of the National Kidney Foundation, the Priscilla Kincaid Smith Award of The APSN, and the Oreopoulos Award of the International Society for Peritoneal Dialysis.

Dr. Li received his MBBS from the University of Hong Kong and received physician training from The Chinese University of Hong Kong. He obtained his MRCP and completed his research fellowship at Hammersmith Hospital, Royal Postgraduate Medical School in London. He served as chief of nephrology at the Prince of Wales Hospital from 2002 to 2020.

Health Disparities Expert to Provide Perspective on Improving Access to Kidney Transplantation

Sumit Mohan, MD, MPH, FASN

A transplant expert and health equity researcher will deliver the Christopher R. Blagg, MD, Endowed Lectureship in Kidney Diseases and Public Policy on the topic "Metrics and the Challenge of Improving Access to Kidney Transplantation" on Saturday, November 4. The lecture will be presented during a special session titled "ETC Home Stretch? The ESKD Treatment Choices Model."

Sumit Mohan, MD, MPH, FASN, is a professor of medicine and epidemiology at Columbia University and the director of the kidney transplant program as well as the Director of Quality and Outcomes Research for the Transplant Initiative at New York-Presbyterian Hospital.

Dr. Mohan's clinical and research career has focused on efforts to lower health disparities, improve outcomes for patients with kidney diseases, boost access to transplantation, and enhance organ utilization. His research has directly informed public policy at the federal level related to patients with kidney diseases, including access to outpatient dialysis for acute kidney injury and elimination of early outcomes as a regulatory measure for transplant center recertification. His work on the inappropriate discard of deceased donor kidneys has helped bring significant attention to this problem nationally including the focus in the White House executive order to lower the discard of deceased donor kidneys. His research has been funded by the National Institutes of Health, the National Science Foundation, and the American Society of Transplantation (AST), among others.

Dr. Mohan serves on multiple committees for ASN, the United Network for Organ Sharing, Scientific Registry of Transplant Recipients, and the National Kidney Foundation (NKF), among others. He has contributed to several technical expert panels for the Centers for Medicare & Medicaid Services and has presented his research to the National Academies of Sciences, Engineering, and Medicine.

He has received the Excellence in Kidney Transplantation Award from the NKF and the Clinical Scientist Award from the AST for his research related to kidney transplantation.

Dr. Mohan received his medical degree from Kasturba Medical College in Manipal, India, and his MPH from the University of Northern Colorado. He completed his internal medicine residency followed by a nephrology and hypertension fellowship at Harlem Hospital Center, an affiliate of Columbia University. He then pursued a renal transplant fellowship at Columbia University Irving Medical Center.

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

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

Patient Advocate with Personal Experience to Speak on Dialysis

Amanda Grandinetti, MPH

A patient who has experienced dialysis and transplant and is also an outcomes researcher will speak on "PROs and PROMs Are What Matter Most to Patients" at the Celeste Castillo Lee Endowed Lectureship on Saturday, November 4. The lecture will be presented during a session titled "Innovation in Dialysis: Better Together."

Amanda Grandinetti, MPH, is a research methodologist and PhD candidate specializing in patient-reported outcomes in drug and device development. With a career dedicated to incorporating the patient perspective and outcomes into all aspects of health care delivery, Ms. Grandinetti is passionate about helping kidney patients access high-quality, affordable care. She describes her commitment to kidney advocacy as not just a hobby but a way of life.

Ms. Grandinetti experienced focal segmental glomerulosclerosis as a child and then kidney failure as a young adult. She underwent hemodialysis before receiving a kidney transplant from a friend in 2013, which was unsuccessful after 3 weeks. She then underwent peritoneal dialysis while pursuing her master's degree. In 2014, she received her second transplant from another friend, and has since maintained kidney function.

Ms. Grandinetti currently serves on the board of directors of the Kidney Health Initiative and previously served as chair and vice chair of the Kidney Health Initiative Patient and Family Partnership Council.

She has extensive experience in both nonprofit and industry settings, collaborating with pharmaceutical companies, such as the former Goldfinch Bio, AstraZeneca, and ProKidney, to integrate patient-reported outcome measures into device and drug development. Ms. Grandinetti has also participated in technical expert panels led by the Centers for Medicare & Medicaid Services and has been a peer reviewer for the U.S. Department of Defense medical research programs.

Her diverse background in evidence-based research and clinical quality provides her with a unique perspective in her kidney advocacy efforts.

She received a BS in psychology and a master's degree in public health from Elmhurst University in Illinois. She is pursuing a doctorate in health sciences from Northern Illinois University with her dissertation focused on patient-reported outcome measures.

Organ Rejection to Be Subject of Murphy Lectureship

Flavio Vincenti, MD

A leader in kidney and pancreas transplantation for almost 50 years, Flavio Vincenti, MD, will provide fresh insights in the Barbara T. Murphy, MD BAO BCh, Endowed Lectureship on Saturday, November 4, in a talk titled "Novel Therapeutic Targets to Control Humoral Responses in Desensitization and ABMR." The lecture will be presented during a session titled "New Look at Antibody-Mediated Rejection."

Dr. Vincenti is professor of clinical medicine at the University of California San Francisco (UCSF).

He has published more than 250 peer-reviewed publications and has been a principal investigator of trials supported by the National Institutes of Health, the Immune Tolerance Network, the UCSF Innovation Ventures Philanthropy Fund (InVent Fund), and industry. His research interests focus on novel biologics, desensitization with novel drugs, and recurrent focal segmental glomerulosclerosis. He has written a series of articles on the complications of transplants and has been a leading investigator on the use of anti-interleukin 2 receptor monoclonal antibodies and costimulation blockade. He is a proponent of minimizing immunosuppressive drugs after transplants.

Dr. Vincenti has been an active member of the American Society of Transplantation (AST), serving as president and on its board of directors and helped establish its Clinical Trials Committee and expanded the collaboration of AST with international transplant societies.

He previously served as associate editor of *CJASN* and the *American Journal of Transplantation* and on the editorial board of *Transplantation* and the *American Journal of Kidney Diseases*.

Dr. Vincenti received a lifetime achievement award from the AST and was honored by the National Kidney Foundation of Northern California for his contributions to transplantation and treatment of kidney failure.

He completed his medical training, internship, and residency at the American University of Beirut Medical Center in Lebanon. He then did a nephrology fellowship at Emory University School of Medicine in Atlanta, GA. He came to UCSF for a transplant nephrology fellowship and has been on the staff of the kidney transplant service at UCSF since 1976.

Basic science and clinical research advance patient care

Submit Applications for Research Funding

Submit your innovative ideas and research plans to the following programs funded by KidneyCure.

Deadline to submit is Wednesday, December 6, 2023 at 2:00 p.m. EST.

- **KidneyCure Pre-Doctoral Fellowship Program** provides support for PhD students to conduct kidney-related research with guidance from a mentor.
- **Ben J. Lipps Research Fellowship Program** provides funding to nephrology fellows for original and meritorious research conducted under the guidance of a sponsor and is fully endowed by contributions provided by Fresenius Medical Care, ASN, the American Renal Patient Care Foundation, Inc., Amgen, Baxter, and the PKD Foundation.
- **Transition to Independence Grants Program** helps young faculty become independent researchers and is supported by contributions provided by ASN, Akebia Therapeutics, Inc., Otsuka and Visterra, and individual donors.
- **William and Sandra Bennett Clinical Scholars Program** provides support for a clinician-educator to conduct a project to advance all facets of nephrology education and teaching.

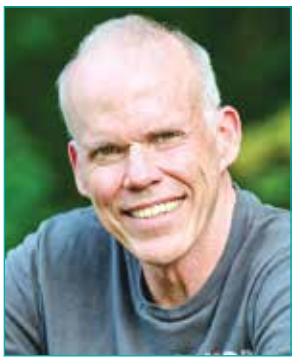
For details and online applications, visit the KidneyCure website, www.kidneycure.org/grants/funding.aspx or scan the QR code.

KidneyCure
Fund it. Find it.

PLENARY SESSION

STATE-OF-THE-ART LECTURE

Climate Activist Will Headline Plenary Session



Bill McKibben

One of the country's foremost climate change activists, Bill McKibben, will deliver a state-of-the-art lecture, titled "Too Hot: Human Bodies and Inhuman Temperatures," on Sunday, November 5.

Mr. McKibben came to prominence with the publication of his groundbreaking 1989 book *The End of Nature*, which is regarded as the first book for a general audience about climate change. He has been at the forefront as an environmental leader ever since.

A contributing writer to *The New Yorker*, his work appears regularly in periodicals from *The New York Times* to *Rolling Stone*, and he has written 20 books. He serves as the Schumann Distinguished Scholar in Environmental Studies at Middlebury College in Vermont.

Mr. McKibben helped found 350.org, the first global, grassroots campaign against climate change, which has organized protests on every continent, including Antarctica. He is also a founder of Third Act, a group aimed at organizing people over the age of 60 to work on climate and racial justice.

He played a leading role in launching the opposition to big oil pipeline projects, such as Keystone XL, and in the fossil fuel divestment campaign, which has become the biggest anti-corporate campaign in history, convincing endowments worth more than $40 trillion to step back from oil, gas, and coal.

He was awarded the Right Livelihood Award, sometimes called the "alternative Nobel," in the Swedish parliament. He has received the Gandhi Peace Prize as well as honorary degrees from 20 colleges and universities. *Foreign Policy* named him to its inaugural list of the world's 100 most important global thinkers.

His latest book is *The Flag, the Cross, and the Station Wagon: A Graying American Looks Back at His Suburban Boyhood and Wonders What the Hell Happened*.

Mr. McKibben lives in the mountains above Lake Champlain, where he and his wife, writer Sue Halpern, spend as much time as possible outdoors. In 2014, biologists recognized his career by naming a new species of woodland gnat—*Megophthalmidia mckibbeni*—in his honor.

ASN Announces Midcareer Award Winners

ASN's Midcareer Awards recognize individuals who have made substantial and significant contributions in a variety of areas early in their professional lives.

Presented on Sunday, November 5, these awards recognize up to three winners in each of five categories: clinical service, education, leadership, mentorship, and research.

Distinguished Clinical Service Award

Michael Heung, MD, MS, FASN

Dr. Heung is professor of medicine, clinical chief of nephrology, and medical director of the acute dialysis program at the University of Michigan in Ann Arbor.

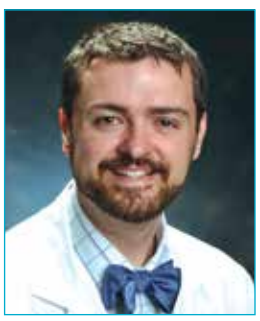
His research and clinical interests have focused on acute kidney injury (AKI) and critical care nephrology. His particular areas of interest include optimizing safety of continuous renal replacement therapy, determining predictors of renal recovery following AKI, exploring novel approaches to detecting fluid overload, and investigating pharmacokinetics in patients who are critically ill with AKI.

As an investigator at the University of Michigan Kidney Epidemiology and Cost Center, Dr. Heung examines AKI measures and outcomes on several federally funded projects, including the U.S. Renal Data System, the Veterans Affairs kidney disease registry, and the Centers for Disease Control and Prevention chronic kidney disease surveillance system.

He currently serves ASN on the AKINow initiative, the COVID-19 Committee, and the Current and Emerging Threats Workgroup. He is associate editor of *Advances in Chronic Kidney Disease*. He has received many teaching and mentorship awards.

Dr. Heung obtained his medical degree from Boston University Chobanian & Avedisian School of Medicine and served as chief resident during his internal medicine residency at the University of Cincinnati. He then completed his nephrology fellowship at the University of Michigan. He also received a master's degree from the University of Michigan School of Public Health.

Eric L. Wallace, MD, FASN



Dr. Wallace is professor of medicine, co-medical director of home dialysis, and medical director of the rare genetic kidney disease programs at The University of Alabama at Birmingham (UAB).

Recognizing the promise of telehealth to deliver services to remote areas, in 2015, he began providing one of the first comprehensive telehealth visits to an older patient on home dialysis in a rural area. The success of this approach led to Dr. Wallace becoming the medical director of telehealth for The UAB health system in 2017.

He has initiated numerous telehealth programs, such as for stroke and critical care, that have significantly improved delivery of care and revenue in rural hospitals in Alabama. He oversaw the transition of care to telehealth during the COVID-19 pandemic, which revealed a 280-fold increase in telehealth across the health system. Dr. Wallace has continued to focus on sustaining telehealth and delivery of care to those with geographic barriers to accessing care.

His research has focused on eliminating geographic and socioeconomic barriers to specialized care, with an emphasis on home dialysis and rare diseases, such as Fabry disease. He is expanding the telemedicine platform he established for his studies on home dialysis to create a network and establish processes to allow physicians at UAB to provide care across the state to patients whose travel is limited by geographic or financial constraints. He hopes these efforts can help address physician workforce distribution issues and access to care across the country.

Dr. Wallace received his MD from The UAB School of Medicine, where he also completed an internal medicine residency and served as chief resident. After completing a clinical fellowship in nephrology at Vanderbilt University, Dr. Wallace joined the faculty at UAB.

PLENARY SESSION

Distinguished Educator Award

Anna M. Burgner, MD, MEHP

Dr. Burgner is assistant professor of medicine and director of the nephrology fellowship program at Vanderbilt University Medical Center.

She has worked diligently over the past 10 years to bring innovation to medical education and transform training in nephrology. She co-directs the Excellence in Teaching program, a 2-year, longitudinal curriculum focused on developing internal medicine residents' skills in medical education. Dr. Burgner is responsible for expanding the program to include all medicine fellowship programs.

She has implemented innovations in Vanderbilt's nephrology fellowship program to include training in performing kidney biopsies and multidisciplinary management of dialysis access complications.

Dr. Burgner has also been involved in several international social media-based nephrology education initiatives. For the past 7 years, she has been on the Executive Committee for NephMadness, a nephrology educational initiative inspired by college basketball's March Madness. She is also on the board of directors of the Nephrology Journal Club, NephJC, a nonprofit organization dedicated to enhancing free open access medical education pertaining to nephrology, hypertension, and transplantation.

She has served on multiple national committees focused on education. She co-chairs the ASN In-Training Examination Committee and is a member of the ASN Workforce and Training Committee. During the COVID-19 pandemic lockdowns, she helped to transition the annual ASN Training Program Directors Retreats to quarterly, virtual town halls by sitting on planning committees, moderating breakout sessions, and giving presentations. She is also on the editorial board of the *American Journal of Kidney Diseases* and associate editor of *Nephrology News & Issues*.

Dr. Burgner received her MD from Indiana University School of Medicine, followed by a residency and nephrology fellowship at Vanderbilt University Medical Center. She also completed a Master of Education in the Health Professions program through Johns Hopkins University.

Distinguished Leader Award

Kenar D. Jhaveri, MD, FASN

Dr. Jhaveri is professor of medicine at the Donald and Barbara Zucker School of Medicine at Hofstra/Northwell and associate chief of the Division of Kidney Diseases and Hypertension at Northwell Health.

As associate division chief, Dr. Jhaveri has been instrumental in developing a glomerular disease center and onco-nephrology and cardio-renal services. He recently launched the trailblazing Galdi fellowship, an advanced fellowship in onco-nephrology and glomerular diseases.

In the early days of the pandemic in New York, he spearheaded fast adaptations in clinical care and led research on COVID-19-related acute kidney injury.

A leading figure in onconephrology and glomerular disease research and treatment, Dr. Jhaveri is a founding member and past president of the newly formed American Society of Onconephrology and a founding member of the International Society of Glomerular Disease. He has published more than 200 articles on these topics as well as other domains in nephrology, including social media and medical education.

He is the editor-in-chief of *Kidney News* and serves on the editorial boards of *CJASN*, *Kidney International*, and the *American Journal of Kidney Diseases*.

Dr. Jhaveri's efforts to bring innovation to education include introducing case-based debates to the ASN Fellows in Training Bowl, a monthly online "GN Chat," and the amusing teaching portal "Detective Nephron," periodically featured in *Kidney News*. He has served on several ASN education committees and teaches creatively via multiple channels, including his "Nephron Power" blog. He has a prominent social media presence with 10,000 followers on the platform X, formerly known as Twitter.

Dr. Jhaveri received his medical degree from the State University of New York (SUNY) Upstate Medical University. He completed his residency at the Yale New Haven Hospital and his nephrology fellowship at the New York-Presbyterian Weill Cornell Medical Center.

Jason Cobb, MD

Dr. Cobb is associate professor of medicine in the Division of Renal Medicine and associate director of the nephrology fellowship program at Emory University School of Medicine.

His research has focused on quality improvement in medical education as well as developing projects to address health disparities, particularly exploring conditions observed at high volumes at Emory University Hospital, such as lupus nephritis, HIV, and calciphylaxis, which disproportionately affect racial and ethnic minority groups.

In his educational efforts for ASN, Dr. Cobb has served on the Diversity, Equity, and Inclusion Committee and the Workforce and Training Committee. He has represented ASN in activities of the National Collaborative for Improving the Clinical Learning Environment and in Equity Matters of the Accreditation Council for Graduate Medical Education. As a principal investigator for an ASN grant for its Kidney Mentoring and Assessment Program for Students (MAPS), he explored outreach to medical students to encourage interest in nephrology.

Dr. Cobb has been active with ASN Kidney Week, organizing, reviewing patient safety abstracts and home dialysis oral presentations, as well as moderating a session on health care equity in kidney diseases.

At Emory University, he serves as a member of the Medical School Performance Evaluation Committee and faculty advisor for Kidney MAPS and the Kidney Disease Screening and Awareness Program.

Dr. Cobb received his medical degree from Emory University School of Medicine, where he completed his internal medicine residency and served as chief fellow during his nephrology fellowship.

Jeffrey Perl, MD, MSc

Dr. Perl is a staff nephrologist at St. Michael's Hospital and associate professor of medicine at the University of Toronto, Canada.

His research, clinical practice, and teaching all focus on home dialysis, including improving access, survival, quality of life, and general clinical outcomes.

Dr. Perl is a primary investigator in the international Peritoneal Dialysis Outcomes and Practice Patterns Study (PDOPPS) and co-principal investigator of the Optimizing the Prevention of Peritoneal Dialysis-Associated Peritonitis in the U.S. (OPPUS) study.

He co-chairs the ASN Home Dialysis Steering Committee and previously chaired the Home Dialysis Subcommittee of the ASN COVID-19 Response Team. He served the International Society of Nephrology as chair of the Young Nephrologists Committee and co-chair of the North America and Caribbean Regional Board. He has been active with the National Kidney Foundation, including serving as chair and course director of clinical meetings.

Dr. Perl is editor-in-chief of *Peritoneal Dialysis International* and recently co-chaired the Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference on Home Dialysis. He has served on the editorial boards of *CJASN*, *Kidney360*, *Kidney Medicine*, and the *American Journal of Kidney Diseases*.

Among many honors, he has received the John Maher Young Investigator Award from the International Society for Peritoneal Dialysis and several teaching awards from the University of Toronto and St. Michael's Hospital.

Dr. Perl received his MD from the University of Toronto and a master's degree in clinical epidemiology from the Harvard T.H. Chan School of Public Health. He completed internal medicine training, a nephrology fellowship, a research fellowship, and a clinical research fellowship at the University of Toronto.

Distinguished Mentor Award

Ann M. O'Hare, MD

Dr. O'Hare is professor of medicine, director of the faculty mentoring program, and an investigator at the Cambia Palliative Care Center of Excellence at the University of Washington (UW). She is also a staff physician at the Veterans Affairs (VA) Puget Sound Health Care System in Seattle, a core investigator and acting associate director at the VA Health Services Research & Development Centers of Innovation, an investigator at the Kidney Research Institute (a collaboration between the UW Department of Medicine and Northwest Kidney Centers), and an affiliate investigator at Kaiser Permanente Northwest Research Institute.

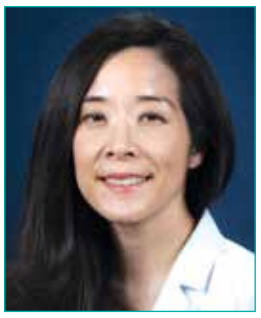
Dr. O'Hare's clinical and research interests focus on the management of chronic kidney disease (CKD) in older individuals, as well as palliative and end-of-life care in older adults with kidney diseases.

She has served ASN as chair of the Geriatric Nephrology Advisory Group and as a member of the Program Committee and the Grants Committee. She has served on the Program Committee of National Kidney Foundation clinical meetings. She has been on Advisory Committees on CKD of the National Institutes of Health and the Centers for Disease Control and Prevention. She was a member of the committee that wrote the VA/Department of Defense Practice Guideline for Management of Chronic Kidney Disease in Primary Care.

Dr. O'Hare is on the editorial boards of *CJASN*, *JASN*, the *American Journal of Kidney Diseases, Advances in Chronic Kidney Disease*, the *Canadian Journal of Kidney Health and Disease*, and *JAMA Internal Medicine* and previously was associate editor of *CJASN*.

She received her medical degree from the University of Virginia, followed by an internal medicine residency at Stanford University Medical Center and a nephrology fellowship at the University of California, San Francisco.

Connie Rhee, MD, MSc



Dr. Rhee is associate professor of medicine and public health and interim chief of the Division of Nephrology, Hypertension, and Kidney Transplantation at the University of California, Irvine School of Medicine. She is also director of clinical and translational research, medical director of dialysis, and vice-chair of research in the Department of Medicine.

Dr. Rhee leads a robust research program of clinical trials and prospective and retrospective observational studies focused on the intersection of kidney diseases, nutrition, and endocrinology and metabolism. Her studies, centered on endo-nephrology and the conservative and preservative management of advanced kidney diseases, have been supported by multiple National Institutes of Health, National Kidney Foundation, American Thyroid Association, and industry grants. She has published more than 200 manuscripts to date.

Dr. Rhee mentors a wide cadre of trainees in the areas of nephrology, nutrition science, endocrinology and metabolism, public health, biostatistics, and related disciplines.

She is incoming editor-in-chief of *CJASN* and currently serves on the editorial board. She serves as associate editor of *BMC Nephrology*, *Cardiorenal Medicine*, and *Seminars in Dialysis* and is also on the editorial boards of the *Journal of Renal Nutrition* and *Kidney International*.

Her contributions to the field have been recognized with several awards, including the National Kidney Foundation and Council on Renal Nutrition Joel D. Kopple Award.

Dr. Rhee completed her medical school training at the Northwestern University Feinberg School of Medicine and her residency and chief residency at the Oregon Health & Science University. She pursued a clinical nephrology fellowship and postdoctoral research training at the Brigham and Women's Hospital/Massachusetts General Hospital. She received a Master of Science in Epidemiology from the Harvard T.H. Chan School of Public Health.

Distinguished Researcher Award

Thomas J. Carroll, PhD

Dr. Carroll is a professor in the Department of Internal Medicine and a member of the Division of Nephrology at The University of Texas (UT) Southwestern Medical Center.

He is internationally recognized for his research in kidney development and polycystic kidney disease. His most widely cited work explores the mechanisms by which members of the Wnt family of glycoproteins regulate the formation of new nephrons in the developing kidney.

He also published a paper describing a signaling mechanism in which stromal epithelial cells regulate kidney progenitor cell differentiation and proliferation through modulation of the Hippo signaling pathway. This work on the signaling mechanisms involved in kidney induction during development has important implications for kidney diseases and possible regenerative strategies.

