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Rare Disease Registries Provide a Powerful Tool for Patients, Researchers, and Clinicians

By Bridget M. Kuehn

It took Richard Nelson 23 years to find the cause of the rare genetic kidney disease that had affected his father, himself, and three of his five siblings. For years his physicians at the Mayo Clinic thought he was experiencing polycystic kidney disease. But 7 years ago, they realized that a different rare genetic kidney disease called mucin-1 (MUC-1) kidney disease was likely to blame and referred him to a team of clinicians and researchers from the Broad Institute in Cambridge, MA, and Wake Forest University School of Medicine in Winston-Salem, NC.

Nelson's journey is typical of what many patients and families with rare genetic forms of kidney diseases face as they seek answers and treatment. "There are hundreds of thousands of people in the world [who] are alone, desperate, and suffering who have no answers," Nelson said.

But patient advocates, clinicians, and scientists across the country are leveraging rare kidney disease patient registries to help patients find answers faster and to accelerate the development of treatments for rare kidney diseases, including MUC-1 kidney disease and Dent disease.

Nelson and his family have joined more than 1000 families and 2000 people from all over the world participating in the Wake Forest Rare Inherited Kidney Disease registry (1). The registry has helped scientists identify five genes that cause rare, inherited, autosomal-dominant kidney diseases (2). The registry has also yielded new insights about the natural history of MUC-1 kidney disease and is laying the necessary groundwork for a clinical trial of an experimental treatment expected to begin within the next 2 years.

"It gives all of us a tremendous amount of hope because we can see incrementally how we are helping to move things forward," said Nelson, who is chairman and trustee of the Rare Kidney Disease Foundation, an organization he helped found in 2018.

Anthony Bleyer, MD, MS, a professor at Wake Forest University School of Medicine and leader of its Rare Inherited Kidney Disease team, began hunting for genetic causes of rare, inherited kidney diseases in 1995 while

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Study Explores Mortality and Years of Life Lost in Children with Kidney Failure

By Tracy Hampton

Children who develop kidney failure and receive a kidney transplant have excellent 5- and 10-year survival rates, but little is known about their lifetime survival. In research recently published in *JASN*, investigators assessed mortality rates in a population-based study of children with kidney failure in Australia and New Zealand and quantified the years of life lost (YLL) due to kidney failure in childhood (1). "Quantification of YLL would aid clinicians in their discussions with parents and caregivers about the future of a child with kidney failure," the authors wrote. "It would also assist policy makers who use expected length of life in conjunction with quality of life to support funding and policy decisions."

When the investigators developed a model that mirrors the lived experience of children with kidney failure, who typically transition between dialysis and transplant and back again before death, they found that YLL were substantially higher than those for patients with many other chronic diseases that develop in childhood.

Their model involved patient data from the CELESTIAL study, a binational, population-based cohort study of all people with treated kidney failure in both Australia (1980–2019) and New Zealand (1988–2019) listed in the Australia and New Zealand Dialysis and Transplant Registry. Patient data in the CELESTIAL study were linked to national death registers to determine the date and cause of death.

Among the 2013 children identified with incident

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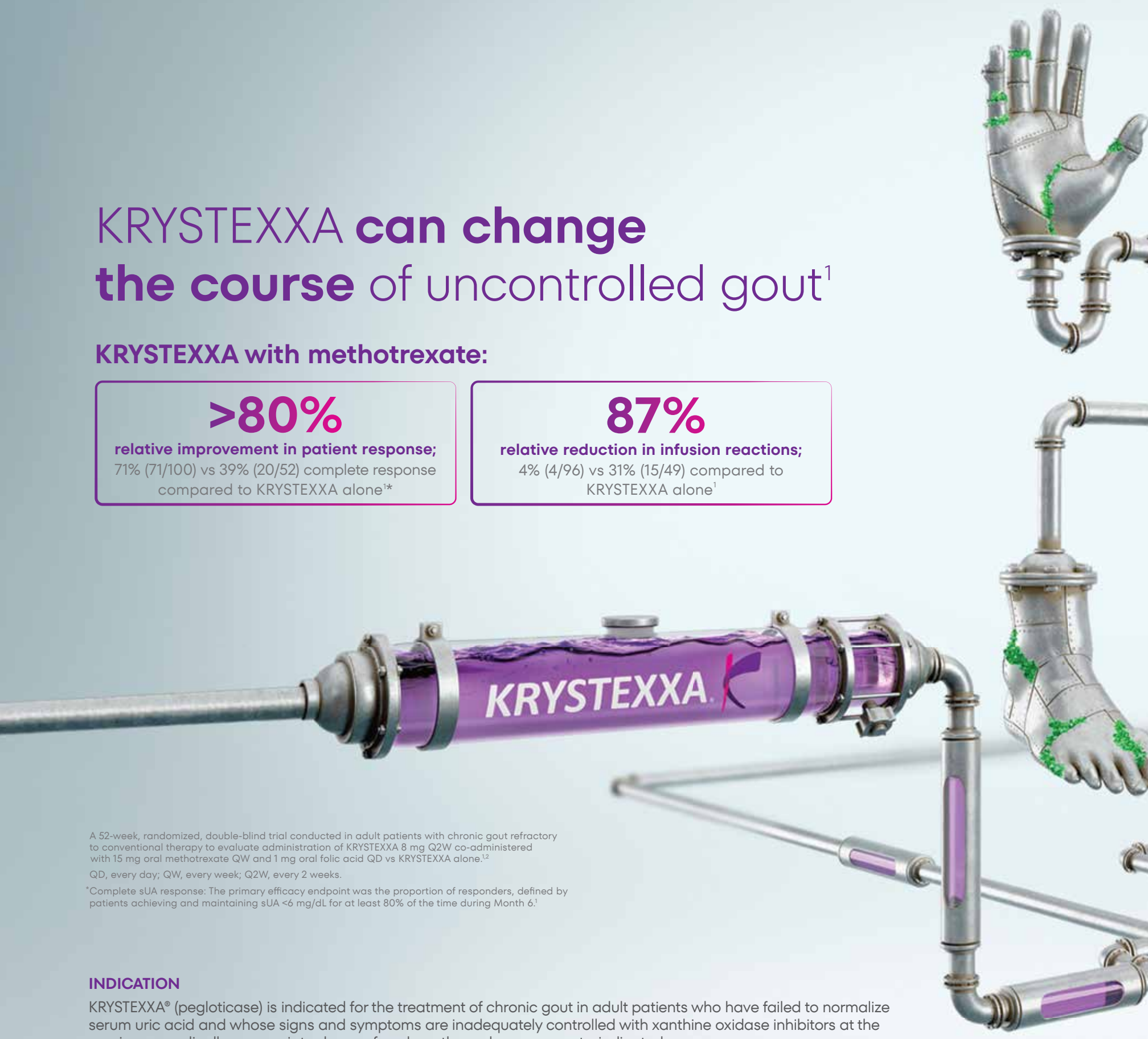
Inside

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.

HORIZON.

KRYSTEXXA®
pegloticase

KRYSTEXXA® (pegloticase) injection, for intravenous use

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

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

See full prescribing information for complete boxed warning.

- **Anaphylaxis and infusion reactions have been reported to occur during and after administration of KRYSTEXXA.**
- **Anaphylaxis may occur with any infusion, including a first infusion, and generally manifests within 2 hours of the infusion. However, delayed hypersensitivity reactions have also been reported.**
- **KRYSTEXXA should be administered in healthcare settings and by healthcare providers prepared to manage anaphylaxis and infusion reactions.**
- **Pre-medicate with antihistamines and corticosteroids and closely monitor for anaphylaxis for an appropriate period of time after administration of KRYSTEXXA.**
- **Monitor serum uric acid levels prior to each infusion and discontinue treatment if levels increase to above 6 mg/dL, particularly when 2 consecutive levels above 6 mg/dL are observed.**
- **Screen patients at risk for G6PD deficiency prior to starting KRYSTEXXA. Hemolysis and methemoglobinemia have been reported with KRYSTEXXA in patients with G6PD deficiency. KRYSTEXXA is contraindicated in patients with G6PD deficiency.**

INDICATIONS AND USAGE

KRYSTEXXA® (pegloticase) is indicated for the treatment of chronic gout in adult patients refractory to conventional therapy.

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

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

CONTRAINDICATIONS

KRYSTEXXA is contraindicated in:

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

WARNINGS AND PRECAUTIONS

Anaphylaxis

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

During pre-marketing clinical trials with KRYSTEXXA alone, KRYSTEXXA was not discontinued following 2 consecutive serum uric acid levels above 6 mg/dL. Anaphylaxis was reported with a frequency of 6.5% (8/123) of patients treated with KRYSTEXXA every 2 weeks and 4.8% (6/126) for the every 4-week dosing regimen. There were no cases of anaphylaxis in patients receiving placebo. Anaphylaxis generally occurred within 2 hours after treatment.

Diagnostic criteria of anaphylaxis were skin or mucosal tissue involvement, and, either airway compromise, and/or reduced blood pressure with or without associated symptoms, and a temporal relationship to KRYSTEXXA or placebo injection with no other identifiable cause. Manifestations included wheezing, peri-oral or lingual edema, or hemodynamic instability, with or without rash or urticaria, nausea or vomiting. Cases occurred in patients being pre-treated with one or more doses of an oral antihistamine, an intravenous corticosteroid and/or acetaminophen. This pre-treatment may have blunted or obscured symptoms or signs of anaphylaxis and therefore the reported frequency may be an underestimate.

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

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

Infusion Reactions

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

During pre-marketing 24-week controlled clinical trials with KRYSTEXXA alone, KRYSTEXXA was not discontinued following 2 consecutive serum uric acid levels above 6 mg/dL. Infusion reactions were reported in 26% of patients treated with KRYSTEXXA 8 mg every 2 weeks, and 41% of patients treated with KRYSTEXXA 8 mg every 4 weeks, compared to 5% of patients treated with placebo. These infusion reactions occurred in patients being pre-treated with an oral antihistamine, intravenous corticosteroid and/or acetaminophen. This pre-treatment may have blunted or obscured symptoms or signs of infusion reactions and therefore the reported frequency may be an underestimate.

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

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

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

G6PD Deficiency Associated Hemolysis and Methemoglobinemia

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

Gout Flares

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

During pre-marketing, 24-week controlled clinical trials with KRYSTEXXA alone, the frequencies of gout flares were high in all treatment groups, but more so with KRYSTEXXA treatment during the first 3 months of treatment, and decreased in the subsequent 3 months of treatment. The percentages of patients with any flare for the first 3 months were 74%, 81%, and 51%, for KRYSTEXXA 8 mg every 2 weeks, KRYSTEXXA 8 mg every 4 weeks, and placebo, respectively. The percentages of patients with any flare for the subsequent 3 months were 41%, 57%, and 67%, for KRYSTEXXA 8 mg every 2 weeks, KRYSTEXXA 8 mg every 4 weeks, and placebo, respectively. Patients received gout flare prophylaxis with colchicine and/or nonsteroidal anti-inflammatory drugs (NSAIDs) starting at least one week before receiving KRYSTEXXA.

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

Congestive Heart Failure

KRYSTEXXA has not been formally studied in patients with congestive heart failure, but some patients in the pre-marketing, 24-week controlled clinical trials experienced exacerbation of congestive heart failure. Two cases of congestive heart failure exacerbation occurred during the trials in patients receiving treatment with KRYSTEXXA 8 mg every 2 weeks. No cases were reported in placebo-treated patients. Four subjects had exacerbations of pre-existing congestive heart failure while receiving KRYSTEXXA 8 mg every 2 weeks during the open-label extension study.

Exercise caution when using KRYSTEXXA in patients who have congestive heart failure and monitor patients closely following infusion.

Re-treatment with KRYSTEXXA

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

ADVERSE REACTIONS

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

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

Clinical Trials Experience

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

Co-administration with Methotrexate

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

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

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

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

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

[a] Included one case of anaphylaxis

KRYSTEXXA ALONE

The data described below reflect exposure to KRYSTEXXA in patients with chronic gout refractory to conventional therapy in two replicate randomized, placebo-controlled, double-blind 24-week clinical trials: 85 patients were treated with KRYSTEXXA 8 mg every 2 weeks; 84 patients were treated with KRYSTEXXA 8 mg every 4 weeks; and 43 patients were treated with placebo. These patients were between the ages of 23 and 89 years (average 55 years); 173 patients were male and 39 were female; and 143 patients were White/Caucasian, 27 were Black/African American, 24 were Hispanic/Latino and 18 were all other ethnicities. Common co-morbid conditions among the enrolled patients included hypertension (72%), dyslipidemia (49%), chronic kidney disease (28%), diabetes (24%), coronary artery disease (18%), arrhythmia (16%), and cardiac failure/left ventricular dysfunction (12%).

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

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

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

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

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

Immunogenicity

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

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

During pre-marketing 24-week controlled clinical trials with KRYSTEXXA alone, anti-pegloticase antibodies developed in 92% of patients treated with KRYSTEXXA every 2 weeks, and 28% for placebo. Anti-PEG antibodies were also detected in 42% of patients treated with KRYSTEXXA. High anti-pegloticase antibody titer was associated with a failure to maintain pegloticase-induced normalization of uric acid. The impact of anti-PEG antibodies on patients' responses to other PEG-containing therapeutics is unknown.

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

Postmarketing Experience

The following adverse reactions have been identified during postapproval use of KRYSTEXXA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship.

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

DRUG INTERACTIONS

Methotrexate

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

PEGylated products

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

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

Data

Animal Data

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

Lactation

Risk Summary

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

Pediatric Use

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

Geriatric Use

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

Renal Impairment

No dose adjustment is required for patients with renal impairment. In a 52-week, randomized, double-blind trial which evaluated KRYSTEXXA co-administered with methotrexate compared to KRYSTEXXA alone, 85% of patients had chronic kidney disease based on estimated glomerular filtration rate (eGFR) of ≥ 40 to < 90 mL/min/1.73 m² at baseline. In the pre-marketing 24-week controlled clinical trials with KRYSTEXXA alone, a total of 32% (27 of 85) of patients treated with KRYSTEXXA 8 mg every 2 weeks had a creatinine clearance of ≤62.5 mL/min. No overall differences in efficacy were observed.

OVERDOSAGE

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

PATIENT COUNSELING INFORMATION

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

Anaphylaxis and Infusion Reactions

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

Glucose-6-phosphate dehydrogenase (G6PD) Deficiency

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

Gout Flares

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

Manufactured by:
Horizon Therapeutics Ireland DAC
Dublin, Ireland

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Rare Disease Registries Provide a Powerful Tool

Continued from cover

treating a large North Carolina family who was referred to him for care for autosomal-dominant kidney disease and gout, which had affected multiple generations. In 2002, Bleyer and colleague Thomas Hart, DDS, PhD, identified genetic mutations in a gene encoding a protein called uromodulin (UMOD) that caused this inherited form of kidney disease (3). "We thought it was really rare," Bleyer said. "There had been about 15 families described in the literature in the United States."

Bleyer decided to build a patient registry to learn more about the condition and help patients and families with the condition. He and the team he assembled, including Associate Project Managers Victoria Robins, RN, a nurse, and Kendrah Kidd, MS, a research scientist who developed the database for the registry, sought referrals from academic centers and independent physicians and set up a website to help patients find the registry directly. The registry started with 5 to 10 families and has grown steadily since to include patients from around the world. Twenty-five percent of families in the registry found the Rare Inherited Kidney Disease team independently through an internet search (4). Patients and physicians may also email the team at kidney@wakehealth.edu.

Over time, they discovered that a subset of the families did not have a mutation in the UMOD gene. These families also did not have gout despite having a similar disease presentation with no proteinuria and bland urinary sediment. To identify a genetic cause, Bleyer teamed up with Eric Lander, PhD, founding director emeritus at the Broad Institute. Using DNA collected from the participants in the registry, in 2013, they identified a mutation hidden deep in the gene, encoding a protein, called MUC-1, as the cause (5).

In 2019, Anna Greka, MD, PhD, associate professor of medicine at Harvard Medical School and a member of the Broad Institute, and her colleagues helped explain how the mutation causes the disease (6). Greka showed that the MUC-1 gene mutation causes misshapen proteins to form and accumulate inside cells that line the tubules in the kidneys. The tubules are a vital part of the kidney's filtering units or nephrons. "It's like an accumulation of toxic trash that can never be removed," she said. "Ultimately, the tubule cells die, which results in the nephron not being able to function anymore."

Even though patients with MUC-1 kidney disease are born with this mutation, it can take decades for symptoms of the condition to appear, Greka said. She explained that 2 million nephrons in the kidney provide humans with more kidney-filtering capacity than they need to survive, which is why individuals can donate one kidney. But as misshapen proteins accumulate, a growing number of nephrons die. "If you have enough of those nephrons coming offline, eventually the kidney doesn't work," she said.

But Greka also demonstrated—using kidney organoids grown from patients from the registry who agreed to participate in the study—that administering an experimental drug could clear the mangled proteins. The team has licensed this experimental treatment to a startup company working in stealth mode to bring it to the clinic. A clinical trial is expected to start sometime in the next 2 years, Greka said. In the meantime, she and her colleagues are working on better understanding the disease and searching for other potential treatments.

"Our job is to continue to dig deeper into the mechanism and understand it further because that may give us a handle on another therapy," she said. Patients continue to be critical partners in the work. Greka said she and her colleagues frequently host patients in the laboratory, and the visits help patients understand the research process and help inspire the researchers to continue to dig.

Bleyer, Greka, and their collaborators now have a longitudinal study underway that collects and analyzes serum creatinine from participating patients every 4 months. The study will provide vital information about the natural history of the disease and help lay the groundwork for future clinical trials. Greka explained that the study would help identify biomarkers that can be used in the trial to determine if the drug is working. "The registry is of enormous value in being able to advance our discoveries in the clinic and hopefully make meaningful therapies for patients," Greka said.

Already, the registry is yielding insights that are helping answer key questions for patients. For example, data from the registry showed that women with autosomal-dominant tubulointerstitial kidney diseases are less likely to have hypertension during pregnancy than women with other forms of kidney diseases and have good maternal and fetal outcomes (7).

