ASN American Society of Nephrology

# Kidney News

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# "One Big Beautiful Bill Act" Brings Sweeping Reforms for Kidney Disease Care and Coverage

By Lauren Ahearn and Suzanne Watnick

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The "One Big Beautiful Bill Act" (HR 1), passed into law on July 4, 2025, represents a broad budget reconciliation package with significant changes across various policy areas including tax reform, extending 2017 tax cuts, and substantial cuts to health care, which impact Medicaid, the Children's Health Insurance Program, and Affordable Care Act (ACA) Marketplaces.

To offset the cost of extended tax cuts and implement new tax deductions, this legislation aimed to reduce government expenditures in other areas. The Congressional Budget Office estimates that over 11 million individuals would lose Medicaid coverage, cutting over $700 billion in Medicaid funding and altering ACA Marketplaces (1). These changes have raised considerable concerns among patient advocacy and health professional organizations, including ASN, which argue that HR 1 will severely impact access to affordable health insurance coverage and vital nutrition benefits for millions of Americans, particularly those with chronic conditions like kidney diseases.

## Cuts to Medicaid: A critical blow to vulnerable populations

Medicaid—a vital lifeline for millions—plays a particularly crucial role for individuals with and at risk for chronic kidney disease (CKD) and kidney failure, as well as those who have undergone kidney transplant. With approximately 37 million Americans affected by CKD and over 800,000 living with kidney failure, Medicaid provides essential coverage for the high-cost treatments, such as kidney transplant, which can exceed $400,000, not including $10,000–$14,000 annually for lifelong immunosuppressant medications. Roughly 30% of individuals with kidney failure rely on Medicaid for their care. HR 1 outlines several provisions that would significantly diminish Medicaid's reach and effectiveness, potentially leading to increased costs, reduced access to care, and life-threatening consequences for many of the nation's most vulnerable patients.

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# **Algorithms to Action:** AI Expands Application in Nephrology

By Karen Blum

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From smart thermostats to ChatGPT to online shopping recommendations based on your recent purchases, the use of artificial intelligence (AI) is becoming ubiquitous in today's society. When it comes to incorporation of AI in health care, nephrology has lagged behind other imaging-heavy specialties such as cardiology and radiology. But nephrologists are catching up, and there is a lot of excitement, experts say.

Nephrology is "very well-suited for AI," said Prabhat Singh, MD, FASN, a nephrologist and physician partner at Kidney Specialists of South Texas in Corpus Christi and coauthor of a recent review paper on AI in nephrology (1). "We, as nephrologists, love numbers. And numbers [are] something we can put into algorithms. It's a very data-driven field, especially dialysis."

Navdeep Tangri, MD, PhD, professor of medicine at the University of Manitoba in Canada, agreed. "There's a unique opportunity in nephrology because we have imaging data, like MRIs [magnetic resonance imaging] and ultrasounds of kidneys, we have kidney biopsies, we have histology and pathology, and we generate a ton of lab data," said Tangri, who also heads ASN's Partnership for Responsible AI in Kidney Health Steering Committee, which started in 2024. "We want nephrologists to lead the charge in development and implementation of AI in their health systems."

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# Inside

# Can your patients with lupus nephritis achieve renal remission (CRR) with BENLYSTA (belimumab)?

**In the BLISS-LN study, renal remission (CRR) was defined as[1,2]:**

- **eGFR ≥90 mL/min/1.73 m$^2$**
  **or eGFR no worse than 10% below the preflare value**
- **and**
  **uPCR <0.5 g/g**
- **and**
  **not a treatment failure***

**Renal remission is defined as complete renal response (CRR)** and was a secondary endpoint in the 104-week BLISS-LN study.[1]

**Primary endpoint:** Renal response defined as eGFR ≥60 mL /min/1.73 m$^2$ or eGFR no worse than 20% below preflare value, uPCR ≤0.7, and not a treatment failure at Week 104. Significantly more BENLYSTA patients (n=223) achieved renal response vs placebo (n=223); 43% vs 32%, respectively (*P*=0.031).

* Treatment failures were defined in the BLISS-LN study as patients who received prohibited therapy due to inadequate control of their lupus nephritis symptoms or renal flare management.[1]

AZA = azathioprine; BLISS-LN = Belimumab International SLE Study in Lupus Nephritis; CI = confidence interval; CYC = cyclophosphamide; eGFR = estimated glomerular filtration rate; IV = intravenous; LN = lupus nephritis; MMF = mycophenolate mofetil; OR = odds ratio; ST = standard therapy; uPCR = urine protein:creatinine ratio.

## INDICATION

BENLYSTA is indicated for patients aged ≥5 with active systemic lupus erythematosus (SLE) or active lupus nephritis who are receiving standard therapy. BENLYSTA is not recommended in patients with severe active central nervous system lupus.

## IMPORTANT SAFETY INFORMATION

### CONTRAINDICATION

Previous anaphylaxis with BENLYSTA.

### WARNINGS AND PRECAUTIONS

**Serious Infections:** Serious and sometimes fatal infections have been reported and occurred more frequently with BENLYSTA. Use caution in patients with severe or chronic infections, and consider interrupting therapy in patients with a new infection.

Progressive Multifocal Leukoencephalopathy (PML): Cases of JC virus-associated PML resulting in neurological deficits, including fatal cases, have been reported. If PML is suspected, immunosuppressant therapy, including BENLYSTA, must be suspended until PML is excluded. If confirmed, stop immunosuppressant therapy, including BENLYSTA.

**Hypersensitivity Reactions (Including Anaphylaxis):** Acute hypersensitivity reactions, including anaphylaxis and death, and infusion-related reactions have been reported. Generally, reactions occurred within hours of the infusion but may occur later, including in patients who have previously tolerated BENLYSTA. Non-acute hypersensitivity reactions (eg, rash, nausea, fatigue, myalgia, headache, and facial edema) typically occurred up to a week after infusion. Monitor patients during and after treatment and be prepared to manage anaphylaxis and infusion-related reactions. Be aware of the risk of hypersensitivity reactions, which may present as infusion-related reactions. Discontinue immediately in the event of a serious reaction. With intravenous administration, if an infusion reaction develops, slow or interrupt the infusion.

**Depression and Suicidality:** Depression and suicidality were reported in patients receiving BENLYSTA. Before adding BENLYSTA, assess patients' risk of depression and suicide and monitor them during treatment. Instruct patients/caregivers to contact their HCP if they experience new/worsening depression, suicidal thoughts/behavior, or other mood changes.

**Malignancy:** There is an increased risk of malignancies with the use of immunosuppressants. The impact of BENLYSTA on the development of malignancies is unknown.

**Immunization:** Live vaccines should not be given for 30 days before or concurrently with BENLYSTA as clinical safety has not been established.

In the BLISS-LN study, patients on ST + MMF or ST + CYC were

# 74% more likely

**to achieve complete renal response (renal remission)** at Week 104 with BENLYSTA[1,3]

(30% vs. 20% for placebo + ST, OR=1.74; 95% CI: 1.11, 2.74; *P*=0.0167)

**Study design:** BLISS-LN was a Phase III study of 448 adult patients with active lupus nephritis (confirmed biopsy-proven Class III, IV, V, or V in combination with III or IV) who were randomized to BENLYSTA 10 mg/kg + ST or placebo. Therapy was administered by IV infusion on Days 0, 14, and 28, and at 4-week intervals thereafter through Week 104. ST was defined as: MMF + high- dose steroids, followed by MMF + low-dose steroids or CYC + high-dose steroids, followed by AZA + low-dose steroids.[1]

**References: 1.** Furie R, *et al*. *N Engl J Med*. 2020;383(12):1117-1128. **2.** Furie R, *et al*. *N Engl J Med*. 2020;383(Suppl):1-15. **3.** Data on File, GSK.

**Learn more about the renal remission (CRR) data for lupus nephritis**

**Use With Biologic Therapies:** Available data do not support the safety and efficacy of concomitant use of BENLYSTA with rituximab in patients with SLE. An increased incidence of serious infections and post-injection systemic reactions in patients receiving BENLYSTA concomitantly with rituximab compared to patients receiving BENLYSTA alone has been observed. The safety and efficacy of BENLYSTA concomitantly with other biologic therapies, including B-cell-targeted therapies, have not been established. Caution should be exercised if BENLYSTA is administered in combination with other biologic therapies.

## ADVERSE REACTIONS

The most common serious adverse reactions in adult SLE clinical trials were serious infections; some were fatal. The most common adverse reactions (≥5%) were nausea, diarrhea, pyrexia, nasopharyngitis, bronchitis, insomnia, pain in extremity, depression, migraine, pharyngitis, and injection site reactions (subcutaneous injection).

Adverse reactions reported in clinical trials with SLE pediatric patients (≥5 years) and adult patients with lupus nephritis were consistent with those observed in adult SLE trials.

## USE IN SPECIFIC POPULATIONS

**Pregnancy:** There are insufficient data in pregnant women to establish whether there is drug-associated risk for major birth defects or miscarriage. After a risk/benefit assessment, if prevention is warranted, women of childbearing potential should use contraception during treatment and for ≥4 months after the final treatment.

Pregnancy Registry: HCPs are encouraged to refer patients and pregnant women are encouraged to enroll themselves by calling 1-877-311-8972 or visiting https://mothertobaby.org/ongoing-study/benlysta-belimumab/.

**Please see Brief Summary of full Prescribing Information for BENLYSTA on the following pages.**

To report SUSPECTED ADVERSE REACTIONS, contact GSK at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Benlysta (belimumab)
*Intravenous Use 120 mg/vial*
*Subcutaneous Use 200 mg/mL*

GSK


PMUS-BELJRNA240005 July 2024
Produced in USA.

# BRIEF SUMMARY

**BENLYSTA (belimumab) for injection, for intravenous use.**
**BENLYSTA (belimumab) injection, for subcutaneous use.**

*The following is a brief summary only; see full prescribing information for complete product information.*

## 1 INDICATIONS AND USAGE

BENLYSTA (belimumab) is indicated for the treatment of:

- patients aged 5 years and older with active systemic lupus erythematosus (SLE) who are receiving standard therapy, and
- patients aged 5 years and older with active lupus nephritis who are receiving standard therapy.

**Limitations of Use**

The efficacy of BENLYSTA has not been evaluated in patients with severe active central nervous system lupus. Use of BENLYSTA is not recommended in this situation.

## 4 CONTRAINDICATIONS

BENLYSTA is contraindicated in patients who have had anaphylaxis with belimumab.

## 5 WARNINGS AND PRECAUTIONS

**5.1 Serious Infections:** Serious and sometimes fatal infections have been reported in patients receiving immunosuppressive agents, including BENLYSTA. Overall, the incidence of serious infections in controlled trials was similar in patients receiving BENLYSTA compared with placebo, whereas fatal infections occurred more frequently in patients receiving BENLYSTA *[see Adverse Reactions (6.1)]*.

Consider the risk and benefit before initiating treatment with BENLYSTA in patients with severe or chronic infections. Consider interrupting therapy with BENLYSTA in patients who develop a new infection while receiving it and monitor these patients closely.

Progressive Multifocal Leukoencephalopathy (PML): Cases of JC virus-associated PML resulting in neurological deficits, including fatal cases, have been reported in patients with SLE receiving immunosuppressants, including BENLYSTA. Risk factors for PML include treatment with immunosuppressant therapies and impairment of immune function. Consider the diagnosis of PML in any patient presenting with new-onset or deteriorating neurological signs and symptoms and consult with a neurologist or other appropriate specialist as clinically indicated. In patients with suspected PML, immunosuppressant therapy, including BENLYSTA, must be suspended until PML has been excluded. If PML is confirmed, immunosuppressant therapy, including BENLYSTA, must be discontinued.

**5.2 Hypersensitivity Reactions, including Anaphylaxis:** Acute hypersensitivity reactions, including anaphylaxis and death, and infusion-related reactions have been reported in association with BENLYSTA *[see Adverse Reactions (6.1)]*. These events generally occurred within hours of the infusion; however, they may occur later. Non-acute hypersensitivity reactions including rash, nausea, fatigue, myalgia, headache, and facial edema, have been reported and typically occurred up to a week following the most recent infusion. Hypersensitivity, including serious reactions, has occurred in patients who have previously tolerated infusions of BENLYSTA. Limited data suggest that patients with a history of multiple drug allergies or significant hypersensitivity may be at increased risk.

Due to overlap in signs and symptoms, it was not possible to distinguish between hypersensitivity reactions and infusion-related reactions in all cases. In the controlled clinical trials of BENLYSTA administered intravenously in adults with SLE, some patients (13%) received premedication, which may have mitigated or masked a hypersensitivity response or infusion-related reaction; however, there is insufficient evidence to determine whether premedication diminishes the frequency or severity of hypersensitivity reactions or infusion-related reaction.

BENLYSTA for intravenous use should be administered by healthcare providers prepared to manage anaphylaxis and infusion-related reactions. Healthcare providers should be aware of the risk of hypersensitivity reactions, which may present as infusion-related reactions. In the event of a serious reaction, discontinue BENLYSTA immediately and administer appropriate medical therapy. With intravenous administration, the infusion rate may be slowed or interrupted if the patient develops an infusion reaction. Monitor patients during infusion and for an appropriate period of time after intravenous administration of BENLYSTA. Consider administering premedication as prophylaxis prior to intravenous dosing *[see Dosage and Administration (2.2) of full prescribing information]*.

Inform patients receiving BENLYSTA of the signs and symptoms of hypersensitivity reactions and instruct them to seek immediate medical care should a reaction occur.

**5.3 Depression and Suicidality:** In controlled clinical trials, depression and suicidality were reported in patients receiving BENLYSTA *[see Adverse Reactions (6.1)]*. Assess the risk of depression and suicide considering the patient's medical history and current psychiatric status before treatment with BENLYSTA and continue to monitor patients during treatment. Instruct patients receiving BENLYSTA (and caregivers, if applicable) to contact their healthcare provider if they experience new or worsening depression, suicidal thoughts or behavior, or other mood changes. Consider the risk and benefit of continued treatment with BENLYSTA for patients who develop such symptoms.

**5.4 Malignancy:** There is an increased risk of malignancies with the use of immunosuppressants. The impact of treatment with BENLYSTA on the development of malignancies is not known *[see Adverse Reactions (6.1)]*.

Consider the individual benefit-risk in patients with known risk factors for the development or reoccurrence of malignancy prior to prescribing BENLYSTA. In patients who develop malignancies, consider the risk and benefit of continued treatment with BENLYSTA.

**5.5 Immunization:** Because of its mechanism of action, BENLYSTA may interfere with the response to immunizations. Live vaccines should not be given for 30 days before or concurrently with BENLYSTA as clinical safety has not been established. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving BENLYSTA or the effect of BENLYSTA on new immunizations.

**5.6 Concomitant Use with Other Biologic Therapies:** Available data do not support the safety and efficacy of concomitant use of BENLYSTA with rituximab in patients with SLE. An increased incidence of serious infections and post-injection systemic reactions in patients receiving BENLYSTA concomitantly with rituximab compared to patients receiving BENLYSTA alone has been observed *[see Adverse Reactions (6.1)]*. The safety and efficacy of BENLYSTA concomitantly with other biologic therapies, including B-cell-targeted therapies, have not been established. Caution should be exercised if BENLYSTA is administered in combination with other biologic therapies *[see Warnings and Precautions (5)]*.

## 6 ADVERSE REACTIONS

The following serious adverse reactions are described below and in the Warnings and Precautions section:

- **Serious Infections** *[see Warnings and Precautions (5.1)]*
- **Hypersensitivity Reactions, including Anaphylaxis** *[see Warnings and Precautions (5.2)]*
- **Depression and Suicidality** *[see Warnings and Precautions (5.3)]*
- **Malignancy** *[see Warnings and Precautions (5.4)]*

### 6.1 Clinical Trials Experience with Intravenous Administration

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

*Adult Patients with SLE:* The data described in Table 1 reflect exposure to BENLYSTA administered intravenously plus standard therapy compared with placebo plus standard therapy in 2,133 adult patients with SLE in 3 controlled trials (Trials 1, 2, and 3). Patients received BENLYSTA plus standard therapy at doses of 1 mg/kg (n=673), 4 mg/kg (n=111; Trial 1 only), or 10 mg/kg (n=674), or placebo plus standard therapy (n=675) intravenously over a 1-hour period on Days 0, 14, 28, and then every 28 days. In 2 of the trials (Trial 1 and Trial 3), treatment was given for 48 weeks, while in the other trial (Trial 2) treatment was given for 72 weeks *[see Clinical Studies (14.1 in full prescribing information)]*. Because there was no apparent dose-related increase in the majority of adverse events observed with BENLYSTA, the safety data summarized below are presented for the 3 intravenous doses pooled, unless otherwise indicated; the adverse reaction table displays the results for the recommended intravenous dose of 10 mg/kg compared with placebo.

In these trials, 93% of patients treated with BENLYSTA plus standard therapy reported an adverse event compared with 92% treated with placebo plus standard therapy.

The most common serious adverse events were serious infections (6% and 5.2% in the groups receiving BENLYSTA and placebo plus standard therapy, respectively), some of which were fatal.

The most commonly reported adverse events, occurring in ≥5% of patients in clinical trials, were nausea, diarrhea, pyrexia, nasopharyngitis, bronchitis, insomnia, pain in extremity, depression, migraine, and pharyngitis.

The proportion of patients who discontinued treatment due to any adverse reaction during the controlled clinical trials was 6.2% for patients receiving BENLYSTA plus standard therapy and 7.1% for patients receiving placebo plus standard therapy. The most common adverse reactions resulting in discontinuation of treatment (≥1% of patients receiving BENLYSTA or placebo) were infusion reactions (1.6% BENLYSTA and 0.9% placebo), lupus nephritis (0.7% BENLYSTA and 1.2% placebo), and infections (0.7% BENLYSTA and 1% placebo).

