ASN American Society of Nephrology

KidneyNews

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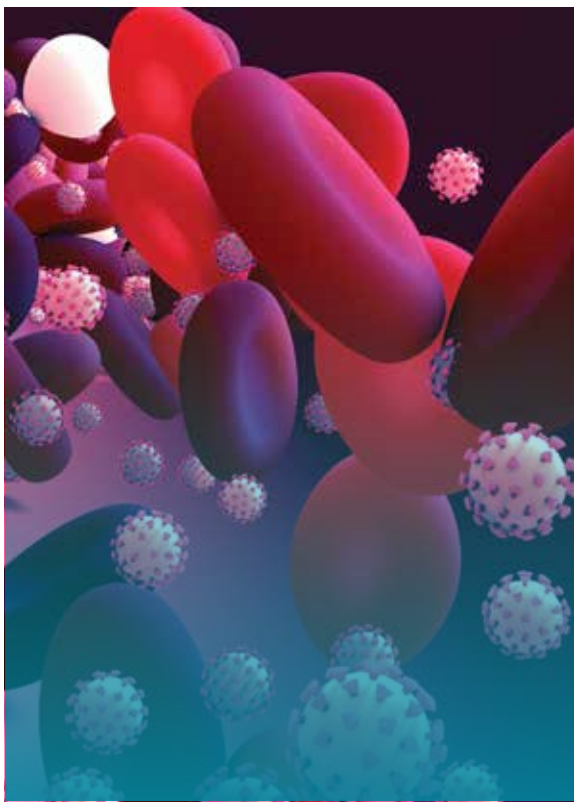
After COVID-19, Dialysis Patients Maintain Immune Response for at Least Six Months, Researchers Find



Most dialysis patients who have been infected with SARS-CoV-2 maintain protective antibody levels over 6 months' follow-up, including subgroups at risk of impaired immunity, reports a study in *Annals of Internal Medicine* (1).

The study investigators used remainder plasma samples from 2215 hemodialysis patients from 1200 dialysis facilities across the United States. Fifty-three percent of patients lived in majority-minority neighborhoods and 44% in low-income neighborhoods (at least 20% below the federal poverty level).

All samples included in the study were positive for SARS-CoV-2 receptor-binding domain (RBD) total antibodies, tested using the highly sensitive and specific Siemens semiquantitative assay in July 2020. Follow-up samples from routine monthly laboratory tests were used to monitor RBD immunoglobulin G (IgG) index values over 6 months. Persistence of RBD antibodies was assessed, including analysis by antibody response level, age, race/ethnicity, and diabetes status.

Ninety-three percent of patients had a detectable response, defined as an IgG index value of 1 or greater. In July 2020, 60% of patients had high IgG index values (10 or greater). About three-fourths of patients in this group continued to have high index levels throughout follow-up.

Follow-up samples for these individuals showed a "small and continuous decline" in RBD IgG levels. Adjusted median values fell from 21 in July 2020 to 13 in December 2020. This pattern was consistent in subgroups defined by age, sex, race/ethnicity, and diabetes status. Patients with consistently undetectable antibody responses were more likely to be White, to be in the younger (18 to 44 years) or older (over 80 years) age groups, and to have diabetes and hypoalbuminemia.

"Our study is the largest to describe longitudinal humoral response in a population that reflects groups most affected by SARS-CoV-2 infection," the researchers write. They note some important limitations, including the lack of data on symptoms or reverse transcription-polymerase chain reaction testing. The study was also limited to patients who survived COVID-19.

The findings suggest that nearly all seroprevalent dialysis patients have a detectable RBD IgG response through at least 6 months' follow-up. There is no indication of shorter-lived antibody responses among subgroups at highest risk of impaired immunity, such as older adults or those with diabetes. The investigators conclude, "Our study...provides a benchmark for clinicians and re-

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Naming and Eliminating Systemic and Institutional Racism in Nephrology Training

By Abinet Aklilu, Jason Cobb, Javier A. Neyra, and Nimrit Goraya

There is no better time than now to start naming and eliminating systemic and institutional racism in nephrology training. Public displays of racial injustice recently captured on traditional and social media have finally brought attention to racism and racial disparities in various sectors of our community including healthcare and medical education. The impact of racism extends to our patients in the form of poor access to care and inadequate care delivery, often due to unconscious biases that lead to perpetuation of mistrust and unjust inequitable care (1). And these gaps in care were further exposed in the current pandemic (2, 3).

The landscape of racial diversity in nephrology has shown no significant growth over the past 20 years (4, 5). In 2000, 4.6% of trainees identified as Black (6). In 2010, the combined percentage of underrepresented minorities (URMs) in nephrology including Black, American Indian/Alaska Native, or Native Hawaiian/Pacific Islander was 6%, and 6.9% were Hispanic (7). This remained unchanged in 2020, during which 4.6% of nephrology trainees, 4.7% internal medi-

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Inside

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After COVID-19

Continued from page 1

searchers assessing humoral response after infection or vaccination in susceptible populations."

Reference

1. Anand S, et al. Serial SARS-CoV-2 receptor-binding domain antibody responses in patients receiving dialysis. *Ann Intern Med* [published online ahead of print May 18, 2021]. doi: 10.7326/M21-0256; https://www.acpjournals.org/doi/10.7326/M21-0256

Systemic and Institutional Racism

Continued from page 1

cine (IM) residents, and 7.6% medical students identified as Black; 7% of nephrology trainees, 6.7% of IM residents, and 6.7% of medical students identified as Hispanic; and American Indian/Alaska Native or Native Hawaiian/Pacific Islanders make up <1% of trainees at all levels (8, 9).

The training program director (TPD) and associate PD (APD) positions of nephrology fellowship programs mirror these trends. In 2020–2021, only 1.4% of the TPDs, 6.4% of APDs, and 3.7% of division directors are Black. Similarly, 4.1% of TPDs, 4.6% of APDs, and 2.7% of division directors are Hispanic (10). Perhaps this is not surprising, as 3.6% of full-time medical school faculty in 2018 were Black, and 5.5% were Hispanic (11). Minorities are highly underrepresented in our field and are out of proportion to the makeup of the US population despite the disproportionately higher adjusted prevalence of end-stage kidney disease (ESKD) in minorities and despite evidence suggesting improved patient satisfaction and outcomes with race-concordant patient-provider encounters (12, 13).

In our efforts toward building a culturally competent nephrology community, training programs play a crucial role (Table 1).

Prior to proposing potential options, we first revisit the concept of institutional racism, which was coined by Stokely Carmichael in the 1960s. This theory brought to light the more pervasive type of racism that is tough to eradicate and represents a constellation of societal factors ingrained into the fabric of our systems and culture that are downstream effects of slavery and segregation and create disadvantages and hurdles on an individual's journey through life, work, and education because of their race.

Understanding the meaning and impact of institutional racism in the United States requires a reflection on the well-recognized downstream effects of 4 centuries of oppression of individuals as slaves, disparities in access to healthcare and education that result from segregation, and the unconscious biases people tend to harbor toward the unknown. Unconscious bias affects one's interaction with other individuals who are of a different background and influences decisions made about them. As humans first and physicians second, we are all prone to make assumptions about individuals that are often inaccurate and make impactful decisions based on those assumptions (14). In clinical practices, this can cause us to disqualify people from potentially life-prolonging treatment. In medical education, unconscious bias affects ranking and recruitment at all levels.

Diversity in leadership impacts diversity down to the training level. For example, lack of diversity in nephrology division leadership can affect representation in training program leadership, which can impact URMs in nephrology fellowship. The lack of diversity in their clinical learning environment (CLE) can negatively influence URM medical students and residents about choosing nephrology as a career path. Racism can be pervasive in our recruitment efforts, as unconscious biases can influence who we invite for nephrology fellowship interviews. Once applicants are invited, our biases can influence our applicant rankings, as rigid interview assessments can potentially be unfair to URM applicants. In addition, URM nephrology fellows can be impacted by an exclusive CLE where isolation and a lack of social support can affect fellow performance. Unconscious biases can negatively impact evaluations of URM nephrology fellows. The Accreditation Council for Graduate Medical Education (ACGME) has mandated efforts in diversity and teaching learners about healthcare disparities (14, 15).

Training programs have an important role in mitigating institutional racism, as they can build a culturally competent workforce through unconscious bias training, discussions, inviting experts in the area, and diversifying the workforce. Destigmatizing bias, recognizing it as a natural response we have, and focusing on strategies to recognize it and keep it in check are first steps. As such, the road to achieving cultural competency starts with cultural humility—a lifelong commitment to self-evaluation, i.e., acknowledging one may not fully understand another individual's background and challenges but is open to explore and learn to impact care of the underserved community (14, 16).

ASN's Diversity, Equity, and Inclusion and Workforce and Training Committees have collaborated to create dialogue and constructive programs that can impact racism in nephrology training. ASN's Town Hall, "Addressing Racism in Kidney Care and Training," held in March 2021, was the first of its kind and a step forward. Racial disparities in the workforce were highlighted, and a new URM pipeline program has been proposed to promote recruitment into the field at the grassroots level (3). The Kidney Mentoring and Awareness Program for Students (MAPS) was sponsored by the ASN Workforce Committee from 2013 to 2015, and the society continues to provide resources for institutions that wish to start their own chapter. Currently, the Tutored Research and Education

for Kidney Scholars (TREKS) program at the University of Chicago has a disparities and outreach module. In addition, there are plans to provide educational resources including unconscious bias training with nephrology-specific clinical vignettes that can be used to train decision-makers, including division leadership and interviewers of nephrology fellowship applicants. Furthermore, the production of a report providing statistics on racial disparities in nephrology on all levels, including leadership, workforce, training programs, and patients, is expected.

To ensure accountability in the efforts toward building a more diverse workforce at all levels of training and leadership, we also propose a metric of performance: a diversity score. The aim of this score is for nephrology divisions to self-evaluate and reflect on areas of improvement. Although it is encouraging to see this topic start to gain the attention it deserves, it will take time to see improvement up to the leadership level. It is time to come together and put an end to institutional racism in nephrology training and build a culturally competent community to ensure equitable care—an individualized but unbiased care.

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The authors are current members of the ASN Diversity, Equity, and Inclusion Committee. There are no other conflicts of interest to disclose.

Table 1. Top 5 suggestions for training programs

1. Training
- Incorporating health equity and cultural competency training into the education curriculum
- Implementing unconscious bias training
- Inviting speakers with expertise in health equity and cultural competency
- Providing self-evaluation tools (proposed diversity score)
- Providing and nurturing a safe space for sharing experiences
- Bringing students, residents, and fellows to the discussion table (i.e., diversity and inclusion, recruitment, quality improvement, clinical competency committees)

2. Workforce
- Providing scheduled platforms for discussion, self-reflection, and brainstorming
- Inviting health equity champions including those from other specialties
- Providing self-assessment tools
- Creating health diversity, equity, and inclusion leadership positions within nephrology divisions

3. Recruitment
- Advocating for less stringent test score criteria for otherwise deserving applicants
- Opening doors for international medical graduates
- Presenting incentives to retain fellows of URM backgrounds as faculty including providing access to research grants to deserving fellows

4. Research and advocacy
- Focusing on data-driven care and encouraging research
- Arranging quality improvement projects and community work
- Collaborating with other departments such as public health, global health
- Creating a Research Oversight Committee looking into appropriate representation in research studies

5. Mentorship
- Providing opportunities to mentor undergraduate or medical students from different backgrounds
- Linking fellows with former graduates of URM background
- Expanding kidney MAPS and proposing URM pipeline program for mentoring and recruiting URM students and residents into nephrology training programs

References

1. Norton JM, et al. Social determinants of racial disparities in CKD. *J Am Soc Nephrol* 2016; 27:2576–2595. doi: 10.1681/ASN.2016010027
2. Kim D, et al. Racial and ethnic disparities in excess deaths among persons with kidney failure during the COVID-19 pandemic, March–July 2020. A*m J Kidney Dis* 2021; 77:827–829. doi: 10.1053/j.ajkd.2021.02.003
3. Bayliss GP, et al. Kidney mentoring and assessment program for students: A guide for engaging medical students in nephrology. *Clin Kidney J* 2019; 12:761–766. doi: 10.1093/ckj/sfz108
4. Lederer E, Lebowitz J. Current state of the workforce in nephrology. *Adv Chronic Kidney Dis* 2020; 27:281–290. e1. doi: 10.1053/j.ackd.2020.07.007
5. Rosenberg ME. Adult nephrology fellowship training in the United States: Trends and issues. *J Am Soc Nephrol* 2007; 18:1027–1033. doi: https://doi.org/10.1681/ASN.2006101169
6. Chavon O, et al. Race disparities in U.S. nephrology fellowship training. *Clin J Am Soc Nephrol* 2011; 6:390–394. doi: 10.2215/CJN.04450510
7. Brotherton SE, Etzel SI. Graduate medical education, 2010–2011. *JAMA* 2011; 306:1015–1030. doi: 10.1001/jama.2011.1236
8. Brotherton SE, Etzel SI. Graduate medical education, 2019–2020. *JAMA* 2020; 324:1230–1250. doi:10.1001/jama.2020.14635
9. Association of American Medical Colleges. Diversity in Medicine: Facts and figures 2019. Executive Summary. 2019. www.aamc.org/data-reports/workforce/report/diversity-medicine-facts-and-figures-2019
10. ASN, personal communication, March 2021.
11. Association of American Medical Colleges. Table B5. Number of active MD residents, by race/ethnicity (alone or in combination) and GME specialty. 2020. www.aamc.org/data-reports/students-residents/interactive-data/report-residents/2020/table-b5-md-residents-race-ethnicity-and-specialty
12. Johansen KL, et al. US Renal Data System 2020 Annual Data Report: Epidemiology of Kidney Disease in the United States. *Am J Kidney Dis* 2021; 77 (4 Suppl 1):A7–A8. doi: 10.1053/j.ajkd.2021.01.002
13. Cooper LA, Powe NR. Disparities in patient experiences, health care processes, and outcomes: The role of patient-provider racial, ethnic, and language concordance. The Commonwealth Fund. July 2004. https://collections.nlm.nih.gov/master/borndig/101669869/Disparities%20in%20patient%20experiences%20health%20care%20processes%20and%20outcomes.pdf
14. Casey BR, et al. Role of the clinical learning environment in preparing new clinicians to engage in quality improvement efforts to eliminate health care disparities. *Am J Health Syst Pharm* 2020; 77:39–46. doi: 10.1093/ajhp/zxz251
15. Accreditation Council for Graduate Medical Education. ACGME program requirements for graduate medical education in nephrology. July 1, 2020. www.acgme.org/Portals/0/PFAssets/ProgramRequirements/148_Nephrology_2020.pdf?ver=2020-06-29-162357-583
16. Tervalon M, Murray-García J. Cultural humility versus cultural competence: A critical distinction in defining physician training outcomes in multicultural education. *J Health Care Poor Underserved* 1998; 9:117–125. doi: 10.1353/hpu.2010.0233

Higher Allograft Failure Rate for Biologically Related Donor-Recipient Pairs

After accounting for human leukocyte antigen (HLA) mismatch and other factors, survival of living-donor kidney allografts is longer for transplants from unrelated donors compared to related donors—particularly for Black or African American donor-recipient pairs, reports a study in *JAMA Network Open*.

The researchers analyzed 72,980 adult living-donor kidney transplants, identified using Organ Procurement and Transplantation Network data from 2000 through 2014, with follow-up to 2020. The median donor age was 41 years; 60% were women. In 59% of transplants, donors and recipients had some degree of biologic relationship.

Rates of death-censored allograft failure were compared for biologically related and unrelated pairs, with adjustment for number of HLA mismatches and other characteristics, including primary diagnosis of cystic kidney disease and donor race (African American versus non-African American).

Donors in biologically related pairs were younger (39 versus 44 years), less likely to be women (58% versus 64%), and less likely to be White (62% versus 77%). Recipients in related pairs were younger (48 versus 50 years), more likely to be women (42% versus 35%), and less likely to have cystic kidney disease (6% versus 15%). Biologically related pairs had fewer HLA mismatches: 3 versus 5.

Allograft failure occurred in 17% of unrelated and 19% of related transplants; recipient death rates were also 17% and 19%, respectively. After adjustment for HLA mismatch, the rate of death-censored allograft failure was significantly higher for the biologically related pairs: hazard ratio (HR) 1.26.

The association was attenuated but remained significant after adjustment for donor and recipient characteristics (HR 1.06) and study era (HR 1.05). On analysis stratified by donor race, the increase in death-censored allograft failure was significant only for transplants from African American donors: HR 1.12.

The proportion of living-donor kidney transplants in the United States has increased substantially over the past 2 decades. The effects of this trend on allograft outcomes remain unclear.

The new analysis shows a higher allograft failure rate among recipients of living-related kidney transplants from biologically related donors. The association persists after accounting for donor and recipient characteristics, including HLA mismatch. "These findings suggest that kidney donors who are related to their recipients may share genetic or socioenvironmental predispositions to kidney disease that shorten allograft longevity," the researchers write [Husain SA, et al. Association between donor-recipient biological relationship and allograft outcomes after living donor kidney transplant. *JAMA Netw Open* 2021; 4:e215718. doi: 10.1001/jamanetworkopen.2021.5718].

KidneyX Receives Record-Breaking Bipartisan Support

By Zachary Kribs and Ryan Murray

KidneyX, the public-private partnership between the American Society of Nephrology (ASN) and the US Department of Health and Human Services (HHS) to accelerate innovation in the diagnosis, prevention, and treatment of kidney diseases, was included in President Biden's first annual budget proposal for fiscal year 2022 (FY 22), announced by the Biden-Harris administration on May 28, 2020. Following the largest showing of support to date from members of the US House of Representatives and Senate—an effort led by Rep. Suzan DelBene of Washington, Rep. Larry Bucshon of Indiana, Rep. Terri Sewell of Alabama, Rep. Brian Babin of Texas, Sen. Ben Cardin of Maryland, and Sen. Todd Young of Indiana—the Biden administration's inclusion of KidneyX in its annual budget proposal cements a legacy of robust bipartisan support of the program across presidential administrations and both chambers of Congress.

Citing KidneyX's track record of success in "catalyzing both the HHS Advancing American Kidney Health Initiative and interest among patients, caregivers, doctors, startups, investors, and industry to solve important problems for the real-world benefit of kidney disease patients," the budget proposes a continued federal investment of $5 million in FY 22 for KidneyX. The Congressional Justification argues that KidneyX is worthy of funding as it "sends a strong signal to the innovation community and to patients that advancing artificial kidney development is a top national public health priority, worthy of additional investment."

In addition to the crucial support displayed by the Biden-Harris administration, KidneyX has received vital bicameral and bipartisan support in Congress. Nearly 60 representatives and 11 senators—the largest number of members of Congress on record supporting KidneyX—sent letters to the Senate and House Labor, Health and Human Services, Education, and Related Agencies Appropriations Subcommittees calling for a $25 million investment in KidneyX. Both the House and Senate letters highlight the recent progress made by the program in "incentivizing innovators to fill unmet patient needs through a series of prize competitions, de-risking the commercialization process by fostering coordination among federal agencies and creating a sense of urgency on behalf of patients and families," demonstrated by the success of the previous 4 prize competitions run by KidneyX. The letters note the racial health disparities and extra risk of COVID-19 among people with kidney diseases and raise the development of a wearable or implantable artificial kidney through KidneyX as a worthwhile investment.

The advocacy efforts of ASN and key partner organizations within the kidney community led to KidneyX securing $5 million in congressional appropriations in both FY 20 and FY 21, totaling $10 million since the start of the program, a testament to the efforts of the kidney community and congressional champions. Although Congress has complete discretion at what level to fund various federal agencies as dictated by the US Constitution, the president's budget serves as a key indicator for the administration's priorities. KidneyX's inclusion in the budget serves as a vote of confidence for the program coming out of the presidential transition.

This prioritization was confirmed at a recent congressional hearing on President Biden's FY 22 budget. Noting that she was "particularly pleased" by the inclusion of KidneyX in the budget, Rep. DelBene described her hope that the administration match the $25 million in private-sector funding provided to KidneyX to date, asking HHS Secretary Xavier Becerra what support can be expected "from the administration in the coming years," especially given the "striking example of the health disparities in our country" posed by kidney diseases and the impact of COVID-19 on kidney health. Secretary Becerra responded that in the budget, the administration does "make a commitment to continue KidneyX, because it's so important that we try to address these types of conditions as quickly and early as possible and as you mentioned, oftentimes, it disproportionately impacts communities of color."

The congressional letters and the program's inclusion in President Biden's budget proposal reflect KidneyX's successful efforts to accelerate innovation in the prevention, diagnosis, and treatment of kidney diseases. To date, KidneyX has supported more than 50 innovators across four prize competitions in 22 states. Building on the achievements of previous competitions, KidneyX launched the Artificial Kidney Prize in 2020 as a long-term commitment to accelerate the development of an artificial kidney that can be worn or implanted. Winners of the Artificial Kidney Prize's Phase 1 will be announced during summer 2021, and KidneyX will begin accepting submissions for Phase 2 in fall 2021. The United States is uniquely positioned, through KidneyX, with an opportunity to be the global leader in the development of the world's first artificial kidney, an innovation that is needed across the world by the 850 million people living with kidney diseases. ASN will continue to advocate that KidneyX receive $25 million in congressional funding to aid its efforts to support the development of the artificial kidney. ■

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†14.5% vs 9.2% with placebo in adults with eGFR ≤75 to ≥25 mL/min/1.73 m^2; HR 0.61 (95% CI: 0.51–0.72); *P*<0.0001.[1,3]
‡6.8% vs 4.7% with placebo in adults with eGFR ≤75 to ≥25 mL/min/1.73 m^2; HR 0.69 (95% CI: 0.53–0.88); *P*=0.0035.[1,3]

Study design: DAPA-CKD was a randomized, double-blind, placebo-controlled, multicenter clinical trial of 4304 adults with eGFR 25-75 mL/min/1.73 m^2, and UACR 200-5000 mg/g, with or without T2D, randomly assigned to receive FARXIGA (10 mg once daily) or placebo for a median follow-up of 2.4 years.[3]

INDICATIONS AND LIMITATIONS OF USE for FARXIGA® (dapagliflozin)

FARXIGA is indicated:

- as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
- to reduce the risk of hospitalization for heart failure in adults with type 2 diabetes mellitus and either established cardiovascular (CV) disease or multiple CV risk factors
- to reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure (NYHA class II-IV) with reduced ejection fraction
- to reduce the risk of sustained eGFR decline, end-stage kidney disease, cardiovascular death, and hospitalization for heart failure in adults with chronic kidney disease at risk of progression

FARXIGA is not recommended for patients with type 1 diabetes mellitus. It may increase the risk of diabetic ketoacidosis in these patients.

FARXIGA is not recommended for use to improve glycemic control in adults with type 2 diabetes mellitus with an eGFR less than 45 mL/min/1.73 m^2. FARXIGA is likely to be ineffective in this setting based upon its mechanism of action.

FARXIGA is not recommended for the treatment of chronic kidney disease in patients with polycystic kidney disease or patients requiring or with a recent history of immunosuppressive therapy for kidney disease. FARXIGA is not expected to be effective in these populations.

IMPORTANT SAFETY INFORMATION

Contraindications

- Prior serious hypersensitivity reaction to FARXIGA
- Patients on dialysis

Warnings and Precautions

- **Ketoacidosis in Diabetes Mellitus** has been reported in patients with type 1 and type 2 diabetes receiving FARXIGA. In placebo-controlled trials of patients with type 1 diabetes, the risk of ketoacidosis was increased in patients who received SGLT2 inhibitors compared to patients who received placebo. Some cases were fatal. Assess patients who present with signs and symptoms of metabolic acidosis for ketoacidosis, regardless of blood glucose level. If suspected, discontinue FARXIGA, evaluate and treat promptly. Before initiating FARXIGA, consider risk factors for ketoacidosis. Patients on FARXIGA may require monitoring and temporary discontinuation in situations known to predispose to ketoacidosis
- **Volume Depletion:** FARXIGA can cause intravascular volume depletion which may manifest as symptomatic hypotension or acute transient changes in creatinine. Acute kidney injury requiring hospitalization and dialysis has been reported in patients with type 2 diabetes receiving SGLT2 inhibitors, including FARXIGA. Patients with impaired renal function (eGFR less than 60 mL/min/1.73 m^2), elderly patients, or patients on loop diuretics may be at increased risk for volume depletion or hypotension. Before initiating FARXIGA in these patients, assess volume status and renal function. After initiating therapy, monitor for signs and symptoms of hypotension and renal function
- **Urosepsis and Pyelonephritis:** SGLT2 inhibitors increase the risk for urinary tract infections (UTIs) and serious UTIs have been reported with FARXIGA. Evaluate for signs and symptoms of UTIs and treat promptly
- **Hypoglycemia:** FARXIGA can increase the risk of hypoglycemia when coadministered with insulin and insulin secretagogues. Consider lowering the dose of these agents when coadministered with FARXIGA
- **Necrotizing Fasciitis of the Perineum (Fournier's Gangrene):** Rare but serious, life-threatening cases have been reported in patients with diabetes mellitus receiving SGLT2 inhibitors including FARXIGA. Cases have been reported in females and males. Serious outcomes have included hospitalization, surgeries, and death. Assess patients presenting with pain or tenderness, erythema, swelling in the genital or perineal area, along with fever or malaise. If suspected, institute prompt treatment and discontinue FARXIGA
- **Genital Mycotic Infections:** FARXIGA increases the risk of genital mycotic infections, particularly in patients with prior genital mycotic infections. Monitor and treat appropriately

Adverse Reactions

In a pool of 12 placebo-controlled studies, the most common adverse reactions (≥5%) associated with FARXIGA 5 mg, 10 mg, and placebo respectively were female genital mycotic infections (8.4% vs 6.9% vs 1.5%), nasopharyngitis (6.6% vs 6.3% vs 6.2%), and urinary tract infections (5.7% vs 4.3% vs 3.7%).

Use in Specific Populations

- **Pregnancy:** Advise females of potential risk to a fetus especially during the second and third trimesters
- **Lactation:** FARXIGA is not recommended when breastfeeding

DOSING

To improve glycemic control, the recommended starting dose is 5 mg orally once daily. Dose can be increased to 10 mg orally once daily for additional glycemic control.

For all other indications, the recommended dose is 10 mg orally once daily.

Please see Brief Summary of Prescribing Information on adjacent pages.

*You are encouraged to report negative side effects of AstraZeneca prescription drugs to the FDA. Visit **www.FDA.gov/medwatch** or call 1-800-FDA-1088.*

CI=confidence interval; CKD=chronic kidney disease; DAPA-CKD=Dapagliflozin And Prevention of Adverse outcomes in Chronic Kidney Disease; eGFR=estimated glomerular filtration rate; FDA=Food and Drug Administration; HR=hazard ratio; NYHA=New York Heart Association; SGLT2i=sodium-glucose cotransporter 2 inhibitor; RRR=relative risk reduction; T2D=type 2 diabetes; UACR=urine albumin-to-creatinine ratio.

References: 1. FARXIGA® (dapagliflozin) [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2021. **2.** FARXIGA granted Breakthrough Therapy Designation in US for chronic kidney disease [press release]. Published October 2, 2020. Accessed March 17, 2021. https://www.astrazeneca-us.com/media/press-releases/2020/farxiga-granted-breakthrough-therapy-designation-in-us-for-chronic-kidney-disease.html **3.** Heerspink HJL et al. *N Engl J Med.* 2020;383(15):1436-1446.

AstraZeneca

FARXIGA® (dapagliflozin) tablets, for oral use

Initial U.S Approval: 2014

BRIEF SUMMARY of PRESCRIBING INFORMATION.

For complete prescribing information, consult official package insert.

INDICATIONS AND USAGE

FARXIGA (dapagliflozin) is indicated:

- As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
- To reduce the risk of hospitalization for heart failure in adults with type 2 diabetes mellitus and either established cardiovascular disease or multiple cardiovascular risk factors.
- To reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure (NYHA class II-IV) with reduced ejection fraction.
- To reduce the risk of sustained eGFR decline, end-stage kidney disease, cardiovascular death, and hospitalization for heart failure in adults with chronic kidney disease at risk of progression.

Limitations of Use

- FARXIGA is not recommended for patients with type 1 diabetes mellitus. It may increase the risk of diabetic ketoacidosis in these patients *[see Warnings and Precautions (5.1) in the full Prescribing Information]*.
- FARXIGA is not recommended for use to improve glycemic control in adults with type 2 diabetes mellitus with an eGFR less than 45 mL/min/1.73 m^2. FARXIGA is likely to be ineffective in this setting based upon its mechanism of action.
- FARXIGA is not recommended for the treatment of chronic kidney disease in patients with polycystic kidney disease or patients requiring or with a recent history of immunosuppressive therapy for kidney disease. FARXIGA is not expected to be effective in these populations.

DOSAGE AND ADMINISTRATION

Prior to Initiation of FARXIGA

Assess renal function prior to initiation of FARXIGA therapy and then as clinically indicated *[see Warnings and Precautions (5.2) in the full Prescribing Information]*.

Assess volume status and, if necessary, correct volume depletion prior to initiation of FARXIGA *[see Warnings and Precautions (5.2) and Use in Specific Populations (8.5, 8.6) in the full Prescribing Information]*.

Recommended Dosage

See Table 1 for dosage recommendations based on estimated glomerular filtration rate (eGFR).

Table 1: Recommended Dosage

eGFR (mL/min/1.73 m^2)	Recommended Dose
eGFR 45 or greater	To improve glycemic control, the recommended starting dose is 5 mg orally once daily. Dose can be increased to 10 mg orally once daily for additional glycemic control*. For all other indications, the recommended starting dose is 10 mg orally once daily.
eGFR 25 to less than 45	10 mg orally once daily*.
eGFR less than 25	Initiation is not recommended, however patients may continue 10 mg orally once daily to reduce the risk of eGFR decline, ESKD, CV death and hHF.
On dialysis	Contraindicated.

* FARXIGA is not recommended for use to improve glycemic control in adults with type 2 diabetes mellitus with an eGFR less than 45 mL/min/1.73 m^2. FARXIGA is likely to be ineffective in this setting based upon its mechanism of action.

hHF: hospitalization for heart failure, CV: Cardiovascular, ESKD: End Stage Kidney Disease.

CONTRAINDICATIONS

- History of a serious hypersensitivity reaction to FARXIGA, such as anaphylactic reactions or angioedema *[see Adverse Reactions (6.1) in the full Prescribing Information]*.
- Patients on dialysis *[see Use in Specific Populations (8.6) in the full Prescribing Information]*.