Breaking down silos

A new collaboration between the Dent Disease Foundation and RareX is underway to grow a new registry for Dent disease (8). This rare, inherited kidney disease causes kidney stones, proteinuria, and chronic kidney disease. RareX is the research arm of a nonprofit organization called Global Genes that works to provide information and resources for individuals affected by rare diseases (9).

The RareX registry platform is already home to disease registries, including approximately 2200 patients, primarily individuals with rare, neurodevelopmental disorders. The platform is now expanding into kidney diseases to bring together registry data on many rare diseases in a consistent format that a range of scientists can use. Karmen Trzupek, BS, MS, senior director of scientific programs at Global Genes, explained that a single institution often operates rare disease registries with limited funding and infrastructure. Pharmaceutical companies may hold other data, she said. The data may not be in a standardized or structured format or easily accessible by others, which can limit the usefulness of the data to other researchers, Trzupek explained. "RareX breaks down those silos," said Jill Goodrich, co-executive director of the Dent Disease Foundation.

RareX has built its platform with a consistent structure and format for all its registries. It creates standardized surveys for collecting "head-to-toe" data about symptoms and natural disease history. For example, some individuals with Dent disease also have intellectual disabilities or sleep difficulties. The RareX platform has symptom surveys usable across conditions. "By bringing together lots of rare disease communities, we can leverage some of the shared symptoms across diseases," Trzupek said. Combining numerous rare diseases also ensures that resources are available even for conditions with fewer affected individuals or less interest from researchers or drug companies.

Enabling disease-agnostic research allows scientists to develop new insights into rare diseases and the symptoms they cause. For example, Goodrich noted that her father had Dent disease but died without a diagnosis because, at the time, his symptoms were not traditionally associated with the disease. But more recent discoveries have given scientists a more expansive view of the potential Dent disease symptoms, she said.

"Things that you wouldn't think were connected are now being connected," Goodrich said. Those connections may help identify people who otherwise might go undiagnosed.

Bringing together larger groups of patients with rare diseases may also make the conditions more appealing to researchers or pharmaceutical companies, said Jennifer Meyer, RN, co-executive director of the Dent Disease Foundation. The RareX initiative is funded by philanthropies and through work commissioned by pharmaceutical companies to help assimilate data from disparate sets or identify potential trial participants, Trzupek said. But patient data are not sold. "Patients own their data and choose how [they are] used," Trzupek said.

The Dent Disease Foundation has worked closely with researchers at the Wake Forest Institute for Regenerative Medicine and experts from the Mayo Clinic's Rare Kidney Stone Consortium Registry, which also houses a Dent disease registry (10).

There are currently 20 patients with Dent disease enrolled in the RareX registry. The Dent Disease Foundation is recruiting more patients to enroll through its website (8). Older studies suggest that approximately 250 families are affected by Dent disease worldwide, Meyer said. But she and Goodrich believe the number is much greater based on their networking with patients and Dent disease specialists at meetings such as ASN's Kidney Week. Goodrich explained that even within families affected by Dent disease, individuals may not understand the X-linked, recessive inheritance of Dent disease. So, they may not suspect other relatives' symptoms are caused by Dent disease. "RareX allows us to make the connections needed to administer relief to our community and hopefully find a cure," Goodrich said.

"Tip of the iceberg"

The patients currently enrolled in the Wake Forest registry likely represent just the "tip of the iceberg" of patients with rare, inherited kidney diseases affecting the tubules, Greka said. She said many patients likely do not know they have the disease. Bleyer estimated that 1% of patients with kidney failure have a UMOD mutation, and a similar number have MUC-1 mutations. Based on the registry data, Bleyer estimated that there are 28,000 patients in the United States with MUC-1 kidney diseases and another 28,000 with kidney diseases caused by UMOD mutations.

Bleyer and Greka urged clinicians and patients to seek genetic testing for patients with unexplained kidney diseases, particularly if there is a family history. Greka suggested that physicians and patients should also pursue testing in cases with bland urinary sediment without proteinuria, even in people without a family history or in individuals with prevalent conditions such as diabetes or obesity that may increase the risk of kidney diseases. "With rapidly expanding access to genetic testing in the United States, we should all be thinking about the genetic underpinnings of diseases in our patients and sending them for those tests," she said.

Genetic testing for 120 genetic kidney diseases, including UMOD, is widely available through commercial laboratories, Greka said. The Broad Institute offers free genetic testing for the MUC-1 mutation for individuals with a family history of kidney diseases and a bland urinary sediment because traditional genetic testing does not capture this mutation. Greka said she and her colleagues are also developing ways to make the testing more widely available.

There is also a great need to grow the registries. Nelson noted that participants regularly receive email updates through the registry, keeping them abreast of the latest developments and giving them opportunities to participate in research. Growing the registries may also increase the likelihood of successful clinical trials that lead to new treatments and provide more insight about the diseases, Greka said. Nelson added that finding and recruiting more families and inviting them to participate are key objectives of the foundation. "We are focused on building this community and finding more [families]," Nelson said. "By throwing in together, we can absolutely affect the outcome and support progress." ■

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Study Explores Mortality and Years of Life Lost in Children with Kidney Failure

Continued from cover

kidney failure, there were 394 deaths (20%) over 30,082 person-years of follow-up with a median follow-up of 13.1 years. Overall, 288 children (14%) underwent preemptive kidney transplantation, and 1497 (74%) underwent kidney transplantation after a median 1.1 years on dialysis. A total of 228 (11%) were never transplanted.

Most patients were older than 10 years of age at the time of kidney failure diagnosis (61%), and the most common cause of kidney failure was congenital anomalies of the kidney and urinary tract (39%), followed by glomerulonephritis (34%), cystic kidney diseases (10%), and other causes (17%). The median number of treatment transitions (moving from dialysis to transplant or vice versa) was 2, and most children (71%) spent more than half of their follow-up time with a functioning transplant. The greatest probability of death was during treatment with dialysis.

Compared with the general population, excess deaths among patients were 41 times higher than expected during 1980–1984 and fell to 22 times higher during 1995–1999 and then to 17 times higher during 2015–2019. Among patients who received transplants, excess deaths were 23 times higher than expected in 1980–1984. This fell to 16 times during 1995–1999 and then to 13 times during 2015–2019. Mortality rates were 12.2 per 1000 person-years in male patients and 14.3 per 1000 person-years in female patients. Mortality rates were highest in the first 3–6 months after kidney failure (34.5 per 1000 person-years), and mortality rates for those younger than 2 years old when diagnosed with kidney failure were 7.5 times the rate of those aged 2–5 years, 39 times the rate of those aged 11–14 years, and 10 times the rate of those aged 15 years or older.

YLL were higher with younger age at kidney failure diagnosis and in female patients. For those who were 5 years old when diagnosed with kidney failure, YLL were 29.6 years in female patients and 21.3 years in male patients. When aged 15 years at the time of kidney failure diagnosis, YLL were 25.0 years in female patients and 17.3 years in male patients. YLL were higher for those diagnosed in 1980–1998 than in those diagnosed in 1999–2019. Children diagnosed with kidney failure in the contemporary era had an extra 5.8 years of life compared with those in the historical era; however, females experienced less improvement in their YLL than males, widening the preexisting sex disparity.

> [A]lthough females tend to outlive males in the general population, the opposite appears to occur among individuals diagnosed with kidney failure as children.

The study's investigators found that although females tend to outlive males in the general population, the opposite appears to occur among individuals diagnosed with kidney failure as children. Sex disparities in the treatment and outcomes of kidney diseases may be involved—for example, it is known that women with kidney failure are less likely to receive transplants than men. Indeed, in this study, female pediatric patients had less access to transplantation, particularly preemptive transplantation, than did male patients. Differences in hormones, immune function, and donor and recipient size may also play a role in sex differences in kidney transplant outcomes.

The study adds to other research, including a study from the US Renal Data System, which calculated that for American children with kidney failure, the expected YLL are 40–55 years if treated with dialysis and 12–20 years if treated with transplantation; however, dialysis and transplantation were considered separately and not as part of a treatment continuum (2).

"The key findings of our study were (1) kidney failure in childhood was associated with substantial YLL, ranging from 16 to 32 years depending on age at kidney failure and sex; (2) female patients lose ≥7 more life years than male patients irrespective of age at diagnosis; and (3) while the excess mortality rate in children with kidney failure remains extremely high, it has been improving over time," the authors wrote. They stressed that despite the potential YLL, many children and adolescents with kidney failure enjoy numerous life years ahead of them, allowing them to participate in important life events—from completing their education, to raising a family, to attaining professional goals.

"This study offers hope to patients and their families that children with kidney failure can grow up and reach significant life milestones. We need more research on how to help these children transition through the different stages of life successfully with kidney disease and how to better support their life participation at all ages," said lead author Melanie L. Wyld, MBBS, MBA, MPH, PhD, FRACP, a kidney and transplant physician at The University of Sydney and Westmead Hospital, in New South Wales.

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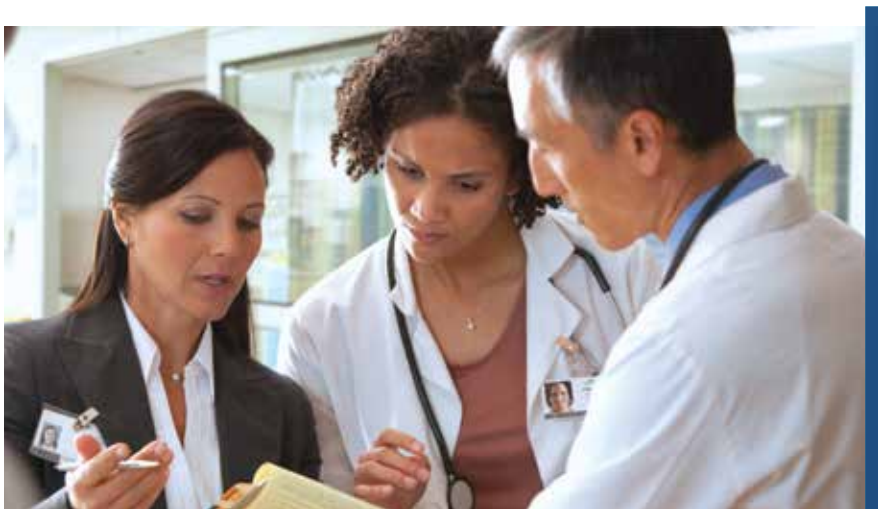

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ARTIFICAL INTELLIGENCE DEVELOPMENTS

By Girish N. Nadkarni and Jamie S. Hirsch

As digital technology advances, the role of artificial intelligence (AI) and informatics in health care continues to grow. As a "numbers" discipline, these technologies have the potential to revolutionize the way we approach kidney health and the diagnosis, treatment, and prevention of kidney diseases. In this special issue of *Kidney News*, we explore the promise of informatics and AI in kidney care and highlight some of the most exciting developments in this field.

In "Nudging Toward Progress: The State of Clinical Decision Support in Nephrology," Kyle O'Connor and Dr. Wilson explore the integration of risk prediction in clinical care. This article highlights the potential benefits of using clinical decision support systems to improve patient outcomes and reduce costs, while highlighting the importance of robust evaluation for patient safety and outcomes. In another article, Dr. Town explores the use of information technology in pediatric nephrology education.

Drs. Bajaj and Koyner's article, "Artificial Intelligence and Acute Kidney Injury," delves into the use of multimodal data in predicting acute kidney injury (AKI). The article highlights the potential of AI to integrate data from various sources and provide clinicians with more accurate and timely predictions of AKI.

Drs. James and Pannu explore the development of new apps that leverage AI to improve the management of AKI. This article highlights the potential of these apps to provide patients and clinicians with real-time insights into their health status, and to improve the overall quality of care for AKI patients.

Dr. Sakhuja and I [Dr. Nadkarni] introduce us to reinforcement learning ("Reinforcement Learning in Kidney Disease"), a branch of AI, and explore the potential of reinforcement learning to optimize treatment strategies for kidney diseases. We highlight the potential of AI to learn from patient data and provide personalized treatment plans that can lead to improved patient outcomes.

Finally, "Digital Health Equity and CKD" highlights the importance of ensuring that AI-powered health care solutions and digital applications are accessible to all patients, regardless of their socioeconomic status. In this article, Dr. Samal and co-authors emphasize the need for policymakers to prioritize digital health equity in the development and deployment of AI-powered health care solutions.

Overall, the articles in this special issue provide a comprehensive overview of the promise of informatics, digital tools, and AI in kidney diseases while laying out limitations and issues. In particular, the authors provide excitement and hope for our field, while stressing the need for rigorous evaluation and monitoring to ensure safety, equity, and effectiveness. We hope that this issue will inspire readers to explore the potential of informatics and AI in their own research and clinical practice. ■

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Nudging Toward Progress: The State of Clinical Decision Support in Nephrology

By Kyle D. O'Connor and F. Perry Wilson

Clinical decision support (CDS) tools have increased in number and complexity as the electronic health record (EHR) has increased in capability. CDS tools come in many forms, including best practice alerts, customized documentation templates, order sets, and warning systems of potential harm. The promise of these tools is to provide clinicians with appropriate, useful, and actionable information at the point of care. The implementation of these tools follows a framework known as "The Five 'Rights' of CDS": 1) the right information, 2) to the right people, 3) through the right channels, 4) in the right format, and 5) at the right points in the workflow (1). The framework encourages the spirit of end-user feedback in the design of CDS tools in the EHR to avoid false positives and "alert fatigue" (2).

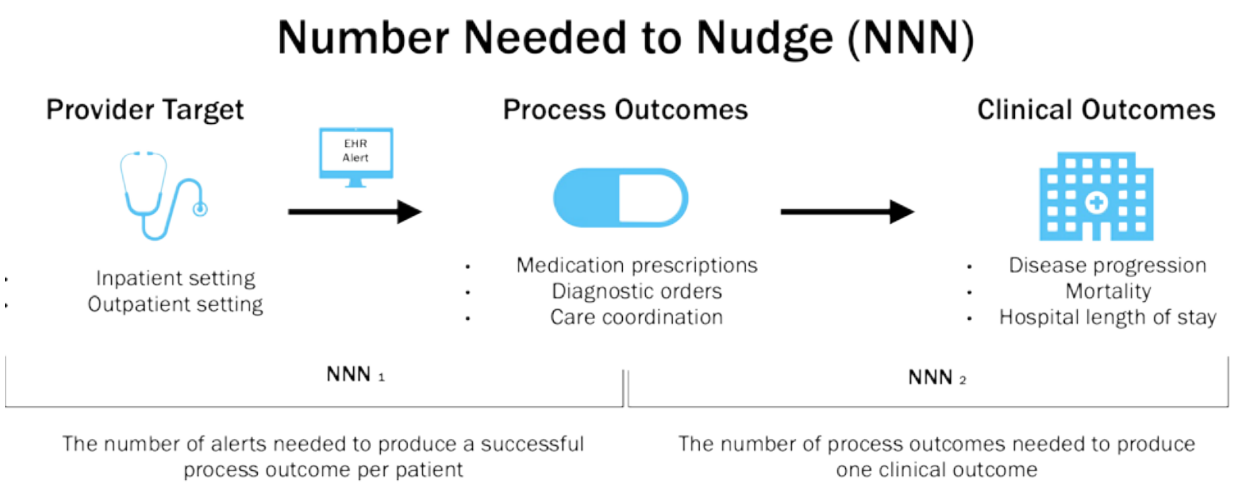
Several pragmatic randomized controlled trials have investigated EHR alerts across multiple disease states and settings. Selby et al. (3) found that EHR alerts, in addition to a care bundle and an educational program, improved acute kidney injury (AKI) recognition, performance of urinalyses, and increased review of medications in adult patients who were hospitalized. Furthermore, Ghazi et al. (4), in the outpatient Pragmatic Trial of Messaging to Providers About Treatment of Heart Failure (PROMPT-HF), demonstrated that EHR alerts linked with an order-set option increased guideline-directed medical therapy class prescription in patients with heart failure. Interestingly, the Electronic Alerts for Acute Kidney Injury Amelioration (ELAIA-1) study found that EHR alerts for AKI *increased* mortality within a subgroup of non-teaching hospitals, underscoring the need for randomized trials for CDS (5), even when the intervention may seem to be "common sense."

Ultimately, these studies indicate that CDS can be quite effective at changing process outcomes (e.g., medication orders) but, to date, have more mixed results in terms of clinical outcomes. To avoid alert fatigue, wherein providers begin to ignore even helpful alerts due to alert proliferation, there must be efforts to minimize the number needed to nudge (NNN), or the number of alerts needed for a successful response per patient (Figure 1). Overall, CDS interventions seek to promote an established process of care that is a best practice and yet is currently under-utilized. CDS interventions should be robustly evaluated in the context of randomization, where feasible, to show they can affect the process and, preferably, downstream clinical outcomes. At all stages, end users should be involved. ■

Kyle D. O'Connor, MS, is with the Clinical and Translational Research Accelerator, Yale School of Medicine, and F. Perry Wilson, MD, MSCE, is with the Clinical and Translational Research Accelerator and Section of Nephrology, Department of Internal Medicine, Yale School of Medicine, New Haven, CT.

Mr. O'Connor reports no conflicts of interest. Dr. Wilson reports receiving grants R01DK113191 and R01HS027626 from the National Institutes of Health and research support from AstraZeneca for trials that use clinical decision support.

Figure 1. Avoiding alert fatigue



The NNN is a statistical concept capturing the number of alerts or "nudges" needed as an intervention to produce a successful outcome per individual patient. For a process outcome to change a clinical outcome, an NNN would need to be minimized to avoid "alert fatigue." NNN1 reflects the number of alerts needed to produce a successful response for the process outcome. NNN2 is the number of process outcomes to produce one clinical outcome.

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What Is the Future of Artificial Intelligence in Nephrology?