Adverse reactions, regardless of causality, occurring in at least 3% of patients with SLE who received BENLYSTA 10 mg/kg plus standard therapy and at an incidence at least 1% greater than that observed with placebo plus standard therapy in 3 controlled trials (Trials 1, 2, and 3) were: nausea 15% and 12%; diarrhea 12% and 9%; pyrexia 10% and 8%; nasopharyngitis 9% and 7%; bronchitis 9% and 5%; insomnia 7% and 5%; pain in extremity 6% and 4%; depression 5% and 4%; migraine 5% and 4%; pharyngitis 5% and 3%; cystitis 4% and 3%; leukopenia 4% and 2%; viral gastroenteritis 3% and 1%.

*Infections*: In the controlled clinical trials of BENLYSTA administered intravenously in adults with SLE, the overall incidence of infections was 71% in patients receiving BENLYSTA compared with 67% in patients receiving placebo. The most frequent infections (>5% of patients receiving BENLYSTA) were upper respiratory tract infection, urinary tract infection, nasopharyngitis, sinusitis, bronchitis, and influenza. Infections leading to discontinuation of treatment occurred in 0.7% of patients receiving BENLYSTA and 1% of patients receiving placebo.

In a randomized, double-blind, placebo-controlled, 104-week trial of active lupus nephritis in adults receiving BENLYSTA administered intravenously (N=448), the overall incidence of infections was 82% in patients receiving BENLYSTA compared with 76% in patients receiving placebo.

*Serious Infections:* In controlled trials of BENLYSTA administered intravenously in adults with SLE, the incidence of serious infections was 6% in patients receiving BENLYSTA and 5.2% in patients receiving placebo. The most frequent serious infections included pneumonia, urinary tract infections, cellulitis, and bronchitis. Fatal infections occurred in 0.3% (4/1,458) of patients receiving BENLYSTA and in 0.1% (1/675) of patients receiving placebo.

In a randomized, double-blind, placebo-controlled, 52-week, postmarketing safety trial of BENLYSTA administered intravenously in adults with SLE (N=4,003), the incidence of serious infections was 3.7% in patients receiving BENLYSTA compared with 4.1% in patients receiving placebo. Serious infections leading to discontinuation of treatment occurred in 1% of patients receiving BENLYSTA and in 0.9% of patients receiving placebo. Fatal infections occurred in 0.45% (9/2,002) of patients receiving BENLYSTA and in 0.15% (3/2,001) of patients receiving placebo, where the incidence of all-cause mortality was 0.50% (10/2,002) in patients receiving BENLYSTA and 0.40% (8/2,001) in patients receiving placebo.

*Hypersensitivity Reactions, including Anaphylaxis*: In the controlled clinical trials of BENLYSTA administered intravenously in adults with SLE, hypersensitivity reactions (occurring on the same day of infusion) were reported in 13% (191/1,458) of patients receiving BENLYSTA and 11% (76/675) of patients receiving placebo. Anaphylaxis was observed in 0.6% (9/1,458) of patients receiving BENLYSTA and 0.4% (3/675) of patients receiving placebo. Manifestations included hypotension, angioedema, urticaria or other rash, pruritus, and dyspnea.

*Infusion-Related Reactions*: In the controlled clinical trials of BENLYSTA administered intravenously in adults with SLE, adverse events associated with the infusion (occurring on the same day of the infusion) were reported in 17% (251/1,458) of patients receiving BENLYSTA and 15% (99/675) of patients receiving placebo. Serious infusion reactions (excluding hypersensitivity reactions) were reported in 0.5% of patients receiving BENLYSTA and 0.4% of patients receiving placebo and included bradycardia, myalgia, headache, rash, urticaria, and hypotension. The most common infusion reactions (≥3% of patients receiving BENLYSTA) were headache, nausea, and skin reactions.

*Depression and Suicidality*: In controlled clinical trials of BENLYSTA administered intravenously in adults with SLE (N=2,133), psychiatric events were reported more frequently with BENLYSTA (16%) than with placebo (12%), primarily related to depression-related events (6.3% BENLYSTA; 4.7% placebo), insomnia (6% BENLYSTA; 5.3% placebo), and anxiety (3.9% BENLYSTA; 2.8% placebo). Serious psychiatric events were reported in 0.8% (12/1,458) of patients receiving BENLYSTA and 0.4% (3/675) of patients receiving placebo. Serious depression was reported in 0.4% (6/1,458) of patients receiving BENLYSTA and 0.1% (1/675) of patients receiving placebo. Two suicides (0.1%) were reported in patients receiving BENLYSTA (one with 10 mg/kg and one with 1 mg/kg).

In a randomized, double-blind, placebo-controlled, 52-week, postmarketing safety trial of BENLYSTA administered intravenously in adults with SLE (N=4,003), serious psychiatric events were reported in 1% (20/2,002) of patients receiving BENLYSTA and 0.3% (6/2,001) of patients receiving placebo. Serious depression was reported in 0.3% (7/2,002) of patients receiving BENLYSTA and in <0.1% (1/2,001) receiving placebo. The overall incidence of serious suicidal ideation or behavior or self-injury without suicidal intent was 0.7% (15/2,002) of patients receiving BENLYSTA and 0.2% (5/2,001) of patients receiving placebo. On the Columbia-Suicide Severity Rating Scale (C-SSRS), 2.4% (48/1,974) of patients receiving BENLYSTA reported suicidal ideation or behavior compared with 2% (39/1,988) of patients receiving placebo. No suicide was reported in either group.

The intravenous trials above did not exclude patients with a history of psychiatric disorders.

*Malignancy*: In the controlled clinical trials of BENLYSTA administered intravenously in adults with SLE, malignancies (including non-melanoma skin cancers) were reported in 0.4% of patients receiving BENLYSTA and 0.4% of patients receiving placebo. In the intravenous controlled clinical trials, malignancies, excluding non-melanoma skin cancers, were observed in 0.2% (3/1,458) and 0.3% (2/675) of patients receiving BENLYSTA and placebo, respectively.

*Black/African-American Patients*: The safety of BENLYSTA 10 mg/kg administered intravenously plus standard therapy (n=331) compared with placebo plus standard therapy (n=165) in Black patients with SLE (Trial 4) was consistent with the known safety profile of BENLYSTA administered intravenously plus standard therapy in the overall population *[see Clinical Studies (14.1) of full prescribing information]*.

*Adult Patients with Lupus Nephritis*: The safety of BENLYSTA 10 mg/kg administered intravenously plus standard therapy (n=224) compared with placebo plus standard therapy (n=224) was evaluated in adults with lupus nephritis for up to 104 weeks (Trial 5) *[see Clinical Studies (14.2) of full prescribing information]*. The adverse reactions observed were consistent with the known safety profile of BENLYSTA administered intravenously plus standard therapy in patients with SLE. Cases of myelosuppression, including febrile neutropenia, leukopenia, and pancytopenia, were observed in subjects who received induction therapy with cyclophosphamide followed by maintenance therapy with azathioprine, or mycophenolate.

*Pediatric Patients:* The safety of BENLYSTA administered intravenously plus standard therapy (n=53) compared with placebo plus standard therapy (n=40) was evaluated in 93 pediatric patients with SLE (Trial 6). The adverse reactions observed were consistent with those observed in adults with SLE *[see Clinical Studies (14.3) of full prescribing information]*.

Clinical Trials with Subcutaneous Administration in Adults: The data described below reflect exposure to BENLYSTA administered subcutaneously plus standard therapy compared with placebo plus standard therapy in 836 patients with SLE in a controlled trial (Trial 7). In addition to standard therapy, patients received BENLYSTA 200 mg (n=556) or placebo (n=280) (2:1 randomization) once weekly for up to 52 weeks *[see Clinical Studies (14.4) of full prescribing information]*.

In the trial, 81% of patients treated with BENLYSTA plus standard therapy reported an adverse event compared with 84% treated with placebo plus standard therapy. The proportion of patients who discontinued treatment due to any adverse reaction during the controlled clinical trial was 7.2% of patients receiving BENLYSTA plus standard therapy and 8.9% of patients receiving placebo plus standard therapy.

The safety profile observed for BENLYSTA administered subcutaneously plus standard therapy was consistent with the known safety profile of BENLYSTA administered intravenously plus standard therapy, with the exception of local injection site reactions.

*(continued on next page)*

Benlysta (belimumab)

*Infections*: In a controlled trial of BENLYSTA administered subcutaneously in adults with SLE (N=836), the overall incidence of infections was 55% in patients receiving BENLYSTA compared with 57% in patients receiving placebo. The most commonly reported infections with BENLYSTA administered subcutaneously were similar to those reported with BENLYSTA administered intravenously.

*Serious Infections*: In a controlled trial of BENLYSTA administered subcutaneously in adults with SLE (N=836), the incidence of serious infections was 4.1% in patients receiving BENLYSTA and 5.4% in patients receiving placebo. Fatal infections occurred in 0.5% (3/556) of patients receiving BENLYSTA and in none of the patients receiving placebo (0/280).

*Depression and Suicidality*: In a controlled trial of BENLYSTA administered subcutaneously in adults with SLE (N=836), which excluded patients with a history of psychiatric disorders, psychiatric events were reported in 6% of patients receiving BENLYSTA and 11% of patients receiving placebo. Depression-related events were reported in 2.7% (15/556) of patients receiving BENLYSTA and 3.6% (10/280) of patients receiving placebo. Serious psychiatric events were reported in 0.2% (1/556) of patients receiving BENLYSTA and in no patients receiving placebo. There were no serious depression-related events or suicides reported in either group. On the C-SSRS, 1.3% (7/554) of patients receiving BENLYSTA reported suicidal ideation or behavior compared with 0.7% (2/277) of patients receiving placebo.

*Malignancy*: In a controlled clinical trial of BENLYSTA administered subcutaneously in adults with SLE (N=836), the reports of malignancies were similar to those reported with BENLYSTA administered intravenously.

*Injection Site Reactions*: In a controlled clinical trial of BENLYSTA administered subcutaneously in adults with SLE (N=836), the frequency of injection site reactions was 6.1% (34/556) for patients receiving BENLYSTA plus standard therapy and 2.5% (7/280) for patients receiving placebo plus standard therapy. These injection site reactions (most commonly pain, erythema, hematoma, pruritus, and induration) were mild to moderate in severity. The majority (94%) did not necessitate discontinuation of treatment.

*Concomitant Use of Rituximab in Adults:* BENLYSTA administered subcutaneously in combination with rituximab was studied in a Phase III, randomized, double-blind, placebo-controlled, 104-week study in adult patients with SLE. Patients were randomized to 1 of the 3 treatment arms: BENLYSTA with a single cycle of rituximab (n=144); BENLYSTA with placebo (n=72); BENLYSTA plus standard therapy (n=76). In general, adverse reactions were consistent with the known safety profile of BENLYSTA and rituximab. When compared with BENLYSTA and placebo or BENLYSTA plus standard therapy, BENLYSTA in combination with rituximab was associated with higher frequency of serious adverse events (13.9%, 19.7%, 22.2%), serious infections (2.8%, 5.3%, 9%), and post-injection systemic reactions (9.7%, 5.3%, 13.2%).

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

• Fatal anaphylaxis *[see Warnings and Precautions (5.2)]*.

## 7 DRUG INTERACTIONS

Formal drug interaction studies have not been performed with BENLYSTA. In clinical trials BENLYSTA was administered concomitantly with other drugs, including corticosteroids, antimalarials, immunomodulatory and immunosuppressive agents (including azathioprine, cyclophosphamide, methotrexate, and mycophenolate), angiotensin pathway antihypertensives, HMG-CoA reductase inhibitors (statins), and/or non-steroidal anti-inflammatory drugs (NSAIDs) without evidence of a clinically meaningful effect of these concomitant medications on belimumab pharmacokinetics. The effect of belimumab on the pharmacokinetics of other drugs has not been evaluated *[see Clinical Pharmacology (12.3) of full prescribing information]*.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Pregnancy Exposure Registry: There is a pregnancy exposure registry that evaluates pregnancy outcomes in women with lupus exposed to BENLYSTA during pregnancy. Healthcare professionals are encouraged to refer patients and pregnant women are encouraged to enroll themselves by calling 1-877-311-8972 or visiting https://mothertobaby.org/ongoing-study/benlysta-belimumab/.

Risk Summary: Available data on use of BENLYSTA in pregnant women, from observational studies, published case reports, and postmarketing surveillance, are insufficient to determine whether there is a drug-associated risk for major birth defects or miscarriage. There are risks to the mother and fetus associated with SLE *(see Clinical Considerations)*. Monoclonal antibodies, such as belimumab, are actively transported across the placenta during the third trimester of pregnancy and may affect immune response in the in utero-exposed infant *(see Clinical Considerations)*. In an animal combined embryo-fetal and pre- and post-natal development study with monkeys that received belimumab by intravenous administration, there was no evidence of fetal harm with exposures approximately 9 times (based on intravenous administration) and 20 times (based on subcutaneous administration) the exposure at the maximum recommended human dose (MRHD). Belimumab-related findings in monkey fetuses and/or infants included reductions of B-cell counts, reductions in the density of lymphoid tissue B-lymphocytes in the spleen and lymph nodes, and altered IgG and IgM titers. The no-adverse-effect-level (NOAEL) was not identified for these findings; however, they were reversible within 3 to 12 months after the drug was discontinued *(see Data)*. Based on animal data and the mechanism of action of belimumab, the immune system in infants of treated mothers may be adversely affected. It is unknown, based on available data, whether immune effects, if identified, are reversible *[see Clinical Pharmacology (12.1) of full prescribing information]*.

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

Clinical Considerations

*Disease-Associated Maternal and/or Embryo/Fetal Risk:* Pregnant women with SLE are at increased risk of adverse pregnancy outcomes, including worsening of the underlying disease, premature birth, miscarriage, and intrauterine growth restriction. Maternal lupus nephritis increases the risk of hypertension and preeclampsia/eclampsia. Passage of maternal autoantibodies across the placenta may result in adverse neonatal outcomes, including neonatal lupus and congenital heart block.

*Fetal/Neonatal Adverse Reactions:* Monoclonal antibodies are increasingly transported across the placenta as pregnancy progresses, with the largest amount transferred during the third trimester. Risks and benefits should be considered prior to administering live or live-attenuated vaccines to infants exposed to BENLYSTA in utero. Monitor an infant of a treated mother for B-cell reduction and other immune dysfunction *[see Warnings and Precautions (5.5)]*.

Data *[see Data (in 8.1) of full prescribing information]*.

### 8.2 Lactation

Risk Summary: No information is available on the presence of belimumab in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for BENLYSTA, and any potential adverse effects on the breastfed child from BENLYSTA or from the underlying maternal condition. *[See Lactation (in 8.2) of full prescribing information]*.

### 8.3 Females and Males of Reproductive Potential

Contraception: Following an assessment of benefit versus risk, if prevention of pregnancy is warranted, females of reproductive potential should use effective contraception during treatment and for at least 4 months after the final treatment.

**8.4 Pediatric Use:** Safety and effectiveness of BENLYSTA have been established for the treatment of SLE and lupus nephritis in pediatric patients 5 to 17 years old.

Use of BENLYSTA in pediatric patients with SLE is supported by evidence from pharmacokinetic (PK) and efficacy results from a pediatric study (Trial 6), as well as PK exposure and extrapolation of the established efficacy of BENLYSTA plus standard therapy from the Phase 3 intravenous studies in adults with SLE. A randomized, double-blind, placebo-controlled, PK, efficacy, and safety study (Trial 6) to evaluate intravenously administered BENLYSTA 10 mg/kg plus standard therapy compared with placebo plus standard therapy over 52 weeks was conducted in 93 pediatric patients with SLE. The proportion of pediatric patients achieving an SRI-4 response was higher in patients receiving BENLYSTA plus standard therapy compared with placebo plus standard therapy. Pediatric patients receiving BENLYSTA plus standard therapy also had a lower risk of experiencing a

severe flare compared with placebo plus standard therapy *[see Clinical Studies (14.3)]*. Pharmacokinetics were evaluated in a total of 53 pediatric patients with SLE and were consistent with the adult population with SLE *[see Clinical Pharmacology (12.3)]*.

Use of BENLYSTA in pediatric patients with active lupus nephritis is based on the extrapolation of efficacy from the intravenous study in adults (n=224) with active lupus nephritis, and supported by pharmacokinetic data from intravenous studies in adults (n=224) with active lupus nephritis and from pediatric patients (n=53) with SLE. Estimated belimumab exposures for pediatric patients were comparable to adults with active lupus nephritis *[see Clinical Pharmacology (12.3)]*.

Use of BENLYSTA, administered subcutaneously in pediatric patients (5 to less than 18 years of age and weighing at least 15 kg) with SLE, is supported by evidence from an open-label pharmacokinetic trial (subcutaneous administration of BENLYSTA in pediatric patients with SLE) and Trial 6 (a pharmacokinetic, efficacy, and safety study of intravenous dosing in pediatric patients with SLE). The pharmacokinetics of belimumab, following subcutaneous administration in pediatric patients, are estimated to be similar to adults who receive BENLYSTA subcutaneously and pediatric patients who receive BENLYSTA intravenously *[see Clinical Pharmacology (12.3)]*.

The safety and effectiveness of the subcutaneous administration of BENLYSTA, in pediatric patients less than 18 years of age with active lupus nephritis, have not been established. The safety and effectiveness of BENLYSTA have not been established in pediatric patients less than 5 years of age.

