ASN American Society of Nephrology

Kidney News

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US Preventive Services Task Force Will Consider CKD Screening Recommendation

USPSTF Responds Positively to Request from Coalition for Kidney Health

By Eric Seaborg

The US Preventive Services Task Force (USPSTF) will consider adding screening for chronic kidney disease (CKD) as a potential recommendation in response to a nomination from the Coalition for Kidney Health. The coalition submitted its request in December 2021 and received a response in February 2022, stating that USPSTF has added "Screening for CKD" to its "list of preventive services topics under active consideration."

The positive response kicks off a thorough, multi-year review, according to Miriam Godwin, health policy director at the National Kidney Foundation (NKF), whom the coalition designated as its contact person in its request to USPSTF. Godwin said that the coalition is asking that USPSTF bring its screening recommendations into concordance with established evidence-based guidelines from the NKF and the American Diabetes Association, which recommend that high-risk individuals be screened for CKD.

The letter from USPSTF notes that the task force has a large portfolio of suggested topics "to work on as part of its deliberative process, and it may take some time" to turn its attention to CKD. The letter only commits the task force to "begin the process of determining when to begin work on a new recommendation," and it will decide later whether it will "prioritize" CKD to consider this year.

Turned down in 2012

USPSTF last reviewed kidney screening in 2012 and concluded that "the evidence on routine screening for CKD in asymptomatic adults is lacking and that the balance of benefits and harms cannot be determined." But the coalition notes that this nomination is different because "rather than general population or mass screening," it wants the task force to consider current evidence that supports testing of individuals at risk for CKD, including those with diabetes, hypertension, cardiovascular disease, family history of kidney diseases, or a history of acute kidney injury.

In the 2012 review, the task force found little evidence of a benefit from early intervention and even "convincing evidence…that medications used to treat early CKD may have adverse effects." But the drug-treatment realm has changed

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ASN Commits to Reconsidering Future of Nephrology

By Eric Seaborg

ASN plans to lead the kidney community in reconsidering "every aspect of the future of nephrology" over the next 8 months, ASN President Susan E. Quaggin, MD, said in a March letter to the American Board of Internal Medicine (ABIM) Nephrology Board and the Accreditation Council for Graduate Medical Education (ACGME).

Quaggin was responding to separate messages from the two organizations asking for ASN's input on major revisions of their certification and training program requirements.

In a letter to Quaggin in January, the ABIM Nephrology Board wrote, "For some time the nephrology community has grappled with whether or not certain procedures (temporary dialysis catheters and kidney biopsies) should remain a required procedure for nephrology fellows to learn to perform competently and whether other requirements should be strengthened like training for peritoneal and home hemodialysis." The letter asked for ASN to share its views on these and other procedures by February 25.

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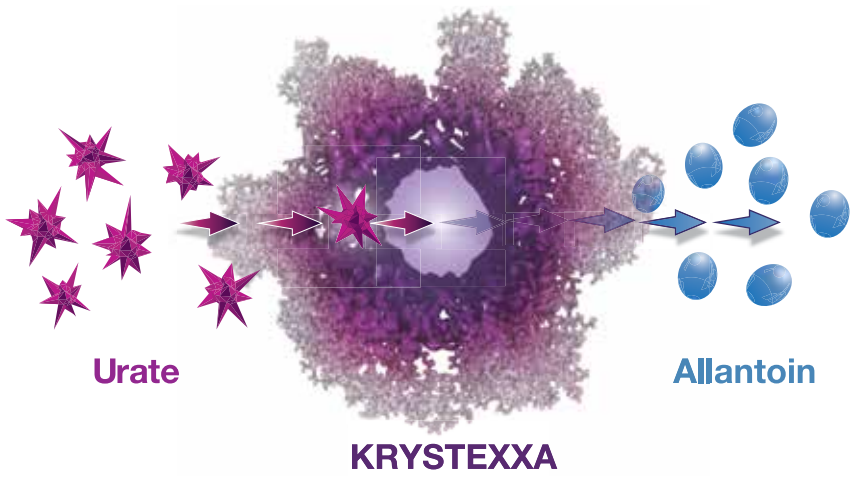
Inside

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



Artist's renditions.

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

INDICATION AND IMPORTANT SAFETY INFORMATION

INDICATIONS AND USAGE

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

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

IMPORTANT SAFETY INFORMATION

WARNING: ANAPHYLAXIS AND INFUSION REACTIONS

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

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

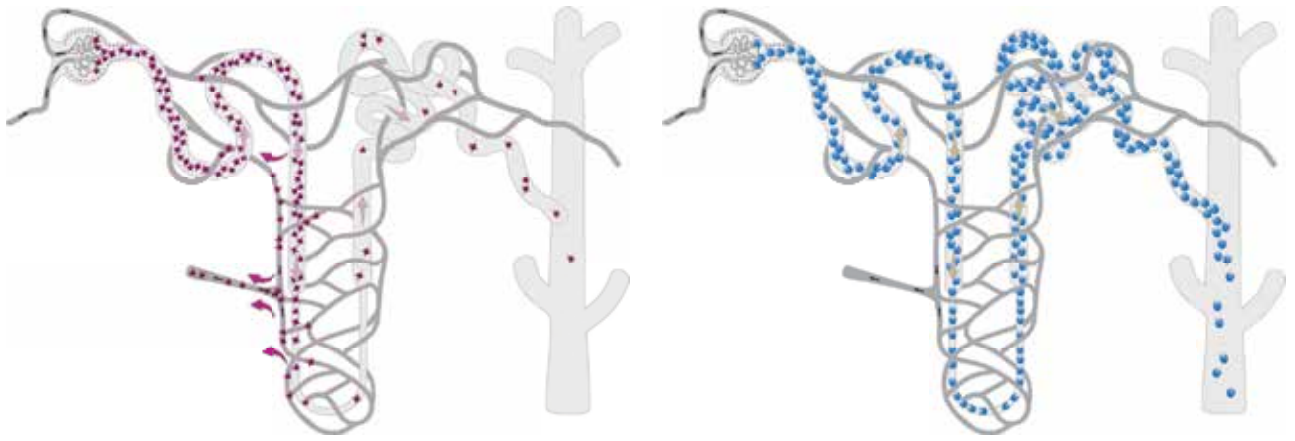
Concomitant use of KRYSTEXXA and oral urate-lowering agents may blunt the rise of sUA levels. Patients should discontinue oral urate-lowering agents and not institute therapy with oral urate-lowering agents while taking KRYSTEXXA.

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

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

HORIZON

URICASE ENZYME THAT CONVERTS URATE



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

vs

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

TO LEARN MORE, VISIT KRYSTEXXAHCP.COM

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

CONTRAINDICATIONS: G6PD DEFICIENCY ASSOCIATED HEMOLYSIS AND METHEMOGLOBINEMIA

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

GOUT FLARES

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

CONGESTIVE HEART FAILURE

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

ADVERSE REACTIONS

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

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

KRYSTEXXA®
pegloticase

KRYSTEXXA® pegloticase

(pegloticase injection), for intravenous infusion

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

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

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

INDICATIONS AND USAGE

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

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

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

CONTRAINDICATIONS

Glucose-6-phosphate dehydrogenase (G6PD) deficiency

WARNINGS AND PRECAUTIONS

Anaphylaxis

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

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

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

Infusion Reactions

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

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

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

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

G6PD Deficiency Associated Hemolysis and Methemoglobinemia

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

Gout Flares

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

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

Congestive Heart Failure

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

Re-treatment with KRYSTEXXA

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

ADVERSE REACTIONS

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

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

Clinical Trials Experience

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

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

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

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

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

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

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

Immunogenicity

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

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

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

Postmarketing Experience

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

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

Data

Animal Data

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

Lactation

Risk Summary

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

Pediatric Use

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

Geriatric Use

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

Renal Impairment

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

OVERDOSAGE

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

PATIENT COUNSELING INFORMATION

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

General Information

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

Anaphylaxis and Infusion Reactions

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

Glucose-6-phosphate dehydrogenase (G6PD) Deficiency

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

Gout Flares

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

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ASN Commits to Reconsidering Future of Nephrology

Continued from cover

On January 18, ACGME sent a message to program directors relaying that it was beginning "a major revision of the current program requirements" for many internal medicine subspecialties, including nephrology. It invited written "comments on specific topics" with a March 3 deadline.

Quaggin responded in March to both organizations with the same letter calling these invitations "exciting opportunities" but requesting an 8-month pause in the deadlines to provide time for ASN to facilitate a discussion in the kidney community on the future of nephrology. Quaggin committed to issue final recommendations by October and share them with "the entire kidney community during ASN Kidney Week" at the start of November.

ASN sees these requests as an opening to resolve several outstanding questions that have been nagging nephrologists for years, according to ASN Executive Vice President Tod Ibrahim. "Many of these conversations have been taking place for quite some time. There hasn't been any pressure to come to consensus, and, as a result, we haven't come to consensus as a community. Perhaps setting a deadline and saying, in the next 8 months we will reach agreement, is the only way we will," he said.

But Ibrahim added that it was not possible to untangle the specific issues from the web without considering the whole. "Our feeling was, you can't reach consensus on procedures until you know what the overall specialty is going to look like. We are going to work from the big picture to the details," Ibrahim said. "We have gone back and forth with ABIM and ACGME on these issues, and it is never clear what the first step is. It is a little bit of a circular process. So, part of what we are trying to do is to break that cycle. The experts in the specialty should determine what the future looks like and then work with the educational regulators to help ensure high-quality training and high-quality certification," he said.

Quaggin's letter commits ASN to "convene the kidney community, representatives from ABIM and ACGME, and other stakeholders during the next 8 months" to carry out the following objectives:

1) Decide the core skills, knowledge, and experiences in kidney medicine that every nephrology fellow must learn during fellowship training
2) Evaluate whether all nephrology fellows should have the same training and initial certification examination (regardless of their clinical interests) or should have a way to differentiate themselves professionally through a standalone subspecialist certification by ABIM
3) Assess which subspecialties of nephrology have evolved to the point of requiring formal training and certification
4) Identify potential gaps in training of nephrology fellows who trained during the COVID-19 pandemic
5) Determine how to ensure that nephrology training, certification, and practice promote diversity, equity, and inclusion while pursuing health care justice
6) Begin to articulate how future nephrology training, certification, and practice can align with other members of the kidney health care team
7) Articulate the future expectations for nephrology fellowship training programs based on the above goals

ABIM and ACGME appear likely to embrace this process. Jerry Vasilias, PhD, executive director of the ACGME Review Committee for Internal Medicine, responded in early March that his committee's leadership has "no issue or concern with pausing the major revision of the program requirements for nephrology for approximately 8 months."

The next ABIM nephrology board meeting was scheduled to be held after this edition of *Kidney News* went to press, but ABIM nephrology board member Matthew Sparks, MD, agreed that "the time is now" to reconsider the issues mentioned in Quaggin's letter: "I can't speak on behalf of the board, but I would support this process. We want to listen to the community and key stakeholders."

Correction and Clarification

The February *Kidney News* article "A Call to Action for Physicians: Become Informed and Empowered, and Begin to Heal Thyself" includes the statement, "The RUC [American Medical Association (AMA) Relative Value Update Committee] is a group of 32 physicians and other health care professionals who advise CMS [Centers for Medicare & Medicaid Services] on how to value various medical services. The advice of the RUC is nearly always accepted by CMS, yet nephrology is not currently represented on the committee."

In reality, nephrology has access to the RUC, because the Renal Physicians Association (RPA) is a member of the AMA House of Delegates, and Adam J. Weinstein, MD, was elected to one of the two 2-year internal medicine rotating seats of the RUC at its January 12–15, 2022, meeting (1). *Kidney News* congratulates Dr. Weinstein, who serves as Chief Medical Information Officer for DaVita, on his recent appointment and apologizes for the oversight.

Additionally, RPA's Health Care Payment Committee maintains a liaison with the AMA Current Procedural Terminology (CPT) advisory panel (2), which is another way the nephrology community can influence the RUC.

References

1. RVS Update Committee (RUC). Composition of the RVS Update Committee (RUS). American Medical Association. https://www.ama-assn.org/about/rvs-update-committee-ruc/composition-rvs-update-committee-ruc
2. Health Care Payment Committee, Renal Physicians Association (RPA). https://www.renalmd.org/page/healthcarepaycommit

CKD Screening

Continued from cover

radically in the intervening decade with the advent of efficacious new medications, several experts told *Kidney News*.

"We have many more effective tools than we did in 2012," said Frank "Chip" Brosius, MD, a professor in the Division of Nephrology at the University of Arizona in Tucson. "Back in 2012, essentially all we had was blood pressure control, good blood sugar control in those that have diabetes, and then either an ACE [angiotensin-converting enzyme] inhibitor or angiotensin-receptor blocker in at least some of the CKD patients. Now we have these newer classes of medications that were brought out 15 years ago as diabetes drugs."

Sodium glucose co-transporter 2 (SGLT2) inhibitors and glucagon-like peptide 1 (GLP-1) receptor agonists were once considered niche drugs, but they gained widespread acceptance when "the cardiovascular outcome studies that included kidney endpoints started coming out about 6 years ago. It became clear that at least these two classes of medications had pretty profound cardiovascular protection for chronic kidney disease patients and also had positive effects on preserving kidney function," Brosius said.

Two common tests

The request letter from the coalition also notes that CKD screening is practical because it can be implemented by a primary care clinician using two readily available tests: estimated glomerular filtration rate based on serum creatinine and urine albumin-creatinine ratio. NKF's Godwin said a USPSTF recommendation would be significant because many primary care physicians look to it for guidance.

Brosius agreed that if the USPSTF includes CKD screening in its recommendations, then primary care physicians will be more cognizant of its importance and pay more attention to the potential consequences. Serum creatinine is part of the standard testing panel that patients undergo for many primary care visits—including annual physicals—but too often, abnormal results are ignored. "The doctor doesn't recognize it or doesn't recognize its importance and doesn't tell the patient," Brosius said. Similarly, obtaining "an albumin-creatinine ratio in the urine just doesn't happen at anywhere near the level that it should," he said.

A screening recommendation would raise the awareness among primary care physicians to pay more attention to these tests, Brosius said, with the potential benefit of beginning early intervention while the condition is more manageable. "Despite being preventable and treatable, CKD is too often not intensively managed until a patient has progressed to kidney failure," the coalition letter notes. "An estimated 37 million Americans have CKD, and the vast majority are unaware."

In the 10 years since the 2012 decision, rates of kidney diseases have continued to grow in tandem with the greatly rising rates of diabetes. CKD has grown to become the ninth leading cause of death in the United States.

Countering racial inequities

Another aspect of medicine that has changed drastically since 2012 is the recognition of systemic racial inequity and the resolve to take action to combat it, particularly in the kidney community, according to David L. White, regulatory and quality officer at the American Society of Nephrology. Increased screening would help to address inequity, because Americans of Black race are significantly more likely than those who are White to have diabetes—the leading cause of CKD—as well as more likely to experience its downstream consequences, including kidney failure and death.

The agreement by USPSTF to consider screening for CKD is the first step in a well-defined and exhaustive process. "[It is] a highly evidence-based body and really process oriented," Godwin said. "There are public review periods with opportunities for public comment." The Coalition for Kidney Health and other organizations will ensure that nephrologists are well represented in the review process, Godwin said.

"The absence of a current CKD screening recommendation exacerbates the lack of attention paid to the growing kidney disease public health crisis and contributes to the low rates of CKD diagnosis in the primary care setting," the coalition letter notes. It continues, "We believe that the opportunity to improve outcomes for CKD patients warrants a CKD screening recommendation for patients at high risk of CKD." ■

ASN President's Update
Close the Gap—Time for a Kidney Health Check

By Susan E. Quaggin

"Doc, I was told I have stage 5 kidney disease. What happened to stages 1 through 4?"

Almost every nephrologist, including myself, has had this heartbreaking and far too common question asked of them by patients receiving their diagnosis of kidney disease for the first time. Even worse: A patient first learns about kidney function coincident with placement of a catheter to initiate urgent dialysis.

Not surprisingly, these diagnoses trigger a mixture of emotions: fear, anxiety, disbelief . . . anger. It is time we do better.

The first diagnosis of kidney disease as kidney failure is truly a failure—of the system. It should come as no surprise that underserved communities with lack of access to health care services and timely intervention are vastly over-represented in this category.

One decade ago, the US Preventive Services Task Force (USPSTF) reviewed the literature and current knowledge available (at that time) to support population-based screening for chronic kidney disease (CKD). In its summary statement, the task force concluded that no data existed to support a recommendation that intervening early in CKD is beneficial (1).

In 2013, the American College of Physicians (ACP) published its guidelines on screening for kidney diseases in the *Annals of Internal Medicine*, advising against testing for proteinuria in adults with or without diabetes who are currently taking an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin II receptor blocker (ARB) (2). Bruce A. Molitoris, MD, FASN, ASN president at the time, responded with an article highlighting the potential dangers, weaknesses, and risks inherent in the recommendations by ACP (3).

Ten years later, in February 2022, USPSTF added "Screening for CKD" to the list of preventive services topics under "active consideration" following nomination and wide support from ASN, the National Kidney Foundation (NKF), other members of the kidney community, and members of Congress (4). Although the task force's decision to re-evaluate its decade-old finding is a hopeful advance for patients and the community, there is no guarantee that CKD screening will be prioritized this year. In its response letter, the task force acknowledged that kidney diseases are a serious public health issue and emphasized that kidney diseases disproportionately affect communities of color but did not indicate a timeline for reconsidering its position.

It is important to recognize that several members of the kidney community have argued against screening of asymptomatic patients, citing studies that identifying CKD does not alter management of patients as long as blood pressure and glucose are controlled (5). Of course, these studies report on those lucky enough—no, *those privileged enough*—to have access to health care when they received their diagnoses of hypertension or diabetes and who were lucky and privileged enough to receive appropriate treatments. As outlined in the KDIGO (Kidney Disease: Improving Global Outcomes) report, which makes the case for CKD screening in at-risk individuals, the authors point out that the burden of CKD falls on the socially disadvantaged and vulnerable (6).