Dr. Carroll's laboratory has been supported by grants from the National Institutes of Health, and he has been recognized for his mentorship of new investigators and junior faculty members. His early work was recognized by a Carl Gottschalk Career Development Award from ASN and a scientist development grant from the American Heart Association.

He has served ASN on a Kidney Week Organizing Committee and as a session chair and abstract reviewer. He served on the editorial board of the *American Journal of Physiology–Renal Physiology*.

Dr. Carroll earned his doctorate in zoology from The UT at Austin and completed a postdoctoral fellowship at Harvard University. He joined The UT Southwestern faculty in 2004 and was promoted to tenured professor in 2016.

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Dr. de Boer's research focuses on the causes, development, progression, and consequences of diabetic kidney disease. Using methods that span clinical epidemiology, physiology studies, and clinical trials, he has made contributions in the areas of epidemiology of diabetic kidney disease, prevention and treatment of kidney diseases in diabetes, metabolic abnormalities in chronic kidney disease, and the role of impaired mineral metabolism in the pathogenesis of chronic kidney disease and cardiovascular diseases. He has helped define the effects of intensive diabetes therapy on kidney diseases and the key role played by kidney diseases in the cardiovascular complications of diabetes.

Dr. de Boer has published more than 400 manuscripts in the field. He serves as deputy editor of *CJASN* and associate editor of *Contemporary Clinical Trials*.

As a member of the American Diabetes Association (ADA) Professional Practice Committee, he helped write ADA's Standards of Medical Care in Diabetes. He co-chaired the committee that created the Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease.

Dr. de Boer received his medical degree from the Oregon Health & Science University School of Medicine and a master's degree in epidemiology from the UW School of Public Health and Community Medicine. He completed an internal medicine internship and residency at the University of California, San Francisco, and clinical and research fellowships in nephrology at UW.

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C3G, complement 3 glomerulopathy; IgA, immunoglobulin A.

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A New Biomarker for Acute Interstitial Nephritis: A Potential, Important Step Forward

By Krishnakumar Hongalgi, Naoru Koizumi, and Loay Salman

The field of nephrology can benefit from advances in noninvasive diagnostic tools (1). Although the use of careful history, physical examination, and urine microscopy is essential in the evaluation of patients with acute kidney injury (AKI) (2), we often need a kidney biopsy to confirm the diagnosis of entities such as acute interstitial nephritis (AIN). This diagnosis of AIN can often be challenging, with available, noninvasive tests suffering from poor accuracy. To improve the diagnostic dilemma, Moledina et al. (3) provided a potential key step forward in establishing a diagnostic test for AIN. Using aptamer-based urine proteomics, they demonstrated that a urine measurement of chemokine C-X-C motif ligand 9 (CXCL9) can be used to identify patients with AIN. CXCL9 is a chemokine induced mainly by interferon production, resulting in predominantly lymphocyte infiltration to the local tissue (4). Using the discovery and the validation cohorts composed of patients with AKI from AIN and non-AIN, Moledina and colleagues (3) showed that CXCL9 is uniquely elevated in the urine of patients with tubulointerstitial inflammation rather than glomerular involvement, making it a potentially valuable biomarker for AIN (5).

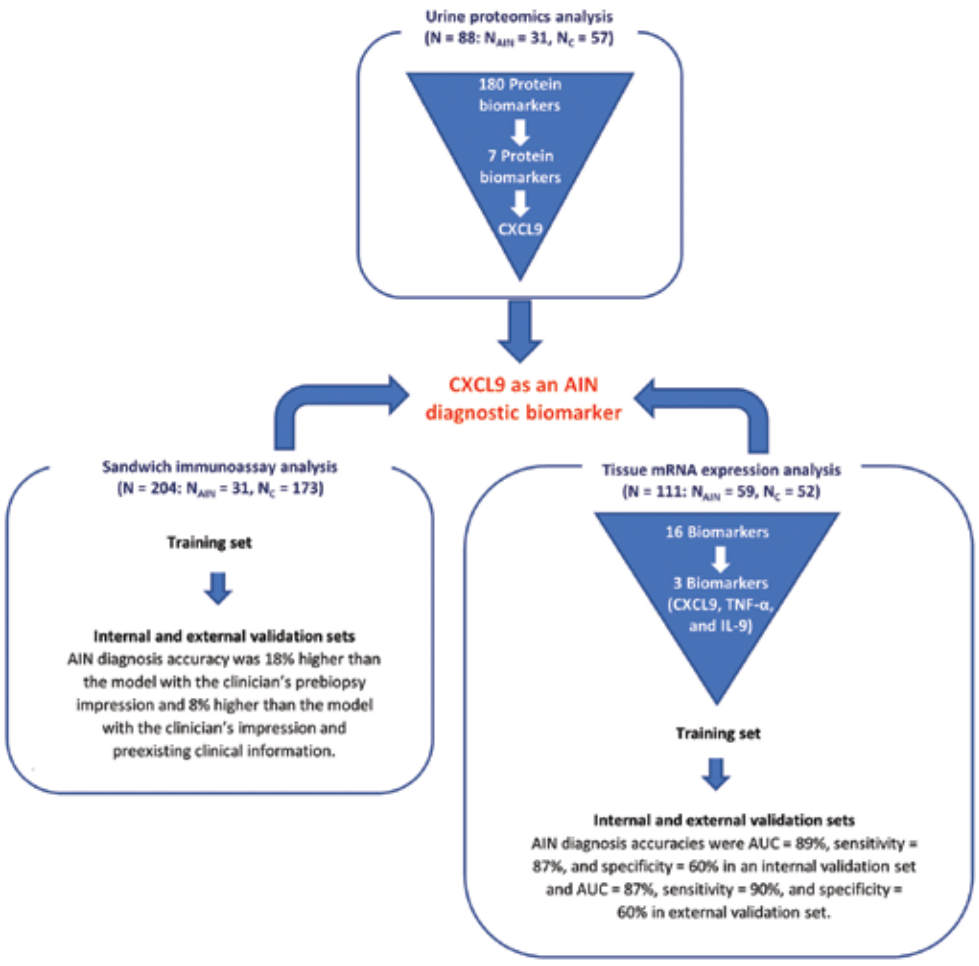
The study offered specific findings regarding CXCL9 (Figure 1). First, urinary CXCL9 offered the best accuracy among 180 candidate proteins identified using an unbiased proteomic analysis of the urine, with levels 7.6 times higher in AIN compared with the control group. Second, 31 out of 204 consecutive biopsies done for AKI were found to have AIN. Urinary CXCL9, as part of a sandwich immunoassay, was discriminatory, with levels eight times higher compared with acute tubular injury and 5.5-fold higher in those who had other causes of AKI. Third, the association of urinary CXCL9 and AIN was tested using a logistic regression model. The highest quartile was not only six times higher in AIN but also affirmed the previously validated diagnostic model for AIN. Fourth, urinary CXCL9 was not only superior to previously identified urinary biomarkers tumor necrosis factor α (TNF-α) and interleukin 9 (IL-9) but when combined, improved the predictability of AIN. Fifth, elevated urinary CXCL9 was associated with increased CXCL9 mRNA expression in kidney biopsy tissue. Sixth, the association between urinary CXCL9 and AIN remained consistent in two external cohorts. The study suggested that a urinary CXCL9:urinary creatinine ratio below 14.2 ng/g could be used to rule out AIN, a urinary CXCL9:urinary creatinine ratio above 58.9 ng/g could be used to rule in AIN, and biopsy could be considered between 14.2 and 58.9 ng/g.

The findings by Moledina et al. (3) could help to facilitate the use of a noninvasive urine test measuring CXCL9. Advantages of this new test would also include avoiding steroids and related side-effects as well as preventing discontinuation of critical medications when AIN is ruled out. If the sensitivity of this test is confirmed by future studies, a kidney biopsy may not be necessary for diagnosis of AIN.

The findings by Moledina et al. could help to facilitate the use of a noninvasive urine test measuring CXCL9.

Studies with a larger sample size are needed now to confirm the diagnostic capacity of CXCL9 in AIN in general and in the setting of various causes of AIN. ■

Figure 1. Findings regarding CXCL9



AUC, area under the curve; NC, number of controls. Based on data from Moledina et al. (3).

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The authors report no conflicts of interest.

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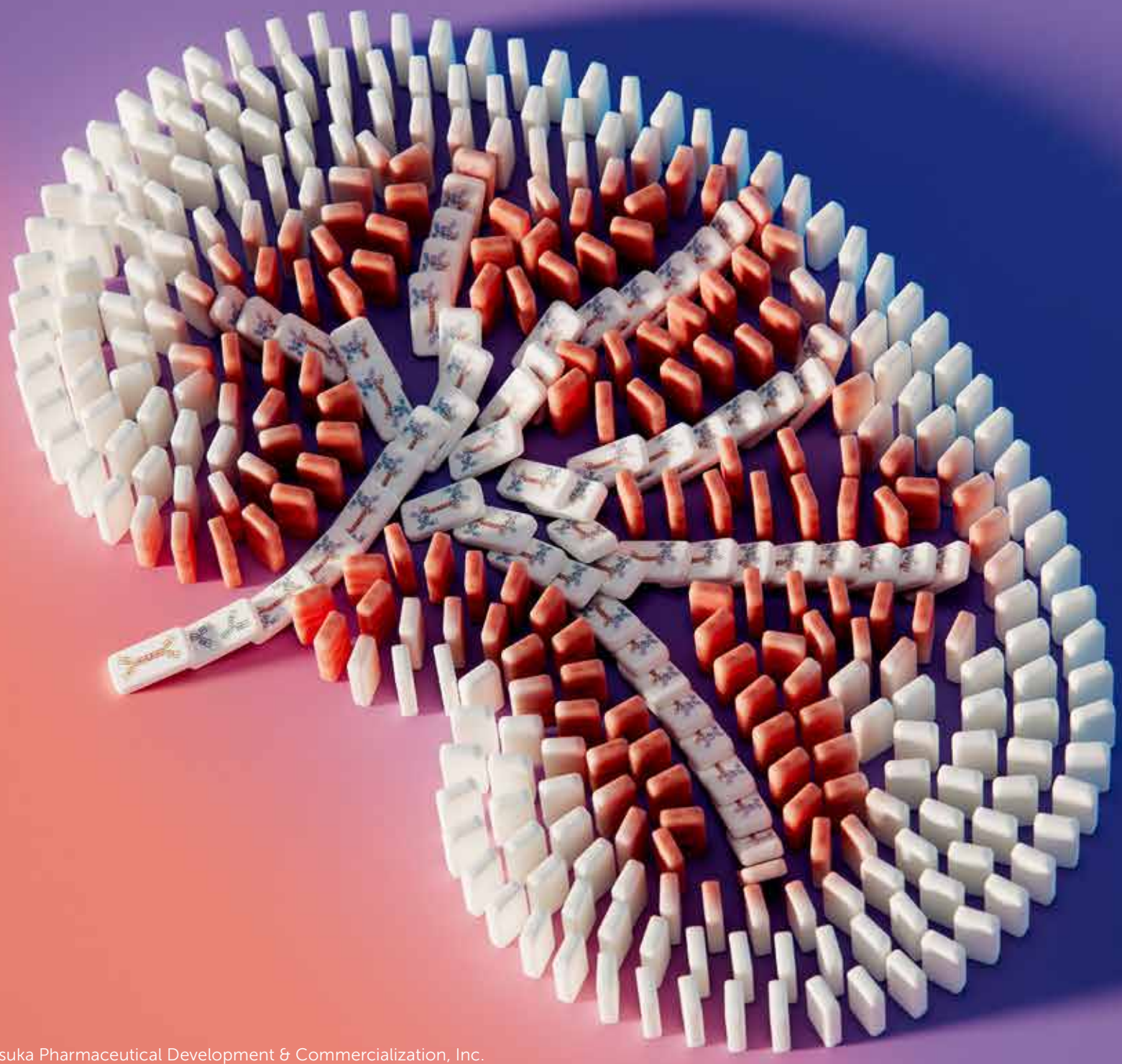

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INDICATIONS AND USAGE

ENVARSUS XR is indicated for the prophylaxis of organ rejection in de novo kidney transplant patients in combination with other immunosuppressants.

ENVARSUS XR is also indicated for the prophylaxis of organ rejection in kidney transplant patients converted from tacrolimus immediate-release formulations in combination with other immunosuppressants.

IMPORTANT SAFETY INFORMATION

WARNING: MALIGNANCIES AND SERIOUS INFECTIONS

Increased risk for developing serious infections and malignancies with ENVARSUS XR or other immunosuppressants that may lead to hospitalization or death

CONTRAINDICATIONS

ENVARSUS XR is contraindicated in patients with known hypersensitivity to tacrolimus.

Please see Brief Summary of full Prescribing Information on next pages.

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ENVARSUS XR® (tacrolimus extended-release tablets), for oral use

Initial U.S. Approval: 1994

BRIEF SUMMARY: See package insert for full prescribing information.

WARNING: MALIGNANCIES AND SERIOUS INFECTIONS

Increased risk for developing serious infections and malignancies with ENVARSUS XR or other immunosuppressants that may lead to hospitalization or death. *[see Warnings and Precautions (5.1, 5.2)].*

1 INDICATIONS AND USAGE

1.1 Prophylaxis of Organ Rejection in De Novo Kidney Transplant Patients

ENVARSUS XR is indicated for the prophylaxis of organ rejection in kidney transplant patients in combination with other immunosuppressants *[see Clinical Studies (14.1)]*.

1.2 Prophylaxis of Organ Rejection in Stable Kidney Transplant Patients Converting from Immediate-Release Formulations

ENVARSUS XR is indicated for the prophylaxis of organ rejection in kidney transplant patients converted from tacrolimus immediate-release formulations, in combination with other immunosuppressants *[see Clinical Studies (14.2)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

- ENVARSUS XR (tacrolimus extended-release tablets) is not interchangeable or substitutable with tacrolimus extended-release capsules, tacrolimus capsules, and tacrolimus for oral suspension. Under or overexposure to tacrolimus may result in graft rejection or other serious adverse reactions *[see Warnings and Precautions (5.3)]*. ENVARSUS XR should not be used without the supervision of a physician with experience in immunosuppressive therapy.
- ENVARSUS XR should be taken on an empty stomach consistently at the same time of the day, preferably in the morning to ensure consistent and maximum possible drug exposure, at least 1 hour before a meal or at least 2 hours after a meal *[see Clinical Pharmacology (12.3)]*.
- Advise patients to swallow ENVARSUS XR tablets whole with fluid (preferably water); patients must not chew, divide, or crush the tablets.
- If a dose is missed, instruct the patient to take it as soon as possible within 15 hours after missing the dose. Beyond the 15-hour time frame, instruct the patient to wait until the usual scheduled time to take the next regular daily dose. Instruct the patient not to double the next dose.
- Patients should avoid eating grapefruit or drinking grapefruit juice or alcoholic beverage while taking ENVARSUS XR *[see Drug Interactions (7.2)]*.

2.2 Dosing in De Novo Kidney Transplant Patients

The recommended starting dose of ENVARSUS XR in de novo kidney transplant patients is 0.14 mg/kg/day. Titrate ENVARSUS XR dosage based on clinical assessments of rejection and tolerability and to achieve whole blood trough concentration ranges (see **Table 1**).

Table 1. Recommended Tacrolimus Whole Blood Trough Concentration Ranges in Kidney Transplant Patients with Antibody Induction

Time Period Post Transplant	Target Tacrolimus Whole Blood Trough Concentration Ranges
During Month 1	6 to 11 ng/mL
> Month 1	4 to 11 ng/mL

2.3 Dosing for Conversion from Tacrolimus Immediate-Release Formulations

To convert from a tacrolimus immediate-release product to ENVARSUS XR, administer ENVARSUS XR once daily at a dose that is 80% of the total daily dose of the tacrolimus immediate-release product. Monitor tacrolimus whole blood trough concentrations and titrate ENVARSUS XR dosage to achieve whole blood trough concentration ranges of 4 to 11 ng/mL.

2.4 Dosing Adjustments in African-American Patients, Patients with Hepatic Impairment, Drug Interactions

African-American patients, compared to Caucasian patients, may need to be titrated to higher ENVARSUS XR dosages to attain comparable trough concentrations *[see Use in Specific Populations (8.8), Clinical Pharmacology (12.3)]*.

Due to reduced clearance and prolonged half-life seen in patients with severe hepatic impairment (Child-Pugh ≥10) these patients may require a lower starting dosage of ENVARSUS XR *[see Clinical Pharmacology (12.3)]*.

Dose adjustments of ENVARSUS XR may be necessary when administered concomitantly with CYP3A inducers or CYP3A inhibitors or cannabidiol *[see Warnings and Precautions (5.9, 5.13), Drug Interactions (7.2, 7.3)]*.

2.5 Therapeutic Drug Monitoring

Measure tacrolimus whole blood trough concentrations at least two times on separate days during the first week after initiation of dosing and after any change in dosage, after a change in co-administration of CYP3A inducers and/or inhibitors or cannabidiol *[see Drug Interactions (7)]*, or after a change in renal or hepatic function. When interpreting measured concentrations, consider that the time to achieve tacrolimus steady state is approximately 7 days after initiating or changing the ENVARSUS XR dose.

Monitor tacrolimus whole blood trough concentrations using a validated assay [e.g., immunoassays or high-performance liquid chromatography with tandem mass spectrometric detection (HPLC/MS/MS)]. The immunosuppressive activity of tacrolimus is mainly due to the parent drug rather than to its metabolites. Immunoassays may react with metabolites as well as the parent drug. Therefore, whole blood tacrolimus trough concentrations obtained with immunoassays may be numerically higher than concentrations obtained with an assay using HPLC/MS/MS. Comparison of the whole blood tacrolimus trough concentrations of patients to those described in the prescribing information and other published literature must be made with knowledge of the assay method(s) employed.

4 CONTRAINDICATIONS

ENVARSUS XR is contraindicated in patients with known hypersensitivity to tacrolimus.

5 WARNINGS AND PRECAUTIONS

5.1 Lymphoma and Other Malignancies

Immunosuppressants, including ENVARSUS XR, increase the risk of developing lymphomas and other malignancies, particularly of the skin. The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent. Examine patients for skin changes and advise to avoid or limit exposure to sunlight and UV light by wearing protective clothing and using a sunscreen with a high protection factor.

Post-transplant lymphoproliferative disorder (PTLD), associated with Epstein-Barr Virus (EBV), has been reported in immunosuppressed organ transplant patients. The risk of PTLD appears greatest in those individuals who are EBV seronegative. Monitor EBV serology during treatment.

5.2 Serious Infections

Immunosuppressants, including ENVARSUS XR, increase the risk of developing bacterial, viral, fungal, and protozoal infections, including opportunistic infections. These infections may lead to serious, including fatal, outcomes. Serious viral infections reported include:

- Polyomavirus-associated nephropathy (especially due to BK virus infection),
- JC virus-associated progressive multifocal leukoencephalopathy (PML), and
- Cytomegalovirus (CMV) infections: CMV seronegative transplant patients who receive an organ from a CMV seropositive donor are at highest risk of CMV viremia and CMV disease.

Monitor for the development of infection and adjust the immunosuppressive regimen to balance the risk of rejection with the risk of infection *[see Adverse Reactions (6.1)]*.

5.3 Not Interchangeable with Other Tacrolimus Products-Medication Errors

Medication errors, including substitution and dispensing errors, between tacrolimus capsules and tacrolimus extended-release capsules were reported outside the U.S. This led to serious adverse reactions, including graft rejection, or other adverse reactions due to under- or over-exposure to tacrolimus. ENVARSUS XR is not interchangeable or substitutable with tacrolimus extended-release capsules, tacrolimus capsules or tacrolimus for oral suspension. Instruct patients and caregivers to recognize the appearance of ENVARSUS XR tablet *[see Dosage Forms and Strengths (3)]* and to confirm with their healthcare provider if a different product is dispensed or if dosing instructions have changed.

5.4 New Onset Diabetes after Transplant

ENVARSUS XR caused new onset diabetes after transplant (NODAT) in kidney transplant patients, which may be reversible in some patients. African-American and Hispanic kidney transplant patients are at an increased risk. Monitor blood glucose concentrations and treat appropriately *[see Adverse Reactions (6.1) and Use in Specific Populations (8.8)]*.

5.5 Nephrotoxicity due to ENVARSUS XR and Drug Interactions

ENVARSUS XR, like other calcineurin-inhibitors, can cause acute or chronic nephrotoxicity. Consider dosage reduction in patients with elevated serum creatinine and tacrolimus whole blood trough concentrations greater than the recommended range.

The risk for nephrotoxicity may increase when ENVARSUS XR is concomitantly administered with CYP3A inhibitors (by increasing tacrolimus whole blood concentrations) or drugs associated with nephrotoxicity (e.g., aminoglycosides, ganciclovir, amphotericin B, cisplatin, nucleotide reverse transcriptase inhibitors, protease inhibitors) *[see Adverse Reactions (6.1, 6.2), Drug Interactions (7.2)]*. Monitor renal function and consider dosage reduction if nephrotoxicity occurs.

5.6 Neurotoxicity

ENVARSUS XR may cause a spectrum of neurotoxicities. The most severe neurotoxicities include posterior reversible encephalopathy syndrome (PRES), delirium, seizure, and coma; others include tremors, paresthesias, headache, mental status changes, and changes in motor and sensory functions *[see Adverse Reactions (6.1, 6.2)]*. As symptoms may be associated with tacrolimus whole blood trough concentrations at or above the recommended range, monitor for neurologic symptoms and consider dosage reduction or discontinuation of ENVARSUS XR if neurotoxicity occurs.

5.7 Hyperkalemia

Mild to severe hyperkalemia, which may require treatment, has been reported with tacrolimus including ENVARSUS XR. Concomitant use of agents associated with hyperkalemia (e.g., potassium-sparing diuretics, ACE inhibitors, angiotensin receptor blockers) may increase the risk for hyperkalemia *[see Adverse Reactions (6.1)]*. Monitor serum potassium levels periodically during treatment.

5.8 Hypertension

Hypertension is a common adverse reaction of ENVARSUS XR therapy and may require antihypertensive therapy *[see Adverse Reactions (6.1)]*. Some antihypertensive drugs can increase the risk for hyperkalemia *[see Warnings and Precautions (5.7)]*. Calcium-channel blocking agents may increase tacrolimus blood concentrations and require dosage reduction of ENVARSUS XR *[see Drug Interactions (7.2)]*.

5.9 Risk of Rejection with Strong CYP3A Inducers and Risk of Serious Adverse Reactions with Strong CYP3A Inhibitors

The concomitant use of strong CYP3A inducers may increase the metabolism of tacrolimus, leading to lower whole blood trough concentrations and greater risk of rejection. In contrast, the concomitant use of strong CYP3A inhibitors may decrease the metabolism of tacrolimus, leading to higher whole blood trough concentrations and greater risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation) *[see Warnings and Precautions (5.6, 5.10)]*. Therefore, adjust ENVARSUS XR dose and monitor tacrolimus whole blood trough concentrations when coadministering ENVARSUS XR with strong CYP3A inhibitors (e.g., including but not limited to telaprevir, boceprevir, ritonavir, ketoconazole, itraconazole, voriconazole, clarithromycin) or strong CYP3A inducers (e.g., including but not limited to rifampin, rifabutin) *[see Dosage and Administration (2.4, 2.5), Drug Interactions (7.2)]*.