Concept by* KN *Editorial Board member Matthew A. Sparks and* KN *Editor-in-Chief Kenar D. Jhaveri

By ChatGPT

Artificial intelligence (AI) has the potential to revolutionize the field of nephrology, which is the study of the kidneys and their functions. With the increasing availability of electronic medical records, imaging data, and genomic data, AI can be used to analyze large amounts of data and extract meaningful insights to improve the diagnosis, treatment, and prevention of kidney diseases. Here are some of the potential applications of AI in nephrology:

1. Diagnosis: AI can be used to analyze patient data, including lab results, imaging studies, and clinical notes, to improve the accuracy of diagnosis of kidney diseases. AI algorithms can also help identify patients who are at high risk of developing kidney diseases.
2. Treatment: AI can help nephrologists select the best treatment option for each patient, based on their individual characteristics and medical history. For example, AI algorithms can help identify which medications will be most effective for a particular patient or which patients are likely to benefit from a particular type of dialysis.
3. Monitoring: AI can be used to monitor patients with kidney diseases and detect changes in their condition in real-time. This can help prevent complications and allow for early intervention when necessary.
4. Predictive analytics: AI can help predict which patients are at risk of developing kidney diseases, allowing for earlier intervention and prevention of complications.
5. Drug discovery: AI can be used to discover new drugs for the treatment of kidney diseases. AI algorithms can analyze large amounts of genomic and proteomic data to identify novel targets for drug development.

Overall, the future of AI in nephrology is promising, as it has the potential to improve the accuracy of diagnosis, treatment, and prevention of kidney diseases, leading to better outcomes for patients. However, it is important to ensure that AI is used ethically and responsibly and that patient privacy is protected. ■

ChatGPT is an artificial intelligence chatbot developed by OpenAI and launched in November 2022. It is built on large language models and has been fine-tuned (an approach to transfer learning) using both supervised and reinforcement learning techniques.

Information Technology in Pediatric Nephrology Education: The Comeback Kids

By Ryan Town

Nephrologists have been leaders in incorporating information technology in the medical educational space and leveraging social media in new and exciting ways. Online medical education in nephrology began with blogs containing the musings of a few great educators and has since blossomed into an impressive array of high-quality and engaging educational material, communities, and events (1). It has never been easier to connect with colleagues, share insights about the latest research, and disseminate educational material.

Understandably, a large majority of educational material in nephrology has been produced by and—crucially—*for* adult nephrologists. However, there are clear benefits in having pediatric-specific educational material. There are significant changes in kidney physiology over the course of the lifespan, with the most dramatic changes occurring during childhood. There are important differences in pediatric kidney disease epidemiology, presentation, and progression; the etiologies and impacts of comorbidities; and in prescribing practices. These variations make it difficult for pediatric specialists to use much of the existing online educational content.

The pediatric nephrology community is relatively small, with approximately 1100 board-certified pediatric nephrologists in the United States, and it is facing a significant workforce shortage. Creating high-quality online educational content can be time consuming, technically difficult, and costly and may not be weighed as heavily in promotional criteria as more traditional educational materials, such as reviews or book chapters. For a heavily academic specialty facing growing clinical needs, research demands, and ever-tighter budgets, this has not proven to be a recipe for spurring innovation in education. With perceived complexity and inadequate didactics being a barrier to trainee interest in the field, there is a risk that these problems will only continue to compound.

High-quality, online, pediatric nephrology educational content certainly exists but often is confined to the literature, is siloed away in expensive textbooks, requires a login or even a paid subscription, is commingled with adult nephrology content, or is simply hard to find unless one knows where to look. Despite these challenges, there have been some positive developments. The Kidney Chronicles: A Pediatric Nephrology Podcast, produced and hosted by Dr. Emily Zangla, a fellow at the University of Minnesota (Minneapolis), has breathed some life into the pediatric nephrology FOAMed space with expert

interviews on a range of interesting and important topics. The American Society of Pediatric Nephrology (ASPN) has made some inroads in recent years, hosting regular pathology and radiology webinars, small group sessions, and seminars for its members. It has also created an interest group focusing on free open-access medical education (ASPNFOAM), which develops and shares "tweetorials" and "infographics." The Neonatal Kidney Collaborative has organized a collection of educational material regarding acute kidney injury and kidney replacement therapy in neonates. For the most part, though, the impetus has been on individuals to identify, appraise, and organize pediatrics-relevant content. These barriers limit the potential audience and frustrate users and creators.

To address these concerns, we created kidney.wiki, a new home for pediatric nephrology education and the winner of the ASN 2022 Innovations in Kidney Education Contest. This website, which is free and open to anyone, is custom built from the ground up to serve the needs of learners and practitioners of pediatric nephrology. It contains easy-to-use calculators as well as enduring educational modules that are designed to be read and understood quickly at the point of care.

The site also acts as an educational platform of sorts: There is a centralized repository—dubbed the Kidney Education Network—that provides links and descriptions for popular nephrology educational sites. The top of each page contains links to relevant guidelines, review articles, podcasts, videos, note templates, patient information, and more, and users can effortlessly share additional educational content as it is created and discovered. Making it easier to share and access resources will provide a better user experience and promote the work of creators, encouraging the production of more high-quality educational material.

Pediatric nephrology has many accomplished educators and a very enthusiastic and supportive community (Table 1). By working together, we can continue to create tools and educational resources that will help us keep up with a burgeoning academic literature, do our jobs more efficiently, teach more effectively, and promote our important field. ■

Ryan Town, MD, is with Stanford School of Medicine, Stanford, CA.

The author reports no conflicts of interest.

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Table 1. Free, open access educational resources in pediatric nephrology

Name	Content type	URL
The Kidney Chronicles	Podcast	zangl015.podbean.com
Neonatal Kidney Collaborative	Recorded presentations	babykidney.org
International Pediatric Nephrology Association	Recorded presentations, slides	theipna.org/resources/education-materials/
American Society of Pediatric Nephrology	Tweetorials, podcast	aspneph.org/aspnfoam-group/ aspneph.podbean.com/
Canadian Association of Paediatric Nephrologists	Resident handbook	capneph.ca/trainees/paediatric-nephrology-handbook.html
kidney.wiki	Enduring educational material, curated resources	https://kidney.wiki

Artificial Intelligence and Acute Kidney Injury

By Tushar Bajaj and Jay L. Koyner

Artificial intelligence (AI) in nephrology has begun to demonstrate potential clinical utility including machine learning for acute kidney injury (AKI) risk prediction, identification, phenotyping, and imaging transcriptomics. Machine learning has shown promise as a method to transform vast quantities of data into tools capable of predicting important patient outcomes (AKI, need for dialysis, and mortality).

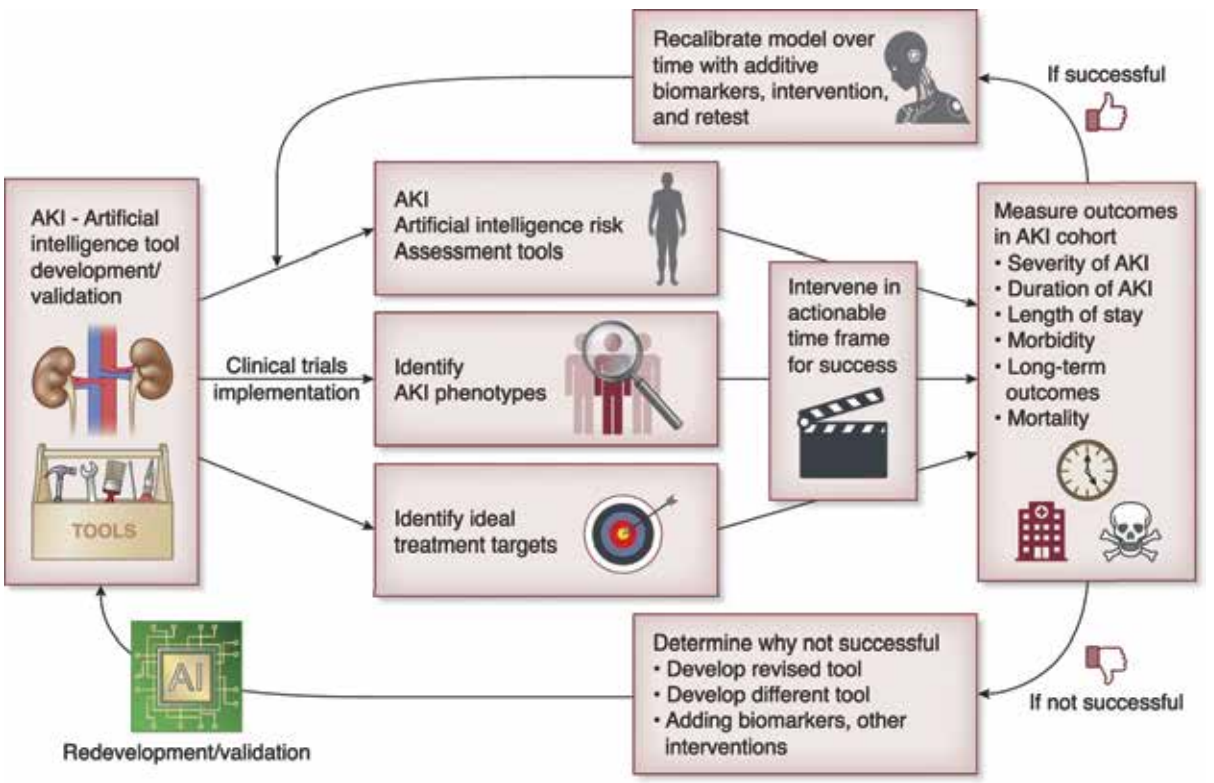
The current gold standard for diagnosis of AKI relies on serum creatinine and urine output, both of which are flawed (1). Similarly, no other novel biomarker of AKI has been consistently shown to improve outcomes after detecting early AKI. This gap in AKI care opens opportunities for machine learning to create AKI risk prediction algorithms and improve outcomes.

Many risk scores have already been published, using methods such as gradient boosting, neural networks, deep learning, and random forests to identify high-risk patients. Many of these AI applications can accurately predict AKI up to 24–48 hours before changes in serum creatinine (2–4). These studies have taken place in variable clinical settings, including the entire hospital, adult intensive care units, and among perioperative patients. Advanced learning techniques have also been implemented to detect patterns within specific AKI settings, with some work identifying two to three different, distinct sub-phenotypes within large cohorts of patients with sepsis-associated AKI (5).

Importantly, just because a risk score can accurately predict AKI outcomes in one cohort does not mean it can in other settings. Many risk scores have high specificity and negative predictive value; however, the scores uniformly suffer from lower-than-optimal positive predictive values (20%–50%), which has limited their wide-scale implementation. Future risk scores may use advanced learning techniques (e.g., natural language processing) to optimize the positive predictive value to successfully identify patients at high risk for severe AKI, rather than the current scores that excel at identifying patients at low risk for severe AKI (e.g., "ruling out" AKI). Regardless of the test characteristics, data on the clinical implementation and validation of these AI-AKI scores are lacking.

In the near future, the Kidney Precision Medicine Project will obtain kidney biopsies from patients with AKI, and analyses of these samples with AI techniques may lead to tools that are even more accurate to assist bedside physicians (6) (Figure 1). It is essential, as these tools are developed and validated to minimize bias. The future of AI in AKI requires controlled, clinical trials paired with clinically meaningful outcomes. ■

Figure 1. Flow chart for an AI-AKI tool



Reprinted from Bajaj and Koyner (7).

Tushar Bajaj, MD, and Jay L. Koyner, MD, are with the University of Chicago, IL.

Dr. Bajaj reports ownership interest in Cidara Therapeutics and Merck & Co., Procore Technologies, and Tilray Brands. Dr. Koyner reports receiving research funding from the National Institutes of Health, bioMérieux, and Fresenius Medical Care.

No AI tool was used to write this article.

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Decreased Proteinuria with Sparsentan in IgA Nephropathy

The dual endothelin (ET) and angiotensin (AT) receptor antagonist sparsentan lowers proteinuria in patients with immunoglobulin A (IgA) nephropathy, according to preliminary phase 3 trial data reported in *The Lancet*.

The authors report a planned interim analysis from the ongoing PROTECT trial, which enrolled patients at 134 sites in 18 countries. Eligible patients had biopsy-confirmed IgA nephropathy with proteinuria of 1.0 g/day or greater, despite at least 12 weeks of maximized renin-AT inhibitor therapy. Patients were randomly assigned to treatment with sparsentan, 400 mg once daily, or as an active control, irbesartan. The groups were stratified by a baseline estimated glomerular filtration rate (eGFR) and urinary protein excretion. Changes in the urine protein-creatinine ratio were measured in 24-hour urine samples.

Analysis included 280 of 404 treated patients who had attended the 36-week visit. The mean age was 46 years; the mean eGFR, 57.0 mL/min/1.73 m^2; and the median urine protein excretion, 1.8 g/day. On efficacy analysis, geometric mean least-squares change in the urine protein-creatinine ratio was –49.8% in patients assigned to sparsentan versus –15.1% with irbesartan, for a relative reduction of 41%. Complete remission of proteinuria occurred in 21% of patients with sparsentan versus 8% with irbesartan: odds ratio (OR), 3.1. Partial remission rates were 70% and 40%, respectively, with the OR, 4.5. Rates of treatment-emergent adverse events were high but similar between groups. There were no cases of severe edema, heart failure, liver toxicity, or edema-related treatment discontinuation.

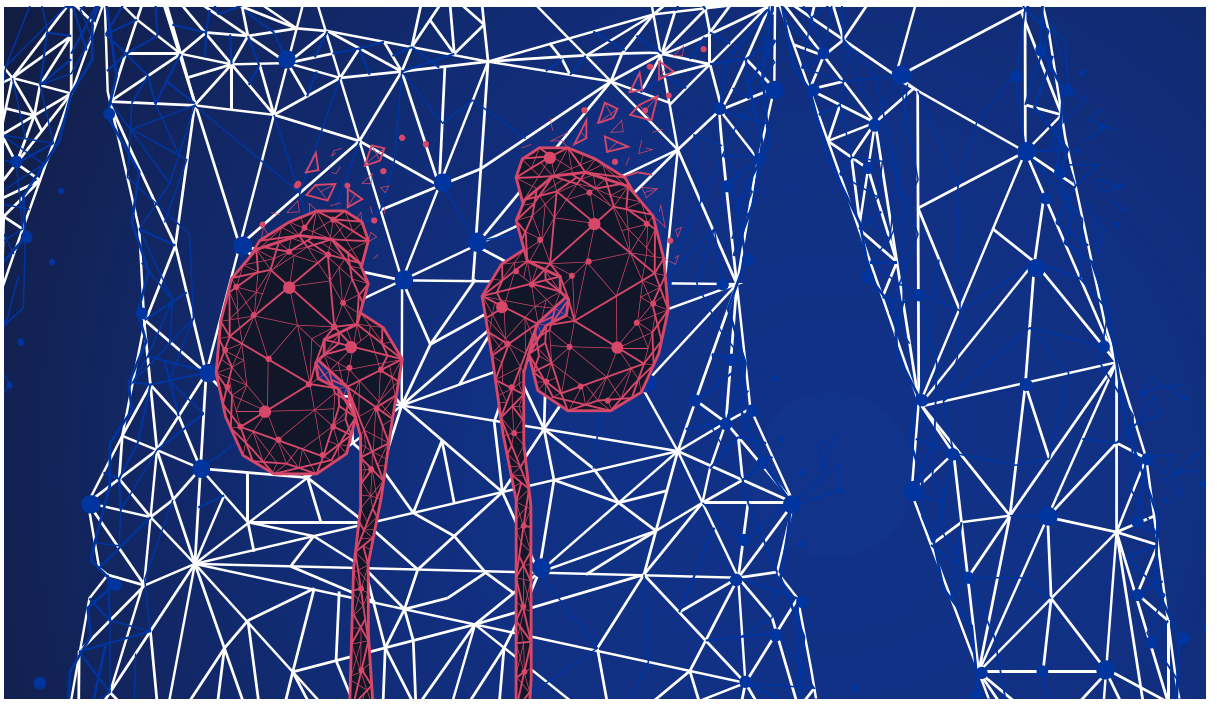
Sparsentan selectively targets the ET receptor A (ET_A) and AT II subtype 1 receptor (AT_1), which contribute to the pathophysiology of IgA nephropathy. In a previous trial in patients with focal segmental glomerulosclerosis, sparsentan reduced proteinuria compared with irbesartan.

The PROTECT data show a similar effect in patients with IgA nephropathy at high risk of disease progression due to continued proteinuria. Safety outcomes appear similar to those of irbesartan. Planned 2-year assessments will evaluate the long-term nephroprotective effects of sparsentan. ■

Heerspink HJL, et al. Sparsentan in patients with IgA nephropathy: A prespecified interim analysis from a randomised, double-blind, active-controlled clinical trial. *Lancet* 2023; 401:1584–1594. doi: 10.1016/S0140-6736(23)00569-X

Current and Emerging Applications of Digital Health for AKI

By Matthew T. James and Neesh Pannu



Digital health technologies include big data analytics, electronic health records (EHRs)/clinical information systems (CISs), mobile-health applications, connected devices, wearables, and computer modeling. Acute kidney injury (AKI) is a common clinical syndrome in which several digital health innovations are increasingly encountered and continue to emerge.

Many jurisdictions have leveraged hospital EHRs and laboratory information management systems to implement AKI detection algorithms that deliver AKI e-alerts to promote patient safety in clinical care and for use in AKI surveillance systems (1) (Figure 1). With increasing volume, veracity, and storage of health data, there has been a proliferation of prediction models developed for AKI (2) and its downstream clinical outcomes (3). As access to high-performance computing resources increases, these predictive models are increasingly being developed using machine learning algorithms that leverage the wealth of structured and unstructured data available from modern clinical data systems (4, 5). EHRs/CISs are ubiquitous in modern health systems and have been leveraged to deliver point-of-care, computerized, clinical decision support to care providers for AKI prevention and early intervention (6, 7). Recent examples also illustrate how electronic clinical data can be used to deliver audit and feedback reports and dashboards that process information on recent clinical performance to providers to encourage practice improvement for AKI prevention (8, 9).