Furthermore, the studies that do not support screening predate the overwhelming and numerous positive clinical trials demonstrating the power of "flozins" (sodium glucose co-transporter 2 inhibitors [SGLT2i]) to prevent mortality, kidney function decline, and cardiovascular disease in people with kidney diseases, regardless of whether the patient has diabetes (see EMPA-REG and CREDENCE trials) (7). In fact, data from the DAPA-CKD trial were so spectacular that the US Food and Drug Administration (FDA) granted breakthrough status for the use of this SGLT2i in patients with CKD, with or without diabetes—the first time ever for a kidney-targeted therapy. Recently, the flozins have been joined by additional classes of medications, including the nonsteroidal mineralocorticoid receptor antagonists and glucagon-like peptide 1 (GLP1) agonists, which have been added to the ever-growing menu of beneficial kidney treatments (see FIDELIO trial) (Figure 1).

Indeed, the ACP guidelines that recommended against screening for proteinuria in patients with diabetes and CKD (i.e., diabetic kidney disease [DKD]) contradict more current guidelines from the American Diabetes Association and KDIGO, which recommend SGLT2i and/or finerenone for patients with proteinuria on therapeutic renin-angiotensin system (RAS) blockade. (Please note that ACP's guidelines expired after 10 years and are no longer in effect.) The outdated belief that "early identification of CKD is pointless because we have no therapies" no longer applies.

That is not to say screening of the general population—particularly low-risk individuals—is automatically warranted or that the importance of having USPSTF revisit the issue should be discounted. However, it is hard to imagine that screening the one in three Americans at risk of kidney diseases—so-called "case finding"—is not warranted. The use of creatinine in combination with urine albumin (uACR) measurement in patients at risk formed the basis of the request to USPSTF by ASN, NKF, other members of the kidney community, and members of Congress.

In the United States, a majority of "crash starts" for dialysis in hospitals occur in patients from underserved communities, where social and political determinants of health determine who has access to care and to treatments that can protect the kidneys and save lives. The failure to detect kidney diseases in these populations is yet one more example of pervasive racism in the health care system. How can we do better?

In Canada, the Can-SOLVE CKD Network launched a program to promote kidney health in First Nations communities (8). Kidney Check provides point-of-care testing for kidney function (creatinine and urine protein), hypertension, and diabetes. Built on the central symbol of *Meyayawin* (getting better), the project is guided by an Elder, with truth and reconciliation recommendations, a diverse and inclusive team, and shared concepts, such as Two-Eyed Seeing, which recognizes that Indigenous and Western knowledge can exist in parallel (9). A single finger-prick blood sample and urine protein analysis on-site provide real-time results and a kidney health plan, tailored to the patient's needs (10).

Similar to at-risk communities in the United States, the First Nations communities are at higher risk of kidney diseases and kidney failure than the general population. In both Canada and the United States, one in every 10 people is estimated to have kidney diseases, whereas in Canadian First Nations communities, that number increases to one in three. In the United States, individuals of Black race or African Americans are almost four times more likely to develop kid-

ney failure than Americans of White race, even though their CKD prevalence is not higher overall—an unacceptable statistic (11).

What concrete steps can we take?

1 We must impel change to current screening recommendations for kidney diseases and kidney health in light of the powerful, new therapies that can dramatically slow progression of kidney diseases and the recognition that we are likely to see increased burden of CKD post-COVID.

Why limit screening to the identification of kidney diseases? Instead, why not pivot the messaging to "screening for kidney health"? International Society of Nephrology Past-President Adeera Levin, MD, points out that knowing you have healthy kidneys can provide peace of mind while expanding the eligible pool of living donors to help address the desperate need for kidneys. Why should knowing the status of your kidney health be any different than knowing your other numbers, such as glucose, lipids, and blood pressure? Isn't it time to take a stand that kidney health matters?

Even though the timeline for this year's USPSTF CKD screening consideration is not clear, we need your voice and your support to request recommendations are revisited and prioritized this year. You can request to be put on the USPSTF mailing list for updates (see https://www.uspreventiveservicestaskforce.org/uspstf/email-updates). You can suggest individuals for nomination to serve on the task force (see https://www.ahrq.gov/cpi/about/otherwebsites/uspstf/nominate.html). And, as we wait for a national recommendation, you can continue to educate, raise awareness, learn about, and implement the new therapies and spread the concept of kidney health. If you have ideas about how to amplify the message, please email them to me at president@asn-online.

2 We must better serve patients, physicians, and other health professionals by providing transparent, consistent, and up-to-date guidance that will improve kidney health.

Current guidelines and recommendations do not effectively address kidney health today, and updated guidelines are urgently needed for primary care physicians. For more than three decades, overwhelming evidence demonstrates that an ACEi or ARB slows progression of kidney diseases, yet only 25%–40% of patients who should be receiving these therapies are receiving them (12, 13). As recently as 2016–2019, only 10%–40% of patients with diabetes are even checked for albuminuria, an essential element for risk stratification and therapeutic selection (12, 14). In light of these statistics, it should come as no surprise that in the period from 2000 to 2019, the number of end stage kidney disease (ESKD) cases reported in the United States increased 41.8% (15). Effective management of diabetes and hypertension, including kidney disease testing and management as part of diabetes care in at-risk populations, will prevent ESKD.

A strong, overarching, and clear recommendation for kidney disease screening that focuses specifically on the kidneys—that is inclusive of all patients at risk—would send a strong message that kidney health for all matters. This focus would help push primary care organizations and the professionals they represent to revisit their guidelines, which is key to reach those who must intervene early. This step is essential for implementation of new therapies, because we know many patients with kidney diseases have multiple indications, such as heart failure or proteinuria.

Patrick O. Gee, Jr., PhD, a patient advocate and member of the ASN Diabetic Kidney Disease Collaborative, provides a compelling case to explain why kidney health must be elevated and screening at-risk patients prioritized: "I was diagnosed with diabetes and managed by an endocrinologist, receiving a diagnosis of stage 3b CKD 10 years in. Shockingly, in that 10-year period since my diabetes diagnosis, I was never told diabetes is the leading cause of kidney failure. I started peritoneal dialysis later that year." This unacceptable outcome underscores why the inclusion of kidney screening recommendations that are siloed and placed within recommendations for the management of other diseases is not enough and inadvertently harms patients. Missing an opportunity to intervene early will lead to lives and kidneys lost.

3 We must eliminate health injustice.

We must advocate for health care justice throughout our society and within our institutions. To accomplish this goal, we must apply advanced technologies and pursue partnerships with community leaders to create equitable kidney care and reimagine kidney screening and education. The Canadian-led Kidney Check project is one example that might be adapted in other at-risk communities throughout North America.

In the United States, it is encouraging to note the Indian Health Service (IHS) has bettered the national average by dedicating resources for intervention and implementation. IHS has optimized protective kidney treatments, with an estimated 80% of patients with DKD receiving standard of care with an ACEi or ARB compared with only 25%–40% nationally (16).

As kidney professionals, as a medical specialty society, and as a profession, we must pledge to be accountable and work tirelessly to effect change. We must help everyone understand the increased incidence of kidney diseases, reduce late or missed diagnoses, and improve access to the best treatments for all who can benefit. Our community must act now to reduce preventable deaths, chronic illness, and severe disability.

We are a specialty that now has the power to prevent kidney failure and premature death. We are a specialty that now has the power to reverse unacceptable disparities in care. It is time to act.

The kidney revolution has begun. ■

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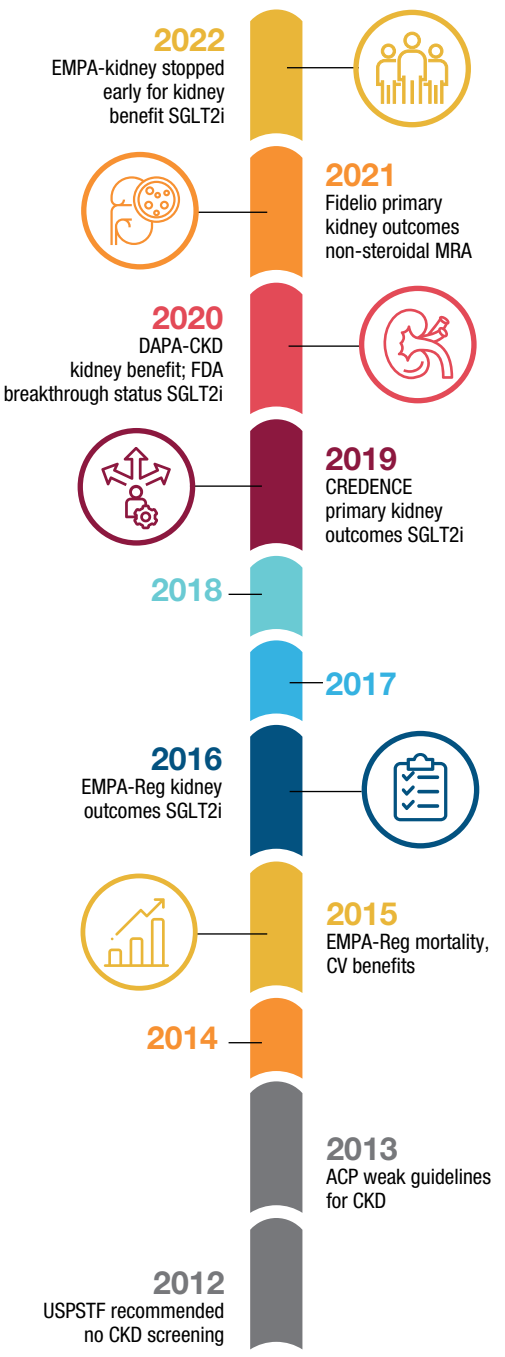
Figure 1. Timeline: Options for managing chronic kidney disease



Positive clinical trials (colors) that impact CKD management since the USPSTF last statement on screening for CKD and ACP guidelines on screening for kidney diseases (gray). CV, cardiovascular; MRA, mineralocorticoid receptor antagonist.

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INDICATIONS AND USAGE

PARSABIV is indicated for the treatment of secondary hyperparathyroidism (HPT) in adult patients with chronic kidney disease (CKD) on hemodialysis.

Limitations of Use:

PARSABIV has not been studied in adult patients with parathyroid carcinoma, primary hyperparathyroidism, or with chronic kidney disease who are not on hemodialysis and is not recommended for use in these populations.

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PARSABIV is contraindicated in patients with known hypersensitivity to etelcalcetide or any of its excipients. Hypersensitivity reactions, including face edema and anaphylactic reaction, have occurred with PARSABIV *[see Adverse Reactions (6) in PARSABIV full prescribing information]*.

WARNINGS AND PRECAUTIONS

Hypocalcemia

PARSABIV lowers serum calcium *[see Adverse Reactions (6.1) in PARSABIV full prescribing information]* and can lead to hypocalcemia, sometimes severe. Significant lowering of serum calcium can cause paresthesias, myalgias, muscle spasms, seizures, QT interval prolongation, and ventricular arrhythmia.

QT Interval Prolongation and Ventricular Arrhythmia

In the combined placebo-controlled studies, more patients treated with PARSABIV experienced a maximum increase from baseline of greater than 60 msec in the QTcF interval (0% placebo versus 1.2% PARSABIV). In these studies, the incidence of a maximum post-baseline predialysis QTcF > 500 msec in the placebo and PARSABIV groups was 1.9% and 4.8%, respectively *[see Adverse Reactions (6.1) in PARSABIV full prescribing information]*. Patients with congenital long QT syndrome, history of QT interval prolongation, family history of long QT syndrome or sudden cardiac death, and other conditions that predispose to QT interval prolongation and ventricular arrhythmia may be at increased risk for QT interval prolongation and ventricular arrhythmias if they develop hypocalcemia due to PARSABIV. Closely monitor corrected serum calcium and QT interval in patients at risk receiving PARSABIV.

Seizures

Significant reductions in corrected serum calcium may lower the threshold for seizures. Patients with a history of seizure disorder may be at increased risk for seizures if they develop hypocalcemia due to PARSABIV. Monitor corrected serum calcium in patients with seizure disorders receiving PARSABIV.

Risk of Hypocalcemia with Other Serum Calcium Lowering Products

Concurrent administration of PARSABIV with another oral calcium-sensing receptor agonist could result in severe, life-threatening hypocalcemia. Patients switching from cinacalcet to PARSABIV should discontinue cinacalcet for at least 7 days prior to initiating PARSABIV *[see Dosage and Administration (2.4) in PARSABIV full prescribing information]*. Closely monitor corrected serum calcium in patients receiving PARSABIV and concomitant therapies known to lower serum calcium.

Monitoring Serum Calcium and Patient Education

Measure corrected serum calcium prior to initiation of PARSABIV. Do not initiate in patients if the corrected serum calcium is less than the lower limit of normal. Monitor corrected serum calcium within 1 week after initiation or dose adjustment and every 4 weeks during treatment with PARSABIV *[see Dosage and Administration (2.2) in PARSABIV full prescribing information]*. Educate patients on the symptoms of hypocalcemia and advise them to contact a healthcare provider if they occur.

Management of Hypocalcemia

If corrected serum calcium falls below the lower limit of normal or symptoms of hypocalcemia develop, start or increase calcium supplementation (including calcium, calcium-containing phosphate binders, and/or vitamin D sterols or increases in dialysate calcium concentration). PARSABIV dose reduction or discontinuation of PARSABIV may be necessary *[see Dosage and Administration (2.2) in PARSABIV full prescribing information]*.

Worsening Heart Failure

In clinical studies with PARSABIV, cases of hypotension, congestive heart failure, and decreased myocardial performance have been reported. In clinical studies, heart failure requiring hospitalization occurred in 2% of PARSABIV-treated patients and 1% of placebo-treated patients. Reductions in corrected serum calcium may be associated with congestive heart failure, however, a causal relationship to PARSABIV could not be completely excluded. Closely monitor patients treated with PARSABIV for worsening signs and symptoms of heart failure.

Upper Gastrointestinal Bleeding

In clinical studies, two patients treated with PARSABIV in 1253 patient-years of exposure had upper gastrointestinal (GI) bleeding noted at the time of death while no patient in the control groups in 384 patient-years of exposure had upper GI bleeding noted at the time of death. The exact cause of GI bleeding in these patients is unknown, and there were too few cases to determine whether these cases were related to PARSABIV.

Patients with risk factors for upper GI bleeding (such as known gastritis, esophagitis, ulcers, or severe vomiting) may be at increased risk for GI bleeding while receiving PARSABIV treatment. Monitor patients for worsening of common GI adverse reactions of nausea and vomiting associated with PARSABIV *[see Adverse Reactions (6.1) in PARSABIV full prescribing information]* and for signs and symptoms of GI bleeding and ulcerations during PARSABIV therapy. Promptly evaluate and treat any suspected GI bleeding.

Adynamic Bone

Adynamic bone may develop if PTH levels are chronically suppressed. If PTH levels decrease below the recommended target range, the dose of vitamin D sterols and/or PARSABIV should be reduced or therapy discontinued. After discontinuation, resume therapy at a lower dose to maintain PTH levels in the target range *[see Dosage and Administration (2.1) in PARSABIV full prescribing information]*.

ADVERSE REACTIONS

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

- Hypocalcemia *[see Warnings and Precautions (5.1) in PARSABIV full prescribing information]*
- Worsening Heart Failure *[see Warnings and Precautions (5.2) in PARSABIV full prescribing information]*
- Upper Gastrointestinal Bleeding *[see Warnings and Precautions (5.3) in PARSABIV full prescribing information]*
- Adynamic Bone *[see Warnings and Precautions (5.4) in PARSABIV full prescribing information]*

Clinical Trials Experience

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

The data in Table 2 are derived from two placebo-controlled clinical studies in patients with chronic kidney disease and secondary hyperparathyroidism on hemodialysis. The data reflect exposure of 503 patients to PARSABIV with a mean duration of exposure to PARSABIV of 23.6 weeks. The mean age of patients was approximately 58 years, and 60% of the patients were male. Of the total patients, 67% were Caucasian, 28% were Black or African American, 2.6% were Asian, 1.2% were Native Hawaiian or Other Pacific Islander, and 1.6% were categorized as Other.

Table 2 shows common adverse reactions associated with the use of PARSABIV in the pool of placebo-controlled studies. These adverse reactions occurred more commonly on PARSABIV than on placebo and were reported in at least 5% of patients treated with PARSABIV.

Table 2: Adverse Reactions Reported in ≥ 5% of PARSABIV-Treated Patients

Adverse Reaction*	Placebo (N = 513)	PARSABIV (N = 503)
Blood calcium decreased[a]	10%	64%
Muscle spasms	7%	12%
Diarrhea	9%	11%
Nausea	6%	11%
Vomiting	5%	9%
Headache	6%	8%
Hypocalcemia[b]	0.2%	7%
Paresthesia[c]	1%	6%

*Included adverse reactions reported with at least 1% greater incidence in the PARSABIV group compared to the placebo group

[a] Asymptomatic reductions in calcium below 7.5 mg/dL or clinically significant asymptomatic reductions in corrected serum calcium between 7.5 and < 8.3 mg/dL (that required medical management)

[b] Symptomatic reductions in corrected serum calcium < 8.3 mg/dL

[c] Paresthesia includes preferred terms of paresthesia and hypoesthesia

Other adverse reactions associated with the use of PARSABIV but reported in < 5% of patients in the PARSABIV group in the two placebo-controlled clinical studies were:

- Hyperkalemia: 3% and 4% for placebo and PARSABIV, respectively.
- Hospitalization for Heart Failure: 1% and 2% for placebo and PARSABIV, respectively.
- Myalgia: 0.2% and 2% for placebo and PARSABIV, respectively.
- Hypophosphatemia: 0.2% and 1% for placebo and PARSABIV, respectively.