5.10 QT Prolongation

ENVARSUS XR may prolong the QT/QTc interval and cause Torsade de Pointes. Avoid ENVARSUS XR in patients with congenital long QT syndrome. Consider obtaining electrocardiograms and monitoring electrolytes (magnesium, potassium, calcium) periodically during treatment in patients with congestive heart failure, bradyarrhythmias, those taking certain antiarrhythmic medications or other products that lead to QT prolongation, and those with electrolyte disturbances (e.g., hypokalemia, hypocalcemia, or hypomagnesemia).

When coadministering ENVARSUS XR with other substrates and/or inhibitors of CYP3A, a reduction in ENVARSUS XR dosage, monitoring of tacrolimus whole blood concentrations, and monitoring for QT prolongation is recommended *[see Dosage and Administration (2.5), Drug Interactions (7.2)]*.

5.11 Immunizations

Whenever possible, administer the complete complement of vaccines before transplantation and treatment with ENVARSUS XR.

Avoid the use of live attenuated vaccines during treatment with ENVARSUS XR (e.g., intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines).

Inactivated vaccines noted to be safe for administration after transplantation may not be sufficiently immunogenic during treatment with ENVARSUS XR.

5.12 Pure Red Cell Aplasia

Cases of pure red cell aplasia (PRCA) have been reported in patients treated with tacrolimus. All of these patients reported risk factors for PRCA such as parvovirus B19 infection, underlying disease, or concomitant medications associated with PRCA. A mechanism for tacrolimus-induced PRCA has not been elucidated. If PRCA is diagnosed, consider discontinuation of ENVARSUS XR.

5.13 Cannabidiol Drug Interactions

When cannabidiol and ENVARSUS XR are co-administered, closely monitor for an increase in tacrolimus blood levels and for adverse reactions suggestive of tacrolimus toxicity. A dose reduction of ENVARSUS XR should be considered as needed when ENVARSUS XR is co-administered with cannabidiol *[see Dosage and Administration (2.4, 2.5), Drug Interactions (7.3)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse drug reactions are discussed in greater detail in other sections of the labeling:

- Lymphoma and Other Malignancies *[see Boxed Warning, Warnings and Precautions (5.1)]*
- Serious Infections *[see Boxed Warning, Warnings and Precautions (5.2)]*
- New Onset Diabetes after Transplant *[see Warnings and Precautions (5.4)*]
- Nephrotoxicity due to ENVARSUS XR and Drug Interactions *[see Warnings and Precautions (5.5)]*
- Neurotoxicity *[see Warnings and Precautions (5.6)]*
- Hyperkalemia *[see Warnings and Precautions (5.7)]*
- Hypertension *[see Warnings and Precautions (5.8)]*
- QT Prolongation *[see Warnings and Precautions (5.10)]*
- Pure Red Cell Aplasia *[see Warnings and Precautions (5.12)]*

6.1 Clinical Studies Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice. In addition, the clinical studies were not designed to establish comparative differences across study arms with regards to the adverse reactions discussed below.

Study 1- Phase 3 Clinical Study in De Novo Kidney Transplant Recipients

Study 1 (NCT 01187953), was a Phase 3 randomized study in de novo kidney transplant patients that were treated with ENVARSUS XR (N=268) or tacrolimus [immediate-release] capsules (N=275) and concomitant immunosuppressants in a double-blind, randomized, multinational study *[see Clinical Studies (14.1)]*. The proportion of patients who discontinued treatment due to adverse reactions was 8.6% and 9.8% in the ENVARSUS XR and tacrolimus capsules treatment groups, respectively, through 12 months of treatment. The most common adverse reactions leading to discontinuation of study drug in the ENVARSUS XR treatment group were esophagitis, polyomavirus-associated nephropathy, graft dysfunction, complications of transplanted kidney, and diabetes mellitus, each resulting in 0.7% discontinuations among ENVARSUS XR treatment patients. In Study 1, de novo kidney transplant patients who received a starting dose of 0.17 mg/kg/day, which is higher than the recommended ENVARSUS XR starting dose of 0.14 mg/kg/day, exceeded the recommended target tacrolimus trough concentrations as high as 57 ng/mL during the first 1 to 2 weeks posttransplant *[see Dosage and Administration (2.2)]*.

Infections

The overall incidence of infections, serious infections, and infections with identified etiology reported in de novo kidney transplant recipients treated with ENVARSUS XR or tacrolimus [immediate-release] capsules in Study 1 are shown in **Table 2**.

Table 2. Percentage of Patients with Infections Through 1 Year Post-Kidney Transplant in Study 1 [a]

	ENVARSUS XR ± steroids, IL-2 receptor antagonist induction therapy, MMF/ MPS or AZA N=268	Tacrolimus [immediate-release] capsules ± steroids, IL-2 receptor antagonist induction therapy, MMF/MPS or AZA N=275
All Infections	70%	65%
Urinary Tract Infections	29%	27%
Respiratory Infections	28%	24%
Bacterial Infections	13%	18%
Cytomegalovirus Infections	11%	9%
Fungal Infections	9%	8%
Gastrointestinal Infections	6%	4%
BK virus [b]	6%	9%
Serious Infections	26%	24%

MMF/MPS- Mycophenolate mofetil/mycophenolate sodium; AZA-azathioprine

[a] Study 1 was not designed to support comparative claims of ENVARSUS XR compared to tacrolimus [immediate-release] capsules for the adverse reactions reported in this table.

[b] BK virus-associated nephropathy (BKVAN) occurred in 1.5% (4/268) and 0.7% (2/275) in the ENVARSUS XR and tacrolimus capsules treatment groups, respectively.

New Onset Diabetes After Transplantation

New onset diabetes after transplantation (NODAT) was defined by the composite occurrence of fasting plasma glucose values ≥126 mg/dL, 2-hour post-prandial plasma glucose of at least 200 mg/dL (in oral glucose tolerance test) on two or more consecutive occasions post-baseline, insulin requirement for ≥31 days, an oral hypoglycemic agent use ≥31 days, or HbA_{1c} ≥6.5% (at least 3 months after randomization) among kidney transplant patients with no medical history of diabetes. The incidence of NODAT for Study 1 through one year post-transplant is summarized in **Table 3** below *[see Warnings and Precautions (5.4)]*.

Table 3. Percentage of Patients with NODAT Through 1 Year Post-Kidney Transplant in Study 1 [a]

	ENVARSUS XR ± steroids, IL-2 receptor antagonist induction therapy, MMF/ MPS or AZA (N=88)	Tacrolimus [immediate-release] capsules ± steroids, IL-2 receptor antagonist induction therapy, MMF/MPS or AZA (N=74)
Composite NODAT [b]	21%	15%
HbA_{1c} ≥6.5%	13%	8%
Fasting Plasma Glucose Values ≥126 mg/dL on 2 consecutive occurrences	8%	11%
Oral hypoglycemic use	7%	5%
Insulin use ≥31 days	1%	4%

MMF/MPS- Mycophenolate mofetil/mycophenolate sodium; AZA-azathioprine

[a] Study 1 was not designed to support comparative claims of ENVARSUS XR compared to tacrolimus [immediate-release] capsules for the adverse reactions reported in this table.

[b] Analyses restricted to patients at risk for NODAT.

Common Adverse Reactions

The incidence of adverse reactions that occurred in ≥10% of ENVARSUS XR-treated patients compared to tacrolimus [immediate-release] capsules through one year of treatment in Study 1 is shown by treatment group in **Table 4**.

Table 4. Adverse Reactions (≥ 10%) in Kidney Transplant Patients Through 1 Year Post-Transplant in Study 1[a]

Adverse Reaction	ENVARSUS XR N=268	Tacrolimus [immediate-release] capsules N=275
Diarrhea	31%	34%
Anemia	26%	29%
Urinary Tract Infection	25%	25%
Hypertension	23%	23%
Tremor	19%	17%
Constipation	18%	25%
Diabetes Mellitus	16%	14%
Peripheral Edema	16%	21%
Hyperkalemia	15%	11%
Headache	15%	10%
Hypophosphatemia	13%	15%
Leukopenia	13%	14%
Nausea	13%	15%
Insomnia	13%	11%
Increased Blood Creatinine	12%	14%
Hypomagnesemia	12%	12%
Hypokalemia	12%	12%
Hyperglycemia	11%	12%

[a] Study 1 was not designed to support comparative claims of ENVARSUS XR compared to tacrolimus [immediate-release] capsules for the adverse reactions reported in this table.

Study 2- Phase 2 Clinical Study in De Novo Kidney Transplant Recipients

Study 2 (NCT00765661) was an open-label Phase 2 study conducted in de novo kidney transplant patients randomized to once daily ENVARSUS XR (N=32) or twice daily tacrolimus [immediate-release] capsules (N=31). The study was conducted in the US and patients received an organ from a deceased or living donor. Pharmacokinetics were evaluated during the first 2 weeks with an additional 50-week treatment and follow-up to evaluate safety and efficacy *[see Clinical Studies (14.1)]*.

The starting dosage was 0.14 mg/kg/day (given once daily) for ENVARSUS XR and 0.2 mg/kg/day (given twice daily) for tacrolimus [immediate-release] capsules. On Day 2 predose, the proportion of patients in the ENVARSUS XR group with tacrolimus trough concentration that were within, above, and below 6 to 11 ng/mL was 53%, 11%, and 37%, respectively. The starting dose of 0.14 mg/kg/day in Study 2 formed the basis of dosing recommendations in de novo kidney transplant patients.

There were no deaths or graft failures in Study 2. Two patients in each arm discontinued due to adverse events. The most common adverse reactions included infections and cardiovascular events, and were generally similar to those reported in Study 1.

Study 3- Phase 3 Clinical Studies in Stable Kidney Transplant Recipients Converted from Tacrolimus Capsules

In Study 3 (NCT00817206) stable kidney transplant patients were treated with ENVARSUS XR (N=162) or tacrolimus [immediate-release] capsules (N=162) and concomitant immunosuppressants in an open-label, randomized, multinational study *[see Clinical Studies (14.2)]*. The proportion of patients who discontinued treatment due to adverse reactions was 7.4% and 1.2% in the ENVARSUS XR and tacrolimus capsules treatment groups, respectively, through 12 months of treatment. The most common adverse reactions leading to discontinuation of study drug in the ENVARSUS XR treatment group was cardiac arrest (2 events).

Infections

The overall incidence of infections, serious infections, and infections with identified etiology reported in stable kidney transplant recipients treated with ENVARSUS XR or tacrolimus capsules are shown in **Table 5**.

Table 5. Percentage of Stable Patients with Infections Through 1 Year Post-Treatment in Study 3 [a]

	ENVARSUS XR ± steroids, MMF/MPS or AZA N=162	Tacrolimus [immediate-release] capsules ± steroids, MMF/MPS or AZA N=162
All Infections	46%	48%
Respiratory Infections	26%	28%
Urinary Tract Infections	10%	14%
Bacterial Infections	7%	5%
Fungal Infections	4%	4%
Gastrointestinal Infections	4%	5%
BK virus [b]	2%	2%

(continued)

Table 5. Percentage of Stable Patients with Infections Through 1 Year Post-Treatment in Study 3 [a]

	ENVARSUS XR ± steroids, MMF/MPS or AZA N=162	Tacrolimus [immediate-release] capsules ± steroids, MMF/MPS or AZA N=162
Cytomegalovirus Infections	2%	1%
Serious Infections	8%	9%

MMF/MPS- Mycophenolate mofetil/mycophenolate sodium; AZA-azathioprine

[a] The stable kidney transplant study was not designed to support comparative claims of ENVARSUS XR compared to tacrolimus capsules for the adverse reactions reported in this table.

[b] BK virus associated nephropathy (BKVAN) occurred in 1.2% (2/162) and 0.6% (1/162) in the ENVARSUS XR and tacrolimus capsules treatment groups, respectively.

New Onset Diabetes After Transplantation

New onset diabetes after transplantation (NODAT) was defined by the composite occurrence of fasting plasma glucose values ≥126 mg/dL, 2-hour postprandial plasma glucose of at least 200 mg/dL (in oral glucose tolerance test) on 2 or more consecutive occasions post-baseline, insulin requirement for ≥31 days, an oral hypoglycemic agent use ≥31 days, or HbA_{1c} ≥6.5% (at least 3 months after randomization) among kidney transplant patients with no medical history of diabetes. The incidence of NODAT for the stable kidney transplant study through one year post-transplant is summarized in **Table 6** below *[see Warnings and Precautions (5.4)]*.

Table 6. Percentage of Stable Patients with NODAT Through 1 Year Post-Treatment in Study 3 [a]

	ENVARSUS XR ± steroids, MMF/MPS or AZA (N=90)	Tacrolimus [immediate-release] capsules ± MMF/MPS or AZA (N=95)
Composite NODAT [b]	10%	11%
HbA_{1C} ≥6.5%	3%	7%
Fasting Plasma Glucose Values ≥126 mg/dL on 2 consecutive occurrences	8%	6%
Oral hypoglycemic use	1%	1%
Insulin use ≥31 days	1%	0%

MMF/MPS- Mycophenolate mofetil/mycophenolate sodium; AZA-azathioprine

[a] The stable kidney transplant study was not designed to support comparative claims of ENVARSUS XR compared to tacrolimus capsules for the adverse reactions reported in this table.

[b] Analyses restricted to patients at risk for NODAT.

Common Adverse Reactions

In Study 3, the most common (≥10%) adverse reactions observed with Envarsus XR were diarrhea (14%), and blood creatinine increased (12%).

6.2 Postmarketing Experience

The following adverse reactions have been reported from marketing experience with tacrolimus in the U.S. and outside the U.S. 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 to drug exposure. The following reactions have been included due to either their seriousness, frequency of reporting or strength of causal connection to ENVARSUS XR:

- Blood and Lymphatic System Disorders: Agranulocytosis, decreased blood fibrinogen, disseminated intravascular coagulation, hemolytic anemia, hemolytic uremic syndrome, leukopenia, febrile neutropenia, pancytopenia, prolonged activated partial thromboplastin time, pure red cell aplasia *[see Warnings and Precautions (5.12)]*, thrombocytopenic purpura, thrombotic thrombocytopenic purpura, thrombotic microangiopathy
- Cardiac Disorders: Atrial fibrillation, atrial flutter, cardiac arrhythmia, cardiac arrest, electrocardiogram T wave abnormal, flushing, myocardial hypertrophy, myocardial infarction, myocardial ischaemia, pericardial effusion, QT prolongation, supraventricular extrasystoles, supraventricular tachycardia, Torsade de Pointes, deep limb venous thrombosis, ventricular fibrillation
- Ear Disorders: Hearing loss including deafness
- Eye Disorders: Blindness, optic neuropathy, photophobia, optic atrophy
- Gastrointestinal Disorders: Abdominal pain, colitis, dysphagia, gastrointestinal perforation, impaired gastric emptying, intestinal obstruction, mouth ulceration, peritonitis, stomach ulcer
- Hepatobiliary Disorders: Bile duct stenosis, cholangitis, cirrhosis, fatty liver, hepatic cytolysis, hepatic failure, hepatic necrosis, hepatic steatosis, jaundice, hemorrhagic pancreatitis, necrotizing pancreatitis, venoocclusive liver disease, hepatitis (acute and chronic)
- Hypersensitivity Reactions: Hypersensitivity, Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria
- Immune System Disorders: Graft versus host disease (acute and chronic)
- Metabolism and Nutrition Disorders: Glycosuria, increased amylase, pancreatitis
- Musculoskeletal and Connective Tissue Disorders: Myalgia, polyarthritis, rhabdomyolysis
- Neoplasms: Lymphoma including EBV-associated lymphoproliferative disorder, PTLD *[see Warnings and Precautions (5.1)]*; leukemia
- Nervous System Disorders: Carpal tunnel syndrome, cerebral infarction, coma, dysarthria, flaccid paralysis, hemiparesis, mental disorder, mutism, nerve compression, posterior reversible encephalopathy syndrome (PRES) *[see Warnings and Precautions (5.6)]*, progressive multifocal leukoencephalopathy (PML) sometimes fatal *[see Warnings and Precautions (5.2)]*, quadriplegia, speech disorder, status epilepticus, syncope
- Renal and Urinary Disorder: Acute renal failure, hemorrhagic cystitis, hemolytic uremic syndrome, micturition disorder
- Respiratory, Thoracic and Mediastinal Disorders: Acute respiratory distress syndrome, interstitial lung disease, lung infiltration, pulmonary embolism, pulmonary hypertension, respiratory distress, respiratory failure
- Skin and Subcutaneous Tissue Disorders: Hyperpigmentation, photosensitivity, pruritus, rash

7 DRUG INTERACTIONS

7.1 Mycophenolic Acid

When ENVARSUS XR is prescribed with a given dose of mycophenolic acid (MPA) product, exposure to MPA is higher with ENVARSUS XR coadministration than with cyclosporine coadministration with MPA, because cyclosporine interrupts the enterohepatic recirculation of MPA while tacrolimus does not. Monitor for MPA associated adverse reactions and reduce the dose of concomitantly administered MPA products as needed.

7.2 Effects of Other Drugs/Substances on ENVARSUS XR

Table 7. Effects of Other Drugs/Substances on ENVARSUS XR[a, d]

Drug/Substance Class or Name	Drug Interaction Effect	Recommendations
Grapefruit or grapefruit juice[b]	May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation) *[see Warnings and Precautions (5.6, 5.9, 5.10)]*	Avoid grapefruit or grapefruit juice
Alcohol	May modify the rate of tacrolimus release	Avoid alcoholic beverages
Strong CYP3A Inducers[c], such as: Antimycobacterials (e.g., rifampin, rifabutin), anticonvulsants (e.g., phenytoin, carbamazepine and phenobarbital), St John's Wort	May decrease tacrolimus whole blood trough concentrations and increase the risk of rejection *[see Warnings and Precautions (5.9)]*	Increase ENVARSUS XR dose and monitor tacrolimus whole blood trough concentrations *[see Dosage and Administration (2.5) and Clinical Pharmacology (12.3)]*
Strong CYP3A Inhibitors[c], such as: Protease inhibitors (e.g., nelfinavir, telaprevir, boceprevir, ritonavir or ritonavir containing products), azole antifungals (e.g., voriconazole, posaconazole, itraconazole, ketoconazole), antibiotics (e.g., clarithromycin, troleandomycin, chloramphenicol), nefazodone, cobicistat	May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation) *[see Warnings and Precautions (5.6, 5.9, 5.10)]*	Reduce ENVARSUS XR dose (for voriconazole and posaconazole, give one-third of the original dose) and adjust dose based on tacrolimus whole blood trough concentrations *[see Dosage and Administration (2.5) and Clinical Pharmacology (12.3)]*
Mild or Moderate CYP3A Inhibitors, such as: antibiotics (e.g., erythromycin), calcium channel blockers (e.g., verapamil, diltiazem, nifedipine, nicardipine), amiodarone, danazol, ethinyl estradiol, cimetidine, lansoprazole and omeprazole, azole antifungals (e.g., clotrimazole, fluconazole, isavuconazole), imatinib, nilotinib, letermovir	May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation) *[see Warnings and Precautions (5.6, 5.9, 5.10)]*	Monitor tacrolimus whole blood trough concentrations and reduce ENVARSUS XR dose if needed *[see Dosage and Administration (2.5) and Clinical Pharmacology (12.3)]*
Other drugs, such as: Magnesium and aluminum hydroxide antacids Metoclopramide	May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation) *[see Warnings and Precautions (5.6 and 5.10)]*	Monitor tacrolimus whole blood trough concentrations and reduce ENVARSUS XR dose if needed *[see Dosage and Administration (2.5) and Clinical Pharmacology (12.3)]*
Mild or Moderate CYP3A Inducers, such as: Methylprednisolone, prednisone	May decrease tacrolimus concentrations	Monitor tacrolimus whole blood trough concentrations and reduce ENVARSUS XR dose if needed *[see Dosage and Administration (2.5)]*

[a] ENVARSUS XR dosage adjustment recommendation based on observed effect of coadministered drug on tacrolimus exposures *[see Clinical Pharmacology (12.3)]*, literature reports of altered tacrolimus exposures, or the other drug's known CYP3A inhibitor/inducer status

[b] High dose or double strength grapefruit juice is a *strong* CYP3A inhibitor; low dose or single strength grapefruit juice is a *moderate* CYP3A inhibitor

[c] Strong CYP3A inhibitor/inducer, based on reported effect on exposures to immediate-release tacrolimus along with supporting *in vitro* CYP3A inhibitor/inducer data, or based on drug-drug interaction studies with midazolam (sensitive CYP3A probe substrate)

[d] A drug interaction study with voriconazole was conducted for ENVARSUS XR *[see Clinical Pharmacology (12.3)]*. No other drug-drug interaction studies were conducted with ENVARSUS XR.

Direct Acting Antiviral (DAA) Therapy

The pharmacokinetics of tacrolimus may be impacted by changes in liver function during DAA therapy, related to clearance of HCV virus. Close monitoring and potential dose adjustment of tacrolimus is warranted to ensure continued efficacy.

7.3 Cannabidiol

The blood levels of tacrolimus may increase upon concomitant use with cannabidiol. When cannabidiol and ENVARSUS XR are co-administered, closely monitor for an increase in tacrolimus blood levels and for adverse reactions suggestive of tacrolimus toxicity. A dose reduction of ENVARSUS XR should be considered as needed when ENVARSUS XR is co-administered with cannabidiol *[see Dosage and Administration (2.5) and Warnings and Precautions (5.13)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy registry that monitors pregnancy outcomes in women exposed to ENVARSUS XR during pregnancy. The Transplantation Pregnancy Registry International (TPRI) is a voluntary pregnancy exposure registry that monitors outcomes of pregnancy in female transplant recipients and those fathered by male transplant recipients exposed to immunosuppressants including tacrolimus. Healthcare providers are encouraged to advise their patients to register by contacting the Transplantation Pregnancy Registry International at 1-877-955-6877 or https://www.transplantpregnancyregistry.org.

Risk Summary

Tacrolimus can cause fetal harm when administered to a pregnant woman. Data from postmarketing surveillance and TPRI suggest that infants exposed to tacrolimus in utero are at a risk of prematurity, birth defects/congenital anomalies, low birth weight, and fetal distress *[see Human Data]*. Advise pregnant women of the potential risk to the fetus.

Administration of oral tacrolimus to pregnant rabbits and rats throughout the period of organogenesis was associated with maternal toxicity/lethality, and an increased incidence of abortion, malformation and embryofetal death at clinically relevant doses (0.7 to 3.7 times the recommended clinical dose [0.14 mg/kg/day], on a mg/m^2

basis). Administration of oral tacrolimus to pregnant rats after organogenesis and throughout lactation produced maternal toxicity, effects on parturition, reduced pup viability and reduced pup weight at clinically relevant doses (1.2 to 3.7 times the recommended clinical dose, on a mg/m² basis). Administration of oral tacrolimus to rats prior to mating, and throughout gestation and lactation produced maternal toxicity/lethality, marked effects on parturition, embryofetal loss, malformations, and reduced pup viability at clinically relevant doses (1.2 to 3.7 times the recommended clinical dose, on a mg/m² basis). Interventricular septal defects, hydronephrosis, craniofacial malformations and skeletal effects were observed in offspring that died *[see Animal Data]*.