**8.5 Geriatric Use:** Clinical studies of BENLYSTA did not include sufficient numbers of subjects aged 65 or older to determine whether they respond differently from younger subjects. Use with caution in geriatric patients.

**8.6 Renal Impairment:** No dosage adjustment is recommended in patients with renal impairment.

**8.7 Hepatic Impairment:** No dosage adjustment is recommended in patients with hepatic impairment.

**8.8 Racial Groups:** In Trial 2 and Trial 3 (intravenous dosing), SLE SRI-4 response rates were lower for Black patients receiving BENLYSTA plus standard therapy relative to Black patients receiving placebo plus standard therapy *[see Clinical Studies (14.1) of full prescribing information]*.

In Trial 4 (intravenous dosing), a 2:1 randomized, placebo-controlled trial in Black patients, SLE Responder Index (SRI-S2K) response rates were higher for Black patients receiving BENLYSTA plus standard therapy (49%) relative to Black patients receiving placebo plus standard therapy (42%). However, the treatment difference was not statistically significant *[see Clinical Studies (14.1) of full prescribing information]*.

In Trial 7 (subcutaneous dosing), SRI-4 response was 45% (26/58) in Black patients receiving BENLYSTA plus standard therapy compared with 39% (13/33) in Black patients receiving placebo plus standard therapy *[see Clinical Studies (14.4) of full prescribing information]*.

The safety profile of BENLYSTA in Black patients was consistent with the known safety profile of BENLYSTA administered in the overall population *[see Adverse Reactions (6.1)]*.

## 10 OVERDOSAGE

There is limited experience with overdosage of belimumab.

## 12 CLINICAL PHARMACOLOGY

### 12.6 Immunogenicity

In Trials 2 and 3 (intravenous dosing in adults with SLE), anti-belimumab antibodies were assessed during the respective 52-week and 76-week, placebo-controlled periods and detected in 4 of 563 (0.7%) patients receiving BENLYSTA 10 mg/kg and in 27 of 559 (4.8%) patients receiving BENLYSTA 1 mg/kg. The reported frequency for the group receiving 10 mg/kg may underestimate the actual frequency due to lower assay sensitivity in the presence of high drug concentrations. Neutralizing antibodies were detected in 3 patients receiving BENLYSTA 1 mg/kg. Three patients with anti-belimumab antibodies experienced mild infusion reactions of nausea, erythematous rash, pruritus, eyelid edema, headache, and dyspnea; none of the reactions were life-threatening. In Trial 4 (intravenous dosing in adult Black patients), anti-belimumab antibodies were detected in 2 of 321 (0.6%) patients receiving BENLYSTA 10 mg/kg during the 52-week, placebo-controlled period. In Trial 5 (intravenous dosing in adults with lupus nephritis), there was no formation of anti-belimumab antibodies in 224 patients receiving BENLYSTA 10 mg/kg plus standard therapy during the 104-week, placebo-controlled period. In Trial 6 (intravenous dosing in pediatric patients with SLE), there was no formation of anti-belimumab antibodies in 53 patients receiving BENLYSTA 10 mg/kg plus standard therapy during the 52-week, placebo-controlled period. In Trial 7 (subcutaneous dosing in adults with SLE), there was no formation of anti-belimumab antibodies in 556 patients receiving BENLYSTA 200 mg during the 52-week, placebo-controlled period.

The clinical relevance of the presence of anti-belimumab antibodies is not known.

## 13 NONCLINICAL TOXICOLOGY

**13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility:** Long-term animal studies have not been performed to evaluate the carcinogenic potential of belimumab. Effects on male and female fertility have not been directly evaluated in animal studies.

## 17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use) of full prescribing information.

Serious Infections: Inform patients that BENLYSTA may decrease their ability to fight infections, and that serious infections, including some fatal ones, occurred in patients receiving BENLYSTA in clinical trials. Instruct patients to tell their healthcare provider if they develop signs or symptoms of an infection *[see Warnings and Precautions (5.1)]*.

Progressive Multifocal Leukoencephalopathy: Advise patients to contact their healthcare professional if they experience new or worsening neurological symptoms such as memory loss, confusion, dizziness or loss of balance, difficulty talking or walking, or vision problems *[see Warnings and Precautions (5.1)]*.

Hypersensitivity Reactions/Anaphylaxis: Educate patients on the signs and symptoms of hypersensitivity reactions and infusion-related reactions. Instruct patients to immediately tell their healthcare provider if they experience symptoms of an allergic reaction during or after the administration of BENLYSTA. Inform patients about possible delayed reactions that may include a combination of symptoms such as rash, nausea, fatigue, muscle aches, headache, and/or facial swelling that may occur after administration of BENLYSTA and advise them to contact their healthcare provider *[see Warnings and Precautions (5.2)]*.

Depression and Suicidality: Instruct patients/caregivers to contact their healthcare provider if they experience new or worsening depression, suicidal thoughts, or other mood changes *[see Warnings and Precautions (5.3)]*.

Immunizations: Inform patients that they should not receive live vaccines while taking BENLYSTA. Response to vaccinations could be impaired by BENLYSTA *[see Warnings and Precautions (5.5)]*.

Pregnancy Registry: Inform patients that there is a pregnancy registry to evaluate fetal outcomes of pregnant women with lupus exposed to BENLYSTA *[see Use in Specific Populations (8.1)]*.

Pregnancy: Inform female patients of reproductive potential that BENLYSTA may impact the immune system in infants of treated mothers and to inform their prescriber of a known or suspected pregnancy *[see Use in Specific Populations (8.1)]*.



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# "One Big Beautiful Bill Act" Brings Sweeping Reforms for Kidney Disease Care and Coverage

*Continued from cover*

**A key concern is the addition of cost-sharing for Medicaid beneficiaries.** HR 1 would allow for cost-sharing of up to $35 per service for individuals above the federal poverty line, with an overall cap of 5% of their income. While primary care and mental health services are exempt from this specific charge, this provision could create substantial financial burdens for patients undergoing dialysis, who often require treatments three times a week for hemodialysis and daily therapy for peritoneal dialysis. The kidney community is still assessing how this may apply to the dialysis environment. For people with CKD who are not on dialysis, including those with a kidney allograft, this can represent a substantial barrier to care. For individuals managing a chronic illness that necessitates frequent medical interventions, copayments can accumulate rapidly and potentially deter people from seeking necessary care. This cumulative cost, coupled with other medical needs, could become prohibitive for many patients with limited income and could jeopardize their adherence to life-sustaining therapies.

**Another controversial aspect of HR 1 is the mandate for work or "community engagement"** for adult Medicaid expansion populations. Although the intent might be to encourage self-sufficiency, early experiences with such mandates in other contexts have shown enrollment declines without generating meaningful cost savings. For individuals with chronic illnesses, particularly those with the debilitating effects of kidney diseases or those undergoing dialysis, meeting stringent work requirements may be physically impossible or severely challenging. This provision risks stripping essential health coverage from those who are already struggling with significant health issues, pushing them further into medical and financial insecurity.

**HR 1 also includes a reduction in federal matching funds from 90% to 80% for states that cover undocumented individuals.** This reduction in federal support will force states to either absorb the increased costs themselves, leading to potential budget shortfalls, or reduce the total amount of services that they can provide. This directly raises concerns about access to crucial services like dialysis for those who are often already in vulnerable positions and rely on such programs for life-saving care.

**HR 1 requires twice-annual recertification of Medicaid eligibility**, increasing the burden on states to verify eligible beneficiaries from once to twice a year. While seemingly an administrative adjustment, this change could divert significant resources from direct patient care services to administrative tasks. States would need to invest more in personnel and systems for eligibility verification, potentially at the expense of funding for actual medical treatments, preventive care, or outreach programs. This added administrative complexity could also lead to eligible individuals losing coverage due to paperwork hurdles or delays in the recertification process, even if they remain eligible.

**The provision that disallows new provider taxes and gradually lowers existing ones** is another issue posing a financial burden. Provider taxes are a mechanism that some states use to generate revenue that can then be used to draw down federal Medicaid matching funds. By restricting and phasing out these taxes, the bill will reduce the amount of federal dollars on which states can rely. This means that some states will be compelled to make difficult choices, such as reducing essential services, cutting administrative costs, or increasing state taxes to maintain their Medicaid programs. This could disproportionately affect states with already strained budgets or those with a high proportion of Medicaid beneficiaries, ultimately impacting the availability and quality of health care services.

**Amidst these proposed cuts, HR 1 does include a provision to establish a "Rural Health Transformation Program" with a $50 billion fund**, allocating $10 billion per year for 5 years. The Rural Health Transformation Program fund will not make direct payments to rural hospitals, as past congressionally directed relief funds have done. Instead, the new law will fund states, and states will need the approval of Mehmet Oz, MD, administrator of the Centers for Medicare & Medicaid Services (CMS), for how they can spend the funds. By law, states are permitted to use portions of this fund to recruit and retain health professionals, upgrade information technology, and implement innovative payment models. However, there is no specific requirement for states to direct funds to rural hospitals or for CMS to approve expenditures for rural hospitals. The administrator also has discretion to approve use of funds for nonrural activities.

This program was reportedly created to mitigate some of the concerns about the negative impact of Medicaid cuts on rural health care infrastructure. Although it may be a positive step, it remains to be seen if this allocation will be sufficient to offset the widespread detrimental effects of the Medicaid cuts, particularly in rural communities where hospitals are already closing at an alarming rate. Furthermore, regardless of what is funded, the rural program's allotments end in 5 years, whereas Medicaid cuts are permanent. ASN and the American Kidney Fund highlighted in a joint letter (2) that 190 rural hospitals in 34 Medicaid expansion states are already at immediate risk of closure, and the Medicaid cuts in HR 1 could exacerbate this crisis.

## Other key provisions with far-reaching implications

Beyond the significant Medicaid changes, HR 1 also includes several other provisions that have raised alarms among health care advocates, particularly concerning their potential impact on health care access, the future health care workforce, and vulnerable populations.

**This includes new caps on federal student loans**, specifically Stafford loans, with limits that are set at a maximum of $100,000 for graduate students and $200,000 for professional students, with a lifetime maximum of $257,000. Additionally, HR 1 ends Grad PLUS loans. These limits could significantly curtail the ability of aspiring health care professionals, particularly those from lower socioeconomic backgrounds, to pursue careers in fields like nephrology, which already faces workforce shortages. The substantial cost of medical education often necessitates borrowing large sums of money, and these new limits could deter talented individuals from entering essential medical specialties, ultimately impacting the availability of specialists to care for patients with complex conditions.

**HR 1 also outlines changes to ACA Marketplace enrollment processes**, mandating manual re-enrollment and creating additional paperwork. This increased administrative burden will make it more cumbersome for marketplace enrollees to maintain their coverage. For individuals with chronic conditions who rely on continuous coverage for managing their health, these changes could lead to lapses in insurance, interruptions in treatment, and potentially adverse health outcomes. Access to the ACA Marketplace coverage is crucial for millions of Americans, especially those eligible for premium tax credits, as it allows them to access preventive care and manage chronic conditions, thereby reducing the risk of developing or progressing kidney disease.

**Furthermore, HR 1 includes reductions in Supplemental Nutrition Assistance Program (SNAP) benefits.** The One Big Beautiful Bill Act reduces funding for SNAP by $300 billion, representing the largest cut in the program's 50-year history. This cut would affect over 40 million people, including children, seniors, and adults with disabilities. SNAP is vital for helping millions of Americans, including individuals on dialysis with limited income, to feed themselves and their families. Food insecurity is a significant challenge for people on dialysis; a recent survey by the American Kidney Fund reveals that 61% of people undergoing dialysis with limited income reported food insecurity. The Congressional Budget Office estimates that these cuts could result in 1.3 million people losing or having their SNAP benefits reduced each month. Such reductions could have severe consequences for the nutritional well-being of vulnerable populations, directly impacting their health and ability to manage chronic diseases.

**Finally, the legislation fails to adequately address physician payment under the Medicare Physician Fee Schedule.** Although HR 1 does include a temporary, 1-year, 2.5% payment increase for physicians and other professionals paid under the Medicare Physician Fee Schedule, this is seen as a "patch" rather than a permanent solution. Organizations like the American Medical Association and ASN have advocated for a more permanent resolution to the long-standing issue of inadequate physician payment. This perpetuates concerns about the financial viability of medical practices, particularly those serving Medicare patients, and could jeopardize patient access to care in the long run. Ensuring a sufficient and stable health care workforce, especially in specialties like nephrology, is critical for addressing the growing needs of Americans with kidney diseases.

In conclusion, the One Big Beautiful Bill Act covers a wide range of policy areas with significant impacts on the landscape of health care and social safety nets in the United States. Although some provisions, like the Rural Health Transformation Program, offer potential positive impact, the overwhelming concerns revolve around the substantial cuts to Medicaid, the increased burdens on beneficiaries, and the potential for a diminished health care workforce. ASN, along with patient advocacy groups and health professional organizations, opposes these cuts and changes, arguing that they would have devastating consequences for vulnerable populations, especially those living with chronic diseases and disabilities. The collective impact of these provisions could lead to a substantial increase in the uninsured population, exacerbation of health disparities, and a weakening of the health care system's ability to provide essential care to those who need it most. ■

To keep track of ASN's policy efforts, follow coverage in *Kidney News* and the ASN podcast feed, and visit ASN's Kidney Health Advocacy webpage (https://www.asn-online.org/policy/kidney-health.aspx). For real-time updates from ASN Policy, follow @ASNAdvocacy on X.

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# Algorithms to Action

*Continued from cover*

AI is rapidly transforming the delivery of kidney care through predictive analytics, machine learning, deep learning, and generative AI technologies, Tangri said.

In nephrology, much AI-related work has been in dialysis, said Len Usvyat, PhD, senior vice president and head of the Renal Research Institute, a wholly owned subsidiary and innovation hub from Fresenius Medical Care. In Fresenius Medical Care-affiliated entities, there are over three dozen algorithms in play, depending on the region, to help predict, for example, which patients are likeliest to be hospitalized for fluid- or infectious-related reasons. The models run on a nightly basis through the company's data systems, processing thousands of variables. Then, a clinical team reviews the predictions on a daily basis to determine what interventions may be necessary for those patients with a higher risk of an impending hospitalization and why the models think so, so that the physician can intervene. AI, in this setting, is just one tool, along with mathematical modeling, computational medicine, and technology, which together are expanding clinicians' ability to manage complex patients, Usvyat explained.

The following descriptions are other examples of ways that AI is being tested or incorporated into nephrology practices:

- **Patient summaries and messages.** Ambient AI scribes "listening" in the background during doctor–patient encounters generate summaries that are reviewed by doctors and are inputted in patients' electronic health records (EHRs), cutting down on physician "pajama time" documentation after hours. Some centers are using AI programs to generate responses to patient messages or queries sent through online portals, which can be reviewed by medical staff before sending.
- **Pathology.** Digital pathology has been increasingly used as a clinical tool for imaging and processing pathology slides. AI techniques can then be used to enhance analysis of pathology slides for diagnosis, prediction of prognosis, treatment, and other clinical purposes (2).
- **Dialysis.** Dialysis generates a lot of patient-related data, which are attractive from an AI and machine-learning standpoint, Singh said. Natural language processing software can extract relevant information that can be used to train algorithms to improve dialysis performance or predict complications. Some studies have demonstrated models that identify common hemodialysis-related symptoms (3), predict risk for intradialytic hypotension (4) or risk of hospitalization and mortality (5, 6), or optimize management of anemia by recommending doses of erythropoietin-stimulating agents (7). Beyond numeric data, AI also can be used to analyze ultrasounds or other images to identify vascular access complications such as aneurysms or to monitor audio signals generated by dialysis machines (8, 9), Tangri said.
- **Acute kidney injury (AKI).** The heterogeneous nature of the pathophysiology leading to AKI poses a significant challenge in developing algorithms or statistical models to detect early AKI, Singh said. Some studies have looked at machine learning or unsupervised learning (analyzing data to discover hidden patterns) to predict AKI in patients who have undergone heart surgery (10). Another study used AI to risk-stratify patients with immunoglobin A nephropathy who are at higher risk of progression to AKI (11) or to help refine current systems to help identify AKI and patients at high risk of progressing. Integrating AI into EHRs can help with real-time monitoring and risk stratification for people with AKI, recommending evidence-based interventions like fluid adjustments or medications (12), Tangri explained.
- **Chronic kidney disease (CKD).** AI or machine learning-driven algorithms integrated with EHRs may help in earlier recognition of CKD, especially in primary care settings, which can trigger referrals to nephrologists and improve patient outcomes, said Singh. Some published studies have highlighted an AI model that can predict progression of diabetic kidney disease (13) or machine learning that may predict complications from diabetes (14). Another study has identified individuals with a higher risk of Fabry disease (15). Commercial AI models such as PulseData use laboratory data, genetic tests, patient symptoms, and biomarkers to help predict CKD progression with good accuracy (16). The KidneyIntelX test platform, integrated into the EHRs at the Mount Sinai Health System in New York City, incorporates plasma biomarkers, 27 laboratory values, 20 diagnostic codes, 30 medications, and vital signs to help detect CKD progression (17). AI also is making its way into screening for CKD, through retina imaging (18) and home testing kits (19), Tangri noted.
- **Kidney transplant.** AI has been applied in nearly all aspects of kidney transplantation, from organ allocation to immunosuppression to pathology, Singh said. One recent study used a prediction system to forecast the long-term risk of allograft failure, showing the tool performed better than nephrologists (20). AI algorithms could be used to improve donor-recipient matching. One tool helped assist transplant physicians in deciding whether to accept or reject marginal kidney offers and to predict waitlist and post-transplant survival (21). In organ allocation, an AI framework called continuous distribution, which uses a point system to prioritize patients on the lung transplant waitlist, has been incorporated by the Organ Procurement and Transplantation Network (22). That tool could be applied to kidneys or other organs, Singh said.
- **Education.** Language models such as chatbots have been piloted to provide health information for patients on dialysis, Tangri said, and could be used to generate multilingual content for diverse patient populations. AI also could be used in fellowship training to "help integrate diverse educational content, [offer] clinical scenarios and real-time data to enhance training precision, and support personalized learning strategies," he noted (23). Instead of hiring local actors as standardized patients, virtual AI standardized patients can allow clinicians to interact and ask questions (24), said Lili Chan, MD, MS, an associate professor of nephrology at the Icahn School of Medicine at Mount Sinai, in New York City. Furthermore, physicians can use an online platform called OpenEvidence, which pulls information from peer-reviewed journals, to ask clinical questions, explained Wisit Cheungpasitporn, MD, FASN, a nephrologist with the Mayo Clinic in Rochester, MN.
- **Social determinants of health.** AI potentially could be used to extract information from patient clinical notes to identify individuals needing transportation or housing resources. Chan conducts an ongoing study in this area, developing a rule-based system to look for terms like "shelter" or "mold in the home" and extracting data from surveys and physician interviews that are already being conducted. People may not be able to identify small nuances or changes in patterns as easily as an AI program, she said.
- **Clinical trials.** AI can be used to create digital twins to simulate a clinical trial, especially for rare diseases, Cheungpasitporn said. "This approach can help refine patient selection, personalize trial design, and predict safety and efficacy outcomes in silico before exposing participants to risk, thereby potentially improving trial efficiency and reducing costs," he explained.