WARNINGS AND PRECAUTIONS

Ketoacidosis in Patients with Diabetes Mellitus

Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization have been identified in patients with type 1 and type 2 diabetes mellitus receiving sodium-glucose cotransporter 2 (SGLT2) inhibitors, including FARXIGA *[see Adverse Reactions (6.1) in the full Prescribing Information]*. In placebo-controlled trials of patients with type 1 diabetes mellitus, the risk of ketoacidosis was increased in patients who received SGLT2 inhibitors compared to patients who received placebo. Fatal cases of ketoacidosis have been reported in patients taking FARXIGA. FARXIGA is not indicated for the treatment of patients with type 1 diabetes mellitus *[see Indications and Usage (1) in the full Prescribing Information]*.

Patients treated with FARXIGA who present with signs and symptoms consistent with severe metabolic acidosis should be assessed for ketoacidosis regardless of presenting blood glucose levels as ketoacidosis associated with FARXIGA may be present even if blood glucose levels are less than 250 mg/dL. If ketoacidosis is suspected, FARXIGA should be discontinued, the patient should be evaluated, and prompt treatment should be instituted. Treatment of ketoacidosis may require insulin, fluid, and carbohydrate replacement.

In many of the postmarketing reports, and particularly in patients with type 1 diabetes, the presence of ketoacidosis was not immediately recognized, and the institution of treatment was delayed because the presenting blood glucose levels were below those typically expected for diabetic ketoacidosis (often less than 250 mg/dL). Signs and symptoms at presentation were consistent with dehydration and severe metabolic acidosis and included nausea, vomiting, abdominal pain, generalized malaise, and shortness of breath. In some but not all cases, factors predisposing to ketoacidosis, such as insulin dose reduction, acute febrile illness, reduced caloric intake, surgery, pancreatic disorders suggesting insulin deficiency (e.g., type 1 diabetes, history of pancreatitis or pancreatic surgery), and alcohol abuse were identified.

Before initiating FARXIGA, consider factors in the patient history that may predispose to ketoacidosis, including pancreatic insulin deficiency from any cause, caloric restriction, and alcohol abuse.

For patients who undergo scheduled surgery, consider temporarily discontinuing FARXIGA for at least 3 days prior to surgery *[see Clinical Pharmacology (12.2, 12.3) in the full Prescribing Information]*.

Consider monitoring for ketoacidosis and temporarily discontinuing FARXIGA in other clinical situations known to predispose to ketoacidosis (e.g., prolonged fasting due to acute illness or post-surgery). Ensure risk factors for ketoacidosis are resolved prior to restarting FARXIGA. Educate patients on the signs and symptoms of ketoacidosis and instruct patients to discontinue FARXIGA and seek medical attention immediately if signs and symptoms occur.

Volume Depletion

FARXIGA can cause intravascular volume depletion which may sometimes manifest as symptomatic hypotension or acute transient changes in creatinine. There have been post-marketing reports of acute kidney injury, some requiring hospitalization and dialysis, in patients with type 2 diabetes mellitus receiving SGLT2 inhibitors, including FARXIGA. Patients with impaired renal function (eGFR less than 60 mL/min/1.73 m^2), elderly patients, or patients on loop diuretics may be at increased risk for volume depletion or hypotension. Before initiating FARXIGA in patients with one or more of these characteristics, assess volume status and renal function. Monitor for signs and symptoms of hypotension, and renal function after initiating therapy.

Urosepsis and Pyelonephritis

Serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization have been reported in patients receiving SGLT2 inhibitors, including FARXIGA. Treatment with SGLT2 inhibitors increases the risk for urinary tract infections. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated *[see Adverse Reactions (6) in the full Prescribing Information]*.

Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues

Insulin and insulin secretagogues are known to cause hypoglycemia. FARXIGA may increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue *[see Adverse Reactions (6.1) in the full Prescribing Information]*. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when these agents are used in combination with FARXIGA.

Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)

Reports of necrotizing fasciitis of the perineum (Fournier's Gangrene), a rare but serious and life-threatening necrotizing infection requiring urgent surgical intervention, have been identified in postmarketing surveillance in patients with diabetes mellitus receiving SGLT2 inhibitors, including FARXIGA. Cases have been reported in both females and males. Serious outcomes have included hospitalization, multiple surgeries, and death.

Patients treated with FARXIGA presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise, should be assessed for necrotizing fasciitis. If suspected, start treatment immediately with broad-spectrum antibiotics and, if necessary, surgical debridement. Discontinue FARXIGA, closely monitor blood glucose levels, and provide appropriate alternative therapy for glycemic control.

Genital Mycotic Infections

FARXIGA increases the risk of genital mycotic infections. Patients with a history of genital mycotic infections were more likely to develop genital mycotic infections *[see Adverse Reactions (6.1) in the full Prescribing Information]*. Monitor and treat appropriately.

ADVERSE REACTIONS

The following important adverse reactions are described below and elsewhere in the labeling:

- Ketoacidosis in Patients with Diabetes Mellitus *[see Warnings and Precautions (5.1) in the full Prescribing Information]*
- Volume Depletion *[see Warnings and Precautions (5.2) in the full Prescribing Information]*
- Urosepsis and Pyelonephritis *[see Warnings and Precautions (5.3) in the full Prescribing Information]*
- Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues *[see Warnings and Precautions (5.4) in the full Prescribing Information]*
- Necrotizing Fasciitis of the Perineum (Fournier's Gangrene) *[see Warnings and Precautions (5.5) in the full Prescribing Information]*
- Genital Mycotic Infections *[see Warnings and Precautions (5.6) in the 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 to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

FARXIGA has been evaluated in clinical trials in patients with type 2 diabetes mellitus, in patients with heart failure, and in patients with chronic kidney disease. The overall safety profile of FARXIGA was consistent across the studied indications. Severe hypoglycemia and diabetic ketoacidosis (DKA) were observed only in patients with diabetes mellitus.

Clinical Trials in Patients with Type 2 Diabetes Mellitus

Pool of 12 Placebo-Controlled Studies for FARXIGA 5 and 10 mg for Glycemic Control

The data in Table 1 is derived from 12 glycemic control placebo-controlled studies in patients with type 2 diabetes mellitus ranging from 12 to 24 weeks. In 4 studies FARXIGA was used as monotherapy, and in 8 studies FARXIGA was used as add-on to background antidiabetic therapy or as combination therapy with metformin *[see Clinical Studies (14.1) in the full Prescribing Information]*.

These data reflect exposure of 2338 patients to FARXIGA with a mean exposure duration of 21 weeks. Patients received placebo (N=1393), FARXIGA 5 mg (N=1145), or FARXIGA 10 mg (N=1193) once daily. The mean age of the population was 55 years and 2% were older than 75 years of age. Fifty percent (50%) of the population were male; 81% were White, 14% were Asian, and 3% were Black or African American. At baseline, the population had diabetes for an average of 6 years, had a mean hemoglobin A1c (HbA1c) of 8.3%, and 21% had established microvascular complications of diabetes. Baseline renal function was normal or mildly impaired in 92% of patients and moderately impaired in 8% of patients (mean eGFR 86 mL/min/1.73 m^2).

Table 2 shows common adverse reactions associated with the use of FARXIGA. These adverse reactions were not present at baseline, occurred more commonly on FARXIGA than on placebo, and occurred in at least 2% of patients treated with either FARXIGA 5 mg or FARXIGA 10 mg.

Table 2: Adverse Reactions in Placebo-Controlled Studies of Glycemic Control Reported in ≥2% of Patients Treated with FARXIGA

Adverse Reaction	% of Patients		
	Pool of 12 Placebo-Controlled Studies		
	Placebo N=1393	FARXIGA 5 mg N=1145	FARXIGA 10 mg N=1193
Female genital mycotic infections*	1.5	8.4	6.9
Nasopharyngitis	6.2	6.6	6.3
Urinary tract infections†	3.7	5.7	4.3
Back pain	3.2	3.1	4.2
Increased urination‡	1.7	2.9	3.8
Male genital mycotic infections§	0.3	2.8	2.7

Table 2: Adverse Reactions in Placebo-Controlled Studies of Glycemic Control Reported in ≥2% of Patients Treated with FARXIGA (cont'd)

Adverse Reaction	% of Patients		
	Pool of 12 Placebo-Controlled Studies		
	Placebo N=1393	FARXIGA 5 mg N=1145	FARXIGA 10 mg N=1193
Nausea	2.4	2.8	2.5
Influenza	2.3	2.7	2.3
Dyslipidemia	1.5	2.1	2.5
Constipation	1.5	2.2	1.9
Discomfort with urination	0.7	1.6	2.1
Pain in extremity	1.4	2.0	1.7

* Genital mycotic infections include the following adverse reactions, listed in order of frequency reported for females: vulvovaginal mycotic infection, vaginal infection, vulvovaginal candidiasis, vulvovaginitis, genital infection, genital candidiasis, fungal genital infection, vulvitis, genitourinary tract infection, vulval abscess, and vaginitis bacterial. (N for females: Placebo=677, FARXIGA 5 mg=581, FARXIGA 10 mg=598).

† Urinary tract infections include the following adverse reactions, listed in order of frequency reported: urinary tract infection, cystitis, *Escherichia* urinary tract infection, genitourinary tract infection, pyelonephritis, trigonitis, urethritis, kidney infection, and prostatitis.

‡ Increased urination includes the following adverse reactions, listed in order of frequency reported: pollakiuria, polyuria, and urine output increased.

§ Genital mycotic infections include the following adverse reactions, listed in order of frequency reported for males: balanitis, fungal genital infection, balanitis candida, genital candidiasis, genital infection male, penile infection, balanoposthitis, balanoposthitis infective, genital infection, and posthitis. (N for males: Placebo=716, FARXIGA 5 mg=564, FARXIGA 10 mg=595).

Pool of 13 Placebo-Controlled Studies for FARXIGA 10 mg for Glycemic Control

FARXIGA 10 mg was also evaluated in a larger glycemic control placebo-controlled study pool in patients with type 2 diabetes mellitus. This pool combined 13 placebo-controlled studies, including 3 monotherapy studies, 9 add-on to background antidiabetic therapy studies, and an initial combination with metformin study. Across these 13 studies, 2360 patients were treated once daily with FARXIGA 10 mg for a mean duration of exposure of 22 weeks. The mean age of the population was 59 years and 4% were older than 75 years. Fifty-eight percent (58%) of the population were male; 84% were White, 9% were Asian, and 3% were Black or African American. At baseline, the population had diabetes for an average of 9 years, had a mean HbA1c of 8.2%, and 30% had established microvascular disease. Baseline renal function was normal or mildly impaired in 88% of patients and moderately impaired in 11% of patients (mean eGFR 82 mL/min/1.73 m^2).

Volume Depletion

FARXIGA causes an osmotic diuresis, which may lead to a reduction in intravascular volume. Adverse reactions related to volume depletion (including reports of dehydration, hypovolemia, orthostatic hypotension, or hypotension) in patients with type 2 diabetes mellitus for the 12-study and 13-study, short-term, placebo-controlled pools and for the DECLARE study are shown in Table 3 *[see Warnings and Precautions (5.2)]*.

Table 3: Adverse Reactions Related to Volume Depletion* in Clinical Studies in Patients with Type 2 Diabetes Mellitus with FARXIGA

	Pool of 12 Placebo-Controlled Studies			Pool of 13 Placebo-Controlled Studies		DECLARE Study	
	Placebo	FARXIGA 5 mg	FARXIGA 10 mg	Placebo	FARXIGA 10 mg	Placebo	FARXIGA 10 mg
Overall population N (%)	N=1393 5 (0.4%)	N=1145 7 (0.6%)	N=1193 9 (0.8%)	N=2295 17 (0.7%)	N=2360 27 (1.1%)	N=8569 207 (2.4%)	N=8574 213 (2.5%)
Patient Subgroup n (%)							
Patients on loop diuretics	n=55 1 (1.8%)	n=40 0	n=31 3 (9.7%)	n=267 4 (1.5%)	n=236 6 (2.5%)	n=934 57 (6.1%)	n=866 57 (6.6%)
Patients with moderate renal impairment with eGFR ≥30 and <60 mL/min/ 1.73 m^2	n=107 2 (1.9%)	n=107 1 (0.9%)	n=89 1 (1.1%)	n=268 4 (1.5%)	n=265 5 (1.9%)	n=658 30 (4.6%)	n=604 35 (5.8%)
Patients ≥65 years of age	n=276 1 (0.4%)	n=216 1 (0.5%)	n=204 3 (1.5%)	n=711 6 (0.8%)	n=665 11 (1.7%)	n=3950 121 (3.1%)	n=3948 117 (3.0%)

* Volume depletion includes reports of dehydration, hypovolemia, orthostatic hypotension, or hypotension.

Hypoglycemia

The frequency of hypoglycemia by study in patients with type 2 diabetes mellitus *[see Clinical Studies (14.1) in the full Prescribing Information]* is shown in Table 4. Hypoglycemia was more frequent when FARXIGA was added to sulfonylurea or insulin *[see Warnings and Precautions (5.4) in the full Prescribing Information]*.

Table 4: Incidence of Severe Hypoglycemia* and Hypoglycemia with Glucose < 54 mg/dL† in Controlled Glycemic Control Clinical Studies in Patients with Type 2 Diabetes Mellitus

	Placebo/Active Control	FARXIGA 5 mg	FARXIGA 10 mg
Monotherapy (24 weeks)	**N=75**	**N=64**	**N=70**
Severe [n (%)]	0	0	0
Glucose <54 mg/dL [n (%)]	0	0	0
Add-on to Metformin (24 weeks)	**N=137**	**N=137**	**N=135**
Severe [n (%)]	0	0	0
Glucose <54 mg/dL [n (%)]	0	0	0
Add-on to Glimepiride (24 weeks)	**N=146**	**N=145**	**N=151**
Severe [n (%)]	0	0	0
Glucose <54 mg/dL [n (%)]	1 (0.7)	3 (2.1)	5 (3.3)
Add-on to Metformin and a Sulfonylurea (24 Weeks)	**N=109**	**-**	**N=109**
Severe [n (%)]	0	-	0
Glucose <54 mg/dL [n (%)]	3 (2.8)	-	7 (6.4)

Table 4: Incidence of Severe Hypoglycemia* and Hypoglycemia with Glucose < 54 mg/dL† in Controlled Glycemic Control Clinical Studies in Patients with Type 2 Diabetes Mellitus (cont'd)

	Placebo/Active Control	FARXIGA 5 mg	FARXIGA 10 mg
Add-on to Pioglitazone (24 weeks)	**N=139**	**N=141**	**N=140**
Severe [n (%)]	0	0	0
Glucose <54 mg/dL [n (%)]	0	1 (0.7)	0
Add-on to DPP4 inhibitor (24 weeks)	**N=226**	**–**	**N=225**
Severe [n (%)]	0	–	1 (0.4)
Glucose <54 mg/dL [n (%)]	1 (0.4)	–	1 (0.4)
Add-on to Insulin with or without other OADs‡ (24 weeks)	**N=197**	**N=212**	**N=196**
Severe [n (%)]	1 (0.5)	2 (0.9)	2 (1.0)
Glucose <54 mg/dL [n (%)]	43 (21.8)	55 (25.9)	45 (23.0)

* Severe episodes of hypoglycemia were defined as episodes of severe impairment in consciousness or behavior, requiring external (third party) assistance, and with prompt recovery after intervention regardless of glucose level.

† Episodes of hypoglycemia with glucose <54 mg/dL (3 mmol/L) were defined as reported episodes of hypoglycemia meeting the glucose criteria that did not also qualify as a severe episode.

‡ OAD = oral antidiabetic therapy.

In the DECLARE study *[see Clinical Studies (14.2) in the full Prescribing Information]*, severe events of hypoglycemia were reported in 58 (0.7%) out of 8574 patients treated with FARXIGA and 83 (1.0%) out of 8569 patients treated with placebo.

Genital Mycotic Infections

In the glycemic control trials, genital mycotic infections were more frequent with FARXIGA treatment. Genital mycotic infections were reported in 0.9% of patients on placebo, 5.7% on FARXIGA 5 mg, and 4.8% on FARXIGA 10 mg, in the 12-study placebo-controlled pool. Discontinuation from study due to genital infection occurred in 0% of placebo-treated patients and 0.2% of patients treated with FARXIGA 10 mg. Infections were more frequently reported in females than in males (see Table 1). The most frequently reported genital mycotic infections were vulvovaginal mycotic infections in females and balanitis in males. Patients with a history of genital mycotic infections were more likely to have a genital mycotic infection during the study than those with no prior history (10.0%, 23.1%, and 25.0% versus 0.8%, 5.9%, and 5.0% on placebo, FARXIGA 5 mg, and FARXIGA 10 mg, respectively). In the DECLARE study *[see Clinical Studies (14.2) in the full Prescribing Information]*, serious genital mycotic infections were reported in <0.1% of patients treated with FARXIGA and <0.1% of patients treated with placebo. Genital mycotic infections that caused study drug discontinuation were reported in 0.9% of patients treated with FARXIGA and <0.1% of patients treated with placebo.

Hypersensitivity Reactions

Hypersensitivity reactions (e.g., angioedema, urticaria, hypersensitivity) were reported with FARXIGA treatment. In glycemic control studies, serious anaphylactic reactions and severe cutaneous adverse reactions and angioedema were reported in 0.2% of comparator-treated patients and 0.3% of FARXIGA-treated patients. If hypersensitivity reactions occur, discontinue use of FARXIGA; treat per standard of care and monitor until signs and symptoms resolve.

Ketoacidosis in Patients with Diabetes Mellitus

In the DECLARE study *[see Warnings and Precautions (5.1) and Clinical Studies (14.2) in the full Prescribing Information]*, events of diabetic ketoacidosis (DKA) were reported in 27 out of 8574 patients in the FARXIGA-treated group and 12 out of 8569 patients in the placebo group. The events were evenly distributed over the study period.

Laboratory Tests

Increases in Serum Creatinine and Decreases in eGFR

Initiation of SGLT2 inhibitors, including FARXIGA causes a small increase in serum creatinine and decrease in eGFR. These changes in serum creatinine and eGFR generally occur within two weeks of starting therapy and then stabilize regardless of baseline kidney function. Changes that do not fit this pattern should prompt further evaluation to exclude the possibility of acute kidney injury *[see Warnings and Precautions (5.2) in the full Prescribing Information]*. In two studies that included patients with type 2 diabetes mellitus with moderate renal impairment, the acute effect on eGFR reversed after treatment discontinuation, suggesting acute hemodynamic changes may play a role in the renal function changes observed with FARXIGA.

Increase in Hematocrit

In the pool of 13 placebo-controlled studies of glycemic control, increases from baseline in mean hematocrit values were observed in FARXIGA-treated patients starting at Week 1 and continuing up to Week 16, when the maximum mean difference from baseline was observed. At Week 24, the mean changes from baseline in hematocrit were –0.33% in the placebo group and 2.30% in the FARXIGA 10 mg group. By Week 24, hematocrit values >55% were reported in 0.4% of placebo-treated patients and 1.3% of FARXIGA 10 mg-treated patients.

Increase in Low-Density Lipoprotein Cholesterol

In the pool of 13 placebo-controlled studies of glycemic control, changes from baseline in mean lipid values were reported in FARXIGA-treated patients compared to placebo-treated patients. Mean percent changes from baseline at Week 24 were 0.0% versus 2.5% for total cholesterol, and -1.0% versus 2.9% for LDL cholesterol in the placebo and FARXIGA 10 mg groups, respectively. In the DECLARE study *[see Clinical Studies (14.2) in the full Prescribing Information]*, mean changes from baseline after 4 years were 0.4 mg/dL versus -4.1 mg/dL for total cholesterol, and -2.5 mg/dL versus -4.4 mg/dL for LDL cholesterol, in FARXIGA-treated and the placebo groups, respectively.

Decrease in Serum Bicarbonate

In a study of concomitant therapy of FARXIGA 10 mg with exenatide extended-release (on a background of metformin), four patients (1.7%) on concomitant therapy had a serum bicarbonate value of less than or equal to 13 mEq/L compared to one each (0.4%) in the FARXIGA and exenatide-extended release treatment groups *[see Warnings and Precautions (5.1) in the full Prescribing Information]*.

DAPA-HF Heart Failure Study

No new adverse reactions were identified in the DAPA-HF heart failure study.

DAPA-CKD Chronic Kidney Disease Study

No new adverse reactions were identified in the DAPA-CKD study in patients with chronic kidney disease.

Postmarketing Experience

Additional adverse reactions have been identified during postapproval use of FARXIGA in patients with diabetes mellitus. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Ketoacidosis
- Acute Kidney Injury
- Urosepsis and Pyelonephritis
- Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)
- Rash

DRUG INTERACTIONS

Positive Urine Glucose Test

Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors as SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests. Use alternative methods to monitor glycemic control.

Interference with 1,5-anhydroglucitol (1,5-AG) Assay

Monitoring glycemic control with 1,5-AG assay is not recommended as measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on animal data showing adverse renal effects, FARXIGA is not recommended during the second and third trimesters of pregnancy.

Limited data with FARXIGA in pregnant women are not sufficient to determine drug-associated risk for major birth defects or miscarriage. There are risks to the mother and fetus associated with poorly controlled diabetes and untreated heart failure in pregnancy *(see Clinical Considerations)*.

In animal studies, adverse renal pelvic and tubule dilatations, that were not fully reversible, were observed in rats when dapagliflozin was administered during a period of renal development corresponding to the late second and third trimesters of human pregnancy, at all doses tested; the lowest of which provided an exposure 15-times the 10 mg clinical dose *(see Data)*.

The estimated background risk of major birth defects is 6 to 10% in women with pre-gestational diabetes with a HbA1c greater than 7% and has been reported to be as high as 20 to 25% in women with HbA1c greater than 10%. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryofetal risk

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, preeclampsia, spontaneous abortions, preterm delivery and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.

Data

Animal Data

Dapagliflozin dosed directly to juvenile rats from postnatal day (PND) 21 until PND 90 at doses of 1, 15, or 75 mg/kg/day, increased kidney weights and increased the incidence of renal pelvic and tubular dilatations at all dose levels. Exposure at the lowest dose tested was 15-times the 10 mg clinical dose (based on AUC). The renal pelvic and tubular dilatations observed in juvenile animals did not fully reverse within a 1-month recovery period.

In a prenatal and postnatal development study, dapagliflozin was administered to maternal rats from gestation day 6 through lactation day 21 at doses of 1, 15, or 75 mg/kg/day, and pups were indirectly exposed *in utero* and throughout lactation. Increased incidence or severity of renal pelvic dilatation was observed in 21-day-old pups offspring of treated dams at 75 mg/kg/day (maternal and pup dapagliflozin exposures were 1415-times and 137-times, respectively, the human values at the 10 mg clinical dose, based on AUC). Dose-related reductions in pup body weights were observed at greater or equal to 29-times the 10 mg clinical dose (based on AUC). No adverse effects on developmental endpoints were noted at 1 mg/kg/day (19-times the 10 mg clinical dose, based on AUC). These outcomes occurred with drug exposure during periods of renal development in rats that corresponds to the late second and third trimester of human development.

In embryofetal development studies in rats and rabbits, dapagliflozin was administered throughout organogenesis, corresponding to the first trimester of human pregnancy. In rats, dapagliflozin was neither embryolethal nor teratogenic at doses up to 75 mg/kg/day (1441-times the 10 mg clinical dose, based on AUC). Dose related effects on the rat fetus (structural abnormalities and reduced body weight) occurred only at higher dosages, equal to or greater than 150 mg/kg (more than 2344-times the 10 mg clinical dose, based on AUC), which were associated with maternal toxicity. No developmental toxicities were observed in rabbits at doses up to 180 mg/kg/day (1191-times the 10 mg clinical dose, based on AUC).

Lactation

Risk Summary

There is no information regarding the presence of dapagliflozin in human milk, the effects on the breastfed infant, or the effects on milk production. Dapagliflozin is present in the milk of lactating rats *(see Data)*. However, due to species specific differences in lactation physiology, the clinical relevance of these data are not clear. Since human kidney maturation occurs *in utero* and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney.

Because of the potential for serious adverse reactions in breastfed infants, advise women that use of FARXIGA is not recommended while breastfeeding.

Data

Dapagliflozin was present in rat milk at a milk/plasma ratio of 0.49, indicating that dapagliflozin and its metabolites are transferred into milk at a concentration that is approximately 50% of that in maternal plasma. Juvenile rats directly exposed to dapagliflozin showed risk to the developing kidney (renal pelvic and tubular dilatations) during maturation.

Pediatric Use

Safety and effectiveness of FARXIGA in pediatric patients under 18 years of age have not been established.

Geriatric Use

No FARXIGA dosage change is recommended based on age.

A total of 1424 (24%) of the 5936 FARXIGA-treated patients were 65 years and older and 207 (3.5%) patients were 75 years and older in a pool of 21 double-blind, controlled, clinical studies assessing the efficacy of FARXIGA in improving glycemic control in type 2 diabetes mellitus. After controlling for level of renal function (eGFR), efficacy was similar for patients under age 65 years and those 65 years and older. In patients ≥65 years of age, a higher proportion of patients treated with FARXIGA for glycemic control had adverse reactions of hypotension *[see Warnings and Precautions (5.2) and Adverse Reactions (6.1) in the full Prescribing Information]*.

In both the DAPA-HF and DAPA-CKD studies, safety and efficacy were similar for patients age 65 years and younger and those older than 65. In the DAPA-HF study, 2714 (57%) out of 4744 patients with HFrEF were older than 65 years. In the DAPA-CKD study, 1818 (42%) out of 4304 patients with CKD were older than 65 years.

Renal Impairment

FARXIGA was evaluated in 4304 patients with chronic kidney disease (eGFR 25 to 75 mL/min/1.73 m^2) in the DAPA-CKD study. FARXIGA was also evaluated in 1926 patients with an eGFR of 30 to 60 mL/min/1.73 m^2 in the DAPA-HF study. The safety profile of FARXIGA across eGFR subgroups in these studies was consistent with the known safety profile *[see Adverse Reactions (6.1) and Clinical Studies (14.3 and 14.4) in the full Prescribing Information]*.

FARXIGA was evaluated in two glycemic control studies that included patients with type 2 diabetes mellitus with moderate renal impairment (an eGFR of 45 to less than 60 mL/min/1.73 m^2 *[see Clinical Studies (14.1) in the full Prescribing Information]*, and an eGFR of 30 to less than 60 mL/min/1.73 m^2, respectively). Patients with diabetes and renal impairment using FARXIGA may be more likely to experience hypotension and may be at higher risk for acute kidney injury secondary to volume depletion. In the study of patients with an eGFR 30 to less than 60 mL/min/1.73 m^2, 13 patients receiving FARXIGA experienced bone fractures compared to none receiving placebo. Use of FARXIGA for glycemic control in patients without established CV disease or CV risk factors is not recommended when eGFR is less than 45 mL/min/1.73 m^2 *[see Dosage and Administration (2.2) in the full Prescribing Information]*.

Efficacy and safety studies with FARXIGA did not enroll patients with an eGFR less than 25 mL/min/1.73 m^2. FARXIGA is contraindicated in patients on dialysis.

Hepatic Impairment

No dose adjustment is recommended for patients with mild, moderate, or severe hepatic impairment. However, the benefit-risk for the use of dapagliflozin in patients with severe hepatic impairment should be individually assessed since the safety and efficacy of dapagliflozin have not been specifically studied in this population *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*.

OVERDOSAGE

There were no reports of overdose during the clinical development program for FARXIGA.

In the event of an overdose, contact the Poison Control Center. It is also reasonable to employ supportive measures as dictated by the patient's clinical status. The removal of dapagliflozin by hemodialysis has not been studied.

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The Future of Education in Nephrology RIGHT HERE, RIGHT NOW

By Sam Kant and Matthew Sparks

The past year has been an arduous one. Amid the pandemic, we swiftly evolved in delivering our primary mission: patient care and education. The need for physical distancing did not culminate into any separation of trainees from education, with the majority of trainees agreeing that the educational endeavors of their programs were unaffected as a result of the pandemic (1). Local institutions and national organizations, led by prominent educators, continued to conduct conferences via innovative virtual platforms with high-quality content reaching audiences all over the globe. This edition of *Kidney News* is dedicated to trainees and educators as we take a step into the next decade—the decade of nephrology. Each article is either spearheaded by or incorporates the viewpoint of the fellow.

Susan Quaggin and Paul Palevsky highlight how the American Society of Nephrology and National Kidney Foundation are continuing to pursue the goal of Putting Fellows First. This also echoes the renaming of the *Kidney News* Fellows Corner section to the Fellows First section, thus showing the continued concerted effort of the field to prioritize trainees in nephrology. This issue of *Kidney News* features perspectives from a wide range of individuals from various career stages. Importantly, they each incorporate trainees into the narrative.

During the last decade, free open-access medical education (FOAMed) platforms have grown immensely and have now become an invaluable resource for trainees and practicing physicians alike (2). Several FOAMed programs are highlighted in this issue including the Nephrology Social Media Collective (NSMC) internship (Isabelle Dominique Tomacruz et al.), NephSIM Nephrons (Elinor C. Mannon et al.), and the GlomCon virtual fellowship (Edward Kwakyi et al.). As nephrology diversifies into various subspecialty streams, we explore the current landscape of glomerular disease (David Massicotte-Azarniouch et al.), kidney transplantation (Fitsum Hailemariam et al.), critical care (Kristin Hoover et al.), ultrasound (Matthew Wysocki et al.), home dialysis (Nidhi Aggarwal et al.), and palliative care (Tripta Kaur and Holly M. Koncicki) education in nephrology. The American Board of Internal Medicine (ABIM) nephrology subspecialty exam continues to be essential in assessing competency in nephrology. Concerns about how and what should be tested and discussions about optimal preparation strategies, along with recent trends in pass rates, are all discussed (Nityasree Srialluri and Stephen Sozio). Finally, as a homage to Homer Smith, who famously said, "Superficially, it might be said that the function of the kidneys is to make urine; but in a more considered view one can say that the kidneys make the stuff of philosophy itself," Sana Shaikh and Jay Seltzer discuss the resurgence in the practice of examining this philosophical product—urine.

The time is now to continue and double down on our efforts to prioritize education in nephrology.

Our specialty has been at the forefront of dismantling inequities and racism in medicine. Abinet Akilu et al. discusses measures to eliminate institutional and systemic racism in medical training in nephrology (see front page). Women in medicine continue to transform all aspects of nephrology. Anika Lucas et al. highlight the challenges faced by women in the workforce and suggest steps to overcome them.

As education in nephrology continues its expansive march in the future, each sphere of progress will extend into the cause central to all of us—the patients. The time is now to continue and double down on our efforts to prioritize education in nephrology. ■

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Conflicts of interest: Matthew Sparks is co-program director of the NSMC internship, Advisory Board member of NephSIM, faculty member of the GlomCon virtual fellowship, and member of the American Board of Internal Medicine, Nephrology Board.