The background risk of major birth defects and miscarriage in the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo-Fetal Risk

Risks during pregnancy are increased in organ transplant recipients.

The risk of premature delivery following transplantation is increased. Pre-existing hypertension and diabetes confer additional risk to the pregnancy of an organ transplant recipient. Pre-gestational and gestational diabetes are associated with birth defects/congenital anomalies, hypertension, low birth weight and fetal death.

Cholestasis of pregnancy (COP) was reported in 7% of liver or liver-kidney (LK) transplant recipients, compared with approximately 1% of pregnancies in the general population. However, COP symptoms resolved postpartum and no long-term effects on the offspring were reported.

Maternal Adverse Reactions

ENVARSUS XR may increase hyperglycemia in pregnant women with diabetes (including gestational diabetes). Monitor maternal blood glucose levels regularly *[see Warnings and Precautions (5.4)]*.

ENVARSUS XR may exacerbate hypertension in pregnant women and increase preeclampsia. Monitor and control blood pressure *[see Warnings and Precautions (5.7, 5.8)]*.

Fetal/Neonatal Adverse Reactions

Renal dysfunction, transient neonatal hyperkalemia and low birth weight have been reported at the time of delivery in infants of mothers taking ENVARSUS XR.

Labor or Delivery

There is an increased risk for premature delivery (<37 weeks) following transplantation and maternal exposure to ENVARSUS XR.

Data

Human Data

There are no adequate and well controlled studies on the effects of tacrolimus in human pregnancy.

Safety data from the TPRI and postmarketing surveillance suggest infants exposed to tacrolimus in utero have an increased risk for miscarriage, pre-term delivery (<37 weeks), low birth weight (<2500 g), birth defects/congenital anomalies and fetal distress.

TPRI reported 450 and 241 total pregnancies in kidney and liver transplant recipients exposed to tacrolimus, respectively. The TPRI pregnancy outcomes are summarized in **Table 8**. In the table below, the number of recipients exposed to tacrolimus concomitantly with mycophenolic acid (MPA) products during the preconception and first trimester periods is high (27% and 29% for renal and liver transplant recipients, respectively). Because MPA products may also cause birth defects, the birth defect rate may be confounded and this should be taken into consideration when reviewing the data, particularly for birth defects. Birth defects observed include cardiac malformations, craniofacial malformations, renal/urogenital disorders, skeletal abnormalities, neurological abnormalities and multiple malformations.

Table 8. TPRI Reported Pregnancy Outcomes in Transplant Recipients with Exposure to Tacrolimus

	Kidney	Liver
Pregnancy Outcomes*	**462**	**253**
Miscarriage	24.5%	25%
Live births	**331**	**180**
Pre-term delivery (< 37 weeks)	49%	42%
Low birth weight (< 2500 g)	42%	30%
Birth defects	8%†	5%

*Includes multiple births and terminations.

†Birth defect rate confounded by concomitant MPA products exposure in over half of offspring with birth defects.

Additional information reported by TPRI in pregnant transplant patients receiving tacrolimus included diabetes during pregnancy in 9% of kidney recipients and 13% of liver recipients and hypertension during pregnancy in 53% of kidney recipients and 16.2% of liver recipients.

Animal Data

Administration of oral tacrolimus to pregnant rabbits throughout organogenesis produced maternal toxicity and abortion at 0.32 mg/kg (0.7 times the recommended clinical dose based on body surface area). At 1 mg/kg (2.3 times the recommended clinical dose) embryofetal lethality and fetal malformations (ventricular hypoplasia, interventricular septal defect, bulbous aortic arch, stenosis of ductus arteriosus, omphalocele, gallbladder agenesis, skeletal anomalies) were observed. Administration of 3.2 mg/kg oral tacrolimus (3.7 times the recommended clinical dose) to pregnant rats throughout organogenesis produced maternal toxicity/lethality, embryofetal lethality and decreased fetal body weight in the offspring of C-sectioned dams; and decreased pup viability and interventricular septal defect in offspring of dams that delivered.

In a peri/postnatal development study, oral administration of tacrolimus to pregnant rats during late gestation (after organogenesis) and throughout lactation produced maternal toxicity, effects of parturition, and reduced pup viability at 3.2 mg/kg (3.7 times the recommended clinical dose); among these pups that died early, an increased incidence of kidney hydronephrosis was observed. Reduced pup weight was observed at 1 mg/kg (1.2 times the recommended clinical dose).

Administration of oral tacrolimus to rats prior to mating, and throughout gestation and lactation produced maternal toxicity/lethality, embryofetal loss and reduced pup viability at 3.2 mg/kg (3.7 times the recommended clinical dose). Interventricular septal defects, hydronephrosis, craniofacial malformations and skeletal effects were observed in offspring that died. Effects on parturition (incomplete delivery of nonviable pups) were observed at 1 mg/kg (1.2 times the recommended clinical dose) *[see Nonclinical Toxicology (13.1)]*.

8.2 Lactation

Risk Summary

Controlled lactation studies have not been conducted in humans; however tacrolimus has been reported to be present in human milk. The effects of tacrolimus on the breastfed infant, or on milk production have not been assessed. Tacrolimus is excreted in rat milk and in peri-/postnatal rat studies, exposure to tacrolimus during the postnatal period was associated with developmental toxicity in the offspring at clinically relevant doses *[see Pregnancy (8.1), Nonclinical Toxicology (13.1)]*.

The development and health benefits of breastfeeding should be considered along with the mother's clinical need for ENVARSUS XR and any potential adverse effects on the breastfed child from ENVARSUS XR or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Contraception

ENVARSUS XR can cause fetal harm when administered to pregnant women. Advise female and male patients of reproductive potential to speak with their healthcare provider on family planning options including appropriate contraception prior to starting treatment with ENVARSUS XR *[see Use in Specific Populations (8.1), Nonclinical Toxicology (13.1)]*.

Infertility

Based on findings in animals, male and female fertility may be compromised by treatment with ENVARSUS XR *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

The safety and effectiveness of ENVARSUS XR in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of ENVARSUS XR did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In Studies 1, 2 and 3, there were 37 patients 65 years of age and older, and no patients were over 75 years *[see Clinical Studies (14)]*. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Renal Impairment

The pharmacokinetics of tacrolimus in patients with renal impairment was similar to that in healthy subjects with normal renal function. However, due to its potential for nephrotoxicity, monitoring of renal function in patients with renal impairment is recommended; tacrolimus dosage should be reduced if indicated *[see Warnings and Precautions (5.5) and Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

The mean clearance of tacrolimus was substantially lower in patients with severe hepatic impairment (mean Child-Pugh score: >10) compared to healthy subjects with normal hepatic function *[see Clinical Pharmacology (12.3)]*. With greater tacrolimus whole blood trough concentrations in patients with severe hepatic impairment, there is a greater risk of adverse reactions and dosage reduction is recommended *[see Dosage and Administration (2.4)]*. For patients with moderate hepatic impairment, monitor tacrolimus whole blood trough concentrations. For patients with mild hepatic impairment, no dosage adjustments are needed.

8.8 Race

African-American patients may need to be titrated to higher ENVARSUS XR dosages to attain comparable trough concentrations compared to Caucasian patients. The pharmacokinetics of ENVARSUS XR were evaluated in a study of 46 stable African-American kidney transplant recipients converted from tacrolimus immediate-release to ENVARSUS XR and indicated that an 80% conversion factor is appropriate for African-American patients *[see Dosage and Administration (2.4), Clinical Pharmacology (12.3)]*.

African-American and Hispanic kidney transplant patients are at an increased risk for new onset diabetes after transplant. Monitor blood glucose concentrations and treat appropriately *[see Warnings and Precautions (5.4)]*.

10 OVERDOSAGE

Postmarketing cases of overdose with tacrolimus have been reported. Overdosage adverse reactions included:

- nervous system disorders (tremor, headache, confusional state, balance disorders, encephalopathy, lethargy and somnolence)
- gastrointestinal disturbances (nausea, vomiting, and diarrhea)
- abnormal renal function (increased blood urea nitrogen and elevated serum creatinine)
- urticaria
- hypertension
- peripheral edema, and
- infections (one fatal postmarketing case of bilateral pneumopathy and CMV infection was attributed to tacrolimus extended-release capsules overdose).

Based on the poor aqueous solubility and extensive erythrocyte and plasma protein binding, it is anticipated that tacrolimus is not dialyzable to any significant extent; there is no experience with charcoal hemoperfusion. The oral use of activated charcoal has been reported in treating acute overdoses, but experience has not been sufficient to warrant recommending its use. General supportive measures and treatment of specific symptoms should be followed in all cases of overdosage.

The risk information provided here is not comprehensive. To learn more, see full prescribing information at www.envarsusxr.com/pi

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TĀCcare Intervention Reduces Dialysis-Related Symptoms

A technology-assisted, stepped, collaborative care intervention called TĀCcare provides a clinically meaningful reduction in debilitating symptoms for patients undergoing hemodialysis, according to a clinical trial report in *JAMA Internal Medicine*.

The TĀCcare randomized trial included 160 patients with end stage kidney disease (ESKD) on long-term hemodialysis with at least moderate levels of fatigue, pain, and/or depression. The patients were 88 men and 72 women, mean age 58 years, enrolled at two sites in New Mexico and Pennsylvania. Race and ethnicity included 52% White patients, 28% Black, 18% Hispanic, and 13% American Indian.

TĀCcare focused on individualized treatment targeting any or all of the three symptoms of interest, following a stepped approach to treatment intensification with shared decision-making. The intervention included 12 weekly sessions of cognitive behavioral therapy (CBT), delivered via telemedicine at home or in a hemodialysis center. Pharmacotherapy for pain and/or depression was added if clinically indicated or preferred by the patient, with dose escalation based on evidence-based protocols.

Patients assigned to the attention control group received six telehealth sessions of health education. Co-primary outcomes of changes in fatigue, average pain severity, and depression were evaluated at 3 months, with follow-up to 12 months.

At 3 months, the TĀCcare group had "statistically and clinically significant reductions" in fatigue, mean difference (MD) was 2.81 on the Functional Assessment of Chronic Illness Therapy–Fatigue scale, and pain severity of MD was −0.96 on the Brief Pain Inventory. There was also a "statistically significant but small" improvement in depression: MD, −1.73 on the Beck Depression Inventory II.

Improvements in fatigue and pain were sustained at 6 months: MD, 3.73 and −1.49, respectively. Adverse events were rare and similar between groups. Most patients in the TĀCcare group preferred CBT over pharmacotherapy; adherence to CBT was high.

Patients experiencing long-term hemodialysis had a high burden of symptoms, which are commonly underrecognized and undertreated. The TĀCcare intervention was designed to provide a flexible approach to addressing these gaps in symptom management.

The new trial shows significant and lasting reductions in fatigue and pain symptoms for patients on hemodialysis assigned to TĀCcare. The researchers write, "Leveraging telemedicine to deliver CBT that targets symptom clusters... may provide a scalable and resource-efficient approach to improve patient-centered outcomes among patients with ESKD who are undergoing long-term hemodialysis" [Jhamb M, et al. Effects of technology assisted stepped collaborative care intervention to improve symptoms in patients undergoing hemodialysis: The TĀCcare randomized clinical trial. *JAMA Intern Med* 2023; 183:795–805. doi: 10.1001/jamainternmed.2023.2215].

Intradialytic Exercise Improves Physical Functioning

For patients with kidney failure on dialysis, supervised exercise training during dialysis sessions leads to improvements on key functional tests, according to a clinical trial report in *NEJM Evidence*.

The randomized Dialysis Training Therapy (DiaTT) trial enrolled 1211 patients with chronic kidney failure undergoing hemodialysis at 21 German centers. The mean age was 66 years, and approximately 60% of patients were men. Patients at intervention centers received intradialytic exercise for 60 minutes during three weekly dialysis sessions. This included 30 minutes of endurance exercise using a bed-cycle ergometer and 30 minutes of resistance exercise using elastic bands, exercise bells, and dumbbells.

Patients at control centers received routine dialysis care. Performance on the 60-second sit-to-stand test (STS60) was assessed after 12 months, along with other exercise performance measures. Data analysis included 917 patients.

Performance on the STS60 improved from 16.2 to 19.2 repetitions in the exercise group compared with a decline from 16.2 to 14.7 repetitions in controls. The exercise group also had improvements of −1.1 seconds on the timed up-and-go test and 37.5 minutes on the 6-minute walk test.

The exercise intervention was associated with improvements in the physical summary score and vitality subscale of the 36-item Short Form Health Survey, with no change in other subscales. The exercise group also had fewer annual hospital days: median 2 versus 5 days. Adverse events were similar between groups, including events during dialysis sessions.

The DiaTT trial supports the benefits of supervised, intradialytic exercise sessions in a real-world hemodialysis setting, with significant improvements in physical functioning measures. The study included the development and implementation of a home-based exercise program in response to disruptions caused by the COVID-19 pandemic [Anding-Rost K, et al. Exercise during hemodialysis in patients with chronic kidney failure. *NEJM Evid* 2023; 2:1–11. https://evidence.nejm.org/doi/pdf/10.1056/EVIDoa2300057].

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- Complimentary Refreshment Breaks
- Exhibitor Spotlights
- Fellows-in-Training (FIT) Bowl
- Headshot Lounge
- 3,000+ Posters with Moderated Poster Sessions
- Welcome Reception
- Wi-Fi Service

Welcome Reception

Thursday, November 2, 6:00 p.m. – 7:00 p.m.

ASN welcomes you to Philadelphia with a reception in the exhibit hall.

Support provided by Calliditas Therapeutics.

ASN Communities Lounge – Booth 1131

A focal point of your exhibit hall experience, visit the lounge to learn more about ASN Communities, meet kidney leaders, network with peers, and unwind at the relaxation zone.

FIT Bowl

Which nephrology training team will reign supreme? Stop by and watch teams test their knowledge against their peers. The FIT Bowl is a two-day, single elimination tournament held in the ASN Futures Theater in the exhibit hall. *Seating is limited.*

Thursday, November 2	**10:30 a.m. – 12:30 p.m.**	**Elimination Rounds**
Friday, November 3	**10:30 a.m. – 11:30 a.m.**	**Semi-Finals**
	11:30 a.m. – 12:30 p.m.	**Finals**

Supported provided by Calliditas Therapeutics.

Headshot Lounge

Stop by booth 505 on Friday, November 3 from 9:30 a.m. – 2:30 p.m. for a complimentary professional headshot.

Exhibitor Spotlight Schedule

Join your colleagues for the latest advances in nephrology practices, products, services, and technologies presented in two theaters on the exhibit hall floor (no continuing education credit). Seating is limited and available on a first-come, first-served basis.

All presentations include breakfast or lunch.

Thursday, November 2

10:00 a.m. – 10:45 a.m. **Theater 1**

The Dual Dilemma: Navigating Cardiorenal Risk in CKD Associated with T2D

Presented by Bayer

11:00 a.m. – 11:45 a.m. **Theater 2**

IgA Nephropathy: Where We Are Now and Where We Are Going

Presented by Chinook Therapeutics, A Novartis Company

12:00 p.m. – 12:45 p.m. **Theater 1**

Replacing RASi in IgA Nephropathy: Unique Therapy Targets Two Pathways, with a Patient's Perspective

Presented by Travere Therapeutics

1:00 p.m. – 1:45 p.m. **Theater 2**

Terlipressin and Albumin Use in Hepatorenal Syndrome

Presented by Mallinckrodt Pharmaceuticals

Friday, November 3

10:00 a.m. – 10:45 a.m. **Theater 1**

Guideline Considerations for Early Treatment in Lupus Nephritis & Updates on Anemia of CKD

Presented by GSK

11:00 a.m. – 11:45 a.m. **Theater 2**

A New Paradigm: Rethinking Hyperphosphatemia Management

Presented by ardelyx

Friday, November 3

12:00 p.m. – 12:45 p.m. **Theater 1**

Overcoming the Challenges of Phosphate Management with a High-Potency Approach

Presented by Fresenius Medical Care Renal Pharmaceuticals

1:00 p.m. – 1:45 p.m. **Theater 2**

Early Identification and Management in ADPKD Featuring Dialogue with a Patient Ambassador

Presented by Otsuka America Pharmaceutical, Inc.

Saturday, November 4

10:00 a.m. – 10:45 a.m. **Theater 1**

Understanding the Complexity of Patients With CKD: Implications for Management

Presented by AstraZeneca

11:00 a.m. – 11:45 a.m. **Theater 2**

A Closer Look at Kidney Preservation in Lupus Nephritis

Presented by Aurinia

12:00 p.m. – 12:45 p.m. **Theater 1**

Jardiance® (empagliflozin) tablets: A Peer Review of the Latest Clinical Data and Dosing Recommendations

Presented by Boehringer Ingelheim | Lilly

1:00 p.m. – 1:45 p.m. **Theater 2**

Genetics in Nephrology: What Are We Missing?

Presented by natera

An Overview of ASN's Excellence in Patient Care

By Alan Kliger (chair of the Excellence in Patient Care Advisory Committee) and Susie Stark (vice president) and Shane Perry (project specialist) on behalf of the Excellence in Patient Care

Excellence in Patient Care (EPC) focuses on ASN's clinical priorities to provide high-quality care for people with kidney diseases. Through all of its projects, EPC embraces three aims:

1. To ensure all people with kidney diseases receive the best evidence-based care possible
2. To champion patient experiences, preferences, and values by actively engaging people with kidney diseases in EPC activities
3. To advance equitable access to high-quality kidney care by promoting diversity, equity, and inclusion and pursuing health care justice

Since its inception in 2016, EPC has sought to educate, train, and promote best practices in quality care for people with kidney diseases, with the focus on clinical nephrology. The timeline (Figure 1) displays the evolution of work from the beginning of EPC in 2016 through 2023, along with the partnership groups supporting these activities.

Over time, these efforts have broadened to include implementation of new therapies, exploration of ways to improve the delivery of dialysis, and collaboration with other organizations and agencies to improve kidney health. Early intervention and care coordination are pillars of these many initiatives. As illustrated in the organization chart (Figure 2), EPC and its initiatives operate across a spectrum of clinical care and quality improvement.

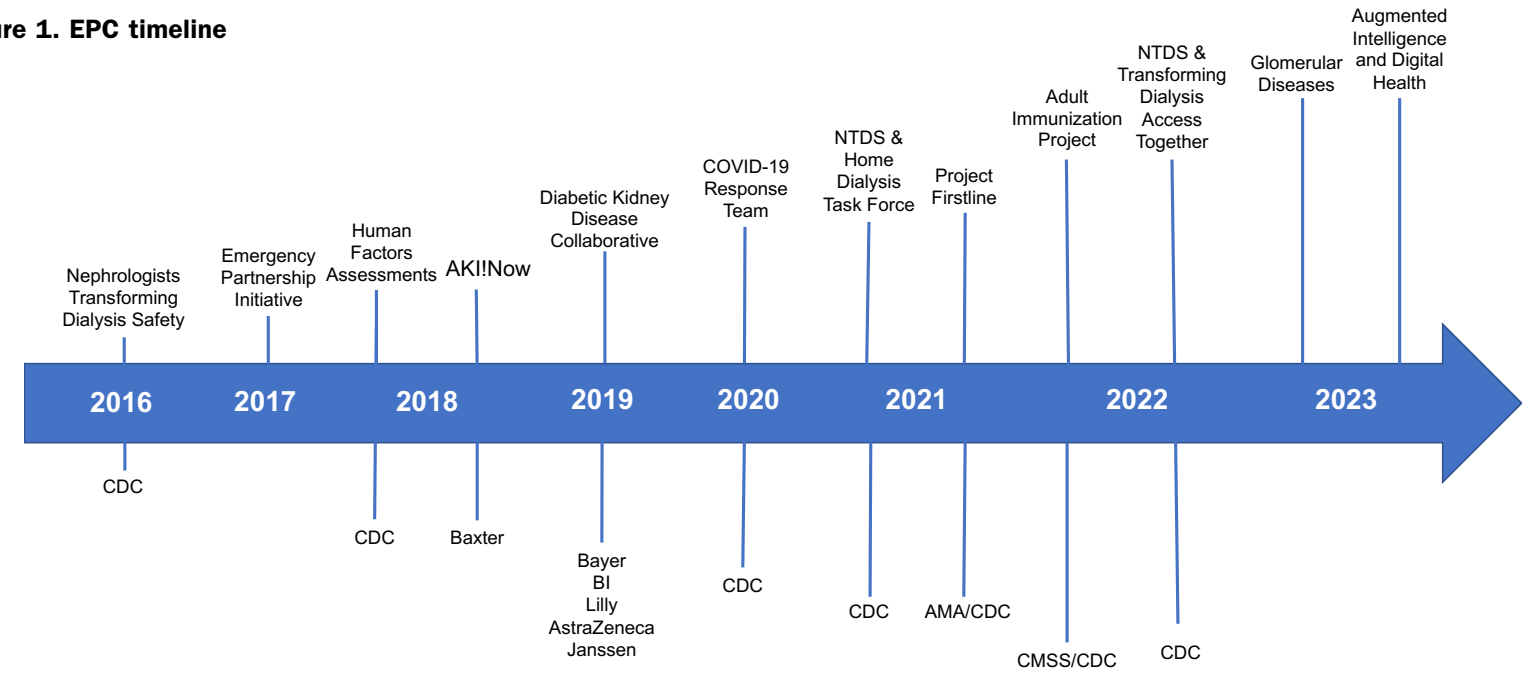
Embracing ASN values to first consider what is best for people with kidney diseases, EPC has engaged patients and caregivers as members of each EPC initiative to better understand and improve the experience of individuals with kidney diseases, as better and earlier education for patients can lead to improved outcomes. Across its initiatives, EPC has engaged with numerous patient and family advocates to gain the patient perspective on living with kidney diseases and to explore ways to improve patient education and health.

EPC recognizes and thanks all of the volunteers working tirelessly to improve the care for people with kidney diseases. To learn more about the important and exciting work being conducted by EPC and these dedicated professionals and patients (Table 1), please explore the articles found in this edition of *Kidney News*.