## Hurdles remain, collaboration needed

It is not AI alone that could improve clinical care; it is how clinicians respond to and act on the information it provides, Usvyat said. Tangri advised that nephrologists should move forward with two overarching principles: 1) the goal of benefiting patients and 2) always keeping a physician in the loop—having ultimate authority over the machine.

To that end, it appears that these algorithms do make a difference, said Tangri: "What we see is that when you flag somebody as high risk, and you show a set of recommendations to the physician, they change their practice." But AI is still learning and could, for example, interpret small increases in creatinine as AKI that actually result from dehydration or other causes, Singh cautioned.

There are still a number of hurdles—including physician skepticism—to overcome before the tools are adopted more widely, Singh said. "As physicians, we are risk-averse. We are on the conservative side. The first thing we are taught is, 'Do no harm,' so when you really don't understand something, you try to be on the conservative side," he added. Some health care professionals are worried about privacy, wondering where data input into these systems is going. Others are concerned over safety "because the way these algorithms are made and developed…you really don't know how they are reasoning," Singh advised.

One criticism of large language models like ChatGPT is that they can pull information from anywhere online, and sometimes "hallucinate," offering fabricated references or data. Usvyat said that at the Renal Research Institute, he and his colleagues use a process that narrows the data field from which the program can pull information, limiting it to curated sources.

While research on AI is expanding, not a lot of that research moves into implementation, Chan said, in part, because it is hard to gain access to sufficient patient data to externally validate models: "I'm really excited to see how different groups can work together to get their research models into clinical practice. As we develop shared data models, and people are more aware of AI and quantum health ecosystems, there's going to be more of an investment in sharing or federated learning (training on decentralized data from multiple entities) or different ways for people to work together."

Going forward, clinicians are trying to incorporate various types of data—genetics, omics, and imaging, both structured and unstructured—into multimodal AI models that can advance personalized medicine, Cheungpasitporn said.

With the "overwhelming learning curve" for patients new to dialysis, Tangri said, "I look forward to the ability to create more personalized teaching materials and handouts on the fly for my patients. I think that's an underexplored area in patient education." For example, patients could be given such resources and then be able to interact with an AI agent or chatbot for more information.

The nephrology community needs to invest in training a competent workforce to drive the next generation of AI innovation and practice, Singh urged. He frequently observes medical residents entering patient symptoms into ChatGPT to generate potential differential diagnoses. Although the generated responses are often accurate, "this is where a human in the loop comes in," he said. "We have to tell trainees, 'You should know which decision to take and which not to take.'"

There are many opportunities for the community to learn more about AI in nephrology. A position paper on the responsible use of AI to improve kidney care is being developed by the ASN AI workgroup, and Kidney Week 2025 in Houston, TX, will feature a plenary session and Advances in Research Conference early program focused on AI. Interested members can also connect in ASN Communities (https://community.asn-online.org). ■

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# Rethinking Statins in Dialysis: Evidence of Absence or Clinical Equipoise?

By Mohammad Shahzeb Khan and Tariq Shafi

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Ask a nephrologist about statins in people with kidney failure requiring kidney replacement therapy by dialysis (KRT-D), and the usual response is: "Not recommended unless already on it." Now, consider this not uncommon scenario: A 60-year-old with type 2 diabetes, on KRT-D for 1 year and on the transplant waitlist, is admitted to a hospital with a myocardial infarction (MI) and undergoes percutaneous coronary intervention (PCI) with stents. The post-MI ejection fraction is 30%, and the patient is removed from the waitlist. Guideline-recommended care for chronic kidney disease (CKD) not on dialysis includes statins, but it was not prescribed. Could initiating a statin after dialysis have prevented the MI (primary prevention)? Should a statin be started now to prevent further events (secondary prevention)?

Clinical guidelines aim to guide care, but not all statements carry the same weight. The 2013 Kidney Disease: Improving Global Outcomes (KDIGO) lipid guideline states: "In adults with dialysis-dependent CKD, we suggest that statins or statin/ezetimibe combination not be initiated. (2A)" (1). This statement has been widely interpreted in practice to mean "not recommended unless already on it." However, this is a level 2 "suggestion" indicating an area of uncertainty and thus not a level 1 "recommendation." The interpretation of this statement is: Based on available data from rigorous clinical trials (grade A), we suggest (level 2) that initiating statins in KRT-D may not be beneficial, but we also do not see any harm. This is a suggestion and not a recommendation; patient-level factors and clinical judgment must drive individualized decisions. Would management have differed if this nuance had been appreciated? Could the MI and removal from the waitlist have been avoided?

The debate around statin use in KRT-D has persisted since the 2013 KDIGO guideline. The language, despite being graded as a weak suggestion, has hardened into dogma and has been codified into clinical habit. To our knowledge, no new randomized clinical trials (RCTs) have emerged to challenge this paradigm. However, a recent study by Yeh et al. reignited the conversation (2). Using Taiwan's National Health Insurance data, the authors examined 7618 people with KRT-D who had an MI and PCI. Two-thirds were not on statins (defined as >90 days of use), but statin therapy was associated with a 23% lower risk of all-cause mortality (hazard ratio, 0.77; 95% confidence interval, 0.71–0.84). While the observational design did not account for selection bias and residual confounding, the study highlights a real-world consequence: Patients who would meet the criteria for level 1A statin use in the general population are not being treated solely because they are on dialysis (3). A cardiology commentary on the study reaffirms the underlying misguided dogma considering all people with KRT-D as a homogenous group, despite wide variability in comorbidity burden, treatment goals, and prognosis (4).

RCTs inform guidelines, but their results are generally applicable to the populations they enrolled. The three major trials that informed the KDIGO KRT-D lipid guideline did not focus on the incident KRT-D population, and all trials excluded patients with recent atherosclerotic cardiovascular disease (ASCVD) events. SHARP (NCT00125593) was a trial of primary prevention, with a signal toward benefit in KRT-D (5). The 4D (6) and AURORA (NCT00240331) (7) trials had a mix of patients with and without prevalent ASCVD. For the patient described at the start of this article, SHARP suggests potential benefit, but 4D and AURORA results are not applicable.

Absence of evidence is not evidence of absence (Figure). The limitations of these trials, combined with statins' favorable safety profile and strong evidence in the general population, demonstrate that the 2A suggestion from KDIGO should not be treated as a prohibition. Until definitive evidence exists, we must individualize ASCVD prevention in KRT-D, and perhaps, with the safety profile of statins, erring on the side of treatment is appropriate. The equipoise in this area, along with the dire need for robust clinical trial evidence, remains quite evident. ■

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The authors report no conflicts of interest.

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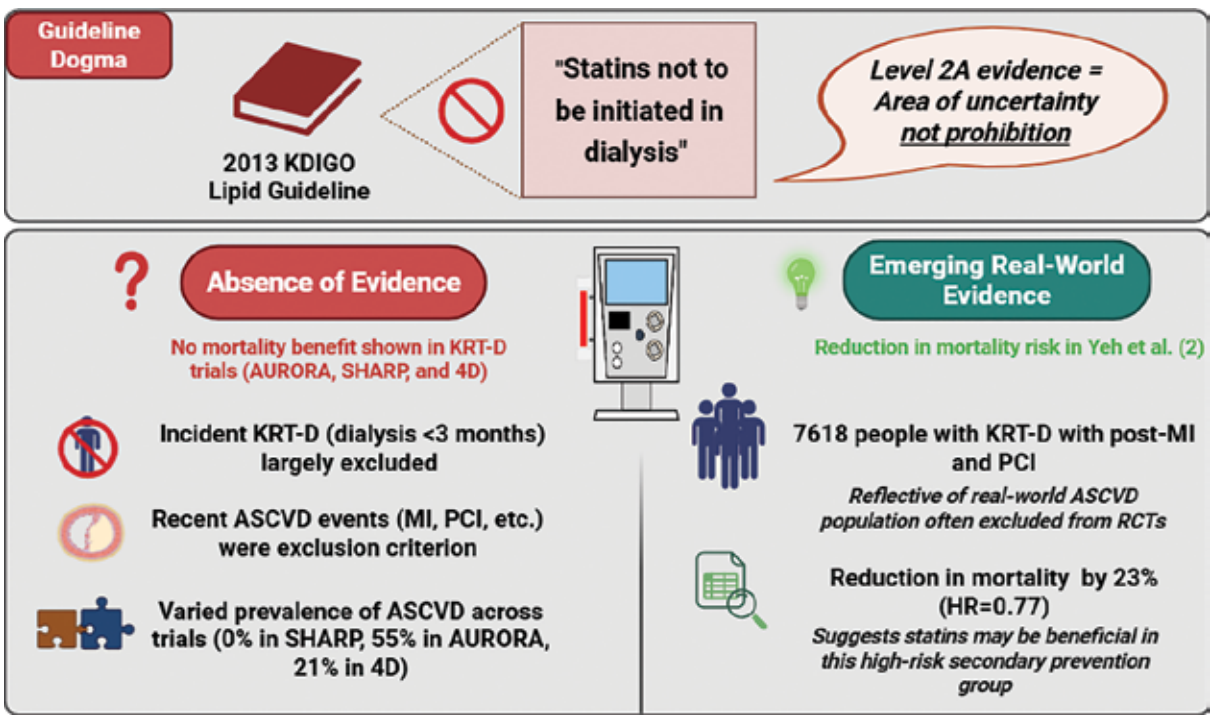
**Figure. Why statin trials in dialysis may not inform care for all**




4D, Die Deutsche Diabetes Dialyse Studie (German Diabetes and Dialysis Study); AURORA, A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Haemodialysis: An Assessment of Survival and Cardiovascular Events; HR, hazard ratio; SHARP, Study of Heart and Renal Protection.

# GLP-1 Receptor Agonists in Dialysis: The Obesity Paradox in the Incretin Era

By Evan Zeitler

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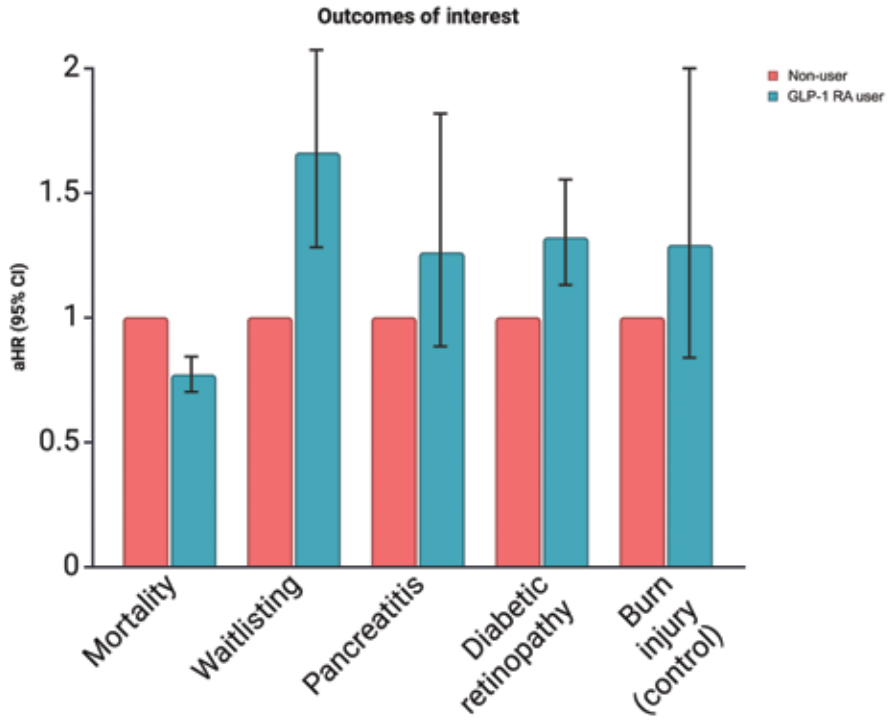
Over 60% of individuals treated with maintenance dialysis have diabetes, and over 40% have obesity, contributing to increased morbidity and mortality. New therapies, primarily incretin mimetics (e.g., semaglutide), have revolutionized the management of obesity and diabetes in the general population and in people with nondialysis chronic kidney disease, as evidenced by both the SELECT (NCT03574597) (1) and FLOW (NCT03819153) (2) studies. As is often the case, though, people on dialysis have been left behind, as nephrologists have traditionally been wary of weight loss among them due to the "obesity paradox" (i.e., a greater mortality rate among people on dialysis with lower body mass index).

However, in a recent national cohort study in *CJASN*, Orandi and colleagues provide compelling real-world evidence that glucagon-like peptide-1 receptor agonists (GLP-1 RAs) may offer substantial clinical benefit for individuals on dialysis (3). Analyzing US Renal Data System data from over 151,000 people with type 2 diabetes between 2013 and 2021, the authors demonstrate that GLP-1 RA use was associated with a 23% reduction in all-cause mortality and a 66% increased likelihood of kidney transplant waitlisting (Figure). Strikingly, GLP-1 RA was associated with an increased likelihood of transplant waitlisting (adjusted hazard ratio [aHR], 1.66), an association that was most pronounced in those with obesity (aHR, 2.05). These benefits were observed despite relatively modest weight loss and were robust across multiple sensitivity analyses, including models adjusting for confounding and immortal time bias.

**Figure. Adjusted hazard ratios for selected outcomes of interest, with nontreated patients as the reference group**




Use of a GLP-1 RA was associated with decreased mortality and increased likelihood of transplant waitlisting, while also correlating with an increased risk of diabetic retinopathy. CI, confidence interval.

Data adapted from Orandi et al. (3). Figure created with BioRender.

The study did not uncover new safety signals. No increased risk was found for acute pancreatitis, biliary complications, or medullary thyroid cancer, although the follow-up time was limited. There was a 32% increased risk of diabetic retinopathy in people with diabetes on dialysis, consistent with other studies of intensive glucose-lowering in people with diabetes (4). Burn injuries (a negative control outcome) were not significantly different between groups.

Limitations of the work include the low uptake of GLP-1 RAs in the cohort (only ~3% initiated therapy). Importantly though, most treated patients were prescribed dulaglutide, as compared with newer agents like semaglutide or tirzepatide, which have demonstrated superior efficacy for both weight loss and cardiovascular disease risk reduction, suggesting that this work may underestimate the benefit of current GLP-1 RA regimens. In addition, only Medicare-eligible patients were included, which may somewhat limit its generalizability.

Still, this rigorously performed analysis of a large, representative national cohort provides the strongest evidence to date that the benefits of GLP-1 RA demonstrated in other populations may extend to those treated with dialysis. These data are tantalizing, as many interventions have failed to alter the staggering mortality rate for this population. Impressively, the GLP-1 RA may not only extend life but also enhance access to the most definitive therapy for kidney failure: transplantation.

This study strengthens the foundation for future investigation, in particular clinical trials, to clarify fully the impact of the incretin mimetics in this high-risk population. Now, more than ever, nephrology clinicians and investigators should re-examine long-held assumptions—like the obesity paradox—and explore the potential of novel metabolic therapies to reshape the landscape of dialysis care. ■

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# An Ever-Changing Landscape: Medicare Reimbursement of Dialysis Care

By Allison C. Reaves

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People with a diagnosis of kidney failure (also known as end stage renal disease [ESRD]) who have paid Medicare taxes are eligible for Medicare, regardless of age. In fact, the majority of people living with ESRD and receiving maintenance dialysis are enrolled in Medicare (more than 80% of existing patients and more than 60% of those starting dialysis) (1), a program administered by the Centers for Medicare & Medicaid Services (CMS), a federal agency within the US Department of Health and Human Services that falls under the purview of the Executive Branch. The policies that have shaped Medicare reimbursement for dialysis have evolved over time with two primary, interconnected goals: maintaining quality while minimizing costs.