Description of Selected Adverse Reactions

Hypocalcemia

In the combined placebo-controlled studies, a higher proportion of patients on PARSABIV developed at least one corrected serum calcium value below 7.0 mg/dL (7.6% PARSABIV, 3.1% placebo), below 7.5 mg/dL (27% PARSABIV, 5.5% placebo), and below 8.3 mg/dL (79% PARSABIV, 19% placebo). In the combined placebo-controlled studies, 1% of patients in the PARSABIV group and 0% of patients in the placebo group discontinued treatment due to an adverse reaction attributed to a low corrected serum calcium.

Hypophosphatemia

In the combined placebo-controlled studies, 18% of patients treated with PARSABIV and 8.2% of patients treated with placebo had at least one measured phosphorus level below the lower normal limit (i.e., 2.2 mg/dL).

QTc Interval Prolongation Secondary to Hypocalcemia

In the combined placebo-controlled studies, more patients treated with PARSABIV experienced a maximum increase from baseline of greater than 60 msec in the QTcF interval (0% placebo versus 1.2% PARSABIV). The patient incidence of maximum post-baseline predialysis QTcF > 500 msec in the placebo and PARSABIV groups was 1.9% and 4.8%, respectively.

Hypersensitivity

In the combined placebo-controlled studies, the subject incidence of adverse reactions potentially related to hypersensitivity was 4.4% in the PARSABIV group and 3.7% in the placebo group. Hypersensitivity reactions in the PARSABIV group were pruritic rash, urticaria, and face edema.

Immunogenicity

As with all peptide therapeutics, there is potential for immunogenicity. The detection of anti-drug binding antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to etelcalcetide with the incidence of antibodies to other products may be misleading.

In clinical studies, 7.1% (71 out of 995) of patients with secondary hyperparathyroidism treated with PARSABIV for up to 6 months tested positive for binding anti-etelcalcetide antibodies. Fifty-seven out of 71 had pre-existing anti-etelcalcetide antibodies.

No evidence of altered pharmacokinetic profile, clinical response, or safety profile was associated with pre-existing or developing anti-etelcalcetide antibodies.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no available data on the use of PARSABIV in pregnant women. In animal reproduction studies, effects were seen at doses associated with maternal toxicity that included hypocalcemia. In a pre- and post-natal study in rats administered etelcalcetide during organogenesis through delivery and weaning, there was a slight increase in perinatal pup mortality, delay in parturition, and transient effects on pup growth at exposures 1.8 times the human exposure for the clinical dose of 15 mg three times per week. There was no effect on sexual maturation, neurobehavioral, or reproductive function in the rat offspring. In embryo-fetal studies, when rats and rabbits were administered etelcalcetide during organogenesis, reduced fetal growth was observed at exposures 2.7 and 7 times exposures for the clinical dose, respectively.

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

Data

Animal Data

There were no effects on embryo-fetal development in Sprague-Dawley rats when etelcalcetide was dosed at 0.75, 1.5, and 3 mg/kg/day by the intravenous route during organogenesis (pre-mating to gestation day 17) at exposures up to 1.8 times human exposures at the clinical dose of 15 mg three times per week based on AUC. No effects on embryo-fetal development were observed in New Zealand White rabbits at doses of etelcalcetide of 0.375, 0.75, and 1.5 mg/kg by the intravenous route (gestation day 7 to 19), representing up to 4.3 times human exposures based on AUC. In separate studies at higher doses of 4.5 mg/kg in rats (gestation days 6 to 17) and 2.25 mg/kg in rabbits (gestation days 7 to 20), representing 2.7- and 7-fold clinical exposures, respectively, there was reduced fetal growth associated with maternal toxicities of hypocalcemia, tremoring, and reductions in body weight and food consumption.

In a pre- and post-natal development study in Sprague-Dawley rats administered etelcalcetide at 0.75, 1.5, and 3 mg/kg/day by the intravenous route (gestation day 7 to lactation day 20), there was a slight increase in perinatal pup mortality, delay in parturition, and transient reductions in post-natal growth at 3 mg/kg/day (representing 1.8-fold human exposures at the clinical dose of 15 mg three times per week based on AUC), associated with maternal toxicities of hypocalcemia, tremoring, and reductions in body weight and food consumption. There were no effects on sexual maturation, neurobehavioral, or reproductive function at up to 3 mg/kg/day, representing exposures up to 1.8-fold human exposure based on AUC.

Lactation

Risk Summary

There are no data regarding the presence of PARSABIV in human milk or effects on the breastfed infant or on milk production. Studies in rats showed [^{14}C]-etelcalcetide was present in the milk at concentrations similar to plasma. Because of the potential for PARSABIV to cause adverse effects in breastfed infants including hypocalcemia, advise women that use of PARSABIV is not recommended while breastfeeding.

Data

Presence in milk was assessed following a single intravenous dose of [^{14}C]-etelcalcetide in lactating rats at maternal exposures similar to the exposure at the human clinical dose of 15 mg three times per week. [^{14}C]-etelcalcetide-derived radioactivity was present in milk at levels similar to plasma.

Pediatric Use

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

Geriatric Use

Of the 503 patients in placebo-controlled studies who received PARSABIV, 177 patients (35.2%) were ≥ 65 years old and 72 patients (14%) were ≥ 75 years old.

No clinically significant differences in safety or efficacy were observed between patients ≥ 65 years and younger patients (≥ 18 and < 65 years old). No differences in plasma concentrations of etelcalcetide were observed between patients ≥ 65 years and younger patients (≥ 18 and < 65 years old).

OVERDOSAGE

There is no clinical experience with PARSABIV overdosage. Overdosage of PARSABIV may lead to hypocalcemia with or without clinical symptoms and may require treatment. Although PARSABIV is cleared by dialysis, hemodialysis has not been studied as a treatment for PARSABIV overdosage. In the event of overdosage, corrected serum calcium should be checked and patients should be monitored for symptoms of hypocalcemia, and appropriate measures should be taken *[see Warnings and Precautions (5.1) in PARSABIV full prescribing information]*.

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Ionized Magnesium (Mg^{++})
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Electrolytes (Na^{+}, K^{+}, Ca^{++}, Cl^{-}) are all measured as ions because that is their only clinically active form. Now Mg^{++} can be measured the same way.

Ionized Magnesium (Mg^{++}), not Total Magnesium (tMg), is the only physiologically active form of magnesium. Magnesium bound to protein, or chelated to phosphate, citrate, sulfate, or carbonate is inactive.

tMg is an unreliable substitute for Mg^{++}. Mg^{++} may be abnormal while tMg is normal, and vice versa.[1,2]

Mg^{++}, and Ca^{++} can now be measured in the lab or at the point of care to provide a complete electrolyte analysis: Na^{+}, K^{+}, Ca^{++}, Mg^{++}, Cl^{-}, HCO_3^{-}

If you are measuring K^{+} and Ca^{++}, you should also be measuring Mg^{++}

Mg^{++}, Ca^{++}, and K^{+} ion abnormalities are common in critical care medicine.

Mg^{++}, Ca^{++}, and K^{+} ions are interdependent and play a role in numerous disease processes, including diabetes, hypertension, kidney disease, cardiovascular disease, cardiac arrhythmia, and sepsis.

Mg^{++} is a vasodilator, Ca^{++} is a vasoconstrictor. Both are synergistic in maintaining vascular and bronchial smooth muscle tone.

Mg^{++} ion is an antagonist to Ca^{++} ion entry into cardiomyocytes.[3]

Serial monitoring of Mg^{++}, Ca^{++}, and K^{+} ions are all important in correcting or avoiding cardiac arrhythmias and cardiomyocyte necrosis.[4,5,6]

Hypokalemia may be unresponsive to potassium repletion unless hypomagnesemia is first corrected.[7]

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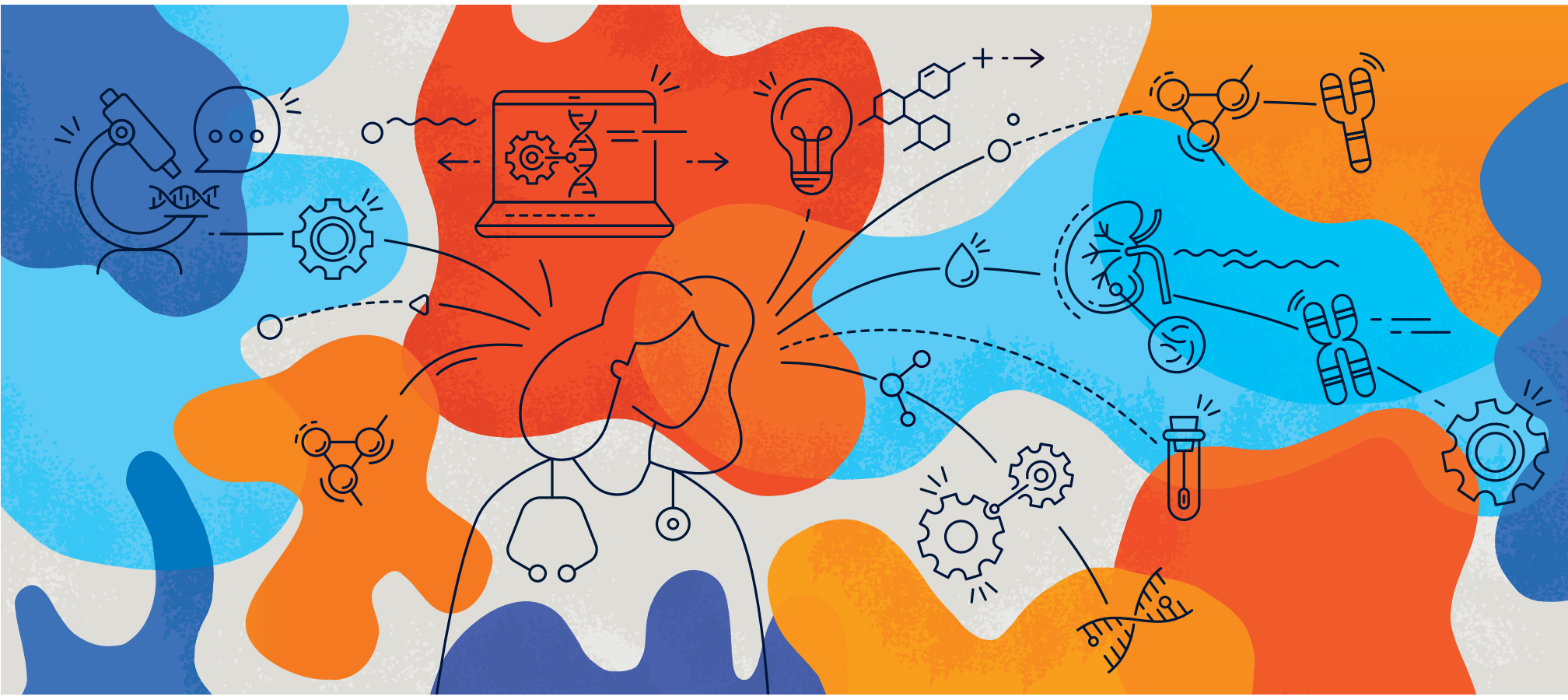

PRIORITIZING AND INVESTING IN BASIC SCIENCE RESEARCH

Are Critical Steps to Advancing Therapies for Kidney Diseases

By Matthew A. Sparks and Jennie J. Lin

Basic science is fundamental to advancing medicine and improving health outcomes. It is an exciting time to be engaged in basic and translational research focusing on kidney diseases. Novel research tools and methodologies are available to answer questions that have long eluded scientists. Moreover, we are seeing investments in kidney-related research by pharmaceutical companies, industry, societies, and governments. Examples of these investments include the Kidney Precision Medicine Project (KPMP), funded by the National Institute of Diabetes and Digestive and Kidney Diseases; the Transformative Research in Diabetic Nephropathy (TRIDENT) study, which is a private-public partnership; the Kidney Innovation Accelerator (KidneyX) prize; and the Nephrotic Syndrome Study Network (NEPTUNE), among others.

How does nephrology stack up to other disciplines? It is imperative that we, as a community, continue to advocate and prioritize funding and support of basic science research throughout the continuum of one's career. This issue of *ASN Kidney News* explores the needs of early career scientists, who are just starting to build their careers, to ensure they develop a strong foundation to propel them forward. This is juxtaposed to other disciplines. Although the increase in investment is welcome, more funding, support, and opportunities are urgently needed. Moreover, our research community, just like the clinical workforce, should reflect the population and patients we serve. Thus, there is an urgent call to ensure that diversity and inclusion are prioritized in nephrology. We will hear from a recently formed grassroots organization, Black in Physiology, with a mission to nurture, fortify, recruit, and strengthen the professional and scientific development of physiologists who are of Black race.

Biomedical research is advancing at an impressive rate. For example, single-cell RNA sequencing, first described in 2009 (1, 2) and once considered a novel methodology, is now a common technique that has made its way into many laboratories as a result of refinements in the technique, enhanced data storage/analysis capabilities, and the availability of reagents at an affordable cost. Single-cell RNA sequencing takes a snapshot in time of all of the mRNA transcripts that are produced by a single cell. This is repeated, for example, in thousands of individual cells after making a single-cell suspension of a sample. The advantage is that we can now better characterize cell populations in an unbiased manner. Whereas in the past, we relied on a combination of two to three known markers, now we find subtypes and sometimes completely novel cell lineages.

In this issue of *ASN Kidney News*, we dive even deeper into single-cell technologies and discuss the emerging area of what is called spatial transcriptomics in which single-cell sequencing is performed on the tissue level, thus allowing researchers to understand how geography and cell-to-cell interactions occur. Although more scientific progress is needed, we witnessed the implantation of a genetically modified pig kidney into a human with a nonfunctioning brain, which did not result in immediate rejection—a barrier that had plagued researchers for decades. Recently, the use of stem cell-derived islet cells for type 1 diabetes in human studies was reported. How close are we? These topics are discussed in this issue. Moreover, the connection between the kidney and other organ systems continues to garner attention. The heart, lungs, immune system, and emerging data on the microbiome are discussed. We also examine the use of human stem cell-derived organoids or "mini-kidneys" and their impact on research in the kidney space. Lastly, we discuss ferroptosis—a type of programmed cell death dependent on iron and characterized by lipid peroxide accumulation—and emerging research on how this process might be manipulated in the future for therapies targeted at kidney diseases.

This issue of *ASN Kidney News* offers a small glimpse into recent developments in basic science research related to kidney diseases. We are hopeful that with continued support and investment, these advances will lead to improved therapies for patients with kidney diseases. ■

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The authors report no conflicts of interest.

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Acknowledging the Challenges Faced by Trainees Building Careers in Kidney Research

By Jermaine G. Johnston and Elinor C. Mannon

The start of a new year often signals a time for reflection. As we move through 2022, we again may find ourselves asking: What is the state of nephrology research? How are trainees fairing as they build their own independent careers in this field? There are many sources of support that assist trainees at all levels as they hone the skills necessary for scientific investigation. However, this career path is not without challenges, including, but not limited to, scientific investigation funding, time that is dedicated for investigation, support to build a professional network, and the current lack of diversity in academia.

Although strong fiscal support for trainees exists in nephrology, there are stark realities that those pursuing a long-term career in kidney research face. At the societal level, ASN provides approximately $3 million annually to fund young researchers, fellows, and educators in nephrology through KidneyCure (1). The American Society of Clinical Oncology awarded over $9 million in 2020 for research support (2), and the American College of Rheumatology will be committing nearly $13 million to fund awards in fiscal year (FY) 2022 (3). Funding for kidney research also exists at the national level. The total estimated investment in kidney disease for FY 2022 by the US National Institutes of Health (NIH) is approximately $685 million. Although this estimate continues a trend of increased funding for nephrology research (4, 5), the amount pales in comparison to the estimated FY 2022 funding supplied by NIH toward other research areas, such as cancer ($7.4 billion), lung research ($2.3 billion), and heart disease ($1.6 billion) (Figure 1) (5). The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) has also disbursed many fellowship, career development, and training awards over a 10-year span (6). Recently, NIDDK reshaped its T32 programs to propel kidney, urologic, and hematologic training and research through its U2C/TL1 Institutional Network Awards (7). This program will eliminate divisional single-discipline T32 awards and instead prioritize funding awards that span multiple institutions and disciplines (for example, hematology, urology, and nephrology). It is currently unclear how this shift will ultimately impact the long-term funding opportunities available to those investigating kidney function, health, and disease.

Opportunities for investigation are also critical to scientists' growth at all levels. Finding time for research can be difficult, as trainees are often pulled in many directions. Clinical demands, teaching workloads, and other institutional requirements can compete with (and at worst, derail) trainees' plans for novel scientific investigation. It is important for mentors, program directors, departments, and institutions to provide trainees and young investigators with opportunities to spend time performing experiments and writing manuscripts and grant applications. These tasks are essential components for budding scientists as they work toward independence.

Avenues through which scientists at different career stages can share their research and participate in networking opportunities are important. ASN provides several opportunities for this, first and foremost through ASN's Kidney Week, the premier meeting for nephrologists and kidney researchers. ASN's partnership with another prominent scientific organization, the American Physiological Society (APS), has led to the creation of the Basic Research Forum for Emerging Kidney Scientists. This Kidney Week pre-meeting is an early-career event that allows nephrology trainees and early-career investigators of diverse backgrounds a platform to share their basic science research with experts in their field. This event also creates opportunities for small-group networking and career development through panel-based talks or mock study sections. The triennial APS/ASN Control of Renal Function in Health and Disease conference, occurring this summer, is another example of a venue that provides basic researchers the opportunity to present their work in a public platform.