Visit the EPC website (https://epc.asn-online.org/) for more information on all of its initiatives. ■

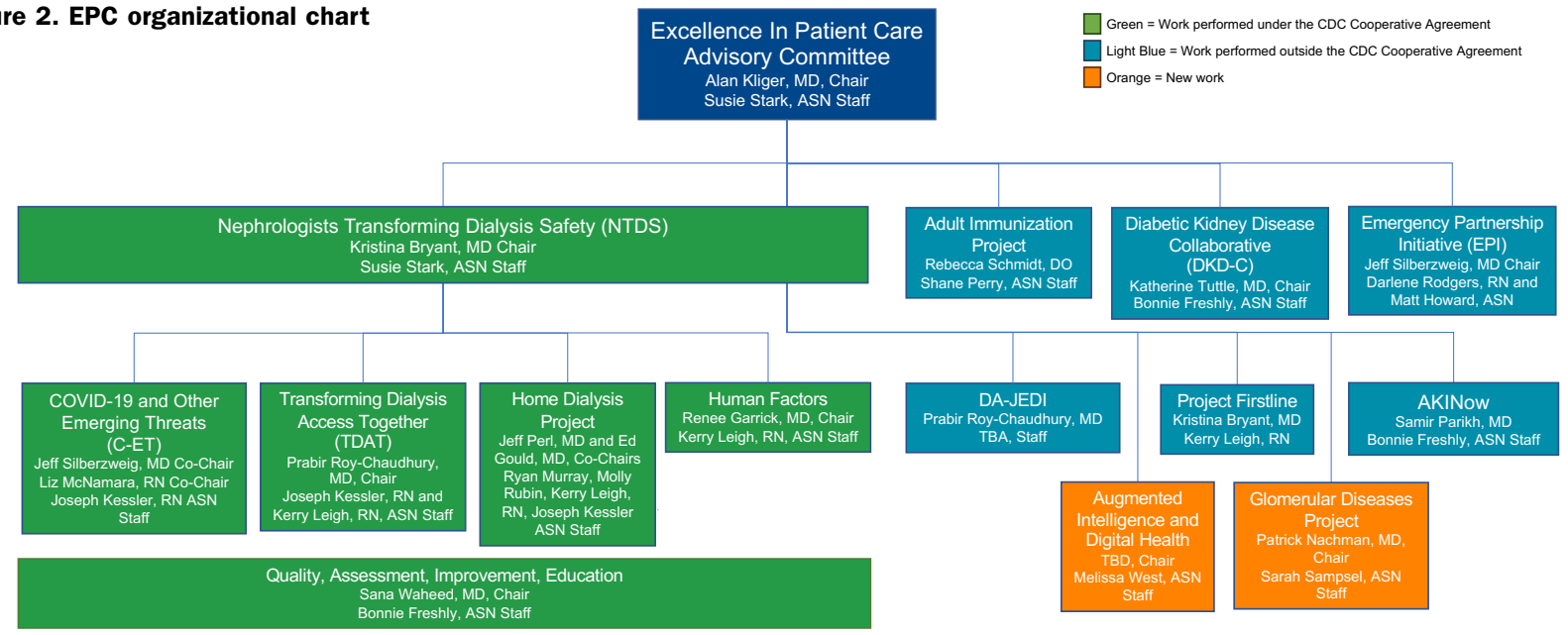
Continued on page 44 >

Figure 1. EPC timeline



AMA, American Medical Association; BI, Boehringer Ingelheim; CMSS, Council of Medical Specialty Societies.

Figure 2. EPC organizational chart



An Overview of EPC *Continued from page 43*

Table 1. EPC projects featured in this issue of *Kidney News*

Project		Focus and purpose
Nephrologists Transforming Dialysis Safety (NTDS)	**Current and Emerging Threats (C-ET)**	C-ET supports the work of NTDS specifically in the area of current and emerging bacterial, viral, and fungal threats, which impact immunocompromised individuals with chronic kidney disease.
	Transforming Dialysis Access Together (TDAT)	The mission of the TDAT initiative is to enhance the quality of life for people with kidney failure by engaging kidney care team members, patients, and nephrologists as leaders in transformational change to improve practices, education, and policies around hemodialysis and peritoneal dialysis accesses.
	Human Factors Engineering (HFE)	The goal of the HFE initiative is to better understand the impact of human factors in the dialysis setting by undertaking facility assessments to identify facilitators and barriers to increased patient and staff safety, including infection prevention and control.
	Home Dialysis Project (HDP)	The mission of the HDP is to improve awareness and outcomes of home dialysis therapies by enhancing education of kidney care professionals and trainees, addressing disparities in access to home dialysis, and advocating for policies that improve access to all dialysis treatment options to promote the highest quality of care.
	Quality, Assessment, Improvement, and Education (QAIE)	The purpose of the QAIE is to produce infection prevention-related education, including publications, virtual presentations, and national webinars, and to advance the use of online learning modules.
Emergency Partnership Initiative (EPI)		The ASN EPI is a coalition of organizations allied to provide support to people with kidney diseases affected by disasters
Adult Immunization Project (AIP)		The mission of the AIP is to promote the adoption of the Centers for Disease Control and Prevention's Standards for Adult Immunization Practice in nephrology care and to facilitate uptake of routine vaccinations recommended for people with kidney diseases.
Diabetic Kidney Disease Collaborative (DKD-C)		The purpose of the DKD-C is to convene experts and work collaboratively to address the urgent and unmet needs in the diagnosis and treatment of people with diabetic kidney disease.
Acute Kidney Injury (AKINow)		The mission of AKINow is to promote excellence in the prevention and treatment of acute kidney injury (AKI) by building a foundational program that transforms the delivery of AKI care, reduces morbidity and mortality, and improves long-term outcomes.
Project Firstline		Project Firstline provides innovative and accessible infection control education for all frontline health care workers to protect patients and staff from infectious disease threats in health care.
Glomerular Diseases Collaborative (GD-C)		ASN is expanding its EPC portfolio, adding glomerular diseases (GD) to promote quality, improve access to patient care, and address gaps in knowledge and training. A launch date has not yet been established.
Augmented Intelligence and Digital Health (AIDH)		ASN is also adding an Augmented Intelligence and Digital Health initiative to its EPC portfolio. Work on the development of this project is expected to begin after Kidney Week 2023. A launch date has not yet been established.

EPC recognizes Kristina Bryant, MD, for her leadership with the Nephrologists Transforming Dialysis Safety (NTDS) initiative, which serves to provide guidance on much of the work being completed under EPC. The mission of NTDS is to enhance the quality of life for people with kidney failure by engaging nephrologists as team leaders in transformational change that continuously improves the safety of life-sustaining dialysis.

An Evolution of Current and Emerging Threats

By Jeffrey I. Silberzweig, Liz McNamara, and Joseph Kessler on behalf of the C-ET Steering Committee

When the novel coronavirus was identified in 2019 and impacted the world in 2020, ASN's Excellence in Patient Care (EPC) formed a "COVID-19 Response Team." The purpose of this group was to bring together nephrology leaders and offer a common space to communicate, collaborate, and gain understanding of the unique and critical needs for patients with kidney diseases. The COVID-19 Response Team was able to offer support for the entire kidney community with consistent, trusted, timely information and education. Workgroups were formed to focus activities across four domains:

- Acute Hospital Kidney Care
- Home Dialysis
- Outpatient Dialysis
- Transplant

Highlights of work completed by the COVID-19 Response Team include:

- Online Learning Modules
  - COVID-19 Lessons from the Kidney Community https://epc.asn-online.org/learning_course/covid-19-lessons-from-the-kidney-community/
  - COVID-19 Toolkit for Nephrology Clinicians: Preparing for a Surge https://epc.asn-online.org/learning_course/covid-19-toolkit-for-nephrology-clinicians-preparing-for-a-surge/
  - Pursuing Mental Wellness: The Impact of COVID-19 on Dialysis Facility Staff https://epc.asn-online.org/learning_course/pursuing-mental-wellness-the-impact-of-covid/
- Resource Library, grouped by category https://epc.asn-online.org/projects/covid-19/covid-19-resource-library/
  - ASN COVID-19 Resources
  - CDC [Centers for Disease Control and Prevention] COVID-19 Information
  - CMS [Centers for Medicare & Medicaid Services] COVID-19 Updates
  - COVID-19 Immunization
  - COVID-19 Vaccines and Therapeutics
  - Other Health Care Organizations on COVID-19
  - Publications Focusing on COVID-19
- Webinar: COVID-19 Therapeutics and the Kidney Transplant Community https://epc.asn-online.org/videos/covid-19-therapeutics-and-the-kidney-transplant-community/

Following the expiration of the COVID-19 Public Health Emergency on May 11, ASN's EPC incorporated COVID-19 as a focus in the Current and Emerging Threats (C-ET) initiative. C-ET was created to enhance the quality of life for people with kidney diseases by engaging nephrologists and nephrology leaders in transformational change that continuously improves the safety of life-sustaining dialysis, specifically in the area of current and emerging bacterial, viral, and fungal threats.

Current activities within the C-ET Steering Committee and its workgroups include:

1. A compendium to address multi-drug-resistant organisms, specifically *Candida auris* and tuberculosis, among populations with end stage kidney disease, with more organisms to be included in future iterations. This resource will provide information on the organism, recommendations for care, and frequently asked questions.
2. A virtual "COVID-19 After-Action" meeting is being planned for November 13, 2023. This meeting will review the impact of the pandemic on patients with kidney diseases, review successes to the response of the pandemic, and discuss opportunities for improvement for future threats. Ensuring that a broad range of perspectives is shared, ASN's EPC is partnering with the CDC, the White House, academic and private-practice nephrologists, transplant nephrologists, surgeons, dialysis company chief medical and nursing officers, kidney community groups, patients, and other government agencies.
3. A "Leadership in Crisis and Uncertainty" pilot, based on the clinical dyad leadership model, is being planned for launch in the fall of 2023. This important training will provide nephrology leaders essential skills for future times of crisis and position them differentially to guide teams through the uncertainty.

Visit the CE-T website (https://epc.asn-online.org/projects/current-and-emerging-threats/) to explore all of the resources that C-ET Workgroups have to offer. ■

Dialysis Access Education Initiative Launched in 2022

By Prabir Roy-Chaudhury, Vandana Dua Niyyar, and Joseph Kessler on behalf of the Transforming Dialysis Access Together Steering Committee

ASN's Transforming Dialysis Access Together (TDAT) Initiative launched in 2022 and is working to improve practices, provide education, and promote policies centered around dialysis access.

The TDAT Steering Committee is also developing a summit to explore diversity, equity, inclusion, and the pursuit of health care justice with respect to dialysis access.

The TDAT Medical Training Workgroup, led by Vandana Dua Niyyar, MD, FASN, and Matthew Sparks, MD, FASN, is developing a dialysis access train-the-trainer curriculum. This work includes a "discovery and curating" of current educational offerings and a needs assessment. Training program directors and second-year fellows were asked to participate in this discovery phase. The first round will be a request for information on current programs and feedback on how to improve training. The second phase will be a focus group, set for mid-October, in which participants can opine on the current state of—and provide solutions to improve—training. This information will be compiled and used to inform the creation of a train-the-trainer curriculum. In 2024, ASN will host training program directors or designees to receive this program with the purpose of incorporating the instruction into their educational offerings.

The Education Workgroup, led by Dr. Niyyar and Gerald Beathard, MD, PhD, FASN, is producing a series of modern educational modules to improve knowledge and competency across all members of the multidisciplinary kidney care team. The first module to be released will be on the "Assessment of Dialysis Vascular Access" (i.e., physical examination). To create a comprehensive, interactive training module on physical examination of vascular access, ASN will partner with a multimedia company to develop state-of-the-art videos and animations. This work is expected to begin in the fall of 2023 with the educational module released in early 2024.

TDAT . . . is working to improve practices, provide education, and promote policies centered around dialysis access.

The Quality Improvement Workgroup, led by Dr. Niyyar and Gordon McLennan, MD, FSIR, is creating an overview document that explores "the meaning of quality from patients' perspectives as it relates to dialysis access." We expect this initiative to shed new light on the issues that are truly important for patients regarding vascular access care.

Visit the TDAT webpage (https://epc.asn-online.org/projects/tdat/) for more information on this initiative. ■

Human Factors Engineering and Infection Prevention in Dialysis

By Renee Garrick and Kerry Leigh on behalf of the Human Factors Steering Committee

ASN Nephrologists Transforming Dialysis Safety entered into a contract with the Centers for Disease Control and Prevention (CDC) in 2018 to begin assessing human factors related to infection prevention in the dialysis setting. Human factors engineering is a discipline concerned with the design of tools, machines, and systems that consider human capabilities, limitations, and characteristics to improve safety and allow for effective human use.

In the first year, ASN physician volunteers and staff, CDC representatives, and human factors engineers from the Virginia Tech Carilion School of Medicine visited six outpatient dialysis facilities across the country. Using human factors approaches, the teams assessed areas of care that may lead to potential infection-control issues in in-center hemodialysis facilities. This work continued with four additional assessments that were conducted in the second year of the contract. A manuscript describing findings from the initial six assessments is soon to be submitted for publication.

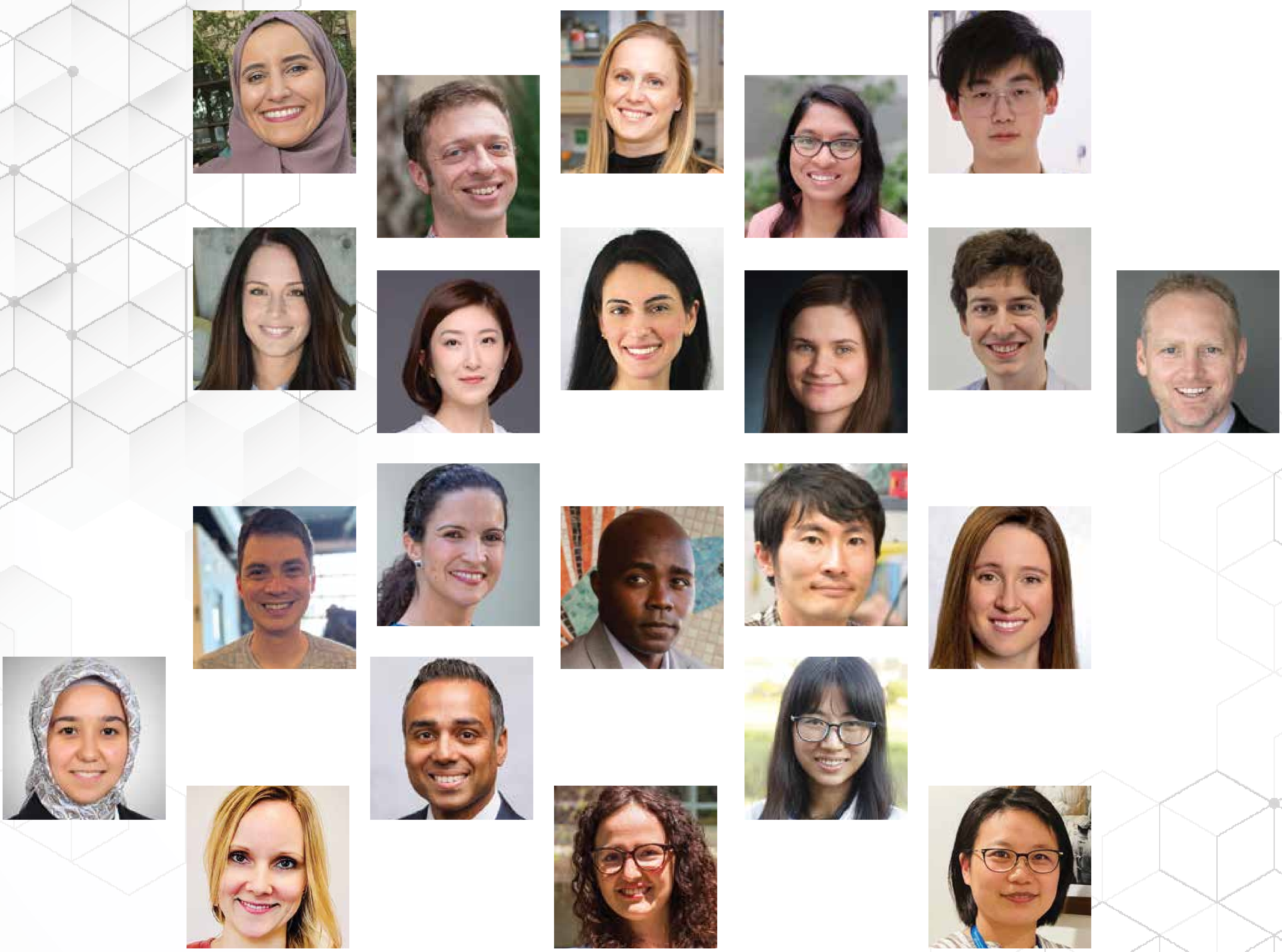
In 2020, ASN was asked to extend its work in this area to look at infection control and prevention in the home dialysis setting. Visits to dialysis facilities were interrupted by the pandemic, but planning continued throughout 2022. In 2023, a team of ASN and CDC staff and human factors engineers visited four home dialysis facilities and 13 patient homes, completing the human factors assessments in home dialysis.

Facility staff and patients who participated in the home assessments were welcoming and provided honest input into their individual infection-prevention practices through demonstration and discussion. The engineers are now compiling human factors findings from the home dialysis assessments into a report for review by the CDC. ■

Left to right: Yuhao Peng (Carilion Clinic), Sarah Parker (Virginia Tech), facility peritoneal dialysis nurse (back facing camera), Kerry Leigh (ASN staff), and Nicole Gualandi (CDC staff) during a human factors visit to a home dialysis facility, 2023.

KidneyCure congratulates the talented group of individuals awarded grants in 2023.

With support from ASN members, industry partners, and nephrology leaders, KidneyCure provides over $3,000,000 annually to young researchers, fellows, and educators at the most critical stages of their careers – giving life and momentum to ideas that would otherwise be lost.



Make a difference today.

Support these trailblazers and future kidney leaders by visiting www.kidneycure.org.

KidneyCure

Fund it. Find it.

ASN-Harold Amos Medical Faculty Development Program

Aiming to increase diversity among future leaders, the ASN-Harold Amos Medical Faculty Development Program provides four years of research and career development support to a nephrologist from a historically disadvantaged background.

Anthony Muiru, MD, MPH
University of California San Francisco
Does Your ZIP Code Matter More Than Your Genetic Code? The Relative Importance of Structural Racism vs. APOL1 Risk Variants in Explaining Black and White Racial Disparities in Kidney Disease

ASN Pre-Doctoral Fellowship Program

The ASN Pre-Doctoral Fellowship Program provides funding to early career-stage PhD students to conduct original research projects and make contributions to the understanding of kidney biology and disease.

Wafaa Albalawy*
University of Pittsburgh
The Role of SGLT2 Inhibitors in Proximal Tubule Function

Matthew Kavanaugh*
University of Kansas School of Medicine
O-GlcNAc in Ciliary Homeostasis and Autosomal Dominant Polycystic Kidney Disease

Ben J. Lipps Research Fellowship Program

The Ben J. Lipps Research Fellowship Program supports nephrology fellows who will advance the understanding of kidney biology and disease and is fully endowed by contributions provided by Fresenius Medical Care, ASN, the American Renal Patient Care Foundation, Inc., Amgen, Baxter, and the PKD Foundation.

Richard Babicz, MD
Massachusetts General Hospital
A Novel Aquaporin-2 Signaling Pathway as a Target for Disorders of Renal Water Balance
Jared J. Grantham Research Fellowship Award

Lashodya Dissanayake, MD, PhD*
University of South Florida
The Role of Uric Acid Homeostasis in Salt-sensitive Hypertension
Dimitrios G. Oreopoulus Research Fellowship Award

Zeping Gui, MD
University of Pittsburgh
The Role and Mechanisms of Innate Allorecognition in Renal Allograft Rejection
George B. Rathmann Research Fellowship Award

Jielu Hao, MD*
Mayo Clinic
A Paradigm of Cilia-mediated Senescence in Promoting Disease Progression After Acute Kidney Injury
Donald E. Wesson Research Fellowship Award

Mitra Jamshidian, MD
University of California San Francisco
The Effect of SGLT2i on Blood Pressure and Serum Potassium in a Real-World Setting
Ben J. Lipps Research Fellowship Award

Jonathan Levinsohn, MD, PhD*
Children's Hospital of Philadelphia
Genomics of Human Kidney Development and Early Maturation
Ben J. Lipps Research Fellowship Award

Ana Onuchic-Whitford, MD
Brigham and Women's Hospital
Allele-specific Expression in Proteinuric Kidney Disorders: Investigating a Novel Disease Mechanism
Sharon Anderson Research Fellowship Award

Merve Postalcioglu, MD
University of California San Francisco
Associations of Urine Epidermal Growth Factor with the Onset and Progression of Chronic Kidney Disease
Ben J. Lipps Research Fellowship Award

Esilida Sula Karreci, MD*
Beth Israel Deaconess Medical Center
Molecular and Cellular Involvement of the Renin Angiotensin Aldosterone System in APOL1 Kidney Disease
Ben J. Lipps Research Fellowship Award

Xiaoqiong Wei, PhD*
University of Virginia
Regulation of Podocyte Adhesion by SEL1L-HRD1 ERAD Via Integrin
Ben J. Lipps Research Fellowship Award

Transition to Independence Grants Program

The Transition to Independence Grants Program helps young investigators achieve independent research careers and is supported by contributions provided by ASN, Akebia Therapeutics, Inc., Otsuka and Visterra, and individual donors.

Cary Boyd-Shiwarski, MD, PhD
University of Pittsburgh
The Role of Calcineurin Inhibitors on Blood Pressure and Potassium Homeostasis Through WNK Body Molecular Condensates
Carl W. Gottschalk Research Scholar Grant

Georgina Gyarmati, MD, MPH
University of Southern California
Role of the Newly Discovered Neuroendothelial Cells in Renal Physiology and Disease
Carl W. Gottschalk Research Scholar Grant

Malgorzata Kasztan, PhD
University of Alabama at Birmingham
The Role of Endothelin-1 in Renal Iron Handling in Sickle Cell Disease
Norman Siegel Research Scholar Grant

Matthew Lanktree, MD, PhD
McMaster University
Multi-omics in PEXIVAS: Using Precision Medicine to Improve Risk Stratification in ANCA Vasculitis
Carl W. Gottschalk Research Scholar Grant

Laisel Martinez, PharmD, MS*
University of Miami
The Contribution of Catheter-derived Inflammation to Arteriovenous Fistula Failure
KidneyCure Diversity, Equity, Inclusion, and Justice Research Scholar Grant

Yoshiharu Muto, MD, PhD*
Washington University in St. Louis
Role of Methionine Cycle in Remodeling of Epigenetic Landscape in Acute Kidney Injury and Failed Repair
Carl W. Gottschalk Research Scholar Grant

Insa Schmidt, MD, MPH*
Boston University and Boston Medical Center
A Deep Learning Framework for the Automated Assessment of Kidney Pathology and Prognosis
Carl W. Gottschalk Research Scholar Grant

Anand Srivastava, MD, MPH
University of Illinois at Chicago
Functional MRI for Enhanced Phenotyping of CKD
Carl W. Gottschalk Research Scholar Grant

Jing Zhao, MD, MS
Brigham and Women's Hospital
Implication of Melanocortin 2 Receptor (MC2R) in Transplant Tolerance
John Merrill Research Scholar Grant

** Kidney Week 2023 oral and/or poster abstract presenter*

Home Dialysis Project: Innovative Approaches to Training and Infection Prevention

By Jeffrey Perl, Edward Gould, and Kerry Leigh on behalf of the Home Dialysis Project Steering Committee

Participants attending an HDU course in the fall of 2023.

ASN partners with Home Dialysis University for a nephrology fellows training program.

ASN and Home Dialysis University (HDU) have partnered to provide an innovative, educational experience for nephrology fellows. This approach begins with a multi-day, in-person, immersive, didactic, and small-group learning experience at HDU, followed by an 11-month, virtual, case-based educational series.

Drs. Graham Abra, Christopher Chan, Janice Lea, and Anjali Saxena developed and will moderate the virtual series. The curriculum for the virtual series follows that of the HDU course and includes key topics specific to peritoneal and home hemodialysis, such as setting a home dialysis prescription, volume management, and the prevention and management of non-infectious and infectious complications.