Underlying these goals is a longstanding priority of US health care policy to make dialysis accessible and affordable for people who need it. Medicare coverage of dialysis began in 1973. In the years that followed, concerns mounted regarding the costs of providing dialysis care in a fee-for-service model (2, 3). In 1981, reimbursement was transitioned to fixed or "bundled" payments. These early bundled payments included dialysis services only. In 2011, in the setting of high medication utilization, payments were expanded to include medications such as erythropoietin-stimulating agents (Figure) (2, 3). The following year, the ESRD Quality Incentive Program (QIP) was implemented. The introduction of this program reflected concerns that bundled payments might incentivize medication underutilization and inadequate dialysis (2, 3). One of several dialysis value-based purchasing programs, the QIP ties performance scores on quality measures to a maximum 2% cut in dialysis facilities' Medicare fee-for-service reimbursement (4). The number of measures has increased as the QIP program has evolved, and, despite the concern that some measures may not accurately reflect quality (5), few measures have been removed. Of note, there is a 2-year lag between collection of data and QIP penalties, which may limit the responsiveness of facilities to their scores (6). Only a small percentage of facilities (1.6% in payment year 2019) receive the maximum payment reduction each year (7), and penalization has not been associated with improvements in performance scores (8).

In recent years, the landscape of Medicare reimbursement for dialysis has undergone substantial change. With the passage of the 21st Century Cures Act, people with ESRD, who had previously been largely limited to enrollment in traditional Medicare, were allowed to enroll in Medicare Advantage (MA) plans starting in 2021 (9). MA enrollment among people with ESRD increased by more than 70% between 2020 and 2022 (10). In MA, private health plans administering Medicare enter into a payment model with CMS, whereby they receive risk-adjusted capitated (fixed) payments and are allowed to keep any savings they accrue. This approach raises concerns for "cherry picking" low-risk beneficiaries (11) and increases incentives for MA plans to optimize coding for risk adjustment, referred to as "upcoding," which recent evidence shows has resulted in significantly greater revenues for MA plans than fee-for-service Medicare (12). Importantly, MA plans represent a departure from the standardization of benefits and reimbursement in traditional Medicare, raising concerns for equitable access to dialysis care. For example, one study found that MA patients traveled farther and to lower-quality dialysis facilities compared with traditional Medicare patients in the same zip code (13).

The emergence of MA as a primary player in dialysis reimbursement raises important questions about priorities for dialysis care going forward. If equitable access to high-quality care is to remain a goal, new systems and programs will be needed to monitor the quality of care received by patients enrolled in MA because existing performance-based models were developed using data from traditional Medicare. Additionally, it will be imperative to ensure that patients enrolled in Medicaid–Medicare Dual Eligible Special Needs MA plans maintain at least the same access to dialysis care that they had under traditional Medicare. MA plans also should be evaluated for potential benefits that may enhance dialysis care. For example, an increasing number of MA plans offer nonemergency medical transportation benefits (14), which may be of great value to some patients on dialysis.

More than 50 years ago, the United States made a substantial commitment toward ensuring that people with ESRD who had paid Medicare taxes had access to dialysis care. Continuing to build on this legacy and improve dialysis care going forward requires understanding the potential benefits and challenges of the ever-evolving Medicare dialysis reimbursement policy. ■

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**Figure. The Medicare ESRD Prospective Payment System bundled payment for dialysis services**


Created from CMS (https://www.cms.gov/medicare/payment/prospective-payment-systems/end-stage-renal-disease-esrd).

# Dietary Strategies for Kidney Health in Diabetic Kidney Disease: Precision Nutrition for Glycemic Control and Kidney Protection

By Yoko Narasaki and Connie Rhee

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Chronic kidney disease (CKD) is one of the most prevalent complications of diabetes, affecting 30%–40% of people with type 1 and type 2 diabetes (T1D and T2D). Given the heightened morbidity and mortality of diabetic kidney disease (DKD), a multifaceted approach is needed to reduce its cardiovascular-kidney-metabolic (CKM) complications. In addition to evidence-based pharmacotherapies, such as renin-angiotensin-aldosterone system inhibitors, sodium-glucose cotransporter-2 inhibitors, and glucagon-like peptide-1 receptor agonists, dietary interventions are a foundational cornerstone in the management of DKD (1–3).

## Kidney nutrition in DKD

### Low-protein diets

In diabetes, chronic hyperglycemia causes afferent arteriolar dilation as well as local renin-angiotensin-aldosterone system activation and efferent arteriole vasoconstriction, leading to glomerular hyperfiltration and glomerular hypertension as major risk factors for CKD development and progression. Higher amino acid and dietary protein intake (DPI) also causes dilation of afferent arterioles, glomerular hyperfiltration, and increased intraglomerular pressure leading to glomerular damage in CKD, which may be exacerbated in diabetes (4). Hence, low-protein diets (LPDs) have an important role in ameliorating DKD progression by reducing glomerular hyperfiltration and hypertension.

Clinical practice guidelines (CPGs) support the use of LPDs in people with CKD who are nondialysis dependent (NDD) to reduce kidney disease progression and mortality, although with varying DPI thresholds (Table). Although the 2020 Kidney Disease Outcomes Quality Initiative (KDOQI) CPG for Nutrition in CKD recommends LPDs (0.55–0.60 g/kg/day) or supplemented very LPDs (VLPDs; 0.28–0.43 g/kg/day with ketoacids) for metabolically stable adults with stages 3–5 NDD-CKD without diabetes to reduce kidney failure and death, in those with diabetes, the guideline recommends a slightly higher DPI threshold (0.60–0.80 g/kg/day) to maintain stable nutritional status and optimize glycemic control (2). The International Society of Renal Nutrition and Metabolism has endorsed these recommendations but also suggests a more streamlined DPI target (0.60–0.80 g/kg/day), irrespective of CKD etiology (5). Similarly, the 2024 Kidney Disease: Improving Global Outcomes (KDIGO) CPG does not distinguish DPI recommendations according to diabetes status (6). This guideline recommends a DPI of 0.80 g/kg/day in stages 3–5 NDD-CKD and also includes a practice point, endorsing prescription of a supplemented VLPD (0.30–0.40 g/kg/day with ketoacids) under close supervision.

### Plant-based diets

In addition to the amount of DPI, the source of dietary protein may have an important bearing on kidney protection and glycemic control in DKD. Plant-based versus animal-based protein sources are higher in fiber, lower in saturated fat, and have been shown to improve glycemic control in T2D. There is also emerging data that plant-based diets reduce incident CKD, CKD progression, and CKD-related complications, including metabolic acidosis, hyperphosphatemia, uremic toxin burden, accumulation of advanced glycation end-products, and insulin resistance (Figure).

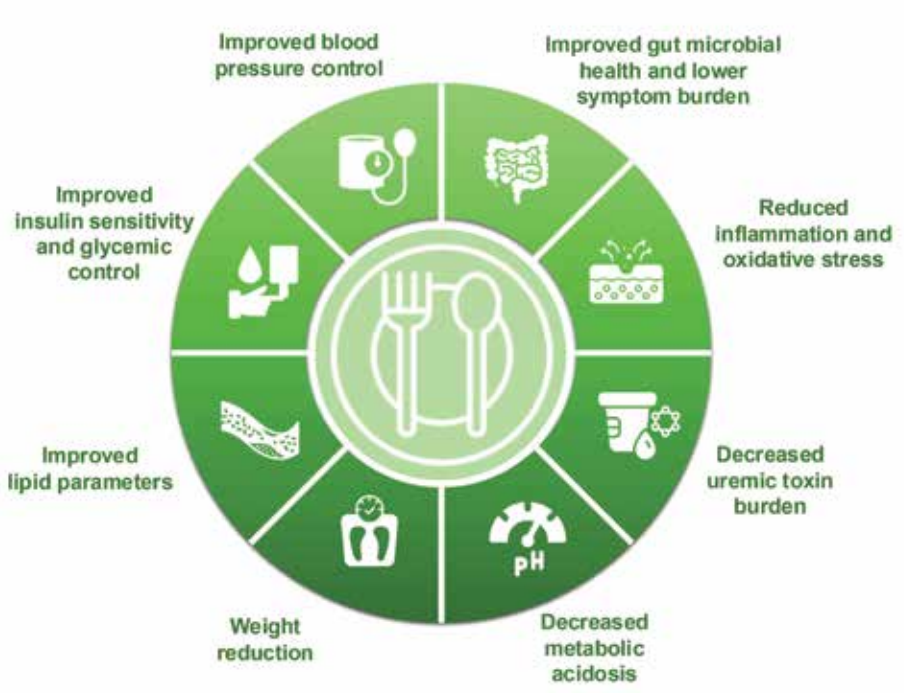
Although the 2020 KDOQI guideline indicates that there is insufficient evidence to recommend a particular protein type (plant versus animal) with respect to nutritional status, calcium or phosphorus, or dyslipidemia in CKD, it supports greater fruit and vegetable consumption to decrease body weight, blood pressure, and net acid production (2). For people with or at risk for diabetes, the 2025 American Diabetes Association Standards of Care in Diabetes recommends greater intake of plant-based protein sources as part of an overall diverse eating pattern to reduce cardiovascular disease (1). The 2024 KDIGO CKD guideline's practice point also promotes healthy and diverse diets with higher consumption of plant-based foods (6).

There have been several randomized controlled trials (RCTs) in people with CKD who are nondiabetic showing benefits of plant-based diets in reducing CKD progression. One RCT randomized 207 people with CKD who were nondiabetic to a supplemented vegetarian VLPD versus a standard LPD. Those in the vegetarian VLPD group had lower risk of the primary composite endpoint (kidney replacement therapy or >50% reduction in estimated glomerular filtration rate) compared with the LPD group (7). Another RCT randomized older adults with stage 5 NDD-CKD who were nondiabetic to a supplemented vegan VLPD versus dialysis. Those in the vegan VLPD group had delayed kidney replacement therapy initiation by a median of approximately 11 months, greater 1-year survival, and lower hospitalization risk (8). Although existing trials of plant-based LPDs in DKD are limited by small sample size, short duration, or noninclusion of participants with impaired kidney function, those in the plant-based groups showed improvement in kidney parameters (glomerular hyperfiltration, proteinuria) and cardio-metabolic indices (hyperglyemia, dyslipidemia, and inflammation). To address these gaps, there is an ongoing National Institutes of Health multicenter RCT—the Plant-Focused Nutrition in Patients With Diabetes and Chronic Kidney Disease (PLAFOND) study—that is evaluating the efficacy and safety of plant-based LPDs versus conventional LPDs in DKD (9).

**Table. Dietary protein intake recommendations for nondialysis-dependent chronic kidney disease (NDD-CKD)**

| Guideline | Stages 3–5 NDD-CKD without diabetes mellitus (DM) | Stages 3–5 NDD-CKD with DM |
|---|---|---|
| 2020 KDOQI Clinical Practice Guideline for Nutrition in Chronic Kidney Disease | In adults who are metabolically stable, the recommendation is dietary protein restriction with or without ketoacid analogs to reduce risk for kidney failure and death and improve quality of life:<br>· an LPD of 0.55–0.60 g/kg/day or<br>· a VLPD of 0.28–0.43 g/kg/day with additional ketoacid analogs to meet protein requirements (0.55–0.60 g/kg/day). | It is reasonable to prescribe, under close clinical supervision, a DPI of 0.60–0.80 g/kg/day to maintain a stable nutritional status and optimize glycemic control. |
| 2020 International Society of Renal Nutrition and Metabolism commentary | It is reasonable for clinicians to aim for the lower end of a streamlined target of 0.60–0.80 g/kg/day, regardless of CKD etiology. | |
| 2024 KDIGO Clinical Practice Guideline for the Evaluation and Management of CKD | · Recommendation: Maintain a protein intake of 0.80 g/kg/day.<br>· Practice point: In adults with CKD who are willing and able and who are at risk of kidney failure, consider prescribing, under close supervision, a VLPD (0.30–0.40 g/kg/day), supplemented with essential amino acids or ketoacid analogs (up to 0.60 g/kg/day). | |

**Figure. Plant-based LPDs and CKM indices in DKD**




## Precision nutrition strategies in DKD

Successful implementation of plant-based LPDs in DKD requires precision nutrition strategies that tailor dietary interventions based on an individual's unique clinical, metabolic, and lifestyle profile (10). As balancing glycemic control, reducing DPI, and maintaining adequate energy intake may be overwhelming for patients, multidisciplinary collaboration with specialty-trained dietitians and/or accredited nutrition professionals, who can adapt CPGs to individuals' needs and preferences, is essential for enhancing patient engagement.

Precision nutrition strategies also use clinical biomarkers, real-time data (continuous glucose monitoring), wearable devices (assessing physical activity and physiologic parameters), and personal preferences and factors to inform dietary interventions in DKD (10). These approaches include laboratory assessments (blood and 24-hour urine measurements of sodium, phosphorus, potassium, urea nitrogen, and albumin as surrogate dietary intake markers) and body composition measurements (to assess nutritional requirements). As a convenient, automated method for comprehensive glycemic monitoring, continuous glucose monitoring is also a useful tool in tailoring dietary interventions in DKD by assessing individuals' glycemic responses to foods (postprandial spikes, nocturnal hypoglycemia, and glucose variability) and guiding precise dietary composition, meal planning, nutrient timing, and portion sizes. Personalized education and motivational interviewing can also be used to incorporate cultural food preferences, lifestyle, and social determinants of health to optimize adherence and long-term behavior modification. Food-exchange lists are also useful in precision nutrition by swapping foods with similar nutritional content to allow for flexible meal planning within CPG parameters and by empowering patients to make informed food choices using food equivalency. In summary, precision nutrition approaches are a critical aspect of enhancing the effectiveness of plant-based LPDs to mitigate the CKM complications and optimize the health and well-being of people with DKD. ■

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# Understanding New Pharmacologic Therapies for Primary Hyperoxaluria

By Gregory L. Braden and Daniel L. Landry

https://doi.org/10.62716/kn.001112025

Primary hyperoxaluria (PH) comprises a rare group of bi-allelic autosomal recessive disorders of glyoxylate metabolic processing leading to overproduction of oxalate. Chronic deposition of oxalate can cause systemic oxalosis, resulting in recurrent nephrolithiasis, nephrocalcinosis, and chronic kidney disease, necessitating dialysis and the need for liver and/or kidney transplant (1). PH type 1 (PH1) is the most common disorder, accounting for 70%–80% of PH cases, and is due to mutations in the *AGXT* gene that inhibit hepatic peroxisomal alanine–glyoxylate aminotransferase (AGT), which can be pyridoxine-sensitive, leading to an increase in liver glyoxylate being shunted to form oxalate via liver lactate dehydrogenase A (LDH-A) (Figure) (2). PH2 results from mutations in the enzyme glyoxylate reductase/hydroxypyruvate reductase (GRHPR), which converts glyoxylate to glycolate, leading to overproduction of oxalate (1–3).

Best-practice guidelines for PH therapy include vigorous fluid intake (2–3 L/body surface area/day); inhibitors of calcium oxalate crystallization such as potassium citrate, magnesium, and neutral phosphate (that must be avoided in individuals with chronic kidney disease); and a diet low in oxalate (1). High-dose pyridoxine can significantly lower hepatic oxalate production in a subset of patients with PH1 with G170R, G41A, F152I, and I244T variants and should be tried in all patients with PH1 for 3 months, whereby 30% of these patients will have a pyridoxine response defined by lowering urinary oxalate. Pyridoxine is not effective in patients with PH2.

There is now hope for better outcomes in PH from two new US Food and Drug Administration-approved, subcutaneously administered, liver-directed RNA interference drugs. Lumasiran increases glycolate by degrading mRNA, encoding glyoxylate oxidase, which prevents glyoxylate formation that leads to reduced hepatic oxalate production (4). Lumasiran in children and adults induced a mean reduction of 65% in daily urinary oxalate excretion in PH1 and mean normalization in 84% of patients after 6 months of therapy (4). However, variations in the ability of lumasiran to inhibit glycolate oxidase were found by isotope infusion studies in patients with PH1 with a range of 55%–91% inhibition, which correlates with their effects on daily urinary oxalate excretion (5). Another subcutaneous agent, nedosiran, inhibits LDH-A in the cytoplasm of hepatocytes by degrading LDH-A mRNA, which reduces the production of LDH-A. Since the LDH-A enzyme is the final common pathway for liver oxalate production, it was developed for use in all three types of PH. In the PHYOX2 study, nedosiran in patients with PH1 produced sustained reductions in daily urinary oxalate excretion, but no consistent effect was found in patients with PH2 (6). The PHYOX4 study showed only a 24% reduction in daily urinary oxalate excretion by nedosiran in patients with PH3 (7). Wanders and colleagues hypothesized that patients with PH2 and PH3 may have other nonliver sources of oxalate production, which would not be inhibited by nedosiran (2).

More recently, Cox and colleagues have reported on a novel, first-of-its-kind, oral mRNA inhibitor of LDH-A, CHK-336 (Chinook Therapeutics [a Novartis company], Seattle, WA) (8). This study highlights the incredible detail to which innovative research continues to progress for the treatment of PH with a focus on the inhibition of liver LDH-A. In this study, three animal species (mice, rats, and monkeys) had proven liver-target distribution by organic anion transport proteins. In addition, the researchers confirmed that human hepatocytes had significant CHK-336 uptake. CHK-336 reduced urinary oxalate to mean normal levels, measured as urinary oxalate-creatinine ratios in a mouse model of PH1. The authors concluded that CHK-336 has the potential to be useful in all three types of PH.

CHK-336 was tested in 104 normal human subjects using single doses ranging from 15 mg to 500 mg in a once-daily dose, and the researchers found no significant side effects. They performed a 14-day daily dosing, ranging from 300 mg to 500 mg. Multiple dosing with 60 mg/day was well-tolerated. However, one patient who received 125 mg/day developed severe anaphylaxis that was not well-described (proprietary information).

Novartis has purchased Chinook, and in a combined merger with Versant Ventures, the company has spun off Borealis Biosciences, which will further develop RNA interference therapies. It is unclear whether CHK-336 will be undergoing further tests and development at this time.

