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Evidence Grows for High-Quality, Plant-Heavy Diets for Kidney Health, Despite High Protein Push

By Bridget M. Kuehn

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As evidence supporting varied plant-forward diets to protect kidney health grows, experts caution that new US dietary guidelines promoting higher intakes of red meat, full-fat dairy, and protein overall may pose risks to individuals with chronic kidney disease (CKD).

The latest version of the "Dietary Guidelines for Americans, 2025–2030" was released in January 2026 (1). It contains many uncontroversial recommendations, which are widely supported by medical and nutrition organizations, including that Americans should consume more whole foods, including fruits and vegetables, and less salt and added sugars and limit intake of highly processed foods. But it also promotes much higher protein intake—1.2–1.6 g/kg body weight/d—than previous US dietary guidelines have recommended. That protein consumption target is substantially higher than the 0.8 g protein recommended for people with CKD who are not on dialysis in the Kidney Disease: Improving Global Outcomes (KDIGO) guideline (2) and in the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) nutrition guideline (3). The recommendations are also higher than the already high average US daily intake of 1.2–1.4 g/kg/d.

"It's actually dangerous to say that we should be eating more protein, especially at the levels they are recommending," said Holly Mattix-Kramer, MD, MPH, professor of public health sciences and medicine at Loyola University of Chicago, IL. "In persons with [a] reduced nephron number, you really have to worry about people eating excessive amounts of animal protein."

Protein risks

Mattix-Kramer explained that most of the protein that people eat is absorbed as amino acids from the stomach or small intestine, but 5%–10% is processed in the colon,

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Refills to Health Advice: AI's Expanding Role Raises Mixed Reactions Among Nephrologists

By Karen Blum

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Upon hearing about a pilot program in Utah allowing residents to renew their prescriptions through an artificial intelligence (AI) platform—without needing to call their doctors—Lili Chan, MD, MS, said her prevailing thought was: *Really?*

She said she still has the "same amount of skepticism" as her initial reaction. "Their selling point is that AI is going to somehow make it faster and easier for people to get their refills," said Chan, an associate professor of nephrology at the Icahn School of Medicine at Mount Sinai in New York City.

Although Chan acknowledged that her academic center has strong information technology support and the ability for patients to request refills through the patient portal, the Utah program is acting on the premise "that [people] have to wait to get an appointment with their [practitioners] in order to request that refill, which generally is not true," she said. "The only time we wouldn't refill is if we haven't seen the patient in a year, because many things can change over the course of a year." However, Chan noted that there may be a role for this program in resource-limited settings.

Through the yearlong Utah program (1), which started in December 2025, the state's Office of Artificial Intelligence Policy partnered with Doctronic, allowing the company's AI platform to legally prescribe refills for a $4 charge per renewal. Although the company requires physicians to review the first 250 prescriptions in each drug class before going autonomous, it is an issue that has sparked mixed feelings among nephrologists.

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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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Evidence Grows for High-Quality, Plant-Heavy Diets

Continued from cover

leading to the formation of uremic solids that must be excreted by the kidneys (4). These uremic solids may also interact with endothelial cells in the blood vessels, increase inflammation, and accelerate atherosclerosis, contributing to cardiovascular risks.

"Uremic solids accelerate vascular aging processes and can worsen nephron loss in addition to just the overall aging of the body, so eating too much protein is not good for people who have CKD," Mattix-Kramer said. Excess protein intake can also contribute to excess calorie intake, she noted.

Individuals on dialysis are advised to eat higher levels of protein (about 1.2 g/kg/d) to help maintain muscle mass, Mattix-Kramer explained. But protein restriction is recommended for people with CKD to help prevent glomerular hyperfiltration along with its adverse effects on the kidney and its potential to contribute to long-term kidney decline, said Shivam Joshi, MD, a fellow and medical advisory board member at the National Kidney Foundation and adjunct assistant professor at the New York University Grossman School of Medicine in New York City. Animal-based proteins may also exacerbate hyperfiltration, he said. Joshi noted that the average American diet is already considered high in protein.

"To tell a population to eat even more than that is concerning, especially when 90% of people with CKD do not know they have it," Joshi said. "It also creates confusion for those who have CKD and know it as to what to do."

Annabel Biruete, PhD, RD, FASN, a registered dietitian and assistant professor at Purdue University in West Lafayette, IN, noted that overall, the new US dietary guidelines' focus on whole foods, fruits and vegetables, and healthy fats is consistent with the evidence and previous guidelines. But she raised concerns about potential confusion among people living with kidney diseases and others who are trying to use the upside-down pyramid in the new guideline to make dietary choices.

The upside-down pyramid—with red meat and dairy prominently at the top left, vegetables and fruits at the top right, and whole grains seemingly "downgraded" at the very bottom—may be hard to interpret or may have unintended consequences, Biruete noted. Other recent US dietary guidelines have used the MyPlate graphic to more clearly communicate appropriate food proportions, she said. In keeping with past US dietary guidelines, the latest version recommends keeping saturated fat intake below 10% of total calories. However, prioritizing red meat and dairy based on the pyramid image could cause individuals to quickly exceed that limit, Biruete noted.

"We know that a diet doesn't have to be vegan in order to be a healthy diet, but we usually try to recommend not overconsuming a lot of animal-based products because of several things, particularly saturated fats," she explained. She noted that the guidelines do mention plant-based proteins and the importance of gut heath; however, the imagery focuses on animal sources.

High protein push

Extremely high protein intake, such as that popular among bodybuilders in the 1990s, involving protein and creatine supplements, can overwhelm the body's ability to clear protein, leading to kidney damage even among people without kidney disease, Mattix-Kramer noted.

Yet, in recent years, high protein diets have regained popularity as a tool for weight loss or to manage diabetes despite the potential to cause new or worsening kidney disease, according to an analysis by Joshi and colleagues (5). He noted that this is driven in part by a misunderstanding of the role of carbohydrates in diabetes and obesity, which has led to the promotion of a string of low carbohydrate diets.

The latest push for higher protein consumption may also reflect both political and commercial considerations, Joshi noted. He explained that food industry and restaurant stakeholders' interests, as well as the economic benefits of America's high food consumption, particularly of highly processed foods, may be barriers to more evidence-based national dietary recommendations. "It is a good political answer for America's health problems, but it is not actually the correct scientific answer," he said. "It would be economically unpalatable and politically unpalatable to tell people, 'You need to eat fruits and vegetables three times a day, emphasize fiber, et cetera.'"