All of these factors provide a foundation for career development and advancement, but it is important to understand that support is multi-faceted. Support also involves opportunities to increase inclusion for groups underrepresented in medicine (URiM). According to the National Science Foundation, people who are URiM made up a small percentage of the 6008 US citizens and permanent residents who received a doctorate in biological and biomedical sciences in 2020: individuals who are Black or African American, 265 (4.4%); Hispanic or Latino, 521 (8.7%); and American Indian or Alaska Native, 9 (0.2%) (8). Although the percentage of individuals in URiM groups with academic doctoral positions has increased over the past 20 years, some percentages remain considerably small as of 2019, with 8.9% of URiM individuals holding doctoral positions (9).

Training a diverse workforce is critical for innovation and growth. Recognizing the need for this, ASN has created the Loan Mitigation Pilot Program (LMPP), which will focus on URiM groups in the first year. Although more needs to be done across the field to promote and sustain the inclusion of people from different backgrounds, the LMPP is an effort to increase diversity of the nephrology workforce to match the patient population (10). Similarly, loan-mitigation awards for those interested in pursuing research as part of their long-term careers may facilitate the growth of a diverse research environment in nephrology.

The path to creating and sustaining a career as an independent investigator in kidney research is not always a straightforward journey, and a gauntlet of challenges exists along the way. There are strong sources of support that exist already at the societal and national levels, but increased institutional intervention can complement these opportunities to enhance the experiences of trainees as they progress in their training. Our passion and will to make the communities around us a reflection of our continued optimism allow us—researchers and clinicians—to be hopeful for our future careers and for the field of nephrology as a whole. ■

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Dr. Johnston and Ms. Mannon are Organizing Committee members for the Basic Research Forum for Emerging Kidney Scientists as part of the early program for ASN Kidney Week. Ms. Mannon was a recipient of a KidneyCure 2021 ASN Predoctoral Fellowship Award. The authors report no other conflicts of interest.

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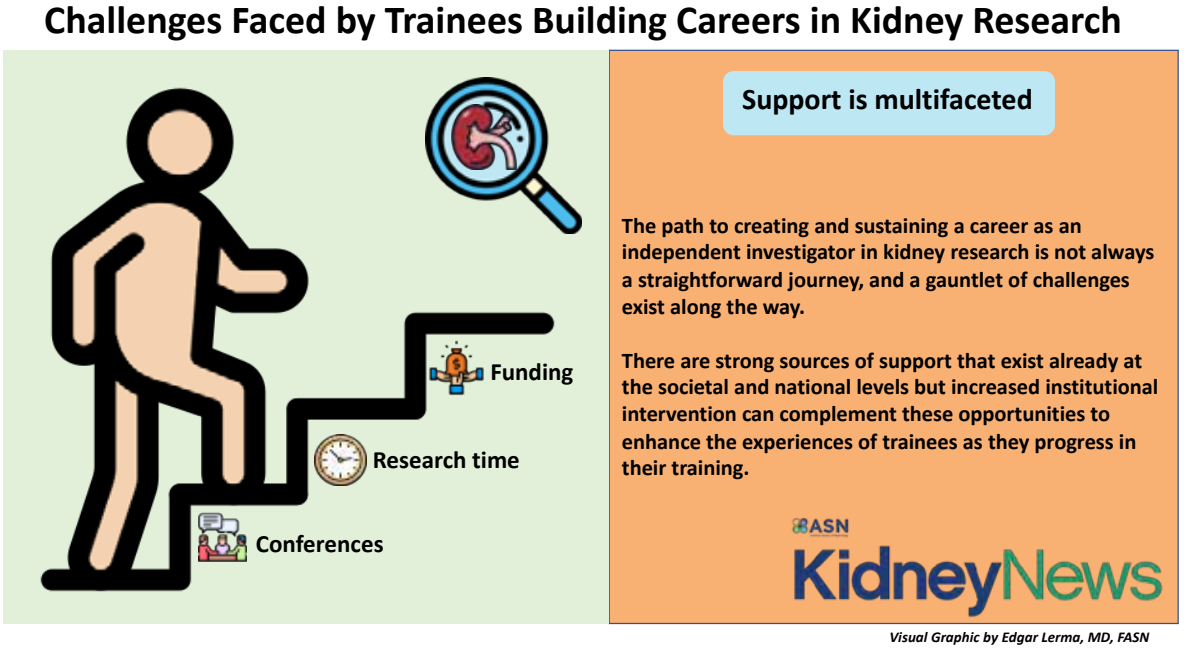
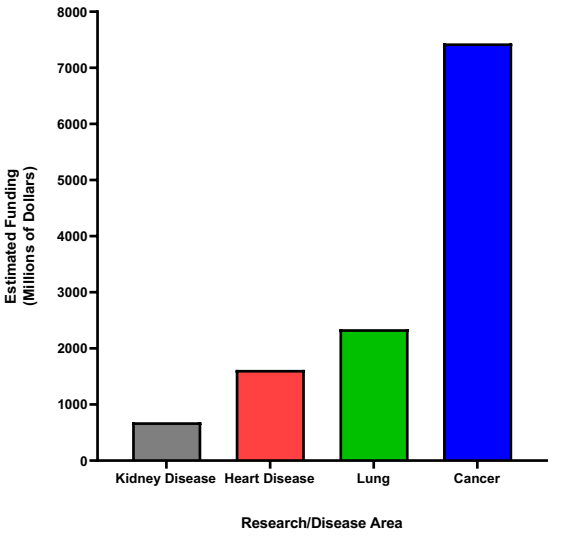


Figure 1. Estimates of funding for various research, condition, and disease categories for FY 2022



Estimates for research/disease areas listed in the graph are based on actual data of research, condition, and disease categories (5).

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Microbiome Research in Kidney Diseases: Listening in on the Gut-Immune System Crosstalk

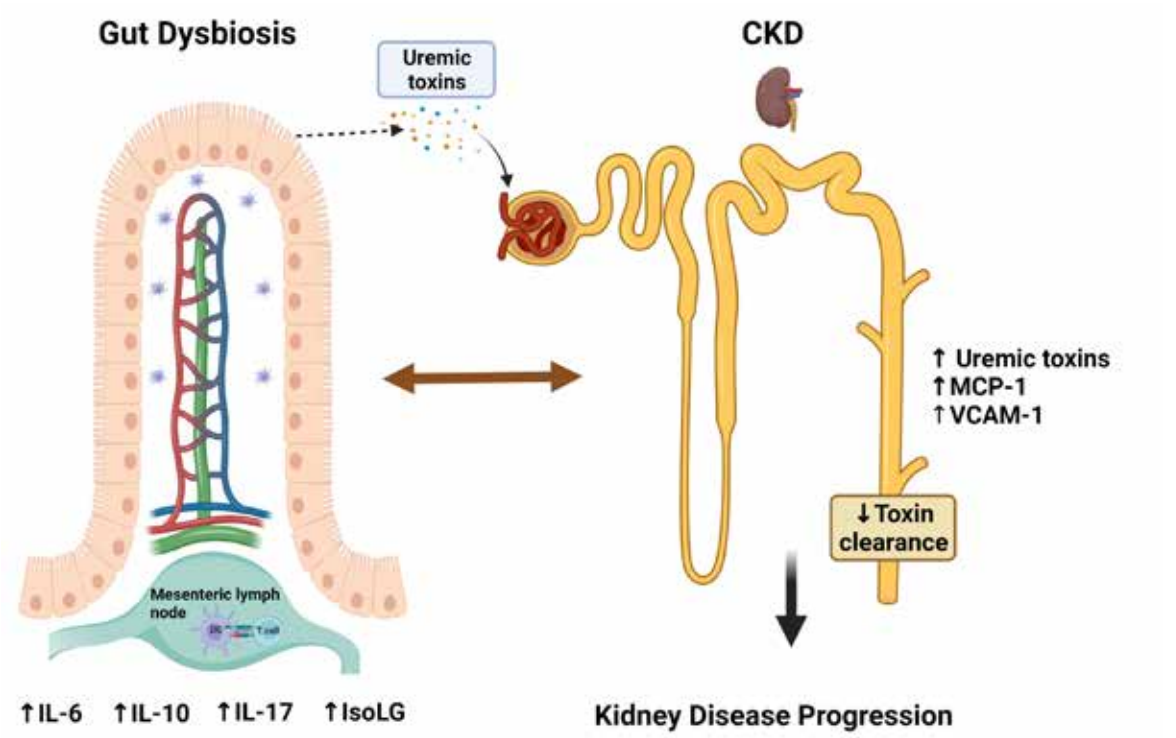
By Jeanne A. Ishimwe, Valentina Kon, and Annet Kirabo

Persistent systemic inflammation is a hallmark of chronic kidney disease (CKD) and several of its risk factors, including diabetes and hypertension. The gut microbiome is defined as the microorganisms and their genetic material in the intestinal tract. Emerging evidence has substantiated the gut microbiome as a key mediator of inflammation in various pathophysiologic states, including kidney diseases (1, 2). Patients with kidney failure on dialysis also exhibit bacterial translocation from the intestines to the circulation, contributing to microinflammation (3). Bacterial translocation is reported in other pathologies, including hypertension and autoimmunity (4, 5). Harnessing the power of the microbiome to treat diseases is promising, especially because this approach is already used as an alternative treatment option for life-threatening diseases such as recurrent *Clostridioides difficile* (6). Although research in the area of the microbiome has made tremendous progress, the mechanisms by which the microbiota (and alterations to gut bacteria) contribute to inflammation and its consequences in the setting of kidney diseases are not fully elucidated.

It is well accepted that there is a bidirectional relationship between the gut and kidney. However, the effect of this crosstalk on kidney function remains an active research question. For example, studies indicate an immunomodulatory role of gut-derived metabolites, including trimethylamine oxide and short-chain fatty acids (7). Alterations in the gut microbiome in mouse models by using antibiotics lead to diminished bacterial production of short-chain fatty acids. These short-chain fatty acids can directly stimulate olfactory receptors present on vascular smooth muscle cells leading to changes in blood pressure (4).

Bacteria in the gut also modulate inflammation through secondary modifications of molecules, such as bile acids and amino acids. For example, tyrosine and tryptophan undergo bacterial modification in the gut to form P-cresol and indole, which are subsequently metabolized by the liver to generate the uremic toxins P-cresyl sulfate and P-indoxyl sulfate. These metabolites highlight the potential importance of the kidney-gut axis in progressive CKD, because their production in the gut may harm the kidneys, just as the inability of the kidneys to clear them may worsen gut dysbiosis and inflammation (Figure 1). The exact mechanism by which these metabolites exert their effects is unclear, but evidence suggests a relationship with proteins involved in endothelial barrier function, the complement system, cell adhesion, phosphate homeostasis, and inflammation (8). Published human studies report a strong correlation between the uremic toxins and inflammatory markers, including monocyte chemoattractant protein 1 and soluble endothelium-associated adhesion molecule 1 (9–11). Moreover, P-cresyl sulfate and P-indoxyl sulfate are toxic in many cells, including intestinal epithelial cells, where direct exposure increases tumor necrosis factor, cyclooxygenase-2, inducible nitric oxide synthase expression, and nitrotyrosine formation (an end product of reactive oxygen species generation) (12).

Figure 1. The role of inflammation in the kidney-gut crosstalk in kidney diseases



Gut dysbiosis generates uremic toxins, which contribute to inflammation and progression of kidney disease. On the other hand, kidney injury stimulates intestinal lymphangiogenesis and increases mesenteric lymph flow and accumulation of proinflammatory molecules that contribute to systemic inflammation and kidney dysfunction. IsoLG, isolevuglandin; IL, interleukin; MCP-1, monocyte chemoattractant protein 1; VCAM-1, vascular cell adhesion molecule 1; DC, dendritic cell.

Let's segue to another closely linked system: the lymphatics. The lymphatic system plays an important role in the progression of a fibrotic response in the kidney by mediating inflammatory mechanisms. A recent experimental study by our group (13) using mice and rats suggests that the intestinal lymphatic system is a novel link among gut-generated metabolites, inflammation, and progressive kidney diseases. We demonstrated that proteinuric kidney injury (puromycin aminoglycoside-injected rats and Nphs1-hCD25 [podocytes expressing the interleukin-2 (IL-2) receptor] transgenic mice) alters the structure and function of intestinal lymphatics and the composition of the mesenteric lymph. These two models of proteinuric kidney injury demonstrated structural and functional alteration of the lymphatic system. This includes intestinal lymphangiogenesis (or mismatch between blood vessels and lymphatics), lymphatic vessel contractions, and activation of lymphatic endothelial cells.

In addition, the mesenteric lymph of kidney-injured mice had increased T helper 17 lymphocytes (which are pro-inflammatory) and production of several pro-inflammatory cytokines, notably IL-6, IL-10, and IL-17. Moreover, the reactive peroxidation product isolevuglandin (IsoLG) was elevated in mice with proteinuria kidney injury. Interestingly, although these cytokines and IsoLG were identified in the

Continued on page 18 >

Microbiome Research in Kidney Diseases

Continued from page 17

gut, they were not detected in concurrently sampled, peripherally collected plasma (13), suggesting origination from the gut. This concept is supported by findings that exposure of cultured intestinal epithelial cells to myeloperoxidase stimulates the production of IsoLG (Figure 1). In addition to gastrointestinal epithelial cells, dendritic cells stimulate IsoLG formation that activates T lymphocytes (14). In the kidney, lymphangiogenesis accelerates inflammation in the kidney, and blocking the lymphatic growth inhibits recruitment of activated dendritic cells into the renal draining lymph nodes and spleen and attenuates progressive kidney damage (15).

A better understanding of the gut microbiome in inflammation and kidney diseases has the potential to elucidate new therapeutic targets for CKD. Interventions such as administration of 2-aza-tyrosine, which blocks the conversion of tyrosine to phenol and reduces circulating levels of the toxic phenyl sulfate, reduces *Coriobacteriales* and *Erysipelotrichales* microbes that associate with kidney failure and lessens albuminuria in diabetic mice (16). Other strategies include personalized nutrition and synbiotics that can modulate gut-derived molecules, such as uremic toxins, to improve kidney function (17, 18). These strategies improve other diseases that are associated with gut dysbiosis, kidney damage, and inflammation, such as systemic lupus erythematosus (19). The gut clearly plays a role in modulating kidney health. More work is needed to delineate the mechanisms at play, particularly in humans. ■

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Being Black in Physiology

By Keisa W. Mathis, Corey L. Reynolds, and Clintoria R. Williams

According to surveys conducted by the Association of Chairs of Departments of Physiology, the percentage of Black faculty has averaged 1% for the past 20 years (1). This same trend in lack of representation exists for the trainee (graduate student and postdoc) level as well, further complicating the recruitment and retention of the next generation of Black physiologists. It was due to these defaults in the system that in the summer of 2020, Black in Physiology (BiP), an organization committed to nurturing and celebrating Black excellence throughout the physiology community, was created by four charter members. Currently, two BiP Executive Board members are renal physiologists.

The BiP community serves as an inclusive space for not only those who consider themselves Black or African American scientists in physiology or physiology-related fields but also for supporters, allies, and advocates. BiP is represented by several different areas of physiology, including renal, cardiovascular, and integrative. BiP is dedicated to fortifying a community for Black physiologists by enhancing visibility and ensuring that resources, support, and guidance are readily accessible. The current focus of BiP is primarily working with trainees at the graduate student and postdoctoral levels; however, some events and workshops offer information and pearls of wisdom that are valuable to students at all levels, including undergraduates (Figure 1). Since its inception, BiP has been dedicated to using the diverse talents of community members to support the professional and scientific development of Black physiologists. BiP has hosted events on YouTube (https://www.youtube.com/watch?v=AGiSqPJyoL4&ab_channel=KeisaMathis) including discussions on the recruitment, retention, and promotion of Black physiologists (2) as well as how to effectively navigate the early stages of academia (3). BiP also hosted a week of events (BiP Week) in 2020 and 2021 that included panel discussions and workshops around topics such as scientific communication and alternative careers in physiology. Given the current climate and pressures that have been placed on trainees and faculty during the COVID-19 pandemic, BiP Week 2021 thoughtfully included a Mental Health Table Talk, moderated by a licensed therapist.

BiP is dedicated to fortifying a community for Black physiologists by enhancing visibility and ensuring that resources, support, and guidance are readily accessible.

In addition to BiP Weeks, the inaugural Conference for Black Physiologists (C4BP) was held in April 2021. C4BP relayed an abundance of professional development nuggets from Black leaders in academia, industry, and government. Scientific talks and moderated poster sessions were presented by up-and-coming Black leaders in the areas of renal, cardiovascular, reproductive, gastrointestinal, and neuroscience physiology. The week also included several social engagement opportunities, all meant to help enhance attendees' networks and importantly, their net worth.

Future events include a hybrid C4BP 2022 conference that will feature 2 days of virtual events and 1 day of in-person events to coincide with the Experimental Biology (EB) 2022 meeting being held in April in Philadelphia. In-person events will include a featured topic oral presentation session at EB, titled "Diseases That Impact the Black Community: This Is My Why," and an evening social networking event. Future goals of BiP are to continue to provide relevant workshops and sessions and to offer graduate students scholarship and fellowship opportunities. However, because BiP is a nonprofit organization, its success is largely dependent on financial support that it receives from individual and corporate sponsors.

If you would like more information about BiP or to donate, please see our webpage at www.blackinphysiology.com, or follow us on Twitter (@BlackInPhysio), Instagram (@blackinphysio), or Linkedin (Black in Physiology, Inc.). BiP workshop videos can be viewed on YouTube at https://youtu.be/SxgoQF4qFVI. ■

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The authors report no conflicts of interest.