References

1. Pivert KA, et al. Impact of the COVID-19 pandemic on nephrology fellow training and well-being in the United States: A national survey. *Am J Soc Nephrol* 2021; 32:1236–1248. doi: 10.1681/ASN.2020111636
2. Colbert GB, et al. The social media revolution in nephrology education. *Kidney Int Rep* 2018; 3:519–529. doi: 10.1016/j.ekir.2018.02.003

Putting Fellows First

By Paul M. Palevsky and Susan E. Quaggin

Our favorite time of the year is fellowship interview season. Mornings and afternoons spent with talented, young physicians who exhibit unbridled enthusiasm for our specialty. For most nephrologists, that passion never wanes. The future of our specialty depends upon recruiting, teaching, and mentoring exceptional and diverse trainees. Nephrology is uniquely diverse on every possible level, which makes every aspect of the specialty richer and more fulfilling.

We are proud that our specialty can boast a higher proportion of traditionally underrepresented-in-medicine (URiM) trainees compared to our internal medicine counterparts in cardiology, gastroenterology, pulmonary and critical care, hematology/oncology, and rheumatology (1). However, there is still much more to do, and it is unacceptable that Black or African American and Hispanic or Latinx students represented only 6.2% and 5.3%, respectively, of graduating medical school classes in 2019.

At the end of each academic year, it is a privilege to recognize and thank our incredible nephrology fellows. They are the backbone and future of our specialty, and they will go on to make great discoveries that will transform our field, help dismantle systemic racism, and tear down barriers to healthcare while providing expert care to millions of people living with kidney diseases.

Like other members of the kidney community, both the National Kidney Foundation (NKF) and American Society of Nephrology (ASN) support and enhance fellowship training through multiple activities and initiatives. First and foremost, both organizations provide free membership to fellows along with subscriptions to our scientific journals, including the *Journal of the American Society of Nephrology* (*JASN*), *Clinical Journal of the American Society of Nephrology* (*CJASN*), *American Journal of Kidney Diseases* (*AJKD*), *Kidney Medicine,* and *Kidney360*. ASN's Kidney Week and NKF's Spring Clinical Meeting represent our respective major educational activities, with multiple programs in both meetings targeting fellows and other trainees. ASN's Board Review Course and Update, held each summer, provides an additional forum to prepare trainees for the American Board of Internal Medicine (ABIM) nephrology board exam. Nearly every fellow takes the Nephrology In-Training Examination, which is cosponsored by ASN and the National Board of Medical Examiners.

Beyond these more traditional training venues, NKF and ASN have developed and supported a variety of other opportunities to promote and enhance the trainee experience. The journals of both organizations—*AJKD* and *JASN*—have developed editorial fellowship programs to permit trainees and early career investigators to get "under the hood" and learn about the editorial processes of research journals. *CJASN* has a trainee peer-review program to give fellows experience in providing peer review of scientific submissions and gives a Trainee of the Year award to recognize outstanding work based on the editors' selection of the best manuscript during the year submitted with a trainee as first author.

NephMadness has become one of our favorite annual traditions in nephrology, providing an educational diversion during the long days of late winter. Supported by the NKF, *AJKD*, and *AJKD* Blog, NephMadness pits themes in nephrology against each other—taking an initial round of 32 meticulously researched topics through a series of elimination rounds until a final "winner," selected by a panel of experts, is crowned, generating passionate debate over various nephrology topics on Twitter and other social media outlets and, inevitably, tweets about #blueribbonfails.

Local NKF offices support a variety of educational opportunities for trainees that vary from city to city including intra-city and even intra-state conferences, permitting fellows across institutions to meet. NKF sponsors regional and national Young Investigator Forums, providing an opportunity to recognize the best clinical and basic science research by nephrology trainees.

Increasingly, today's fellows participated in ASN's Kidney TREKS (Tutored Research and Education for Kidney Scholars) and Kidney STARS (Students and Residents) programs when they were students and residents. TREKS is a summer program to encourage interest and a love of kidney physiology and medicine among medical students and graduate students, whereas the STARS program coincides with the annual ASN Kidney Week, providing a mentored experience for medical students, graduate students, and residents to experience the very best of nephrology.

Many nephrology and PhD postdoctoral fellows apply to participate in ASN's Karen L. Campbell, PhD, Trainee Support Program for Fellows, which provides travel support to serve as mentors for Kidney STARS during ASN Kidney Week. ASN travel grants permit eligible fellows to attend the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Network of Minority Health Research Investigators Annual Workshop.

The commitment of both NKF and ASN to trainee education runs deep. Both organizations provide grant and funding opportunities to support and encourage fellows, early career scientists, and clinician-educators to pursue research that will transform kidney care.

ASN also supports the Harold Amos Medical Faculty Development Program, a partnership with the Robert Wood Johnson Foundation to increase diversity among future leaders in nephrology by supporting the research and career development of a kidney scholar and future healthcare leader from a historically disadvantaged background. This year, ASN launched a $2.7 million loan-mitigation pilot program targeting residents interested in nephrology, reflecting the vital importance of fellows to advancing treatment, research, and education. The first year of the program targets residents who self-identify as underrepresented in medicine.

These programs are designed to support the nephrology fellows who enrich the work of those of us who interact with them and who do so much to advance care of those with kidney diseases. Moreover, we are personally incredibly grateful to many other members of our community who are also committed to supporting the next generation of nephrologists, scientists, and other health professionals focused on advancing kidney health. We challenge all in the community to continue to put "fellows first" in all that you do. ■

Paul M. Palevsky, National Kidney Foundation President, is Deputy National Program Director, Veterans Health Administration (VHA) Nephrology Program; Chief, Kidney Medicine Section, VA Pittsburgh Healthcare System; and Professor of Medicine and Clinical and Translational Science, Renal-Electrolyte Division, University of Pittsburgh School of Medicine, Pittsburgh, PA. Susan E. Quaggin, ASN President, is Charles Horace Mayo Professor and Chief, Division of Nephrology and Hypertension, and Director, Feinberg Cardiovascular and Renal Research Institute, Northwestern University Feinberg School of Medicine, Chicago, IL.

Reference

1. Santhosh L, Babik JM. Trends in racial and ethnic diversity in internal medicine subspecialty fellowships from 2006 to 2018. *JAMA Netw Open* 2020; 3:e1920482. doi: 10.1001/jamanetworkopen.2019.20482

Nephrology fellows are the backbone and future of our specialty.

The Nephrology Social Media Collective Internship: Cultivating Leaders in the Age of Social Media

By Isabelle Dominique Tomacruz, Corina Teodosiu, Sophia L. Ambruso, and Michelle Lim

The rise of social media (SoMe) and free open-access medical education (#FOAMed)

The internet and social media have revolutionized the way medical information is disseminated, presented, and consumed. There is a rapid uptake of virtual and mobile-optimized modalities, where FOAMed tools are becoming a preferred modality for medical education (1–5). FOAMed differs from traditional medical education in that teaching and learning occur asynchronously within the virtual space, outside of traditional institutions and a lecture-based format. Although virtual education has grown exponentially over the last several decades, gaining the skills to harness social media as an educational platform has largely remained up to the individual, with little guidance. More recently, a few formal month-to-year-long training programs emerged, i.e., the Nephrology Social Media Collective (NSMC) internship, Academic Life in Emergency Medicine (ALiEM), CardioNerds Academy, iMED Track (Internal Medicine), and Digital Communications Fellowship (Pathology), designed to equip healthcare professionals with the tools necessary to use social media effectively in healthcare in their respective fields (6–10).

Enter the NSMC

The NSMC internship was established in 2015 as a year-long, free, online, mentored training program envisioned to "train healthcare professionals to effectively harness social media to be leaders in medicine" (11, 12). This internship enables a diverse and international community of interns, composed of specialists, fellows, residents, nurses, and medical students, to collaborate and engage in virtual projects and activities to become "knowledgeable, proficient, and confident in the use of social media" (12), while maintaining a professional, inclusive, and respectful atmosphere within the virtual community.

Learning activities

The internship runs from January to November of each year, where the interns are divided into 4 mentoring pods and rotate through the four NSMC core rotations:

1. Graphical communications: to create visual abstracts and infographics with the potential of publication in journals
2. Tweetorial and blogposts: to produce and publish tweetorials and blog posts with the Renal Fellow Network and *American Journal of Kidney Diseases* (*AJKD*) blog
3. Podcasting: to contribute to the NSMC podcast, "Tales from the Tubule," under the guidance of experienced podcast producers
4. NephJC (a Twitter-based journal club): to produce visual abstracts and summaries and to participate and host the fortnightly NephJC

Most of the public activities occur on Twitter, whereas the back-channel communication between interns and faculty occurs on a semi-private communication platform (Slack) (13).

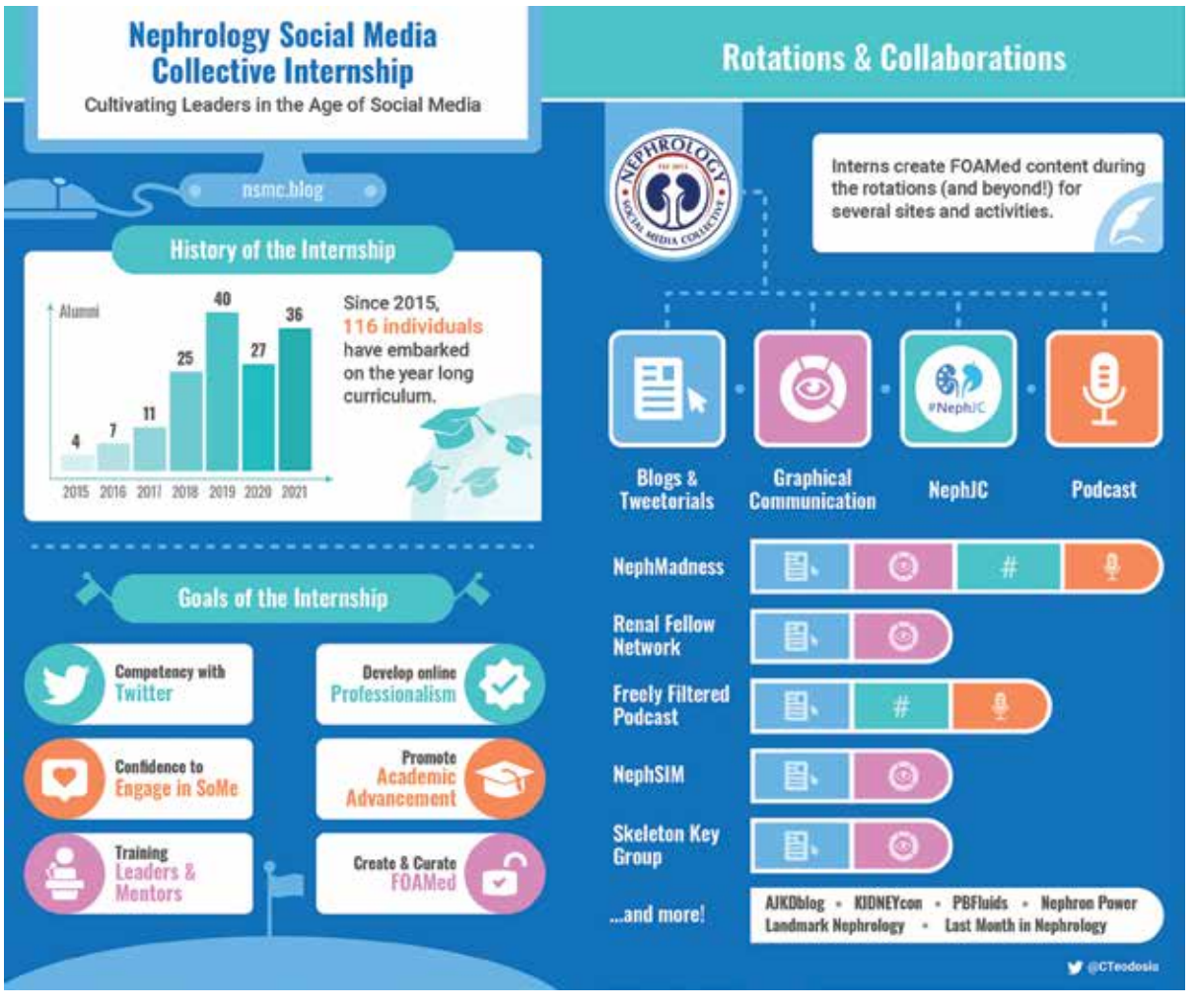
Interns also learn important social media skills—including Online Professionalism, Medical Advocacies, Social Media and Leadership, Twitter & Slack 101, Creating and Producing Podcasts, and Animated Videos—from the faculty and invited speakers during "Open Mic Nights," which take place on Zoom. These sessions are recorded so they can be watched at any time.

In addition to this, interns are encouraged to create FOAMed resources for the highly popular annual online educational game NephMadness and attend a unique educational meeting, KIDNEYcon, held every April, for those interested in participating in hands-on workshops and collaborating and learning more about nephrology. There are also multiple opportunities to work on projects with collaborators who are leaders and pioneers in nephrology education.

Onward and upward

The internship culminates with a graduation ceremony during the American Society of Nephrology's Kidney Week every fall. where faculty, alumni, and graduating interns celebrate the achievements of the past year. Although this signifies the end of the internship, the connections and opportunities created by the internship have provided avenues to collaborate with colleagues from all over the world, serve as leaders on national committees, join editorial boards of journals, give talks in local and international conferences, as well as provide mentorship to younger interns. All of these opportunities serve as a springboard to propel careers and cultivate new generations of leaders and pioneers in nephrology education around the globe.

For more information about the program, visit the website www.nsmc.blog, and look for applications each December. ■



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Dr. Lim is an executive member of the Nephrology Social Media Collective. The other authors report no conflicts of interest.

References

1. Mallin M, et al. A survey of the current utilization of asynchronous education among emergency medicine residents in the United States. *Acad Med* 2014; 89:598–601. doi: 10.1097/ACM.0000000000000170
2. Rope RW, et al. Education in nephrology fellowship: A survey-based needs assessment. *J Am Soc Nephrol* 2017; 28:1983–1990. doi: 10.1681/ASN.2016101061
3. Colbert GB, et al. The social media revolution in nephrology education. K*idney Int Rep* 2018; 3:519–529. doi: 10.1016/j.ekir.2018.02.003
4. Hoskins F. Response to article: "Social-media-enabled learning in emergency medicine: A case study of the growth, engagement and impact of a free open access medical education blog." *Med Teach* 2018; 40:1080. doi: 10.1080/0142159X.2018.1468073
5. Farouk SS, et al. Design, dissemination, and assessment of NephSIM: A mobile-optimized nephrology teaching tool. *J Grad Med Educ* 2019; 11:708–712. doi: 10.4300/JGME-D-19-00443.1
6. Harvard Medical School. Digital education: Twitter, podcasts, visuals, and beyond. Accessed 4/23/21. https://cmeregistration.hms.harvard.edu/events/digital-

education-twitter-podcasts-visuals-and-beyond/event-summary-eb029f12d6ec43d5a48a8ef7d47c876b.aspx?dvce=1
7. Monash University. Technology for education in clinical healthcare (EdTech). Accessed 4/23/21. https://www.monash.edu/healthed-institute/short-courses/edtech
8. A fellowship for the 21st century. Digital Communications Fellowship in Pathology. *The Pathologist*, Texere Publishing Ltd. Accessed 5/17/21. https://thepathologist.com/digital-communications-fellowship
9. Lin M. Academic Life in Emergency Medicine AIR Series. Academic Life in Emergency Medicine. 2014. Accessed on 5/17/21. http://www.aliem.com/aliemap-proved-instructional-resources-air-series
10. CardioNerds. CardioNerds Academy. Accessed 5/17/21. https://www.cardionerds.com/academy/
11. Shah S, Topf J. Mentorship in the digital age: Nephrology social media collective internship. *Clin J Am Soc Nephrol* 2019; 14:294–296. doi: 10.2215/CJN.09970818
12. Ramakrishnan M, et al. Training the public physician: The nephrology social media collective internship. *Semin Nephrol* 2020; 40:320–327. doi: 10.1016/j.semnephrol.2020.04.012
13. Lin J. Picking up the Slack: Collaboration tools to build community and increase productivity in nephrology. *Semin Nephrol* 2020; 40:298–302. doi: 10.1016/j.semnephrol.2020.04.009

NephSIM Nephrons: A Year-Long Virtual Mentorship Program to Foster Interest in Nephrology

By Elinor C. Mannon, Matthew A. Sparks, and Samira S. Farouk

Mentorship and early educational experiences play critical roles in influencing trainees' long-term career goals, and the field of nephrology is no exception. Like any specialty, one's decision to pursue nephrology likely results from a combination of clinical experiences, nephrology education, and mentorship both during medical school and residency. A majority of nephrology fellows previously reported deciding to pursue a nephrology fellowship during residency (1), and 33% of US internal medicine subspecialty fellows who did not choose nephrology identified the lack of a clear mentor as being one of the reasons for not doing so (2). Additionally, almost one-quarter of respondents highlighted how a lack of positive nephrology educational experiences negatively impacted their decision to pursue nephrology as a career (2). Whereas these data reinforce the anecdotal importance of mentorship in specialty selection, opportunities for the creation and establishment of mentor-mentee relationships are not always readily available—particularly within nephrology. Creation of peer-peer networks and trainee-mentor relationships in nephrology may also be difficult given the relatively small number of applicants to nephrology fellowship programs. After the 2020 Nephrology Fellowship Match, 43% of training programs remained unfilled for the 2021 academic year (3). Further, nephrology educational experiences are often limited to preclinical coursework in medical school and both didactics and clinical experiences during internal medicine or pediatric residencies.

To address these needs within nephrology, a 1-year international, virtual mentoring program for trainees (NephSIM Nephrons) was launched in January 2021 (4). The goal of this program is to provide an array of virtual learning and networking experiences throughout the year for trainees of all levels who have an interest in learning more about nephrology as a specialty. Trainees in the program are divided into groups (tubules) of 7–8 and paired with 2–3 volunteer faculty mentors (Figure 1). Trainees and mentors have been paired to try to match similar interests as well as geographical locations. The NephSIM Nephrons faculty consists of 45 nephrologists with diverse geographical and career backgrounds. The 2021 cohort of 112 trainees are located in 24 countries, with 33% of the participants being medical students and 60% being internal medicine or pediatrics residents. Other Nephrons participants include graduate students, as well as several postdoctoral trainees and research assistants.

The 1-year virtual curriculum for trainees (Figure 2) is designed to expose trainees to diverse nephrology educational experiences earlier in their medical careers and provide opportunities to identify and form relationships with nephrologists. Several of these educational sessions highlight nephrology free, open-access medical education (FOAMed) resources such as NephSIM (5), NephMadness (6), and Arkana Live Nephropathology (7) sessions. During quarterly tubule meetings, trainees have the opportunity not only to get to know their faculty mentors but also to discuss neph-

Figure 1. NephSIM Nephrons program structure

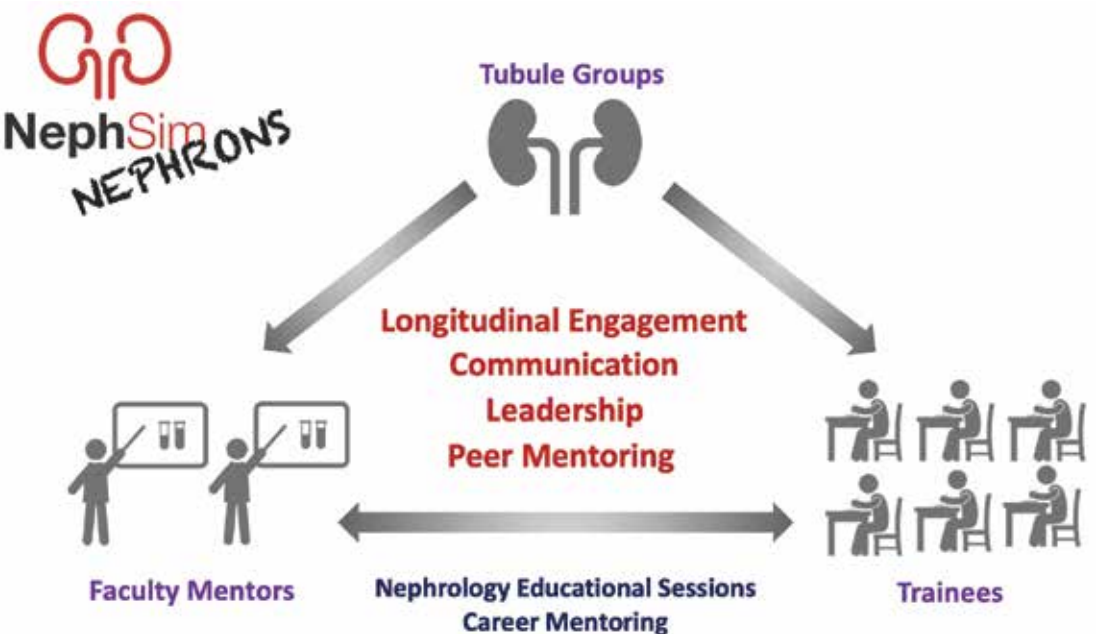
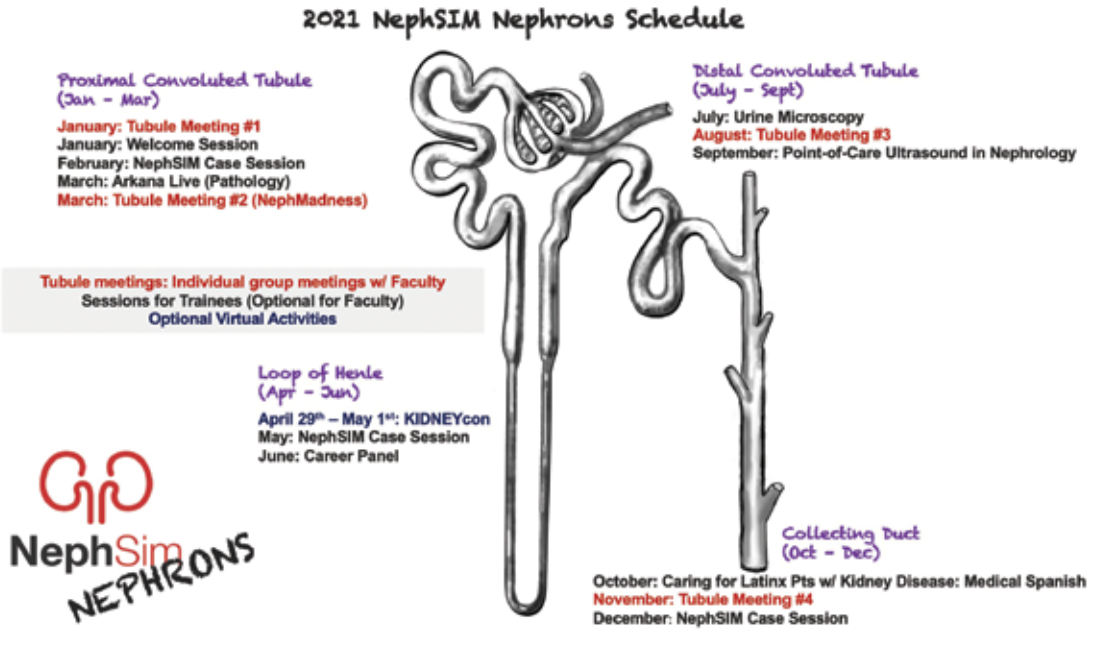


Figure 2. NephSIM Nephrons 1-year virtual curriculum



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NephSIM Nephrons

Continued from page 11

rology cases and topics. Beyond case-based discussions, the diverse career paths of faculty mentors (e.g., physician-scientist, clinician educator, private practice, interventional nephrology, glomerular disease, transplant nephrology) allow trainees to learn about a variety of training opportunities in the field. The diversity of career options within nephrology (8) will be further highlighted during a career panel to be held later in the year.

Feedback from current Nephrons about their experiences has highlighted how participation in this program has positively impacted their decision to pursue nephrology in their long-term career. Carmen Cajina, a medical school graduate in Nicaragua, has found that NephSIM Nephrons "has been a unique and amazing experience. Educational events and meetings with my tubule group have allowed me to enjoy learning and speaking with people passionate about nephrology." Harsha Adnani, a graduate research fellow preparing to begin internal medicine residency at Anne Arundel Medical Center in Annapolis, Maryland, also noted that, "NephSIM Nephrons is a great learning tool for an incoming generation of nephrology enthusiasts. More than anything, I have enjoyed solving clinical cases, learned a ton from the Arkana Live pathology sessions, relished the camaraderie with my tubule team, and the endless opportunities to network. This platform is a gateway to a larger, more diverse community of mentors and educators whose goal is to help and guide you, build confidence to engage in discussions, and show you how fun nephrology can be! NephSIM provides an excellent opportunity to learn from the best in the specialty, and it has certainly advanced my interest in nephrology. I'm so grateful to be a part of this vibrant community."

It is plausible that earlier exposure to and participation in a nephrology mentoring and educational program may increase the number of individuals in the nephrology workforce pipeline. Trainee evaluations, focus groups of both faculty and trainees, and assessment of postgraduate outcomes will be essential in understanding how impactful NephSIM Nephrons may be for trainees. ■

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Conflicts of interest: Elinor C. Mannon is currently enrolled in NephSIM Nephrons. Samira S. Farouk is the cofounder of NephSIM and program director of NephSIM Nephrons. Matthew A. Sparks is an associate program director of NephSIM Nephrons. Drs. Farouk and Sparks are members of the NephMadness Executive Committee and moderators for Arkana Live Nephropathology sessions.

References

1. Shah HH, et al. Career choice selection and satisfaction among US adult nephrology fellows. *Clin J Am Soc Nephrol* 2012; 7:1513–1520. doi: 10.2215/CJN.01620212
2. Jhaveri KD, et al. Why not nephrology? A survey of US internal medicine subspecialty fellows. *Am J Kidney Dis* 2013; 61:540–546. doi: 10.1053/j.ajkd.2012.10.025
3. National Resident Matching Program, Results and Data: Specialties Matching Service 2021 Appointment Year. National Resident Matching Program, Washington, DC, 2021. https://mk0nrmp3oyqui6wqfm.kinstacdn.com/wp-content/uploads/2021/02/SMS_Result_and_Data_2021.pdf
4. NephSIM Nephrons. https://nephsim.com/nephsim-nephrons/
5. Farouk S, et al. Design, dissemination, and assessment of NephSIM: A mobile-optimized teaching tool. *J Grad Med Educ* 2019; 11:708–712. doi: 10.4300/JGME-D-19-00443.1
6. Topf JM, et al. NephMadness: Lessons from seven years on the leading edge of social media medical education. *EMJ Nephrol* 2019; 7:48–53. https://www.emjreviews.com/nephrology/article/nephmadness-lessons-from-seven-years-on-the-leading-edge-of-social-media-medical-education/
7. Hilburg R, et al. Medical education during the coronavirus disease-2019 pandemic: Learning from a distance. *Adv Chronic Kidney Dis* 2020; 27:412–417. doi: 10.1053/j.ackd.2020.05.017
8. The nephrology workforce: The future of kidney care in the United States. *Adv Chronic Kidney Dis* 2020; 27:A1–A8, 277–360. https://www.sciencedirect.com/journal/advances-in-chronic-kidney-disease/vol/27/issue/4

The GlomCon Virtual Fellowship in Glomerular Diseases—A Priceless Innovation in Online Learning

By Edward Kwakyi, Sayna Norouzi, Kate J. Robson, and Harish Seethapathy

I am a newly qualified nephrologist, currently working in the Korle Bu Teaching Hospital (KBTH) in Accra, Ghana. At KBTH, where we run a weekly glomerular diseases clinic, my experience has been rewarding but not without challenges; these include a prolonged turnaround time for kidney biopsy results and choosing reasonable alternatives when standard-of-care medications are not affordable or available.

My experience as a GlomCon fellow has been immeasurable. The opportunity to learn and interact with pacesetters in glomerular diseases has been an invaluable experience. The histopathology sessions with phenomenal nephropathologists have demystified a vital tool that I had previously approached with great uncertainty and trepidation. Interacting virtually with colleagues practicing in diverse socioeconomic and geographic environments has given me great insight into the practicability of clinical solutions and the need to tailor one's practice to suit the prevailing circumstances. The collegiality with my colleagues and approachability of the faculty have helped me learn the nuances of glomerular disease management in a fun, unassuming, and safe environment. Other key attributes that have been emphasized throughout this program are research and presentation skills, which I hope will stand me in good stead when I become the teacher for the next generation. The knowledge and teaching skills I have gained as a GlomCon fellow will go a long way toward improving the outcomes of my patients and contribute significantly to glomerular disease training in Ghana.

—Edward Kwakyi, MD, Korle Bu Teaching Hospital, Accra, Ghana

The art of teaching medicine has evolved continuously since its inception. In the ever-expanding virtual education space, there is a need for high-quality innovative teaching methods that are streamlined to directly benefit patient care. The diagnosis and management of glomerular disease are highly specialized. In the era of super-specialization, the global pooling of data and expertise enables learners to undertake an in-depth journey into glomerular disease diagnosis and management that is often not feasible at a single center. In a large survey of US-based trainees, nearly 40% of fellows felt that they would benefit from further instruction in the diagnosis and management of glomerular disease (1).

The GlomCon organization is an international grass roots initiative for which its philosophy is to promote collaboration among clinicians, pathologists, and researchers to help patients with glomerular disease. With its educational arm—the GlomCon virtual fellowship (est. 2020)—we have tried to incorporate the philosophy of GlomCon with the attributes of a time-worthy online learning program that includes content, expertise, and engagement. The learning experience is further enhanced by the infusion of a student-led learning component into the program. The goal of the fellowship is to advance and complement the education provided by training programs and focus it to benefit patients with glomerular disease in the community.

The GlomCon fellowship, in its inaugural year (2020–2021), admitted 52 fellows from 19 countries to be educated in the diagnosis and management of glomerular diseases by renowned experts in the area (2). The fellowship is made possible by the generosity of nearly 75 international experts who volunteer their time and effort. Due to their various geographical locations, fellows are divided into two groups based on time zones: Nephrin group (America, Europe, Africa) and Podocin group (Asia, Oceania). The groups run concurrently, based on a comprehensive curriculum. The course structure consists of two hour-long sessions that take place every 2 weeks. The sessions are a mix of active and passive learning exercises. The first hour is usually a formal clinical or pathology lecture on the specific subject for the session and involves an extensive question-and-answer portion at the end. During the second hour of the session, fellows convene in pre-formed groups (we call them "houses") and present evidence-based solutions to clinical case scenarios, which had been sent via email a week prior, to discuss them with expert faculty. With the learning entirely virtual, fellows from around the world receive the exact same experience, with equal opportunity for learning, collaborating, and eventually becoming educators and leaders themselves. We believe our graduates will amplify the benefits of the program by focusing their efforts on improving the care of patients with glomerular diseases in our community and globally.