Mobile health applications, connected devices, and wearables are also growing in use and entering clinical use to collect measurements directly from patients, thereby enabling real-time monitoring and intervention strategies for AKI (10, 11). These data can be rapidly processed via artificial intelligence systems with the potential to provide continuous monitoring linked to recommendations for clinical actions. The extension of digital monitoring systems beyond the hospital and into the home holds promise to extend this paradigm into community-onset AKI and through transition from hospital to home to facilitate recovery and rehabilitation after AKI.

Although we expect these exciting digital health tools will rapidly progress in the clinical arenas in which AKI is encountered, innovators cannot simply "flip the on switch" and expect they will be effortlessly taken up into practice, accepted by end-users, and improve health system performance and health outcomes. Effective implementation will require evidence-based, scientific approaches to integrate digital tools within patient self-management strategies and clinical care, based on principles of behavior change and implementation science frameworks that support their uptake by the users of these tools. Incorporation of rigorous evaluation alongside deployment will also be required to demonstrate value for patients and providers and to ensure return on investment for health systems. ■

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Drs. James and Pannu report research funding from the Canadian Institutes of Health Research and Alberta Innovates to implement and evaluate digital health interventions for acute kidney injury.

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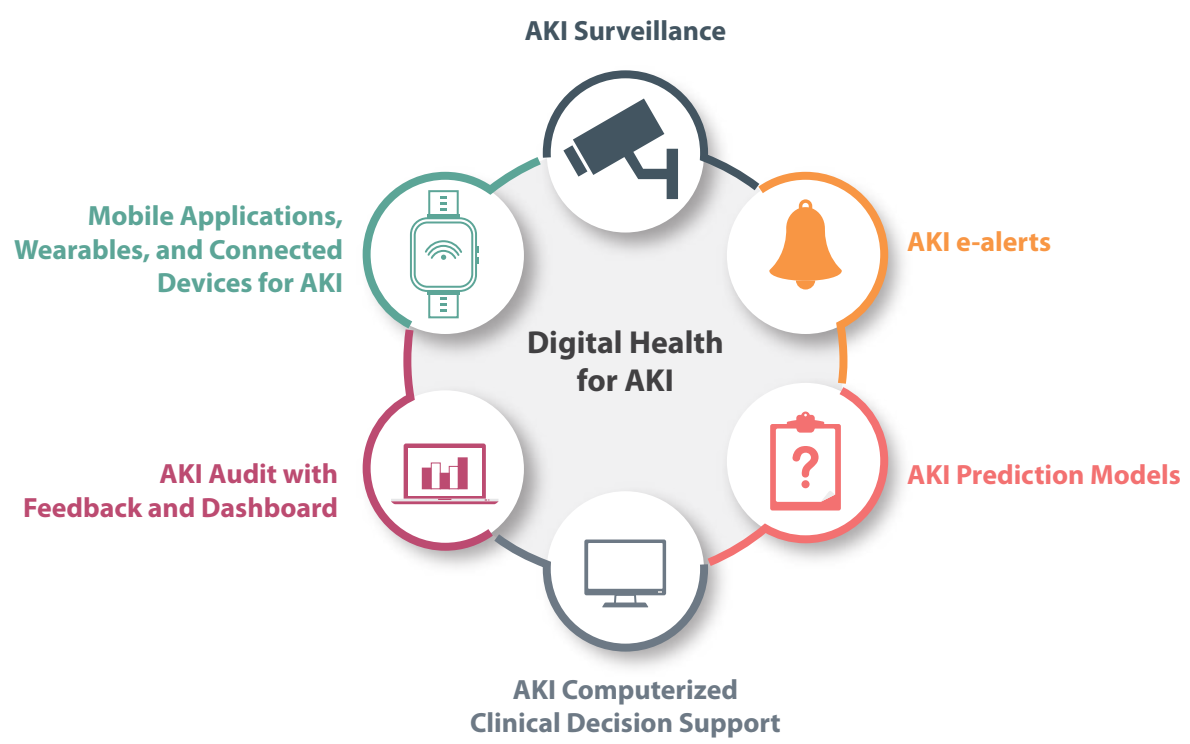
Figure 1. Digital health applications for AKI



Reinforcement Learning in Kidney Diseases

By Ankit Sakhuja and Girish N. Nadkarni

Reinforcement learning (RL) is a branch of machine learning used to solve sequential decision problems (1). It relies on RL algorithm learning correct actions using trial and error, while using feedback from its own actions and experiences. It is analogous to playing chess where each player makes moves or "actions" based on the configuration of the chess board, referred to as "state" in RL. Each action changes the state of the chess board and thus dictates the next action. In RL, the algorithm is trained to identify a sequence of actions, known as "policy," which maximizes the chances of winning by providing the algorithm a "reward" for a win. The goal is to train the algorithm to identify a policy that maximizes the reward.

RL has seen remarkable success in robotics and computer games (2–6). Its emergence in medicine is, however, recent and mostly limited to computer simulations (7, 8). There are many potential applications of RL in kidney health and diseases (Figure 1). For example, RL can be used to individualize dialysis dosing and management of intra-dialytic hypotension. It can also be used to individualize the management of therapies for chronic kidney disease and its complications, such as anemia, bone mineral disease, and in the use of medications to slow the progression of chronic kidney disease. Additionally, RL can be used to individualize the management of acute kidney injury, especially among critically ill patients. Acute kidney injury requires complex management of fluid balance, electrolytes, and hemodynamic support. RL can be used to learn optimal dosing of medications and fluids based on each patient's individual characteristics and response to treatment.

In conclusion, RL is a relatively nascent branch of machine learning that has the potential to revolutionize the management of patients with kidney diseases by individualizing treatment strategies and developing decision support tools for clinicians. ■

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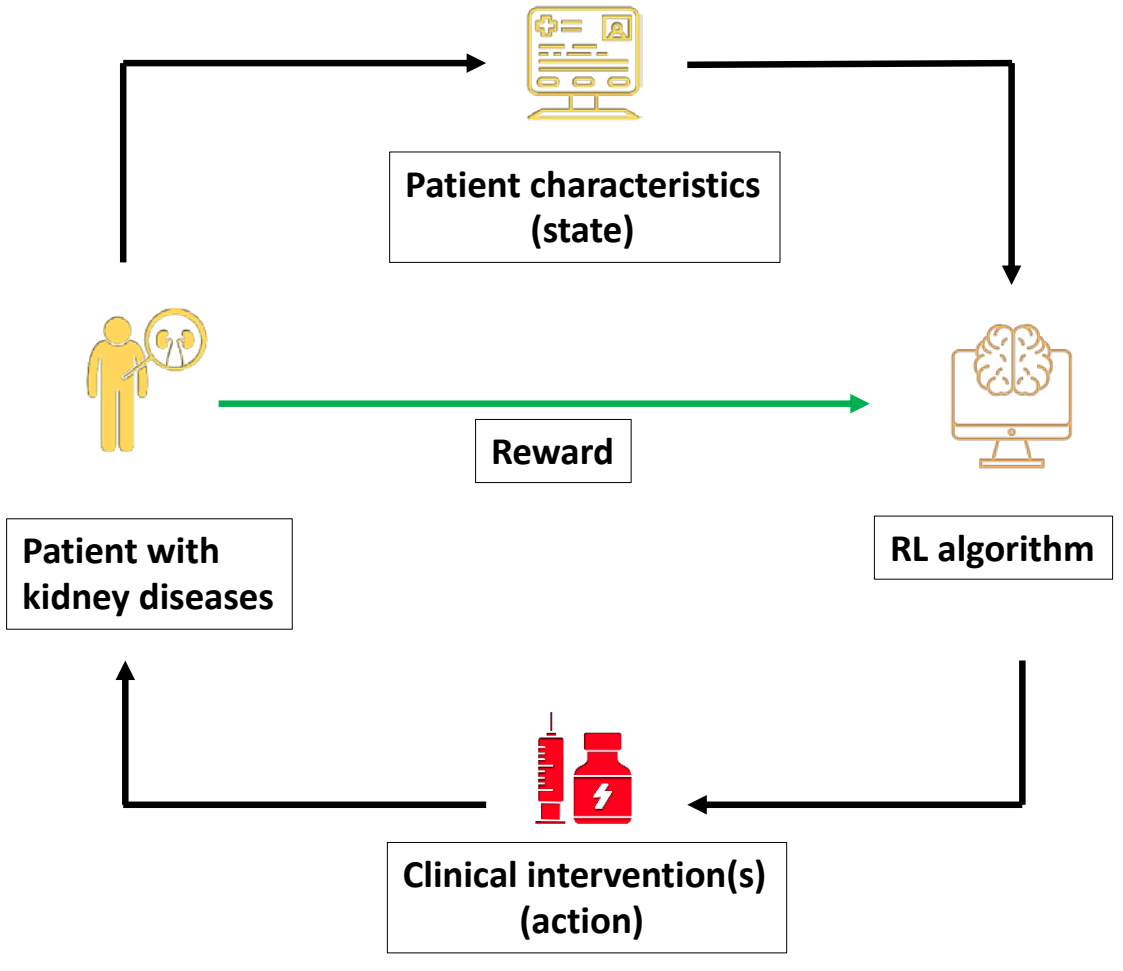
[Reinforcement learning] can be used to learn optimal dosing of medications and fluids.

Figure 1. Applications of RL in kidney health and diseases



In health care, the use of RL translates into RL suggesting clinical interventions ("action") based on a patient's characteristics ("state"). This modifies the patient's state, and the next action now must account for this new state. The reward for the RL algorithm is determined by desired outcomes (survival, improvement of kidney diseases, etc.).

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Digital Health Equity and Kidney Diseases

By Lipika Samal, Jorge A. Rodriguez, and Patricia C. Dykes

Research on digital health has largely focused on clinical decision support tools to help providers. Much of the research related to chronic kidney disease (CKD) has been on closing the "knowing-doing" gap through computerized clinical decision support and other types of quality improvement tools. Now, the focus is moving to risk prediction tools that are either rule based or model based (regression model or machine learning methods). The goal of these tools is to identify patients earlier for intervention (e.g., before development of acute kidney injury [AKI]), with the goal to improve outcomes.

There has been much less research on digital health tools for patients and their families and care partners. This is concerning since, in the ambulatory setting, active patient engagement is of paramount importance. Digital health tools include patient portals tied to electronic health records (EHRs), mobile applications, remote patient monitoring, and other technology for the provision of telehealth services. Using these tools, patient education about kidney diseases could be tailored to each individual patient. For example, the data in the EHR can be used to stage a patient's CKD based on laboratory results for serum creatinine or serum cystatin C and the urine albumin-to-creatinine ratio, which would allow a digital health tool to show stage-appropriate educational materials to the patient. Even more importantly, patients themselves can be the ones to remind their physicians about screening and stage-appropriate monitoring (1).

With the enactment of the 21st Century Cures Act, which supports patients' access to their data, an important step forward is the development of applications that can use interoperability standards. Standards, such as Consolidated Clinical Document Architecture and Fast Healthcare Interoperability Resources, enable the digital health tools to pull in an individual patient's own data regardless of which EHR the physician or hospital system is using. For example, one application uses this approach to present diabetes-relevant data in a low numeracy-appropriate format (2). This functionality can also be used to help patients separate "signal" from "noise." For example, a hospitalization for an acute illness often leads to temporary changes in medications for chronic diseases, including CKD, diabetes, and congestive heart failure. These changes can be highlighted for patients so that they can be prepared to discuss long-term dosage changes with their primary care physician (3). Digital health tools are also part of the strategy to improve post-AKI care through federally funded research (4). Such tools can help patients and their primary care physicians discuss a diagnosis of AKI and potential sequelae.

Digital health equity is the fair and just opportunity for patients to engage with and benefit from digital tools. Digital equity is central to ensuring that the implementation of these technologies does not widen health disparities. The key components of digital equity are broadband internet access and affordability, digital literacy, inclusive design and implementation, supportive reimbursement policies, and inclusion of digital tools and orientation for the use of digital tools in self-management as a standard part of care. There are ongoing, multi-level activities to address these digital gaps (Figure 1). At the federal level, the Infrastructure Investment and Jobs Act promotes the extension of broadband infrastructure, which includes a subsidy program to help patients with their monthly internet costs and devices (5). Health care systems, like the Veterans Administration, have established tablet-loaning programs to help patients who do not have devices (6). Additional focus has been placed on ensuring access to digital tools for patients with limited English proficiency. Some hospital systems have translated their patient portals to multiple languages as a commitment to language equity (7). These efforts represent initial steps to ensure a digitally equitable health care system that supports patient engagement and comprehensive kidney disease care.

In addition, there are quite a few opportunities for individual physicians in health care settings, like office-based clinics. National surveys show that there are disparities in provision of patient portals across racial and ethnic groups but little difference in actual use of portals for those who are offered access (8). Physicians and clinic staff in nephrology clinics can screen patients for digital needs and digital tool use at routine visits. For patients lacking device or broadband access, they can be referred to the Affordable Connectivity Program. Additionally, clinics can use EHR data to identify patients who are not using patient portals and offer training support. Older patients and patients with less education can become portal users through training in the clinic setting (9) or at home (10). One approach is to incorporate a digital navigator who can train patients to use these tools (11).

Digital health equity is another way to combat the environmental, medical, and social factors, as well as the effects of structural racism, that contribute to an increased risk of developing kidney failure. Through these key activities for digital health equity, we can all work together to ensure that patients with vulnerabilities derive benefit from digital health tools. ■

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The authors report no relevant conflicts of interest.

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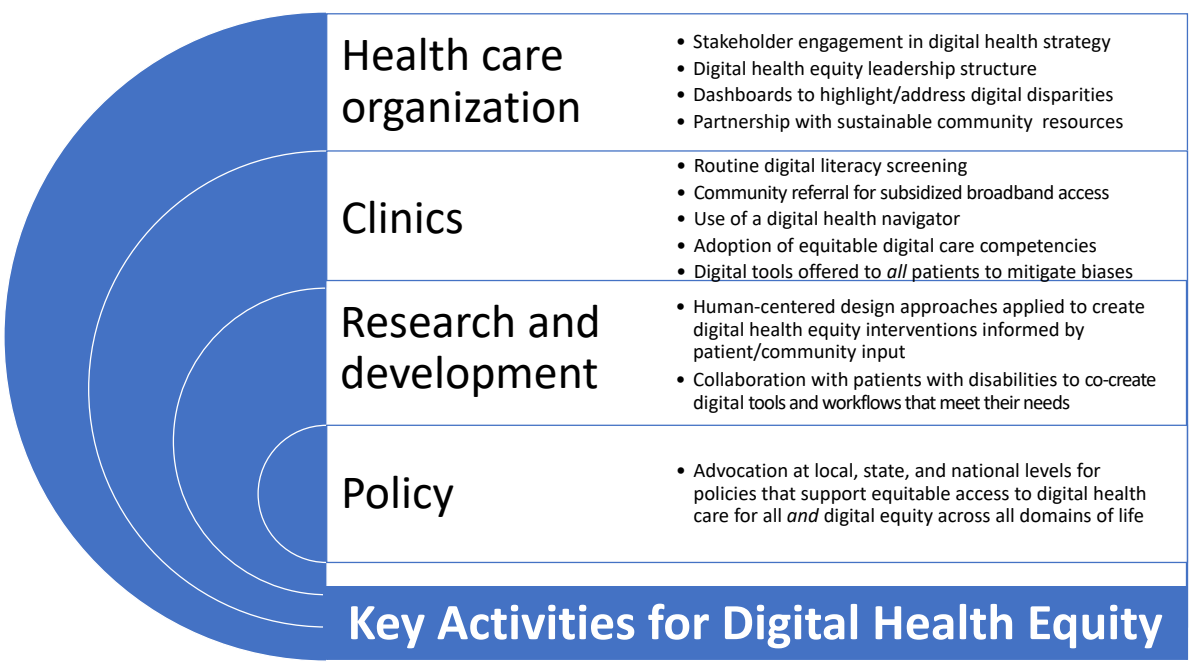
Figure 1. Activities to address digital health equity gaps



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C3G, complement 3 glomerulopathy; IgA, immunoglobulin A.

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ASN Executive Vice President's Update

Assessing KidneyX After Five Years

By Tod Ibrahim

To "boost innovation in the fight against cancer" as part of the reignited Cancer Moonshot, the Biden administration, on Thursday, February 2, 2023, announced CancerX (1). According to the administration, this public-private partnership "will build on previous models deployed by successful HHS [US Department of Health and Human Services] InnovationX program accelerators such as KidneyX [The Kidney Innovation Accelerator]" (2).

In the 5 years between Thursday, April 26, 2018—when ASN and the Trump administration established KidneyX (3)—and the announcement about CancerX earlier this year, HHS has launched several similar initiatives, including InnovationX, LymeX, PandemicX, and PreventionX. These public-private partnerships are housed in the Office of the Assistant Secretary for Health at HHS and structured similarly to highlight unmet needs, support innovation, advance solutions, and build community to overcome challenges that private markets and government agencies cannot solve alone.

Representatives Larry Bucshon, MD (R-IN), and Suzan DelBene (D-WA)—who co-chair the Congressional Kidney Caucus—and Senators Ben Cardin (D-MD) and Todd Young (R-IN) have been tireless advocates for the more than 37 million Americans with kidney diseases. Having successfully secured $20 million in funding to support KidneyX since fiscal year (FY) 2020, they are currently seeking an additional $25 million in funding for FY 2024. Their leadership has also resulted in congressional acclaim for KidneyX, making it synonymous with bold innovation. Due to this bipartisan, bicameral support, it is not surprising that the Biden administration used KidneyX as a model to spur innovation in other diseases, especially as part of reigniting the Cancer Moonshot.