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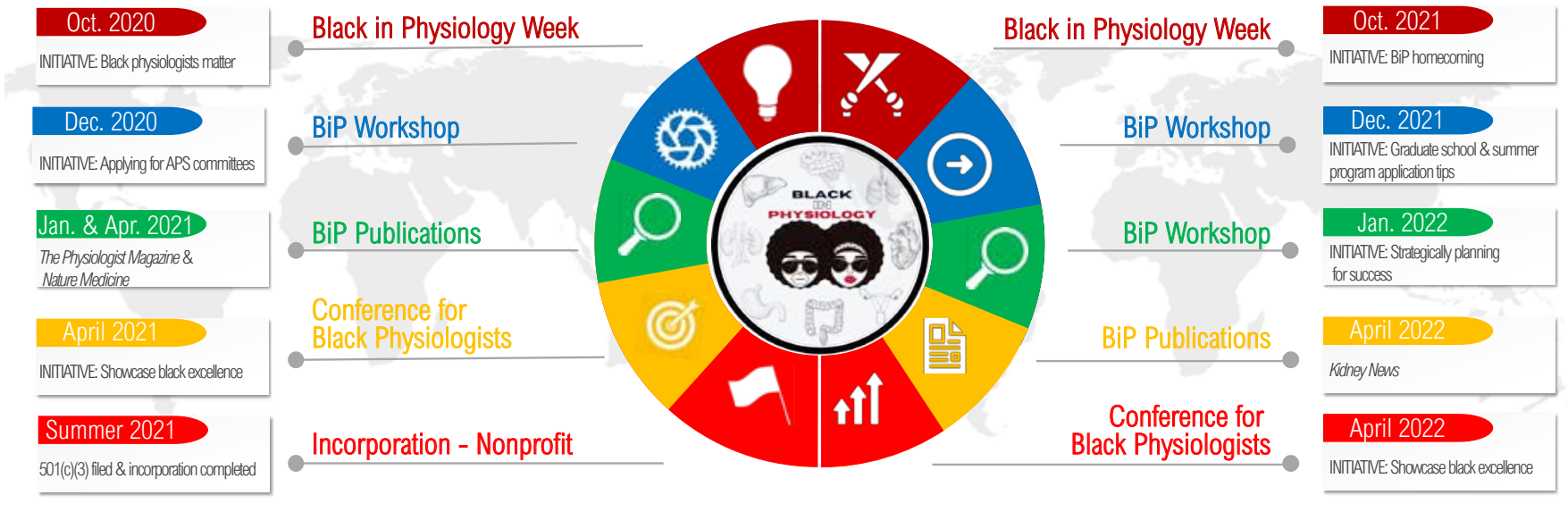
Figure 1. Black in Physiology timeline and accomplishments



APS, American Physiological Society.

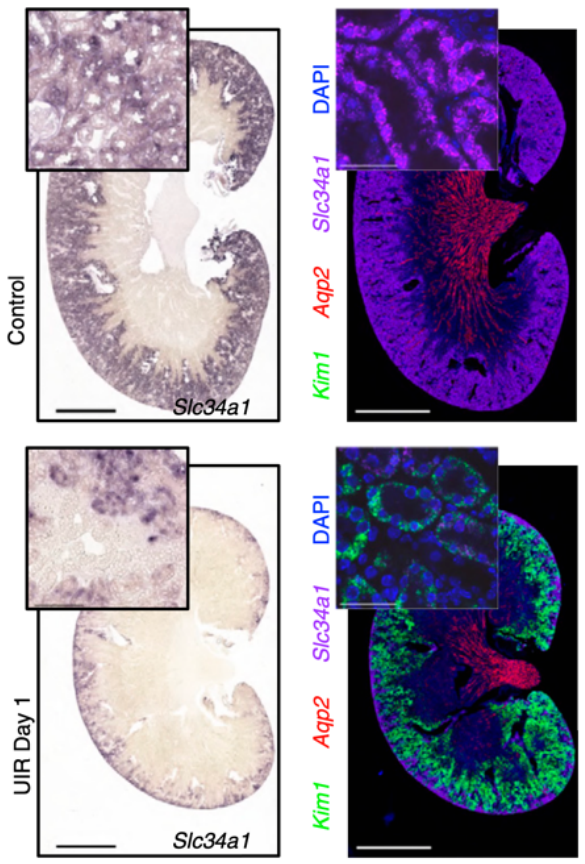
Visualizing the Kidney Transcriptome: Spatial Transcriptomics Take Center Stage

By Eryn E. Dixon

The advancements of single-cell and nucleus RNA sequencing (sc/snRNAseq) have shifted our approach to defining cell types and states relevant to human health. These technologies have provided detailed insight into the transcriptome (all of the expressed messenger RNA [mRNA] of a single cell, tissue, or sample) of a single cell. However, this process, requiring dissociation of tissue to the level of the single cell or nucleus, obscures the structural context of each cell within the tissue. Therefore, sc/snRNAseq studies have been limited by their inability to capture data essential to understanding these cellular microenvironments (surrounding cells, extracellular matrix, and signaling molecules that affect the response of a cell of interest) and the overall transcriptional landscape of the kidney. In response, researchers have been optimizing and implementing new strategies that account for both the two- and three-dimensional architecture of tissues as a whole. These efforts are known as spatially resolved transcriptomics.

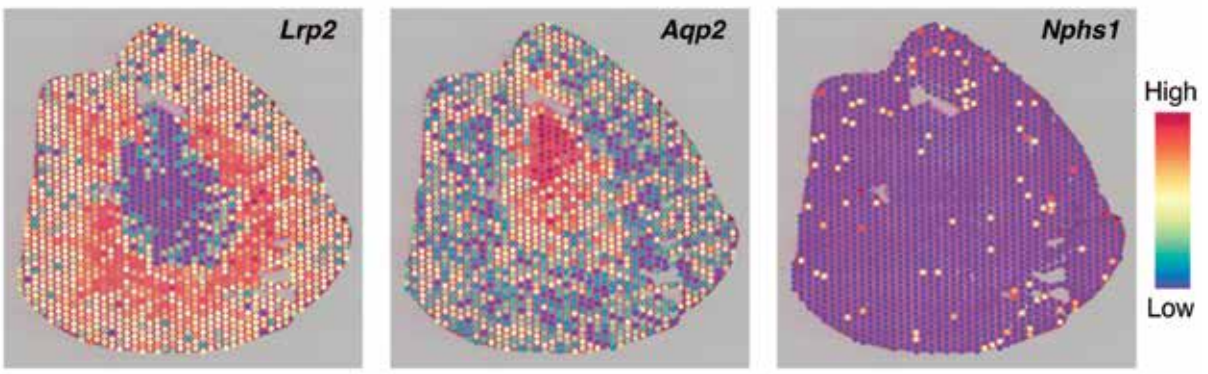
The idea of visualizing transcript localization is not necessarily new. For years, researchers have used techniques, such as in situ hybridization (ISH; a technique for the visualization of a specific segment of a target nucleic acid [DNA or RNA] using a single-stranded DNA or RNA probe that can be detected using radioactivity, enzymes, or immunofluorescence), to localize one gene transcript at a time. But, in recent years, these gold-standard molecular biology techniques have evolved from visualization of single gene targets to robust and technically challenging sequencing methods that support hundreds to thousands of different gene transcripts. Regardless of the method, the driving motivation of this methodology is to cultivate an efficient platform for the visualization of gene expression and localization within intact tissue across the transcriptome.

Figure 1. ISH-based visualization techniques



Representation of gene target localization using ISH-based RNAscope in a mouse kidney. UIR, unilateral ischemia/reperfusion. Reprinted from Rudman-Melnick et al. (2).

Figure 2. Spatially resolved transcriptomics of kidney tissue



Representation of three structural marker genes in a female kidney using 10X Genomics Visium. Reprinted from Dixon et al. (5).

There are two main categories of spatially resolved transcriptomics, including ISH-based and next-generation sequencing (NGS)-based (also known as barcoding-based spatially resolved transcriptomics). Both categories are gaining momentum with the advent of specialized computational analysis pipelines and streamlined processes for sequencing library generation. However, implementation of a specific modality of spatially resolved transcriptomics depends on the research question. For cellular or subcellular localization of a pre-specified profile of target genes, ISH-based spatially resolved transcriptomics will be the best option. To capture transcriptome-wide (unbiased) expression and localization changes in the kidney, NGS-based spatially resolved transcriptomics—a large-scale and high-throughput technology that rapidly determines the whole genome or transcriptome by reading millions of DNA or RNA sequences in parallel instead of previous methods that processed one at a time—would be needed.

ISH-based spatially resolved transcriptomics examples: sequential fluorescence ISH (seqFISH) and MERFISH

ISH-based spatially resolved transcriptomics were built on the foundation of original, gold-standard ISH protocols. Therefore, to scale up the basic ISH protocol, ISH-based spatially resolved transcriptomics use repeated binding, known as serial hybridization, of RNA target-specific primer probes to transcripts of interest, which are imaged to capture the binding of each probe (1). This serial hybridization creates unique molecular identifiers, corresponding to each target, and allows for the identification of hundreds of genes. Following the image capture of these probes, advanced computational analysis integrated with immunofluorescent images of markers that delineate tubule borders, or membrane markers for cell borders, can be used to segment tissue structures down to the cell or even subcellular level, resulting in highly resolved localization of gene targets. These ISH-based spatially resolved transcriptomic approaches have not yet been directly applied to kidney research. However, RNAscope, a similar but lower-throughput technology, has been used to exhibit the localization of multiple target genes (Figure 1). In the future, kidney researchers may be able to leverage the higher sensitivity and throughput of seqFISH, MERFISH, and other related ISH-based spatial transcriptomics to visualize genes of interest with unknown expression patterns by simultaneously looking at the expression and localization of gene panels that characterize potential neighboring cell types.

NGS-based spatially resolved transcriptomics example: Visium

Barcoding-based spatially resolved transcriptomics have rapidly evolved from the seminal work of Ståhl, Salmén, and co-workers (3), where tissue was mounted on a specialized slide, covered with an array of oligonucleotides and positional barcodes. From this tissue slice, cellular mRNA could be captured by the probes underneath it on the slide and synthesized into cDNA (3). Enzymes could then be used to release this cDNA for generation of sequencing libraries, now with a special spatial barcode that can be used to map expression back to a specific area of the tissue. Curated gene targets are not necessary for this approach, and the whole transcriptome can be sequenced, providing an unbiased method for discovery of gene expression and localization changes. This technology, commercially available as the 10X Genomics Visium platform (4), can thus generate transcriptome-wide spatial atlases overlaid on hematoxylin and eosin or immunofluorescent staining (Figure 2). Although the barriers to barcoding-based spatially resolved transcriptomics or Visium technologies have decreased because of open-source computational toolboxes, a substantial remaining disadvantage is the resolution. Arrayed, probe-embedded spots are too large and too distant to resolve single cells, but cellular deconvolution pipelines have helped determine the contributions of multiple cell types.

How can spatially resolved transcriptomics be applied to kidney study in health and disease?

sc/snRNAseq has provided great insight into the cellular composition of the kidney at many different stages in both animal and human models (6, 7). With the identification of new cell types and states, it is critical to investigate how these cells communicate and the physiological relevance of these local signaling microenvironments. For example, how do we better understand the interactions of injured kidney cells with other epithelial cells and the interstitium? In the past year, multiple groups (5, 8, 9) have focused on spatially resolved transcriptomics for various models of acute kidney injury and chronic kidney disease in both mouse and human kidneys. Although these projects differ in model systems, the efforts share similar goals, including the deconvolution of spatially resolved transcriptomics data to the level of the cell and assessment of cell-to-cell interactions. Ultimately, these spatial atlases of sepsis and ischemia reperfusion injury

models demonstrate changes in immune and epithelial cell interactions that are consistent with the disease states they represent (5, 8, 9). Beyond determining localization and expression changes of tubule segment-specific markers and other genes of interest, spatially resolved transcriptomics can reveal how communication within tubule microenvironments responds to genetic variation and disease. The pairing of the spatially resolved transcriptomics pipeline with sc/snRNAseq and other sequencing modalities, such as assay for transposase-accessible chromatin with sequencing (ATAC-seq), will build a multi-dimensional picture of how the kidney responds to health and disease states, leading us closer to defining mechanisms of kidney physiology. ■

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Pancreatic Islet Cell Transplantation: Are We Getting Closer?

By Collin Jordan and Xunrong Luo

For the greater part of the 20th century, exogenous insulin administration and whole organ pancreatic transplantation served as the predominant therapeutic interventions for patients with type 1 diabetes mellitus. The success of the Edmonton group in achieving insulin independence in the early 2000s via islet cell transplantation in a cohort of patients with autoimmune diabetes led to renewed optimism that this treatment could serve as an alternative to solid organ transplantation (1). However, 16 years later, a shortage of donor pancreatic islet cells remains a major challenge in increasing the scale of human allogeneic islet transplantation.

Various novel approaches to alleviate the donor shortage have been studied; however, a promising treatment offered by Vertex Pharmaceuticals seeks to eliminate this obstacle. In collaboration with the lab of Douglas Melton, Xander University Professor at Harvard and an Investigator of the Howard Hughes Medical Institute, Vertex has generated VX-880, an investigational stem cell-derived, fully differentiated pancreatic islet cell replacement therapy for patients with type 1 diabetes (2).

Typically, in whole islet transplantation, purified islets are infused via the hepatic portal vein, upon which they migrate to and engraft in the sinusoids of the liver. For Vertex's clinical trial, the technical mechanism of transplantation remains the same; however, unlike whole islet transplantation, VX-880 is selectively a beta cell therapy. Thus far, it has not been confirmed that beta cells engraft in the same spatial orientation of the liver as do whole islets, given that they are magnitudes smaller in size. Despite this, we know that transplanted beta cells do produce and secrete insulin into the blood immediately following transplantation (Figure 1).

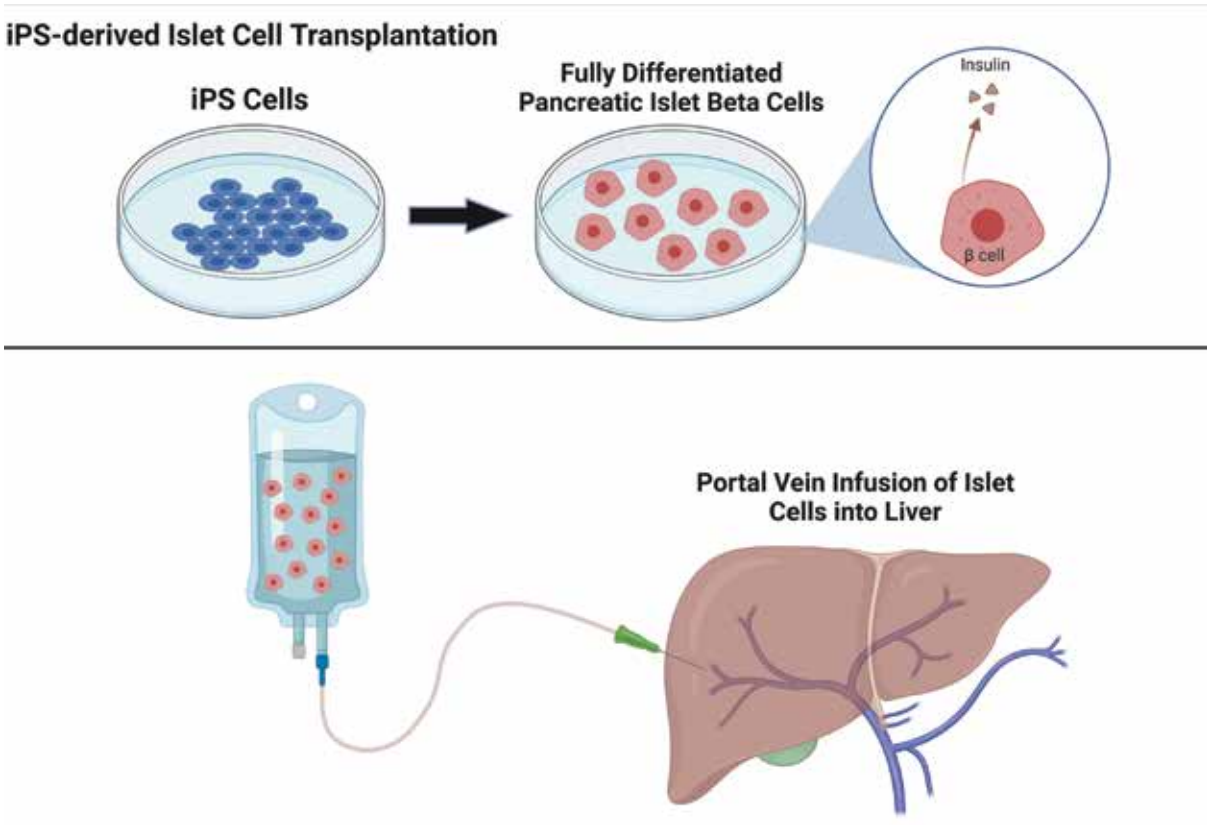
A game-changing therapy, VX-880 has the potential to completely obviate the need for an organ donor. In March 2021, the collaborators initiated a phase 1/2 clinical trial to evaluate the safety, tolerability, and efficacy of VX-880 (3). Seven months later, Vertex issued a press release to announce positive day 90 data for the first patient recruited to the phase 1/2 trial. Brian Shelton, the patient in question, whose identity was revealed in a feature in *The New York Times*, had lived with autoimmune diabetes for nearly 50 years before receiving a single infusion of VX-880 at one-half the target dose (4). In conjunction with immunosuppression therapy, Shelton demonstrated successful engraftment and restoration of insulin production. Furthermore, rapid improvement in fasting and stimulated C-peptide, glycemic control, and HbA1c were observed, along with a 91% decrease in daily exogenous insulin administration. These results are certainly encouraging for the continued progression of the VX-880 clinical studies, although what makes them truly striking is that they were achieved at one-half the target dose.