ASN awarded scholarships to 30 nephrology fellows to participate in the innovative educational program. All scholarship participants began the program by attending an HDU course in the fall of 2023. The virtual series launched in August, following the HDU course, and will conclude in June 2024. Each virtual session features one moderator and one faculty member presenting cases and facilitating case-based discussion with 15 fellows. Faculty for the virtual series include Drs. Joanne Bargman, Joel Glickman, Thomas Golper, Frank Liu, Rajnish Mehrotra, Brent Miller, Jeffrey Perl, Matthew Rivara, Rebecca Seshasai, Isaac Teitelbaum, and Eric Wallace.

A secure website houses educational materials and content for the longitudinal learning program. Drs. Yuvaram Reddy and Wendy Ye are leading development of an evaluation of the in-person session and virtual educational series.

Home Dialysis Scholarship Program by the numbers:

84
applicants

30
scholarship awardees

2
in-person training events

Each event spans 2½ days with approximately 15 hours of instruction followed by an 11-month longitudinal learning program.

PD Core Interventions for Infection Prevention Summit attendees, June 2023.

ASN partners with the CDC and leaders in nephrology to develop Peritoneal Dialysis Core Interventions for Infection Prevention.

In June 2023, the Home Dialysis Project (HDP) hosted a virtual session (held via Zoom) and an in-person summit (held in Atlanta, GA) to develop a list of core interventions for peritoneal dialysis (PD) infection prevention.

The workgroup continues to refine the list and language included in each intervention. Once the draft list of PD core interventions is finalized, the HDP will reach out to stakeholders with a request for comment. The workgroup is interested in creating more detailed documents to support the list of core interventions in the future.

This approach mirrors the Centers for Disease Control and Prevention (CDC) Making Dialysis Safer for Patients Coalition's work in developing the "CDC Approach to BSI [Bloodstream Infection] Prevention in Dialysis Facilities (i.e., the Core Interventions for Dialysis BSI Prevention)" resource.

A Reinvigorated Emergency Partnership Initiative

By Jeffrey I. Silberzweig and Darlene Rodgers on behalf of the EPI Steering Committee

The ASN Emergency Partnership Initiative (EPI) is a coalition of organizations allied to provide support to people with kidney diseases affected by disasters. Motivated by the adage coined by Benjamin Franklin in 1736, "An ounce of preparation is worth a pound of cure," ASN's EPI seeks to help patients, caregivers, and practitioners anticipate and prepare for disasters that are likely to affect the regions where they live. EPI efforts recognize that disasters impact and may exaggerate historic sociodemographic inequities, so this initiative includes a focus on diversity, equity, and inclusion as well as justice.

EPI will continue to serve as a vehicle for care coordination and early intervention via its collaboration with disaster-relief agencies, dialysis companies, state and federal officials, and kidney disease experts. EPI focuses on events throughout the United States and the Caribbean, with an emphasis on disasters that are a result of climactic factors. Recent data show increasing severity of disasters in correlation with climate change. As such, EPI will work toward a better understanding of the relationship between climate change and kidney diseases.

In 2023, EPI engaged with members of its newly seated steering committee and created a new website to host resources, education, and materials in key areas, including:

- Community and federal emergency partners
- Infection prevention and control
- Unique situations

Visit the new EPI webpage (https://epc.asn-online.org/projects/epi/) for resources and information.

The ASN Excellence in Patient Care Quality, Assessment, Improvement, and Education Initiative

By Sana Waheed and Bonnie Freshly on behalf of the QAIE Initiative

The Quality, Assessment, Improvement, and Education (QAIE) Steering Committee collaborates to produce infection-prevention-related educational material, including peer-reviewed publications, virtual presentations, online learning modules, and national webinars.

In late 2022 and early 2023, the workgroup produced a "micro-webinar" series for new practitioners and fellows that covers core concepts in infection prevention in the outpatient hemodialysis setting. Each micro-webinar is less than 30 minutes, making them ideal for lunch-and-learn-style conversations. The series can be viewed on the Excellence in Patient Care (EPC) website (https://epc.asn-online.org/projects/quality-assessment-improvement-education/).

In spring 2023, QAIE members partnered with the American Society of Pediatric Nephrology to design a poster series (in English and Spanish; https://epc.asn-online.org/projects/quality-assessment-improvement-education/https-epc-asn-online-org-projects-quality-assessment-improvement-education-qaie-promoting-vaccine-confidence-in-the-pediatric-kidney-community/) to inspire vaccine confidence in pediatric patients. This poster series was followed by a short video that features a parent advocate, a pediatric nephrologist, and an infectious disease physician sharing their views on the importance of vaccination. Both the poster series and video have been shared throughout the pediatric kidney community, including directly to parent and family groups.

Finally, the steering committee has released the 10th webinar in the Targeting Zero Infections series. The latest installment, which can be viewed on the EPC website, addresses vaccination topics, including lessons learned from the COVID-19 experience, routine recommendations for dialysis patients, and vaccination in special populations. ■

Second Year of the Adult Immunization Project

By Rebecca J. Schmidt and Shane Perry on behalf of the AIP Steering Committee

The ASN Adult Immunization Project (AIP) continued its work with the Council of Medical Specialty Societies (CMSS) on a grant provided by the Centers for Disease Control and Prevention (CDC).

On February 3, 2023, the AIP Steering Committee hosted a virtual focus group with 32 participants, many of whom represented the dialysis corporations and facilities involved in the project.

Participants included were from the following categories:

- Patients (n = 4)
- Physicians (n = 4)
- Nurses, nurse practitioners, social workers, clinic directors, and administrators (n = 12)
- Steering Committee members serving as breakout moderators (n = 4)
- ASN staff (for note taking and support) (n = 8)

The event was 90 minutes in length and included the following program:

- Welcome by Rebecca J. Schmidt, DO, FASN, AIP Steering Committee Chair
- Keynote presentation: "mRNA as Medicine" by Melissa J. Moore, PhD, from a recording made at 2022 Kidney Week
- Breakout sessions by group (kidney professionals in three groups and kidney patients in one group)

Breakout discussion transcripts were reviewed and coded against seven concepts (Table 1). Preliminary data from the ASN AIP Focus Group revealed the frequency of discussion for each concept (Figure 1).

A significant amount of information was acquired from this event, which continues to inform the work of the AIP. In response to the focus group, the AIP Steering Committee is developing the following material to address the needs communicated during the breakout sessions:

1. A guidebook on "How to be a Vaccine Advocate" for staff and patients
2. Videos from kidney professionals and patients sharing vaccination experiences and reasons for choosing a vaccine
3. Visual materials, such as posters, for display at dialysis units, physician offices, patient areas, or other locations
4. Guidance on how to work with state immunization information systems to maximize the utility of these systems at the patient and facility levels

By September 2023, ASN had completed its recruitment of dialysis corporations and facilities for this initiative. Project partners represent large, mid-size, and small dialysis companies across the United States. Onboarding and quality improvement interventions with new dialysis corporations and facilities will occur through the fall, just in time for the 2023–2024 influenza season.

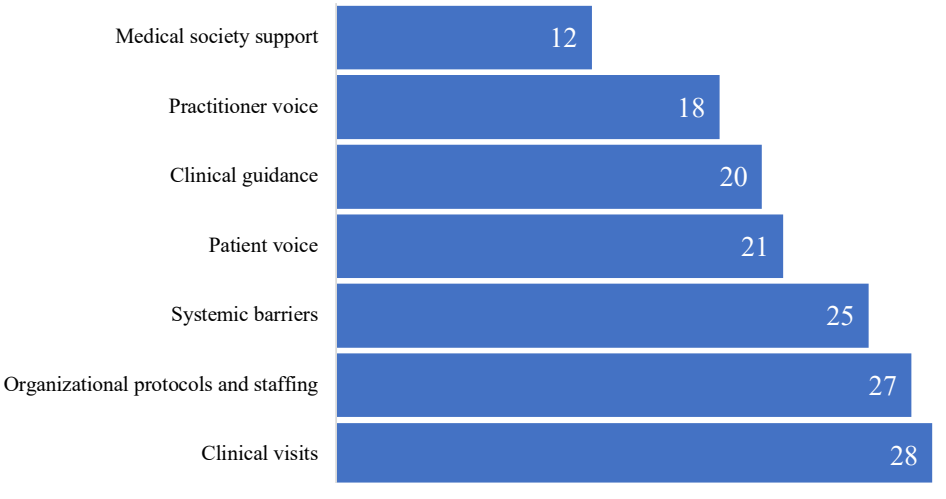
ASN is looking forward to improving processes around the CDC Standards for Adult Immunization Practice (SAIP), increasing immunization rates, and sharing knowledge through this exciting collaborative quality improvement effort with the CMSS and the CDC.

Visit the Adult Immunization Project webpage for updates, information, and materials: https://epc.asn-online.org/projects/aip/. ■

Table 1. AIP Focus Group: Concepts and questions

Concept	Guiding question
Clinical guidance	How does the existence (or lack) of clinical guidance impact vaccination?
Clinical visits	How is SAIP implemented in the practitioner–patient interaction?
Medical society support	What is the respective medical society doing, or what could it do, to support its members and their patients?
Organizational protocols and staffing	How does an organization impact vaccination?
Patient voice	How does the patient impact vaccination?
Practitioner voice	How does a practitioner impact vaccination?
Systemic barriers	How does the health care system impact vaccination?

Figure 1. AIP Focus Group: Frequency of concepts discussed



The ASN Diabetic Kidney Disease Collaborative Initiative: Pursue Kidney Health for All

By Katherine R. Tuttle and Bonnie Freshly on behalf of the DKD-C Steering Committee

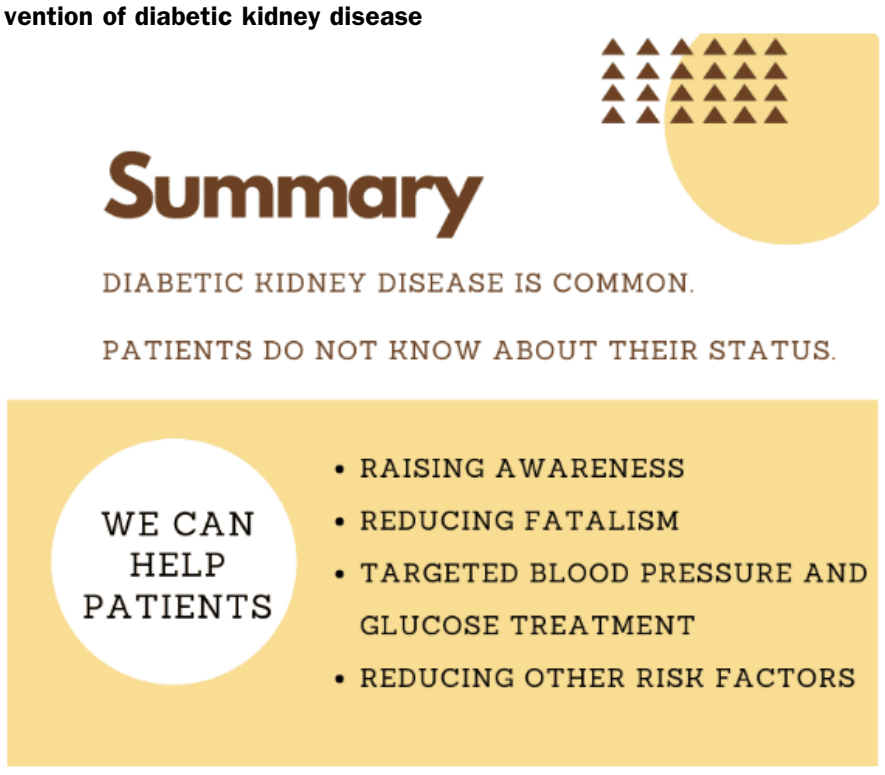
The Diabetic Kidney Disease Collaborative (DKD-C) was launched in 2019 with a mission of "working together to address the urgent and unmet needs in the diagnosis and treatment of people with diabetic kidney disease."

In addition to being the most common cause of kidney failure worldwide, DKD greatly amplifies risks of cardiovascular disease and death (1). A Strategy Conference series was launched in 2020 to determine the role of the nephrologist in diagnosing and treating DKD, to encourage nephrologists to interact proactively with primary care physicians and other specialists to ensure people with DKD receive the best care possible, and to provide education to both practitioners and patients with DKD (2–4).

To support these goals, in 2022, the DKD Steering Committee released an online learning module, "Management of Chronic Kidney Disease in People with Diabetes." This comprehensive resource is intended for all practitioners who care for individuals with kidney diseases and diabetes. Assessment and management of hyperglycemia, hypertension, albuminuria or proteinuria, cardiovascular disease, acute kidney injury, and social determinants of health are addressed with a square focus on the patient journey (Figure 1).

Currently, two new initiatives are underway to expand this educational effort and to promote implementation of the sodium-glucose cotransporter-2 (SGLT2) inhibitor class of agents and other guideline-directed medical therapies. These include glucagon-like peptide-1 receptor agonists and a non-steroidal mineralocorticoid antagonist for DKD. Multiple, large randomized controlled trials have now demonstrated unequivocally that SGLT2 inhibitors prevent loss of kidney function, kidney failure, heart failure and atherosclerotic cardiovascular events, and death in patients with chronic kidney disease with or without diabetes.

Figure 1. Online chapter summary on awareness, detection, and intervention of diabetic kidney disease



Reprinted from ASN's Management of Chronic Kidney Disease in People with Diabetes module, chapter 5 (https://epc.asn-online.org/learning_course/management-of-chronic-kidney-disease-in-people-with-diabetes/).

First, Patrick O. Gee, Sr., PhD, JLC, DKD-C Steering Committee member and longtime patient advocate, is spearheading an adaptation of the practitioner-focused online learning module into a resource designed for people with, and at risk, of kidney diseases and their support or care practitioners. A strong cadre of patient advocates, including Thelma Barber, Precious McCowan, and Virna Elly, will direct the development of content that speaks to patients' most frequent questions and concerns about kidney health, treatment options, and communication with care practitioners.

Second, Frank C. (Chip) Brosius III, MD, and Patrick H. Nachman, MD, FASN, are coordinating a two-pronged study of the cost-effectiveness of SGLT2 inhibitor treatment. The first prong will study the implementation of SGLT2 inhibitors across a cohort of patients with DKD from the Veterans Administration, and the second will focus on SGLT2 inhibitor treatment among employees with diabetes in another large U.S. health care system. These partnerships are aimed to support a sea change in nephrology toward upstream prevention and treatment, rather than late-stage reactionary care, through value-based approaches for people with, and at-risk for, kidney diseases.

The advent of breakthrough therapies for DKD is an unprecedented opportunity to save kidneys, hearts, and lives. "A world without kidney diseases…"—our ASN aspirational motto—is indeed a possibility. The DKD-C invites you to share its resources with your colleagues, patients, and communities to pursue kidney health for all. *It is time to move from knowing to doing.*

DKD-C Steering Committee members

Chair: Katherine R. Tuttle, MD, FASN

Steering Committee members: Christos Argyropoulos, MD, PhD, FASN; Frank C. (Chip) Brosius III, MD; David Cherney, PhD, MD; Patrick O. Gee, Sr., PhD, JLC; Raymond C. Harris, MD, FASN; Alan S. Kliger, MD; Amy Mottl, MD, MPH, FASN; Patrick H. Nachman, MD, FASN; and Susan E. Quaggin, MD, FASN

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The ASN AKINow Initiative: Defining Excellence in the Prevention and Care of Patients with Acute Kidney Injury

By Samir M. Parikh with Michael Heung, Sherry Mansour, Sanjeev Kumar, Anitha Vijayan, Erin Barreto, Jay Koyner, and Bonnie Freshly on behalf of the AKINow Initiative

AKINow was created in the spring of 2019 to address the rising incidence of acute kidney injury (AKI), which is estimated to affect more than 13 million hospitalized people every year around the world (1). AKI survivors have a higher risk of death, rehospitalization, recurrent AKI, chronic kidney disease (CKD), and lower quality of life than patients discharged from the hospital without an AKI diagnosis (2). The mission of AKINow is "to promote excellence in the prevention and treatment of [AKI] by building a foundational program that transforms the delivery of AKI care, reduces morbidity and mortality, and improves long-term outcomes."

Over the past year, AKINow's workgroups have approached this mission through the development of novel educational content and platforms, outreach to the kidney community and engagement with patient advocates, and dissemination of best practice information to both clinicians and individuals affected by AKI.

- The **Public Awareness and Education Workgroup** has completed a scoping literature review, which revealed a dearth of information regarding education for patients who have experienced AKI. Subsequently, the workgroup hosted a focus group session with diverse AKI stakeholders, including patients in May 2023, to identify barriers to AKI education for both patients and practitioners. Areas for improvement that emerged from these discussions included communication among practitioners, better information for patients about the kidneys, clarity on whether a patient is being discharged with an AKI versus an end stage kidney disease diagnosis, and improved information at discharge to facilitate the transition to outpatient care for individuals who are affected. In 2024, along with developing new educational material to address these unmet needs, this workgroup will pursue relationships with non-nephrology societies to increase awareness of AKI.
- The **Basic Science: AKI-Specific Early Interventions Workgroup** is pursuing methods to promote collaborative and inclusive discovery research that translates more effectively to patients. In 2023, the workgroup launched a virtually hosted AKINow Journal Club to foster discussion in the community on emerging, high-impact research. The first Journal Club presented a manuscript, published in *The Journal of Clinical Investigation* (3), on new mechanisms of AKI-to-CKD transitions, and the second discussed a randomized clinical trial of electronic health record alerts to improve AKI prevention and outcomes, published in *Nature Communications* (4). Recordings of the first two Journal Club events are available on the AKINow website (https://epc.asn-online.org/projects/akinow/). The workgroup is also developing a proposal for a new curriculum to lower entry barriers for researchers interested in the application of data science to AKI. This unique program would include the basics of conducting research studies, introduce learners to freely available statistical software, and assist participants in performing their own statistical coding. The program will focus on recruiting students from minority groups and community hospitals who are less likely to have access to the tools needed to conduct research.
- The **AKI Recovery Workgroup** aims to identify challenges and opportunities to improve post-AKI care (5, 6). Survivors of AKI are a high-risk, growing population with poor long-term outcomes. How to care for patients after AKI remains ill-defined and with substantial practice variation. In fall 2021 and spring 2022, the workgroup hosted two focus group sessions to determine gaps in care and to understand the challenges and opportunities in developing evidence-based practice recommendations for the care of survivors of AKI. The workgroup is currently designing a Delphi process to gather insight on survivorship care plans that organize information about recommended follow-up care. This includes how often examinations are needed, required testing, and potential late effects of AKI that should be monitored. The Delphi technique is a method of group decision-making and forecasting that involves successively collating the judgments of experts. Through this process, the group will focus on the population with non-dialysis AKI (patients or family members of patients who have experienced AKI but did not require dialysis) and with practitioner-to-practitioner and practitioner-to-patient communications. The outcome of this process will be two model survivorship care plans (one for patients and a second for practitioners) to guide post-AKI care.
- The **Artificial Intelligence (AI) Workgroup** aims to help clinicians, patients, and researchers use AI to improve the quality, accessibility, affordability, and equity of care. Efforts to mobilize data to improve health care delivery and patient outcomes are rapidly reaching every corner of medicine. ASN's focus on data science and AI commenced in this AKINow workgroup to develop ways to use electronic health data to predict, prevent, and mitigate the impact of AKI in hospitalized patients. This workgroup has evolved, via the ASN's Task Force on Augmented Intelligence and Digital Health recommendation, which focuses on coordinating activities across many of ASN's interest areas beyond AKI to accelerate the integration of digital health into the care of patients with kidney diseases. Prior to establishing ASN's Task Force on Augmented Intelligence and Digital Health, the AKINow AI Workgroup organized several webinars with leaders in the field (from nephrology and beyond) on the basic concepts of augmented intelligence and clinical decision support. These educational offerings can be found on the AKINow website. The workgroup anticipates continuing its support of the larger nephrology community in this area of AI and AKI.

AKI is common, serious, under-recognized, and strongly associated with increased risk of adverse outcomes. Early recognition is essential. Therapies to prevent or treat AKI are sorely needed. Post-AKI recovery care is essential to improve long-term outcomes that significantly impact individuals and society. Such efforts will require close interaction and cross-pollination among patients, scientists, clinicians, academics, and regulatory and industry partners to achieve better AKI outcomes.

AKINow Workgroup members

Chair: Samir M. Parikh, MD, FASN

Public Awareness and Education Workgroup: Michael Heung, MD, MS, FASN – Chair; Linda Awdishu, PharmD, FASN; Rajit K. Basu, MD, MS, FCCM; Jorge Cerdá, MD, MS, FASN; Patricia Kao, MD, MS, MHPE; Marla Levy; Andrew Lewington, BSc (Hons), MBBS, MEd, MD, FRCP; Kathleen Liu, MD, PhD, FASN; Rhonda Moore; Daniel Murphy, MD, MS; Marlies Ostermann, MD, PhD; Ashita Tolwani, MD, MS; and Aarthi Vijaykumar, MD, FASN

Basic Science Workgroup: Sanjeev Kumar, MD, PhD – Co-Chair; Sherry Mansour, MD, MS – Co-Chair; Anupam Agarwal, MD, FASN; Amandeep Bajwa, PhD; Leslie Gewin, MD; Mark D. Okusa, MD, FASN; Laura Onuchic, MD; and Samir M. Parikh, MD, FASN

Recovery Workgroup: Erin Barreto, PharmD, MS, FASN – Co-Chair; Anitha Vijayan, MD, FASN – Co-Chair; Emaad Abdel-Rahman, MD, PhD, FASN; Leslie Gewin, MD; Diana Kwong, MD; Ian McCoy, MD, MS, FASN; Javier A. Neyra, MD, MS, FASN; Jia Ng, MD; and Samuel Silver, MD, MS, FASN

AI Workgroup: Jay Koyner, MD – Chair; Stuart Goldstein, MD, FASN; Kianoush Kashani, MD, MS, FASN; Mei Liu, PhD; Shina Menon, MD; Girish Nadkarni, MD, MPH; Javier Neyra, MD, MS, FASN; Neesh Pannu, MD, MS; Karandeep Singh, MD, MMSc; and Danielle Soranno, MD

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Celebrating the Partnerships and Products of Project Firstline

By Kristina Bryant, Kerry Leigh, and Shane Perry on behalf of the Project Firstline Steering Committee

Project Firstline is a Centers for Disease Control and Prevention-led, national training collaborative for health care infection control, which provides innovative and accessible infection control education for all frontline health care workers for the purpose of protecting their patients, coworkers, and themselves from infectious disease threats in health care.

ASN partnered with the American Medical Association in 2022 to develop a four-part, infection-prevention educational series for frontline workers in dialysis facilities. The series includes educational modules and videos on hand hygiene, personal protective equipment (PPE), injection safety, and environmental cleaning and disinfection (Table 1).

Additional information and access to the infection-prevention modules can be found at https://epc.asn-online.org/projects/project-firstline/.