Biruete noted that the latest guideline was based on a rapid evidence review focused on weight-management studies, which often exclude people with kidney diseases. Concerns about transparency in the development of the new dietary guidelines were raised by the American Society for Nutrition (6). The group, however, supported the new US dietary guidelines' focus on minimally processed, nutrient-dense foods and on limiting added sugar, salt, and saturated fat intake. "[The American Society for Nutrition] supports nutrition guidance that is grounded in science, clearly explains how the evidence was reviewed, and helps people make informed decisions about their health," according to the statement. It also emphasizes the need for guidelines that all US residents can use and policies that make healthy eating easier and more affordable.

Plant-based benefits

Meanwhile, a growing body of evidence supports the benefits of a diet rich in plant-based foods for kidney health. A recent study that assessed dietary intake of 179,508 participants without kidney diseases in the UK Biobank found that those who more closely followed the EAT-Lancet diet, which emphasizes more ecofriendly, lower animal product plant-based diets, were less likely to develop CKD (7). The strength of these kidney-protective benefits increased with how closely participants followed the diet, based on the researcher's assessment of the individual's metabolic and proteomic signatures.

Similarly, a recent review by Biruete and colleagues (8) found growing evidence supporting a shift toward high-quality, varied plant-rich diets to prevent kidney diseases and to support people living with CKD. Biruete noted that in the past, kidney diets have often focused on restricting sodium, potassium, phosphorus, and protein but have overlooked the overall quality of the diet.

"Focusing on the quality of the foods that we're consuming is important," she said. She emphasized the importance of eating a variety of fruits and vegetables, as well as a mix of protein sources and whole grains. Overall, the review focuses on minimally processed foods, but she noted that some processed foods, including fortified grain products, may have a place in a healthy kidney diet. Moderating portion sizes of foods that may be high in added sugars, potassium, or phosphorus may also help. The review also highlights the importance of considering culture and the way foods are prepared. "It's about balance," Biruete said.

Joshi recommends that patients eat lots of fiber-rich foods, such as fruits, vegetables, whole grains, nuts, seeds, and legumes. He also recommends avoiding processed foods, animal proteins, salt, desserts, and sugary beverages. He notes that plant-based diets, emphasizing plant-based proteins, may have beneficial effects on chronic conditions like hypertension, diabetes, or obesity. They also have direct benefits for kidney health. "[Plant-based] foods tend to be more alkaline than acidic, which is favorable because, as kidney function declines, there's an impairment in the kidney's ability to excrete acid," he explained. "These foods have been shown to have less absorbable phosphorus, which is a problem as kidney function becomes less and less, and there may be an effect directly on the kidney."

Joshi noted that there is some debate about whether newer kidney function-preserving medications, like glucagon-like peptide-1 agonists or sodium-glucose cotransporter-2 inhibitors, may help offset some of the risks of high protein diets, but he said that more research is needed. Biruete explained that such medications may affect what and how much people eat, and in some cases, higher protein diets may be recommended. But she noted that there are currently no evidence-based recommendations on the topic.

Mattix-Kramer noted that newer potassium binders, such as Lokelma (AstraZeneca) and patiromer, have been "a godsend" for helping patients manage potassium spikes.

Biruete also said that the US dietary guidelines are not intended as a guideline for chronic diseases but that the guidelines from KDOQI, KDIGO, and the Academy of Nutrition and Dietetics do offer kidney and chronic disease-focused dietary advice. "People who have kidney disease should ignore that [the high protein intake recommendation from the US dietary guidelines] and follow the KDOQI nutrition guidelines, and talk with your doctor," Mattix-Kramer said.

Mattix-Kramer advised that nephrologists should focus on helping patients adopt healthier diets through gradual changes and healthier substitutions, including eating more fruits and vegetables. Both she and Biruete also emphasized the benefits of advice from a renal dietitian, who would likely be up to date on more liberalized dietary recommendations. Mattix-Kramer noted that both Medicare and private insurance companies cover medical nutrition therapy without cost sharing and that studies have shown that this therapy can slow progression from CKD to dialysis, yet only about 10% of patients receive such care (9).

"Every patient with kidney disease would probably benefit from seeing a specialist in kidney nutrition," Biruete said. However, given the limited number of kidney dietitians, focusing on a healthy diet is the most important thing for people with stages 2 or 3A CKD, she said. "Those with stages 3B and higher would benefit most from seeing a renal dietitian." ■

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Pow, Pop, Wham, Bam! NephMadness Is Back

By Matthew Sparks

https://doi.org/10.62716/kn.003112026

NephMadness bursts back onto the scene! BAM! Ready to educate, energize, and electrify the nephrology world! Now in its 14th year, NephMadness 2026 unleashes a striking lineup of teams across eight dynamic regions (Figure).

In the Immunoglobulin A (IgA) Nephropathy region, we feature New B-Cell Targets versus Complement Inhibition, highlighting emerging immunologic strategies shaping the future of glomerular disease treatment. The Complement 3 Glomerulopathy (C3G) region presents C3G Diagnosis versus C3G Treatment, offering a focused look at advances in complement-mediated disease detection and therapeutic innovation. The Cerebronephrology region explores Cerebronephrology in Chronic Kidney Disease (CKD) versus Cerebronephrology in End-Stage Kidney Disease (ESKD), examining how kidney diseases influence neurologic function across the disease spectrum. In the Trolls of Transplantation region, BK Virus (BKV) versus Cytomegalovirus (CMV) underscores two persistent viral adversaries that continue to challenge transplant outcomes. Animal House returns this year with Dogs versus Cats, using comparative physiology to shed light on kidney function across our closest companions. Team Artificial Intelligence discusses Natural Language Processing versus Computational Pathology, demonstrating how machine-learning tools are beginning to transform both clinical data interpretation and tissue diagnostics. Team Point-of-Care Ultrasound (POCUS) highlights POCUS in Acute Kidney Injury (AKI) versus POCUS in ESKD, emphasizing the expanding role of POCUS across acute and CKD settings. Finally, Team Genetics examines Polycystic Kidney Disease (PKD) Masqueraders versus Fabry Treatment, focusing on the diagnostic nuances of genetic kidney diseases and emerging therapeutic approaches. Together, these regions and teams offer a dynamic and forward-looking slate of topics designed to spark thoughtful dialogue and enrich nephrology practice.