Perhaps the most transformative advancement to extrapolate from these early results is the potential for a rapid expansion of the donor islet pool readily available to patients with type 1 diabetes. Without the need for a deceased donor, stem cell-derived VX-880 offers new hope for the large-scale feasibility of clinical islet transplantation. However, beyond that, our ultimate goal should be to deliver islet cell transplantation without the need for a robust immunosuppression regimen, thus mitigating the risk for opportunistic infections among recipients. Whether this comes from Vertex's already-developed encapsulated islets or through another mechanism, such as gene-editing technology or immunoprotective implantation devices, remains to be seen.

Regardless, future trials involving VX-880 must explore the attrition of these stem cell-derived islets after transplantation. Do the cells functionally decline over time? Will a patient potentially need multiple infusions to remain euglycemic? If so, would the multiple infusions precipitate a donor-specific alloimmune response, subsequently driving

Continued on page 22 >

Figure 1.



iPS, induced pluripotent stem cell.

Pancreatic Islet Cell Transplantation

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sensitization of the recipient and thus, making future infusions progressively less effective? These are questions that must be addressed if we are to proclaim VX-880 a landscape-changing cell therapy for autoimmune diabetes. Until then, it will be interesting to follow the continued progression of this trial to see if these results can be generalized to a larger cohort of patients. ■

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The authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest, or non-financial interest, in the subject matter or materials discussed in this manuscript.

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Ferroptosis, an Emerging Therapeutic Target for Acute and Chronic Kidney Diseases

By Koki Abe and Tomokazu Souma

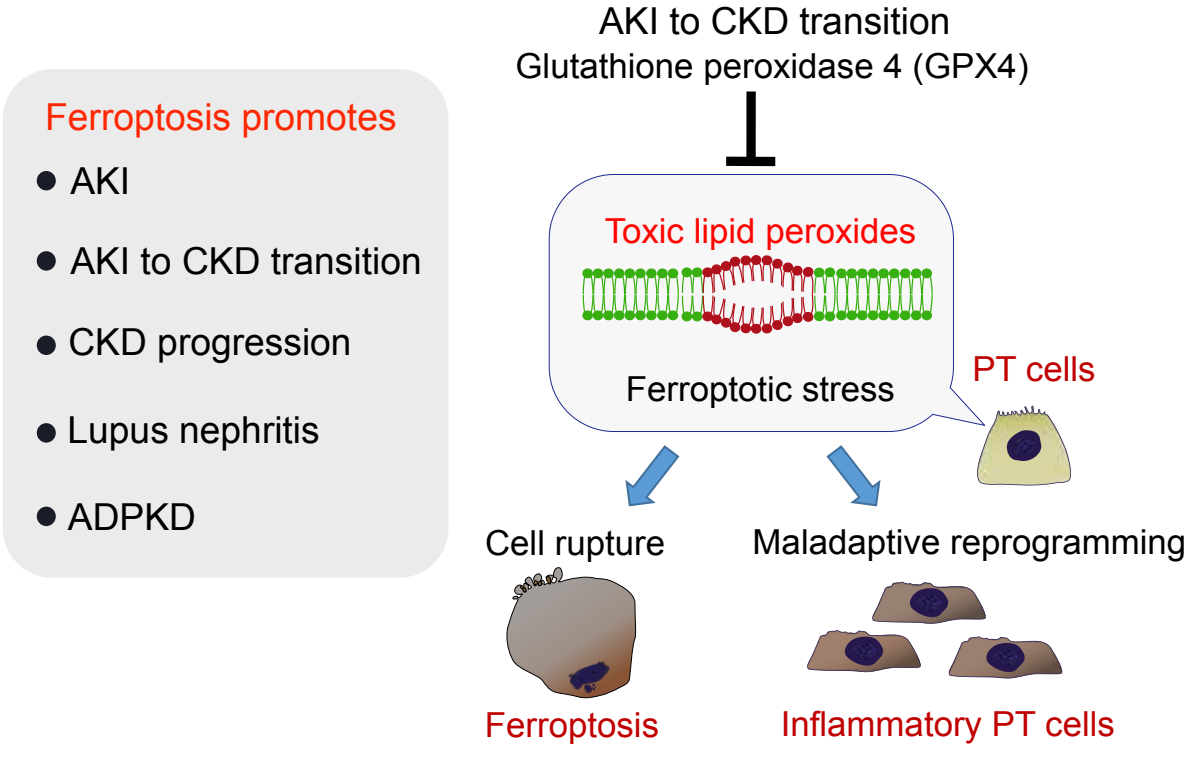
Cell death is a fundamental biological process underlying normal development, homeostasis, and diseases. Regulated cell death is defined as a molecularly controlled cell death that can be modulated (either promoting or preventing) by specific interventions (1). Although apoptosis has been the focus of interest regarding research on regulated cell death and has been historically considered a major cell death pathway in kidney disease processes, there are surprisingly many other ways cells end their lives in a molecularly regulated manner, such as necroptosis, pyroptosis, ferroptosis, and others. Among them, ferroptosis is attracting attention as a critical contributor and a potential novel therapeutic target for many common pathologic states, such as acute and chronic kidney diseases, cardiovascular diseases, neurodegeneration, stroke, chemotherapy-resistant cancers, and more (1, 2).

The term "ferroptosis" was coined in 2012 to describe a distinct form of cell death caused by the pathologic accumulation of toxic lipid peroxides (i.e., oxidized lipids) in an iron-dependent manner (1–3). Accumulation of toxic lipid peroxides worsens the redox status of the cell membrane (ferroptotic stress) and causes plasma membrane damage and subsequent cellular rupture (Figure 1). The glutathione/glutathione peroxidase 4 (GPX4) defense pathway prevents this pathologic consequence by detoxifying toxic lipid peroxides. Ferroptosis is particularly relevant to kidney diseases because the kidney is one of the organs most vulnerable to dysregulation and insufficient activity of GPX4 (4). This was highlighted by examining mice with complete absence (through genetic deletion) of the *Gpx4* gene. Mice without the *Gpx4* gene had massive albuminuria, kidney tubular epithelial cell death, and subsequent mortality just a few weeks after inducing the gene deletion (4). Moreover, recent human studies suggest the potential involvement of the ferroptotic process in acute kidney injury (AKI) and chronic kidney disease (CKD), highlighting its clinical significance (5–8).

The first investigations of the ferroptotic process in nephrology examined its role in AKI. Ferroptosis inhibitors have been shown to diminish the severity of AKI in multiple preclinical (animal) AKI models such as ischemia-reperfusion injury and folic acid-induced nephropathy (1, 9). Our study further identified how the ferroptotic process involves maladaptive repair after AKI using single-cell transcriptomics, a revolutionizing tool to decipher complex biological and pathological processes at single-cell resolution (10). After ischemic and toxic injuries, proximal tubular cells of the kidney alter their cellular state significantly and acquire a proinflammatory state. They also revert to a more primitive state called dedifferentiation (10–14). The accumulation of these inflammatory proximal tubular cells appears to promote kidney inflammation and a maladaptive repair process (10–14). The ferroptotic process uniquely contributes to this dynamic alteration of the proximal tubule cell state (10). Our group found that ferroptotic stress promotes the accumulation of these inflammatory proximal tubule cells inside the severely damaged kidneys, in addition to triggering ferroptotic death of these cells (Figure 1). Our results, using a mouse model, suggest that inhibiting the ferroptotic process holds the potential to disrupt the AKI to CKD transition.

Although most of the currently available data are derived from animal models, emerging evidence supports the pathogenic role of ferroptosis in multiple forms of CKD. By detailed and integrated analyses of genome-wide association studies on kidney function with multiple human transcriptomic and epigenomic datasets, two genes (*DPEP1* and *CHMP1A*) were identified as potential causal genes of CKD progression (6). This mechanistic study using animal models found that these two genes control cellular ferroptosis sensitivity of proximal tubule cells by regulating cellular iron homeostasis. Ferroptosis is also linked with autosomal dominant polycystic kidney diseases (15). Surprisingly, pharmacological induction of the ferroptotic process increased the cyst growth in *Pkd1* null mice by triggering cellular proliferation of cyst-lining epithelial cells in addition to inducing cell death. Conversely, pharmacological inhibition of ferroptosis reduced the cyst size. Clinical and experimental data also show ferroptosis of the neutrophil promotes the pathogenesis of lupus nephritis in mice and likely in humans (7). These data collectively support that ferroptosis inhibition represents an attractive therapeutic strategy to prevent multiple forms of CKD. We also need to be aware that a therapeutic strategy that enhances ferroptosis gains significant attention to treat chemotherapy-resistant cancers, as ferroptosis is identified as a targetable vulnerability of therapy-resistant cancers (16). Therefore, we may see increased AKI incidence due to enhanced tubular toxicity in cancer patients treated with the

Figure 1. Ferroptosis underlies multiple forms of acute and chronic kidney diseases



Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; ADPKD, autosomal dominant polycystic kidney disease; PT cells, proximal tubular cells.

pro-ferroptotic small molecules as a chemosensitizer in the future.

In summary, elucidating and understanding the molecular nexus that controls ferroptosis sensitivity and resistance in the kidney may provide new therapeutic targets for multiple forms of kidney diseases and may aid in identifying protective adjunctive therapies to prevent or mitigate kidney injury related to cancer therapies. ■

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Organoids Advance Kidney Science

By Hongxia Fu and Benjamin S. Freedman

Ten years ago, human kidney organoids were but twinkles in the eyes of a few intrepid inventors. Now, these tiny collections of cells, which bear a striking resemblance to kidney tissue, are well on their way to becoming a standard research tool. As they spread, kidney organoids are also becoming more diverse and gaining new abilities.

The ability of organoids to mimic features of kidney diseases presents new opportunities to discover medications and exciting possibilities for regenerative medicine. To generate the structures more reproducibly and optimize their shapes and sizes, a technique, called cellular extrusion bioprinting, has recently been introduced in which organoid progenitor cells are "printed" in specific patterns (1). Similarly, automated instruments (robots) capable of performing routine cell-culture tasks can be harnessed to produce large batches of organoids in microwell-plate formats for querying hundreds of conditions simultaneously (2). Generating organoids in the lab used to require substantial expertise, but now researchers can purchase a commercially available kit to grow organoids (just add cells) (3). These advances increase the scale and reproducibility of kidney organoid technology.

Organoids naturally contain blood vessel endothelial cells, but these fail to link with the podocytes to form glomeruli and may die over time (2, 4). This endothelium can be increased by treating organoids with vascular endothelial growth factor (2, 4) or by flowing media over the organoids in a microfluidic chamber (5). The most exciting findings, however, are seen when human organoids are implanted beneath the kidney capsule of living mice. Blood vessels from the mice invade the organoid podocytes to produce glomerulus-like structures, which can "sieve" high molecular weight carbohydrates from the blood (4, 6, 7).

The "original" kidney organoids were limited to proximal nephron structures containing podocytes, proximal tubules, and distal tubules in connected segments. Subsequent work described methods to produce structures that resemble primitive collecting ducts, which were combined with the original organoids to produce "higher order" structures (8, 9). The addition of a third population of cells to the mix that represents supporting, connective tissue-like cells similar to those found in the renal interstitium appears to encourage the collecting duct-like structures to grow and branch, at least in mouse organoids, resulting in striking images (Figure 1) (10).

How are kidney organoids currently being used? COVID-19 provides a case in point. In the midst of the pandemic, kidney organoids emerged as powerful models for studying SARS-CoV-2 infection and its potential treatments. A trend in these recent studies is cross-validation of data from organoids with data from clinical cohorts (11, 12). This fruitful back-and-forth produces a more holistic understanding than could be ascertained from either system on its own and is likely to be a common theme as this technology matures.

With advances being made at both the vascular and ureteric ends of the nephron, organoids are rapidly evolving (Figure 2). This evolution presents untapped opportunities to study a variety of kidney disorders and potentially to regrow parts of kidney tissues from autologous cells. A key question is whether organoids can perform kidney functions. It is not yet clear whether organoid grafts have any therapeutic benefit. They also contain fast-growing immature cells that could turn into tumors (7). The next few years will likely prove pivotal in our understanding of these issues as organoids inch closer to the real thing. ■

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Dr. Fu reports no conflicts of interest. Dr. Freedman is an inventor on patent applications licensed to STEMCELL Technologies.

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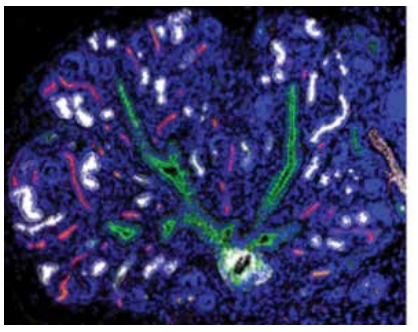
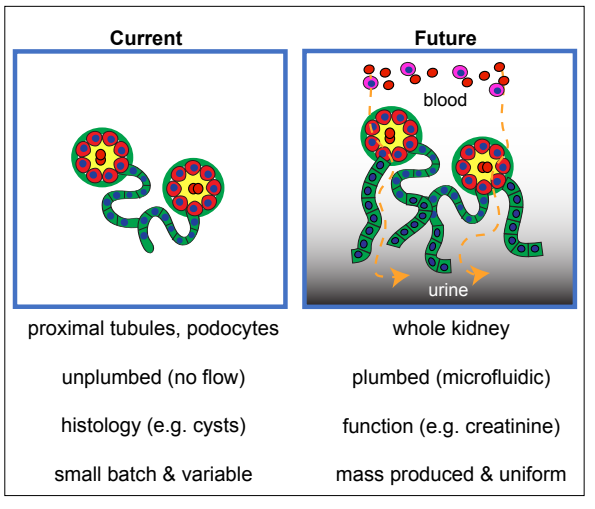
Figure 1. Higher order organoid (0.5 mm diameter) after implantation into a mouse host



Green, collecting duct-like; red, loop of Henle-like; white, proximal tubule-like; blue, all cells. From Tanigawa et al. (10) (unaltered; CC BY 4.0).

Figure 2. Evolution of organoids



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The Nephrotic Syndrome Study Network (NEPTUNE): Heterogeneity Becomes an Opportunity

By Laura H. Mariani, Laura Barisoni, Debbie S. Gipson, Lawrence B. Holzman, Crystal Gadegbeku, John R. Sedor, and Matthias Kretzler

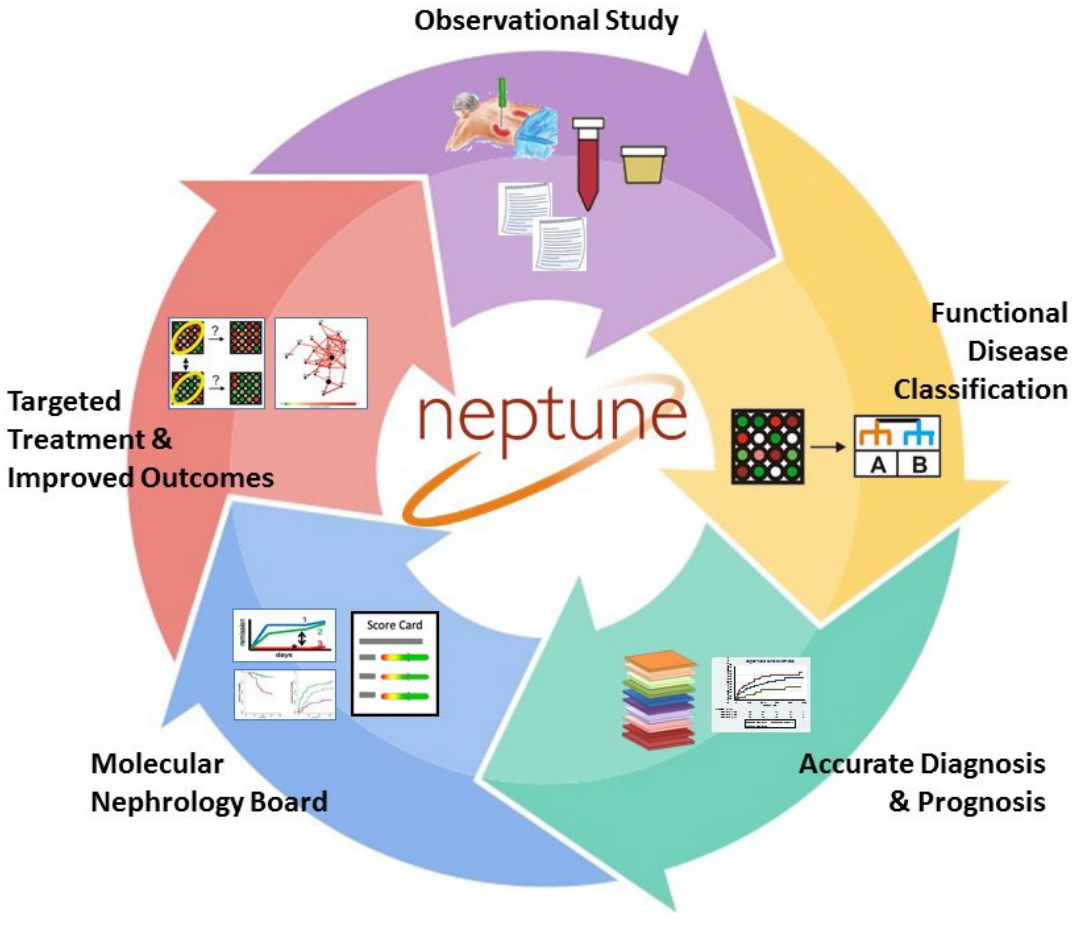
Patients with newly diagnosed nephrotic syndrome due to minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS), and membranous nephropathy (MN) display an impressive amount of variability in disease severity, symptom burden, response to initial therapy, and risk of relapse. Although this heterogeneity is a clinical challenge—frustrating patients and clinicians alike—it is also an opportunity for researchers to partner with patients under routine clinical care to collect the data and biosamples needed to better define mechanistically relevant subgroups. The Nephrotic Syndrome Study Network (NEPTUNE) is a North American multi-center collaborative consortium that was established to develop such a translational research infrastructure with the goal to better understand underlying disease pathogenesis and guide further investigation for targeted therapies (1) (Figure 1).