Table 1. Four-part, infection-prevention series for frontline workers in dialysis facilities

Module	Learning objectives	Link
Hand Hygiene for Infection Prevention in a Dialysis Setting	• Indicate why hand hygiene is important for infection prevention in a dialysis setting. • Recognize some common mistakes that health care workers make regarding hand hygiene that may lead to infection. • Identify what can be done to improve hand hygiene practices in a dialysis setting.	https://edhub.ama-assn.org/cdc-project-firsline/interactive/18754447
Personal Protective Equipment (PPE) for Infection Prevention in a Dialysis Setting	• Indicate why PPE is important in dialysis settings. • Recognize some common mistakes that health care workers make when using PPE that may lead to the spread of germs. • Identify what can be done to improve the proper use of PPE to prevent the spread of germs.	https://edhub.ama-assn.org/cdc-project-firstline/interactive/18754450
Injection Safety for Infection Prevention in a Dialysis Setting	• Indicate why injection safety is important in dialysis. • Recognize some common mistakes that health care workers make when preparing and administering parenteral medications that may lead to infection. • Identify what can be done to improve injection safety practice.	https://edhub.ama-assn.org/cdc-project-firstline/interactive/18754444
Environmental Cleaning and Disinfection for Infection Prevention in a Dialysis Setting	• Indicate why environmental cleaning and disinfection are important in dialysis settings. • Recognize some common mistakes that health care workers make regarding environmental cleaning and disinfection that may lead to infection. • Identify what can be done to improve environmental cleaning and disinfection practices.	https://edhub.ama-assn.org/cdc-project-firstline/interactive/18754441

Leverage AI and Machine Learning in Kidney Care

Explore the new **Artificial Intelligence and Machine Learning in Nephrology** series to understand how the fundamentals and clinical applications will advance kidney health and diseases, including AKI, CKD, and dialysis. In this new special collection, you will review the advantages of using deep learning, natural language processing, and spatial technologies to improve care and maintain your patient's health.

Scan the QR code to read the series.

CJASN®

With support from ASN members, friends and family, industry partners, and leaders in the field, KidneyCure funds trailblazing investigators whose work is leading to better therapies, and someday cures, for the millions impacted by devastating kidney diseases.

Thank you to the following donors for their generous support of KidneyCure:

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The Founders Circle recognizes companies and nonprofit organizations that have made significant contributions in support of foundation programs.

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ASN American Society of Nephrology	Akebia Therapeutics	Otsuka | Visterra Otsuka Group of Companies
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Ben J. Lipps Research Fellowship Program Donors

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The Visionary Circle recognizes individuals who have donated, pledged, or made a bequest of $75,000 or more to the foundation or its programs.

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FILSPARI™
(sparsentan) tablets 200 mg/400 mg

For adults with primary IgA nephropathy at risk of rapid progression*

TURN DOWN PROTEINURIA

FILSPARI™ is the **first and only** single molecule, endothelin-1 and angiotensin II receptor antagonist, binding to the endothelin type A (ET_A) receptor and angiotensin II type 1 (AT_1) receptor.[1]

Proven to provide **superior reduction in proteinuria** vs irbesartan at 36 weeks in a head-to-head study.[1†]

*Generally defined as UPCR of ≥1.5 g/g.

†Results based on an interim analysis from the PROTECT Study, an ongoing, randomized, double-blind, head-to-head, multicenter, global study in 281 patients with biopsy-proven IgA nephropathy. Patients who received FILSPARI (n=141) had an adjusted GM of UPCR of 1.2 g/g at baseline vs 1.2 g/g for patients who received irbesartan (n=140). The adjusted GM of UPCR at Week 36 was 0.7 g/g for FILSPARI-treated patients (n=135) vs 1.0 g/g for irbesartan-treated patients (n=128). The adjusted GMPC from baseline in UPCR at Week 36 was -45% (-51%, -38%) for the FILSPARI group vs -15% (-24%, -4%) for the irbesartan group (*P*<0.0001; ratio of adjusted GM relative to baseline [95% CI]: 0.65 [0.55, 0.77]).[1,2]

CI=confidence interval; GM=geometric mean; GMPC=geometric mean percent change; IgA=immunoglobulin A; UPCR=urine protein-to-creatinine ratio.

Learn more at FILSPARIhcp.com

INDICATIONS & USAGE

FILSPARI™ (sparsentan) is indicated to reduce proteinuria in adults with primary immunoglobulin A nephropathy (IgAN) at risk of rapid disease progression, generally a urine protein-to-creatinine ratio (UPCR) ≥1.5 g/g.

This indication is approved under accelerated approval based on reduction of proteinuria. It has not been established whether FILSPARI slows kidney function decline in patients with IgAN. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory clinical trial.

IMPORTANT SAFETY INFORMATION

BOXED WARNING: HEPATOTOXICITY AND EMBRYO-FETAL TOXICITY

Because of the risks of hepatotoxicity and birth defects, FILSPARI is available only through a restricted program called the FILSPARI REMS. Under the FILSPARI REMS, prescribers, patients and pharmacies must enroll in the program.

Hepatotoxicity

Some Endothelin Receptor Antagonists (ERAs) have caused elevations of aminotransferases, hepatotoxicity, and liver failure. In clinical studies, elevations in aminotransferases (ALT or AST) of at least 3-times the Upper Limit of Normal (ULN) have been observed in up to 2.5% of FILSPARI-treated patients, including cases confirmed with rechallenge.

Measure transaminases and bilirubin before initiating treatment and monthly for the first 12 months, and then every 3 months during treatment. Interrupt treatment and closely monitor patients who develop aminotransferase elevations more than 3x ULN.

FILSPARI should generally be avoided in patients with elevated aminotransferases (>3x ULN) at baseline because monitoring for hepatotoxicity may be more difficult and these patients may be at increased risk for serious hepatotoxicity.

Embryo-Fetal Toxicity

FILSPARI can cause major birth defects if used by pregnant patients based on animal data. Therefore, pregnancy testing is required before the initiation of treatment, during treatment and one month after discontinuation of treatment with FILSPARI. Patients who can become pregnant must use effective contraception before the initiation of treatment, during treatment, and for one month after discontinuation of treatment with FILSPARI.

Contraindications

Use of FILSPARI is contraindicated in patients who are pregnant. Do not coadminister FILSPARI with angiotensin receptor blockers (ARBs), ERAs, or aliskiren.

Please see additional Important Safety Information on adjacent page.

Warnings and Precautions

- **Hepatotoxicity:** Elevations in ALT or AST of at least 3-fold ULN have been observed in up to 2.5% of FILSPARI-treated patients, including cases confirmed with rechallenge. While no concurrent elevations in bilirubin >2-times ULN or cases of liver failure were observed in FILSPARI-treated patients, some ERAs have caused elevations of aminotransferases, hepatotoxicity, and liver failure. To reduce the risk of potential serious hepatotoxicity, measure serum aminotransferase levels and total bilirubin prior to initiation of treatment and monthly for the first 12 months, then every 3 months during treatment.

  Advise patients with symptoms suggesting hepatotoxicity (nausea, vomiting, right upper quadrant pain, fatigue, anorexia, jaundice, dark urine, fever, or itching) to immediately stop treatment with FILSPARI and seek medical attention. If aminotransferase levels are abnormal at any time during treatment, interrupt FILSPARI and monitor as recommended.

  Consider re-initiation of FILSPARI only when hepatic enzyme levels and bilirubin return to pretreatment values and only in patients who have not experienced clinical symptoms of hepatotoxicity. Avoid initiation of FILSPARI in patients with elevated aminotransferases (>3x ULN) prior to drug initiation because monitoring hepatotoxicity in these patients may be more difficult and these patients may be at increased risk for serious hepatotoxicity.
- **Embryo-Fetal Toxicity:** FILSPARI can cause fetal harm when administered to a pregnant patient and is contraindicated during pregnancy. Advise patients who can become pregnant of the potential risk to a fetus. Obtain a pregnancy test prior to initiation of treatment with FILSPARI, monthly during treatment, and one month after discontinuation of treatment. Advise patients who can become pregnant to use effective contraception prior to initiation of treatment, during treatment, and for one month after discontinuation of treatment with FILSPARI.
- **FILSPARI REMS:** For all patients, FILSPARI is available only through a restricted program under a REMS called the FILSPARI REMS because of the risk of hepatotoxicity and embryo-fetal toxicity.
  Important requirements of the FILSPARI REMS program include the following:
  - Prescribers must be certified with the FILSPARI REMS by enrolling and completing training.
  - All patients must enroll in the FILSPARI REMS prior to initiating treatment and comply with monitoring requirements.
  - Pharmacies that dispense FILSPARI must be certified with the FILSPARI REMS and must dispense only to patients who are authorized to receive FILSPARI.

  Further information is available at www.filsparirems.com or 1-833-513-1325.
- **Hypotension:** Hypotension has been observed in patients treated with ARBs and ERAs. There was a greater incidence of hypotension-associated adverse events, some serious, including dizziness, in patients treated with FILSPARI compared to irbesartan. In patients at risk for hypotension, consider eliminating or adjusting other antihypertensive medications and maintaining appropriate volume status. If hypotension develops, despite elimination or reduction of other antihypertensive medications, consider a dose reduction or dose interruption of FILSPARI. A transient hypotensive response is not a contraindication to further dosing of FILSPARI, which can be given once blood pressure has stabilized.
- **Acute Kidney Injury:** Monitor kidney function periodically. Drugs that inhibit the renin-angiotensin system can cause kidney injury. Patients whose kidney function may depend in part on the activity of the renin-angiotensin system (e.g., patients with renal artery stenosis, chronic kidney disease, severe congestive heart failure, or volume depletion) may be at particular risk of developing acute kidney injury on FILSPARI. Consider withholding or discontinuing therapy in patients who develop a clinically significant decrease in kidney function while on FILSPARI.
- **Hyperkalemia:** Monitor serum potassium periodically and treat appropriately. Patients with advanced kidney disease, taking concomitant potassium-increasing drugs (e.g., potassium supplements, potassium-sparing diuretics), or using potassium-containing salt substitutes are at increased risk for developing hyperkalemia. Dosage reduction or discontinuation of FILSPARI may be required.
- **Fluid Retention:** Fluid retention may occur with ERAs, and has been observed in clinical studies with FILSPARI. FILSPARI has not been evaluated in patients with heart failure. If clinically significant fluid retention develops, evaluate the patient to determine the cause and the potential need to initiate or modify the dose of diuretic treatment then consider modifying the dose of FILSPARI.

Most common adverse reactions

The most common adverse reactions (≥5%) are peripheral edema, hypotension (including orthostatic hypotension), dizziness, hyperkalemia, and anemia.

Drug interactions

- **Renin-Angiotensin System (RAS) Inhibitors and ERAs:** Do not coadminister FILSPARI with ARBs, ERAs, or aliskiren. Combined use of these agents is associated with increased risks of hypotension, syncope, hyperkalemia, and changes in renal function (including acute renal failure).
- **Strong and Moderate CYP3A Inhibitors:** Avoid concomitant use of FILSPARI with strong CYP3A inhibitors. If a strong CYP3A inhibitor cannot be avoided, interrupt treatment with FILSPARI. When resuming treatment with FILSPARI, consider dose titration. Monitor blood pressure, serum potassium, edema, and kidney function regularly when used concomitantly with moderate CYP3A inhibitors. Sparsentan is a CYP3A substrate. Concomitant use with a strong CYP3A inhibitor increases sparsentan C_{max} and AUC which may increase the risk of FILSPARI adverse reactions.
- **Strong CYP3A Inducers:** Avoid concomitant use with a strong CYP3A inducer. Sparsentan is a CYP3A substrate. Concomitant use with a strong CYP3A inducer decreases sparsentan C_{max} and AUC, which may reduce FILSPARI efficacy.
- **Antacids and Acid Reducing Agents:** Administer FILSPARI 2 hours before or after administration of antacids. Avoid concomitant use of acid reducing agents (histamine H2 receptor antagonist and PPI proton pump inhibitor) with FILSPARI. Sparsentan exhibits pH-dependent solubility. Antacids or acid reducing agents may decrease sparsentan exposure which may reduce FILSPARI efficacy.
- **Non-Steroidal Anti-Inflammatory Agents (NSAIDs), Including Selective Cyclooxygenase-2 (COX-2) Inhibitors:** Monitor for signs of worsening renal function with concomitant use with NSAIDs (including selective COX-2 inhibitors). In patients with volume depletion (including those on diuretic therapy) or with impaired kidney function, concomitant use of NSAIDs (including selective COX-2 inhibitors) with drugs that antagonize the angiotensin II receptor may result in deterioration of kidney function, including possible kidney failure.
- **CYP2B6, 2C9, and 2C19 Substrates:** Monitor for efficacy of the concurrently administered CYP2B6, 2C9, and 2C19 substrates and consider dosage adjustment in accordance with the Prescribing Information. Sparsentan is an inducer of CYP2B6, 2C9, and 2C19. Sparsentan decreases exposure of these substrates, which may reduce efficacy related to these substrates.
- **P-gp and BCRP Substrates:** Avoid concomitant use of sensitive substrates of P-gp and BCRP with FILSPARI. Sparsentan is an inhibitor of P-gp and BCRP. Sparsentan may increase exposure of these transporter substrates, which may increase the risk of adverse reactions related to these substrates.
- **Agents Increasing Serum Potassium:** Monitor serum potassium frequently in patients treated with FILSPARI and other agents that increase serum potassium. Concomitant use of FILSPARI with potassium-sparing diuretics, potassium supplements, potassium-containing salt substitutes, or other drugs that raise serum potassium levels may result in hyperkalemia.

Use in specific populations

- **Pregnancy / Females and Males of Reproductive Potential:** FILSPARI can cause fetal harm, including birth defects and fetal death, when administered to a pregnant patient and is contraindicated during pregnancy. Advise pregnant patients of the potential risk to the fetus.
  - **Pregnancy Testing:** Verify that patients who can become pregnant are not pregnant prior to initiating FILSPARI, monthly during treatment, and one month after discontinuation of treatment. The patient should contact their physician immediately for pregnancy testing if onset of menses is delayed or pregnancy is suspected. If the pregnancy test is positive, the physician and patient must discuss the risks to their pregnancy and the fetus.
  - **Contraception:** Patients who can become pregnant who are using FILSPARI must use an effective method of contraception prior to initiation of treatment, during treatment, and for one month after discontinuation of treatment with FILSPARI to prevent pregnancy.
- **Lactation:** Advise patients not to breastfeed during treatment with FILSPARI.
- **Hepatic Impairment:** Avoid use of FILSPARI in patients with any hepatic impairment (Child-Pugh class A-C) because of the potential risk of serious liver injury.

For additional Important Safety Information, please see Brief Summary of the full Prescribing Information on the following pages, and the full Prescribing Information, including BOXED WARNING.

References: 1. FILSPARI Prescribing Information. San Diego, CA: Travere Therapeutics, Inc. **2.** Data on file; Travere Therapeutics, Inc.

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TRAVERE™ THERAPEUTICS

Brief Summary of full Prescribing Information for FILSPARI™ (sparsentan) tablets, for oral use

Initial U.S. Approval: 2023

INDICATIONS AND USAGE

FILSPARI is indicated to reduce proteinuria in adults with primary immunoglobulin A nephropathy (IgAN) at risk of rapid disease progression, generally a urine protein-to-creatinine ratio (UPCR) ≥1.5 g/g.

This indication is approved under accelerated approval based on a reduction of proteinuria. It has not been established whether FILSPARI slows kidney function decline in patients with IgAN. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory clinical trial.

WARNING: HEPATOTOXICITY and EMBRYO-FETAL TOXICITY

Because of the risks of hepatotoxicity and birth defects, FILSPARI is available only through a restricted program called the FILSPARI REMS. Under the FILSPARI REMS, prescribers, patients, and pharmacies must enroll in the program.

Hepatotoxicity

Some Endothelin Receptor Antagonists (ERAs) have caused elevations of aminotransferases, hepatotoxicity, and liver failure. In clinical studies, elevations in aminotransferases (ALT or AST) of at least 3-times the Upper Limit of Normal (ULN) have been observed in up to 2.5% of FILSPARI-treated patients, including cases confirmed with rechallenge.

Measure transaminases and bilirubin before initiating treatment and monthly for the first 12 months, and then every 3 months during treatment. Interrupt treatment and closely monitor patients who develop aminotransferase elevations more than 3x ULN.

FILSPARI should generally be avoided in patients with elevated aminotransferases (>3x ULN) at baseline because monitoring for hepatotoxicity may be more difficult and these patients may be at increased risk for serious hepatotoxicity.

Embryo-Fetal Toxicity

FILSPARI can cause major birth defects if used by pregnant patients based on animal data. Therefore, pregnancy testing is required before the initiation of treatment, during treatment, and one month after discontinuation of treatment with FILSPARI. Patients who can become pregnant must use effective contraception before the initiation of treatment, during treatment, and for one month after discontinuation of treatment with FILSPARI.

CONTRAINDICATIONS

Use of FILSPARI is contraindicated in patients who are pregnant.

Do not coadminister FILSPARI with angiotensin receptor blockers (ARBs), ERAs, or aliskiren.

WARNINGS AND PRECAUTIONS

Hepatotoxicity

Elevations in ALT or AST of at least 3-fold ULN have been observed in up to 2.5% of FILSPARI-treated patients, including cases confirmed with rechallenge. While no concurrent elevations in bilirubin >2-times ULN or cases of liver failure were observed in FILSPARI-treated patients in clinical trials, some endothelin receptor antagonists have caused elevations of aminotransferases, hepatotoxicity, and liver failure. To reduce the risk of potential serious hepatotoxicity, measure serum aminotransferase levels and total bilirubin prior to initiation of treatment and monthly for the first 12 months, then every 3 months during treatment.

Advise patients with symptoms suggesting hepatotoxicity (nausea, vomiting, right upper quadrant pain, fatigue, anorexia, jaundice, dark urine, fever, or itching) to immediately stop treatment with FILSPARI and seek medical attention. If aminotransferase levels are abnormal at any time during treatment, interrupt FILSPARI and monitor as recommended.

Consider re-initiation of FILSPARI only when hepatic enzyme levels and bilirubin return to pretreatment values and only in patients who have not experienced clinical symptoms of hepatotoxicity.

Avoid initiation of FILSPARI in patients with elevated aminotransferases (>3x ULN) prior to drug initiation because monitoring hepatotoxicity in these patients may be more difficult and these patients may be at increased risk for serious hepatotoxicity.

Embryo-Fetal Toxicity

Based on data from animal reproduction studies, FILSPARI can cause fetal harm when administered to a pregnant patient and is contraindicated during pregnancy. Advise patients who can become pregnant of the potential risk to a fetus. Obtain a pregnancy test prior to initiation of treatment with FILSPARI, monthly during treatment, and one month after discontinuation of treatment. Advise patients who can become pregnant to use effective contraception prior to initiation of treatment, during treatment, and for one month after discontinuation of treatment with FILSPARI.

FILSPARI REMS

For all patients, FILSPARI is available only through a restricted program under a REMS called the FILSPARI REMS because of the risk of hepatotoxicity and embryo-fetal toxicity.

Important requirements of the FILSPARI REMS include the following:

- Prescribers must be certified with the FILSPARI REMS by enrolling and completing training.
- All patients must enroll in the FILSPARI REMS prior to initiating treatment and comply with monitoring requirements.
- Pharmacies that dispense FILSPARI must be certified with the FILSPARI REMS and must dispense only to patients who are authorized to receive FILSPARI.

Further information is available at www.filsparirems.com or 1-833-513-1325.

Hypotension

Hypotension has been observed in patients treated with ARBs and endothelin receptor antagonists (ERAs) and was observed in clinical studies with FILSPARI. In the PROTECT trial, there was a greater incidence of hypotension-associated adverse events, some serious, including dizziness, in patients treated with FILSPARI compared to irbesartan.

In patients at risk for hypotension, consider eliminating or adjusting other antihypertensive medications and maintaining appropriate volume status.

If hypotension develops, despite elimination or reduction of other antihypertensive medications, consider a dose reduction or dose interruption of FILSPARI. A transient hypotensive response is not a contraindication to further dosing of FILSPARI, which can be given once blood pressure has stabilized.

Acute Kidney Injury

Monitor kidney function periodically. Drugs that inhibit the renin-angiotensin system can cause acute kidney injury. Patients whose kidney function may depend in part on the activity of the renin-angiotensin system (e.g., patients with renal artery stenosis, chronic kidney disease, severe congestive heart failure, or volume depletion) may be at particular risk of developing acute kidney injury on FILSPARI. Consider withholding or discontinuing therapy in patients who develop a clinically significant decrease in kidney function while on FILSPARI.

Hyperkalemia

Monitor serum potassium periodically and treat appropriately. Patients with advanced kidney disease or taking concomitant potassium-increasing drugs (e.g., potassium supplements, potassium-sparing diuretics), or using potassium-containing salt substitutes are at increased risk for developing hyperkalemia. Dosage reduction or discontinuation of FILSPARI may be required.

Fluid Retention

Fluid retention may occur with endothelin receptor antagonists and has been observed in clinical studies with FILSPARI. FILSPARI has not been evaluated in patients with heart failure.

If clinically significant fluid retention develops, evaluate the patient to determine the cause and the potential need to initiate or modify the dose of diuretic treatment then consider modifying the dose of FILSPARI.

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of FILSPARI was evaluated in PROTECT (NCT03762850), a randomized, double-blind, active-controlled clinical study in adults with IgAN.

The data below reflect FILSPARI exposure in 202 patients with a median duration of 73 weeks (up to 110 weeks).

The most common adverse reactions are presented in the table below.

Adverse Reactions[1] Reported in ≥2% in Subjects Treated with FILSPARI

	FILSPARI (N = 202) n (%)	Irbesartan (N = 202) n (%)
Peripheral edema	29 (14)	19 (9)
Hypotension (including orthostatic hypotension)	28 (14)	12 (6)
Dizziness	27 (13)	11 (5)
Hyperkalemia	27 (13)	21 (10)
Anemia	10 (5)	5 (2)
Acute kidney injury	9 (4)	2 (1)
Transaminase elevations[2]	5 (2.5)	4 (2)

[1] Data presented include all Treatment-Emergent Adverse Events reported
[2] Elevations in ALT or AST >3-fold ULN reported as Adverse Events of Interest

Laboratory Tests

Initiation of FILSPARI may cause an initial small decrease in estimated glomerular filtration rate (eGFR) that occurs within the first 4 weeks of starting therapy and then stabilizes.

The incidence of a hemoglobin decrease >2 g/dL compared to baseline and below the lower limit of normal was greater for the FILSPARI arm (11%) compared to the irbesartan arm (5%). This decrease is thought to be in part due to hemodilution. There were no treatment discontinuations due to anemia or hemoglobin decrease in the PROTECT study.

DRUG INTERACTIONS

Renin-Angiotensin System (RAS) Inhibitors and ERAs

Do not coadminister FILSPARI with ARBs, ERAs, or aliskiren.

Combined use of these agents is associated with increased risks of hypotension, syncope, hyperkalemia, and changes in renal function (including acute renal failure).

Strong and Moderate CYP3A Inhibitors

Avoid concomitant use of FILSPARI with strong CYP3A inhibitors. If a strong CYP3A inhibitor cannot be avoided, interrupt treatment with FILSPARI. When resuming treatment with FILSPARI, consider dose titration.

Monitor blood pressure, serum potassium, edema, and kidney function regularly when used concomitantly with moderate CYP3A inhibitors. No FILSPARI dose adjustment is needed.

Sparsentan is a CYP3A substrate. Concomitant use with a strong CYP3A inhibitor increases sparsentan C_{max} and AUC, which may increase the risk of FILSPARI adverse reactions.