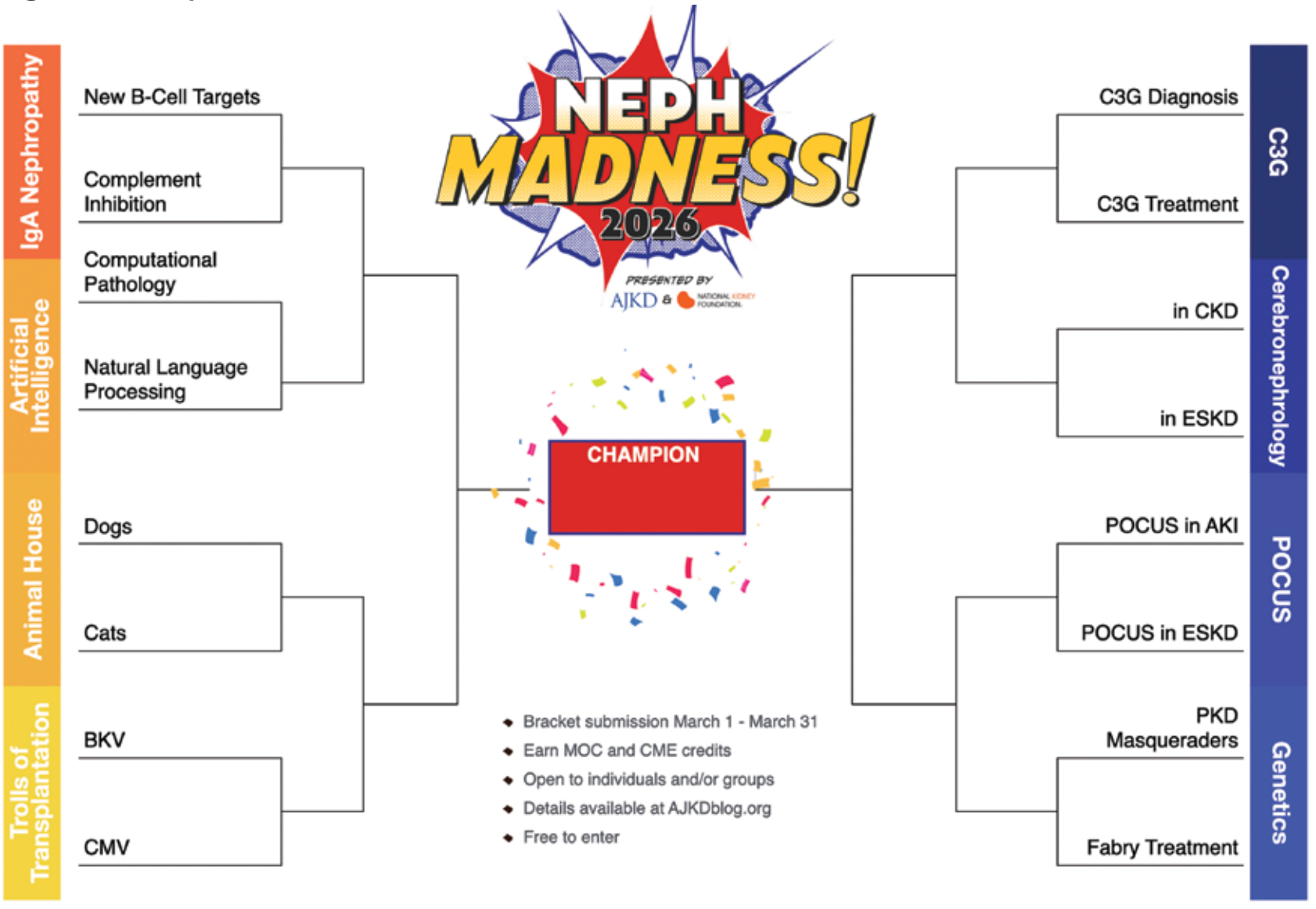
NephMadness is a single-elimination tournament consisting of 16 nephrology concepts divided into 8 distinct regions. The purpose of the tournament is to learn, discuss, and debate each topic, with a little friendly competition! We encourage you and your group to throw a NephMadness party, and we made it easy with a PowerPoint presentation describing each of the concepts. You can engage with the online nephrology community on social media using the hashtag #NephMadness on X, Instagram, or Bluesky. NephMadness will also feature podcasts covering each of the regions in what is called a PodCrawl, featuring podcasts by The Nephron Segment, Freely Filtered, GN in Ten, and the NKF Kidney Commute Podcast.

Do you have what it takes to match the Blue Ribbon Panel? Head to https://ajkdblog.org/ to find more information and enter your bracket.

Matthew Sparks, MD, FASN, is an associate professor of medicine at Duke University, Durham, NC. He is a cocreator of NephMadness and serves on the NephMadness 2026 Executive Team.

The author reports no conflicts of interest.

Figure. 2026 NephMadness tournament bracket



CME, Continuing Medical Education; MOC, Maintenance of Certification.

Refills to Health Advice

Continued from cover

Many of the 192 medications eligible for refills in the program include those commonly prescribed for people with kidney diseases, such as diuretics, anticoagulants, heart failure agents, and sodium-glucose cotransporter-2 inhibitors, said Wisit Cheungpasitporn, MD, FASN, a nephrologist with the Mayo Clinic in Rochester, MN.

"These are not medications I would feel comfortable refilling without some form of patient check-in or lab monitoring," Cheungpasitporn said. "For these drugs, blood pressure, volume status, kidney function, electrolytes, and bleeding risk are part of routine safe care, not optional extras." Refill automation may make sense for specific low-risk medications, he added.

Nirupama Ramkumar, MD, MPH, FASN, an associate professor of nephrology and hypertension at the University of Utah in Salt Lake City, said none of her or her colleagues' patients have tried the pilot yet, but she does have some concerns.

One concern is for people with kidney diseases who take blood pressure medications. "If we're monitoring their blood pressure, we see them in clinic, we can make adjustments," Ramkumar said. If blood pressure is high, patients may need additional pills; if their kidney function is worsening, some medications may need to be discontinued or adjusted. The other concern is for patients who may have a medication allergy or side effects to a medication for which the AI program orders a refill. "There's really no way of monitoring things."

But Navdeep Tangri, MD, PhD, professor of medicine at the University of Manitoba in Canada, said he is in favor of the idea. "There are holes in the current refill system," Tangri said. "It's a pretty manual process, and a patient could miss their refills and end up in real trouble, particularly patients who are on diuretics or blood pressure pills."