The GlomCon fellowship was set to begin accepting applications for its 2021–2022 class around mid-June 2021 (2). There is no cost of enrollment, and fellows are chosen through a merit-based application review. ■

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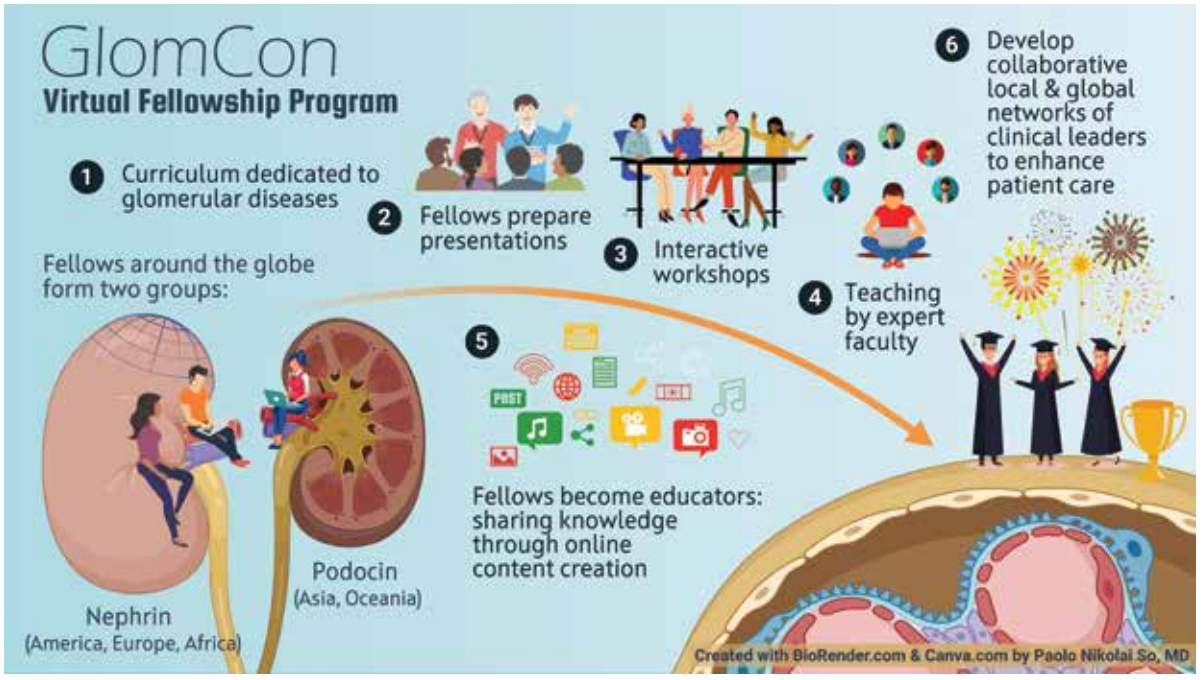
The authors have no conflicts of interest.

References

1. Rope et al. Education in nephrology fellowship: A survey-based needs assessment. *J Am Soc Nephrol* 2017; 28:1983–1990. doi: 10.1681/ASN.2016101061
2. GlomCon*edu*. A new online initiative for nephrology fellows and early-career nephrologists. https://edu.glomcon.org/fellowship



Glomerular Disease Nephrology Training

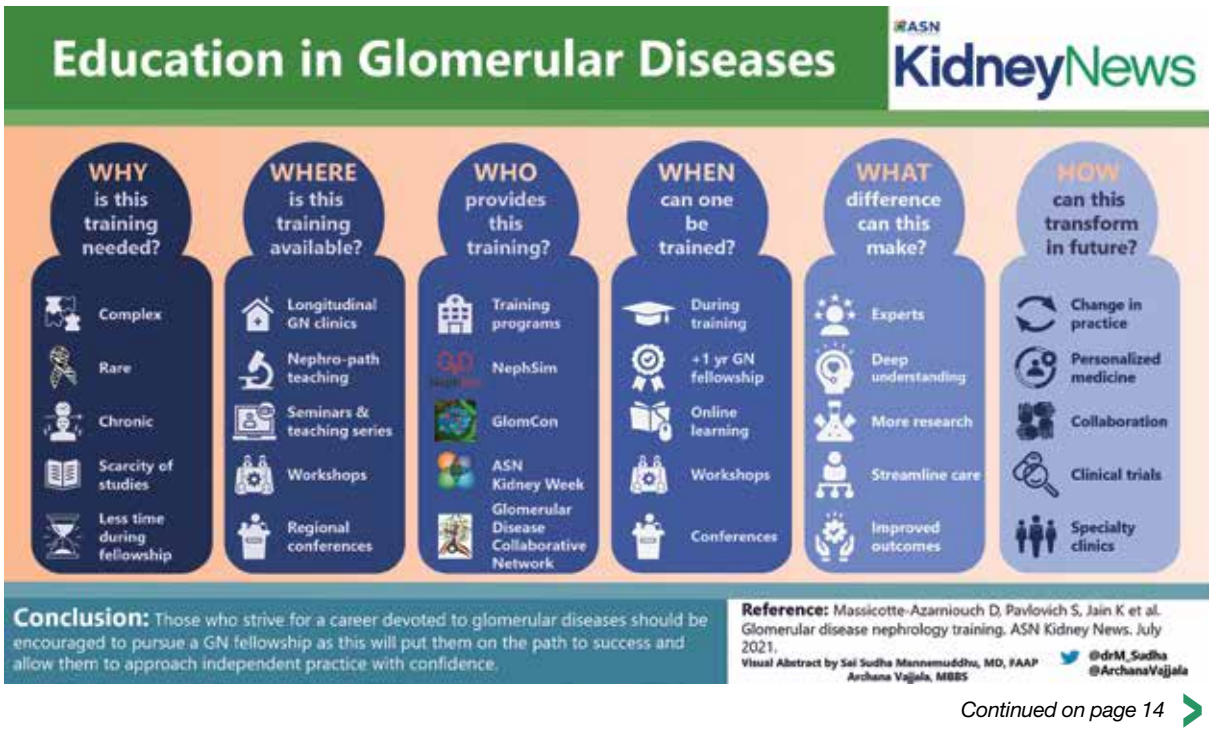
By David Massicotte-Azarniouch, Stephanie S. Pavlovich, and Koyal Jain

Medical knowledge and patient complexity are rapidly growing, particularly in nephrology, one of the most complex medical subspecialties (1). This complexity allows for diversity in practice as nephrologists often develop niche areas of expertise including glomerular diseases, home dialysis, and transplantation, among others. Glomerular diseases are a particularly stimulating aspect of nephrology. The multisystemic nature of these diseases tends to elicit interest from individuals with a strong intellectual curiosity. The ability to effectively treat glomerular diseases, in some cases warding off kidney failure, can make it an extremely rewarding process. In addition, the chronic nature of these diseases leads to a long-term patient-doctor relationship with a strong rapport. Due to the scarcity of large, high-quality studies, physicians are often required to individualize management through involvement of the patient and shared decision-making. Close collaboration with a multidisciplinary medical team (renal pathology, rheumatology, and pulmonology, to name a few) is inherent to the practice, making it both stimulating and diverse. Finally, there are many opportunities for research endeavors and the potential to make a distinct impact with practice-changing knowledge.

The knowledge a nephrology fellow must acquire within a 2-year period is tremendous, making it challenging to ensure competency in areas such as glomerulonephritis (GN) due to rarity and inconsistent exposure, unless pursuing a yearlong GN fellowship. Participation in longitudinal GN clinics may remedy this by ensuring regular exposure and patient follow-up. In addition to this, an emphasis on nephropathology teaching is essential given its integral role in diagnosing and understanding glomerular diseases. Both nephrology trainees and program directors acknowledge the importance of nephropathology education (2, 3). Regular renal biopsy rounds with nephropathologists, or even elective nephropathology rotations, are valuable teaching resources for trainees. Unfortunately, not all training programs have nephropathologists, and biopsies may be sent to other institutions, limiting learning opportunities (2). In such cases, collaboration with centers with nephropathology services would be beneficial by, for example, providing virtual lectures or biopsy reviews. There are also many GN educational sessions at the international, national, and regional levels that should be promoted by program directors. The Glomerular Disease Study & Trial Consortium (GlomCon) offers GN-focused virtual seminars, conferences, and teaching series dedicated to trainees, allowing people from all over the globe to learn from world leaders in the field. Every year at Kidney Week, the American Society of Nephrology offers a comprehensive, multiday glomerular diseases update course. On a regional level, the Glomerular Disease Collaborative Network Annual Conference is offered to trainees from programs in the southeast United States. Program directors should promote these valuable educational resources to their trainees, particularly those who have an interest in the field.

Despite the opportunities available for advancing knowledge in GN outside of a fellowship, nephrology trainees who aspire to achieve proficiency and a niche area of practice in glomerular diseases should consider pursuing 1–2 years of a focused GN fellowship with qualified mentors. Extensive clinical exposure, beyond what can be achieved during 2 years of general nephrology training, is often required to develop expertise prior to independent practice given the rarity of glomerular diseases. GN fellowships allow fellows to gain clinical experience and expose them to the subtleties of managing patients with glomerular diseases and of dealing with immunosuppression. Furthermore, immersing oneself in a specific area for a dedicated period allows one to gain a deep understanding of the scientific literature—how to interpret it and how to apply it to clinical care. GN fellowship training may also provide research experience, clinical or basic science, and the ability to create lifelong collaborative networks. This is an important stepping stone for a career in academic medicine.

Setting up a successful GN practice may be challenging, and a GN fellowship is a great way to appreciate the organizational aspects of setting up a practice. Indeed, many factors need to be taken into consideration prior to establishing a GN clinic, such as reimbursement and patient sharing with other members in the practice group. This may start as a half-day clinic where general nephrologists direct their patients with glomerular diseases. Additionally, providing a multidisciplinary clinic with rheumatology, dermatology, or pulmonology requires proper planning but addresses the multisystemic nature of GN and may improve patient care. Setting up infusion centers for administration of therapies or even a biopsy suite could help make the clinic financially attractive and convenient for patients. With an associated infusion center, the opportunity for research, including clinical trials, also becomes more feasible. Finally, and most important, delivering multidisciplinary care, including allied health professionals such as nurses, dieticians, pharmacists, and social workers, allows one to provide comprehensive pa-



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Glomerular Disease

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tient care and helps facilitate access to medications.

This can all seem like a daunting task but working during a GN fellowship in an environment that can then be used as a model of care is an invaluable opportunity. Therefore, those who strive for a career devoted to glomerular diseases should be encouraged to pursue a GN fellowship, as this will put them on the path to success and allow them to approach independent practice with confidence. ■

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The authors have no conflicts of interest.

References

1. Tonelli M, et al. Comparison of the complexity of patients seen by different medical subspecialists in a universal health care system. *JAMA Netw Open* 2018; 1:e184852. doi: 10.1001/jamanetworkopen.2018.4852
2. Mechery V, et al. Nephropathology education during nephrology fellowship training in the United States. *Kidney Int Rep* 2017; 3:236–241. doi: 10.1016/j.ekir.2017.11.01
3. Rope RW, et al. Education in nephrology fellowship: A survey-based needs assessment. *J Am Soc Nephrol* 2017; 28:1983–1990. doi: 10.1681/ASN.2016101061

The Current State of Transplant Training in Nephrology Fellowships

By Fitsum Hailemariam, Beje Thomas, and Anju Yadav

Kidney transplantation is the optimal treatment for kidney failure (1). As recently as 2019, there were 244,000 kidney transplant recipients (2) with a functioning kidney allograft, and this number continues to grow (3, 4). Thus, it is very important that we strive to ensure our workforce is trained to be able to care for this group of patients. A 2020 review article (5) estimates there are 1200–1400 transplant nephrologists in the United States. There are 149 accredited nephrology training programs in the United States (6) and <50% (63/149) of these with accredited transplant nephrology programs (7). Less than 10% of nephrology fellows usually pursue an additional year of transplant training (Figure 1).

The Accreditation Council for Graduate Medical Education (ACGME) requires a minimum of 2 months of clinical experience during nephrology fellowship training on an active transplant service (ACGME core program requirements, section IV.A.6.a).(2)) in managing all aspects of kidney transplant care (8). This longitudinal care includes preemptive listing or waitlist candidacy assessment; immediate posttransplant care (at least 10 new transplants); and the management of immunosuppression, rejection, and long-term care of the patient with a kidney transplant. To achieve this, the nephrology fellowship program should be a transplant center or have a written agreement with a transplant center (ACGME common program requirements, section II.D.4.c)). Outside rotations for fellows for transplant education should be arranged for trainees.

The ultimate goal of fellowship training is to adequately prepare fellows to be able to provide compassionate, appropriate, and effective peri-transplant care for kidney transplant recipients and kidney donors. When these trainees graduate, they help create a shared care model between transplant centers and general nephrologists. Moreover, reflecting this point, 11% of the American Board of Internal Medicine (ABIM) nephrology subspecialty blueprint for the board examination covers transplant-related topics (9). Thus, the core curriculum of any nephrology fellowship program should heavily emphasize transplantation topics.

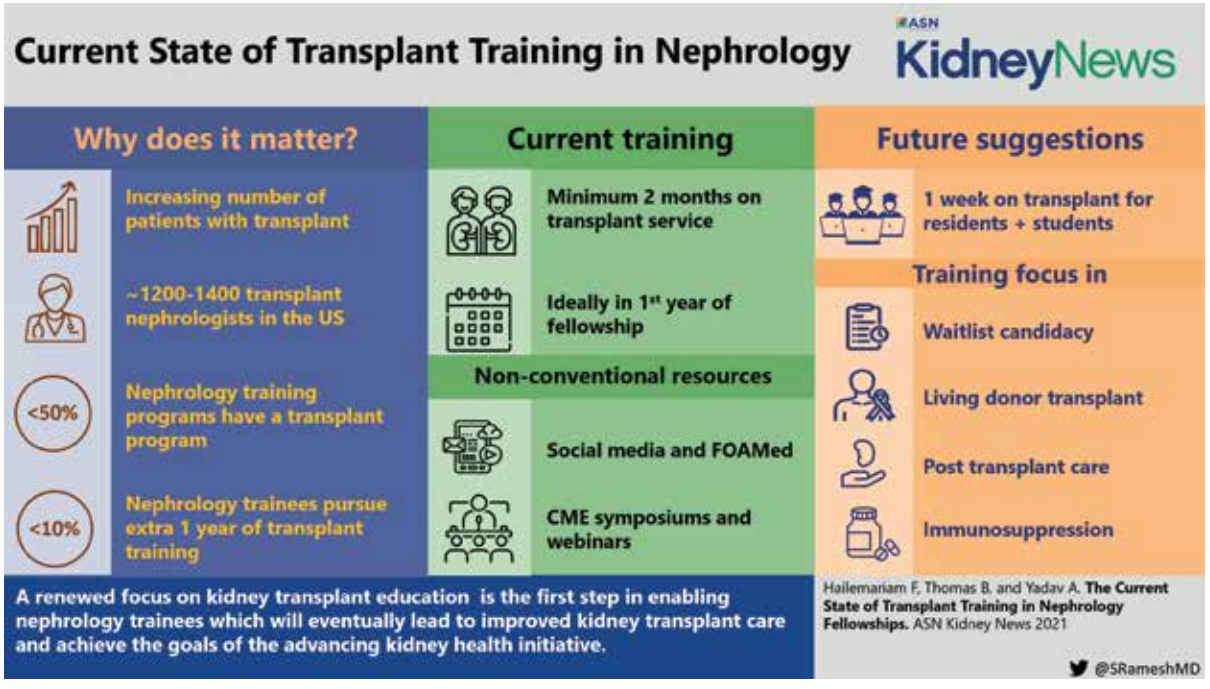
Apart from conventional fellowship training, online education, including the use of social media platforms (FOAMed [free open access medical education]), can be used to supplement the training. Continuing medical education (CME) symposiums and webinars are great tools to stay abreast with advances in kidney transplantation, and a lot of these resources are available on social media platforms for free. Early introduction of kidney transplantation in medical education, at the student or resident level, can spark interest in nephrology and/or transplant. In addition to rotation on consults and dialysis service, exposure to patients with kidney transplant is important, as we have done at our institutes. Out of 4 weeks, students/residents spend 2 weeks in consult service and 1 week each in dialysis and transplant rotation. Regarding nephrology fellows, it would be ideal if there were exposure from early in the first year of fellowship.

The care of the kidney transplant recipient is complex and involves a multidisciplinary team approach that manages medical care, financial, and social work concerns. This makes the recipient an important stakeholder in posttransplant care and outcomes (10), highlighting the importance of more structured transplant education during fellowship. Robust CME opportunities for practicing physicians in general nephrology should be prioritized, and an enhanced transplant representation in national meetings is desired.

In conclusion, a renewed focus on kidney transplant education is the first step in enabling nephrology trainees, which will eventually lead to improved kidney transplant care and achieve the goals of the Advancing American Kidney Health Initiative. ■

When these trainees graduate, they help create a shared care model between transplant centers and general nephrologists.

Figure 1.



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The authors have no conflicts of interest.

References

1. Abecassis M, et al. Kidney transplantation as primary therapy for end-stage renal disease: A National Kidney Foundation/Kidney Disease Outcomes Quality Initiative (NKF/KDOQITM) conference. *Clin J Am Soc Nephrol* 2008; 3:471–480. doi: 10.2215/CJN.05021107

2. United Network for Organ Sharing (UNOS). Transplant trends. More deceased-donor organ transplants than ever. 2021. https://unos.org/data/transplant-trends/
3. United States Renal Data System (USRDS). *2020 USRDS Annual Data Report: Epidemiology of kidney disease in the United States*. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2020. https://adr.usrds.org/2020
4. 2019 Annual Report of the U.S. Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients. *OPTN/SRTR 2019 Annual Data Report: Kidney*. Department of Health and Human Services, Health Resources and Services Administration, Healthcare Systems Bureau, Division of Transplantation, Rockville, MD; United Network for Organ Sharing, Richmond, VA; University Renal Research and Education Association, Ann Arbor, MI. https://srtr.transplant.hrsa.gov/annual_reports/2019/Kidney.aspx
5. Concepcion BP, et al. The transplant nephrology workforce in the United States: Current state and future directions. *Adv Chronic Kidney Dis* 2020; 27:336–343.e1. doi: 10.1053/j.ackd.2020.05.005
6. Brotherton SE, et al. Graduate medical education, 2019–2020. *JAMA* 2020; 324:1230–1250. doi: 10.1001/jama.2020.14635
7. Transplant Nephrology Fellowship Training Accreditation Program, LLC. List of accredited transplant nephrology fellowship programs. Accessed May 25, 2021. http://www.txnephaccreditation.org/programs
8. Accreditation Council for Graduate Medical Education (ACGME). ACGME Program Requirements for Graduate Medical Education in Nephrology. July 1, 2020. https://www.acgme.org/Portals/0/PFAssets/ProgramRequirements/148_Nephrology_2020.pdf?ver=2020-06-29-162357-583
9. American Board of Internal Medicine (ABIM). Nephrology Certification Examination Blueprint. Accessed May, 25, 2021. https://www.abim.org/Media/iohh2ahg/nephrology.pdf
10. Sawinski D, et al. Introduction to kidney transplantation: Long-term management challenges. *Clin J Am Soc Nephrol* [published online ahead of print March 10, 2021]. doi: 10.2215/CJN.13440820; https://cjasn.asnjournals.org/content/early/2021/04/01/CJN.13440820

Critical Care Nephrology: The Formidable Combination

By Kristin Hoover, Amanda Dijanic Zeidman, and Javier A. Neyra

What is nephrology critical care?

The census of hospitalized critically ill patients has risen over the last decades (1). As this population expands, leaders of intensive care units (ICUs) are attempting to diversify the healthcare team. A rapidly expanding area within the diversified ICU team is nephrology critical care. The combination of nephrology and critical care is a seamless amalgamation of physiology, pathobiology, and organ crosstalk, which renders the clinician equipped with expertise in acute kidney injury, acid-base/electrolyte disorders, and volume management (Figure 1).

Importantly, as the critically ill population becomes sicker, reliance on extracorporeal support therapies (kidney replacement therapy, hemoperfusion, immunomodulation, plasma exchange, extracorporeal organ oxygenation or CO_2 removal, etc.) is essential to state-of-the-art care in settings of severe multiorgan failure (2). A deep understanding of the intricacies in the provision of these therapies is a valuable asset to any ICU practice. The COVID-19 pandemic stressed the importance of supply of these therapies and reinvigorated the value of the nephrologist in the ICU (3).

How to train in nephrology critical care

There are two tracks to become dual board certified in nephrology and critical care medicine: 1) 3-year combined fellowship or 2) two separate fellowships in succession. For the combined 3-year fellowship, trainees often have the option of blending the two over the total time in training or completing one field followed by the other. When formally separating the two fellowships, either at the same institution or different institutions, it should be noted that nephrology followed by critical care allows for a 3-year completion time (2-year nephrology, 1-year critical care); however, critical care followed by nephrology results in a 4-year completion time (2 years for both programs), as even with the 2-year critical care base, nephrology training requires an additional 2 years to be board eligible.

An alternative is to become a nephrologist focused on critical care. In this track, trainees customize their fellowship to accommodate more ICU rotations and develop specific skills in bedside ultrasonography and multifaceted organ support. The training can be further complemented by research year(s) for those interested in academic medicine in the scholar track. How does one go about deciding their path? Multiple factors come into play such as location, training opportunities, and work-life balance. However, an important question to ask yourself is: How do you envision your future practice? The answer may be intercalating time as an intensivist and a nephrologist or being a full-time nephrologist focused on the comprehensive spectrum of acute care nephrology.

Why train in nephrology critical care?

A recent survey of clinicians dual certified in nephrology and critical care revealed overall high employment satisfaction, although some participants highlighted difficulties in job search/availability post-training. The survey also noted that about one-half of dual-certified clinicians are currently working in academic medicine (4). This is likely in part due to it being easier to negotiate a dual appointment between two divisions in academic hospitals. There remains no clear structure and less flexibility for this dual appointment in private practice settings, particularly those with close ICU models. The average compensation appears to be higher in dual practice as compared to nephrology alone. The practice of acute care nephrology remains an exciting and innovative field with dynamic collaboration, constant scientific discovery, and evolving technologies. Although we are not needed every day, we can offer complementary expertise when we have a chance. At the end of the day, the intensivist is not only waiting for dialysis but for the acute care nephrologist to come. ■

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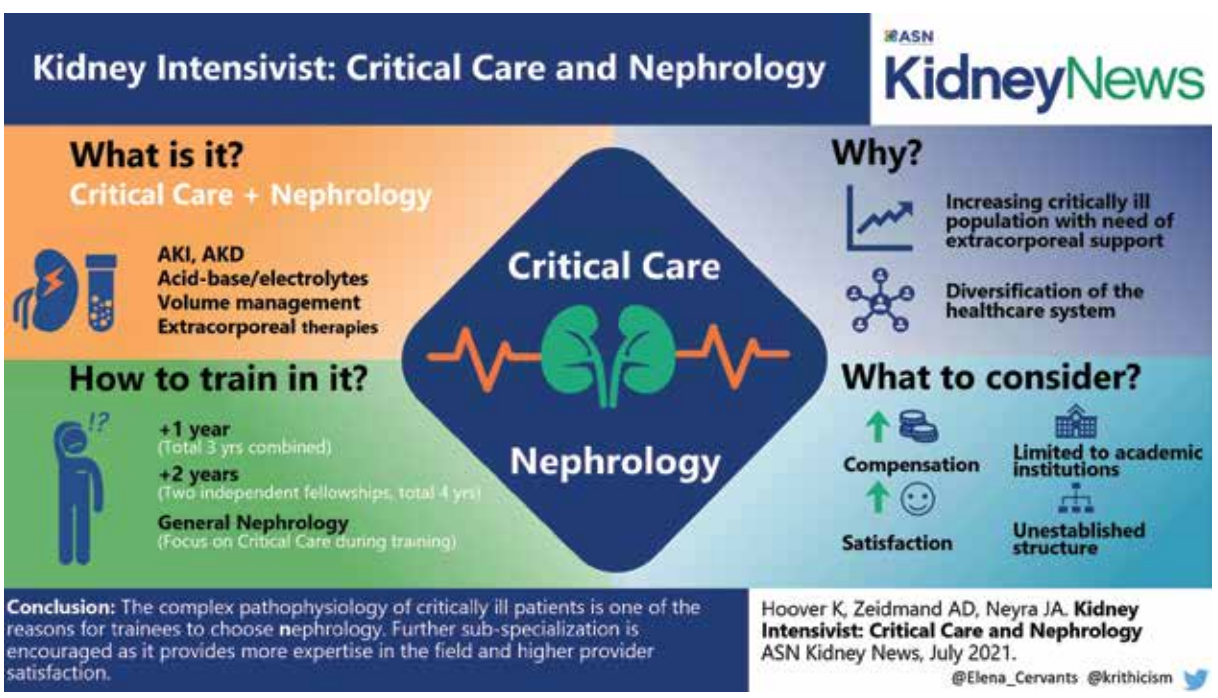
The authors have no conflicts of interest.

References

1. Halpern NA, et al. Trends in critical care beds and use among population groups and Medicare and Medicaid beneficiaries in the United States: 2000–2010. *Crit Care Med* 2016; 44:1490–1499. doi: 10.1097/CCM.0000000000001722
2. Husain-Syed F, et al. Extracorporeal organ support (ECOS) in critical illness and acute kidney injury: From native to artificial organ crosstalk. *Intensive Care Med* 2018; 44:1447–1459. doi: 10.1007/s00134-018-5329-z
3. Neyra JA, et al. Preparedness of kidney replacement therapy in the critically ill during COVID-19 surge. *Kidney Int Rep* 2020; 5:961–964. doi: 10.1016/j.ekir.2020.05.029
4. Zeidman AD, et al. The workforce in critical care nephrology: Challenges and opportunities. *Adv Chronic Kidney Dis* 2020; 27:328–335.e1. doi: 10.1053/j.ackd.2020.07.003

Figure 1.



POCUS— The New Focus in Nephrology Training

By Matthew Wysocki, Natalie McCall, and Anna Burgner

Popularized by cutting-edge research, on the wards, and even on social media, point-of-care ultrasound, or "POCUS," has the potential to change the way we practice medicine. Widely implemented in numerous clinical settings, current ultrasound devices are made to be compact and affordable, and an argument could be made that POCUS should be incorporated into the routine physical exam. Although many specialties of medicine have adopted this tool for everyday practice, it remains absent, underused, or undertaught in many nephrology training programs and practices. In addition, per the 2017 ASN workforce fellow data, 44% of respondents felt their programs lacked ultrasound training (1).

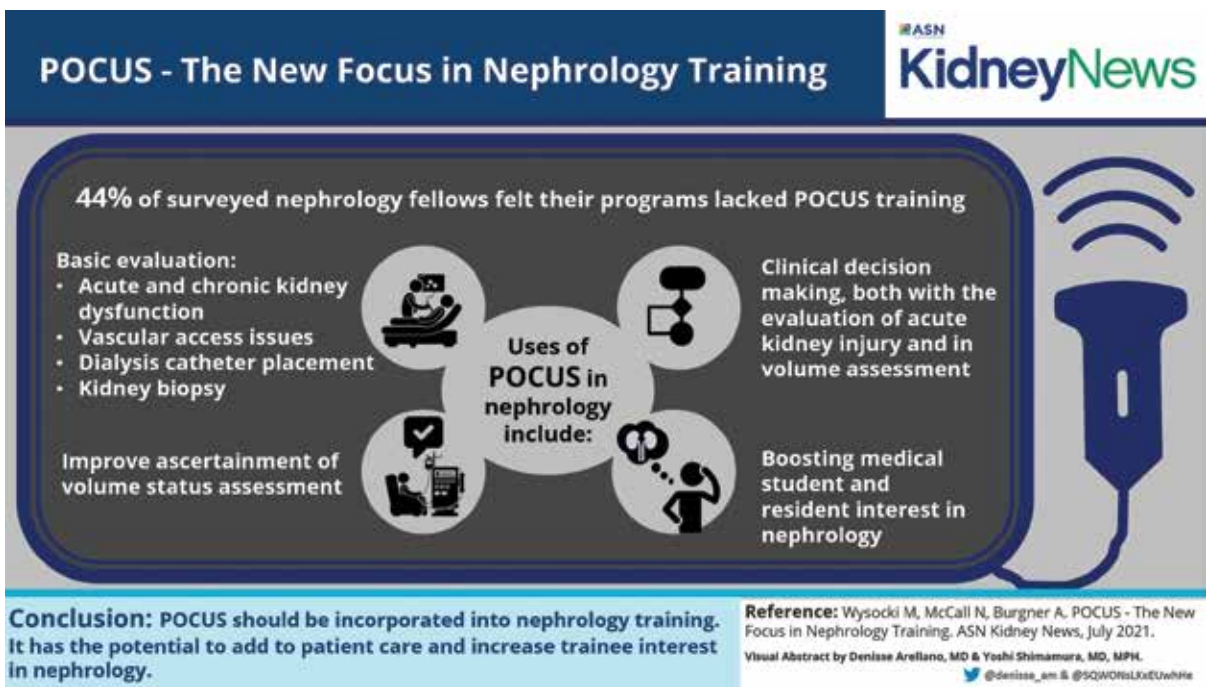
Ultrasound has long been an integral instrument in nephrology and is used in many facets of the field including basic evaluation of acute and chronic kidney dysfunction, vascular access issues, hemodialysis catheter placement, and kidney biopsy. However, less is understood about the role of POCUS performed by the nephrologist and under what circumstances it should be applied. Regardless, there has been a push over the years to incorporate it formally into training. In 2019, Koratala and colleagues (2) shared a model curriculum on how POCUS training can be integrated into a nephrology fellowship. This curriculum was based on the American Society of Diagnostic and Interventional Nephrology (ASDIN) recommendation of 6 weeks of didactic ultrasound interpretation, with the authors suggesting an additional 2 weeks dedicated to teaching POCUS skills, spread out over 2 years. These recommendations reflect the ever-evolving ways of nephrology practice and how ultrasound has shaped it.

The addition of POCUS to nephrology will aid and expedite clinical decision-making, both with the evaluation of acute kidney injury (AKI) and in volume assessment. Assessing for hydronephrosis and nephrolithiasis and even measuring volume status with rapid echocardiography and by scanning for pulmonary B-lines or inferior vena cava (IVC) fullness/collapsibility can all be accomplished with POCUS. A recent study involving the novel venous excess ultrasound model (VExUS), which incorporates the sonographic measurements of IVC and hepatic, portal, and renal vein congestion, showed that AKI risk could be predicted in patients with cardiorenal syndrome (3). The novel renal venous stasis index (RVSI), on the other hand, uses sonographically quantified kidney congestion, which can prognosticate the propensity to develop right heart failure (4). Other studies have shown POCUS being reliable for volume status evaluation among varying kidney functions, especially in predicting intra-dialytic hypotension in dialysis patients (5–7). Furthermore, POCUS skills can be easily taught and are reproducible. POCUS can be effectively implemented in a variety of clinical settings, including the ICU and dialysis unit (7–10). With its application, POCUS has the potential to facilitate AKI evaluation and potentially improve outcomes in patients on dialysis by eliminating some of the guesswork that comes with assessing patients with history and physical exam alone.