Now in its third grant-funding phase, the prospective cohort studies have consented over 1100 patients from 34 centers since 2010. Children and adults are enrolled at the time of the first clinically indicated biopsy, with proteinuria >500 mg/day in phase 1 and >1500 mg/day in phases 2 and 3. Participants who had other kidney disease diagnoses beyond MCD, FSGS, and MN were retained as a relevant comparison group. An additional pediatric cohort of patients not undergoing biopsy but presenting within 30 days of treatment initiation was added in phases 2 and 3 and now includes over 170 children. Patients with secondary glomerular disease (e.g., lupus and myeloma) and solid organ transplant were excluded.

The overarching goal of NEPTUNE has been to aggregate comprehensive, longitudinal clinical and molecular data into a resource for use by the entire scientific community to better unravel the heterogeneity of nephrotic syndrome. NEPTUNE participants are followed prospectively with up to three visits in the first year and two visits per subsequent year, up to 3 years. Multiple unique data elements and biosamples are available, which span the genotype-phenotype continuum. These include demographics, comorbidities, medications, laboratory values, physical exam, patient-reported outcomes, SMS texting, and census tract, as well as whole genome sequencing, targeted proteomics, and urine and blood biosamples. At the time of biopsy, an extra core of tissue is obtained for RNA sequencing (i.e., transcriptomics) after the tissue is manually micro-dissected to separate the glomerular from tubulointerstitial compartments. The kidney tissue slides, stained per usual clinical practice, are scanned into whole slide images and stored in the NEPTUNE Digital Pathology Repository. In the current study phase, NEPTUNE has launched a program to test the matching of disease mechanism biosignatures to enrolling clinical trial drug mechanisms on a patient level. This program allows patient participants to join in the review of research results.

As one example of combining high-dimensional datasets, a recent NEPTUNE study of 221 MCD and FSGS participants leveraged the unique digital pathology data and combined them with clinical outcome and molecular data (2). The NEPTUNE Digital Pathology Scoring system was developed to comprehensively and agnostically quantify structural changes in the biopsy (3). Pathologists enumerate glomeruli across levels and stains before scoring each glomerulus for the presence or absence of various features, called descriptors. In this study, the percentage of glomeruli with each descriptor was calculated for each patient biopsy. A clustering analysis of these data revealed three subgroups, each of which included both MCD and FSGS patients. One of the clusters had lower probability of remission of proteinuria and greater loss of estimated glomerular filtration rate over time. Importantly, the gene expression profile of this poor-outcome group revealed a

Figure 1. Highlights of the NEPTUNE study



unique signature, including potentially targetable pathways of inflammation and immune response.

With studies such as this one and many others leveraging the additional high-dimensional datasets and biosamples, NEPTUNE aims to support a variety of experimental approaches that can move nephrotic syndrome treatment closer to precision medicine. Investigators, internal and external to the consortium, are encouraged to propose ancillary studies (see NEPTUNE-Study.org) to bring this vision to fruition. ■

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Dr. Mariani has served on the advisory board of Reata Pharmaceuticals, Calliditas Therapeutics, and Travere Therapeutics. Dr. Barisoni has received consulting fees from Vertex, Protalix, and Sangamo and is a member of NephCure and Vertex scientific advisory boards. Dr. Gipson reports grants from Travere Therapeutics, Reata Pharmaceuticals, Goldfinch Bio, Novartis, and Boehringer Ingelheim and serves as advisory or consultancy through the University of Michigan with Roche, Genentech, AstraZeneca, and Vertex. Dr. Gadegbeku was Fresenius Kidney Care Episcopal Hospital Dialysis Medical Director until May 2021 and received consulting fees from Bristol Myers Squibb advisory board for clinical trials paid to Temple University. Dr. Kretzler reports grants from the National Institutes of Health, Chan Zuckerberg Initiative, Juvenile Diabetes Research Foundation, AstraZeneca, Novo Nordisk, Eli Lilly, Gilead, Goldfinch Bio, Janssen, Boehringer Ingelheim, Moderna, European Innovative Medicines Initiative, Certa, Chinook, amfAR, Angion, RenalytixAI, Travere Therapeutics, Regeneron, and Ionis and has a licensed patent, PCT/EP2014/073413, "Biomarkers and methods for progression prediction for chronic kidney disease," outside the submitted work. Other authors report no conflicts of interest.

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Mechanism of Heart Protection by SGLT2 Inhibitors, Direct and Indirect Effects

By Jianxiang Xue and Timo Rieg

A series of clinical trials demonstrated promising outcomes of sodium glucose co-transporter 2 (SGLT2) inhibitors, a novel class of antidiabetic drugs, in patients with heart failure (HF), with either reduced ejection fraction or preserved ejection fraction. Of note, these positive outcomes are irrespective of the diabetic status and with rapid onset, suggesting the clinical benefits of SGLT2 inhibition are not fully attributable to glycemic control. Based on various experimental studies, a substantial number of hypotheses have been proposed to explain the beneficial effects of SGLT2 inhibition in HF. These effects can be divided into two groups: indirect systemic effects and direct myocardial effects (Figure 1).

Potential indirect systemic effects include but are not limited to the following:

1) Natriuresis and diuresis induce blood pressure-lowering effects with subsequent reductions in preload and afterload (potentially occurring via lowering of arterial pressure and stiffness), favorably altering ventricular loading conditions. Importantly, natriuresis and diuresis, induced by SGLT2 inhibition, are not associated with a compensatory activation of the renin-angiotensin-aldosterone system.
2) Prevention of cardiac remodeling and associated cardiac fibrosis (a feature of HF), probably owing to systemic hemodynamic and metabolic effects
3) Improvement in endothelial dysfunction and vascular stiffness
4) Increased hematopoiesis with an increase in hematocrit due to enhanced erythropoietin (EPO) production, resulting from improved renal function by SGLT2 inhibition. The increased hematocrit and EPO might exert beneficial effects on mitochondrial function in cardiomyocytes, angiogenesis, and oxygen delivery to the myocardial tissue.
5) Inhibition of sympathetic nervous system activity, which is postulated to be secondary to attenuated renal "stress"
6) Increased circulating proangiogenic progenitor cells
7) Suppression of advanced glycation end-products, which may contribute to improve vascular dysfunction, prevent progressive atherosclerosis, and reduce inflammation
8) Glucosuria improves glucose control and results in body weight and epicardial fat loss, as well as an overall metabolic shift from glucose to ketone body metabolism (specifically increases in β-hydroxybutyrate production).
9) Lowering of uric acid levels

All of these changes contribute to improve cardiac energetics and efficiency, oxidative stress, and inflammation.

Potential direct myocardial effects include but are not limited to the following:

1) Direct inhibition of the cardiac sodium/hydrogen exchanger isoform 1 (NHE1), which alters intracellular Na^+ and Ca^{2+} handling, leading to attenuation of cardiac injury, hypertrophy, and systolic dysfunction. However, whether NHE1 inhibition plays a role in

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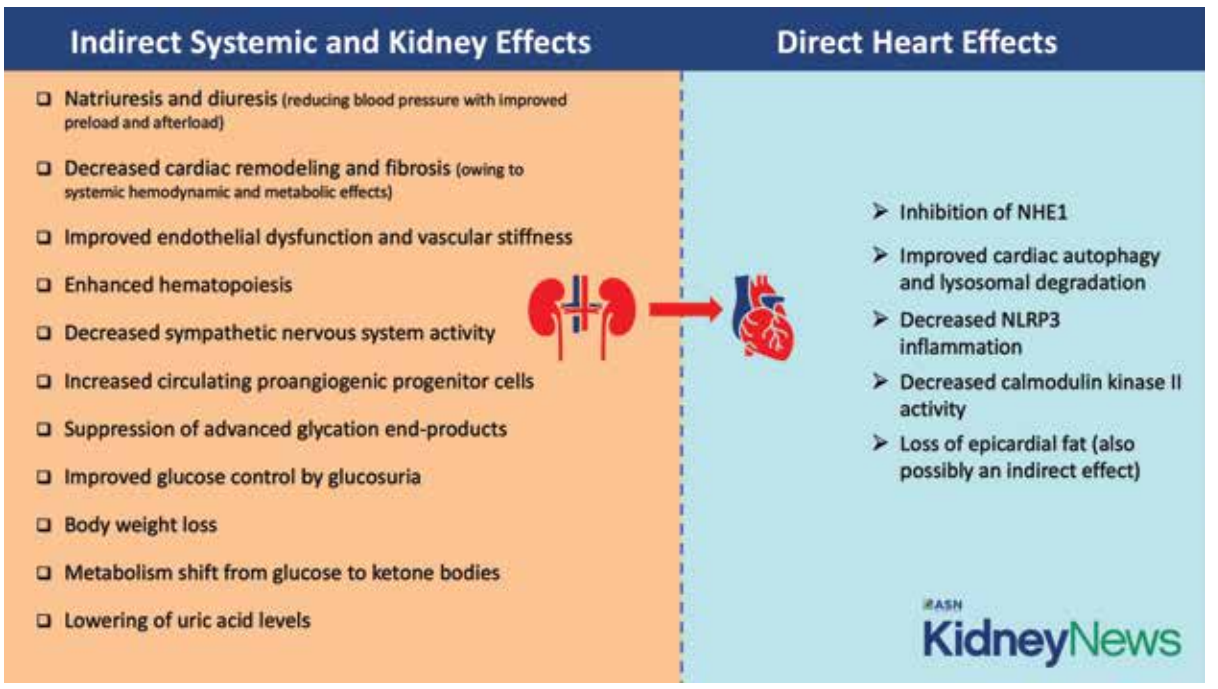
Figure 1. Beneficial effects of SGLT2 inhibition in heart failure



Mechanism of Heart Protection by SGLT2 Inhibitors, Direct and Indirect Effects

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cardiovascular protection by SGLT2 inhibitors is still controversial, and conflicting results have been reported in the literature.

2) Improved cardiac autophagy and lysosomal degradation
3) Inhibition of the nucleotide-binding oligomerization domain, leucine-rich repeat, and pyrin domain-containing 3 (NLRP3) inflammasome
4) A decrease in calmodulin kinase II activity, resulting in improved sarcoplasmic reticulum Ca^{2+} flux and increased contractility

It is clear that none of the aforementioned mechanisms can solely explain the clinical benefits of SGLT2 inhibitors in HF, and all possible mechanisms may play a role at one point or another during the treatment of the disease. Although most of these mechanisms are closely interrelated, it is conceivable that the effects on the kidneys are predominating, and cardiovascular benefits are secondary to this. Consistent with this theory, various clinical trials show that worsening of renal function is associated with a higher risk of both hospitalization for HF (hHF) and atherothrombotic events, and the reduction in hHF by SGLT2 inhibition is greater in patients with lower baseline renal function. These observations support that the reduction in hHF is more likely due to SGLT2 inhibitor-mediated kidney protection.

Although current clinical trials give positive outcomes supporting the efficacy of SGLT2 inhibitors in the prevention of HF, the outcomes do not necessarily translate to efficacy in treatment of HF. It is encouraging that the US Food and Drug Administration just approved empagliflozin (Jardiance®) as a treatment option for a wider range of patients with HF. However, it remains to be determined if these are class effects of SGLT2 inhibitors. ■

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The authors report no conflicts of interest.

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Xenotransplantation: No Longer Just the Future of Transplantation?

By Seth J. Karp

The old tongue-in-cheek maxim that xenotransplantation is, and always will be, the future of transplantation is under withering attack. Three reports within the past few months—one published in a scientific journal (1) and two in the lay press—suggest xenotransplantation success may be at hand. First, a little history.

Xenotransplantation promises an unlimited supply of organs. Conceptually straightforward, the details turn out to be critically important. First attempts at xenotransplantation using pigs were unsuccessful due to, among other issues, the Galα1,3Gal (Gal) epitope on the vascular epithelium. These epitopes induced refractory rejection, leading to organ loss in transplant models. Advances in genetic modification technologies allowed this major hurdle to be surmounted in 2005 with four reports that organs from knockout pigs lacking Gal epitopes did not experience acute or hyperacute rejection in primate models (2–5). Add additional genetic modifications and about 15 years, and the technology has now been brought into humans.

The first publication in a scientific journal reported transplanting pig organs into humans. The study comes from the University of Alabama, where pig kidneys, produced by the company Revivicor, were transplanted into a patient who was declared brain dead (1). Kidney function was not recovered; however, the kidneys did not experience acute or hyperacute rejection, although the vascular lesions were potentially concerning. In a similar scenario, a kidney from a pig was transplanted into a patient with a nonfunctioning brain in New York, and finally and perhaps most excitingly, a pig heart was successfully transplanted into a living human recipient in Maryland and demonstrated function. As of this writing, these last two reports have not been published, and the patient who received the pig heart died a few months after the transplant.

This is incredibly exciting. What happens next? Two major lines of investigation for each type of organ are the following:

1) Immunologic: What immunologic issues accompany the use of pig organs? What are the optimal immunosuppressive regimens? What is the nature of rejection, and how is it treated? Are these organs subject to chronic rejection, and can this be avoided? What additional genetic modifications could improve immunocompatibility?
2) Function: Do pig organs faithfully reproduce the function of the corresponding human organ? In particular for the kidneys, will the higher human blood pressure be an issue in the short or long term? Will filtering and other kidney function be appropriate?

Pig organs may have initial difficulty with any of these issues. Even so, the transplant community supports a deep culture of scientific investigation and innovation. Combined with recent major advances in genetic manipulation, it is reasonable to assume that these hurdles will be overcome over time. Concerns about transplantation-mediated zoonoses (e.g., pig viruses) will remain, and these will need to be assiduously monitored. When the recent studies were reported in major media outlets, comment sections were filled with objections to using pigs as organ farms from an animal rights perspective. These concerns will similarly need to be addressed.

The history of transplantation encompasses a series of major breakthroughs, leading to initially limited benefits, followed by continual improvements producing the reliable, outstanding life-saving therapies we have today. The last few months represent one of these major breakthroughs. There is every reason to believe iterations on this achievement will bring xenotransplantation into the mainstream. ■

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The author reports no conflicts of interest.

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The Kidney Precision Medicine Project (KPMP)
An Update and Vision for the Future

By Steven Menez, Ashveena L. Dighe, and Ian H. de Boer, for the Kidney Precision Medicine Project

The Kidney Precision Medicine Project (KPMP) is a National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)-funded, multi-year collaboration of leading research institutions across the United States that aims to better understand the mechanisms of acute kidney injury (AKI) and chronic kidney disease (CKD) (1).

Our understanding of the pathophysiology of certain kidney diseases has improved dramatically in recent years, with discovery of the genetic mechanisms behind phenotypes, such as non-diabetic focal segmental glomerular sclerosis in patients with high-risk APOL1 genotypes (2). However, CKD and, in particular, AKI are defined broadly using serum creatinine and urine output, which in the acute setting, can be highly inaccurate and imprecise. Therefore, the major goals of KPMP have been to collect research kidney biopsies in an ethical manner from consented individuals with AKI and CKD to achieve the following: 1) create a kidney tissue atlas, 2) define new disease subgroups, and 3) identify new therapeutic targets and pathways of kidney diseases.

The KPMP consortium consists of 1) a central hub that manages study organization, data collection, and data visualization center; 2) clinical sites that prospectively recruit eligible participants with CKD or AKI; and 3) tissue interrogation sites that apply various omics technologies to kidney tissue to construct a comprehensive kidney tissue atlas. Patients with kidney diseases inform and contribute to all aspects of KPMP, including study design, leadership, and dissemination.

Beginning in 2017, the primary aim of the first phase of KPMP was to establish an ethical and safe clinical protocol for collection of biosamples (including kidney tissue, urine, and blood), with optimization and validation of tissue processing, including rigorous quality control (3, 4). Eligible participants have been recruited from three AKI recruitment sites (Columbia University, University of Pittsburgh, and Johns Hopkins-Yale Universities) and three CKD recruitment sites (Cleveland Clinic, University of Texas Southwestern, and Brigham and Women's Hospital-Boston University-Joslin Diabetes Center-Beth Israel Deaconess Medical Center). Biosamples obtained at these various recruitment sites are transferred to the KPMP central biorepository and then sent to tissue interrogation sites for next-generation sequencing, three-dimensional (3D) tissue imaging and cytometry (fluorescence imaging), proteomics, spatial metabolomics, and other advanced technologies (see https://www.kpmp.org/help-docs/technologies). Data are then centrally integrated, standardized, and validated before being added to the ever-growing open-access kidney tissue atlas (see atlas.kpmp.org).

KPMP remains committed to new avenues for scientific discovery, with Opportunity Pool funding available for research groups interested in joining KPMP (see https://www.kpmp.org/opportunity-pool). These have included additional new technologies, enhanced clinical phenotyping (advanced retinal imaging, functional magnetic resonance imaging [MRI], and kidney functional reserve), recruitment of healthy individuals for reference tissue, and a sub-study, enrolling adults hospitalized with COVID-19.

As of March 10, 2022, 150 participants (32 with AKI, 95 with CKD, and 23 healthy volunteers who were donating a kidney or undergoing kidney stone surgery) have consented to participate and have undergone the protocol KPMP kidney biopsy. An additional 89 participants have been enrolled in the COVID-19 blood and urine collection study. KPMP pathology has been remarkably heterogenous, even within groups of patients with "common" presentations of AKI or CKD. Individual clinical-pathological-molecular case evaluations have demonstrated proof of concept that detailed omics interrogation of kidney tissue can add value to traditional pathology (5), data from the kidney atlas have been used to enhance the interpretation of novel biomarker studies (6, 7), and systems biology analyses have generated initial versions of a kidney atlas (8, 9).