The refill program, while AI-based, "is not medical decision-making," he added, but instead an administrative, agentic-type function. "This is not a rocket science thing, and you could put safeguards around which medications you're going to refill and which ones you're not…. We should just compare the performance of the AI for this very simple task to what a human would do—and if it's just as good as a human, then I think it's okay."

ChatGPT and others launch health platforms

The medication refill pilot is one of several recent developments in the medical AI realm. In January, OpenAI launched its new platform ChatGPT Health, through which users can ask health and wellness questions or upload and connect health data such as medical records or information from wellness apps. Another large language model (LLM) company, Anthropic, released Claude for Healthcare, with tools for health care professionals to conduct tasks such as prior authorization, care coordination, and claims appeals. Additionally, medical centers including Stanford Health Care and Penn Medicine have created their own versions of ChatGPT to query their electronic health records (2).

Chan said she has not yet seen her patients using ChatGPT Health, but plenty of patients use LLMs like ChatGPT to interpret lab results, get information on a new diagnosis, or explain symptoms. "I do think [ChatGPT Health] is targeting people who would want to use it, people who are already using wearable technology," she said. "There's still the concern of what advice is really coming out of these [LLMs] and how accurate they are—are they giving people bad or wrong advice?"

People could end up getting wrong information or information that is not specific to their situation, "which could lead to a lot of problems and also a lot of mistrust with the doctors." Still, Chan said, "We do have to have an open mind to having these discussions with people of the limitations of these LLMs, and how they can be wrong."

As a pediatric nephrologist, Abiodun Omoloja, MD, chief medical informatics officer at Dayton Children's Hospital, OH, said most of the patient parents he interacts with now are millennials or part of Generation Z. "It's standard practice for me now to say, 'What did ChatGPT tell you?' I'll be remiss if I don't," Omoloja said during a February webinar on the integration of AI in health care, hosted by the Ohio chapter of the Healthcare Information and Management Systems Society. "I make an assumption that they've already done that before they're walking in…. Meeting that expectation helps, hopefully over time, build trust."

If Omoloja does not agree with suggestions that ChatGPT has provided to the patient family, he makes sure to explain why. "We teach residents these days, especially for cases that are a little bit difficult to solve or [are] taking time, that you have to factor in where the patient is coming from. They're basically consumers."

On the positive side, Tangri said, using platforms like ChatGPT Health could empower patients. He has worked with patients who have used the general ChatGPT or similar models for health information. "I don't discourage people from doing it," Tangri said. For example, if he diagnoses a patient with a rare condition, he is in favor of a person using ChatGPT for more information about the disease. "It's better than looking it up on [search engines] and then going to some completely random page, because it's usually a synthesis of all the information, with more verified sources near the top.

"Activated, informed patients are good for themselves, because they're more likely to follow treatment and do better, but they're also better for doctors," he continued. "While we should continue to do our best to educate and inform our patients about kidney disease[s] and their specific medical condition, we should also use these tools to allow patients to learn more."

To aid in supporting patient care and educating the nephrology workforce on AI, ASN's Partnership for Responsible Augmented Intelligence in Kidney Health (3)—of which Drs. Chan, Cheungpasitporn, and Tangri serve on the steering committee—is hosting two events this spring: a hands-on primer workshop at the New York Academy of Medicine in New York City this month and a conference at the University of California, San Diego, School of Medicine in April.

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STAND for Kidney Health: ASN's Policy Priorities for 2026

By Ryan Murray

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ASN enters 2026 with a refreshed, focused policy agenda designed to move kidney health upstream, strengthen the care continuum, and ensure that scientific discovery translates into better outcomes for people living with kidney diseases. Branded as STAND for Kidney Health, this framework organizes ASN's priorities around five pillars: Start Earlier, Transform Transplant, Accelerate Innovation, Nurture the Workforce, and Deliver Value. Together, these goals reflect ASN's long-standing principles while responding to emerging challenges across care delivery, research, and the health workforce.

Start earlier for kidney health

ASN's first priority is simple but transformative: Identify and treat kidney diseases sooner. Too many individuals still learn that they have kidney disease late in the course of illness, when options are limited and costs are high. In 2026, ASN will continue to advocate for screening people the most at risk and for policies that embed kidney health in upstream chronic care models. This focus includes close collaboration with partners across the kidney community, such as The Coalition for Kidney Health (C4KH) (1), to align messaging, share data, and advance prevention-oriented strategies.

ASN will also explore opportunities to lead "Saving Kidneys, Hearts, and Lives" (2) policy efforts in profession-sanctioned arenas and monitor new chronic care models that include people with or at risk for kidney diseases. By shifting attention earlier in the disease course, ASN aims to improve outcomes and reduce the downstream human and financial costs of kidney failure.

Transform transplant for kidney health

Transplant remains the optimal therapy for many people with kidney failure, yet access is uneven, and the system faces growing pressure. ASN's 2026 agenda focuses on maximizing access to transplantation for every American who would benefit, with special attention to transparency, equity, and efficiency.

ASN will continue to champion reforms that make the transplant system more understandable to patients and care teams, to influence the Organ Procurement and Transplantation Network Modernization Initiative and the Increasing Organ Transplant Access value-based care model, and to address persistent challenges in the kidney allocation system, including the rising discard rate and the growing number of out-of-sequence offers. Legislative priorities include enacting stronger supports for living donors, fighting for robust appropriations to modernize US transplant infrastructure, and fully funding the Living Organ Donation Reimbursement Program.

Looking ahead, ASN will also articulate a xenotransplantation policy agenda, recognizing the potential of this rapidly evolving field. These efforts build on ASN's past transplant advocacy while positioning the community for the next generation of solutions.

Accelerate innovation for kidney health

Innovation is central to ASN's mission, and 2026 will be a pivotal year for advancing kidney research and translating discoveries into care. ASN will lead community efforts to implement the *Transforming Kidney Health Research* report's recommendations (3), including the call for $1.8 billion annually from the federal government to develop scalable therapies and innovations.

ASN will also support robust appropriations for kidney research across federal agencies and highlight the integral role of the Kidney Innovation Accelerator (KidneyX) (4) in the government's approach to kidney care innovation. Incentivizing innovators to meet patient needs, accelerate novel approaches, and adopt existing but underutilized therapies and care models is an important part of this strategy.

Regulatory pathways matter as much as funding. ASN plans to collaborate with the kidney community to improve routes for bringing new therapies to market and to evaluate the policy landscape related to artificial intelligence and its implications for kidney health. The goal is not only more innovation but faster, fairer, and more effective translation to patients.