Strong CYP3A Inducers

Avoid concomitant use with a strong CYP3A inducer. Sparsentan is a CYP3A substrate. Concomitant use with a strong CYP3A inducer decreases sparsentan C_{max} and AUC, which may reduce FILSPARI efficacy.

Antacids and Acid Reducing Agents

Administer FILSPARI 2 hours before or after administration of antacids. Avoid concomitant use of acid reducing agents (histamine H2 receptor antagonist and PPI proton pump inhibitor) with FILSPARI. Sparsentan exhibits pH-dependent solubility. Antacids or acid reducing agents may decrease sparsentan exposure which may reduce FILSPARI efficacy.

Non-Steroidal Anti-Inflammatory Agents (NSAIDs), Including Selective Cyclooxygenase-2 (COX-2) Inhibitors

Monitor for signs of worsening renal function with concomitant use with NSAIDs (including selective COX-2 inhibitors). In patients with volume depletion (including those on diuretic therapy) or with impaired kidney function, concomitant use of NSAIDs (including selective COX-2 inhibitors) with drugs that antagonize the angiotensin II receptor may result in deterioration of kidney function, including possible kidney failure. These effects are usually reversible.

CYP2B6, 2C9, and 2C19 Substrates

Monitor for efficacy of the concurrently administered CYP2B6, 2C9, and 2C19 substrates and consider dosage adjustment in accordance with the Prescribing Information. Sparsentan is an inducer of CYP2B6, 2C9, and 2C19. Sparsentan decreases exposure of these substrates, which may reduce efficacy related to these substrates.

P-gp and BCRP Substrates

Avoid concomitant use of sensitive substrates of P-gp and BCRP with FILSPARI. Sparsentan is an inhibitor of P-gp and BCRP. Sparsentan may increase exposure of these transporter substrates, which may increase the risk of adverse reactions related to these substrates.

Agents Increasing Serum Potassium

Monitor serum potassium frequently in patients treated with FILSPARI and other agents that increase serum potassium. Concomitant use of FILSPARI with potassium-sparing diuretics, potassium supplements, potassium-containing salt substitutes, or other drugs that raise serum potassium levels may result in hyperkalemia.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on data from animal reproductive toxicity studies, FILSPARI can cause fetal harm, including birth defects and fetal death, when administered to a pregnant patient and is contraindicated during pregnancy. Available data from reports of pregnancy in clinical trials with FILSPARI are insufficient to identify a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. In animal reproduction studies, oral administration of sparsentan to pregnant rats throughout organogenesis at 10-times the maximum recommended human dose (MRHD) in mg/day caused teratogenic effects in rats, including craniofacial malformations, skeletal abnormalities, increased embryo-fetal lethality, and reduced fetal weights. Advise pregnant patients of the potential risk to the fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Lactation

Risk Summary

There are no data on the presence of sparsentan in human milk, the effects on the breastfed infant, or the effect on milk production. Because of the potential for adverse reactions, such as hypotension in breastfed infants, advise patients not to breastfeed during treatment with FILSPARI.

Females and Males of Reproductive Potential

Based on data from animal reproductive toxicity studies, FILSPARI can cause fetal harm, including birth defects and fetal death, when administered to a pregnant patient and is contraindicated during pregnancy.

Pregnancy Testing

Verify that patients who can become pregnant are not pregnant prior to initiating FILSPARI, monthly during treatment, and one month after discontinuation of treatment. The patient should contact their physician immediately for pregnancy testing if onset of menses is delayed or pregnancy is suspected. If the pregnancy test is positive, the physician and patient must discuss the risks to their pregnancy and the fetus.

Contraception

Patients who can become pregnant who are using FILSPARI must use an effective method of contraception prior to initiation of treatment, during treatment, and for one month after discontinuation of treatment with FILSPARI to prevent pregnancy.

Pediatric Use

The safety and efficacy of FILSPARI in pediatric patients have not been established.

Geriatric Use

Of the total number of subjects in the PROTECT study of FILSPARI, 15 (7.4%) were 65 and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

Hepatic Impairment

Avoid use of FILSPARI in patients with any hepatic impairment (Child-Pugh class A-C) because of the potential risk of serious liver injury.

OVERDOSAGE

There is no experience with overdose with FILSPARI. Sparsentan has been given in doses up to 1600 mg/day in healthy volunteers, or up to 400 mg/day in patients. Overdose of FILSPARI may result in decreased blood pressure. In the event of an overdose, standard supportive measures should be taken, as required. Dialysis is unlikely to be effective because sparsentan is highly protein-bound.

PATIENT COUNSELING INFORMATION

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

Restricted access

Advise the patient that FILSPARI is only available through a restricted access program called the FILSPARI REMS.

As a component of the FILSPARI REMS, prescribers must review the contents of the FILSPARI Medication Guide with the patient before initiating FILSPARI.

Instruct patients that the risks associated with FILSPARI include:

Hepatotoxicity

Advise patients with symptoms suggesting hepatotoxicity (nausea, vomiting, right upper quadrant pain, fatigue, anorexia, jaundice, dark urine, fever, or itching) to immediately stop taking FILSPARI and seek medical attention.

Embryo-Fetal Toxicity

Educate and counsel patients who can become pregnant about the need to use reliable methods of contraception prior to treatment with FILSPARI, during treatment and for one month after treatment discontinuation. Patients who can become pregnant must have pregnancy tests prior to treatment with FILSPARI, monthly during treatment, and one month after treatment discontinuation.

Patients should be instructed to immediately contact their physician if they suspect they may be pregnant. Patients should seek additional contraceptive advice from a gynecologist or similar expert as needed.

Educate and counsel patients who can become pregnant on the use of emergency contraception in the event of unprotected sex or contraceptive failure.

Advise patients to contact their gynecologist or healthcare provider if they want to change the form of birth control which is used to ensure that another acceptable form of birth control is selected.

Advise the patient that FILSPARI is available only from certified pharmacies that are enrolled in the FILSPARI REMS.

Patients must sign the FILSPARI REMS Patient Enrollment Form to confirm that they understand the risks of FILSPARI.

Lactation

Advise patients not to breastfeed during treatment with FILSPARI.

Drug Interactions

Advise patients to inform their healthcare provider of all concomitant medications, including prescription medications, over-the-counter drugs, vitamins/supplements, herbal products, and grapefruit.

Other Risks Associated with FILSPARI

Inform patients of other risks associated with FILSPARI, including:

- Hypotension: Advise patients to remain hydrated.
- Hyperkalemia: Advise patients not to use potassium supplements or salt substitutes that contain potassium without consulting their healthcare provider.

This information is not comprehensive. Visit FILSPARI.com or call 1-877-659-5518 to obtain the full Prescribing Information.

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02/2023 SPA0112

TRAVERE™ THERAPEUTICS

Unexplained, Recurrent AKI in a Young Man—It Takes a Community

By Roger A. Rodby

A 28-year male from Asia, with no comorbidities; with no family history of kidney diseases; a non-smoker; an occasional alcohol drinker; with no use of nonsteroidal anti-inflammatory drugs/other drugs; and index presentation in October 2020 with nausea, generalized weakness, and on investigation creatinine was 2 mg/dL (no baseline creatinine). With hydration, acute kidney injury (AKI) self-resolved to creatinine 1.1 mg/dL in 1 month.

And so began a thread from a physician in India that was posted in the Open Forum of ASN Communities (1). Eight months later, it happened to the patient again: same symptoms, same AKI, and a similar resolution. An extensive history was taken and was negative for any ingestions, prodromes, fevers, etc. A urinalysis was normal, and a 24-hour urine collection showed 72 mg of proteinuria. Serologic testing included normal antinuclear antibody, cytoplasmic-antineutrophil cytoplasmic antibody (ANCA), and perinuclear-ANCA. Two months later, the patient had the same presentation and outcome. Six months after the initial presentation, he developed gross hematuria, and his creatinine peaked at 2.6 mg/dL. This time, the urinalysis had >100 red blood cell/high-powered field. An antistreptolysin O titer, C3, and C4 were in the normal range. He was then treated with intravenous pulse steroids, and within 1 week, his creatinine level was 1.2 mg/dL and urinalysis completely normalized. Two months following that AKI episode, he developed another AKI to 2.7 mg/dL but no hematuria this time, and a kidney biopsy was performed. It was read as normal kidney parenchyma. The kidney function resolved again within 1 week. For 1 year, he was symptom-free, and then he developed similar vague symptoms and gross hematuria: creatinine, 2.3 mg/dL. Within 1 week, it normalized to 1.1 mg/dL, and hematuria resolved. The patient exercised regularly with both resistance and aerobic training but was unable to associate any of these AKI events to his level of workout routine.

In 2016, ASN opened its online "ASN Communities": a physician blog that allows any ASN member to post a difficult case to which any other ASN member can contribute with comments, suggestions, or advice. This case of totally unexplained AKI is the kind of unusual case that we often see posted in the "Open" Communities forum.

The blog continued with questions from various ASN members of hemolysis, rhabdomyolysis, porphyria, and even paroxysmal nocturnal hemoglobinuria, even though the patient experienced hematuria not pigmenturia. Then, following several posts questioning the kidney biopsy, a contributing nephrologist, also from India, asked for a serum uric acid level. This was largely ignored until he posted his comment: "*A low serum uric acid may be a clue to the development of AKI with exercise or even otherwise due to a URAT1 [urate transporter 1] mutation*," at which point everyone jumped on the hypouricemic bandwagon! A uric acid was ordered and was extremely low at 0.3 mg/dL with a fractional excretion of uric acid of 120%. What then followed were several references to case reports of AKI associated with renal hypouricemia (RHUC) that were often preceded by exercise and sometimes associated with gross hematuria. The symptoms are relatively non-specific with malaise, often with flank pain, and typically with microscopic hematuria but can be gross. Microscopic examination of the urine may show uric acid crystals.

RHUC is a rare genetic condition in which there is impaired tubular transport of uric acid in the proximal tubule. As a result, the serum uric acid is very low (<2%) associated with a high fractional excretion of uric acid (>10%). Type 1 RHUC is caused by a loss-of-function mutation in *SLC22A12*, which encodes the URAT1 uric acid transporter within the apical plasma membrane of the proximal tubule. Type 2 RHUC is related to a mutation in *SLC2A9* (or glucose transporter 9 [GLUT9]), which encodes GLUT9 in the apical and basolateral membranes of the proximal tubule (Figure 1). Type 1 RHUC is more common than type 2 RHUC, but the latter is more severe, with the lowest blood levels of uric acid (2–5). Both have been associated with a clinical syndrome of exercise-induced AKI. These are rare, autosomal-recessive, genetic mutations but can be tested with commercial, renal-oriented, genetic panels that are finding a rapidly expanding role in chronic kidney disease and unexplained AKI, as could have been the case here.

There are two theories that explain exercise-induced AKI seen in RHUC. One is renal tubular uric acid overload with crystal formation brought on by exercise, which increases protein catabolism and thus uric acid production. This increased protein catabolism will also lower the urine pH, which markedly decreases uric acid solubility. Finally, exercise may lead to dehydration and increase urinary concentration, which will further decrease uric acid solubility. These factors could lead to uric acid tubular obstruction and hematuria from crystal-induced damage. Uric acid stones have been occasionally described in RHUC. The second RHUC AKI hypothesis relates to the fact that uric acid has potent antioxidant activity, and this may be lacking in patients with RHUC. Supporting the former explanation—that exercise-induced AKI is a result of an increased uric acid load (exercise) in a dehydrated acidic urine—are the facts that a patient with RHUC and exercise-induced AKI underwent a formal physical fitness test, the uric acid excretion rate increased three-fold from 0.48 mg/min to 1.49 mg/min, and he developed AKI. The patient then received allopurinol, 300 mg/day, for 5 days; the physical fitness test was repeated; the uric acid excretion was lower at 0.28 mg/min and did not increase with exercise (0.22 mg/min); and the patient did not develop AKI (5). Whether there is a role for allopurinol in RHUC-associated AKI is unknown. There was additional discussion in the Communities thread for the use of urine alkalization with sodium bicarbonate, representing more speculation, but interesting nevertheless.

Although it is extremely unlikely that the average nephrologist will ever see a case of RHUC, and even though I find the purported mechanism of AKI associated with RHUC extremely interesting, I would emphasize that this is more than a fascinating case but demonstrates what an asset ASN Communities is to members of ASN. This is a lesson about how international collaboration not only helps a physician solve a mystery—and in doing so, potentially helps a patient—but in the process, also educates a broad "community" of nephrologists. ■

Roger A. Rodby, MD, is a professor of medicine in the Division of Nephrology, Rush University Medical Center, Chicago, IL.

Dr. Rodby serves as a leader in ASN Communities' online Open Forum and is the co-director of ASN's Board Review Course & Update.

References

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2. Jeannin G, et al. Recurrent exercise-induced acute renal failure in a young Pakistani man with severe hypouricemia and *SLC2A9* compound heterozygosity. *BMC Med Genet* 2014; 15:3. doi: 10.1186/1471-2350-15-3
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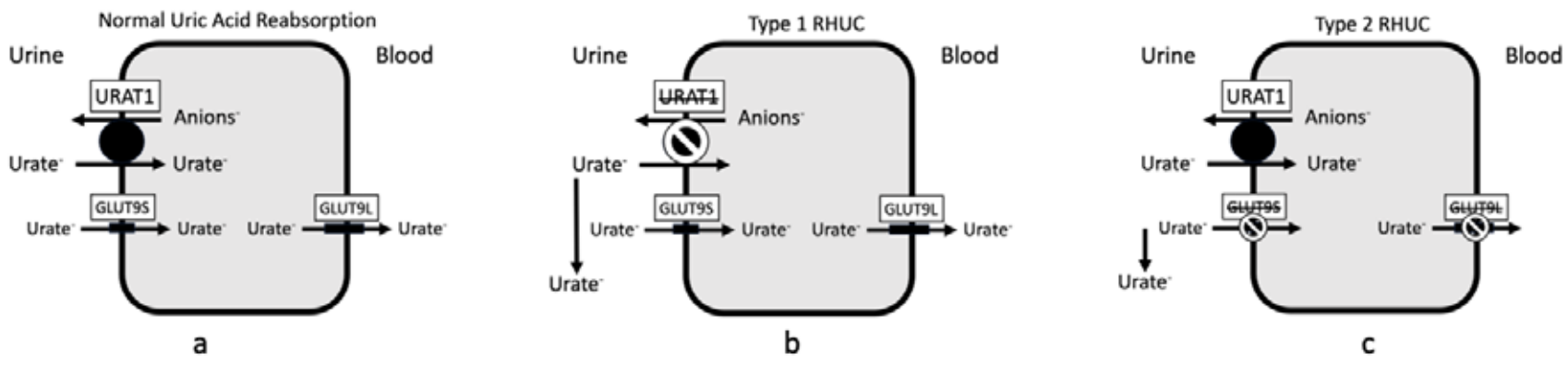
Figure 1. Normal uric acid reabsorption compared with type 1 and type 2 renal hypouricemia



Filtered uric acid is transported back into the blood by two mechanisms. There is an anion exchanger URAT1 on the apical side of the proximal tubule membrane that transports uric acid into the cell. It then exits the cell through the GLUT9 transporter, which exists as a long form (GLUT9L) located on the basolateral proximal tubule membrane and a short form (GLUT9S) located on the apical proximal tubule membrane (a). Defects in either URAT1 (b) or GLUT9 (c) will impair uric acid reabsorption and lead to hypouricemia, increasing the risk for uric acid stones and exercise-induced AKI.

Visit the ASN Communities Lounge at ASN Kidney Week

Community discussions, networking and collaboration.

Meet-and-Greet
10:00 a.m. — 11:00 a.m.

Ed Kashi
Photojournalist and Filmmaker

Thursday, Nov. 2

Overview of Communities — **11:00 a.m. — 12:00 p.m.**
Profile components, account preferences, navigation tips

Mentor Match Program — **12:00 p.m. — 1:00 p.m.**
Enrollment basics, search criteria, building relationships

Networking and Collaboration — **1:00 p.m. — 2:00 p.m.**
Leveraging connections, sharing stories, team projects

Friday, Nov. 3

CMMI Listening Session — **10:00 a.m. — 11:00 a.m.**
Join the Center for Medicare and Medicaid Innovation (CMMI) and ASN to discuss the ESRD Treatment Choices (ETC) Model and the Kidney Care Choices (KCC) Model.

Hot Topics — **11:00 a.m. — 12:00 p.m.**
Chronic Kidney Disease, Transplantation, Home Dialysis

Becoming a Community Leader — **12:00 p.m. — 1:00 p.m.**
Engagement strategies, moderation, replies and follow-through

CMMI Listening Session — **1:00 p.m. — 2:00 p.m.**
Join CMMI representatives and ASN staff to ask questions and discuss issues regarding the ETC Model and KCC Model.

Saturday, Nov. 4

Communities Library — **10:00 a.m. — 11:00 a.m.**
Keyword searching, studies & reports, credible research

Early Career Focus — **11:00 a.m. — 12:00 p.m.**
STARS, TREKS, in-training exam, the nephrology match

Themed Communities — **12:00 p.m. — 1:00 p.m.**
Onco-nephrology, Kidney Transplantation, Women's Health & Research

Open Discussion — **1:00 p.m. — 2:00 p.m.**
New ideas, future directions, lingering questions

Listen and partake in conversations.

ASN Communities

KIDNEY WEEK 2023

Nov. 2–5 | Philadelphia, PA

ASN Career Fair

Meet face-to-face with top employers looking to hire!

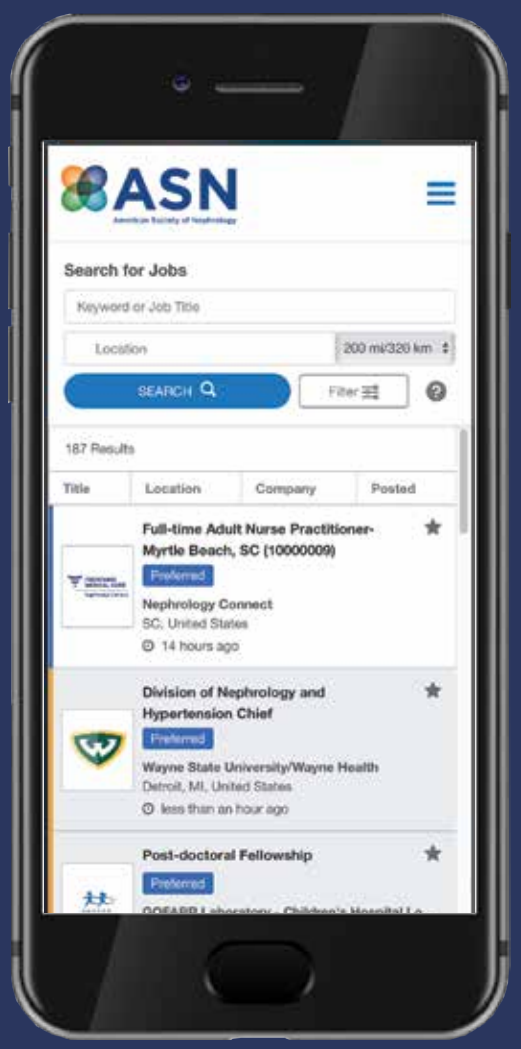
November 2–4, 2023
9:30 a.m. – 2:30 p.m.

Located in the Exhibit Hall

ASN invites you to take part in the ASN Career Fair. Connect with employers and find your next nephrology opportunity. It's FREE to attend!

Be on the lookout for the ASN Featured Employers Guide, including open positions from top employers delivered to your inbox after Kidney Week.

Take charge of your career! Upload or update your resume on the ASN Career Center.



- Get your resume in front of employers hiring nephrology professionals who search the database.
- Search for jobs that are posted right from your smartphone or tablet.
- Be the first to get job alerts when a new position matching your criteria is available.
- Gain resume writing tips and how to prepare for an interview.

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

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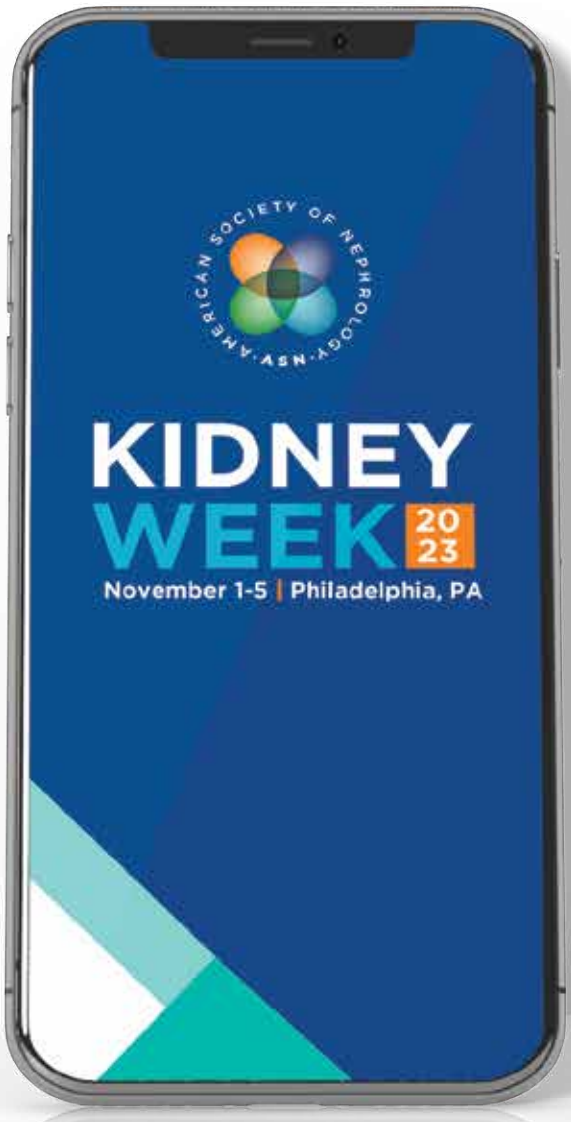

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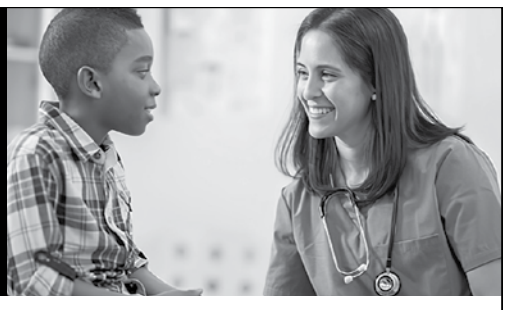

St. Christopher's Hospital for Children
A PARTNERSHIP OF TOWER HEALTH AND DREXEL UNIVERSITY

TOWER HEALTH IS SEEKING A **PEDIATRIC NEPHROLOGIST**

for St. Christopher's Hospital for Children, Philadelphia, PA

St. Christopher's Hospital for Children is seeking a **Pediatric Nephrologist** to join the hospital's pediatric staff of experts.

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For more information, contact:
Beth Calabria, MBA, CPRP,
Sr. Medical Staff Recruiter
484-628-6714
Beth.Calabria@towerhealth.org

To apply, scan the QR Code or go to Careers.TowerHealth.org.
Tower Health is an Equal Opportunity Employer committed to creating a diverse and inclusive environment reflective of the communities we serve.

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Shelley Talbot, Physician Recruiter
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