It is clear that the new RNA inhibitor drugs will require long-term studies of efficacy. However, there is now hope for more favorable outcomes in patients with PH from this new class of liver LDH-A inhibitor drugs. The ability to use oral therapy capable of treating the entire spectrum of PH could be a ground-breaking event that creates hope for an entire population of patients dealing with a rare, life-threatening disease. ■

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The authors report no conflicts of interest.

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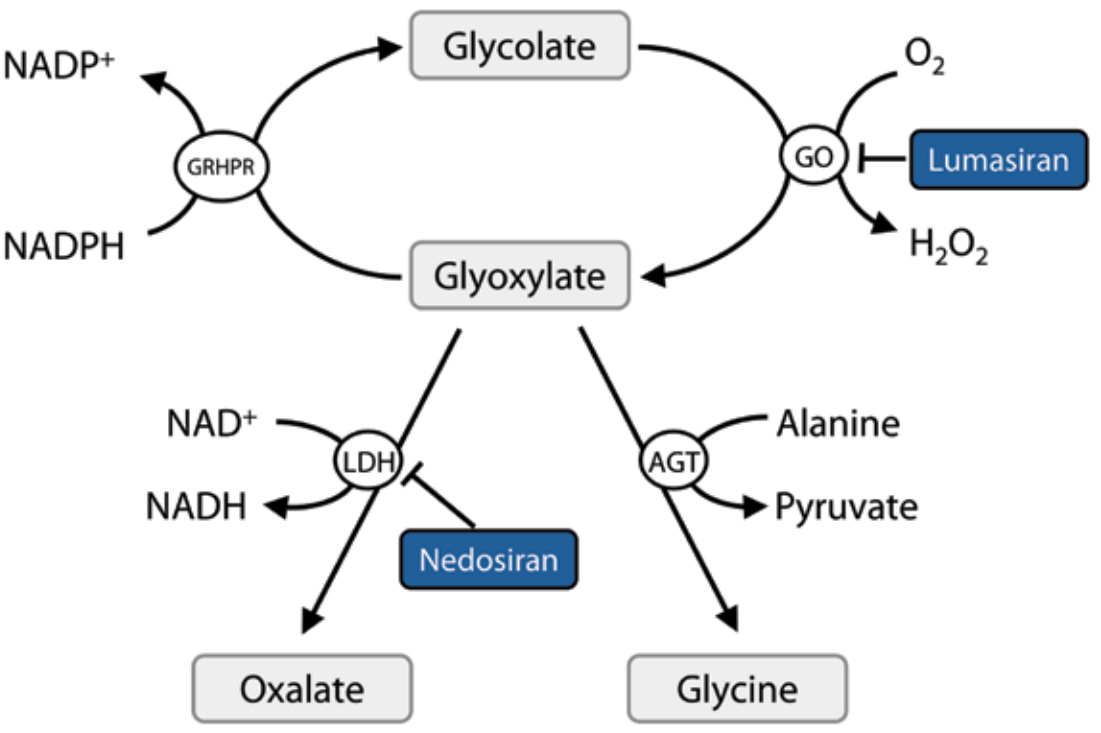
**Figure. Simplified form of glyoxylate metabolism**




GO, glycolate oxidase. Reproduced with permission from Wanders et al. (2).

CREATIVE CORTEX

# The Vortex of Filtration

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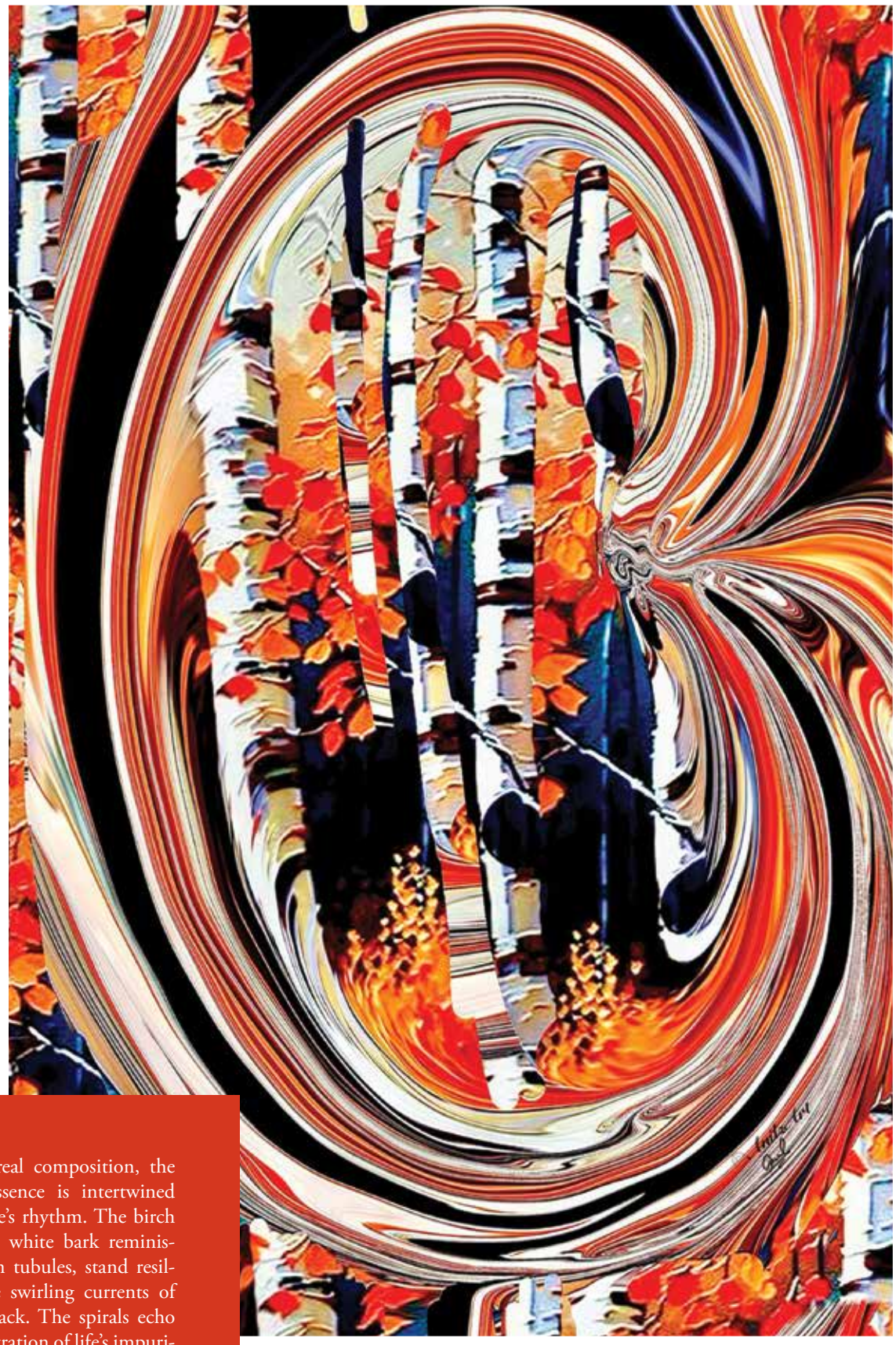

In this surreal composition, the kidney's essence is intertwined with nature's rhythm. The birch trees, their white bark reminiscent of nephron tubules, stand resilient amidst the swirling currents of crimson and black. The spirals echo the relentless filtration of life's impurities, a dance between chaos and clarity. Like autumn leaves surrendering to the wind, waste is relinquished, making way for renewal. This piece speaks of the kidney's silent labor—an eternal vortex of cleansing, sustaining existence with unseen grace. ■

*Artwork by AnilzArt. Anil Saxena, MD, FASN, is a digital artist based in Dubai, United Arab Emirates. His abstract artwork blends trained medical expertise with vibrant color palettes, creating visually captivating landscapes of human identity and transformation. Saxena's work has been exhibited internationally and featured on the covers of medical journals.*

# Sustainable Nephrology: Actions That Can Help Make Nephrology Greener

By Letizia De Chiara and Maria Pippias

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Health systems have a long-term sustainability problem (1). This is largely driven by aging populations and the burden of chronic diseases, also known as noncommunicable diseases, which are associated with long durations and slow progress. The 2030 Agenda for Sustainable Development recognizes noncommunicable diseases as a major unmet challenge for sustainable development (2). This is particularly relevant for people living with kidney diseases. In fact, more than 850 million people worldwide are living with some form of kidney disease—double the number of people who live with diabetes and 20 times the worldwide prevalence of cancer. Yet, gradual and progressive loss of kidney function, termed chronic kidney disease (CKD), often progresses silently until it reaches advanced stages, remaining unrecognized in up to 90% of patients, as standard tests fail to detect subtle or even extensive kidney tissue loss (3). This delay can lead to kidney failure, requiring dialysis or transplantation, with additional significant economic and environmental burdens (1). For these reasons, many recent studies have tried to measure sustainability in CKD/kidney disease management with rather disappointing results, likely due to the complexity of performing such studies (4).

Climate change is both an environmental crisis and a public health emergency. In January 2025, global average surface air temperatures reached a worrying 1.75°C higher than preindustrial levels (5). This followed the warmest year on record, with 2024 temperatures exceeding the aspirational 1.5°C ambition outlined in the Paris Agreement. The health care sector contributes to climate change and is responsible for 5.2% of global greenhouse gas emissions (6). Yet, it also has a moral and ethical responsibility to minimize its environmental impact through sustainable practice, not only to protect patient health today but to contribute to a livable climate in the future.

## What does sustainability mean in CKD management?

Ideally, sustainability in CKD management (as well as with all chronic disease) would involve creating systems and practices that can effectively address the long-term needs of individuals living with CKD, while also considering the broader environmental, social, and economic impacts. This should include preventative measures, early detection, and ongoing care, all within a framework that considers resource limitations, equity, and the health of the environment. Currently, much of the activity of health care systems around reducing their environmental impact relates to infrastructure and systems that support direct clinical care. Additional actions may be focused on promoting healthy lifestyles that address risk factors for CKD such as tighter control of diabetes and hypertension to reduce the incidence of CKD. A meta-analysis of the CREDENCE trial data (NCT02065791) reported that the introduction of sodium-glucose cotransporter-2 inhibitors reduced greenhouse gas emissions through the prevention of hospital admissions and the need for dialysis (7).

Promoting resource allocation and a circular economy is also important. Sustainable solutions must consider the efficient allocation of resources to ensure that care is provided equitably and effectively. Our current economy is largely linear, meaning that resources are extracted and used and then disposed of as waste at the end of their life. In a circular economy, medical devices are designed to be reused as long as possible, reducing waste and pollution (8). When selecting medical equipment, health care professionals should focus on the concept of the "5 Rs": reduce, reuse, reprocess, renew, and recycle (9).

Promoting personalized and precision medicine would also decrease the environmental impact of chronic disease, if effectively applied. Personalized medicine is based on the principle of tailoring the treatment to each patient, allowing for more effective outcomes. This approach would be more impactful in terms of response to therapy and clinical effectiveness, ultimately resulting in decreasing the number of health care visits, routine testing, as well as medications.

Innovation and research can also play central roles. Innovation in the way health care is delivered, by using digital technologies that can help improve both access to and quality of care for patients, could reduce the number of in-person health care visits. Likewise, alternative protocols, with less fractionated treatments that would require fewer treatment days and visits, could also potentially have a lower environmental impact. Finally, exploration of possibilities for recycling, including developing novel processes for products that currently lack recycling options, represent another potential area for innovation.

In essence, sustainability in CKD management involves creating a comprehensive system that is not only effective in addressing the needs of individuals living with chronic conditions but also considers the broader environmental, social, and economic factors that influence health and disease.

Challenges, such as the lack of data on the environmental impact of clinical interventions and devices, remain. However, there are opportunities for engaging health care leadership, staff, and patients to develop and implement changes to make health care more environmentally sustainable. In the future, there may be greater opportunities to consider evidence on the environmental impact—alongside clinical and economic evidence, patient perspectives, social values, and ethics—to support the delivery of clinically effective, cost-effective, and environmentally sustainable care. ■

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The authors report no conflicts of interest.

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# Integrating AI-Based Biomarkers Into Diabetic Kidney Disease Care: Evidence From the KidneyIntelX Precision Program

By Muhammad Yasir Baloch, Charat Thongprayoon, and Wisit Cheungpasitporn

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Despite recent advances in therapies for diabetic kidney disease (DKD), many patients still fail to receive timely and optimized care—often due to therapeutic inertia and inadequate risk stratification in everyday practice (1–3). A 2024 real-world evidence study demonstrates how KidneyIntelX, a machine learning-based platform that integrates biomarkers with clinical data, can help close this gap by identifying patients at high risk earlier and guiding more targeted interventions (1).

KidneyIntelX combines three plasma biomarkers—soluble tumor necrosis factor receptors 1 and 2 and kidney injury molecule-1—with clinical data from electronic health records to predict 5-year risk of progressive kidney function decline (4, 5). In this longitudinal study (NCT04802395), 2569 people with type 2 diabetes and early-stage DKD across the Mount Sinai Health System were followed for at least 12 months after testing.

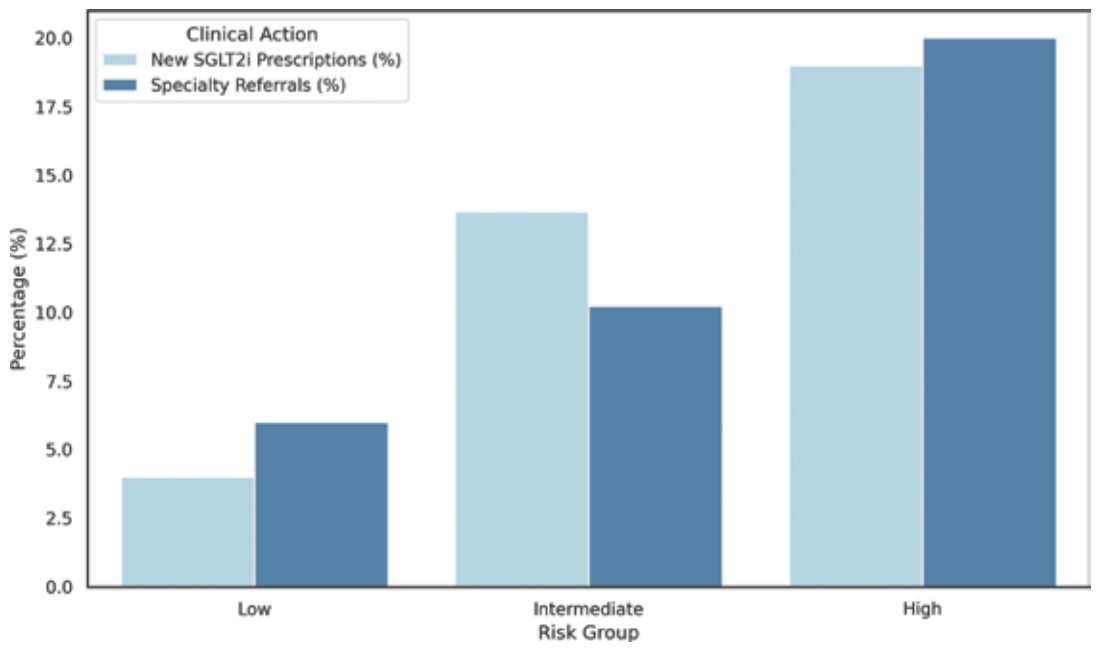
Risk categories (low, intermediate, and high) directly influenced physician decisions and patient engagement. Among patients with high risk, 43% received new prescriptions such as sodium-glucose cotransporter-2 inhibitors (SGLT2is) or glucagon-like peptide-1 receptor agonists—or referrals to specialists within 6 months—compared with 19% of patients with low risk. SGLT2i initiation was nearly five times more likely in the high-risk group (19% versus 4%) (Figure). These actions were associated with clinical gains: the median hemoglobin $A_{1C}$ decreased from 8.2% to 7.5% in the high-risk group, the urine albumin-to-creatinine ratio declined by approximately 20% in overall patients with intermediate risk and by approximately 50% in a subgroup of patients with intermediate risk who received new prescriptions for SGLT2i, and the estimated glomerular filtration rate slope improved across all risk levels (1).

Population health infrastructure, including care navigation teams, pharmacists, and remote monitoring, amplified KidneyIntelX's impact. For example, blood pressure control improved from 33% to 61% among patients with high and intermediate risk who were enrolled in a remote hypertension management program, with an average systolic reduction of 11.8 mm Hg. Notably, integration of predictive risk scores within a care coordination framework enabled timely interventions that would otherwise be delayed in standard care pathways.

Importantly, 98% of patients with high risk appreciated the care navigation team outreach, and 97% reported feeling motivated to act—emphasizing the value of personalized risk communication. Education, coupled with data-driven stratification, improved patient activation and therapeutic alignment with American Diabetes Association and KDIGO (Kidney Disease: Improving Global Outcomes) guidelines (1, 6). Clinical pharmacists also supported treatment intensification and blood pressure control, reinforcing evidence from prior studies showing their impact in chronic kidney disease management (7).

KidneyIntelX enables a sustainable transition toward precision medicine in DKD by facilitating early, risk-informed interventions and by enhancing the coordination of multidisciplinary care. Beyond optimizing the initiation of renoprotective therapies, the model has demonstrated improvements in glycemic control, proteinuria reduction, and attenuation of the estimated glomerular filtration rate decline. These findings underscore the potential for integrating predictive biomarkers and artificial intelligence-based risk stratification into population health frameworks. However, the study does not yet report on long-term clinical endpoints, such as progression to kidney failure, major cardiovascular events, or mortality. These outcomes are anticipated in future analyses as extended follow-up data become available. ■

**Figure. Percentage of patients receiving new SGLT2i prescriptions and specialty referrals within 6 months post-KidneyIntelX testing, stratified by risk group**

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The authors report no conflicts of interest.