Nurture the workforce for kidney health

A strong nephrology workforce is essential to delivering high-quality care. ASN's 2026 priorities recognize the mounting pressures on nephrologists and the broader teams of health professionals. ASN will prioritize increasing compensation for nephrologists and will produce—with the American Nephrology Nurses Association, the National Kidney Foundation, and the Renal Physicians Association—a report by spring 2027 on recommendations to strengthen the US dialysis care team. ASN will also support the American Society of Pediatric Nephrology in addressing challenges unique to the pediatric nephrology workforce shortage.

Beyond the kidney community, ASN plans to collaborate with the broader medical and scientific community on the impact of visa restrictions and immigration policy on nephrology training and staffing. These issues affect not only recruitment but also the diversity and resilience of the nephrology workforce.

Deliver value for kidney health

The final priority connects policy to real-world performance: better outcomes, smarter spending, and a system that works for patients and clinicians. ASN will champion the creation of an Officer of Kidney Health and Transplantation within the Department of Health and Human Services.

ASN will also work to improve kidney health programs across the federal government by reimagining the payment "bundle" for the Medicare End-Stage Renal Disease Prospective Payment System; advocating for access to innovation, data, and high-quality care in Medicare Advantage; and engaging leadership at the Veterans Health Administration to strengthen kidney care for America's veterans. ASN will also address persistent data challenges by pushing for affordable, timely access to data for researchers and policymakers, improved electronic health record interoperability, and the capture of relevant demographic data via the Centers for Medicare & Medicaid Services Form 2728.

Finally, ASN will ensure that quality parameters are appropriate and measured longitudinally for all Americans living with kidney diseases—regardless of payor—so that value is defined by sustained health and equity, not by short-term metrics.

An agenda to move kidney care forward

Taken together, the priorities included in ASN's 2026 STAND for Kidney Health reflect a comprehensive strategy: Prevent disease where possible, fix what's broken, invest in the future, support the people who deliver care, and make the system work better for people living with kidney diseases. From upstream screening to transplant reform and from $1.8 billion in annual research investment to workforce stabilization and more efficient federal programs, the agenda is necessary, ambitious, and overdue.

For ASN members, these priorities provide a roadmap for patient care, research, education, and advocacy in the year ahead. For policymakers and partners, they offer clear, evidence-based actions to improve kidney health nationwide. And for patients and their families, STAND for Kidney Health signals a commitment to earlier care, better access, and more hope. In 2026, ASN is not just standing for kidney health, it is moving forward. ■

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Beyond Survival: 10 Strategic Tips for Building a Sustainable Nephrology Career During Fellowship

By Harsha Adnani

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Halfway through my second year of nephrology fellowship, I am learning that training is more than preparing for board exams. It is where I am forming the habits and patterns that will shape the nephrologist I become. Our specialty faces workforce concerns. A 2020 national survey found that about 30% of nephrology fellows report burnout driven by work-life balance and disruptive work environments (1), and recent ASN data confirm that lifestyle factors, work-life balance, and compensation weigh heavily on career decisions (2). As I move through fellowship, I am trying to build a path that feels sustainable. The following are 10 lessons I am learning as I go.

❶ Define your professional identity early; then test it.

You do not need a final answer, but you do need a working hypothesis. I started fellowship thinking that I had to know exactly what kind of nephrologist I wanted to become. What I am learning instead is that exploration is the work. I currently find dialysis and general nephrology rewarding, and I am pursuing the GlomCon Virtual Fellowship in Glomerular Diseases to deepen my understanding of complex glomerular diseases (3). My interests continue to evolve, and I have made progress by using rotations, clinic choices, and small projects to test them rather than relying on guesswork.

❷ Build a mentorship portfolio, not a single mentor.

In my first few months, I assumed mentorship would develop naturally. When it did not, I started reaching out deliberately and building those relationships myself. I now have a small group of mentors that include a clinical role model, someone willing to discuss contracts and call structure, and those who demonstrate sustainable practice style. Mentorship contributes to career development, and I am seeing that play out (4). Some of my mentors came from conferences, and others came from online groups. Scheduling short, structured meetings to follow up has made these relationships more effective.

The habits and relationships that I am building now feel like the early framework for my future career.

❸ Use second-year flexibility like a limited resource.

Second year feels more open, but the time moves fast. I am serving as chief fellow, so I am learning about operations and quality improvement. I am trying to use the flexibility to gain skills that match my future goals. This includes more outpatient exposure and leadership experience. For trainees with less flexibility, focused projects still help shape training. Writing a simple plan with a few priorities has kept me intentional.

❹ Build sustainable clinical systems early.

I am still learning how to work efficiently. Relying on systems has helped me more than pushing harder. Consistent note templates, a structured consult script, and clearer decisions about what needs attention today have reduced cognitive load. These systems are imperfect, but building them now feels essential before responsibility increases.

❺ Make the dialysis unit your longitudinal classroom.

Initially, I did not appreciate dialysis rotations, but over time, I realized how invaluable they are in teaching the essence of nephrology, transforming it into longitudinal care. I am using this space to sharpen volume assessment, dry-weight reasoning, vascular-access management, and early recognition of complications. I am also learning the operational realities, like transportation barriers and missed treatments, that shape patient outcomes.

❻ Network with intent, and follow through.

Networking initially felt uncomfortable, but it became more natural when I became involved in projects that truly mattered to me. Cohosting a cardiorenal podcast and participating in virtual trainee groups like NephSIM connected me to people through shared work and learning (5). In nephrology's close-knit community, these shared interests create connections. Introducing myself and following up within 48 hours have turned brief conversations into real relationships.

❼ Communicate complexity with clarity.

Clarity is a clinical skill that I am actively developing. When I present cases, I try to start with the question that needs answering. When I teach, I focus on reasoning rather than memorizing data. Doing this with students has helped me improve the way I inform patients.

❽ Learn the business before it shapes you.

I underestimated how important business topics would be. I have been asking attendings about compensation models, call schedules, dialysis responsibilities, and support staff. The 2025 ASN fellow survey shows that lifestyle factors and compensation significantly influence trainee decisions (2). Programs like Nephrology Business Leadership University gave me a clearer understanding of practice economics and contract basics (6). Receiving its social media award showed me how digital presence and professional networking complement business acumen in today's career landscape. This exposure has changed how I view job opportunities and how I plan my next steps.

❾ Protect your nonclinical identity on purpose.

I am still learning how to create structure outside of work. Free time does not magically appear; it requires effort. Scheduling exercise, family time, and hobbies has helped me feel more balanced. Research has linked burnout to patient safety issues and lower-quality care (7). Protecting my time outside the hospital has become a priority rather than an afterthought.