Additionally, in an era where 62% of medical schools are integrating courses in ultrasound education, exposing medical students and residents to POCUS in nephrology will give trainees a hands-on, contemporary glimpse into the complex anatomical and physiological principles that make this field so exciting and unique (11). This modern approach to medicine could increase medical student and resident interest in nephrology and be another area of much desired impact.

It is essential to incorporate POCUS in nephrology training. Our field has the opportunity to reinvent the means we go about in caring for our increasingly complex patients while boosting interest in the nephrology field at the same time. For many fellowship programs, there are currently barriers to implementation including cost, attending physician experience, and available resources. Through collaborative efforts and further research on the impact of POCUS on nephrology, this tool has the potential to be a diagnostic and therapeutic necessity that will become more widely accepted, rendering its exclusion obsolete. ■

The addition of POCUS to nephrology will aid and expedite clinical decision-making, both with the evaluation of acute kidney injury and in volume assessment.



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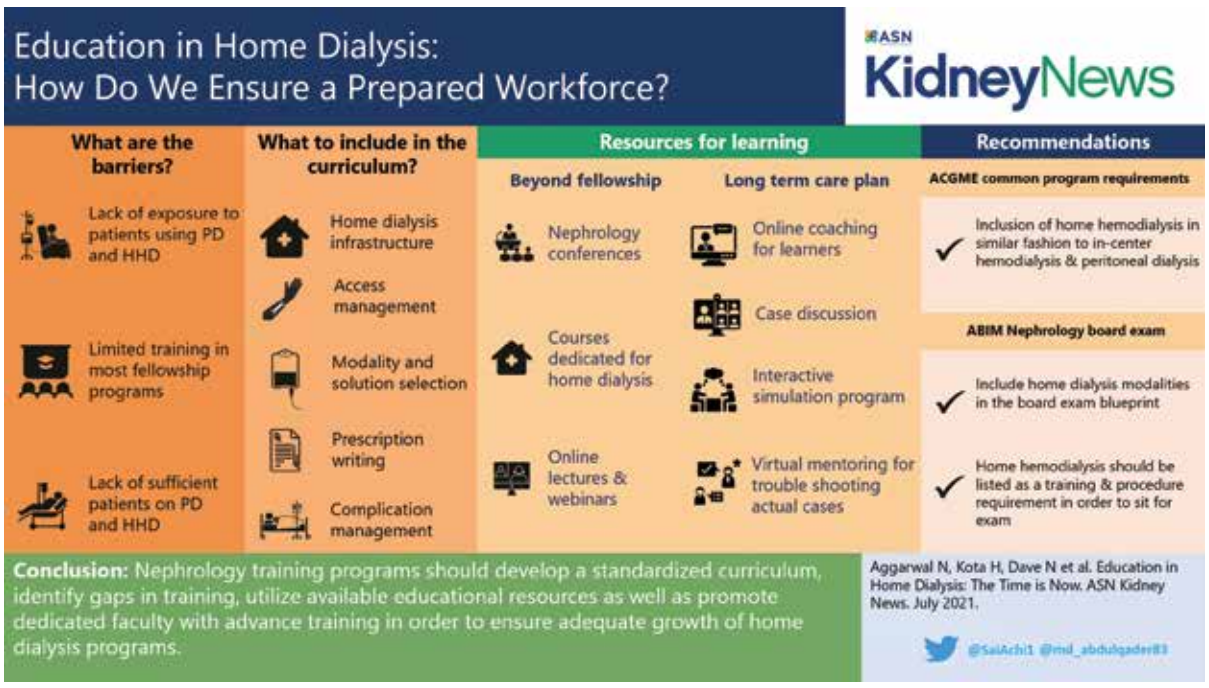
The authors have no conflicts of interest.

References

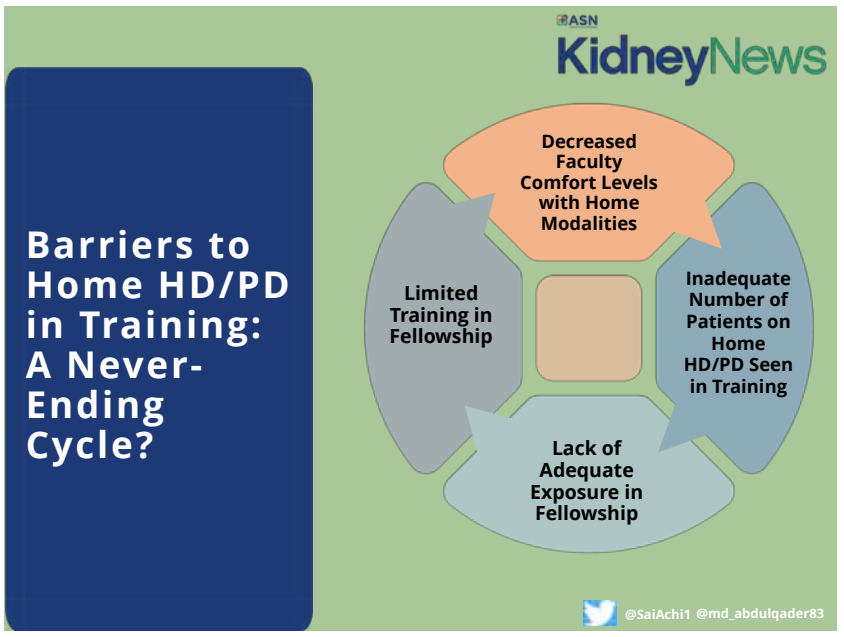
1. Quigley L, et al. Report Highlights. Survey of 2017 nephrology fellows. Prepared for ASN by George Washington University Health Workforce Institute. Accessed May 1, 2021. https://www.asn-online.org/education/training/workforce/Nephrology_Fellow_Survey_Report_2017_Highlights.pdf
2. Koratala A, et al. Integrating point-of-care ultrasonography into nephrology fellowship training: A model curriculum. 2019; 74:1–5. doi: 10.1053/j.ajkd.2019.02.002
3. Bhardwaj V, et al. Combination of inferior vena cava diameter, hepatic venous flow, and portal vein pulsatility index: Venous excess ultrasound score (VEXUS Score) in predicting acute kidney injury in patients with cardiorenal syndrome: A prospective cohort study. *Indian J Crit Care Med* 2020; 24:783–789. doi: 10.5005/jp-journals-10071-23570
4. Husain-Syed F, et al. Doppler-derived renal venous stasis index in the prognosis of right heart failure. J *Am Heart Assoc* 2019; 8:e013584. doi: 10.1161/JAHA.119.013584
5. Khanin Y, et al. Intradialytic hypotension in critically ill patients on hemodialysis with A-line versus B-line pattern on lung ultrasonography. *Kidney Int Rep* [published online ahead of print April 26, 2021]. https://doi.org/10.1016/j.ekir.2021.04.010
6. Covic A, et al. Use of lung ultrasound for the assessment of volume status in CKD. *Am J Kidney Dis* 2018; 71:412–422. doi: 10.1053/j.ajkd.2017.10.009
7. Mallamaci F, et al. Detection of pulmonary congestion by chest ultrasound in dialysis patients. *JACC Cardiovasc Imaging* 2010; 3:586–594. doi: 10.1016/j.jcmg.2010.02.005
8. Zieleskiewicz L, et al. Point-of-care ultrasound in intensive care units: Assessment of 1072 procedures in a multicentric, prospective, observational study. *Intensive Care Med* 2015; 41:1638–1647. doi: 10.1007/s00134-015-3952-5
9. Ben-Baruch Golan Y, et al. Early point-of-care ultrasound assessment for medical patients reduces time to appropriate treatment: A pilot randomized controlled trial. *Ultrasound Med Biol* 2020; 46:1908–1915. doi: 10.1016/j.ultrasmedbio.2020.03.023
10. Gargani L, et al. Efficacy of a remote web-based lung ultrasound training for nephrologists and cardiologists: A LUST trial sub-project. *Nephrol Dial Transplant* 2016; 31:1982–1988. doi: 10.1093/ndt/gfw329
11. Bahner DP, et al. The state of ultrasound education in U.S. medical schools: Results of a national survey. *Acad Med* 2014; 89:1681–1686. doi: 10.1097/ACM.0000000000000414

Education in Home Dialysis: The Time Is Now

By Nidhi Aggarwal, Harshitha Kota, Natasha N. Dave, and Ankur Shah



training is quite inconsistent. We believe home dialysis training during fellowship should be similarly emphasized in the Accreditation Council for Graduate Medical Education (ACGME) common program requirements as is done for kidney transplantation where 2 months of service is mandated, and a minimum of 10 new kidney transplants are to be followed (8). Similar guidance should be provided for home dialysis therapies where it is currently lumped with the 4-month exposure to dialysis in general: "four months of experience with dialysis therapies, both hemodialysis and peritoneal dialysis" (8). Furthermore, the American Board of Internal Medicine (ABIM) should devote more attention to home dialysis modalities, where currently, it is not listed separately on the ABIM Nephrology certification examination blueprint but is presumably contained within several categories (9). Last, in order to sit for the ABIM Nephrology boards, only PD is listed as a procedure requirement and not home HD. The ABIM Nephrology board should similarly list home HD as a training and procedure requirement (10).



Programs should develop a standardized curriculum, identify gaps in training, and use the numerous educational resources to bridge these gaps in order to enhance the educational experience for the fellows. Attention should be focused not only on the management of patients who have chosen a home modality but also on the processes that support that choice, particularly pre-dialysis education. The promotion of dedicated faculty members to undergo advanced training would add to growth of home dialysis programs within the institutions and allow a more meaningful educational experience through direct patient care. ■

Several resources exist to supplement fellowship education. Conferences with extensive didactics on home dialysis include American Society of Nephrology (ASN) Kidney Week, the Annual Dialysis Conference, Nephrology Business Leadership University (NBLU), and the National Kidney Foundation (NKF) Spring Clinical Meeting. Courses such as the Home Dialysis University offer an immersive 2.5-day experience dedicated to all aspects of home dialysis. In addition, online coursework provided by the ASN Dialysis Advisory Group and an industry symposium endorsed by the North American Chapter of the International Society for Peritoneal Dialysis (ISPD) are freely available.

Beyond fellowship, education can also be imparted in the form of lecture series and webinars covering a broad range of topics. One such health educational model is Project ECHO (Extension for Community Healthcare Outcome) in which teleconferencing is used to enhance medical resources in communities that lack specialized care (7). An application in home dialysis was proposed in the landmark NKF-Kidney Disease Outcomes Quality Initiative (KDOQI) report (7). Through this program, clinical experts in home dialysis can provide online coaching for learners. Case studies are discussed to highlight various issues related to patients on home dialysis. Problem-solving techniques can be taught through interactive simulation programs. Virtual mentoring can be made available for troubleshooting actual cases.

Home dialysis education during nephrology fellowship

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Dr. Dave reports serving on a medical advisory board for Tricida Pharmaceuticals.

References

1. Ledebo I, Ronco C. The best dialysis therapy? Results from an international survey among nephrology professionals. *NDT Plus* 2008; 1:403–408. doi: 10.1093/ndtplus/sfn148
2. Berns JS. A survey-based evaluation of self-perceived competency after nephrology fellowship training. *Clin J Am Soc Nephrol* 2010; 5:490–496. doi: 10.2215/CJN.08461109
3. Gupta N, et al. Perceptions of home dialysis training and experience among us nephrology fellows. *Am J Kidney Dis* 2021; 77:713–718.e1. doi: 10.1053/j.ajkd.2020.09.014
4. Wadhwa NK, et al. Does current nephrology fellowship training affect utilization of peritoneal dialysis in the United States? O*pen J Nephrol* 2013; 3:109–114. https://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.1023.1825&rep=rep1&type=pdf
5. Mehrotra R, et al. An analysis of dialysis training in the United States and Canada. *Am J Kidney Dis* 2002; 40:152–160. doi: 10.1053/ajkd.2002.33924
6. Golper TA, et al. Systematic barriers to the effective delivery of home dialysis in the United States: A report from the Public Policy/Advocacy Committee of the North American Chapter of the International Society for Peritoneal Dialysis. *Am J Kidney Dis* 2011; 58:879–885. doi: 10.1053/j.ajkd.2011.06.028
7. Chan CT, et al. Overcoming barriers for uptake and continued use of home dialysis: An NKF-KDOQI

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conference report. A*m J Kidney Dis* 2020; 75:926–934. doi: 10.1053/j.ajkd.2019.11.007
8. Accreditation Council for Graduate Medical Education. ACGME Program Requirements for Graduate Medical Education in Nephrology. July 1, 2020. Accessed May 25, 2021. https://www.acgme.org/Portals/0/PFAssets/ProgramRequirements/148_Nephrology_2020.pdf?ver=2020-06-29-162357-583
9. American Board of Internal Medicine. Nephrology Certification Examination Blueprint. Accessed May 25, 2021. https://www.abim.org/Media/iohh2ahg/nephrology.pdf
10. American Board of Internal Medicine. Nephrology Policies–Training and Procedure Requirements. Accessed May 25, 2021. https://www.abim.org/certification/policies/internal-medicine-subspecialty-policies/nephrology/

Education in Palliative Care during Nephrology Fellowship: Where Are We?

By Tripta Kaur and Holly M. Koncicki

Patients with advanced kidney disease are increasingly older with multiple comorbidities and cognitive and functional impairments and have a limited life expectancy (1). They experience high symptom burden and recurrent hospitalizations and undergo aggressive medical interventions at the end of life with high inpatient mortality and low utilization of hospice services (2). Palliative care, which focuses on the optimization of quality of life, can be delivered alongside chronic kidney disease care. Primary palliative care skills that all nephrology providers should use (2–4) include the following:

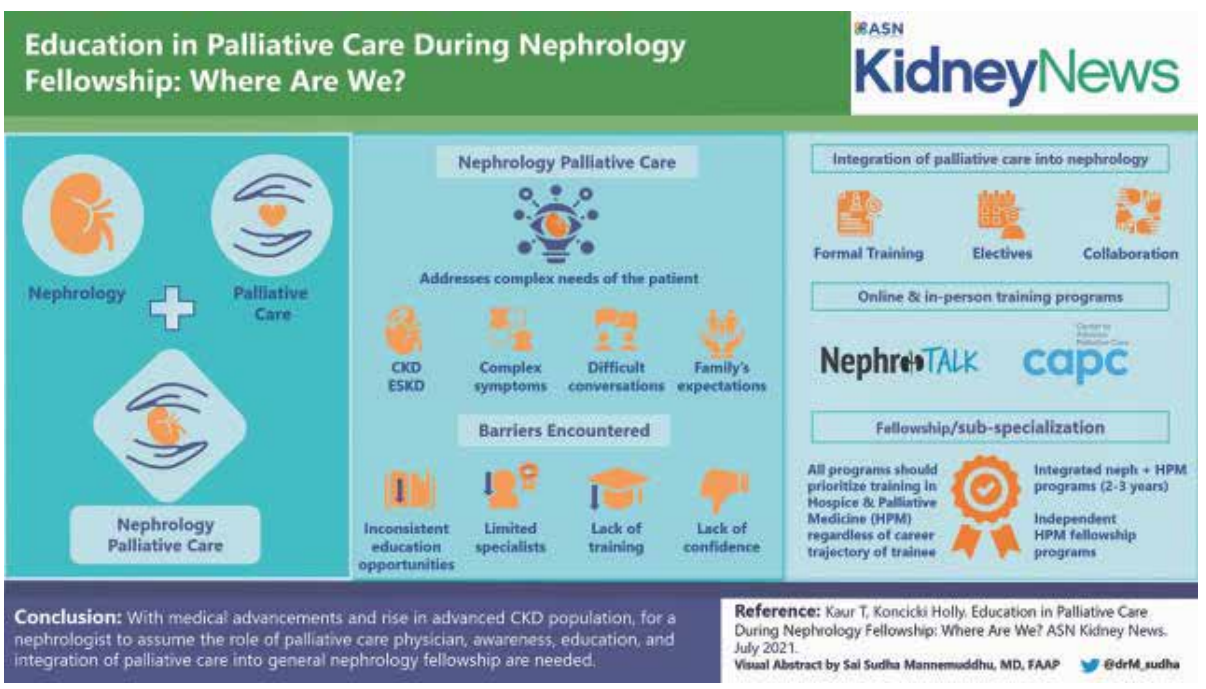
1) education of overall medical condition,
2) evaluation and communication of prognosis,
3) basic goals of care discussions that elicit values and medical wishes to guide consistent treatment plans,
4) advance care planning,
5) identification and management of physical and psychological symptoms, and
6) identification of clinical changes near the end of life.

Nephrology palliative care is a developing subspecialty of nephrology that addresses the more complex needs of patients with advanced kidney disease, including managing complex symptoms, difficult conversations, and discourse over treatment preferences among patients, families, or other providers. There are several barriers in providing nephrology palliative care, ranging from broad misconceptions about the field to healthcare policies limiting feasibility of this care (5, 6). Strikingly, the most fundamental barriers are 1) inconsistent general nephrology education in primary palliative care skills and 2) limited nephrology palliative care specialists. Online nationwide survey-based studies conducted in 2012 and 2013 on second- and third-year nephrology fellows highlighted the lack of primary palliative care training in US nephrology fellowship programs. The majority of nephrology fellows expressed discomfort with primary palliative care due to their lack of educational exposure and felt they would benefit from formal palliative care rotations with a structured curriculum during fellowship (7, 8).

The integration of primary palliative care in general nephrology fellowships is in development. Formal curriculum or palliative care electives have been created in some institutions through collaboration with palliative care, geriatric, and nephrology faculty and are taught by interprofessional (physicians, social workers, and pharmacists) teams (9). There are also several online and in-person training programs including *NephroTalk Conservative Care Curriculum, VitalTalk, Center to Advance Palliative Care (CAPC) Clinical Training, Stanford Palliative Care Training Portal,* and *Coalition for Supportive Care of Kidney Patients* webinar series (10, 11). We believe that institution-based nephrology palliative care curriculums should be incorporated into general nephrology fellowship training programs. An ideal curriculum includes the following: 1) didactics on fundamental concepts of nephrology palliative care, 2) interactive serious illness communication workshops, 3) individualized exposure through active participation and rounding with palliative care teams, and 4) guided implementation of conservative kidney care.

To subspecialize in nephrology palliative care, there are several pathways to obtain dual board eligibility. Currently, there are several 3-year integrated nephrology and hospice and palliative medicine (HPM) fellowship programs, including Mount Sinai Hospital and Stanford University. Starting in July 2021, the University of Pennsylvania, Yale University, and The University of North Carolina are initiating an Accreditation Council for Graduate Medical Education (ACGME) combined 2-year nephrology and HPM fellowship program. Last, the option to pursue an independent HPM fellowship following completion of general nephrology fellowship is available.

With the advancement of medicine, patients with advanced kidney disease are aging and presenting greater medical complexity. The role of the nephrologist is evolving. In order to adapt into this new role, education in nephrology palliative care must continue to grow through awareness, integration into general nephrology fellowships, research, and most important, the willingness to step out of our comfort zones and have difficult conversations. ■



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The authors have no conflicts of interest.

References

1. Gelfand SL, et al. Kidney supportive care: Core curriculum 2020. *Am J Kidney Dis* 2020; 75:793–806. doi: 10.1053/j.ajkd.2019.10.016
2. Koncicki HM, Schell JO. Communication skills and decision making for elderly patients with advanced kidney disease: A guide for nephrologists. *Am J Kidney Dis* 2015; 67:688–695. doi: 10.1053/j.ajkd.2015.09.032
3. Lam DY, et al. A conceptual framework of palliative care across the continuum of advanced kidney disease. *Clin J Am Soc Nephrol* 2019; 14:635–641. doi: 10.2215/CJN.09330818
4. Ramer SJ, Koncicki HM. The nephrologist's responsibility for advance care planning. *Kidney Med* 2020; 2:102–104. doi: 10.1016/j.xkme.2020.02.002
5. Mendu ML, Weiner DE. Health policy and kidney care in the United States: Core curriculum 2020. *Am J Kidney Dis* 2020; 76:720–730. doi: 10.1053/j.ajkd.2020.03.028
6. Kurella Tamura M, et al. Palliative care disincentives in CKD: Changing policy to improve CKD care. *Am J Kidney Dis* 2017; 71:866–873. doi: 10.1053/j.ajkd.2017.12.017
7. Combs SA, et al. Update on end-of-life care training during nephrology fellowship: A cross-sectional national survey of fellows. *Am J Kidney Dis* 2015; 65:233–239. doi: 10.1053/j.ajkd.2014.07.018
8. Shah HH, et al. Palliative care experience of US adult nephrology fellows: A national survey. *Ren Fail* 2014; 36:39–45. doi: 10.3109/0886022X.2013.831718
9. Fulton AT, et al. A novel interprofessional palliative care and geriatrics curriculum for nephrology teams. *Am J Hosp Palliat Care* 2020; 37:913–917. doi: 10.1177/1049909120915462
10. Schell JO, et al. NephroTalk: Evaluation of a palliative care communication curriculum for nephrology fellows. *J Pain Symptom Manage* 2018; 56:767–773.e2. doi: 10.1016/j.jpainsymman.2018.08.002
11. Gelfand SL, et al. Palliative care in nephrology: The work and the workforce. *Adv Chronic Kidney Dis* 2020; 27:350–355.e1. doi: 10.1053/j.ackd.2020.02.007

The ABIM Boards and Fellowship: The Past, Present, and Future

By Nityasree Srialluri and Stephen M. Sozio

The past decade has been a challenging time for nephrology. The increasing demand for kidney care combined with recent match challenges calls for the strengthening of fellowship training. This translates into a need to evaluate nephrology training, with the American Board of Internal Medicine (ABIM) nephrology subspecialization certification traditionally an objective way to accomplish this. The pass rate for the board exam, however, has seen continued struggles, with the 80% pass rate in 2020 being an improvement from the year prior but still the lowest among medicine subspecialties. A recent *Kidney News* article hypothesizes that this decline is potentially due to a combination of factors. These factors include the mismatch between exam content by ABIM question writers and real-world clinical experience and insufficient preparation for the exam by the fellows and/or fellowship programs (1).

So what should programs do to prepare fellows for this high-stakes exam (Table 1)? The ABIM Nephrology Certification Examination blueprint serves as an outline for preparation for both individual fellows and the program core curriculum (2). The In-Training Exam (ITE) can then be used to gauge knowledge gaps, as it has shown to be an independent predictor of performance on the initial certification exam (3). Several tools are at our disposal to enhance education. A 2018 Renal Fellow Network survey showed that the Kidney Self-Assessment Program (KSAP), ASN Board Review Course & Update (BRCU), and Nephrology Self-Assessment Program (nephSAP) are the most popular resources utilized by fellows (4). Fellowship programs should also have protected board question-based sessions, core lecture series, and innovative tools (5) starting early in the first year, with particular emphasis on complex topics such as renal physiology and pathology. Various resources are available that simplify instruction and guide training. A recent article in *Kidney News* by Garcia and Reddy provides an excellent curated list of fellow-friendly resources, highlighting available courses, societies, annual meetings, and development opportunities (6).

Low board pass rate, decrease in procedural competency, and a workforce shortage [are] areas in demand of improvement.

And what does the future hold for board preparation and fellowship? A 2016 national study of nephrology fellows highlighted a need for increased time on education in home dialysis modalities and renal pathology and physiology (7). The current emphasis on promoting and expanding home therapies necessitates that nephrology fellows receive adequate training in home dialysis modalities. It is thus concerning that a study of US nephrology fellows showed an overall perceived preparedness moderate for peritoneal dialysis and low for home hemodialysis (8). This emphasizes a critical need to increase education toward home dialysis modalities through lectures, conferences, and enhanced hands-on outpatient experience. The focus on expanding nephrology education should come with an awareness of the limited time fellows have for independent study, especially when on clinical service. Programs can consider restructuring rotations by incorporating physician extenders to lighten fellows' workload, especially for patients with whom fellows have ample learning opportunities (i.e., patients with end-stage kidney disease on hemodialysis). Finally, the landscape of nephrology is changing, with increased emphasis on onco-nephrology, business, health policy, interventional nephrology, glomerular disease, and critical care nephrology. Assessment of these areas on the ABIM Nephrology Board Exam will require future thoughts.

The changes of the past decade of nephrology fellowship training such as low board pass rate, decrease in procedural competency, and a workforce shortage unveil current areas in demand of improvement. The future of nephrology training should include the development and application of universal novel educational modalities in fellowship to strengthen training and increase interest among upcoming generations of learners. ■

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Table 1. Recommendations for nephrology fellowship programs

Establish a structured board review (e.g., lecture series, question-based conferences).
Use the ASN In-Training Exam to: target specific areas of deficiency in the program, and assess strengths and weaknesses of fellows and identify fellows at risk of requiring additional resources.
Ensure program core curriculum covers the ABIM Nephrology Certification Examination blueprint.
Restructure rotations to offload fellows to allow more time toward education.

The authors have no conflicts of interest.

References

1. Seaborg E. Nephrology certification exam pass rates bounce back … somewhat. *Kidney News* April 2021; 13:1 and 9. https://www.kidneynews.org/view/journals/kidney-news/13/4/article-p1_1.xml
2. American Board of Internal Medicine. Nephrology Certification Exam Blueprint. January 2021. http://www.abim.org/Media/iohh2ahg/nephrology.pdf
3. Jurich D, et al. Performance on the nephrology In-Training Examination and ABIM Nephrology Certification Examination outcomes. *Clin J Am Soc Nephrol* 2018; 13:710–717. doi: 10.2215/CJN.05580517
4. Farouk S. Here they are: The most popular resources used to study for the nephrology board exam. Renal Fellow Network. December 17, 2018. www.renalfellow.org/
5. Jhaveri KD, et al. Novel educational approaches to enhance learning and interest in nephrology. *Adv Chronic Kidney Dis* 2013; 20:336–346. doi: 10.1053/j.ackd.2013.03.006
6. Garcia P, Reddy Y. Tips and tricks for the 2021 nephrology fellows—A curated list of fellow-friendly resources in the United States. *Kidney News* May 2021; 13:20–24. https://www.kidneynews.org/view/journals/kidney-news/13/5/article-p20_6.xml
7. Rope RW, et al. Education in nephrology fellowship: A survey-based needs assessment. *J Am Soc Nephrol* 2017; 28:1983–1990. doi: 10.1681/ASN.2016101061
8. Gupta N, et al. Perceptions of home dialysis training and experience among US nephrology fellows. *Am J Kidney Dis* 2021; 77:713–718.e1. doi: 10.1053/j.ajkd.2020.09.014

The Resurgence of Urine Microscopy

By Sana Shaikh and Jay R. Seltzer

Biochemical and microscopic examination of the urine is routinely utilized in the evaluation of patients with kidney disorders, and urine microscopy—by providing a view into what's happening in the kidneys—may at times be a surrogate for histologic testing and serve as a "liquid biopsy."

Several studies have highlighted the benefits of urine microscopy. In patients with a high pretest probability of acute tubular necrosis (ATN), detection of granular casts or renal tubular epithelial cells (RTECs) has a very high positive predictive value and low negative predictive value (1). Application of a urinary sediment score (composite of number of granular casts and RTECs) for patients with ATN serves as a proxy for severity of acute kidney injury (AKI), as it has a dose-dependent relationship with risk of worsening (2). There is also diagnostic utility of serial microscopy in establishing a diagnosis of ATN and other etiologies of a non-recovering or worsening AKI (3).

In order to increase productivity and ensure reproducibility, most laboratories now utilize automated urine flow cytometry or digital imaging systems. Despite these advances in laboratory automation, manual microscopy, particularly one performed by an experienced nephrologist, is usually better at identifying important elements in the urinary sediment, specifically cellular casts, RTECs, and acanthocytes (4, 5). Nevertheless, the trend toward automation has resulted in fewer nephrologists taking the time to look at the urine themselves.

Fortunately, the past few years have witnessed a gradual resurgence of interest in manual microscopy (Figure 1). The expansion of medical education from classroom learning to social media platforms, such as Twitter, has played an essential role. Availability of smartphone microscope adapters has enabled providers to capture high-quality images of the urine sediment for documentation and education. In 2018, the Renal Fellow Network introduced a regular feature, titled "Urine Sediment of the Month," showcasing images and text contributions from field experts. In 2019, the *American Journal of Kidney Diseases* featured "Urine sediment examination in the diagnosis and management of kidney disease: Core curriculum," an extensive review of performance of urine sediment analysis and its role in patient care (6). More recently, NephMadness 2021 introduced the "liquid biopsy region," highlighting urine microscopy as an important aspect of clinical nephrology.

The incorporation of manual microscopy into day-to-day practice requires proper equipment, experience using different microscopy techniques, and Provider-Performed Microscopy (PPM) certification (https://www.cdc.gov/PPMP), which permits physicians to perform manual microscopy in the office or a laboratory as a part of patient evaluation.

Although there is substantial variability in the interpretation of urine sediment findings among nephrologists (7), continuous medical education, including didactics, computer-based learning, online courses, training workshops, and social media, may help improve interobserver reliability of manual microscopy and ensure continued interest in this time-honored technique. ■

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The authors have no conflicts of interest.

Figure 1. Urine microscopy

From top left clockwise: 1. red blood cell (RBC) cast under brightfield, unstained; 2. acanthocyte darkfield, unstained; 3. RBC cast, brightfield Sternheimer-Malbin (SM) stain; 4. mixed cellular cast containing mostly RBCs, phase contrast, unstained; 5. RBC cast brightfield, SM stain; 6. calcium oxalate dihydrate crystals, darkfield, unstained; 7. RBC cast, brightfield, SM stain; 8. oval fat bodies within cast phase contrast with SM stain; 9. uric acid crystals polarized. Middle left: 10. RBC cast brightfield, SM stain. Middle right: 11. RBC cast brightfield, SM stain. All from Jay R. Seltzer, MD.