To accomplish its mission of accelerating "innovation in the prevention, diagnosis, and treatment of kidney diseases," KidneyX is built on four pillars (3):

1. Offering funding opportunities through prize competitions for unmet needs in kidney diseases
2. Coordinating regulatory and payment policies across HHS—including the National Institutes of Health, Food and Drug Administration (FDA), and Centers for Medicare & Medicaid Services (CMS)—to clarify pathways to commercializing innovations
3. De-risking commercialization to attract outside investment capital and partnerships
4. Creating a sense of urgency on behalf of people with kidney diseases

By evaluating each of these pillars, ASN can help HHS, the rest of the kidney community, the Congressional Kidney Caucus, and the Senate KidneyX champions assess the first 5 years of KidneyX and plan for its future.

Pillar 1: Offering Funding Opportunities. In its first 5 years, KidneyX designed, supported, and completed six separate prize competitions:

- COVID-19 Kidney Care Challenge
- Patient Innovator Challenge, which was funded by the National Kidney Foundation (NKF)
- Redesign Dialysis Phase One
- Redesign Dialysis Phase Two
- Artificial Kidney Prize Phase One
- Artificial Kidney Prize Phase Two

Through these six competitions, KidneyX has awarded approximately $17 million to 75 winners in 26 different US states (as well as one recipient in the United Kingdom, supported directly by ASN). Besides starting to bring new innovators into the kidney community, KidneyX's winners have included university-based start-ups, such as Relavo; researchers from other fields, such as those at VasoBio, who can apply their technologies toward unmet needs in treating kidney diseases; people ineligible for traditional government-funding mechanisms, such as the winners of the Patient Innovator Challenge; and innovators who explicitly sought advances in other artificial organs, such as the liver and heart, toward the development of an artificial kidney.

As you can imagine, ASN and HHS have learned a lot about administering prize competitions during the past 5 years. These insights will help inform future competitions, outreach efforts to attract non-traditional kidney innovators, and potential partnerships with other non-government organizations, as well as allow the KidneyX Steering Committee (Table 1) to consider other mechanisms for offering funding opportunities.

Pillar 2, A: Coordinating Regulatory Policies across HHS. In 2012, ASN partnered with the FDA and more than 75 member organizations to launch the Kidney Health Initiative (KHI). With a mission "to catalyze innovation and the development of safe and effective patient-centered therapies for people living with kidney diseases," KHI identifies surrogate endpoints for the eventual approval of new drugs, strengthens the pipeline of potential therapeutics, creates roadmaps to support product development and early-stage investment, and defines best practices to partner with people living with kidney diseases (4).

To coordinate regulatory policies—particularly for KidneyX's Redesign Dialysis and Artificial Kidney Prize—KHI helps the FDA, ASN, and the rest of the kidney community to frame how innovators improve care and quality of life for people with kidney failure through innovative kidney replacement technologies. Examples of this alignment include: A Technology Roadmap for Innovative Approaches to Kidney Replacement Therapies: A Catalyst for Change (5), Building Capacity to Incorporate Patient Preferences into the Development of Innovative Alternatives to Renal Replacement Therapy (a project that resulted in multiple publications and toolkits) (6), Human Centered Design Toolkit for Kidney Failure (7), and Xenotransplantation: Knowledge and Perception Assessment (which is expected to be finished later this year) (8).

Recognizing the challenges of coordinating regulatory policies, ASN and NKF on Tuesday, November 8, 2022, sent a joint letter to FDA Commissioner Robert M. Califf, MD—who served on the KidneyX Steering Committee before returning to the FDA last year—offering to help address public "concerns about FDA's recent decisions of new drug applications for therapies targeting kidney diseases" (9). ASN and NKF offered to help harmonize "endpoints among kidney patients, researchers, sponsor(s), and FDA"; sponsor "a Patient Focused Drug Development Meeting highlighting the preferences of people living with kidney failure on dialysis"; establish "processes for providing constructive feedback earlier in the regulatory review process to allow sponsors to make necessary adjustments to drug development studies and assure they demonstrate safety and efficacy"; utilize "FDA's labeling authority to convey risks and benefits of a therapeutic to kidney patients and health care professionals"; and ensure "participants in clinical trials designed for people living with kidney diseases accurately reflect the patient population."

Dr. Califf responded to ASN and NKF on Tuesday, February 14, 2023, emphasizing: "FDA recognizes the morbidity and mortality associated with kidney disease, the unmet needs of patients living with kidney disease, and the urgent need to make additional treatment options available, particularly for underserved minorities." He added, "FDA looks forward to continued productive and valued interactions with ASN and NKF to help facilitate the development and availability of effective and safe therapies for people living with kidney disease."

Pillar 2, B: Coordinating Payment Policies across HHS. Based on its ongoing focus on the payment landscape, ASN included recommendations concerning this issue in a response to a CMS Request for Information (CMS-3409-NC) on Tuesday, February 1, 2022 (10). In its response, ASN called on CMS to "elevate the development of artificial kidneys as alternatives to dialysis to a national priority" and to "recognize that innovation is imminent for people with kidney failure but still in an early enough stage to be shaped by public policy." ASN continues to collaborate with experts to identify potential payment pathways for artificial kidneys that can incentivize innovations for this much-needed kidney replacement option.

The broader problem, however, relates to the Medicare program's challenges in paying for innovative medical devices. In 2021, CMS withdrew—and has yet to replace—a federal regulation, "The Medicare Coverage of Innovative Technology (MCIT) Definition of 'Reasonable and Necessary,'" due to concerns raised about insufficient patient protections (11). MCIT would have provided 4 years of Medicare coverage for medical devices approved through the FDA Breakthrough Device Designation (BDD).

According to the FDA, BDD is intended to provide patients and health professionals "with timely access to these medical devices by speeding up their development, assessment, and review, while preserving the statutory standards for premarket approval, 510(k) clearance, and De Novo marketing authorization, consistent with the Agency's mission to protect and promote public health" (12). The FDA uses a 510(k) clearance to demonstrate that a new medical device is similarly safe and effective in comparison with another cleared device with the same intended use.

For years, ASN and other members of the kidney community have also raised concerns about two new payment designations within the Medicare End Stage Renal Disease Prospective Payment System, which is also known as "the bundle." Through the Transitional Drug Add-on Payment Adjustment (TDAPA), eligible new drugs can receive a temporary pass-through payment outside of the bundle, and the Transitional Add-on Payment Adjustment for New and Innovative Equipment and Supplies (TPNIES) is intended to incentivize early adoption of eligible new and innovative equipment, such as home dialysis machines.

For TPNIES, CMS requires evidence of improved care, specifically for people eligible for Medicare coverage. Additionally, by requiring evidence of substantial clinical improvement that is not clearly defined, TPNIES requires an even higher, and less clear, threshold than TDAPA. In fact, the Tablo Hemodialysis System from KidneyX winner Outset Medical is the only medical device to receive TPNIES approval from CMS.

On Thursday, May 11, 2023, the House Committee on Ways and Means' Subcommittee on Health (which has jurisdiction over Medicare) held a hearing on medical innovation and access to care. During the hearing, several members of Congress expressed their concerns about barriers faced by

device companies in obtaining insurance coverage after the FDA BDD, thereby stifling innovation and limiting patient options. Among those demanding clear metrics for insurance coverage was Representative DelBene, who has previously sponsored legislation that would provide traditional Medicare coverage for breakthrough devices.

Pillar 3: De-Risking Commercialization. To encourage investment in the kidney arena, KidneyX has held annual in-person and virtual summits (including one on Monday, June 12, 2023, in Washington, DC), pitch sessions at ASN Kidney Week in 2019 and 2022, and Capital Market Days (in London, England, and virtually) and continues to connect winners and other entrepreneurs with experts in the kidney community. Last month, KidneyX initiated a webinar series on kidney entrepreneurship that focuses on common pitfalls preventing the advancement of kidney technologies with strategies to overcome them, trends shaping the xenotransplantation and artificial kidney markets, current patient flows for dialysis to understand where artificial kidneys can provide the most benefit, and the existing landscape of emerging technologies in home dialysis and kidney transplant (13).

In 2022, the FDA cleared devices developed by two KidneyX prize winners. VenoStent received BDD from the FDA on its innovative vascular access technologies, while Alio received FDA 510(k) clearance "for its remote monitoring system that collects data on skin temperature, auscultation, or internal body sounds, and heart rate" (14). Alio's current focus is remote monitoring for patients on dialysis, but "it is working on clinical studies to validate the system's use for other indications."

In addition to funding the KidneyX Patient Innovator Challenge, NKF in 2022 launched the NKF Innovation Fund, "a new impact investment program aimed at fundamentally disrupting the fight against kidney disease" (15). During its first year, the NKF Innovation Fund supported three KidneyX winners: 34 Lives (formerly Renovera), Kuleana/University of Washington, and Relavo. Relavo has also received $1.25 million in Phase 1 and 2 Small Business Innovation Research funding from the National Science Foundation.

Demonstrating KidneyX's unique potential to excite, catalyze, and activate private markets to support innovation in kidney health, other winners to receive additional funding after their prize award include:

- VenoStent: $2.3 million in seed funding
- VasoBio: $3 million of follow-on grant funding from the California Institute for Regenerative Medicine
- NitriCap Medical: $3.2 million from the Michigan Biomedical Venture Fund
- The Kidney Project/University of California, San Francisco, School of Medicine: $6.7 million from Amgen Ventures, the John and Marcia Goldman Foundation, and other contributors
- Miromatrix Medical: $20 million in Series C financing, followed by $43 million initial public offering (IPO)
- Outset Medical: $277.9 million in its IPO

In evaluating KidneyX, it is important to question whether this level of private funding is enough. Have KidneyX's prize competitions (jointly administered by ASN and HHS) done enough to de-risk commercialization to attract outside investment capital and partnerships? The KidneyX Steering Committee is well positioned to consider this and related questions.

Pillar 4: Creating a Sense of Urgency. On Wednesday, July 10, 2019, the Executive Order on Advancing American Kidney Health (EO 13879) was signed, making it the nation's first presidential directive focused on overarching policy objectives for one disease. On that day, the success of KHI, HHS's commitment to KidneyX, and unified advocacy by ASN and the rest of the kidney community helped make improving kidney health federal policy in the United States.

To "encourage the development of an artificial kidney," the executive order requested that HHS "produce a strategy for encouraging innovation in new therapies through the Kidney Innovation Accelerator (KidneyX), a public-private partnership between the Department and the American Society of Nephrology" (16). This request helped amplify the community's advocacy efforts, galvanize support in Congress, capture the attention of the media and investors, and focus the KidneyX Steering Committee on the Redesign Dialysis and Artificial Kidney Prize.

Beyond the executive order, KidneyX has involved people with kidney diseases in everything it does: serving as members of the KidneyX Steering Committee (NKF Chief Executive Officer Kevin Longino and musical artist David Rush), incorporating the patient perspective as scored criteria in all submissions, including patients as judges on review panels, and offering a Patient Innovator Prize. As KHI Strategy Committee Member Glenda V. Roberts said when she received the ASN President's Medal at Kidney Week 2022, "I think that the most exciting project that's going on is KidneyX, because KidneyX is facilitating innovation."

After 5 years, KidneyX has made considerable progress despite the COVID-19 pandemic, a change in presidential administrations, and an expanded portfolio of innovator accelerators at HHS. During the Biden administration, the Office of the Assistant Secretary for Health at HHS has been responsible for KidneyX as a public-private partnership with ASN. HHS Assistant Secretary for Health Admiral Rachel L. Levine, MD, has been hugely supportive of KidneyX, and ASN members, leadership, staff, and I, as well as the rest of the kidney community, owe her—and Representatives Bucshon and DelBene and Senators Cardin and Young—our gratitude and appreciation.

Given Admiral Levine's support, two consecutive presidential administrations' interest in public-private innovation accelerators, like KidneyX; backing from both the Congressional Kidney Caucus and Senate champions; the Executive Order on Advancing American Kidney Health; and KidneyX's first 5 years of success, the time is right for ASN and the rest of the kidney community to advocate for the establishment of the HHS Office of Kidney Health and Transplantation. The announcement of the Organ Procurement and Transplantation Network Modernization Initiative by HHS's Health Resources and Services Administration on Wednesday, March 22, 2023, creates even more momentum, potential, and need for this approach (17).

As I noted in the April 2023 issue of ASN *Kidney News*, "the oversight, administration, and delivery of care for the more than 37 million Americans with kidney diseases, kidney failure, and kidney transplants are spread across the federal government" (18). Besides offering an ideal home for KidneyX, the HHS Office of Kidney Health and Transplantation would ensure that every HHS entity with a role to play in kidney and transplant health works synergistically. It would also amplify the patient voice and guarantee that ASN and the rest of the kidney community have a centralized way to share their experiences for driving access, accelerating innovation, and maximizing scientific advancements.

With KidneyX as a cornerstone and maximizing access to transplantation a key focus, the HHS Office of Kidney Health and Transplantation would also enhance efforts to offer funding opportunities through prize competitions and other mechanisms, coordinate regulatory and payment policies across HHS, de-risk commercialization to attract outside investment capital and partnerships, and create an even greater sense of urgency on behalf of people with kidney diseases. Such an approach would prove that "we're united 4 kidney health" and committed to intervening earlier, transforming transplant, accelerating innovation, and achieving equity (19). ■

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Table 1. KidneyX Steering Committee

Member	Affiliation
Elazer Edelman, MD, PhD	Massachusetts Institute of Technology
Jennifer Erickson	White House Office of Science and Technology Policy (2015–2017)
Linda F. Fried, MD, MPH, FASN ASN Council Liaison	VA Pittsburgh Healthcare System
RADM Michael Iademarco, MD, MPH Ex Officio	Department of Health and Human Services
Paul E. Klotman, MD	Baylor College of Medicine
Emily Levy, MBA	Synergy Partners
Kevin Longino	National Kidney Foundation
Sandeep Patel, PhD Ex Officio	Biomedical Advanced Research and Development Authority
Saira Ramasastry, MA, MS	Life Sciences Advisory
David Rush	Patient advocate
John R. Sedor, MD, FASN Chair	Cleveland Clinic
Danilo Tagle, PhD Ex Officio	National Institutes of Health National Center for Advancing Translational Sciences
Bruce J. Tromberg, PhD Ex Officio	National Institutes of Health National Institute of Biomedical Imaging and Bioengineering

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Progressive CKD and Adverse Events: New UK Data

In patients with chronic kidney disease (CKD), adverse clinical events increase with disease stage and dialysis status, especially incident dialysis, reports a study in *BMC Nephrology*.

The analysis included data on 310,953 patients with CKD, identified from the UK Clinical Practice Research Datalink from 2004 through 2017. The study focused on selected adverse clinical events that may be difficult to measure in randomized trials. Event rates were compared by dialysis status and modality, baseline CKD stage, and observation period.

At index, 601 patients had dialysis-dependent CKD (DD-CKD). Among those with non-DD (NDD)-CKD, the disease stage was 3a in 71.7% of patients, stage 3b in 23.0%, stage 4 in 4.8%, and stage 5 in 0.4%. The median age was 67 years in the DD-CKD group versus 76 in the NDD-CKD group. Women accounted for 60.4% of patients with NDD-CKD, 39.2% with DD-CKD, and 39.1% with incident DD-CKD (IDD-CKD).

Patients with NDD-CKD had fewer comorbidities, higher hemoglobin, and lower C-reactive protein compared with the DD-CKD or IDD-CKD group. Within the NDD-CKD group, comorbidity was higher at lower estimated glomerular filtration rate levels.

Among patients receiving dialysis, the most frequent adverse clinical events were pneumonia/respiratory infection: incidence rate, 18.0 per 100 patient-years in the DD-CKD group and 19.9 in the IDD-CKD group compared with 9.3 in the NDD-CKD group. Incidence rates and all-event rates were generally higher in patients who were DD, including a 6.5-fold increase in hyperkalemia and a 6.9-fold increase in infection/sepsis in the DD-CKD group. In the IDD-CKD group, these increases were 7.4-fold and 9.4-fold, respectively.

Adverse event rates were higher during more recent observation periods. Mortality during follow-up was higher in the two dialysis groups and in patients with stage 4 or 5 disease in the NDD-CKD group. Adverse events and mortality were higher in patients receiving hemodialysis compared with peritoneal dialysis.

Among patients with CKD, rates of adverse clinical events and mortality are higher in patients who are DD and those with higher-stage CKD. Risks are particularly high in patients with IDD. The researchers conclude: "Our findings highlight the need to monitor patients with CKD for comorbidities and complications, as well as signs or symptoms of clinical adverse events, such as hyperkalemia, hypoglycemia, retinal disorders, seizures, and infection/sepsis." ■

Little DJ, et al. Rates of adverse clinical events in patients with chronic kidney disease: Analysis of electronic health records from the UK Clinical Practice Research Datalink linked to hospital data. *BMC Nephrol* 2023; 24:91; doi: 10.1186/s12882-023-03119-z

Patient Outcomes and Dialysis Care Models

By Nurit Katz-Agranov

The prevalence of end stage kidney disease and the demand for dialysis services have been steadily increasing worldwide (1), with projections indicating that this trend will continue to rise (1, 2). Although the ability to provide dialysis has improved patient life expectancy (3, 4), those who require dialysis have inferior outcomes compared with the general population, emphasizing the importance of implementing strategies to improve these outcomes. Although many factors shown to affect patient outcome in dialysis programs cannot be changed, such as geography, facility location, and patient comorbidities, there are many others that can be modified (5) (Table 1).

The Peer Kidney Care Initiative, an important enterprise to identify some of these factors, was created in 2014 by the chief medical officers of 14 U.S. dialysis provider organizations and the Chronic Disease Research Group (4). Several studies have evaluated several modifiable factors in dialysis care that improve patient outcomes, such as high use of surgical vascular access and increased dialysis time (6). The impact of both structural characteristics of dialysis programs and delivery of care by nephrologists on patient outcomes has also increasingly become a topic of interest.