❿ Process the emotional weight of nephrology.

Nephrology involves chronic illness, moral distress, and frequent end-of-life decisions. Moral distress is common among fellows (8). I have felt it myself. Talking with cofellows, taking a few minutes to debrief after difficult cases, and being honest about the impact on my well-being have helped me stay grounded. Processing these experiences is part of staying compassionate without losing balance.

I am sharing these lessons as someone who is still in training and still learning. The habits and relationships that I am building now feel like the early framework for my future career. With purposeful planning, supportive mentorship, and attention to both clinical and personal growth, I believe trainees can build careers in nephrology that stay fulfilling over time. ■

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Reeling in the Years: Fish Oil Lowers Cardiovascular Risk in Hemodialysis

By Chrystel Pawly and Daniel Edmonston

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Despite substantial progress in lowering cardiovascular risk among individuals with nondialysis chronic kidney disease (CKD), many therapies that improve cardiovascular outcomes in this population have either not translated cleanly to maintenance dialysis (e.g., statins) or have not been evaluated in dedicated cardiovascular outcomes trials in dialysis, as is the case for most of the current guideline-directed medical therapies in nondialysis CKD (1, 2). Against this backdrop, the Protection Against Incidences of Serious Cardiovascular Events Study With Daily Fish Oil Supplementation (PISCES) trial is uniquely consequential.

Recently published in *The New England Journal of Medicine*, PISCES evaluated whether omega-3 polyunsaturated fatty acids reduced serious cardiovascular events in individuals receiving maintenance hemodialysis compared with placebo (3). The mechanistic rationale is compelling: Dialysis is associated with markedly reduced circulating eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) levels, and individuals with kidney failure face an extreme burden of inflammation, thrombosis, arrhythmia, and sudden cardiac death (4). Omega-3 fatty acids target these pathways through putative anti-inflammatory, antithrombotic, plaque-stabilizing, and anti-arrhythmic effects.

In this multicenter, randomized double-blind trial, 1228 patients undergoing hemodialysis were assigned to omega-3 fatty acids supplementation or placebo and were followed up for 3.5 years. The primary outcome was the rate of serious cardiovascular events, analyzed using a recurrent-event framework to capture the cumulative burden of disease. Patients receiving fish oil experienced a striking reduction in events compared with those in the placebo group: 0.31 versus 0.61 events per 1000 patient-days, corresponding to a 43% lower risk of serious cardiovascular events (hazard ratio, 0.57; 95% confidence interval, 0.47–0.70). The benefits of fish oil were consistent across individual components of the composite endpoint and sensitivity analyses; emerged early during follow-up; and were not accompanied by safety concerns, including serious bleeding events.

The implications are notable. First, although confirmatory trials are warranted, the barrier to clinical adoption is rather low. Fish oil is familiar, generally well-tolerated, does not require changes to the dialysis prescription, and falls outside of the Medicare dialysis reimbursement bundles. Understanding the predominant mechanisms of benefit (e.g., anti-arrhythmic effects, vascular protection, or decreased inflammation) would strengthen confidence in implementation and uptake and help target patients most likely to benefit. PISCES also raises an important question of timing: Should omega-3 therapy be initiated earlier in the course of CKD to prevent avoidable cardiovascular risk? Dedicated trials in advanced, nondialysis CKD are now needed.

Finally, the intervention used in PISCES should not be conflated with over-the-counter fish oil supplements. Prescription-grade omega-3 formulations deliver standardized, high-dose EPA and DHA with consistent bioavailability, whereas many over-the-counter products vary widely in purity, potency, and composition (e.g., the EPA to DHA ratio).

Perhaps the most important takeaway from PISCES is that cardiovascular outcomes trials in dialysis can succeed and that we should continue to cast a wider net. ■

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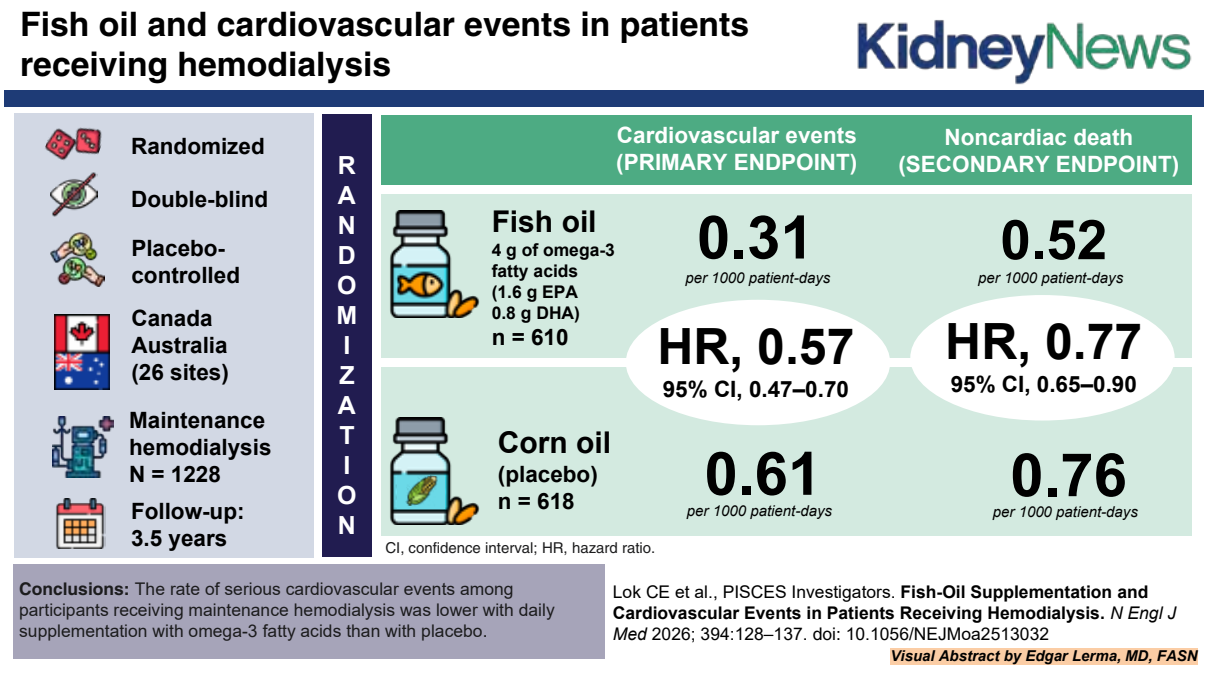

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ADVANCES IN DIALYSIS

Technology, Artificial Intelligence, and the Future of Kidney Replacement Therapy

By Wisit Cheungpasitporn and Suman Behera

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Dialysis is undergoing a period of accelerated transformation driven by technological innovation, artificial intelligence (AI), digital intelligence, and a renewed focus on patient-centered care. Advances in machine automation, remote monitoring, AI-enabled decision support, and novel kidney replacement platforms are no longer incremental improvements. They represent a fundamental shift in how dialysis is designed, delivered, and continuously optimized across in-center, home, and hybrid settings.