Resources

NephSIM, How to spin urine guide: https://nephsim.com/how-to-spin-urine/NephSIM

Urine microscopy image gallery: https://nephsim.com/image-gallery/

Renal Fellow Network, Urine Sediment of the Month series: https://www.renalfellow.org/category/urine-sediment-of-the-month/

References

1. Perazella MA, et al. Diagnostic value of urine microscopy for differential diagnosis of acute kidney injury in hospitalized patients. *Clin J Am Soc Nephrol* 2008; 3:1615–1619. doi: 10.2215/CJN.02860608
2. Perazella MA, et al. Urine microscopy is associated with severity and worsening of acute kidney injury in hospitalized patients. *Clin J Am Soc Nephrol* 2010; 5:402–408. doi: 10.2215/CJN.06960909
3. Varghese V, et al. Diagnostic utility of serial microscopic examination of the urinary sediment in acute kidney injury. *Kidney360* February 2021; 2:182–191. doi: https://doi.org/10.34067/KID.0004022020
4. Cho J, et al. Comparison of five automated urine sediment analyzers with manual microscopy for accurate identification of urine sediment. *Clin Chem Lab Med* 2019; 57:1744–1753. doi: 10.1515/cclm-2019-0211
5. Tsai JJ, et al. Comparison and interpretation of urinalysis performed by a nephrologist versus a hospital-based clinical laboratory. *Am J Kidney Dis* 2005; 46:820–829. doi: 10.1053/j.ajkd.2005.07.039
6. Cavanaugh C, et al. Urine sediment examination in the diagnosis and management of kidney disease: Core curriculum 2019. *Am J Kidney Dis* 2019; 73:258–272. doi: 10.1053/j.ajkd.2018.07.012
7. Palsson R, et al. Assessment of interobserver reliability of nephrologist examination of urine sediment. *JAMA Netw Open* 2020; 3:e2013959. doi: 10.1001/jamanetworkopen.2020.13959

Women in Nephrology: Progress and Goals

By Anika Lucas, Mala Sachdeva, Ellie Kelepouris, and Lisa M. Curtis

Over 60 years ago, nephrology was established as a medical specialty. In 1966, the American Society of Nephrology (ASN) was founded by 17 men (1). Although there were many notable women researchers and physicians caring for women with kidney disease at that time, there was an apparent gender gap in leadership. Interestingly, women were trailblazers in the field of nephrology even before it was recognized as a distinct specialty. Women such as Phyllis Adele Bott, Margaret Mylle, Muriel MacDowell, and Dr. Alma Elizabeth Hiller made profound contributions to our understanding of renal physiology (2). Pauline M. Hald authored one of the first papers on how to measure electrolytes in 1946, but it was not until 1972 that a woman nephrologist became an international leader. Dr. Priscilla Kincaid-Smith, an astute researcher on analgesic nephropathy, was the first woman president of the International Society of Nephrology (ISN) (3).

Women nephrologists recognized the critical need for representation and mentorship in our field. On December 5, 1983, Dr. Nancy Gary, Dr. Lois Katz, Dr. Sandra Levison, and Dr. Mabel Purkerson founded Women in Nephrology (WIN). The main objective was twofold: to enhance professional development and career opportunities for women in this field and to advocate for inclusivity and gender equality throughout the field of nephrology (Figure 1). Since its beginning, WIN has been steadfast in its mission to facilitate career and leadership development and to increase representation of women nephrologists. WIN has sponsored an annual professional development series as part of the ASN pre-Kidney Week meetings in past years and additional workshops, as well as the annual Dr. Nancy Gary luncheon lecture during Kidney Week meetings. Career development workshops sponsored by WIN have also been held at other national kidney organizations, including the National Kidney Foundation (NKF), the Renal Physicians Association (RPA), and, this year, at the ISN World Congress of Nephrology. An annual WIN Leadership Conference with purposes to create mentorship and networking opportunities and facilitate leadership training was begun by WIN in 2020. The second annual Leadership Conference is planned for September 24, 2021, in Birmingham, AL. The first WIN Speakers Bureau, including women and men nephrologists with specialized expertise in many areas of nephrology, was created by WIN this past year in response to the need identified by event organizers and repeated requests for suggested names received by WIN. Although WIN has actively provided mentorship on a case-by-case basis since its inception, a new formal Mentor Match program was initiated a few years ago.

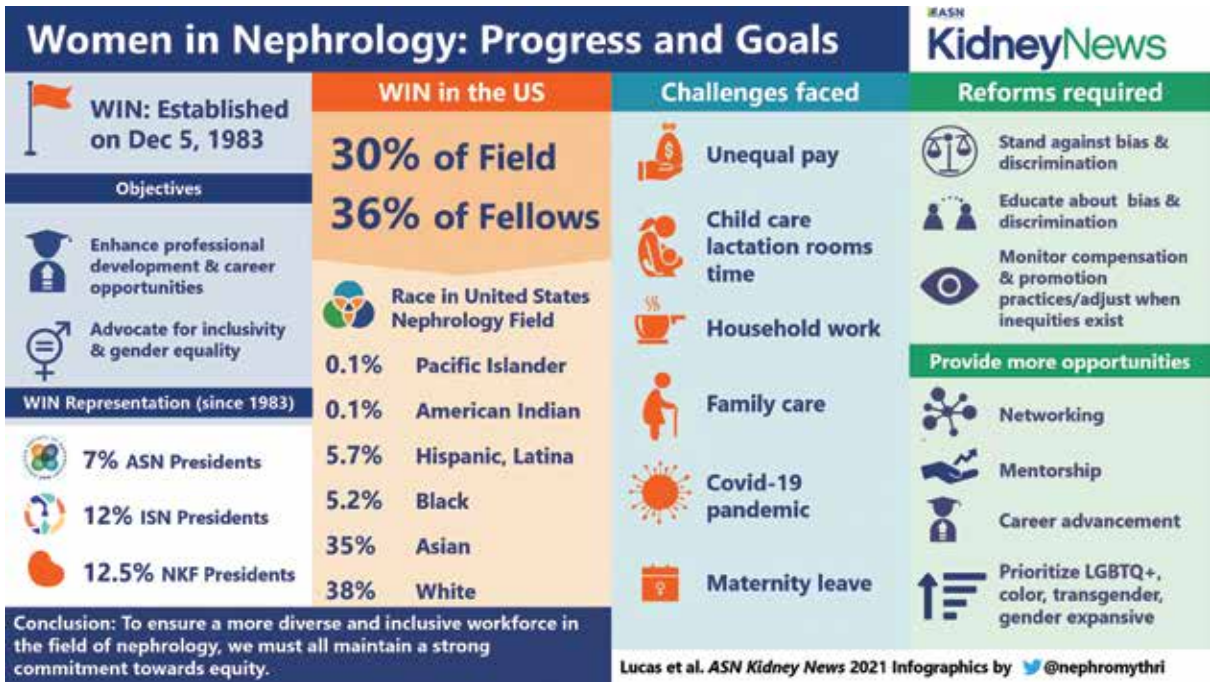
Since the creation of WIN, there have been 4 (of 55, or 7%) female presidents of the ASN, including the current president, Dr. Susan Quaggin, and others serving on the Council in preparation for the presidency; 3 (of 24, or 12.5%) female physician presidents of the NKF, with a past leader of WIN serving as president-elect this year; and at least 1 chairwoman of the NKF. Women have also served as presidents of the ISN (3 of 25, or 12%) (4), including the current president who is a WIN leadership alumna. Through the efforts of WIN in collaboration with ASN and its Diversity, Equity, and Inclusion Committee, the number of women moderators increased by 47% and women speakers by 40% at Kidney Week in 2019 (5). There are more women in leadership roles locally, serving as medical school deans, Department of Medicine chairs, division chiefs in nephrology, program directors, and associate program directors. The advancement of women in the field of nephrology is the result of the dedicated and determined efforts of many individuals as well as organizations such as WIN, ASN, NKF, RPA, and ISN. The use of social media to contribute to women's career advancement cannot be underestimated, as many women have used social media to build global networks and create opportunities for self-promotion. The establishment of a professional online presence will increasingly be important in advancing careers (6).

Although we have made some progress toward gender equity in the field of nephrology, there are still important challenges we have yet to overcome. We must sustain the woman leadership pipeline to reflect the diversity of patients with chronic kidney disease (CKD) and to provide diverse role models for trainees. In 2020, only 27% of academic women physicians were professors, whereas 59% of women were instructors. There is also a great need for women of color in nephrology. Black women make up 5.2% of faculty; American Indian or Alaskan Native 0.1%; Asian women 35%; Hispanic, Latina, or Spanish women 5.7%; and Native Hawaiian or Pacific Islander 0.1%, whereas White women are 38% of women faculty (7). Pay equity continues to be a major issue (8). According to the 2020 Medscape Nephrologist Compensation Report, male nephrologists still make 18% more than women (9). Although men spent on average 7.1 more hours than women with patients, gender disparities in compensation continue to exist in both academic centers and private practices (9). Gender equity also encompasses the support of women who choose to become mothers. Maternity leave, lactation rooms, and additional support for childcare continue to be important areas of concern for many women nephrologists, contributing to added stress. The COVID-19 pandemic, coupled with continued disproportionate responsibility for family care by women (e.g., elder- and childcare, household work), presented additional barriers to the advancement of women in our field, as many expanded their care-taking roles in the home. The pandemic highlighted these challenges by upending the precarious patchwork of support for home-based care that women have utilized in the past to sustain careers. Although COVID-19 put in stark relief the impact of the burden of household demand on productivity, one feature of the pandemic may offer future advantages that are particularly relevant to women. With the advent of virtual talks, many women who have declined opportunities due to household demands may be able to utilize the flexibility of doing these talks from their home base. Continuing to provide this advantage may have significant implications on the advancement of those previously underrepresented in these offerings. The long-term consequences, positive and negative, of the COVID-19 pandemic on productivity and promotion of women are crucial areas for further investigation. Reflection on ways to continue implementation of these flexible paradigms in the future is warranted.

Gender equity also includes increased representation. Achieving equity will require intention at all levels (Table 1) to enhance inclusion and avoid selecting only "who you know." Although 50% of medical students are women, only 36% of nephrology fellows were women

We must sustain the woman leadership pipeline to reflect the diversity of patients with CKD and to provide diverse role models for trainees.

Figure 1.



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Women in Nephrology

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in 2019 (10). It is prudent that we extend our recruitment efforts to include women across the pipeline from fellows to clinicians and physician-scientists in every facet of nephrology. To promote interest and retention of women in our field, rigorous efforts must be made to reduce burnout; increase opportunities for networking, partnership, mentorship, and sponsorship; and provide real-world role models. Generous parental leave, tenure clock stoppage or extension, research, and pay equity must also be a priority (4). These potential areas for change represent opportunities to improve life-work integration and to transform the culture of medicine.

To ensure a more diverse and inclusive workforce in the field of nephrology, we must all maintain a strong commitment toward equity. This means taking a steadfast stand against discrimination and bias and providing additional training on bias and discrimination for trainees, program directors, clinicians, researchers, and society leaders. Moreover, it entails the establishment of multiple measures to promote transparency and accountability such as monitoring and tracking systems to evaluate compensation and promotion practices. Finally, additional opportunities for networking, mentorship, and career advancement that are intentionally inclusive of LGBTQ+ women, women of color, transgender women, and gender-expansive people in nephrology must be our priority. ■

Table 1. Gender equity includes increased representation

Roles	Suggestions to enhance representation of women in nephrology
Division chiefs	• Engage proactively in combating bias by striving for parity in selection or nomination for honors, speaking, or leadership opportunities and in compensation practices. • Use a formal mechanism of mentorship (e.g., mentoring committees) with established benchmarks and reporting structure. • Include participation in mentoring committees beyond immediate division members. • Actively foster an environment of inclusion by engaging in explicit discussions of bias and the value of diversity to enhancing all outcomes—for patients, careers, and institutions. • Value mentoring and teaching activities by recognition in annual reviews and compensation. • Advocate for and implement flexible work arrangements when possible to improve life-work integration. • Foster interaction across different arenas of careers, e.g., research and patient care; basic and clinical scientific research; and industry, academia, and private practice. • Be attuned to life-work integration needs (e.g., schedule meetings at times other than early morning, evening).
Program directors	• Engage proactively in combating bias by striving for parity in selection or nomination for honors, speaking, or leadership opportunities. • Use a formal mechanism of mentorship (e.g., mentoring committees) with established benchmarks and reporting structure. • Include participation in mentoring committees beyond immediate division members. • Encourage training in soft skills of career development. • Provide protected time for career development. • Be open to the career aspirations of the mentee. • Be attuned to life-work integration needs (e.g., schedule meetings at times other than early morning, evening).
Journal editors	• Utilize speakers bureaus to identify less well-known individuals. • Diversify makeup of organizational committees. • Establish benchmarks to strive for diversity. • Utilize virtual formats to increase inclusion. • Strive for parity in selection of associate editors.
Conference organizers	• Utilize speakers bureaus to identify less well-known individuals. • Diversify makeup of organizational committees. • Establish benchmarks to strive for diversity. • Utilize virtual formats to increase inclusion. • Strive for parity in selection of speakers, as well as moderators.
Mentors/sponsors	• Place value on the mentoring relationship by committing time and energy to the relationship. • Utilize formal plans for career advancement that include goals and benchmarks. • Engage in regular meetings to ensure achievement of goals and benchmarks. • Advocate for opportunities for the mentee. • Be open to the career aspirations of the mentee.
Individuals	• Seek out guidance on career development from diverse sources. • Engage in continued education on soft skills of careers. • Critically address decisions to accept or decline opportunities. • Establish and foster networks. • Identify and engage with mentors and role models for each career opportunity contemplated (private practice, academia, industry, administration, leadership). • Negotiate effectively to establish value in all career endeavors. • Engage regularly in open and honest discussions with mentors, sponsors.

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Conflicts of interest: Drs. Sachdeva, Kelepouris, and Curtis are members of the Women in Nephrology Executive Council.

References

1. Lederer E. Women in nephrology today. *Clin J Am Soc Nephrol* 2018; 13:1755–1756. doi: 10.2215/CJN.07650618
2. Martín-Gómez MA, et al. The role of women throughout the history of nephrology. *Nefrologia (Engl Ed)* 2019; 39:15–17. doi: 10.1016/j.nefro.2018.08.006
3. Eknoyan G. Women: Medicine, their kidneys, and nephrology. *Adv Chronic Kidney Dis* 2013; 20:382–389. doi: 10.1053/j.ackd.2013.03.003
4. Weinstock Brown W, Anderson S. Women in nephrology leadership. *Adv Chronic Kidney Dis* 2018; 25:519–522. doi: 10.1053/j.ackd.2018.08.014
5. Malieckal DA, et al. Trends in the proportions of women program chairs, moderators, and speakers at American Society of Nephrology Kidney Week 2011–2019. *Clin J Am Soc Nephrol* 2020; 15:265–266. doi: 10.2215/CJN.08140719
6. Dave NN, et al. An introduction and guide to becoming a social media savvy nephrologist. *Nephrol Dial Transplant* 2020, 1–7. doi: 10.1093/ndt/gfaa067; https://academic.oup.com/ndt/advance-article/doi/10.1093/ndt/gfaa067/5834661
7. Association of American Medical Colleges. Diversity and Inclusion. Diversity in Medicine: Facts and Figures 2019. Table 13. Practice Specialty, Males by Race/Ethnicity, 2018. https://www.aamc.org/data-reports/workforce/data/table-13-practice-specialty-males-race/ethnicity-2018
8. Butkus R, et al. Achieving gender equity in physician compensation and career advancement: A position paper of the American College of Physicians. *Ann Intern Med* 2018; 168:721–723. doi: 10.7326/M17-3438
9. Martin KL. Medscape Nephrologist Compensation Report 2020. May 20, 2020. https://www.medscape.com/slideshow/2020-compensation-nephrologist-6012736
10. Brotherton SE, Etzel SI. Graduate medical education, 2019–2020. *JAMA* 2020; 324:1230–1250. doi: 10.1001/jama.2020.14635

INVOKANA®: the FIRST SGLT2i proven to slow the progression of DKD in adults with DKD* and T2D and the ONLY SGLT2i indicated to reduce the risk of 3-point MACE (heart attack, stroke , and CV death) in adults with T2D and established CVD[1-5]

*With albuminuria >300 mg/day.

INVOKANA® is the first SGLT2i indicated to reduce the risk of end-stage kidney disease[1,6]

CREDENCE

30% RRR

Relative risk reduction of the primary composite of:

- **End-stage kidney disease†** (dialysis, transplant, or eGFR <15)
- **Doubling of serum creatinine**
- **Renal death‡**
- **CV death**

Patients with DKD* and T2D

HR=0.70 (95% CI: 0.59, 0.82); *P*=0.00001

Placebo + ACEi or ARB therapy (n=2199)
Event rate: 6.1 (per 100 patient-years)

INVOKANA® 100 mg + ACEi or ARB therapy (n=2202)
Event rate: 4.3 (per 100 patient-years)

‡There were not enough events to evaluate the risk of renal death (placebo, n=5; INVOKANA®, n=2). **INVOKANA® is not indicated to reduce the risk of renal death.**

INVOKANA® is the only SGLT2i to demonstrate a reduction in the relative risk of all components of MACE in 2 clinical trials[1,5,6,7‖]

CREDENCE

20% RRR§

Patients with DKD* and T2D

HR=0.80 (95% CI: 0.67, 0.95); *P*=0.01

Placebo + ACEi or ARB therapy (n=2199)
Event rate: 4.9 (per 100 patient-years)

INVOKANA® 100 mg + ACEi or ARB therapy (n=2202)
Event rate: 3.9 (per 100 patient-years)

CANVAS

18% RRR§

Patients with T2D and CVD

HR=0.82 (95% CI: 0.72, 0.95); *P*=0.008

Placebo + standard of care (n=2900)
Event rate: 4.13 (per 100 patient-years)

INVOKANA® 100 mg and 300 mg + standard of care (n=3756)
Event rate: 3.41 (per 100 patient-years)

Relative risk reduction in the composite of 3-point major adverse cardiac events[1,7]:

- **Heart attack**
- **Stroke**
- **CV death**

‖Prespecified secondary endpoint for CREDENCE; prespecified primary endpoint for CANVAS.

In the landmark renal CREDENCE trial, INVOKANA® demonstrated a proven safety profile in patients with an eGFR of 30 to <90[1,6]

- Similar overall AEs with INVOKANA® vs placebo (35.1 vs 37.9 per 100 patient-years). Male GMI incidence was 0.84 vs 0.09 per 100 patient-years, respectively. DKA incidence was 0.22 vs 0.02 per 100 patient-years, respectively.¶ No imbalance in fracture or amputation. Hypotension incidence was 2.8% vs 1.5%, respectively. Hypoglycemia incidence was 4.43 vs 4.89 per 100 patient-years, respectively#

In the CV outcomes CANVAS Program, INVOKANA® demonstrated a proven safety profile in patients with T2D and established CVD[5]

- Similar overall AEs with INVOKANA® vs placebo (10.43 vs 12.00 per 100 patient-years). Male GMI incidence was 3.49 vs 1.08 per 100 patient-years, respectively. DKA incidence was 0.06 vs 0.03 per 100 patient-years, respectively. Hypoglycemia incidence was 5.00 vs 4.64 per 100 patient-years, respectively

AEs=adverse events; CANVAS=Canagliflozin Cardiovascular Assessment Study; CREDENCE=Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation; CV=cardiovascular; CVD=cardiovascular disease; DKA=diabetic ketoacidosis; DKD=diabetic kidney disease; GMI=genital mycotic infection; HR=hazard ratio; MACE=major adverse cardiovascular events; RRR=relative risk reduction; SGLT2i=sodium-glucose co-transporter 2 inhibitor; T2D=type 2 diabetes.

Learn more at INVOKANAhcp.com

Study designs: CREDENCE was a randomized, double-blind, placebo-controlled, parallel group, multicenter, event-driven clinical trial. The trial compared the effects of INVOKANA® 100 mg vs placebo in 4401 men and women with type 2 diabetes and diabetic kidney disease (described as chronic kidney disease with eGFR 30 to <90 mL/min/1.73 m^2 and albuminuria [ratio of albumin to creatinine >300 to 5000 mg/g]) who were already taking a stable, maximum-tolerated, or labeled dose (for ≥4 weeks prior to randomization) of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB). The mean eGFR of patients was 56.2 mL/min/1.73 m^2 and the median urinary albumin-to-creatinine ratio was 927 mg/g. The primary efficacy outcome was the composite of end-stage kidney disease (dialysis, transplant, or eGFR <15 mL/min/1.73 m^2), doubling of serum creatinine, or renal or cardiovascular (CV) death. Prespecified secondary outcomes included a composite of CV death or hospitalization for heart failure; a composite of heart attack, stroke, or CV death; hospitalization for heart failure; and a composite of end-stage kidney disease, doubling of the serum creatinine level, or renal death.[6]

The CANVAS Program was an integrated analysis of 2 trials (the CANVAS trial and the CANVAS-R trial) with a total of 10,142 men and women with type 2 diabetes. Of the participants, 96.0% completed the trial and vital status was confirmed for 99.6%. The mean follow-up for the CANVAS Program was 188.2 weeks, while the length of follow-up was 295.9 weeks and 108.0 weeks in the CANVAS and CANVAS-R trials, respectively. Participants were either ≥30 years of age with a history of symptomatic atherosclerotic cardiovascular disease or ≥50 years of age with ≥2 risk factors** for cardiovascular disease. The primary efficacy outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.[5]

**≥2 of the following risk factors for CVD: duration of diabetes ≥10 years, systolic blood pressure >140 mm Hg while they were receiving ≥1 antihypertensive agents, currently smoking, microalbuminuria or macroalbuminuria, or HDL cholesterol level <1 mmol/L (38.7 mg/dL).

INDICATIONS

INVOKANA® is indicated:

- as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
- to reduce the risk of major adverse cardiovascular events (cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke) in adults with type 2 diabetes mellitus and established cardiovascular disease (CVD)
- to reduce the risk of end-stage kidney disease (ESKD), doubling of serum creatinine, cardiovascular (CV) death, and hospitalization for heart failure in adults with type 2 diabetes mellitus and diabetic nephropathy with albuminuria greater than 300 mg/day

Limitations of Use

INVOKANA® is not recommended in patients with type 1 diabetes mellitus. It may increase the risk of diabetic ketoacidosis in these patients.

INVOKANA® is not recommended for use to improve glycemic control in adults with type 2 diabetes mellitus with an eGFR less than 30 mL/min/1.73 m^2. INVOKANA® is likely to be ineffective in this setting based upon its mechanism of action.

SELECT IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

- Serious hypersensitivity reaction to INVOKANA®, such as anaphylaxis or angioedema
- Patients on dialysis

Please read additional Important Safety Information and Brief Summary of full Prescribing Information for INVOKANA® on the following pages.

eGFR is measured in mL/min/1.73 m^2.
*With albuminuria >300 mg/day.
†End-stage kidney disease was defined as dialysis for ≥30 days, kidney transplantation, or an eGFR <15 mL/min/1.73 m^2 sustained for ≥30 days.
§RRR was calculated using the following formula: 100 x (1−HR).
¶All potential ketone-related events were adjudicated for diabetic ketoacidosis by an independent adjudication committee on the basis of clinical presentation and predefined biochemical measures.
#In all glycemic control trials of INVOKANA®, hypoglycemia was defined as any event, regardless of symptoms, in which biochemical hypoglycemia was documented (any glucose value ≤70 mg/dL) or any hypoglycemic episode was considered severe. Severe hypoglycemia was defined as an event consistent with hypoglycemia in which the patient required the assistance of another person to recover, lost consciousness, or experienced a seizure (regardless of whether biochemical documentation of a low glucose value was obtained).[1]

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Invokana® (canagliflozin) tablets

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Invokana®
(canagliflozin) tablets

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Limitations of Use

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IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

- Serious hypersensitivity reaction to INVOKANA®, such as anaphylaxis or angioedema
- Patients on dialysis

WARNINGS AND PRECAUTIONS

- **Lower-Limb Amputation:** An increased risk of lower-limb amputations associated with INVOKANA® use versus placebo was observed in CANVAS (5.9 vs 2.8 events per 1000 patient-years) and CANVAS-R (7.5 vs 4.2 events per 1000 patient-years), two randomized, placebo-controlled trials evaluating patients with type 2 diabetes who had either established cardiovascular disease or were at risk for cardiovascular disease. The risk of lower-limb amputations was observed at both the 100-mg and 300-mg once-daily dosage regimens.

  Amputations of the toe and midfoot (99 out of 140 patients with amputations receiving INVOKANA® in the two trials) were the most frequent; however, amputations involving the leg, below and above the knee, were also observed (41 out of 140 patients with amputations receiving INVOKANA® in the two trials). Some patients had multiple amputations, some involving both lower limbs.

  Lower-limb infections, gangrene, and diabetic foot ulcers were the most common precipitating medical events leading to the need for an amputation. The risk of amputation was highest in patients with a baseline history of prior amputation, peripheral vascular disease, and neuropathy. Before initiating INVOKANA®, consider factors in the patient history that may predispose to the need for amputations, such as a history of prior amputation, peripheral vascular disease, neuropathy, and diabetic foot ulcers. Counsel patients about the importance of routine preventative foot care. Monitor patients for signs and symptoms of infection (including osteomyelitis), new pain or tenderness, sores, or ulcers involving the lower limbs, and discontinue if these complications occur.
- **Volume Depletion:** INVOKANA® can cause intravascular volume contraction, which may sometimes manifest as symptomatic hypotension or acute transient changes in creatinine. There have been postmarketing reports of acute kidney injury which are likely related to volume depletion, some requiring hospitalizations and dialysis, in patients with type 2 diabetes mellitus receiving SGLT2 inhibitors, including INVOKANA®. Patients with impaired renal function (eGFR less than 60 mL/min/1.73 m^2), elderly patients, or patients on loop diuretics may be at increased risk for volume depletion or hypotension. Before initiating INVOKANA® in patients with one or more of these characteristics, assess and correct volume status. Monitor for signs and symptoms of volume depletion after initiating therapy.
- **Ketoacidosis:** Ketoacidosis, a serious life-threatening condition requiring urgent hospitalization, has been identified in patients with type 1 and 2 diabetes mellitus receiving SGLT2 inhibitors, including INVOKANA®. In placebo-controlled trials of patients with type 1 diabetes, the risk of ketoacidosis was increased in patients who received SGLT2 inhibitors compared to patients who received placebo. The risk of ketoacidosis may be greater with higher doses. Fatal cases of ketoacidosis have been reported in patients taking INVOKANA®. Before initiating INVOKANA®, consider factors in patient history that may predispose to ketoacidosis. For patients who undergo scheduled surgery, consider temporarily discontinuing INVOKANA® for at least 3 days prior to surgery. Monitor for ketoacidosis and temporarily discontinue in other clinical situations known to predispose to ketoacidosis. Ensure risk factors for ketoacidosis are resolved prior to restarting therapy. Educate patients on the signs and symptoms of ketoacidosis and instruct patients to discontinue INVOKANA® and seek medical attention immediately if signs and symptoms occur.
- **Urosepsis and Pyelonephritis:** Serious urinary tract infections, including urosepsis and pyelonephritis, requiring hospitalization have been reported in patients receiving SGLT2 inhibitors, including INVOKANA®. Treatment with SGLT2 inhibitors increases this risk. Evaluate for signs and symptoms and treat promptly.
- **Hypoglycemia With Concomitant Use With Insulin and Insulin Secretagogues:** Insulin and insulin secretagogues are known to cause hypoglycemia. INVOKANA® may increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with INVOKANA®.

Please read Brief Summary of full Prescribing Information for INVOKANA® on the following pages.

Invokana®
(canagliflozin) tablets

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- **Necrotizing Fasciitis of the Perineum (Fournier's Gangrene):** Necrotizing fasciitis of the perineum, a rare but serious and life-threatening necrotizing infection requiring urgent surgical intervention, has been identified in postmarketing surveillance in female and male patients with diabetes mellitus receiving SGLT2 inhibitors, including INVOKANA®. Serious outcomes have included hospitalization, multiple surgeries, and death. If suspected, start treatment immediately with broad-spectrum antibiotics and, if necessary, surgical debridement. Discontinue INVOKANA®.
- **Genital Mycotic Infections:** INVOKANA® increases risk of genital mycotic infections, especially in uncircumcised males or patients with prior infections. Monitor and treat appropriately.
- **Hypersensitivity Reactions:** Hypersensitivity reactions, including angioedema and anaphylaxis, were reported with INVOKANA®; these reactions generally occurred within hours to days after initiation. If reactions occur, discontinue INVOKANA®, treat, and monitor until signs and symptoms resolve.
- **Bone Fracture:** Increased risk of bone fracture, occurring as early as 12 weeks after treatment initiation, was observed in patients using INVOKANA®. Prior to initiation, consider factors that contribute to fracture risk.

DRUG INTERACTIONS

- **UGT Enzyme Inducers:** Co-administration with rifampin lowered INVOKANA® exposure, which may reduce the efficacy of INVOKANA®. For patients with eGFR ≥60 mL/min/1.73 m^2, if an inducer of UGTs (eg, rifampin, phenytoin, phenobarbital, ritonavir) is co-administered with INVOKANA®, increase the dose to 200 mg (taken as two 100 mg tablets) once daily in patients currently tolerating INVOKANA® 100 mg. The dose may be increased to 300 mg once daily in patients currently tolerating INVOKANA® 200 mg and who require additional glycemic control.

  For patients with eGFR <60 mL/min/1.73 m^2, if an inducer of UGTs is co-administered with INVOKANA®, increase the dose to 200 mg (taken as two 100 mg tablets) once daily in patients currently tolerating INVOKANA® 100 mg. Consider adding another antihyperglycemic agent in patients who require additional glycemic control.
- **Digoxin:** There was an increase in the AUC and mean peak drug concentration of digoxin when co-administered with INVOKANA® 300 mg. Monitor appropriately.
- **Positive Urine Glucose Test:** Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.
- **Interference With 1,5-Anhydroglucitol (1,5-AG) Assay:** Monitoring glycemic control with 1,5-AG assay is not recommended in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.

USE IN SPECIFIC POPULATIONS

- **Pregnancy:** INVOKANA® is not recommended in pregnant women, especially during the second and third trimesters.
- **Lactation:** INVOKANA® is not recommended while breastfeeding.
- **Pediatric Use:** Safety and effectiveness in patients <18 years of age have not been established.
- **Geriatric Use:** Patients ≥65 years had a higher incidence of adverse reactions related to reduced intravascular volume, particularly with the 300-mg dose; more prominent increase in the incidence was seen in patients who were ≥75 years. Smaller reductions in HbA1c relative to placebo were seen in patients ≥65 years.
- **Renal Impairment:** The efficacy and safety of INVOKANA® for glycemic control were evaluated in a trial that included patients with moderate renal impairment (eGFR 30 to <50 mL/min/1.73 m^2). These patients had less overall glycemic efficacy, and patients treated with 300 mg per day had increases in serum potassium, which were transient and similar by the end of the study. Patients with renal impairment using INVOKANA® for glycemic control may be more likely to experience hypotension and may be at a higher risk for acute kidney injury. INVOKANA® is contraindicated in patients with ESKD on dialysis.
- **Hepatic Impairment:** INVOKANA® has not been studied in patients with severe hepatic impairment and is not recommended in this population.

OVERDOSAGE

- In the event of an overdose, contact the Poison Control Center and employ the usual supportive measures.

ADVERSE REACTIONS

- The most common adverse reactions associated with INVOKANA® (5% or greater incidence) were female genital mycotic infections, urinary tract infections, and increased urination.

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Please read Brief Summary of full Prescribing Information for INVOKANA® on the following pages.