For example, some studies have evaluated the impact of frequency and duration of provider-patient visits in hemodialysis programs on patient outcomes (7, 8), with variable results (9). Others evaluated whether a dialysis program structure affects patient outcomes (10, 11). To date, there has been no large-scale study, however, to evaluate the impact of nephrologist staffing models on patient outcomes, a topic that has been addressed by Silver and colleagues (12). The authors identified the wide variations in nephrology staffing models and sought to evaluate whether this factor impacts patient outcomes in a large, population-based cohort of over 14,000 individuals receiving hemodialysis in Ontario, Canada. In this retrospective study, Silver and coworkers (12) compared patient outcomes between dialysis programs that used a single, primary nephrologist model with those that used a group of nephrologists on a rotating basis. After adjusting for several predefined patient and center characteristics, no differences were found in rates of mortality, kidney transplantation, or home dialysis initiation between the groups (Figure 1). In dialysis programs with high patient volumes (>500 patients) and in those with medically complex patients (Charlson Comorbidity Index ≥4), the authors did find an interaction between the single nephrologist model and mortality, suggesting that these factors may need to be considered when considering staffing models.

The results of this study suggest a multidisciplinary approach is required to optimize patient outcomes in dialysis programs and that continuity of care alone, while important, is not enough. Worth mentioning, as noted by the authors, is hat this study did not assess patient-reported outcome measures, an important point to consider (13). Previous studies evaluating the effect of face-to-face time between patients and providers in dialysis centers have found that length of visits, rather than frequency of visits, was associated with better patient-reported outcome measures, suggesting communication skills were more important for patient satisfaction (14).

The concerning trajectory of the incidence of dialysis initiation worldwide highlights the importance of identifying and optimizing patient care models in dialysis programs. Whereas the abundance of research on this topic has been done at a population-based level, interpretating results must be done cautiously, as there are many confounders that are difficult to adjust for in this study design. Such confounders may include several treatment protocols that vary among programs (i.e., anemia/iron protocols, mineral and bone disorder protocols, the transplant-referral process, etc.), a limitation that was also noted appropriately by the authors.

Improvement initiatives implemented within individual dialysis centers have the potential to enhance objective patient outcomes by targeting factors that are specific to the patient population served by that center. Finally, it is crucial to keep in mind that the identification of factors that improve patient outcomes is just the initial stage, and it is essential to follow through with implementation to effectively achieve the desired change. This is not a simple task, as some factors, such as dialysis frequency and time, require change at the level of health policymakers because reimbursement is currently pre-set for three times weekly for in-center hemodialysis (15). This complexity of policy change further emphasizes the importance of building strong evidence for change to improve outcomes of patients requiring dialysis. ■

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Table 1. Factors affecting patient outcomes in dialysis programs

Pre-dialysis care:	• Established care in nephrology clinic prior to dialysis initiation
Dialysis modalities/practices:	• Access • Dialysis times • Dialysis prescriptions
Delivery of care:	• Length of patient-provider encounter
Structure of dialysis centers:	• Medical center-based vs. clinic-based

Generalizability of these findings is challenging because study populations vary widely between studies, both in geography/study location as well as in inclusion criteria. For example, while some studies assessed patients who were new to dialysis initiation, which is notoriously known to have increased mortality rates, other studies included only patients on maintenance hemodialysis.

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Figure 1. Does longitudinal care provided by a single nephrologist in dialysis centers improve patient outcomes?

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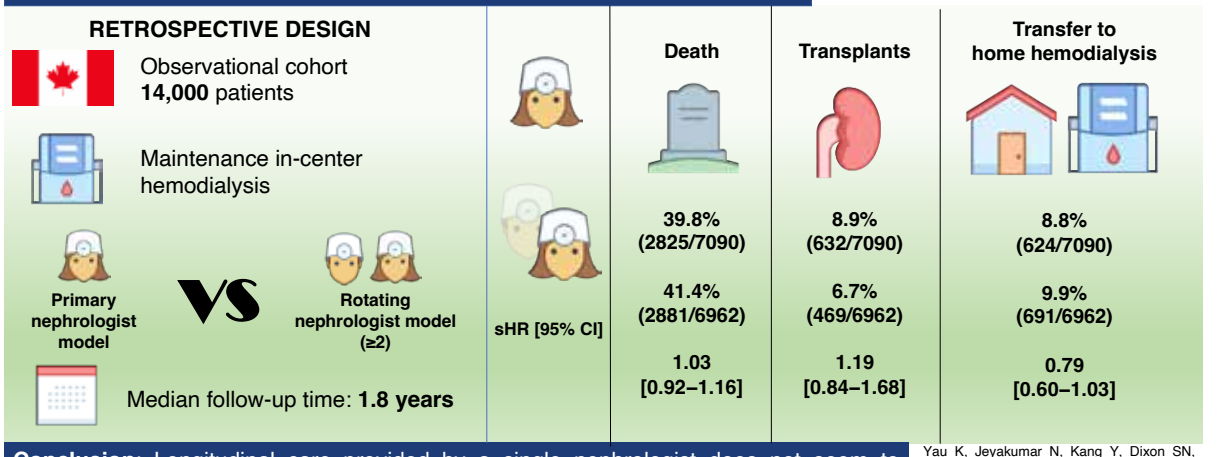

Conclusion: Longitudinal care provided by a single nephrologist does not seem to improve patient outcomes in dialysis programs, making both primary nephrologist models and rotating nephrologist models equally acceptable in delivery of care to patients in dialysis programs. CI, confidence interval; sHR, subdistribution hazard ratio.

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Promoting Clinical Trials on Pediatric Chronic Kidney Disease

By Howard Trachtman

The need

Chronic kidney disease (CKD) is a rare but serious condition in children and adolescents (1). The causes of CKD often differ from those that are common in adults with a far greater contribution of congenital abnormalities of the kidney and urinary tract (CAKUT) and a far less significant role for diabetic nephropathy and hypertensive nephrosclerosis. Although CKD is not nearly as prevalent in children as in adults, the effects on well-being and long-term health outcomes are just as profound in the pediatric population (2).

First, a recent study indicates that the natural history of glomerular disorders like focal segmental glomerulosclerosis (FSGS) is very similar in children, adolescents, and adults with a parallel trajectory of estimated glomerular filtration rate decline over time in the three age groups (3). Second, the onset of CKD early in life can have a wide range of irreversible, deleterious effects on somatic and neurocognitive development (4, 5). CKD in childhood interferes with normal pubertal development and the attainment of full growth stature. Finally, adolescence can be associated with compromised adherence to prescribed treatments leading to suboptimal care (6). Except for a few genetic disorders, such as oxalosis and atypical hemolytic uremic syndrome, there are no U.S. Food & Drug Administration (FDA)-approved therapies for pediatric CKD. This results in off-label use of most medications without clear-cut guidelines about indication and dosage. Taken together, all of these considerations argue persuasively for the need to conduct well-designed clinical trials in the pediatric population for those with CKD. Because this is a rare condition, it will require innovative design and analytic approaches to enhance the feasibility and successful completion of proposed trials. Closer engagement with the patient community will be needed to foster their full participation in this effort.

Bioethical considerations

It is essential that clinical trials for pediatric CKD be conducted within a sound bioethical framework. There is a justifiable concern when testing novel therapies in neonates, children, and adolescents who represent a vulnerable population, but one that is in need of more effective therapeutics. The risks of adverse effects that may have long-term ramifications are greater in children than in adults. The concerns about disrupting normal development are unique to childhood. The uncertainty about whether children, adolescents, and their families fully comprehend the nature of their disease and about the potential hazards and benefits of a clinical trial needs to be taken into account in planning trials for pediatric CKD. However, this caution needs to be balanced by consideration of the actual impact of the disease in children versus adults. Additional studies like the one by Gipson et al. (3) would fill gaps in knowledge and provide a strong rationale for inclusion of pediatric patients in clinical trials. Performing additional studies would be relevant in a number of diseases such as autosomal-dominant polycystic kidney disease, Alport syndrome, and diabetic kidney disease, which begin at birth or in childhood. Finally, more attention to the lived experience of pediatric patients with CKD and a broader assessment of perceived risk and benefit by patients and care providers would promote a more grounded analysis of the ethical justification for testing novel therapies in pediatric patients. Autonomy is a dynamic variable in pediatrics, and the voices and wishes of adolescents regarding their participation in trials need to be heard.

Approaches

- *Patient identification*: The are a number of approaches that can be adopted to foster the conduct of clinical trials in pediatric CKD. Early case identification is critical to enable the documentation of patients who might qualify for enrollment in trials. Because of the relative rarity of CKD in children, routine measurement of serum creatinine concentration and urinary protein excretion is less likely to be routinely performed in children than in adults. However, computable phenotypes have been developed for identification of cases of glomerular disease and nephrotic syndrome using the electronic health record (7). Expanding these methods to include CKD would broaden the population to include glomerular and non-glomerular diseases, an important consideration in pediatrics.

In addition, it is important to educate and engage prospective trial participants about the clinical significance of CKD. This condition is often clinically silent without evident symptoms and, thus, unrecognized in its initial stages, and the adverse consequences are not fully appreciated. Moreover, children and adults are different, and the community should be made to understand the need to define optimal therapies specifically in children and adolescents. There is a great need to target these efforts to 1) minority and underrepresented populations who are wary of participating in trials due to historical and present-day injustices in the health care system and 2) misinformed populations who are wary of participating in clinical trials due to medical misinformation and inaccurate open-source content.

- *Registries*: Regional, national, and international registries represent an invaluable resource to assess the incidence, prevalence, and geographical distribution of kidney diseases in children (8). Importantly, these joint enterprises help delineate the natural history of the specific entities, a key consideration in clinical trial design and the estimation of the projected benefit of a new test therapy. Prominent examples include the European registry for autosomal recessive polycystic kidney disease and the PodoNet (Clinical, Genetic and Experimental Research into Hereditary Diseases of the Podocyte) registry for steroid-resistant nephrotic syndrome. Longitudinal, observational, cohort studies NEPTUNE (9) and CureGN (10) amplify this effort by compiling deep clinical and laboratory phenotyping of enrolled patients—in this case, children with nephrotic syndrome. Similar efforts need to be extended to the sizable number of children with CAKUT, which like FSGS, probably represents a heterogeneous group of disorders with distinctive mechanisms of kidney injury and damage. This will advance the scientific understanding of this disorder and lay the groundwork for more effective therapies.

Trial design

Because of the rarity of CKD in children, it is imperative that the trial design is optimized to help ensure successful enrollment and completion of studies. Novel approaches to dose finding and planned transition from phase 2 to phase 3 trials can expedite the successful completion of trials and minimize the sample size required. The definition of appropriate end points to assess efficacy of novel therapies is a vital concern in pediatric CKD because the rate of disease progression and the incidence of clinically relevant events are less than in adults. Examples include validated mea-surements of oxalate excretion in clinical trials for primary hyperoxaluria (11). Incorporation of novel measures such as patient-reported outcomes may be especially pertinent in pediatric CKD. Adaptive designs and Sequential, Multiple Assignment, Randomized Trial (SMART) approaches are relevant in pediatric CKD because the limited number of patients reinforces the need to maximize what can be learned from each trial participant (12). Platform trials with an adaptive design, a common protocol, harmonized methods for sample acquisition and outcomes, and a concurrent control group would improve the efficiency of clinical trials in pediatric CKD (13). The designation of select pediatric nephrology divisions as clinical trial centers of excellence may provide a way to direct financial and institutional resources to those sites that are most likely to succeed in this work.

Extrapolation and in vitro studies

Because of the limited number of pediatric patients with CKD and the extent of resources available to conduct clinical trials, alternative sources of information can be used to guide the implementation of clinical trials. Extrapolation from adult clinical trials and trial experience may be warranted in circumstances where the mechanism of action and handling of the drug are likely to be similar in children and adults. In addition, newer technologies such as organoids or Kidney on a Chip provide in vitro systems to test the efficacy of new agents in model systems that can shed light on potential application in pediatric CKD. The FDA has provided guidance for clinical investigators to ensure that they use these non-standard methods in an appropriate and meaningful manner (14).

Initiatives

A number of initiatives are underway to meet the urgent challenge of promoting clinical trials in pediatric CKD. The Kidney Health Initiative (KHI) is a program sponsored by ASN that brings together nephrologists, industry partners, and the FDA into a shared space where they can discuss and implement strategies to facilitate clinical trials in nephrology. A Pediatric Working Group within the KHI is charged with addressing these issues from a pediatric perspective. Work is underway to survey key stakeholders about areas of priority for research in three distinct areas: 1) CKD in general, 2) transplantation, and 3) rare diseases. As a timely example, the importance of evaluating sodium-glucose cotransporter-2 inhibitors (SGLT2is) for the treatment of pediatric CKD has emerged as a significant clinical problem that warrants immediate attention. Although SGLT2is have been demonstrated to be safe and effective renoprotective agents in nearly all forms of adult CKD, there are limited data in children, underscoring the need to address this issue in a timely manner with well-designed, feasible trials.

In addition, the KHI Pediatric Working Group is

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Promoting Clinical Trials

Continued from page 25

compiling a tool kit that can be a resource to guide nephrologists and sponsors when they consider conducting a trial in pediatric CKD. It will include key components that should be considered, such as preclinical studies (including juvenile toxicity), use of in vitro systems, the value of extrapolation, issues surrounding drug formulation and bioavailability, standard case report forms, and a template informed consent form and site contracts. This tool kit is envisioned to be a living resource that can be updated based on changes in the science and regulatory framework.

The Pediatric Inclusion in the Evaluation of Novel Therapies (PIONEER) Group represents a parallel effort initiated with the support of NephCure Kidney International (NKI) (15). It brings together pediatric nephrologists, representatives of the FDA, and patient advocates and is geared to advance clinical trials in pediatric CKD. It is conceived of as a service to the pediatric nephrology community to provide guidance to investigators considering a trial for a specific disease entity. One of the advantages of PIONEER is that it includes nephrologists from the United States and Europe and is poised to help clinical researchers working in these two distinct regulatory environments.

Finally, it is universally recognized that inclusion of the patient voice is a vital component in any attempt to conduct clinical trials in pediatric CKD. Involvement of parents, caregivers, and patients from the earliest stages of trial development ensures that the study addresses questions that are truly of concern to the patient community. Issues of practicality such as the number of study visits, the nature of the laboratory assessment, availability of an open-label extension, and provision of resources to help the parents (e.g., accounting for time away from work, babysitting, and travel costs) can be thoughtfully evaluated before enrolling the first patient. Getting it right at the start is the best way to avoid sluggish recruitment and the need for protocol amendments. Pragmatic trials and studies conducted within the community are additional strategies to promote trials in pediatric CKD. These steps will increase access to and patient acceptance of clinical trials, the extent of their participation, and the timely completion of studies. NKI and other patient-advocacy groups are invaluable partners, both as champions for needed trials and promoters for studies that have been launched. The groups address the unmet clinical and health needs of children with nephrotic syndrome just as the Alport Syndrome Foundation, the Polycystic Kidney Disease (PKD) Foundation, and the Oxalosis and Hyperoxaluria Foundation advocate on behalf of those affected with their specific disorder. There are many other patient voices in the CKD community, and together, they enrich the conversation and are important pro-clinical trial forces.

Conclusion

There is no denying the need to conduct well-designed clinical trials in pediatric CKD. Although it is a relatively rare condition, the health consequences are profound, and economic costs of the condition continue to rise. The manifestations of pediatric CKD are manifold, but there are only a limited number of approved therapies. Advances in basic science, trial design, and analytic methods have come together to create an environment that can foster this effort. Initiatives within the broad nephrology community are pulling together the human and institutional resources needed to ensure the success of this work. Finally, patients and their caregivers have emphatically voiced their support for this work. It is now incumbent on pediatric nephrologists to take full advantage of all of the constructive forces at play and not let the opportunity to move the field forward pass us by. ■

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Fosl1 Is Upregulated During AKI and Ameliorates Proximal Tubule Injury via α-Klotho

By Ignacio Portales-Castillo and Javier A. Neyra

Acute kidney injury (AKI) is a common condition that is characterized by necrosis of certain renal tubular cells, particularly in the proximal tubule, as well as modification of cellular signaling in remaining tubular cells to promote tissue repair. Nonetheless, the clinical context, severity, and duration of AKI may contribute to irreversible kidney parenchymal damage and fibrosis, which ultimately leads to chronic kidney disease. At the cellular level, evidence of failed proximal tubule repair includes persistent expression of markers such as the hepatitis A virus cellular receptor (Havcr1), keratin 20 (Krt20), and/or the vascular cell adhesion molecule 1 (Vcam1) (1). Therefore, an area of considerable interest is the identification of protective cellular signatures during AKI.

In a recent issue of *Kidney International*, Cuarental et al. (2) used proximal tubule cell models as well as rodent models of AKI to identify a significant and consistent upregulation of Fosl1 during the early phase of kidney injury. Fosl1 is a leucine zipper protein that forms part of the canonical activator protein-1 transcription factor complex. The authors demonstrated that Fosl1 is abundant in the proximal tubule cells and can bind directly to the α-klotho gene to promote its expression. To study the relevance of Fosl1 during AKI, the authors selectively deleted Fosl1 in the proximal tubule. Compared with wild-type (WT) mice, Fosl1-deficient mice had more severe kidney injury after exposure to either cisplatin or folic acid, which is consistent with a protective role of FosI1 during AKI. As would be predicted, mice lacking Fosl1

also had lower expression and levels of α-klotho during AKI compared with WT mice. Treatment with exogenous α-klotho ameliorated the kidney injury produced by cisplatin or folic acid in mice lacking Fosl1, supporting a pathobiological mechanism by which Fosl1 exerts its protective functions upstream of α-klotho.

These results provide a novel, direct link to previous observations that α-klotho reduction contributes to incidence and progression of AKI. α-Klotho has important functions in the kidney as a mediator of fibroblast growth factor 23 actions and systemically as a pleiotropic protein with anti-aging, anti-fibrotic, and antioxidant properties. The study by Cuarental et al. (2) provides key insights into the protective role of increased proximal tubule Fosl1 as an adaptive response during AKI via upregulation of α-klotho. Overall, this study underpins a new strategy for α-klotho-centered therapeutics in AKI that requires further translational investigation. ■

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The authors report no conflicts of interest.