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## What Health Outcomes Are Most Important to Older Adults With CKD?

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For older adults with advanced chronic kidney disease (CKD), fatigue and life expectancy are the factors most strongly affecting preferred health outcomes, with important implications for shared decision-making, reports a study in the *American Journal of Kidney Diseases*.

The researchers performed a "discrete choice" experiment including 85 participants, aged 65 years or older, receiving outpatient treatment for advanced (stage 4 or 5) CKD. The study questionnaire focused on five attributes: fatigue, life expectancy, level of independence, hospital admissions, and hospital visits. Patients' priorities for health outcomes were assessed, along with the trade-offs that they would be willing to make to achieve one attribute over another.

Among the total patients (mean age, 77 years; 65% males) at the time of the study, 37% had no expressed treatment preference, 33% preferred conservative care, and 15% each preferred dialysis or transplantation.

Fatigue was the attribute with the greatest relative influence on patients' choice, accounting for 26% of total importance. This was followed by life expectancy (23%) and hospital admissions (20%). For level of independence and hospital visits, relative importance was 16% and 15%, respectively. Findings include some age-related variations: Younger patients placed the highest priority on avoiding fatigue, whereas avoiding hospital admissions was the most important goal for the oldest patients.

On analysis of trade-offs affecting treatment decisions, patients indicated that they would accept a 46% reduction in the chance of 3-year survival, five extra hospital admissions per year, or 86 extra hospital visits per year to avoid having any fatigue as opposed to severe fatigue. To gain a 10% increase in probability of survival, patients would accept one additional hospital admission and 20 additional hospital visits per year.

In subgroup analyses, avoiding hospital admissions was the top-rated attribute for patients aged 85 years or older (relative importance, 33%), in contrast to younger patients (aged 65–74 years), for which it was the lowest-rated factor (relative importance, 15%).

Individuals with advanced CKD face complex decisions regarding their treatment options, shifting from a disease-oriented approach toward a goal-oriented approach that integrates health outcome preferences. The new study identifies five attributes affecting health outcome preferences among older adults with stage 4 or 5 CKD.

"The results of this study can aid the decision-making process for kidney failure therapies by guiding discussions about patient preferences," the researchers conclude [Schoot TS, et al. Health outcome preferences and trade-offs among older adults with advanced CKD: A discrete choice experiment. *Am J Kidney Dis*, published online August 1, 2025. doi: 10.1053/j.ajkd.2025.06.010].

## Adverse Outcomes of ART Pregnancies in Kidney Recipients

https://doi.org/10.62716/kn.001452025

For kidney transplant recipients, many adverse maternal and fetal outcomes are more frequent in pregnancies achieved using assisted reproductive technology (ART) compared with natural conception, reports a study in *Transplantation*.

Using Transplant Pregnancy Registry International data from 1962 to 2022, the researchers identified two groups of kidney transplant recipients with subsequent pregnancies: 77 achieved with ART and 695 through natural conception. Patients with ART pregnancies were older than those with natural conception (median age at conception, 35.0 years versus 30.7 years). Numbers of ART pregnancies increased over time.

On multivariate analysis, patients with ART pregnancies had a higher likelihood of hypertension during pregnancy (odds ratio [OR], 1.57). Risks of pre-eclampsia and gestational diabetes were similar between groups. Women with ART pregnancies were at higher risk of cesarean delivery (OR, 1.60) and preterm birth (before 37 weeks; OR, 2.07).

ART pregnancy was also associated with lower median birthweight (2551 versus 2722 g), lower gestational age at birth (36 versus 37 weeks), and higher neonatal mortality (4.4% versus 0.8%). Rates of miscarriage, live birth, low birthweight, and a birth defect were similar between groups. There was no significant difference in 2-year graft loss (8.4% in patients with ART pregnancies and 5.6% in those with natural conception).

Pregnancy after kidney transplantation poses challenges related to maternal and fetal complications, immunosuppression side effects, and decreased graft function. There are few specific data on outcomes of ART pregnancies after kidney transplantation.

The new registry study finds higher rates of several adverse outcomes among kidney transplant recipients with ART pregnancies compared with natural conception. Despite these risks, the two groups of pregnancies appear to have similar rates for other outcomes. The researchers conclude: "This finding can be valuable for [health care] providers as it helps them offer preconception counseling and informed guidance when assisting individuals who wish to start a family after a kidney transplant" [Shah S, et al. Pregnancy outcomes using assisted reproductive technology in kidney transplant recipients. *Transplantation,* published online July 4, 2025. doi: 10.1097/TP.0000000000005449].

# No Filters: Frailty and the Senescent Kidney

By Antonio Gabriel Corona, Rimon Golovey, and Linda Wang

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There is a growing understanding of the differences between kidney disease and kidney senescence. These differences highlight the importance of contextualizing any evaluation of kidney insufficiency against the overall clinical presentation, which is especially important in older patients. Over the past 15 years, research has identified frailty as a predictor of increased morbidity and mortality. Since frailty is closely associated with increasing age, can frailty be included as a diagnostic adjunct and taken into consideration in the diagnosis and management of acute kidney injury (AKI), particularly in older adults?

In a recent study by Herget-Rosenthal and colleagues, patients 80 years or older (hereinafter "the older population") were found to have a high incidence of AKI, which led to poor outcomes (1). Among their many findings, there are three talking points that this commentary will focus on: 1) the connection between kidney aging and cardiorenal syndrome (CRS), 2) the potential role of frailty in evaluating and possibly even predicting AKI, and 3) the comprehensive geriatric assessment (CGA).

## The senescent kidney

In the study (1), the strongest risk factors, excluding sepsis and shock, for AKI in the older population were higher baseline serum creatinine (SCr) and the continuum of volume depletion and volume overload, especially in the setting of heart failure. This finding mirrors previous data describing the disproportionately high incidence of CRS in older adults and the identification of diuretic use as a significant risk factor (2). So, what makes the aging kidney particularly susceptible to injury from volume depletion, especially in the setting of heart failure?

We are discovering that as we age, our kidneys age as well. This is likely due to a combination of nephron loss and nephrosclerosis, which likely begins much earlier in life. Nephrosclerosis, or arterionephrosclerosis, is a nonspecific microstructural feature in kidney histology that is characterized most distinctively by changes in the arteriolar-glomerular units, namely hyalinosis of afferent arterioles. It is thought that age-related hyalinosis of the interlobular arteries transmitting abnormal pulse waves distally induces fibrointimal hyperplasia in smaller arterioles. This, along with aberrant responses to neuroendocrine molecules, predisposes the vascular tone toward vasoconstriction and hypoperfusion of the kidneys, culminating in glomerular hypertrophy, glomerulosclerosis, and tubular atrophy (3). The collapse of the glomerular tuft is eventually accompanied by the formation of an anastomotic connection between the afferent and efferent arterioles (4). This leads to the loss of glomeruli with shunting of blood flow to the efferent arterioles.

Although it has been established that the eventual outcome of this process is loss of kidney function, these changes may be adaptive responses to senescent changes occurring in the rest of the body. On a systemic scale, aging is associated with decreased systemic perfusion to organs, and this includes kidney blood flow and the corresponding glomerular filtration rate (GFR) (3). The decrease in kidney blood flow is postulated to be a compensatory mechanism to preserve perfusion in other vascular beds, such as the cardiac and cerebral circulatory systems. Blood flow to the brain and heart declines with senescence, and both seem to be more susceptible to clinical impairments compared with the kidneys (5).

This process of kidney senescence closely reflects the findings in Herget-Rosenthal and colleagues' article (1), in which the aging kidney can be "exhausted" in order to preserve the more age-vulnerable cardiovascular system. However, once it reaches a critical point, the ensuing kidney injury is severe. Owing to the depletion of functional reserve, median SCr levels for the older population with AKI do not tend to return to baseline levels after the insult.

Consequently, it is not surprising that heart failure and hypovolemia compound this kidney injury in older adults. In general, volume removal through diuresis remains the mainstay of treatment for heart failure. Diuretic use, however, has been implicated in the development of AKI in CRS (2). The clinical implication of this cardiorenal relationship must involve a more individualized and liberal strategy for volume management in heart failure in the geriatric population. Treatment endpoints, volume assessment, and use of diuretics should be more refined, especially in the older population.

## The role of frailty in AKI

Evaluating kidney function in the older population is challenging. Regardless of the prevalence with advancing age, senile nephrosclerosis does not fully correlate with the decline in measured GFR associated with maturing kidneys. Glomerular hypertrophy, despite loss of overall glomerular density, is implied to play a part in maintaining GFR, initially as a compensatory function. With time, the elevated glomerular capillary pressures have additive tensile stress effects on capillary walls, causing a corresponding higher ultrafiltrate flow in Bowman's space (6). However, the potential injurious nature of this finding in healthy aging is debated.

This brings us to a challenging question of how kidney insufficiency is assessed in older adults. It is expected that the rate and the severity of SCr increase are blunted in older adults due to sarcopenia (7). Cystatin C is becoming more widely used; however, there remains a large discrepancy between GFR measured by SCr and cystatin C of unknown clinical relevance in older adults, which may be partially explained by selective glomerular hypofiltration (8). Herget-Rosenthal and colleagues (1) may have presented another way of detecting and even predicting kidney injury in the older population: frailty.

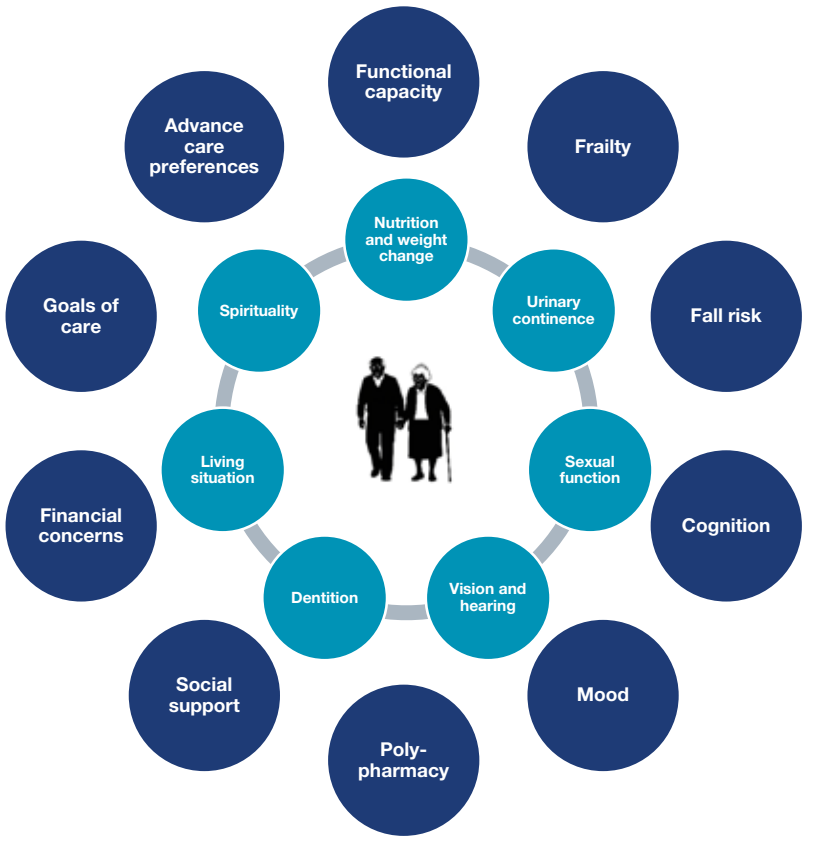
Although there is no standard definition of frailty, it is generally recognized as the hallmark geriatric syndrome that incorporates physical, cognitive, and psychosocial elements that lead to physiological decline and increased vulnerability to adverse events. Age, comorbidity, and disability, although associated with frailty, do not establish the diagnosis of frailty alone. Frailty has been shown to increase disability, institutionalization, and mortality. There is no gold standard for detecting frailty, and there have been multiple screening tools developed for frailty risk assessment, but most have been validated to properly identify patients at the highest risk for adverse outcomes in a variety of clinical settings. The prevalence of frailty has ranged from 6% to 44% depending on the frailty assessment tool used (9), with the highest prevalence among those in the oldest adult age range (generally defined as those aged ≥85 years) (10).

Just as in other syndromes like lupus or vasculitis, diagnosis and monitoring rely on a combination of biomarkers and clinical findings. Kidney injury, with all of its difficulties and challenges, in the older population may be better assessed using a combination of both, especially in scenarios in which SCr does not objectively meet the criteria for AKI in this cohort.

Herget-Rosenthal and colleagues (1) found that the product of the Clinical Frailty Scale (CFS), with age in years, was able to discriminate between older adults with AKI and those without AKI, with reasonable levels of sensitivity and specificity. Although the formula is not validated, and thus, we do not recommend its use at this time, if it were to be validated in the future, it could serve as a helpful adjunct to the diagnosis of AKI in older adults, much like how procalcitonin has been found to be a helpful adjunct to the diagnosis of lower respiratory tract infections.

We can also potentially apply Herget-Rosenthal and colleagues' formula of the CFS score of the patient's age in years once their data are presented (1). Future studies can conceivably provide numerical cutoffs, based on this

**Figure. Comprehensive geriatric assessment**




The CGA is a multidimensional, multidisciplinary process that evaluates an older person's health, well-being, and functional abilities to develop a coordinated plan for treatment, rehabilitation, and long-term care.

predictive model, to aid clinicians to fine-tune therapeutic plans for older adults.

## Frailty and the comprehensive geriatric assessment

We agree with Herget-Rosenthal and colleagues' recommendation that attention should be paid to frailty in the older population (1). To identify individuals with frailty, we also agree with the recommendation put forth by a consensus group consisting of delegates from six major international societies that "all persons older than 70 years and all individuals with significant weight loss (>5%) due to chronic disease should be screened for frailty" (11). This recommendation takes into consideration age but also recognizes that frailty can occur in all ages of individuals depending on other factors. We recommend that frailty should be integrated into AKI diagnosis and risk algorithms. In addition, once an individual has been identified with frailty, we recommend that they undergo a CGA (Figure), which is a multidisciplinary and comprehensive diagnostic and treatment process that identifies medical, cognitive, physical/functional, and psychosocial limitations of older adults in order to develop a coordinated plan to optimize healthy aging. CGAs are the gold standard for frailty assessment and can help with developing and implementing treatment plans that can reduce the risk of developing community-acquired AKIs in older adults with frailty. Therapeutic plans such as nutritional optimization to maintain fluid balance, for example, can be implemented.

It can be considered that older adults with frailty and AKI who are hospitalized might benefit from an inpatient geriatric consult for a CGA, much like how many institutions have a protocol for automatic inpatient geriatric consults for older adults who are admitted for trauma. If the situation calls for more urgent clinical decision-making, the CFS can be used as a rapid evaluation tool for clinicians to use.

The evolving understanding of kidney aging and frailty provides us critical insights into the assessment of kidney injury in older individuals and offers valuable prognostic information, such as 30-day mortality, as outlined in Herget-Rosenthal and colleagues' study (1). This approach opens up a path for more individualized and refined treatment strategies for a vulnerable population. ■

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The authors report no conflicts of interest.

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In Memoriam

# Marianne Leenaerts, MHSA, PhD, Cofounder, Primary Aldosteronism Foundation: Celebrating a Legacy of Advocacy, Compassion, and Vision

By Lisa Schwartz

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On April 1, 2025, the world lost a passionate voice for people with primary aldosteronism (PA). Marianne Leenaerts, MHSA, PhD, cofounder and chief executive officer (CEO) of the Primary Aldosteronism Foundation (PAF), was a champion for patients around the world, leaving behind a legacy of compassion, vision, and unwavering commitment to the foundation's mission.

Leenaerts, a Belgium-born individual living with PA and a public health advocate, lived with purpose and drive. Her career spanned global health policy, knowledge management, and academia. From her role with the United Nations to later work as a consultant and with academic and health care institutions, she encountered some of the world's greatest minds. At the age of 50, the completion of her doctoral degree coincided with the life-changing diagnosis of PA.

## A decades-long journey with PA

For more than 2 decades, Leenaerts lived with undiagnosed PA, facing symptoms such as treatment-resistant hypertension and fatigue. Like so many people living with PA, her condition went undiagnosed and untreated because of limited awareness and clinical understanding of the disease. Her eventual diagnosis came after years of self-advocacy and the intense desire to piece together a very challenging puzzle of severe symptoms that progressively took a toll on her quality of life.

In her farewell message to the PAF community, she wrote, "In retrospect, I had unknowingly harbored the disease most of my life" (1). Of all the roles she held throughout her lifetime, it was that of a patient that perhaps had the most impact, shaping her legacy of resilience and compassion and her drive to effect change.

"Marianne's perspective was rare," said Debbie Kelly, cofounder and secretary of PAF. "She understood the clinical, scientific, and policy landscapes as a PhD, yet always centered her work on the patient experience. As both an advocate and a patient herself, she helped build the Primary Aldosteronism Foundation as a bridge between patients, clinicians, researchers, public health leaders, and industry partners. Her compassion, intellectual rigor, and purposeful collaboration continue to shape the foundation's mission to improve standards of care for all [of] those living with primary aldosteronism."

## Understanding PA

PA (also known as Conn's syndrome) occurs when the adrenal glands make too much aldosterone, a steroid hormone that helps regulate sodium and potassium in the blood. It can lead to severe or treatment-resistant hypertension, low potassium levels, and systemic complications including heart disease, kidney dysfunction, and metabolic disorders. Left untreated, PA can result in a heart attack and kidney failure (2).