References: 1. INVOKANA® [prescribing information]. Titusville, NJ: Janssen Pharmaceuticals, Inc. **2.** Jardiance® [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc. **3.** Farxiga® [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP. **4.** Steglatro™ [prescribing information]. Whitehouse Station, NJ: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. **5.** Neal B, Perkovic V, Mahaffey KW, et al; CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med*. 2017;377(7):644-657. **6.** Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med*. 2019;380(24):2295-2306. Supplementary appendix available at: doi:10.1056/NEJMoa1811744. **7.** Mahaffey KW, Neal B, Perkovic V, et al. Canagliflozin for primary and secondary prevention of cardiovascular events: results from the CANVAS Program (Canagliflozin Cardiovascular Assessment Study). *Circulation*. 2018;137(4):323-334.

INVOKANA®

(canagliflozin) tablets, for oral use

Brief Summary of Prescribing Information.

INDICATIONS AND USAGE

INVOKANA (canagliflozin) is indicated:

- as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
- to reduce the risk of major adverse cardiovascular events (cardiovascular death, nonfatal myocardial infarction and nonfatal stroke) in adults with type 2 diabetes mellitus and established cardiovascular disease (CVD).
- to reduce the risk of end-stage kidney disease (ESKD), doubling of serum creatinine, cardiovascular (CV) death, and hospitalization for heart failure in adults with type 2 diabetes mellitus and diabetic nephropathy with albuminuria greater than 300 mg/day.

Limitations of Use

INVOKANA is not recommended in patients with type 1 diabetes mellitus. It may increase the risk of diabetic ketoacidosis in these patients *[see Warnings and Precautions]*.

INVOKANA is not recommended for use to improve glycemic control in adults with type 2 diabetes mellitus with an eGFR less than 30 mL/min/1.73 m^2. INVOKANA is likely to be ineffective in this setting based upon its mechanism of action.

CONTRAINDICATIONS

- Serious hypersensitivity reaction to INVOKANA, such as anaphylaxis or angioedema *[see Warnings and Precautions and Adverse Reactions]*.
- Patients on dialysis *[see Use in Specific Populations]*.

WARNINGS AND PRECAUTIONS

Lower Limb Amputation: An increased risk of lower limb amputations associated with INVOKANA use versus placebo was observed in CANVAS (5.9 vs 2.8 events per 1000 patient-years) and CANVAS-R (7.5 vs 4.2 events per 1000 patient-years), two randomized, placebo-controlled trials evaluating patients with type 2 diabetes who had either established cardiovascular disease or were at risk for cardiovascular disease. The risk of lower limb amputations was observed at both the 100 mg and 300 mg once daily dosage regimens. The amputation data for CANVAS and CANVAS-R are shown in Tables 3 and 4, respectively *[see Adverse Reactions]*.

Amputations of the toe and midfoot (99 out of 140 patients with amputations receiving INVOKANA in the two trials) were the most frequent; however, amputations involving the leg, below and above the knee, were also observed (41 out of 140 patients with amputations receiving INVOKANA in the two trials). Some patients had multiple amputations, some involving both lower limbs.

Lower limb infections, gangrene, and diabetic foot ulcers were the most common precipitating medical events leading to the need for an amputation. The risk of amputation was highest in patients with a baseline history of prior amputation, peripheral vascular disease, and neuropathy.

Before initiating INVOKANA, consider factors in the patient history that may predispose to the need for amputations, such as a history of prior amputation, peripheral vascular disease, neuropathy and diabetic foot ulcers. Counsel patients about the importance of routine preventative foot care. Monitor patients receiving INVOKANA for signs and symptoms of infection (including osteomyelitis), new pain or tenderness, sores or ulcers involving the lower limbs, and discontinue INVOKANA if these complications occur.

Volume Depletion: INVOKANA can cause intravascular volume contraction which may sometimes manifest as symptomatic hypotension or acute transient changes in creatinine *[see Adverse Reactions]*. There have been post-marketing reports of acute kidney injury which are likely related to volume depletion, some requiring hospitalizations and dialysis, in patients with type 2 diabetes mellitus receiving SGLT2 inhibitors, including INVOKANA. Patients with impaired renal function (eGFR less than 60 mL/min/1.73 m^2), elderly patients, or patients on loop diuretics may be at increased risk for volume depletion or hypotension. Before initiating INVOKANA in patients with one or more of these characteristics, assess and correct volume status. Monitor for signs and symptoms of volume depletion after initiating therapy.

Ketoacidosis: Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization have been identified in clinical trials and postmarketing surveillance in patients with type 1 and type 2 diabetes mellitus receiving sodium glucose co-transporter-2 (SGLT2) inhibitors, including INVOKANA. In placebo-controlled trials of patients with type 1 diabetes, the risk of ketoacidosis was increased in patients who received SGLT2 inhibitors compared to patients who received placebo. The risk of ketoacidosis may be greater with higher doses. Fatal cases of ketoacidosis have been reported in patients taking INVOKANA. INVOKANA is not indicated for the treatment of patients with type 1 diabetes mellitus *[see Indications and Usage]*.

Patients treated with INVOKANA who present with signs and symptoms consistent with severe metabolic acidosis should be assessed for ketoacidosis regardless of presenting blood glucose levels, as ketoacidosis associated with INVOKANA may be present even if blood glucose levels are less than 250 mg/dL. If ketoacidosis is suspected, INVOKANA should be discontinued, patient should be evaluated, and prompt treatment should be instituted. Treatment of ketoacidosis may require insulin, fluid and carbohydrate replacement.

In many of the postmarketing reports, and particularly in patients with type 1 diabetes, the presence of ketoacidosis was not immediately recognized and institution of treatment was delayed because presenting blood glucose levels were below those typically expected for diabetic ketoacidosis (often less than 250 mg/dL). Signs and symptoms at presentation were consistent with dehydration and severe metabolic acidosis and included nausea, vomiting, abdominal pain, generalized malaise, and shortness of breath. In some but not all cases, factors predisposing to ketoacidosis such as insulin dose reduction, acute febrile illness, reduced caloric intake, surgery, pancreatic disorders suggesting insulin deficiency (e.g., type 1 diabetes, history of pancreatitis or pancreatic surgery), and alcohol abuse were identified.

Before initiating INVOKANA, consider factors in the patient history that may predispose to ketoacidosis including pancreatic insulin deficiency from any cause, caloric restriction, and alcohol abuse.

For patients who undergo scheduled surgery, consider temporarily discontinuing INVOKANA for at least 3 days prior to surgery *[see Clinical Pharmacology (12.2, 12.3) in Full Prescribing Information]*.

Consider monitoring for ketoacidosis and temporarily discontinuing INVOKANA in other clinical situations known to predispose to ketoacidosis (e.g., prolonged fasting due to acute illness or post-surgery). Ensure risk factors for ketoacidosis are resolved prior to restarting INVOKANA.

Educate patients on the signs and symptoms of ketoacidosis and instruct patients to discontinue INVOKANA and seek medical attention immediately if signs and symptoms occur.

Urosepsis and Pyelonephritis: There have been postmarketing reports of serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization in patients receiving SGLT2 inhibitors, including INVOKANA. Treatment with SGLT2 inhibitors increases the risk for urinary tract infections. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated *[see Adverse Reactions]*.

Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues: Insulin and insulin secretagogues are known to cause hypoglycemia. INVOKANA may increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue *[see Adverse Reactions]*. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with INVOKANA.

Necrotizing Fasciitis of the Perineum (Fournier's Gangrene): Reports of necrotizing fasciitis of the perineum (Fournier's gangrene), a rare but serious and life-threatening necrotizing infection requiring urgent surgical intervention, have been identified in postmarketing surveillance in patients with diabetes mellitus receiving SGLT2 inhibitors, including INVOKANA. Cases have been reported in both females and males. Serious outcomes have included hospitalization, multiple surgeries, and death.

Patients treated with INVOKANA presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise, should be assessed for necrotizing fasciitis. If suspected, start treatment immediately with broad-spectrum antibiotics and, if necessary, surgical debridement. Discontinue INVOKANA, closely monitor blood glucose levels, and provide appropriate alternative therapy for glycemic control.

Genital Mycotic Infections: INVOKANA increases the risk of genital mycotic infections. Patients with a history of genital mycotic infections and uncircumcised males were more likely to develop genital mycotic infections *[see Adverse Reactions]*. Monitor and treat appropriately.

Hypersensitivity Reactions: Hypersensitivity reactions, including angioedema and anaphylaxis, have been reported with INVOKANA. These reactions generally occurred within hours to days after initiating INVOKANA. If hypersensitivity reactions occur, discontinue use of INVOKANA; treat and monitor until signs and symptoms resolve *[see Contraindications and Adverse Reactions]*.

Bone Fracture: An increased risk of bone fracture, occurring as early as 12 weeks after treatment initiation, was observed in patients using INVOKANA in the CANVAS trial *[see Clinical Studies (14.2) in Full Prescribing Information]*. Consider factors that contribute to fracture risk prior to initiating INVOKANA *[see Adverse Reactions]*.

ADVERSE REACTIONS

The following important adverse reactions are described below and elsewhere in the labeling:

- Lower Limb Amputation *[see Warnings and Precautions]*
- Volume Depletion *[see Warnings and Precautions]*
- Ketoacidosis *[see Warnings and Precautions]*
- Urosepsis and Pyelonephritis *[see Warnings and Precautions]*
- Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues *[see Warnings and Precautions]*
- Necrotizing Fasciitis of the Perineum (Fournier's gangrene) *[see Warnings and Precautions]*
- Genital Mycotic Infections *[see Warnings and Precautions]*
- Hypersensitivity Reactions *[see Warnings and Precautions]*
- Bone Fracture *[see Warnings and Precautions]*

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

Pool of Placebo-Controlled Trials for Glycemic Control: The data in Table 1 is derived from four 26-week placebo-controlled trials where INVOKANA was used as monotherapy in one trial and as add-on therapy in three trials. These data reflect exposure of 1,667 patients to INVOKANA and a mean duration of exposure to INVOKANA of 24 weeks. Patients received INVOKANA 100 mg (N=833), INVOKANA 300 mg (N=834) or placebo (N=646) once daily. The mean age of the population was 56 years and 2% were older than 75 years of age. Fifty percent (50%) of the population was male and 72% were Caucasian, 12% were Asian, and 5% were Black or African American. At baseline the population had diabetes for an average of 7.3 years, had a mean HbA_{1C} of 8.0% and 20% had established microvascular complications of diabetes. Baseline renal function was normal or mildly impaired (mean eGFR 88 mL/min/1.73 m^2).

Table 1 shows common adverse reactions associated with the use of INVOKANA. These adverse reactions were not present at baseline, occurred more commonly on INVOKANA than on placebo, and occurred in at least 2% of patients treated with either INVOKANA 100 mg or INVOKANA 300 mg.

Table 1: Adverse Reactions from Pool of Four 26–Week Placebo-Controlled Studies Reported in ≥ 2% of INVOKANA-Treated Patients*

Adverse Reaction	Placebo N=646	INVOKANA 100 mg N=833	INVOKANA 300 mg N=834
Urinary tract infections‡	3.8%	5.9%	4.4%
Increased urination§	0.7%	5.1%	4.6%
Thirst#	0.1%	2.8%	2.4%
Constipation	0.9%	1.8%	2.4%
Nausea	1.6%	2.1%	2.3%
	N=312	**N=425**	**N=430**
Female genital mycotic infections†	2.8%	10.6%	11.6%
Vulvovaginal pruritus	0.0%	1.6%	3.2%
	N=334	**N=408**	**N=404**
Male genital mycotic infections¶	0.7%	4.2%	3.8%

* The four placebo-controlled trials included one monotherapy trial and three add-on combination trials with metformin, metformin and sulfonylurea, or metformin and pioglitazone.

† Female genital mycotic infections include the following adverse reactions: Vulvovaginal candidiasis, Vulvovaginal mycotic infection, Vulvovaginitis, Vaginal infection, Vulvitis, and Genital infection fungal.

‡ Urinary tract infections include the following adverse reactions: Urinary tract infection, Cystitis, Kidney infection, and Urosepsis.

§ Increased urination includes the following adverse reactions: Polyuria, Pollakiuria, Urine output increased, Micturition urgency, and Nocturia.

¶ Male genital mycotic infections include the following adverse reactions: Balanitis or Balanoposthitis, Balanitis candida, and Genital infection fungal.

\# Thirst includes the following adverse reactions: Thirst, Dry mouth, and Polydipsia.

Note: Percentages were weighted by studies. Study weights were proportional to the harmonic mean of the three treatment sample sizes.

Abdominal pain was also more commonly reported in patients taking INVOKANA 100 mg (1.8%), 300 mg (1.7%) than in patients taking placebo (0.8%).

Placebo-Controlled Trial in Diabetic Nephropathy: The occurrence of adverse reactions for INVOKANA was evaluated in patients participating in CREDENCE, a study in patients with type 2 diabetes mellitus and diabetic nephropathy with albuminuria > 300 mg/day *[see Clinical Studies (14.3) in Full Prescribing Information]*. These data reflect exposure of 2,201 patients to INVOKANA and a mean duration of exposure to INVOKANA of 137 weeks.

- The rate of lower limb amputations associated with the use of INVOKANA 100 mg relative to placebo was 12.3 vs 11.2 events per 1000 patient-years, respectively, with 2.6 years mean duration of follow-up.
- Incidence rates of adjudicated events of diabetic ketoacidosis (DKA) were 0.21 (0.5%, 12/2,200) and 0.03 (0.1%, 2/2,197) per 100 patient-years of follow-up with INVOKANA 100 mg and placebo, respectively.
- The incidence of hypotension was 2.8% and 1.5% on INVOKANA 100 mg and placebo, respectively.

Pool of Placebo- and Active-Controlled Trials for Glycemic Control and Cardiovascular Outcomes: The occurrence of adverse reactions for INVOKANA was evaluated in patients participating in placebo- and active-controlled trials and in an integrated analysis of two cardiovascular trials, CANVAS and CANVAS-R.

The types and frequency of common adverse reactions observed in the pool of eight clinical trials (which reflect an exposure of 6,177 patients to INVOKANA) were consistent with those listed in Table 1.

Percentages were weighted by studies. Study weights were proportional to the harmonic mean of the three treatment sample sizes. In this pool, INVOKANA was also associated with the adverse reactions of fatigue (1.8%, 2.2%, and 2.0% with comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively) and loss of strength or energy (i.e., asthenia) (0.6%, 0.7%, and 1.1% with comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively).

In the pool of eight clinical trials, the incidence rate of pancreatitis (acute or chronic) was 0.1%, 0.2%, and 0.1% receiving comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively.

In the pool of eight clinical trials, hypersensitivity-related adverse reactions (including erythema, rash, pruritus, urticaria, and angioedema) occurred in 3.0%, 3.8%, and 4.2% of patients receiving comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. Five patients experienced serious adverse reactions of hypersensitivity with INVOKANA, which included 4 patients with urticaria and 1 patient with a diffuse rash and urticaria occurring within hours of exposure to INVOKANA. Among these patients, 2 patients discontinued INVOKANA. One patient with urticaria had recurrence when INVOKANA was re-initiated.

Photosensitivity-related adverse reactions (including photosensitivity reaction, polymorphic light eruption, and sunburn) occurred in 0.1%, 0.2%, and 0.2% of patients receiving comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively.

Other adverse reactions occurring more frequently on INVOKANA than on comparator were:

Lower Limb Amputation: An increased risk of lower limb amputations associated with INVOKANA use versus placebo was observed in CANVAS (5.9 vs 2.8 events per 1000 patient-years) and CANVAS-R (7.5 vs 4.2 events per 1000 patient-years), two randomized, placebo-controlled trials evaluating patients with type 2 diabetes who had either established cardiovascular disease or were at risk for cardiovascular disease. Patients in CANVAS and CANVAS-R were followed for an average of 5.7 and 2.1 years, respectively *[see Clinical Studies (14.2) in Full Prescribing Information]*. The amputation data for CANVAS and CANVAS-R are shown in Tables 2 and 3, respectively.

Table 2: CANVAS Amputations

	Placebo N=1441	INVOKANA 100 mg N=1445	INVOKANA 300 mg N=1441	INVOKANA (Pooled) N=2886
Patients with an amputation, n (%)	22 (1.5)	50 (3.5)	45 (3.1)	95 (3.3)
Total amputations	33	83	79	162
Amputation incidence rate (per 1000 patient-years)	2.8	6.2	5.5	5.9
Hazard Ratio (95% CI)	--	2.24 (1.36, 3.69)	2.01 (1.20, 3.34)	2.12 (1.34, 3.38)

Note: Incidence is based on the number of patients with at least one amputation, and not the total number of amputation events. A patient's follow-up is calculated from Day 1 to the first amputation event date. Some patients had more than one amputation.

Table 3: CANVAS-R Amputations

	Placebo N=2903	INVOKANA 100 mg (with up-titration to 300 mg) N=2904
Patients with an amputation, n (%)	25 (0.9)	45 (1.5)
Total amputations	36	59
Amputation incidence rate (per 1000 patient-years)	4.2	7.5
Hazard Ratio (95% CI)	--	1.80 (1.10, 2.93)

Note: Incidence is based on the number of patients with at least one amputation, and not the total number of amputation events. A patient's follow-up is calculated from Day 1 to the first amputation event date. Some patients had more than one amputation.

Renal Cell Carcinoma: In the CANVAS trial (mean duration of follow-up of 5.7 years) *[see Clinical Studies (14.2) in Full Prescribing Information]*, the incidence of renal cell carcinoma was 0.15% (2/1331) and 0.29% (8/2716) for placebo and INVOKANA, respectively, excluding patients with less than 6 months of follow-up, less than 90 days of treatment, or a history of renal cell carcinoma. A causal relationship to INVOKANA could not be established due to the limited number of cases.

Volume Depletion-Related Adverse Reactions: INVOKANA results in an osmotic diuresis, which may lead to reductions in intravascular volume. In clinical trials for glycemic control, treatment with INVOKANA was associated with a dose-dependent increase in the incidence of volume depletion-related adverse reactions (e.g., hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration). An increased incidence was observed in patients on the 300 mg dose. The three factors associated with the largest increase in volume depletion-related adverse reactions in these trials were the use of loop diuretics, moderate renal impairment (eGFR 30 to less than 60 mL/min/1.73 m^2), and age 75 years and older (Table 4) *[see Use in Specific Populations]*.

Table 4: Proportion of Patients With at Least One Volume Depletion-Related Adverse Reaction (Pooled Results from 8 Clinical Trials for Glycemic Control)

Baseline Characteristic	Comparator Group* %	INVOKANA 100 mg %	INVOKANA 300 mg %
Overall population	1.5%	2.3%	3.4%
75 years of age and older†	2.6%	4.9%	8.7%
eGFR less than 60 mL/min/1.73 m^2†	2.5%	4.7%	8.1%
Use of loop diuretic†	4.7%	3.2%	8.8%

* Includes placebo and active-comparator groups

† Patients could have more than 1 of the listed risk factors

Falls: In a pool of nine clinical trials with mean duration of exposure to INVOKANA of 85 weeks, the proportion of patients who experienced falls was 1.3%, 1.5%, and 2.1% with comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. The higher risk of falls for patients treated with INVOKANA was observed within the first few weeks of treatment.

Genital Mycotic Infections: In the pool of four placebo-controlled clinical trials for glycemic control, female genital mycotic infections (e.g., vulvovaginal mycotic infection, vulvovaginal candidiasis, and vulvovaginitis) occurred in 2.8%, 10.6%, and 11.6% of females treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. Patients with a history of genital mycotic infections were more likely to develop genital mycotic infections on INVOKANA. Female patients who developed genital mycotic infections on INVOKANA were more likely to experience recurrence and require treatment with oral or topical antifungal agents and anti-microbial agents. In females, discontinuation due to genital mycotic infections occurred in 0% and 0.7% of patients treated with placebo and INVOKANA, respectively.

In the pool of four placebo-controlled clinical trials, male genital mycotic infections (e.g., candidal balanitis, balanoposthitis) occurred in 0.7%, 4.2%, and 3.8% of males treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. Male genital mycotic infections occurred more commonly in uncircumcised males and in males with a prior history of balanitis or balanoposthitis. Male patients who developed genital mycotic infections on INVOKANA were more likely to experience recurrent infections

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(22% on INVOKANA versus none on placebo), and require treatment with oral or topical antifungal agents and anti-microbial agents than patients on comparators. In males, discontinuations due to genital mycotic infections occurred in 0% and 0.5% of patients treated with placebo and INVOKANA, respectively.

In the pooled analysis of 8 randomized trials evaluating glycemic control, phimosis was reported in 0.3% of uncircumcised male patients treated with INVOKANA and 0.2% required circumcision to treat the phimosis.

Hypoglycemia: In all glycemic control trials, hypoglycemia was defined as any event regardless of symptoms, where biochemical hypoglycemia was documented (any glucose value below or equal to 70 mg/dL). Severe hypoglycemia was defined as an event consistent with hypoglycemia where the patient required the assistance of another person to recover, lost consciousness, or experienced a seizure (regardless of whether biochemical documentation of a low glucose value was obtained). In individual clinical trials of glycemic control *[see Clinical Studies (14.1) in Full Prescribing Information]*, episodes of hypoglycemia occurred at a higher rate when INVOKANA was co-administered with insulin or sulfonylureas (Table 5).

Table 5: Incidence of Hypoglycemia* in Randomized Clinical Studies of Glycemic Control

Monotherapy (26 weeks)	**Placebo (N=192)**	**INVOKANA 100 mg (N=195)**	**INVOKANA 300 mg (N=197)**
Overall [N (%)]	5 (2.6)	7 (3.6)	6 (3.0)
In Combination with Metformin (26 weeks)	**Placebo + Metformin (N=183)**	**INVOKANA 100 mg + Metformin (N=368)**	**INVOKANA 300 mg + Metformin (N=367)**
Overall [N (%)]	3 (1.6)	16 (4.3)	17 (4.6)
Severe [N (%)]†	0 (0)	1 (0.3)	1 (0.3)
In Combination with Metformin (52 weeks)	**Glimepiride + Metformin (N=482)**	**INVOKANA 100 mg + Metformin (N=483)**	**INVOKANA 300 mg + Metformin (N=485)**
Overall [N (%)]	165 (34.2)	27 (5.6)	24 (4.9)
Severe [N (%)]†	15 (3.1)	2 (0.4)	3 (0.6)
In Combination with Sulfonylurea (18 weeks)	**Placebo + Sulfonylurea (N=69)**	**INVOKANA 100 mg + Sulfonylurea (N=74)**	**INVOKANA 300 mg + Sulfonylurea (N=72)**
Overall [N (%)]	4 (5.8)	3 (4.1)	9 (12.5)
In Combination with Metformin + Sulfonylurea (26 weeks)	**Placebo + Metformin + Sulfonylurea (N=156)**	**INVOKANA 100 mg + Metformin + Sulfonylurea (N=157)**	**INVOKANA 300 mg + Metformin + Sulfonylurea (N=156)**
Overall [N (%)]	24 (15.4)	43 (27.4)	47 (30.1)
Severe [N (%)]†	1 (0.6)	1 (0.6)	0
In Combination with Metformin + Sulfonylurea (52 weeks)	**Sitagliptin + Metformin + Sulfonylurea (N=378)**		**INVOKANA 300 mg + Metformin + Sulfonylurea (N=377)**
Overall [N (%)]	154 (40.7)		163 (43.2)
Severe [N (%)]†	13 (3.4)		15 (4.0)
In Combination with Metformin + Pioglitazone (26 weeks)	**Placebo + Metformin + Pioglitazone (N=115)**	**INVOKANA 100 mg + Metformin + Pioglitazone (N=113)**	**INVOKANA 300 mg + Metformin + Pioglitazone (N=114)**
Overall [N (%)]	3 (2.6)	3 (2.7)	6 (5.3)
In Combination with Insulin (18 weeks)	**Placebo (N=565)**	**INVOKANA 100 mg (N=566)**	**INVOKANA 300 mg (N=587)**
Overall [N (%)]	208 (36.8)	279 (49.3)	285 (48.6)
Severe [N (%)]†	14 (2.5)	10 (1.8)	16 (2.7)

* Number of patients experiencing at least one event of hypoglycemia based on either biochemically documented episodes or severe hypoglycemic events in the intent-to-treat population

† Severe episodes of hypoglycemia were defined as those where the patient required the assistance of another person to recover, lost consciousness, or experienced a seizure (regardless of whether biochemical documentation of a low glucose value was obtained)

Bone Fracture: In the CANVAS trial *[see Clinical Studies (14.2) in Full Prescribing Information]*, the incidence rates of all adjudicated bone fracture were 1.09, 1.59, and 1.79 events per 100 patient-years of follow-up to placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. The fracture imbalance was observed within the first 26 weeks of therapy and remained through the end of the trial. Fractures were more likely to be low trauma (e.g., fall from no more than standing height), and affect the distal portion of upper and lower extremities.

Laboratory and Imaging Tests*: Increases in Serum Creatinine and Decreases in eGFR*: Initiation of INVOKANA causes an increase in serum creatinine and decrease in estimated GFR. In patients with moderate renal impairment, the increase in serum creatinine generally does not exceed 0.2 mg/dL, occurs within the first 6 weeks of starting therapy, and then stabilizes. Increases that do not fit this pattern should prompt further evaluation to exclude the possibility of acute kidney injury *[see Clinical Pharmacology (12.1) in Full Prescribing Information]*. The acute effect on eGFR reverses after treatment discontinuation suggesting acute hemodynamic changes may play a role in the renal function changes observed with INVOKANA.

Increases in Serum Potassium: In a pooled population of patients (N=723) in glycemic control trials with moderate renal impairment (eGFR 45 to less than 60 mL/min/1.73 m^2), increases in serum potassium to greater than 5.4 mEq/L and 15% above baseline occurred in 5.3%, 5.0%, and 8.8% of patients treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. Severe elevations (greater than or equal to 6.5 mEq/L) occurred in 0.4% of patients treated with placebo, no patients treated with INVOKANA 100 mg, and 1.3% of patients treated with INVOKANA 300 mg.

In these patients, increases in potassium were more commonly seen in those with elevated potassium at baseline. Among patients with moderate renal impairment, approximately 84% were taking medications that interfere with potassium excretion, such as potassium-sparing diuretics, angiotensin-converting-enzyme inhibitors, and angiotensin-receptor blockers *[see Use in Specific Populations]*.

In CREDENCE, no difference in serum potassium, no increase in adverse events of hyperkalemia, and no increase in absolute (> 6.5 mEq/L) or relative (> upper limit of normal and > 15% increase from baseline) increases in serum potassium were observed with INVOKANA 100 mg relative to placebo.

Increases in Low-Density Lipoprotein Cholesterol (LDL-C) and non-High-Density Lipoprotein Cholesterol (non-HDL-C): In the pool of four glycemic control placebo-controlled trials, dose-related increases in LDL-C with INVOKANA were observed. Mean changes (percent changes) from baseline in LDL-C relative to placebo were 4.4 mg/dL (4.5%) and 8.2 mg/dL (8.0%) with INVOKANA 100 mg and INVOKANA 300 mg, respectively. The mean baseline LDL-C levels were 104 to 110 mg/dL across treatment groups.

Dose-related increases in non-HDL-C with INVOKANA were observed. Mean changes (percent changes) from baseline in non-HDL-C relative to placebo were 2.1 mg/dL (1.5%) and 5.1 mg/dL (3.6%) with INVOKANA 100 mg and 300 mg, respectively. The mean baseline non-HDL-C levels were 140 to 147 mg/dL across treatment groups.

Increases in Hemoglobin: In the pool of four placebo-controlled trials of glycemic control, mean changes (percent changes) from baseline in hemoglobin were -0.18 g/dL (-1.1%) with placebo, 0.47 g/dL (3.5%) with INVOKANA 100 mg, and 0.51 g/dL (3.8%) with INVOKANA 300 mg. The mean baseline hemoglobin value was approximately 14.1 g/dL across treatment groups. At the end of treatment, 0.8%, 4.0%, and 2.7% of patients treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively, had hemoglobin above the upper limit of normal.

Decreases in Bone Mineral Density: Bone mineral density (BMD) was measured by dual-energy X-ray absorptiometry in a clinical trial of 714 older adults (mean age 64 years) *[see Clinical Studies (14.1) in Full Prescribing Information]*. At 2 years, patients randomized to INVOKANA 100 mg and INVOKANA 300 mg had placebo-corrected declines in BMD at the total hip of 0.9% and 1.2%, respectively, and at the lumbar spine of 0.3% and 0.7%, respectively. Additionally, placebo-adjusted BMD declines were 0.1% at the femoral neck for both INVOKANA doses and 0.4% at the distal forearm for patients randomized to INVOKANA 300 mg. The placebo-adjusted change at the distal forearm for patients randomized to INVOKANA 100 mg was 0%.

Postmarketing Experience: Additional adverse reactions have been identified during post-approval use of INVOKANA. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Ketoacidosis

Acute Kidney Injury

Anaphylaxis, Angioedema

Urosepsis and Pyelonephritis

Necrotizing Fasciitis of the Perineum (Fournier's gangrene)

DRUG INTERACTIONS

UGT Enzyme Inducers: Co-administration of canagliflozin with rifampin, a nonselective inducer of several UGT enzymes, including UGT1A9, UGT2B4, decreased canagliflozin area under the curve (AUC) by 51%. This decrease in exposure to canagliflozin may decrease efficacy.

For patients with eGFR 60 mL/min/1.73 m^2 or greater, if an inducer of UGTs (e.g., rifampin, phenytoin, phenobarbital, ritonavir) is co-administered with INVOKANA, increase the dose to 200 mg (taken as two 100 mg tablets) once daily in patients currently tolerating INVOKANA 100 mg. The dose may be increased to 300 mg once daily in patients currently tolerating INVOKANA 200 mg and who require additional glycemic control.

For patients with eGFR less than 60 mL/min/1.73 m^2, if an inducer of UGTs (e.g., rifampin, phenytoin, phenobarbital, ritonavir) is co-administered with INVOKANA, increase the dose to 200 mg (taken as two 100 mg tablets) once daily in patients currently tolerating INVOKANA 100 mg. Consider adding another antihyperglycemic agent in patients who require additional glycemic control *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3) in Full Prescribing Information]*.

Digoxin: There was an increase in the AUC and mean peak drug concentration (C_{max}) of digoxin (20% and 36%, respectively) when co-administered with INVOKANA 300 mg *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*. Patients taking INVOKANA with concomitant digoxin should be monitored appropriately.

Positive Urine Glucose Test: Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors as SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests. Use alternative methods to monitor glycemic control.

Interference with 1,5-anhydroglucitol (1,5-AG) Assay: Monitoring glycemic control with 1,5-AG assay is not recommended as measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.

USE IN SPECIFIC POPULATIONS

Pregnancy: Risk Summary: Based on animal data showing adverse renal effects, INVOKANA is not recommended during the second and third trimesters of pregnancy.