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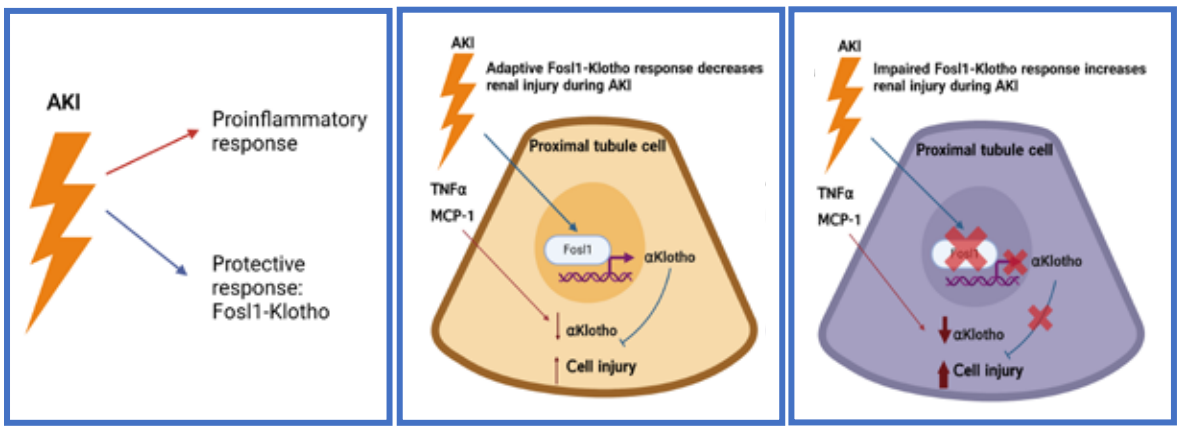
Conceptual impact of Fosl1-Klotho adaptive response in AKI



During AKI, several proinflammatory responses are upregulated, here illustrated by an increase in tumor necrosis factor alpha (TNFα) and monocyte chemoattractant protein-1 (MCP-1). The inflammatory response contributes to cellular injury and also to a decrease in α-klotho. Protective cellular responses during AKI include the upregulation of Fosl1, which via an increase in α-klotho expression ameliorates cellular injury. Deletion of Fosl1 results in more severe downregulation of α-klotho and cellular injury. The visual abstract was created with BioRender.com.

The Role of the Kidney in Cardiovascular Disease Educational Tools Contest, Sponsored by the American Heart Association KCVD, Returns

The American Heart Association (AHA) Council on the Kidney in Cardiovascular Disease (KCVD) is continuing a contest to promote educational tools spanning heart disease and kidney diseases. The role of the kidney in cardiovascular disease (CVD) is widely recognized among nephrologists, but there is scant education about this among primary care practitioners, during medical school, and during residency training. Novel therapies continue to be developed (e.g., sodium glucose co-transporter 2 [SGLT2] inhibitors, for example), and it is imperative to develop new teaching tools that are far reaching in scope and scale.

The Role of the Kidney in Cardiovascular Disease Educational Tools Contest supports the creation of an educational tool aimed at educating physicians/clinicians, trainees, and students about the impact of chronic kidney disease on CVD. The following are contest requirements:

- The teaching tool must enhance the learner's understanding of kidney diseases and CVD to impact clinical decision-making or awareness. The tool can be a video series, interactive website, or a podcast.
- It must teach some aspect about the connection between the kidney and CVD through clinical studies, basic science, translational research, etc.
- One member of the submitting team must be an AHA member. Teams can consist of undergraduate, medical, or PhD students; trainees (resident, fellow, and postdoc); faculty; practicing physicians; researchers; or other health professionals, but one member must have a faculty position in either private practice or at an academic institution. Each member of the team can only be involved in one submission. A corresponding member must be denoted.

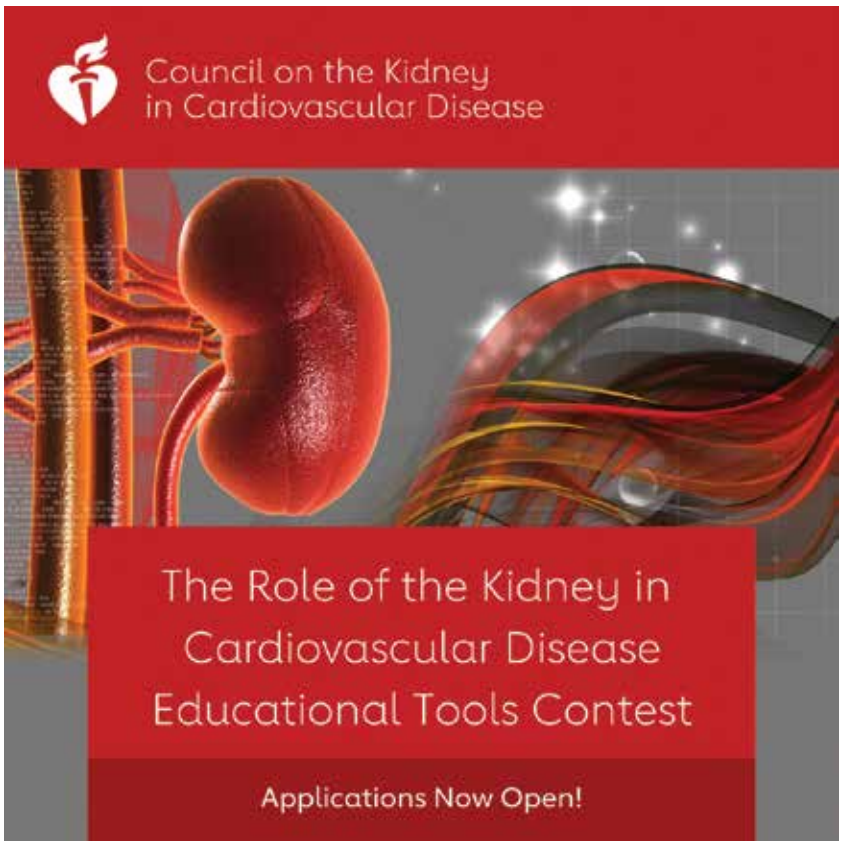
Applications are due July 28, 2023. Please see https://professional.heart.org/en/partners/scientific-councils/kcvd/awards-and-lectures/the-role-of-the-kidney-in-cardiovascular-disease-educational-tools-contest for more information.

The teaching tool will be submitted and judged based on the following merits:

- Kidney and CVD must be featured.
- The tool must be easily accessible.
- The tool must have feasibility for creation (meaning it can be developed).
- A prototype of the tool should be submitted (does not have to be the final product).

Up to three teaching tools will be selected as winners with the following results:

- Each team will receive up to $2000 for further development of the tool.
- AHA's KCVD will publicize the tool.
- Winners will be announced at AHA Scientific Sessions 2023.
- The tool will be linked on the AHA website with a description.
- Each winner will make a video describing the tool. ■



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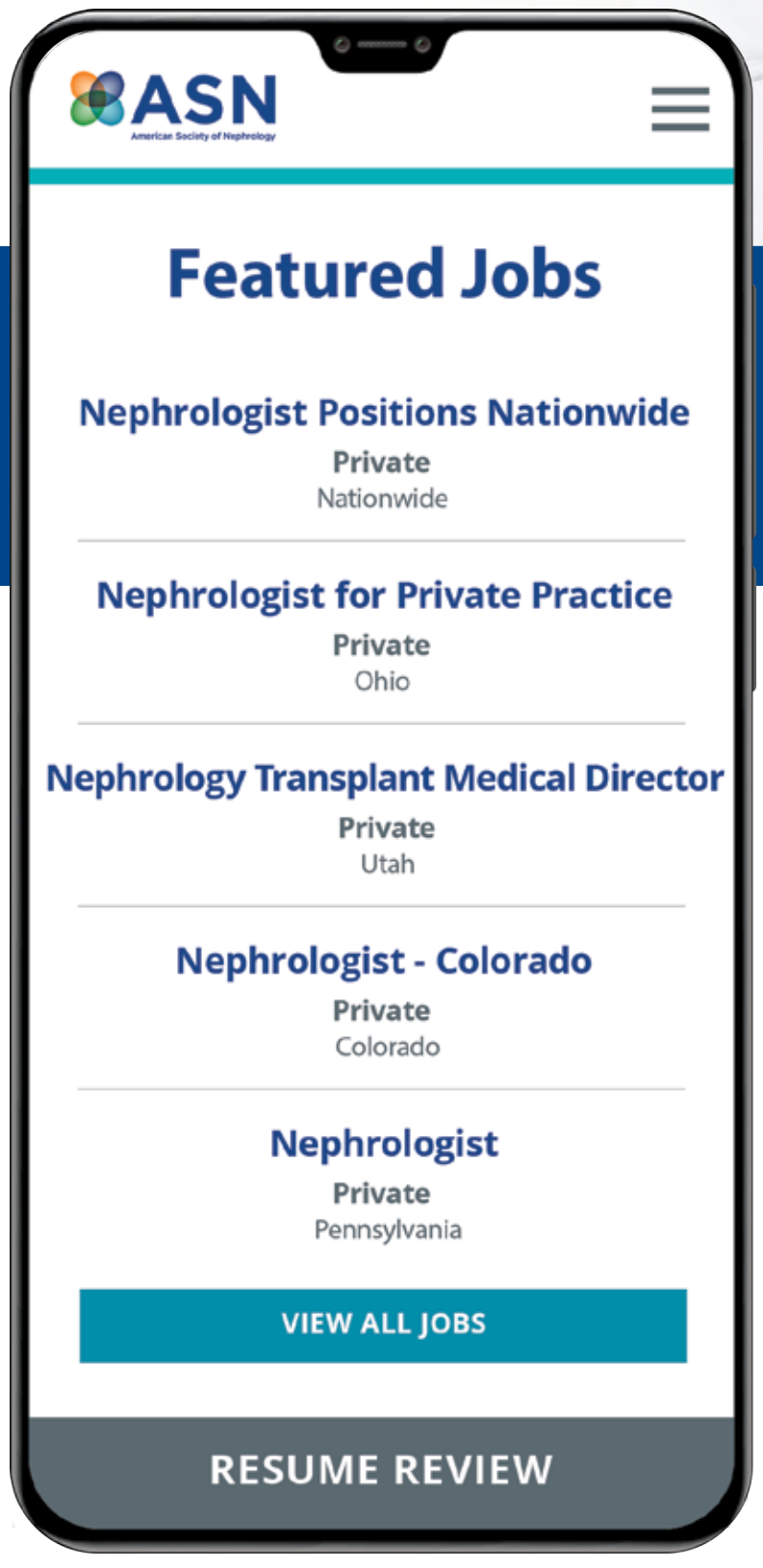

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ASN Responds to FTC Noncompete Clause Proposed Rule

By Scott Bieber

The Federal Trade Commission (FTC) released a proposed rule on January 5, 2023, to prohibit employers from imposing noncompete clauses on workers. In issuing the proposed rule, the FTC cited evidence suggesting noncompete clauses significantly reduce workers' wages, stifle new businesses and new ideas, exploit workers, and hinder economic liberty.

Traditionally, legislation that impacts noncompete clauses for workers exists at a state level, marking this move as a significant effort on a national level. Three states currently have legislation that prevents employers from enforcing noncompetition clauses: California, North Dakota, and Oklahoma. In its release of the proposed rule, the FTC is quick to point out that despite the absence of noncompete clauses in these states, industries that depend on trade secrets and other key investments have flourished there, suggesting that companies are able to find other ways to protect their investments. The proposed rule has a broad reach and is not specific to the health care industry but has the potential to impact physicians and their employers directly (1).

Recent and historical actions by the FTC have shown interest in health care business operations in kidney care, particularly as it relates to dialysis markets and consolidation. Not long ago, the current FTC regulators recognized the impact that dialysis providers can have on industry consolidation and workforce availability for dialysis facilities. In 2021, the FTC intervened in DaVita, Inc., and Total Renal Care, Inc., on acquisition of The University of Utah clinics, citing a concern over reduced competition. In its decision, the FTC also prohibited DaVita from enforcing noncompete agreements and other employee restrictions (2).

Nephrologists are commonly exposed to noncompete clauses in employment agreements and also in contracting agreements for medical director services with dialysis organizations. The degree to which nephrologists are exposed to these agreements and the impact these agreements have on the health care system are largely unknown. Concern does exist, as illustrated by the FTC in the Utah example, that medical director arrangements between locally established physician groups and consolidated dialysis providers can lead to less competition in local dialysis markets. Established dialysis providers typically will have the advantage in locking physician groups into noncompete arrangements, thus restricting access for new dialysis companies to medical director leadership. This practice has the potential, particularly in rural environments, to lead to "dialysis deserts," limiting patient access to care.

Additionally, some academic medical programs have been known to subject junior faculty, directly out of training, to noncompete arrangements at a time when graduating trainees may not fully understand complex contractual agreements. Trainees may feel intimidated or uncomfortable negotiating such agreements with mentors who they respect and trust. Contractual-restrictive covenants are applied more frequently to women and minorities, who may also feel that they are not in a position to negotiate (3). Research has suggested that banning noncompete clauses nationally may help to close gender and racial wage gaps by 3.6% to 9.1% (4).

Following interest from numerous ASN members, the society's Quality Committee—formerly titled the Quality, Patient Safety, and Clinical Practice Committee—reviewed the FTC proposed rule on behalf of ASN members. The ASN Quality Committee aids the policy and advocacy effort of the society with a focus on the regulatory aspects of public policy. The end-product of this effort, along with subsequent review by the ASN Council, was a letter sent by ASN President Michelle A. Josephson, MD, FASN, to the FTC (5). In the letter, ASN highlighted its full support for the proposed rule, focusing on two key issues summarized below.

The unique role of doctors and medical professionals for patients and the community

At the forefront of ASN's response to the FTC proposed rule was a desire, above all else, to preserve the patient-doctor relationship. Nephrologists and other highly trained kidney care professionals provide some of the most complex, long-term, longitudinal care for patients in all of health care. Noncompete arrangements have the potential to disrupt these relationships when health care professionals are forced to relocate due to restrictive covenants.

Recent shifts from independent practice to large group-employed practice and health care consolidation have exposed more physicians to contractional obligations that have the potential to disrupt the patient-physician relationship even further into the future. Noncompete clauses can infringe on the right of the patient to select the physician who they choose. When employment arrangements do not work out as planned, health care professionals deserve the freedom to practice unimpeded in the location that is best for their patients, themselves, and their families. These fundamental, individual rights should outweigh any health care system or business interest.

Unresolved questions for nonprofits

The question of how the proposed rule will apply to nonprofit health care employers is uncertain. There is a suggestion in the proposed rule that nonprofit organizations will be exempt from it. In its letter, ASN points out that a majority of hospitals in the United States are not-for-profit organizations, and dialysis providers are a mix of for-profit and not-for-profit organizations (5). If the proposed rule is applied as suggested—exempting nonprofit organizations—concern exists that an unfair distortion in the labor market may occur, particularly for physicians and other health care workers.

ASN asked the FTC to clarify this issue and expand the proposed rule by including nonprofit health care employers, prohibiting them from binding their employees to noncompete agreements. This approach would level the playing field for all health care employers, including nephrologists.

Differing opinions

The FTC asserts that its authority to regulate noncompete clauses exists under section 5 of the Federal Trade Act, which prohibits unfair methods of competition. Opponents to the proposed rule argue about regulatory overreach by the FTC and assert that such matters should be handled in a more direct fashion by Congress through legislation or remain in the domain of state law. At the time of drafting this article, business and industry seem to be lining up in opposition and are likely to launch efforts to lobby Congress and challenge the final rule in court. It is also unclear if (or how) the FTC will revise the proposed rule based on the feedback it received from ASN and other stakeholders.

Unfortunately, many other advocacy groups that represent physicians and health professionals have articulated mixed responses, been silent, or opposed the FTC rule as proposed. For example, the American Medical Association opposed the proposed rule, citing concerns about the impact it will have on physicians who own and operate medical practices. Whereas concern about the impact the rule may have on small practices and independent nephrologists exits, it may be overstated, as the costs that a small practice would incur in legal fees to enforce a noncompete agreement would likely outweigh any benefit obtained.

When employment arrangements do not work out as planned, health care professionals deserve the freedom to practice unimpeded in the location that is best for their patients, themselves, and their families.

In conclusion, the future of the proposed rule is quite uncertain. Even so, ASN members can take pride in the fact that their professional organization stood with them to support their individual rights and liberties, advocating for the interests of patients and their physicians above those of business entities. ■

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The author reports no conflicts of interest.