Many patients go undiagnosed, as symptoms of the condition are not specific to PA and are often treated as separate conditions (3). PA is missed or misdiagnosed 95% of the time, affecting up to 10% of people with high blood pressure (4). The treatment for PA varies and may include mineralocorticoid receptor antagonists or adrenalectomy. Mineralocorticoid receptor antagonists, however, were not specifically developed for PA.

## Founding PAF

After completing her PhD and on the heels of her diagnosis, Leenaerts began her next chapter as cofounder and CEO of PAF in 2019. The foundation became the first and only global nonprofit organization focused on improving awareness and care for PA, promoting clinical research, building a global network of PA experts, advocating for new clinical guidelines, and providing patient support and education.

In her letter (1), Leenaerts pushed for the medical community to prioritize the adoption of positron emission tomography scans, next-generation drugs, and adrenalectomy surgery for eligible patients. She also outlined key priorities for the field:

1) to accelerate the US Food and Drug Administration's approval and adoption of newer and better targeted drugs for patients with PA;
2) to acknowledge the systemic nature of excess aldosterone instead of confining it to an electrolyte imbalance of cardiorenal consequences; and
3) to establish the actual signs, symptoms, and comorbidities of PA.

She wrote, "The cascading collateral damage of hyperaldosteronism remains nearly impossible to conquer unless patients are candidates for and given the option of successful surgery."

Leenaerts also acknowledged the severe physical and emotional toll of the disease, adding, "First, patients with primary aldosteronism lose their personal life. Next, they lose their social and professional life (some fall on disability insurance, others become bankrupt or homeless). Their struggles last for years and even decades over the course of which the very institution tasked with caring for them fails to acknowledge the severity and extent of the deadly disease that debilitates them. Lack of answers and substandard responses alone cause irreparable trauma."

## A legacy continued

Leenaerts led the foundation until, as she wrote in her message, "...lung cancer was added to an already long list of medical mishaps related to excess aldosterone. By then, my body did not have enough resources left to endure the toxic blow of cancer treatments. To preserve my dignity, I opted to bow out with medical assistance."

Yet, even in her final years, she remained committed to the foundation's efforts, participating in global work groups, writing policy statements, and supporting research. Because of her voice and vision, the next generation of clinicians is now better equipped to recognize and treat PA.

Following her passing, PAF's governing board reaffirmed its commitment to advancing the foundation's mission, stating in an email to stakeholders: "In the spirit of her dedication, the remaining [codirectors] remain fully committed to continuing the vital work Marianne began. We are determined to carry forward our mission, guided by the integrity, purpose, and care she brought to her work."

## An inspiring patient advocate

To those who knew her, Leenaerts was a woman of deep kindness and boundless determination. Her passion inspired a global community to come together around a shared purpose. "Marianne was a tireless champion for patients, embodying a rare blend of compassion, conviction, and relentless drive," said Kelly. "Her impact reached far beyond those living with primary aldosteronism. She also deeply influenced the clinicians, researchers, and industry partners committed to improving their care. Through her example, she fostered a powerful sense of shared purpose across the medical community, reminding us all that advancing patient care isn't just possible, it is essential."

To learn more about PAF, its work, and mission, visit https://primaryaldosteronism.org/. To read Leenaerts' farewell message entitled "So Long," visit https://primaryaldosteronism.org/so-long/.

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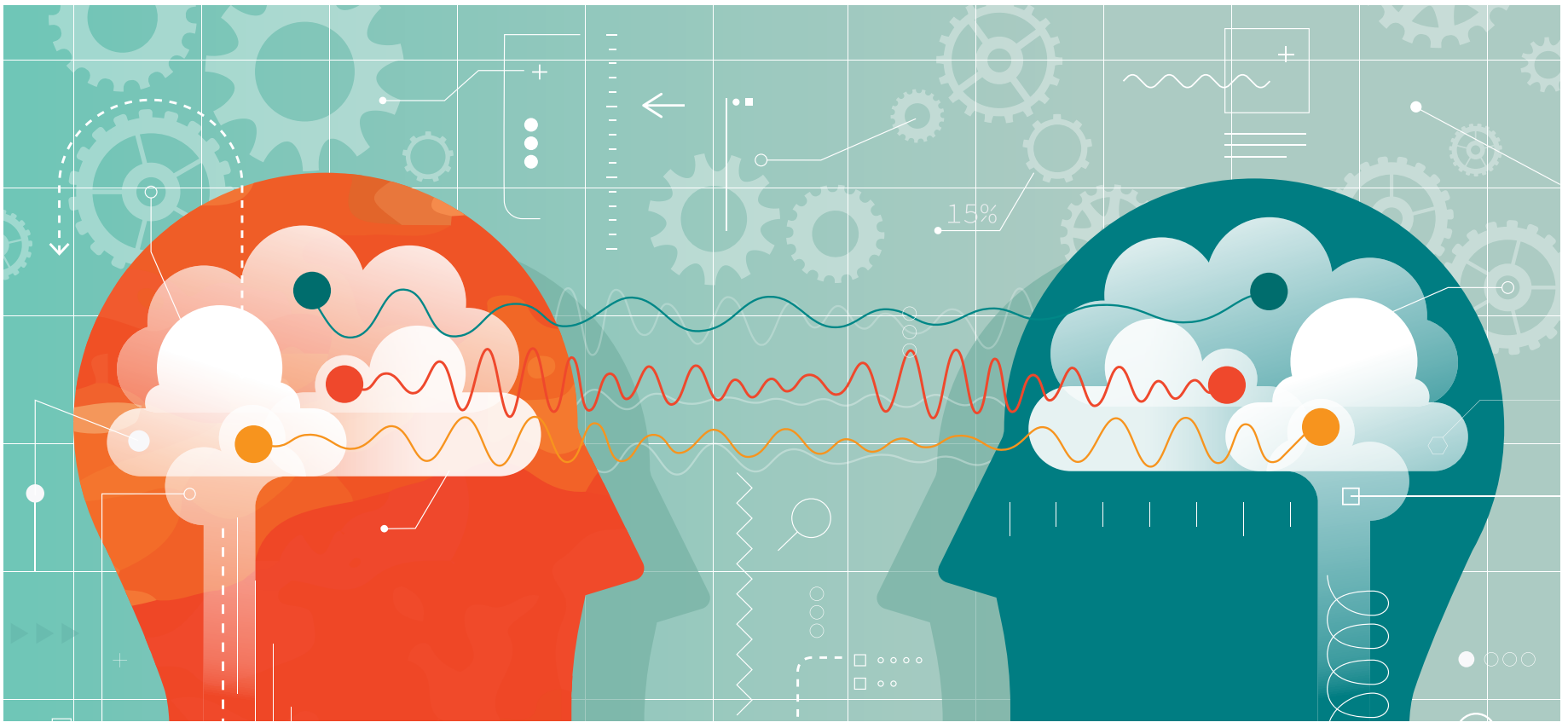

# When AI Speaks Medicine, It Still Misses the Conversation

By Ghassan Bandak and Ankit Sakhuja

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As patients increasingly turn to artificial intelligence (AI) for health information, clinicians are left asking a fundamental question: Can these tools provide answers that are accurate and align with clinical best practices? A recent study published in *JMIR Diabetes* by Ebrahimi and colleagues (1) suggests that the answer for now is *not quite*.

The study explored how well ChatGPT-4 and Google Gemini, two widely available AI tools, answered common patient questions about diabetic nephropathy (DN). The findings point to growing interest in AI's use in patient education (2–4), while also highlighting its current limitations in clinical accuracy and consistency. To simulate real-world patient interactions, the authors first asked AI tools to generate the most common questions that patients might have about DN. From this list, the investigators selected 10 representative questions, ranging from diagnosis and prevention to disease progression and dialysis initiation. Two experienced nephrologists independently answered the questions using a standardized form. Their responses were compared with answers generated by ChatGPT-4 and Google Gemini. An independent academic reviewer, blinded to source identity, scored each response using a five-point scale from "completely inaccurate" to "completely accurate."

## Generally accurate but not in agreement

Across the board, both AI tools and nephrologists received favorable accuracy ratings with no response deemed as "inaccurate" or "irrelevant." Yet, the agreement between AI and human experts told a more complex story. The two nephrologists demonstrated moderate agreement ($\kappa = 0.61$; $p = 0.04$), whereas ChatGPT-4 and Google Gemini showed only weak, statistically insignificant agreement ($\kappa = 0.52$; $p = 0.10$). When compared directly with nephrologists, neither AI model exhibited any agreement. Moreover, ChatGPT-4's consistency between its two runs was also low ($\kappa = -0.08$; $p = 0.80$), suggesting that its answers are subject to change over time, even with the same input.

## AI may inform but cannot yet guide

Despite promising signs that AI can produce largely accurate responses, the study shows that current tools are not yet ready to replace clinical conversations in nephrology. Notably, the accuracy of AI outputs tends to diminish as clinical questions become more specialized. This pattern aligns with prior research demonstrating that although AI models perform well on broad medical knowledge assessments (5), their performance declines on specialized tasks such as nephrology assessments or *International Classification of Diseases* coding (6, 7).

These limitations are particularly consequential in the context of DN, for which decisions about disease progression, timing of interventions such as dialysis initiation, and tailoring of treatment strategies require sophisticated clinical judgment. A chatbot, regardless of its algorithmic prowess, cannot yet replicate that.

## What's next? AI as a partner not a replacement

This study adds to the growing literature that the path forward is not about replacing clinicians with algorithms but about designing AI systems that enhance clinical workflows and keep physicians in the loop (8). In this vision, AI serves as a supportive partner offering information, augmenting decision-making, and improving efficiency, while clinicians continue to exercise judgment, empathy, and oversight.

For now, clinicians should guide patients to treat AI-generated content as a preliminary resource not as a definitive source of medical advice. As these technologies mature, future research must go beyond benchmarking accuracy to explore how AI can be responsibly and meaningfully integrated into the real-world landscape of patient care. ■

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Dr. Bandak reports no conflicts of interest. Dr. Sakhuja reports providing consultancy services to Roche Diagnostics Corporation.

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# Understanding IgA Nephropathy: Insights From a US-Based Retrospective Study

By Zainab Obaidi, Momen Abbasi, and Duvuru Geetha

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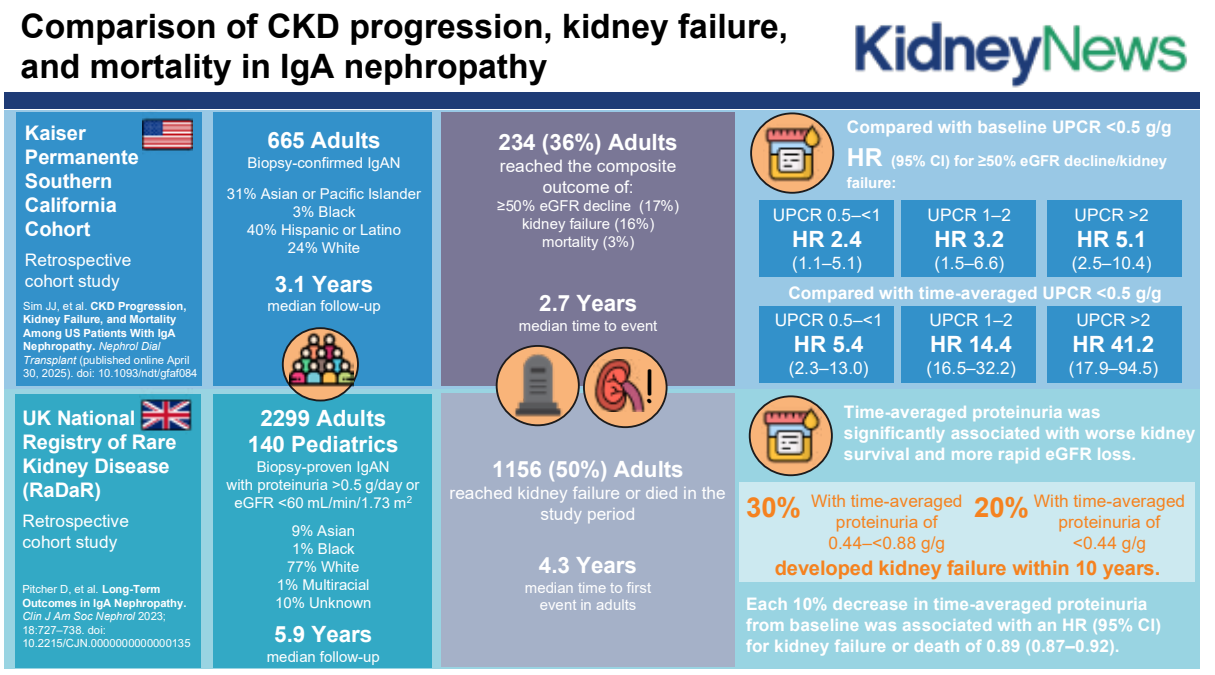


The understanding of immunoglobulin A nephropathy (IgAN) is rapidly evolving, driven by efforts toward earlier diagnosis and intervention. As the leading cause of glomerular disease worldwide and in the United States, with an incidence of 0.4–2.3 per 100,000 annually, identifying factors that predict progression remains a priority (1). Recent research has focused on therapeutic targets, using proteinuria levels and glomerular filtration rate (GFR) decline as surrogate markers. The Kidney Disease: Improving Global Outcomes (KDIGO) guideline is being updated to incorporate emerging evidence, moving beyond the 2021 recommendation of reducing proteinuria below 1 g/g (2). Notably, the National Registry of Rare Kidney Diseases (RaDaR) trial—a UK-based study—highlighted ongoing risks of progression even with proteinuria between 0.4 and 0.8 g/g (3). In this context, we review a recent study by Sim et al., which examines a diverse patient population with IgAN within Kaiser Permanente Southern California (KPSC), focusing on progression timelines to chronic kidney disease, kidney failure, and death (4).

This study analyzed patients with biopsy-confirmed IgAN diagnosed from 2000 to 2022 at KPSC. Inclusion criteria included being 18 years or older with an available urine protein-to-creatinine ratio (UPCR) at diagnosis; missing UPCR at biopsy was estimated using the earliest measurement, with subsequent follow-up values carried forward. The researchers calculated time-weighted UPCR averages until a 50% or more estimated GFR (eGFR) decline. They assessed comorbidities, medication use (angiotensin-converting enzyme inhibitor/angiotensin II receptor [ACEi/ARB], sodium-glucose cotransporter-2 inhibitor [SGLT2i]), and immunosuppressives (prednisone, cyclophosphamide, mycophenolate, and azathioprine). Exclusions included secondary IgA, GFR less than 15 mL/min/1.73 m², dialysis, or prior transplant. The primary outcome was a composite of 50% or more eGFR decline, kidney failure, or death.

The study included 655 adults with a mean age of 45 years, evenly split by sex, and racially diverse: 31% Asian or Pacific Islander, 3% Black, 40% Hispanic or Latino, and 24% White. Approximately 60% used ACEi/ARB, 0.3% SGLT2i, and 40% immunosuppressives within 1 year of biopsy. Hypertension was present in 64% and diabetes in 15%. Baseline UPCR averaged 2.5 g; median UPCR was 1.8 ($p = 0.02$). With a median follow-up of 3.1 years, the median time to an adverse event was 2.7 years.

Overall, 36% reached the composite endpoint: 17% had 50% or more eGFR decline, 16% developed kidney failure, and 3% died. Higher baseline proteinuria correlated with increased incidence rates of the composite outcome (≥50% eGFR decline, kidney failure, and mortality)—136 per 1000 patient-years for UPCR more than 2 g/g versus 29 per 1000 patient-years for UPCR less than 0.5 g/g. Multivariable analysis showed lower GFR, higher UPCR, diabetes, and younger-age increased risk; eGFR less than 15 had the highest hazard ratio (HR): 12.9. Hematuria was noted in 50% of participants within the previous year, persisting over 4 years, but its presence did not significantly alter risk or age at adverse outcomes.

Compared with the RaDaR trial, this study shares similarities: median age (~45 years), baseline GFRs, and chronic kidney disease stage as a key predictor. Both found that higher UPCR (>0.5–1 g/g) and lower GFR increased risk of progression. RaDaR's strength was the inclusion of a GFR slope analysis, suggesting that an annual decline of 3 mL/min/1.73 m² would result in 100% of patients who were diagnosed before age 40 years reaching kidney failure—which was not analyzed in the Sim et al. study (4). This current study confirms that IgAN progresses faster than what was formerly recognized and benefits from more comprehensive UPCR data, as it was available in a greater proportion of patients (23%) than in the RaDaR study and included medications and comorbidities. Limitations include its single-center design, potential confounding by age, survival bias, and absence of data on medication doses or adherence. Despite a shorter median follow-up in this study (3 years versus 10 years), both studies emphasize early intervention, aggressive proteinuria reduction, and GFR preservation. They also underscore the importance of diverse populations and real-world treatment data, especially as newer therapies emerge. ■

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The authors report no conflicts of interest.

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# Algorithms to Action

*Continued from page 10*


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*Case descriptions are for educational purposes only; not real patient cases. There are additional factors to consider determining if Paradise uRDN procedure is right for your patients and may require shared decision making with a team of medical specialists to assess risks and benefits. See Indications below. Refer to the IFU for more information prior to considering the Paradise uRDN treatment.
INDICATION: The Paradise Ultrasound Renal Denervation System (Paradise System)is indicated to reduce blood pressure as an adjunctive treatment in hypertension patients in whom lifestyle modifications and antihypertensive medications do not adequately control blood pressure.



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