Limited data with INVOKANA in pregnant women are not sufficient to determine a drug-associated risk for major birth defects or miscarriage. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy *[see Clinical Considerations]*.

In animal studies, adverse renal pelvic and tubule dilatations that were not reversible were observed in rats when canagliflozin was administered during a period of renal development corresponding to the late second and third trimesters of human pregnancy, at an exposure 0.5-times the 300 mg clinical dose, based on AUC.

The estimated background risk of major birth defects is 6-10% in women with pre-gestational diabetes with a HbA_{1C} >7 and has been reported to be as high as 20-25% in women with a HbA_{1C} >10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations*: Disease-associated maternal and/or embryo/fetal risk*: Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.

Animal Data: Canagliflozin dosed directly to juvenile rats from postnatal day (PND) 21 until PND 90 at doses of 4, 20, 65, or 100 mg/kg increased kidney weights and dose dependently increased the incidence and severity of renal pelvic and tubular dilatation at all doses tested. Exposure at the lowest dose was greater than or equal to 0.5-times the 300 mg clinical dose, based on AUC. These outcomes occurred with drug exposure during periods of renal development in rats that correspond to the late second and third trimester of human renal development. The renal pelvic dilatations observed in juvenile animals did not fully reverse within a 1-month recovery period.

In embryo-fetal development studies in rats and rabbits, canagliflozin was administered for intervals coinciding with the first trimester period of organogenesis in humans. No developmental toxicities independent of maternal toxicity were observed when canagliflozin was administered at doses up to 100 mg/kg in pregnant rats and 160 mg/kg in pregnant rabbits during embryonic organogenesis or during a study in which maternal rats were dosed from gestation day (GD) 6 through PND 21, yielding exposures up to approximately 19-times the 300 mg clinical dose, based on AUC.

Lactation: Risk Summary: There is no information regarding the presence of INVOKANA in human milk, the effects on the breastfed infant, or the effects on milk production. Canagliflozin is present in the milk of lactating rats *[see Data]*. Since human kidney maturation occurs *in utero* and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney.

Because of the potential for serious adverse reactions in a breastfed infant, advise women that use of INVOKANA is not recommended while breastfeeding.

Data: *Animal Data*: Radiolabeled canagliflozin administered to lactating rats on day 13 post-partum was present at a milk/plasma ratio of 1.40, indicating that canagliflozin and its metabolites are transferred into milk at a concentration comparable to that in plasma. Juvenile rats directly exposed to canagliflozin showed a risk to the developing kidney (renal pelvic and tubular dilatations) during maturation.

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Pediatric Use: Safety and effectiveness of INVOKANA in pediatric patients under 18 years of age have not been established.

Geriatric Use: In 13 clinical trials of INVOKANA, 2,294 patients 65 years and older, and 351 patients 75 years and older were exposed to INVOKANA *[see Clinical Studies (14.1) in Full Prescribing Information]*.

Patients 65 years and older had a higher incidence of adverse reactions related to reduced intravascular volume with INVOKANA (such as hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration), particularly with the 300 mg daily dose, compared to younger patients; a more prominent increase in the incidence was seen in patients who were 75 years and older *[see Dosage and Administration (2.1) in Full Prescribing Information and Adverse Reactions]*. Smaller reductions in HbA_{1C} with INVOKANA relative to placebo were seen in older (65 years and older; -0.61% with INVOKANA 100 mg and -0.74% with INVOKANA 300 mg relative to placebo) compared to younger patients (-0.72% with INVOKANA 100 mg and -0.87% with INVOKANA 300 mg relative to placebo).

Renal Impairment: The efficacy and safety of INVOKANA for glycemic control were evaluated in a trial that included patients with moderate renal impairment (eGFR 30 to less than 50 mL/min/1.73 m^2) *[see Clinical Studies (14.1) in Full Prescribing Information]*. These patients had less overall glycemic efficacy, and patients treated with 300 mg per day had increases in serum potassium, which were transient and similar by the end of study. Patients with renal impairment using INVOKANA for glycemic control may also be more likely to experience hypotension and may be at higher risk for acute kidney injury *[see Warnings and Precautions]*.

Efficacy and safety studies with INVOKANA did not enroll patients with ESKD on dialysis or patients with an eGFR less than 30 mL/min/1.73 m^2. INVOKANA is contraindicated in patients with ESKD on dialysis *[see Contraindications and Clinical Pharmacology (12.1) in Full Prescribing Information]*.

Hepatic Impairment: No dosage adjustment is necessary in patients with mild or moderate hepatic impairment. The use of INVOKANA has not been studied in patients with severe hepatic impairment and is therefore not recommended *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*.

OVERDOSAGE

In the event of an overdose, contact the Poison Control Center. It is also reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment as dictated by the patient's clinical status. Canagliflozin was negligibly removed during a 4-hour hemodialysis session. Canagliflozin is not expected to be dialyzable by peritoneal dialysis.

PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

Lower Limb Amputation: Inform patients that INVOKANA is associated with an increased risk of amputations. Counsel patients about the importance of routine preventative foot care. Instruct patients to monitor for new pain or tenderness, sores or ulcers, or infections involving the leg or foot and to seek medical advice immediately if such signs or symptoms develop *[see Warnings and Precautions]*.

Volume Depletion: Inform patients that symptomatic hypotension may occur with INVOKANA and advise them to contact their doctor if they experience such symptoms *[see Warnings and Precautions]*. Inform patients that dehydration may increase the risk for hypotension, and to have adequate fluid intake.

Ketoacidosis: Inform patients that ketoacidosis is a serious life-threatening condition and that cases of ketoacidosis have been reported during use of INVOKANA, sometimes associated with illness or surgery among other risk factors. Instruct patients to check ketones (when possible) if symptoms consistent with ketoacidosis occur even if blood glucose is not elevated. If symptoms of ketoacidosis (including nausea, vomiting, abdominal pain, tiredness, and labored breathing) occur, instruct patients to discontinue INVOKANA and seek medical attention immediately *[see Warnings and Precautions]*.

Serious Urinary Tract Infections: Inform patients of the potential for urinary tract infections, which may be serious. Provide them with information on the symptoms of urinary tract infections. Advise them to seek medical advice if such symptoms occur *[see Warnings and Precautions]*.

Necrotizing Fasciitis of the Perineum (Fournier's Gangrene): Inform patients that necrotizing infections of the perineum (Fournier's gangrene) have occurred with INVOKANA. Counsel patients to promptly seek medical attention if they develop pain or tenderness, redness, or swelling of the genitals or the area from the genitals back to the rectum, along with a fever above 100.4°F or malaise *[see Warnings and Precautions]*.

Genital Mycotic Infections in Females (e.g., Vulvovaginitis): Inform female patients that vaginal yeast infection may occur and provide them with information on the signs and symptoms of vaginal yeast infection. Advise them of treatment options and when to seek medical advice *[see Warnings and Precautions]*.

Genital Mycotic Infections in Males (e.g., Balanitis or Balanoposthitis): Inform male patients that yeast infection of penis (e.g., balanitis or balanoposthitis) may occur, especially in uncircumcised males and patients with prior history. Provide them with information on the signs and symptoms of balanitis and balanoposthitis (rash or redness of the glans or foreskin of the penis). Advise them of treatment options and when to seek medical advice *[see Warnings and Precautions]*.

Hypersensitivity Reactions: Inform patients that serious hypersensitivity reactions, such as urticaria, rash, anaphylaxis, and angioedema, have been reported with INVOKANA. Advise patients to report immediately any signs or symptoms suggesting allergic reaction, and to discontinue drug until they have consulted prescribing physicians *[see Warnings and Precautions]*.

Bone Fracture: Inform patients that bone fractures have been reported in patients taking INVOKANA. Provide them with information on factors that may contribute to fracture risk *[see Warnings and Precautions]*.

Pregnancy: Advise pregnant women, and females of reproductive potential of the potential risk to a fetus with treatment with INVOKANA *[see Use in Specific Populations]*. Instruct females of reproductive potential to report pregnancies to their physicians as soon as possible.

Lactation: Advise women that breastfeeding is not recommended during treatment with INVOKANA *[see Use in Specific Populations]*.

Laboratory Tests: Inform patients that due to its mechanism of action, patients taking INVOKANA will test positive for glucose in their urine *[see Drug Interactions]*.

Missed Dose: If a dose is missed, advise patients to take it as soon as it is remembered unless it is almost time for the next dose, in which case patients should skip the missed dose and take the medicine at the next regularly scheduled time. Advise patients not to take two doses of INVOKANA at the same time.

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Lumasiran Offers a New, Effective Treatment for Primary Hyperoxaluria Type 1 (PH1)

By Stephanie Perez Kerkvliet and Michelle N. Rheault

Primary hyperoxaluria type 1 (PH1) is a rare metabolic disease that leads to oxalate overproduction and results in kidney stones, nephrocalcinosis, kidney failure, and eventually systemic oxalosis. Garrelfs et al. (1) recently published results of the multinational, randomized, double-blind, placebo-controlled ILLUMINATE-A clinical trial evaluating the effectiveness of treating PH1 with lumasiran, an RNA interference (RNAi) agent directed against the mRNA encoding glycolate oxidase in the liver. The trial included 39 participants with PH1, ages 6–60 years (median age 14 years, including 22 pediatric participants), with an estimated glomerular filtration rate (eGFR) greater than or equal to 30 mL/min/1.73 m^2, 26 of whom were randomized to lumasiran treatment. After 6 months of treatment, the least-squares mean percent change in 24-hour urinary oxalate excretion decreased 65.4% in the lumasiran group compared to 11.8% in the placebo group. Moreover, 84% of patients in the lumasiran group had 24-hour urinary oxalate levels no higher than 1.5 times the upper limit of normal compared to 0% of patients in the placebo group ($p < 0.001$). The most common side effect of lumasiran was injection-site reactions (38%), and no severe or serious adverse events occurred. Lumasiran is the first US Food and Drug Administration (FDA)-approved specific treatment for patients with PH1. Lumasiran has not been tested in other genetic forms of PH1 and would not be expected to be efficacious in secondary hyperoxaluria.

Prior to lumasiran, treatment strategies for PH1 focused on preventing oxalate stone formation and slowing disease progression and included hyperhydration, high-dose pyridoxine, and citrate. Despite these burdensome treatments, patients with PH1 often experienced progressive kidney failure. Liver transplant is curative, and patients often receive combined liver and kidney transplants after kidney failure. However, organ transplantation carries many peri- and post-operative risks, and many patients and their families experience transplantation as trading one disease for another. The findings of the ILLUMINATE-A clinical trial offer an apparently safe and effective subcutaneous treatment with the opportunity to improve both disease control and quality of life in patients with PH1. ■

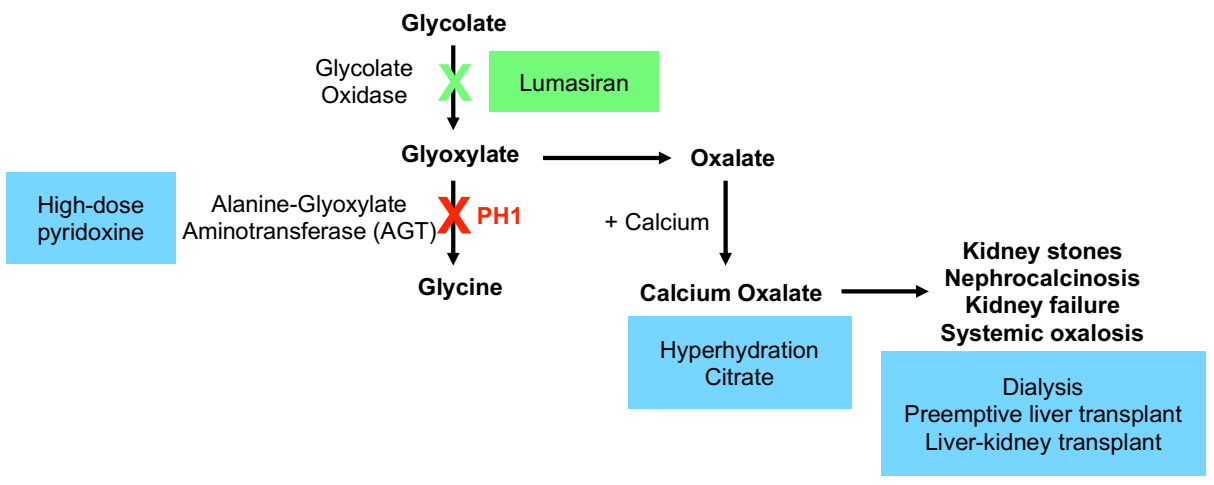
Stephanie Perez Kerkvliet, MD, is a Pediatrics Resident Physician, and Michelle N. Rheault, MD, is Director, Division of Pediatric Nephrology, and Associate Professor of Pediatrics, University of Minnesota Masonic Children's Hospital, in Minneapolis.

Dr. Rheault is the site principal investigator with Advicenne, Travere, Reata, Sanofi, and Genentech. Dr. Perez Kerkvliet has no disclosures.

Reference

1. Garrelfs SF, et al. Lumasiran, an RNAi therapeutic for primary hyperoxaluria type 1. *N Engl J Med* 2021; 384:1216–1226. doi: 10.1056/NEJMoa2021712

Figure 1. Treatments for primary hyperoxaluria type 1 (PH1)



Adding Life to Their Years

By Holly M. Koncicki

Adding life to their years: The current state of pediatric palliative care in CKD," by House and Wightman, calls pediatric nephrologists to action for the integration of palliative care into their practice. In an effort to distinguish palliative care from being inappropriately conflated with "end-of-life care," the rebranding of the nephology-palliative care integration has already occurred in adult nephrology, highlighting the ability of palliative care to be delivered alongside CKD care (1).

By highlighting the effects of pediatric CKD on the child and family unit, the authors describe some challenges similar to adult CKD care, including adverse effects on health-related quality of life and increased symptom burden, as well as the unique needs of children, including subsequent transplants, detrimental effects on well-being, financial stress, and anxiety experienced by siblings and parents. Integration of palliative care into other pediatric chronic illnesses has proven valuable, with improved psychosocial outcomes in oncology; physical and psychological symptoms in patients with cystic fibrosis; and maternal anxiety in children with hypoplastic left heart syndrome. It is time for pediatric nephrologists to spearhead this integration for their patients as well. Continued exposure in fellowship and continuing education can increase pediatric nephrologists' familiarity with primary palliative care skills, including basic symptom management, communication, and incorporation of the patient's perspective in shared decision-making. More complex care needs of patients and families should prompt consultation with specialist palliative care providers, social workers, psychologists, and child life specialists. Similar to the adult integration of nephrology and palliative care (Table 1), the most effective way to deliver this integrated care remains as yet undefined, but through conscious efforts and research, this model can be better delineated to best "add life to the child's years, not simply years to the child's life." ■

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The author has no conflicts of interest.

Reference

1. House TR, Wightman A. Adding life to their years: The current state of pediatric palliative care in CKD. *Kidney360* April 2021. doi: 10.34067/KID.0000282021; https://doi.org/10.34067/KID.0000282021

Table 1. Comparison of adult vs. pediatric palliative care

Similarities	Differences
Palliative care can be delivered at any stage of illness, including alongside curative treatments.	Childhood illness can occur in a broad spectrum of ages varying from perinatal to young adult and may persist through varying stages of development. The palliative care team will need to adapt to the child's evolving emotional maturity and cognitive understanding of the illness.
The palliative care team can help with decision-making and establishing goals of care with the patient and/or surrogate/proxy.	Medical decisions for young children are made by their parents or guardians.
The care model involves an interdisciplinary team including a doctor, nurse, and social worker.	The interdisciplinary team for pediatric palliative care has unique members including a child life specialist.
A focus of care is to improve quality of life by early identification and treatment of symptoms.	Having a serious illness in childhood can present unique features in caring for the child, siblings, and parents. This includes addressing emotional and psychological needs and the potential need for respite care.

Adapted from Center to Advance Palliative Care. Pediatric versus adult palliative care. https://getpalliativecare.org/whatis/pediatric/adult-vs-pediatric-palliative-care/#:~:text=Medical%20decisions%20for%20young%20children,and%2For%20child%20behavioral%20specialist

The Impact of COVID-19 on Undocumented Immigrants Needing Dialysis

By Areeba Jawed

There is mounting evidence of the disproportionate impact of the COVID-19 pandemic on racial and ethnic minorities within the United States (1). Undocumented immigrants represent one of the most marginalized segments of society with access to fewer healthcare resources and thus worse health-related outcomes (2). There are approximately between 5500 and 8857 undocumented immigrants receiving dialysis in the United States based on recent data (3). Undocumented immigrants do not qualify for regular outpatient-scheduled dialysis under Medicare or non-emergency Medicaid, and a majority of undocumented immigrants with chronic kidney disease receive emergent dialysis covered under the Emergency Medical Treatment & Labor Act (EMTALA) (3).

Higher risk of exposure due to nature of emergency dialysis

Due to concerns related to COVID-19 exposure, emergency room (ER) visits among the general population declined by 42% during the early COVID-19 pandemic (4). However, undocumented immigrants are left with no choice but to visit the ER when confronted with life-threatening emergencies related to lack of scheduled dialysis. In one study, undocumented immigrants needing emergent dialysis visited the ER an average of 6 times in 1 month (5). Multiple ER visits often requiring hospitalization, including in the intensive care units, may result in an increased risk of COVID-19 exposure, which needs to be addressed in future studies. The mental and social well-being of these patients, already impacted by the nature of emergent dialysis (6), is likely to decline further when they are forced to visit the ER amid pandemic anxiety, limited supplies of personal protective equipment, uncertainties regarding disease course, and unknown risks.

Potentially worse outcomes with COVID-19-related disease

Data specific to outcomes of COVID-19-related disease in undocumented immigrants on emergent dialysis have not been reported. However, in the general population, Latino individuals are more likely to become infected, hospitalized, and die from COVID-19 compared with White individuals (7), and much of these differences are concentrated in immigrants (8). Hispanic ethnicity is also associated with higher rates of COVID-19 hospitalization and higher excess mortality in Medicare beneficiaries on dialysis (9). Hispanic Latinos constitute the majority of undocumented immigrants. One can postulate that with overall higher mortality and morbidity with emergent dialysis, these patients are likely to have worse outcomes with COVID-19 compared to citizens on dialysis, based on ethnicity and lack of scheduled dialysis (5, 10).

Barriers to seeking medical care

The pandemic has highlighted disparities in the healthcare system, including access to basic healthcare. An estimated 7 million undocumented immigrants are without healthcare insurance after being excluded from the Affordable Care Act. Recent policy initiatives that expand access to COVID-19 treatment, such as the Families First Coronavirus Response Act; the Coronavirus Aid, Relief, and Economic Security Act; and the proposed Take Responsibility for Workers and Families Act, do not alter Medicaid eligibility, thereby excluding undocumented immigrants (11). Historically, due to lack of insurance coverage, these patients and their families have become reliant on the ER for primary care needs. Given the current strain on the healthcare system, patients are being asked to avoid ER visits; however, without access to primary care or mobile testing sites, these patients are placed in limbo. Although most COVID-19 patients can successfully be managed at home, lack of access to primary care may result in unnecessary ER visits as patients struggle with seeking help to diagnose and manage COVID-19-related diseases, adding further emotional strain for these patients.

The fear of deportation, the experiences of stigma, and racial discrimination may limit the willingness of undocumented immigrants to seek the healthcare they need (12). Despite the suspension of the US Citizenship and Immigration Services' (USCIS) new Inadmissibility on Public Charge Grounds rule, which negatively views use of public assistance when considering applications for permanent residence, there is still widespread fear of its application, which may delay patients from seeking emergent dialysis. Patients themselves may also be worried about the risk of coronavirus exposure through the ER and the risk of serious adverse events, such as volume overload, hypoxia, and fatal arrythmias, by increasing the interval days between dialysis treatments.

Social conditions contributing to increased risk of disease

The pandemic resulted in widespread stay-at-home orders across the states to limit disease spread; however, undocumented immigrants make up a disproportionate share of essential workers, which increases their risk of acquiring COVID-19 and limits their ability to work from home (13). Low-income immigrant families frequently have precarious living conditions with multiple family members sharing living arrangements to save money, which makes it challenging to self-isolate in the setting of COVID-19 exposure. Based on a recent analysis, Latino patients with COVID-19 compared with non-Latino individuals were more likely to report working while ill, exposure to someone with COVID-19 in the household, and living with multiple household members (14), which further contributes to increased morbidity and mortality from COVID-19 disease.

Economic strain

Being on dialysis is known to be associated with decreased likelihood of employment (15), with vulnerable groups having an even lower employment rate. Many undocumented immigrants are employed in the service industry and have lost their source of income during the pandemic (16). Furthermore, they will not qualify for federal relief funding in the face of rising unemployment and financial hardship. Immigrants are known to support large families within the United States and may also send resources to families overseas, and thus they are at risk for declining health as they have fewer resources to spend on medications and other healthcare-related needs (17).

The pandemic has highlighted deep-rooted inequities in healthcare access and delivery. Undocumented immigrants receiving emergent dialysis are one of the most vulnerable segments of our population, and efforts should be made to highlight their contributions to our society. A transition from emergent dialysis to scheduled outpatient hemodialysis should be part of the larger efforts to curtail COVID-19 spread and address healthcare disparities during the pandemic and beyond. ■

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References

1. Tai DBG, et al. The disproportionate impact of COVID-19 on racial and ethnic minorities in the United States. *Clin Infect Dis* 2021; 72:703–706. doi: 10.1093/cid/ciaa815
2. Gostin LO. Is affording undocumented immigrants health coverage a radical proposal? *JAMA* 2019; 322:1438–1439. doi: 10.1001/jama.2019.15806
3. Rodriguez R, et al. Estimating the prevalence of undocumented immigrants with end-stage renal disease in the United States. *Clin Nephrol* 2020; 93:108–112. doi: 10.5414/CNP92S119
4. Hartnett KP, et al. Impact of the COVID-19 pandemic on emergency department visits—United States, January 1, 2019–May 30, 2020. *Morb Mortal Wkly Rep* 2020; 69:699–704. doi: 10.15585/mmwr.mm6923e1
5. Cervantes L, et al. Association of emergency-only vs standard hemodialysis with mortality and health care use among undocumented immigrants with end-stage renal disease. *JAMA Intern Med* 2018; 178:188–195. doi: 10.1001/jamainternmed.2017.7039
6. Cervantes L, et al. The illness experience of undocumented immigrants with end-stage renal disease. *JAMA Intern Med* 2017; 177:529–535. doi: 10.1001/jamainternmed.2016.8865
7. Cooper LA, Williams DR. Excess deaths from COVID-19, community bereavement, and restorative justice for communities of color. *JAMA* 2020; 324:1491–1492. doi: 10.1001/jama.2020.19567
8. Riley AR, et al. Excess death among Latino people in California during the COVID-19 pandemic. medRxiv [preprint published online ahead of print January 25, 2021]. doi: 10.1101/2020.12.18.20248434; https://www.medrxiv.org/content/10.1101/2020.12.18.20248434v2
9. Weinhandl ED, et al. Initial effects of COVID-19 on patients with ESKD. *J Am Soc Nephrol* [published online ahead of print April 8, 2021]. doi: 10.1681/ASN.2021010009; https://jasn.asnjournals.org/content/early/2021/04/07/ASN.2021010009
10. Cervantes L, et al. Qualitative interviews exploring palliative care perspectives of Latinos on dialysis. *Clin J Am Soc Nephrol* 2017; 12:788–798. doi: 10.2215/CJN.10260916
11. National Immigration Law Center. Understanding the impact of key provisions of COVID-19 relief bills on immigrant communities. April 1, 2020; 1–15. https://www.fullerton.edu/tdrc/_resources/COVID19-NILC%20Relief%20Bills%20on%20Immigrant%20Communities.pdf
12. Heyman JM, et al. Healthcare access and barriers for unauthorized immigrants in El Paso County, Texas. *Fam Community Health* 2009; 32:4–21. doi: 10.1097/01.FCH.0000342813.42025.a3
13. Jordan M. Farmworkers, mostly undocumented, become 'essential' during pandemic. *The New York Times* Published April 2, 2020. Updated April 10, 2020. https://www.nytimes.com/2020/04/02/us/coronavirus-undocumented-immigrant-farmworkers-agriculture.html
14. Podewils LJ, et al. Disproportionate incidence of COVID-19 infection, hospitalizations, and deaths among persons identifying as Hispanic or Latino—Denver, Colorado March–October 2020. *Morb Mortal Wkly Rep* 2020; 69:1812–1816. doi: 10.15585/mmwr.mm6948a3
15. Erickson KF, et al. Employment among patients starting dialysis in the United States. *Clin J Am Soc Nephrol* 2018; 13:265–273. doi: 10.2215/CJN.06470617
16. Jordan M, Dickerson C. 'Plz cancel our cleaning': Virus leads many to cast aside household help. *The New York Times* March 25, 2020. https://www.nytimes.com/2020/03/25/us/coronavirus-housekeepers-nannies-domestic-undocumented-immigrants.html
17. Page KR, et al. Undocumented U.S. immigrants and COVID-19. *N Engl J Med* 2020; 382:e62. doi: 10.1056/NEJMp2005953

Acute Kidney Injury Common in Children with COVID-19 Multisystem Inflammatory Syndrome

By Bridget M. Kuehn

Acute kidney injury (AKI) is common among children hospitalized with COVID-19 Multisystem Inflammatory Syndrome (MIS-C), but it usually resolves quickly, a trio of recent studies suggests.

Studies have shown that about one-third of adults hospitalized with COVID-19 develop AKI (1). Fewer children have been hospitalized with acute COVID-19 or MIS-C, a rare Kawasaki disease-like syndrome linked with recent COVID-19 infections in children (2). But the three new studies suggest that AKI is also a frequent complication in this age group affecting 8% to 20% of children hospitalized with acute COVID-19 and 18% to 46% of children hospitalized with MIS-C.

"Acute kidney injury was a common finding among pediatric patients with MIS-C, but thankfully it was mild and with a shorter recovery period, which differed significantly with what we've seen with AKI in adults with primary COVID infection," said Natalie Uy, MD, assistant professor in the Division of Pediatric Nephrology at Columbia University Irving Medical Center.

Rapid resolution

One study analyzed data on 157 pediatric patients hospitalized with either acute COVID-19 or MIS-C at one of the four hospitals in the Northwell Health System between early March and mid-August 2020 (3). It found that about 8% of the children hospitalized with acute COVID-19 and 18% of the children hospitalized with MIS-C had AKI. Most children with acute COVID-19 had stage I AKI, and most children with MIS-C had stage I or II AKI.

"The MIS-C patients were overall sicker and had increased inflammation," said lead author Abby Basalely, MD, MS, assistant professor of pediatrics at the Zucker School of Medicine at Hofstra/Northwell and attending pediatric nephrologist at the Cohen Children's Medical Center in New York.

A multi-center retrospective study at three tertiary care centers in Saudi Arabia found that 21% of children admitted for COVID-19 developed AKI, mostly stage I or II (4). About one-third of children with COVID-19 and AKI required intensive care compared with only about 3% of COVID-19 patients without AKI. About 40% of the pediatric patients with both COVID-19 and AKI died. Almost 10% of the children with COVID-19 and kidney injury had kidney impairment at discharge. The patients who developed AKI or kidney impairment at discharge were more likely to have other co-morbid conditions, such as lung or heart diseases, blood disorders, pre-existing kidney disease, diabetes, or cancer. Overall, the authors concluded that AKI was milder in children than adults hospitalized with COVID-19; none of the children required dialysis.

A third study looked at 57 pediatric patients admitted to New York-Presbyterian Morgan Stanley Children's Hospital for MIS-C between mid-April and late September 2020. Nearly half of the children had AKI. The hospital houses the largest pediatric intensive care unit in New York City.

"The majority of the children with AKI had mild AKI that was present on admission," said Uy, who is also a pediatric nephrologist at Morgan Stanley and the study's senior author. "We found that children with AKI and MIS-C have swift resolution of AKI."

Uy and her colleagues also found higher levels of inflammation in the children who developed AKI and that the children with AKI tended to be older and were more likely to have cardiac dysfunction.

The studies were not large enough to determine the exact cause of the MIS-C related AKI. But Basalely suspects that dehydration as a result of the vomiting and diarrhea many patients experienced likely contributed, and that inflammation also plays a role. Uy also cited a potential lack of blood flow to the kidneys, possibly exacerbating decreased cardiac function.

Both Uy and Basalely emphasized the importance of fluid resuscitation for these patients.

"If AKI is diagnosed by the clinician during the admission, try to mitigate it and not to add fuel to the fire," Basalely said. "Consider utilizing medications that are not nephrotoxic and make sure that you're carefully working with your clinical team and pharmacists to renally dose medication."

Long-term questions

The long-term prognosis for pediatric patients who develop AKI as a result of COVID-19 or MIS-C isn't yet clear. But the findings that few children in either study required dialysis and most had recovered at discharge were hopeful.

"We're seeing that hospitalized children have less evidence of kidney injury [than adults]," Basalely said. "That said, a little over 10% of our total population of children with acute COVID-19 and MIS-C had acute kidney injury, which should not go unnoticed because kidney injury in children can—even if it resolves—have implications for kidney health and kidney reserve later in life."

Basalely and her colleagues are following a few children with MIS-C who recovered from AKI but continued to have elevated blood pressure. She recommends physicians monitor blood pressure in pediatric patients who have recovered from MIS-C–related AKI at every visit and that patients or their parents know that having had MIS-C and AKI is an important part of their medical history they should share with all their physicians.

"Surveillance of borderline blood pressure should be a little higher in these patients," she said. ■

References

1. Silver SA, et al. The prevalence of acute kidney injury in patients hospitalized with COVID-19 infection: A systematic review and meta-analysis. *Kidney Med* 2021; 3:83–98.e1. doi: 10.1016/j.xkme.2020.11.008
2. Centers for Disease Control and Prevention. Health Alert Network. Multisystem Inflammatory Syndrome in Children (MIS-C) associated with Coronavirus Disease 2019 (COVID-19). May 14, 2020. https://emergency.cdc.gov/han/2020/han00432.asp
3. Basalely A, et al. Acute kidney injury in pediatric patients hospitalized with acute COVID-19 and Multisystem Inflammatory Syndrome in Children associated with COVID-19. *Kidney Int* [published online ahead of print March 3, 2021]. doi: 10.1016/j.kint.2021.02.026; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7927648/
4. Kari JA et al. Acute kidney injury in children with COVID-19: a retrospective study. *BMC Nephrol* 2021 May 31; 22202. DOI:10.1186/s12882-021-02389-9.
5. Lipton M, et al. Acute kidney injury in COVID-19-associated Multisystem Inflammatory Syndrome in Children (MIS-C). *Kidney360* [published online ahead of print February 3, 2021]. doi: 10.34067/KID.0005372020

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