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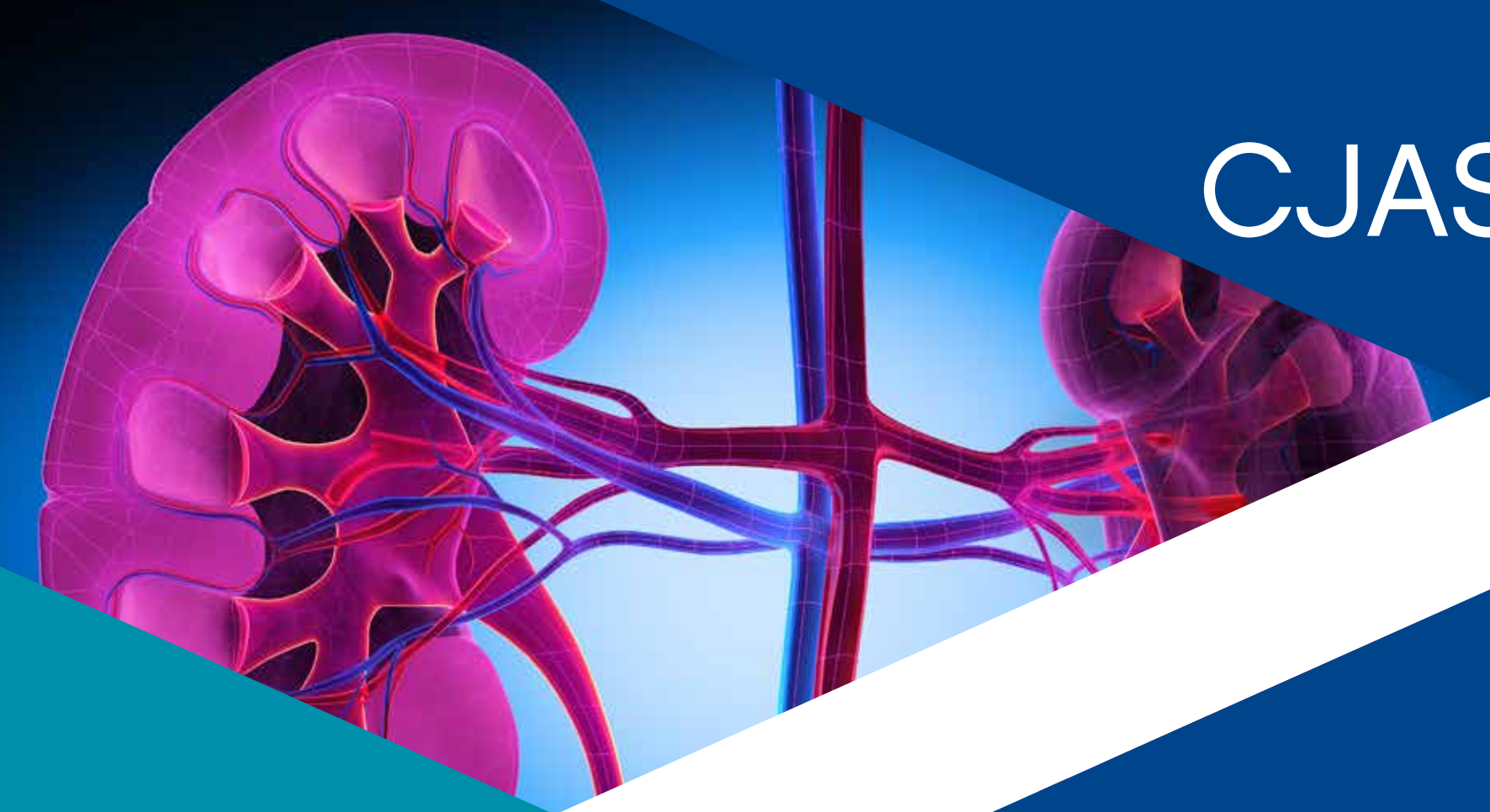

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Low Kidney Function and Proteinuria Separately Linked to Adverse Outcomes After Stroke

In patients with ischemic stroke, the decreased estimated glomerular filtration rate (eGFR) and proteinuria are separately and independently associated with stroke recurrence and death, reports a study in *Stroke*.

The researchers analyzed prospective follow-up data on 12,576 patients with ischemic stroke (41.3% women; mean age, 73 years). Data were drawn from the Japanese Fukuoka Stroke Registry from 2007 to 2019. Patients were classified into groups based on eGFR values of ≥60, 45–59, or <45 mL/min/1.73 m^2, and with proteinuria classified as –, ±/1+, or 2+ or greater.

The measurements of kidney function and kidney damage were evaluated as predictors of recurrent stroke and all-cause mortality. At a median follow-up of 4.3 years, recurrent stroke incidence was 48.0 per 1000 patient-years, and mortality was 67.3 per 1000 patient-years. Chronic kidney disease (CKD), defined as decreased eGFR or the presence of proteinuria, was associated with increased risks of recurrent stroke and death, independent of traditional cardiovascular risk factors.

For recurrent stroke, adjusted hazard ratios (HRs) were 1.22 for patients with an eGFR <45 mL/min/1.73 m^2 (compared with ≥60 mL/min/1.73 m^2) and 1.25 for those with proteinuria of 2+ or greater (compared with absent proteinuria). For all-cause mortality, HRs were 1.45 and 1.62, respectively.

The association of proteinuria with recurrent stroke tended to decrease on analysis considering competing causes of death. The mortality effect of proteinuria was stronger for patients younger than age 75 compared with older patients and for those with non-cardioembolic versus cardioembolic stroke.

Decreasing eGFR and increasing proteinuria are "mutually independent risk factors" for long-term stroke recurrence and death, the findings suggest. The associations are heterogeneous for proteinuria, indicating possible differences in the pathophysiologic mechanisms of the two risks. "Further studies are needed to determine whether interventions targeting CKD can offer additional benefits to poststroke outcomes following ischemic stroke," the researchers write [Ueki K, et al. Decreased estimated glomerular filtration rate and proteinuria and long-term outcomes after ischemic stroke: A longitudinal observational cohort study. *Stroke* 2023; 54:1268–1277; doi: 10.1161/STROKEAHA.122.040958].

AKI Linked to Increased Mortality and Rehospitalization, With or Without CKD

Patients hospitalized with acute kidney injury (AKI) are at elevated risk of rehospitalization and death, whether or not they have chronic kidney disease (CKD), reports a study in the *American Journal of Kidney Diseases*.

The analysis included 471,176 patients with a discharge diagnosis of AKI, propensity score-matched to the same number of patients hospitalized without AKI. Patients were identified from a national claims database (Optum Clinformatics). All were continuously enrolled throughout a 2-year lookback period, during which they were free of AKI hospitalization.

All-cause and selected-cause rehospitalization and mortality were assessed at 90 and 365 days after hospitalization, including possible interactions between AKI and pre-existing CKD. Fifty-one percent of patients hospitalized with AKI were men; the mean age was 73 years. Before index hospitalization, approximately 56% of patients had CKD, 47% had coronary artery disease, and 42% had diabetes.

On propensity score-matched analysis, AKI was associated with an increased rate of all-cause rehospitalization within 90 days: hazard ratio (HR), 1.62. Analysis of specific causes showed significant increases for end stage kidney disease: HR, 6.1; heart failure: HR, 2.81; sepsis: HR, 2.62; pneumonia: HR, 1.47; myocardial infarction: HR, 1.48; and volume depletion: HR, 1.64. Similar patterns were found for 365-day rehospitalization.

All-cause mortality was more than doubled for the AKI group: HR, 2.66 at 90 days and 2.11 at 365 days. Associations of AKI with rehospitalization were similar for patients with and without CKD. The association with mortality was weaker in patients with CKD.

The findings lend new insights into short- and long-term risk of adverse outcomes of AKI in a diverse US patient population. Rehospitalization and mortality risks are elevated at 3 months and 1 year after discharge for patients with AKI compared with matched patients without AKI. "[T]hese results underscore the immediate need for close posthospitalization monitoring of individuals with AKI," the researchers write [Schulman IH, et al. Readmission and mortality after hospitalization with acute kidney injury. *Am J Kidney Dis,* published online ahead of print April 19, 2023. doi: 10.1053/j.ajkd.2022.12.008; https://www.ajkd.org/article/S0272-6386(23)00067-7/fulltext].

More States Provide Kidney Care for Undocumented Immigrants

The number of states providing access to dialysis for undocumented immigrants has increased substantially over the past few years, according to a brief research report in *Annals of Internal Medicine*.

Using Medicaid and Emergency Medicaid (EM) manuals and other sources, the researchers analyzed the inclusion of undocumented immigrants for kidney failure, dialysis, and transplantation between March and October 2022. Data also included interviews with clinicians in each state who had provided kidney replacement therapy to at least two undocumented immigrants over the past 5 years.

The study found that 20 states and the District of Columbia provided statewide coverage for standard outpatient hemodialysis for undocumented immigrants. Hemodialysis was provided through EM in 17 states and through Medicaid or state insurance pools in the rest. Five states—California, Illinois, Massachusetts, Minnesota, and New Mexico—provided coverage for kidney transplantation.

A 2019 study reported that 12 states and the District of Columbia offered coverage for dialysis by including kidney failure as a qualifying condition under EM. In 2022, the number of states providing statewide coverage for hemodialysis in undocumented immigrants increased to 20. "The expansion of dialysis coverage may be due to increasing awareness of poor outcomes with emergency hemodialysis and heightened advocacy efforts," the researchers write [Rizzolo K, et al. Access to kidney care for undocumented immigrants across the United States. *Ann Intern Med*, published online ahead of print April 25, 2023. doi: 10.7326/M23-0202; https://www.acpjournals.org/doi/10.7326/M23-0202].

Expressed Values of Patients Receiving Dialysis May Not Match End-of-Life Care

Patients receiving dialysis who say they value, comfort-based care often end up with advance care planning and end-of-life care that focuses on prolongation of life, reports a study in *JAMA Internal Medicine*.

The survey study included patients receiving maintenance dialysis at centers in the Seattle and Nashville metropolitan areas between 2015 and 2018. Participants responded to a question about the value they would place on comfort-based care and pain relief compared with longevity-focused care, even if it entailed more pain and discomfort if they were to become seriously ill. These expressed values were compared with patient-reported engagement in advance care planning and end-of-life care received through 2020, based on linked kidney registry and Medicare claims data.

The analysis included 933 respondents (mean age, 63 years; 56% male; and 27% Black) with linked registry data. Nearly half of participants (48.4%) said they would value comfort-focused care, whereas 19.2% valued longevity-based care. The remaining 28.1% were unsure about which intensity of care they would value. Those who valued comfort-based care were more likely to say they had not completed an advance directive: estimated probability, 47.5%, compared with 28.1% of those who valued longevity-focused care or were unsure.

Patients who valued comfort-based care were also more likely to report that they had not had discussions about stopping dialysis (estimated probability, 33.3% versus 21.9%) or hospice (28.6% versus 18.2%). Most patients indicated they would want to receive cardiopulmonary resuscitation: estimated probability, 78.0% in those who valued the comfort-based care group and 93.9% in those who valued longevity or were unsure. For mechanical ventilation, estimated probabilities were 52.0% and 77.9%, respectively.

Among patients who died during follow-up, expected probabilities of intensive procedures during the last month of life were 23.5% for those who valued comfort-based care and 26.1% for those who valued longevity-focused care or were unsure. The findings were similar for dialysis discontinuation: 38.3% versus 30.2% and hospice enrollment: 32.2% versus 23.3%, respectively.

The study adds new evidence of a "disconnect" between expressed values for care versus actual care received by patients receiving hemodialysis. Although patients are more likely to express a value for comfort-based care, advance care planning and end-of-life care often reflect a focus on longevity. "These findings suggest important opportunities to improve the quality of care for patients receiving dialysis," the researchers conclude [Wong SPY, et al. Value placed on comfort vs life prolongation among patients treated with maintenance dialysis. *JAMA Intern Med* 2023; 183:462–469; doi: 10.1001/jamainternmed.2023.0265].

Ideal Practice Model for Advanced Care Practitioners in Nephrology at an Academic Institution

By Aisha Batool, Kristin Gajewski, and Kevin Regner

The number of patients with kidney diseases in the United States continues to rise, creating a greater need for nephrology practitioners to provide ongoing management, which requires numerous long-term follow-up visits. According to the U.S. Renal Data System, in 2019, there were over 808,000 patients with kidney failure on dialysis, and the incidence rate had almost doubled from 2000 to 2019, with over 134,000 new starts (1). This increased demand for nephrology providers, coupled with the decline in physician fellowship interest (2), demonstrates an opportunity for nurse practitioners and physician assistants—collectively known as advanced practice providers (APPs)—to meet the needs of this growing patient population.

Nephrology is a multifaceted practice involving patient care in a wide variety of settings that include vast levels of knowledge and skill sets. APPs are highly trained health care providers, and when used to their maximum scope of practice, they can serve this growing patient population by increasing access to care using an independent and collaborative practice. The definition of collaborative practice may vary by state, so practice models must adjust accordingly to the needs and limitations of licensure. Most APPs will have minimal nephrology exposure in their formal education and will gain much of their specialty knowledge with on-the-job training. Nurse practitioners can further obtain the certified nephrology nurse–nurse practitioner-required 2000 hours of experience in nephrology, and physician assistants can consider pursuing a certificate of expertise in nephrology, called the Certificate of Added Qualifications. This is pursued through the physician assistant-certifying body, the National Commission on Certification of Physician Assistants. At our institution (the Medical College of Wisconsin in Milwaukee), APPs play many roles, mainly in collaborative practice in inpatient settings for consult services, outpatient dialysis weekly rounds, and out-patient transplant services.

Patients with kidney failure require complex management of anemia, bone mineral disorders, dialysis access issues, dialysis prescription changes, ongoing education, and coordination with other providers. At our institution, at outpatient hemodialysis units, APPs provide weekly outpatient dialysis unit rounds independently and consult monthly with the physician. A similar approach is used for APPs rounding on stable inpatients already on maintenance hemodialysis admitted for other reasons (Figure 1).

Figure 1. Pictorial representation of ideal practice model with APPs in nephrology

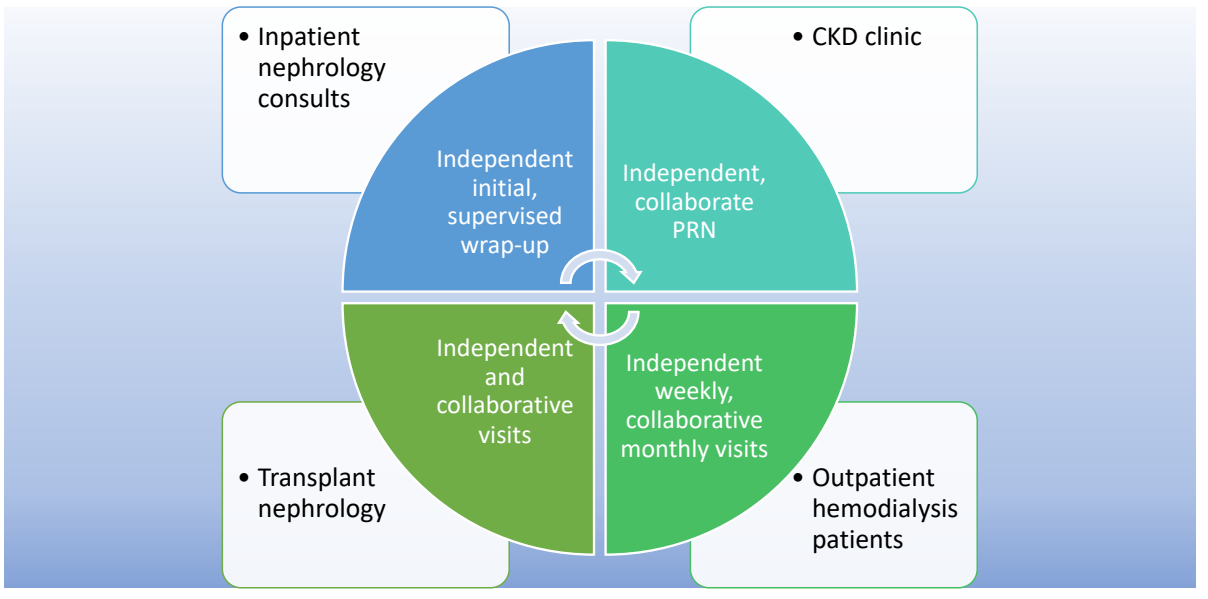

Table 1. Different practice models for APPs in nephrology

Practice models	Description	Practice setting
1. Collaborative	• APP and physician will both see the patient and collaborate the plan of care.	• Inpatient nephrology consults
2. Independent initial, supervised wrap-up	• Physician sees the patient for initial visit to create a plan of care, and APPs will see the patient for follow-up visits.	• Outpatient transplant nephrology • Outpatient and inpatient chronic hemodialysis
3. Tail, established	• The patients need follow-ups over longer periods for continuity of care.	• Outpatient CKD clinic
4. Independent practice	• APP manages a patient independently throughout the continuum of care.	• Outpatient CKD clinic
5. Procedures	• APPs get training and certification for the procedures.	• Dialysis catheter/access placement

Adapted from Chaney et al. (4).

There are many practice models used based on institutions' and departments' needs, as Chaney et al. (4) have explained as well. Among these models (Table 1), the "independent initiation and supervised wrap-up" model is most used in general nephrology consults and transplant services. An inpatient nephrology consultation service has some of the most complex patients needing a high acuity of care. In many academic institutions, APPs serve not only to off- load trainees but also to provide effective care in a timely manner. Using APPs allows physicians to oversee a larger patient population; spend time educating medical students, residents, and fellows; and attend to research and academic responsibilities. Nephrology APPs function in a variety of inpatient settings, which increases autonomy, allows the full use of licensure, and provides an intellectually engaging environment while using on-site continuing education and encouragement.

In outpatient chronic kidney disease (CKD) clinics, APPs generally conduct frequent visits to provide much-needed education for different aspects of management of kidney diseases and coordination, particularly with patients who are nearing dialysis initiation. The variety of providers allows increased access to care for patients who require frequent touch points with their nephrology care team. This can increase reimbursement, such as in the outpatient dialysis setting, and more time spent with the patients will increase patient satisfaction and quality of care.

In the challenging field of kidney transplantation, APPs function in a wide range of practice areas (5). They mostly use an independent initiation and supervised wrap-up model. At our institution, APPs have exhibited a wide range of functions across all practice areas, including transplant evaluation and re-evaluation work-ups and visits; donor evaluations; and communication among family members, interdisciplinary team members, and other providers. APPs are an invaluable workforce when it comes to post-transplant care in outpatient settings to perform focused work-ups for acute rejection, suspected infections, and other complications of kidney transplant recipients.

Given the lack of a standardized training system for APPs in subspecialty practice, each institution follows its own bylaws for use of APPs. It is imperative to implement an on-boarding syllabus, mentorship, and progress model for new hires. Ongoing education of APPs on the team remains crucial to not only their practice but also for education regarding new advancements in the ever-changing field of nephrology. We use "monthly chalk talks," which are specifically geared toward APP education, and APPs also join divisional weekly case conferences along with a journal club as means of continued education. We are including APPs in divisional research projects, and they have proven to be invaluable members of the team.

The scope of practice and responsibilities of nephrology APPs vary among different institutions, particularly in the delivery of dialysis care. APPs' involvement in creation, development, and sustainability of health care delivery design is crucial to nephrology practice given unmet provider needs for increasing patient numbers and unmatched trained physicians in the field. Key to successful implementation of any practice model remains enhancing team care and supporting the full scope of practice for all stakeholders involved. ■

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