KPMP will embark on its second 5 years of activity from 2022 to 2027. During this next phase, both enrollment and tissue interrogation will be scaled up. Based on our participants' generous contributions, KPMP is poised to continue scientific discovery in both AKI and CKD, with further enrichment of the kidney tissue atlas—a publicly available resource (atlas.kpmp.org) where researchers and clinicians can explore many of the findings generated through this consortium (Figure 1). ■

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Dr. de Boer reports consulting for AztraZeneca, Bayer, Boehringer Ingelheim, Cyclerion Therapeutics, George Clinical, Gilead Sciences, Goldfinch Bio, and Ironwood Pharmaceuticals. The other authors report no conflicts of interest.

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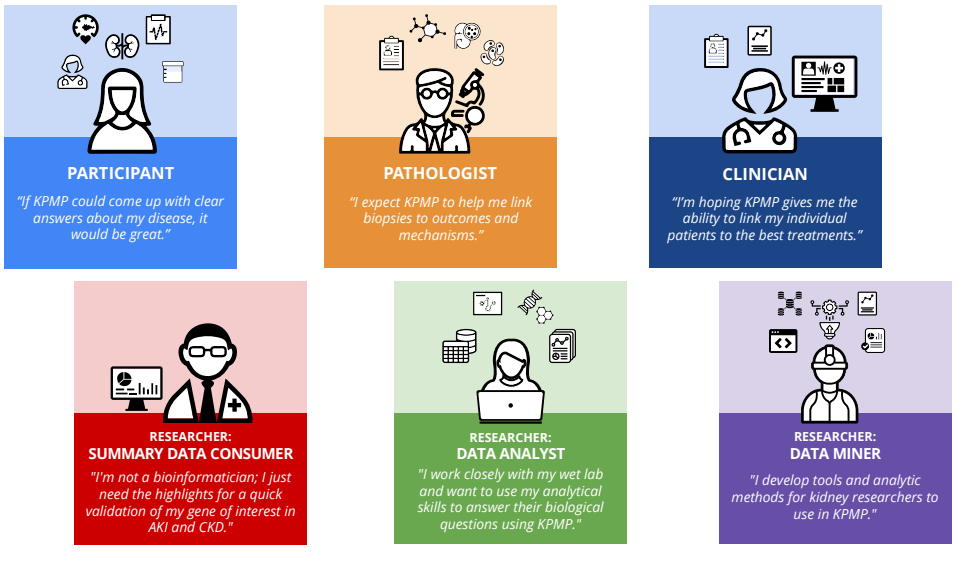
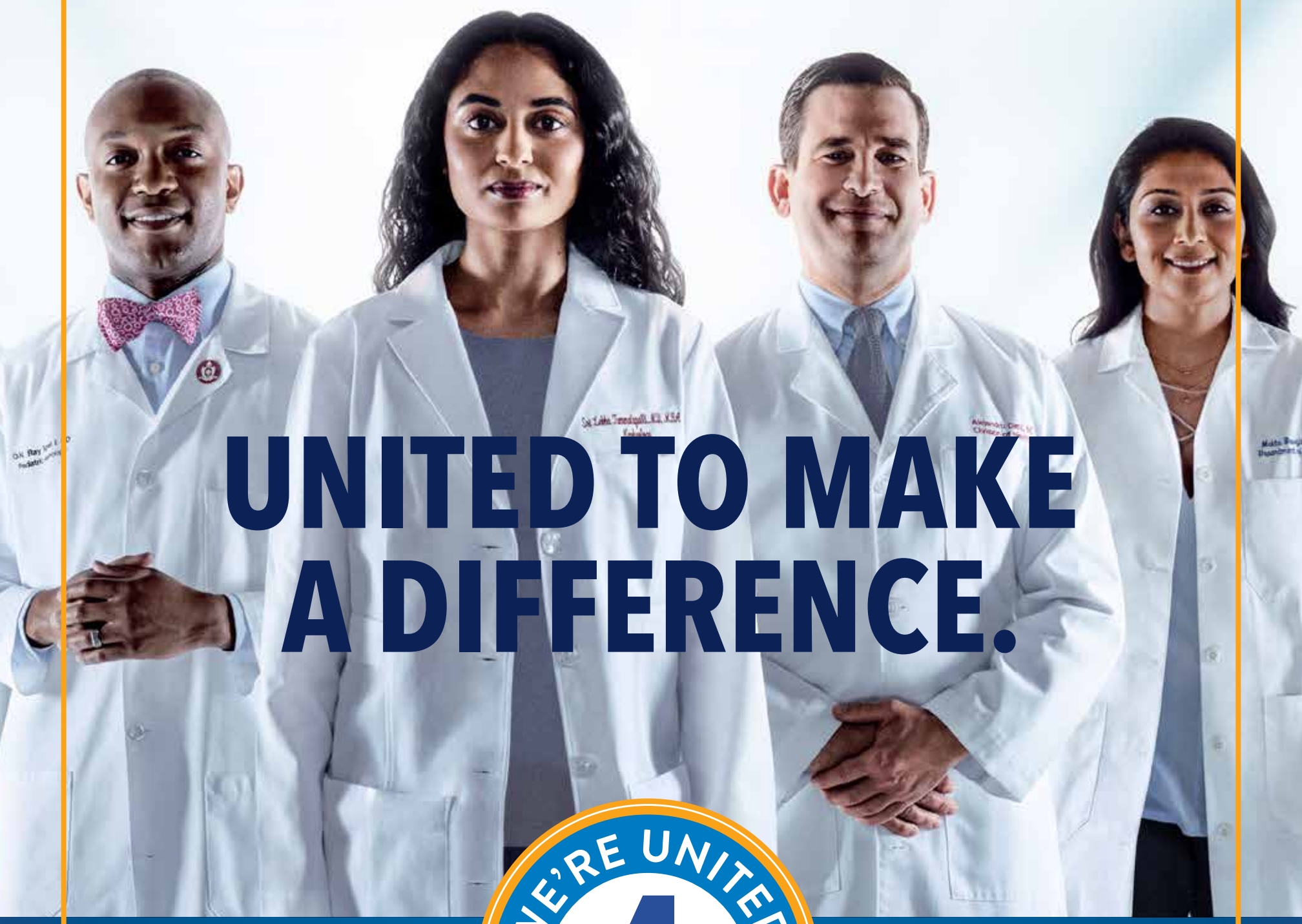
Figure 1. The KPMP is designed to support a wide variety of stakeholders interested in advancing kidney medicine



The Kidney Precision Medicine Project (KPMP) is designed to provide unique granular data on chronic kidney disease (CKD) and acute kidney injury (AKI) for a diverse range of users. Clinical data from participants with CKD or AKI and healthy volunteers, along with kidney pathology and molecular data generated by a wealth of cutting-edge technologies, are openly available at kpmp.org.



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Hypertension in Pregnancy: Diagnosis, Blood Pressure Goals, and Pharmacotherapy: A Scientific Statement from the American Heart Association

By Priti Meena and Silvi Shah

The American Heart Association (AHA) recently published a scientific statement on the diagnosis, blood pressure goals, and pharmacotherapy of hypertension in pregnancy (1). Although hypertensive disorders of pregnancy are associated with high maternal and fetal mortality and morbidity (Figures 1 and 2), little has changed in their diagnosis and treatment in the United States over the past decades. Hypertension in pregnancy continues to be defined as blood pressure ≥140/90 mm Hg by most societies, including the International Society for the Study of Hypertension in Pregnancy (ISSHP), despite lowering the threshold in the general population to 130/80 mm Hg for the diagnosis of stage 1 hypertension by the joint American College of Cardiology (ACC)/AHA guidelines in 2017 (2, 3). The AHA scientific statement on hypertension in pregnancy is timely and much needed, especially with the increasing incidence of women with hypertensive disorders of pregnancy, its associated higher immediate and long-term cardiovascular risks, and variability in anti-hypertensive treatment thresholds—blood pressure ≥160/110 mm Hg by the American College of Obstetricians and Gynecologists (ACOG) and blood pressure ≥140/90 mm Hg by other societies, such as ISSHP (1). Hypertensive disorders of pregnancy are a heterogenous disease, based on their distinct clinical presentations and unique pathological mechanisms, and are classified into chronic hypertension, gestational hypertension, preeclampsia/eclampsia, and preeclampsia superimposed on chronic hypertension (4).

However, there is no clear consensus about the threshold blood pressure for initiating therapy and target blood pressure for titrating anti-hypertensive therapy. The new AHA scientific statement summarizes and synthesizes the various recommendations without endorsing any one in particular. Although the ACOG guidelines recommend initiating anti-hypertensive therapy at a systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥110 mm Hg, with a treatment goal of 120–160 mm Hg systolic/80–110 mm Hg diastolic, most other hypertension societies, such as ISSHP and the National Institute for Health and Care Excellence (NICE), endorse a more aggressive approach and recommend anti-hypertensive therapy when blood pressure is ≥140/90 mm Hg (5, 6). It is arguable that aggressive blood pressure control reduces the risk of severe hypertension and neurological complication of preeclampsia, such as intracerebral hemorrhage in the mother, and may permit prolongation of pregnancies, thereby reducing preterm births. Furthermore, strict blood pressure control may be particularly important for women with multiple pregnancies, who spend several years of their lives being pregnant with uncontrolled hypertension. It is well known that hypertension in pregnancy increases the risk of immediate and postpartum complications, such as acute cardiovascular and cerebrovascular diseases.

Nevertheless, the conclusive evidence regarding the benefits of treating non-severe hypertension for the short duration of pregnancy to prevent maternal morbidity in young women without cardiovascular disease risk is lacking, which may explain the higher blood pressure target threshold by ACOG. Moreover, with aggressive maternal blood pressure control, there are concerns of potential fetal risks due to reductions in utero-placental circulation and in utero exposure to anti-hypertensive medications. Therefore, while awaiting more conclusive data, the AHA scientific statement currently endorses shared, informed decision-making with patients regarding whether similar blood pressure targets recommended outside of pregnancy would be beneficial and safe for the mother and fetus, with attention to risk factors, including preexisting heart or kidney diseases or individuals of Black race and vulnerable ethnicity and with obesity (1).

With the emerging evidence that tighter blood pressure control during pregnancy reduces the risk of severe hypertension without increasing the risk of pregnancy loss and the increasing recognition of morbidity associated with postpartum hypertension and preeclampsia, we recommend lowering blood pressure targets for women with preexisting kidney diseases and initiating anti-hypertensive therapy when the blood pressure is ≥140/90 mm Hg. Nifedipine and labetalol remain widely used first-line drugs for effective treatment. It may also be appropriate to lower the blood pressure threshold for the diagnosis of hypertensive disorders of pregnancies to systolic ≥130 mm Hg or diastolic ≥80 mm Hg, which may better identify women at risk for developing preeclampsia and adverse pregnancy outcomes (7). Lastly, to give optimal care to women with kidney diseases and hypertensive disorders of pregnancy, close collaboration is needed among nephrologists, internists, and obstetrics and gynecology specialists.

In conclusion, there remains a pressing need for evidence-based consensus on a global level for the diagnostic and treatment thresholds for hypertensive disorders of pregnancy. Future research and guidelines should emphasize long-term cardiovascular and kidney diseases risk assessment to further improve women's health during and after pregnancy. ■

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Figure 1. Maternal complications of hypertensive disorders of pregnancy

Short term	Long term
• Mortality	• Hypertension and diabetes mellitus
• Myocardial infarction	• Hyperlipidemia
• Stroke	• Stroke and vascular dementia
• Peripartum cardiomyopathy	• Atrial fibrillation and venous thromboembolism
• Spontaneous coronary artery dissection	• Chronic kidney disease and kidney failure
• Postpartum hemorrhage and placental abruption	• Cardiovascular diseases

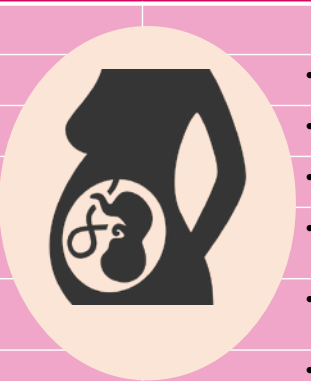


Figure 2. Fetal complications of hypertensive disorders of pregnancy

Short term	Long term
• Small for gestational age	• Cardiovascular disease
• Stillbirth	• Stroke
• Preterm delivery	• Hypertension
	• Higher body mass index

Kidney Health Advocacy Day Advances Key ASN Legislative Priorities

The American Society of Nephrology (ASN) and the American Association of Kidney Patients (AAKP) partnered together for the 10th Annual Kidney Health Advocacy Day on March 23. Advocates from both organizations met virtually with representatives, senators, and their respective staffs to urge Congress to support key legislative priorities including the following:

- supporting kidney health research at the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK),
- funding kidney health innovation for Kidney Innovation Accelerator (KidneyX), and
- protecting living donors to increase organs available for transplant.

Kidney research leads to the discovery of new methods to detect kidney diseases, and an early diagnosis can allow those at risk to be educated on how to slow disease progression and help prevent costly kidney failure requiring dialysis or transplant. Kidney advocates called on Congress to champion a funding increase of no less than $285 million for NIDDK in fiscal year (FY) 2023, which would enable NIDDK to fulfill its mission to conduct and support medical research and research training, to disseminate science-based information on kidneys, and to support the institute's multi-pronged efforts toward the goal of health equity.

Advocates also requested that Congress increase its support for innovation in the prevention, diagnosis, and treatment of kidney diseases by providing $25 million for KidneyX in FY 2023. KidneyX has, so far, received $15 million in federal funding, having most recently received $5 million in FY 2022. Increasing funding by matching ASN's initial $25 million commitment to KidneyX will allow the program to increase the support provided to innovators competing in the current Artificial Kidney Prize competition, as well as invest in other areas of kidney health in need of innovation, such as improving the prevention and diagnosis of kidney diseases.

Lastly, advocates urged Congress to establish protections for living donors, principles laid out in legislation, such as the Living Donor Protection Act (LDPA). A longstanding advocacy priority of ASN and the broader kidney health community, the LDPA guarantees that living donors have access to life, disability, and long-term care insurance with full coverage, without higher premiums, and regardless of insurance status at the time of donation and codifies that the Family and Medical Leave Act protects the employment of living donors after taking time off to donate an organ.

Currently, as many as one in four living donors reports significant difficulty in obtaining life, disability, and long-term care insurance, and fear of a loss of employment after donating an organ is commonly expressed by living donors. The removal of these barriers to living donation is a critical first step to increasing the number of organs available for transplantation. Long-time kidney champions and co-sponsors of the legislation, Sen. Gillibrand, Sen. Cotton, Rep. Nadler, and Rep. Herrera Beutler, are finalizing the text of the legislation, which kidney community stakeholders stand ready to enact into law.

"Vocal constituents are essential in creating meaningful, person-centered policy," said Zachary Kribs, ASN Senior Government Affairs Specialist. "The ASN and AAKP members volunteering to meet with their Congressional delegation help each office gain a better understanding of the current state of kidney care, research, innovation, and are the most important way members of Congress are motivated to create a policy ecosystem that fosters kidney health."

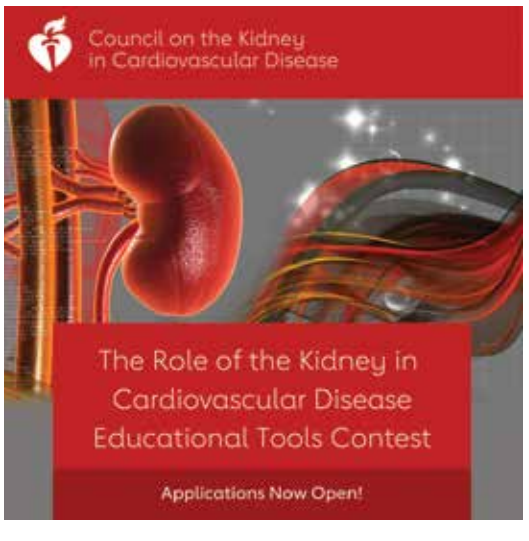
ASN will build on the momentum of Kidney Health Advocacy Day by continuing to collaborate with the kidney health and transplant community to advance key 2022 legislative priorities. Updates on progress made throughout the year will be provided in subsequent issues of *Kidney News* and in real time via @ASNAdvocacy on Twitter. ■

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

By Matthew A. Sparks, MD, on behalf of the AHA KCVD Council

Inspired by the success of the ASN Innovations in Kidney Education Contest, the American Heart Association (AHA) Council on the Kidney in Cardiovascular Disease (KCVD) is launching a contest to promote educational tools spanning heart disease and kidney diseases. Although the role of the kidney in cardiovascular disease (CVD) is widely recognized among nephrologists, there is a paucity of education about this among primary care practitioners, during medical school, and in residency training. Whereas novel therapies are continuing to be developed (sodium glucose co-transporter 2 [SGLT2] inhibitors, for example), it is imperative to develop new teaching tools that can be 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 that chronic kidney disease portends to CVD. The following are contest requirements:



- The teaching tool must enhance the learner's understanding of kidney disease 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 post-doc); faculty; practicing physicians; researchers; or other health professionals. Each member of the team can only be involved in one submission. A corresponding member must be denoted.

Applications are due June 9, 2022; 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 cardiovascular disease 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 Council on the Kidney in Cardiovascular Disease will publicize the tool.
- Winners will be announced at AHA Scientific Sessions 2022.
- The tool will be linked on the AHA website with a description.
- Each winner will make a video describing the tool. ■

Matthew A. Sparks, MD, is Associate Professor of Medicine; Program Director of Nephrology Fellowship; and Lead, Society for Early Education Scholars (SEEDS) program, Department of Medicine, Duke University, and Staff Physician, Durham VA Health Care System, Durham, NC.

Dr. Sparks is past chair of the AHA KCVD Council on Scientific and Clinical Education Lifelong Learning (SCILL) Committee.

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