This "Advances in Dialysis" special section explores emerging concepts that span AI-guided fluid and anemia management, innovations in home and virtual dialysis, digitally enabled hemodiafiltration, incremental and hybrid strategies, and next-generation artificial and bioengineered kidney systems. Together, these contributions emphasize the growing influence of AI-driven and intelligent systems in moving dialysis beyond static protocols toward adaptive, data-informed, and personalized kidney replacement therapy.

As the dialysis ecosystem evolves, advancements in AI, alongside enabling digital and biomedical technologies, will be essential to improving clinical outcomes; enhancing patient autonomy and safety; and supporting scalable, high-quality care delivery. This collection provides clinicians, researchers, and policymakers with a forward-looking perspective on the future of dialysis and underscores the importance of continued innovation, particularly in AI-enabled dialysis care, in shaping the evolution of kidney replacement therapy. ■

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Advances in Portable, Wearable, and Implantable Artificial Kidneys

By Fokko P. Wieringa

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The number of people needing lifesaving kidney replacement therapy (KRT) worldwide is predicted to become 14.5 million in 2030, of whom (if nothing changes) approximately two-thirds will die without access to KRT (largely due to economic, social, infrastructural, ecologic, and political factors) (1). Current routine KRTs include transplantation, peritoneal dialysis (PD), and hemodialysis (HD). Xenotransplantation is rapidly making progress, but a trade-off is that it puts more strain on immune suppression. Besides that, not all patients are medically eligible for transplantation. Technology-based KRTs will thus remain important, but their present forms (PD and HD) are costly and highly dependent on infrastructure, which hampers universal KRT access. Since the 1980s, the technologic KRT field has been facing an increasing "innovation paradox," with little truly fundamental improvements reaching patients (2). American and European organizations for people with kidney diseases want to disrupt this innovation paradox (3). As patients receiving KRT highly desire mobility (4), we might learn from the "African mobile phone revolution," which utilized a leap-frog effect that beat infrastructural limitations, lowered costs, and increased access (5). KRT innovation faces similar challenges, namely bypassing infrastructural limitations (attracting enough investors) while increasing accessibility and affordability for users. In both cases—for miniaturizing phones as well as for miniaturizing KRT devices—chip technology forms an enabler (5, 6).

This article briefly lists several ongoing efforts to realize technology-based milestones of the Kidney Health Initiative roadmap for KRT innovations (7). It is based on several previously published overviews (3, 5, 6, 8–10), which readers are encouraged to explore for more detail.

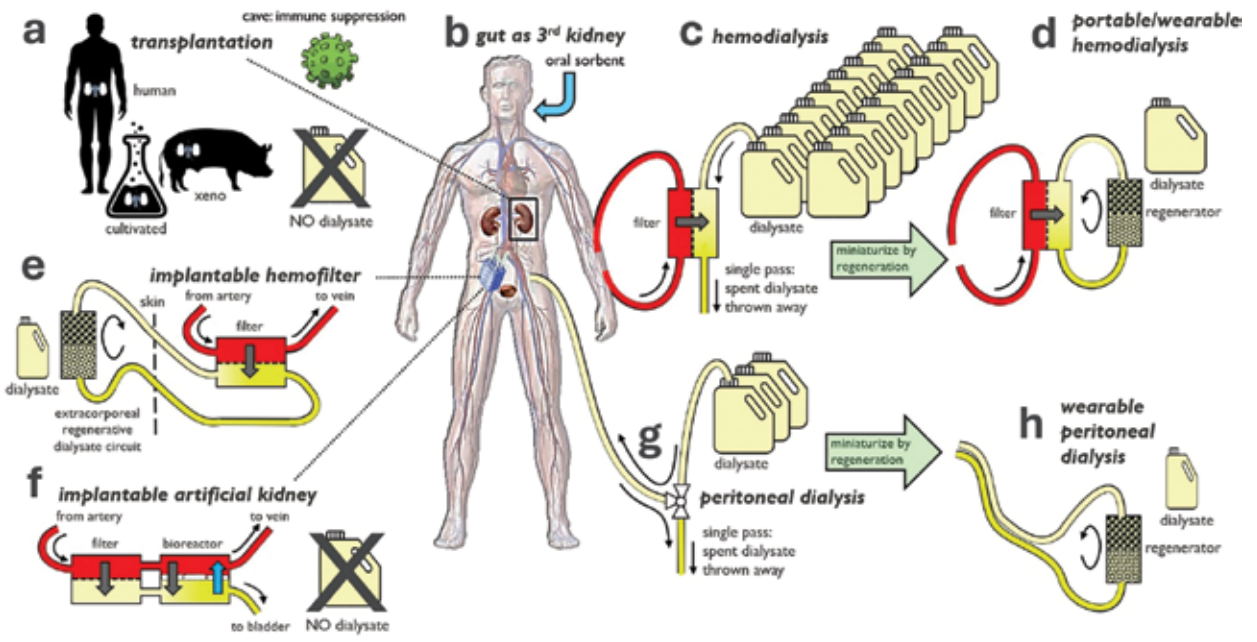
The Figure graphically summarizes the main KRTs that are currently available, together with various ongoing innovative KRT approaches to elevate patient mobility and autonomy. Existing products, products nearing the market, and promising projects in earlier stages include the following:

- **a** Transplantation of human kidneys is the present "first choice" therapy, but there is a structural shortage of donor kidneys, for which xenotransplantation or lab-cultivated kidneys may become solutions. Amazing progress is ongoing in xenotransplantation of organs grown in genetically modified pigs. However, not all patients are suited for a transplant, and, to prevent rejection, patients must be treated with immune-suppressive drugs that increase risks of cancer and infections.
- **b** In addition to traditional phosphorus binders, now also, novel oral sorbents to lower urea and potassium are available (5).
- **c** HD (in a single-pass embodiment) is the most widely applied form of KRT, but it is costly and not very mobile.
- **d** HD with an extracorporeal blood circuit using dialysate regeneration in a closed loop can significantly improve mobility. The firm Nextkidney (the Netherlands) has a product that uses such a concept in multicenter human clinical trials to obtain CE (European Conformity) marking.
- **e** Implanting the HD filter would eliminate the need for an extracorporeal blood circuit. Only an extracorporeal dialysate circuit would then be needed to perform HD. Chip technology is a promising enabler to miniaturize the nanoporous filters needed for such devices. Such concepts are pursued by The Kidney Project at the University of California San Francisco; the firm Nephrodite in Atlanta, GA; and the Artificial Kidney Innovation Lab of the University Medical Center Utrecht, the Netherlands.
- **f** Adding a bioreactor to the implantable hemofiltration filter could (partly) replace tubular functions. Concentrated "urine" is discarded via the bladder. This concept goes beyond the definition of HD within the standard IEC60601-2-16 (6) and once fully developed into a product, would form an autonomous implantable artificial kidney without needing immune suppression. The Kidney Project (9) and Artificial Kidney Innovation Lab (5) are pursuing such concepts, but this will take a longer timeline than approach "e."
- **g** PD (shown in the Figure in its simplest form) does not require an extracorporeal blood circuit but requires quite some dialysate volume. Typically, the dialysate is instilled into the peritoneum, remains there for a few hours, and is then drained (single-pass).
- **h** Similar to HD, PD mobility can be significantly improved by closed-loop dialysate regeneration, preferably in a continuous flow mode. The firms Vivance (Singapore) and Nanodialysis (the Netherlands) have products in human clinical trials similar to this concept.

Clinicians should be aware of the technology readiness level of an approach (6). Adequate funding remains a barrier to getting these approaches to patients (5, 6, 8, 9). *Nature Reviews Nephrology* recently celebrated its 20th anniversary with a collection of perspectives on how nephrology has progressed in the last 2 decades, outlining remaining challenges including funding (10).

Advances in artificial kidneys are constantly developing, and this article will soon become outdated by new advancements. Readers are encouraged to stay updated on home PD and home HD devices through resources such as Home Dialysis Central (11). ■

Figure. Main forms of current and future-projected KRTs



Jerrican symbols qualitatively depict the relative amount of water consumption by the various modalities. Updated and adapted from Wieringa et al. (5).

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Technology-Guided Dry-Weight Management in Dialysis: Current Evidence and the Road Ahead

By Wannasit Wathanavasin, Francesco Pesce, and Charat Thongprayoon

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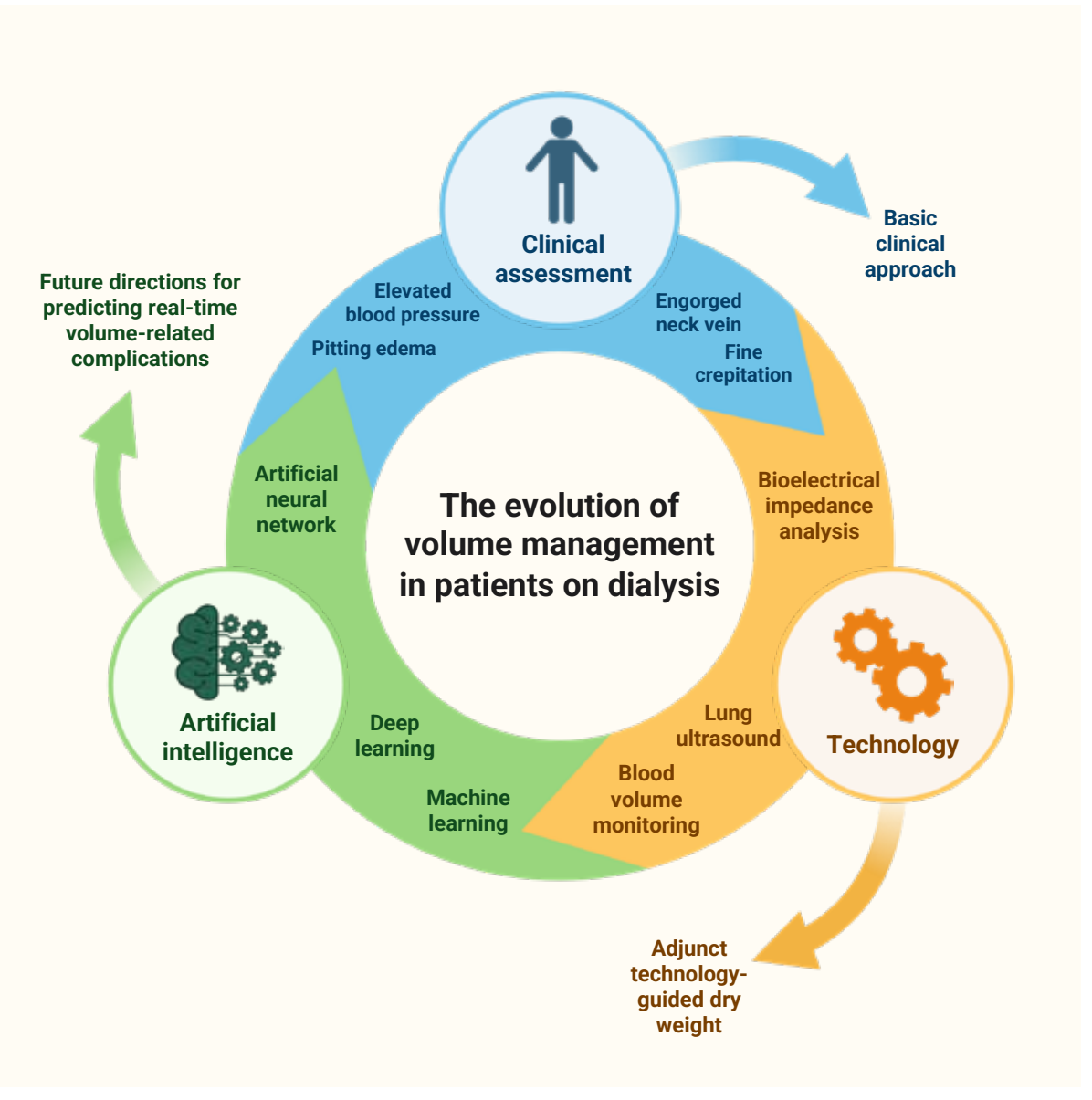
The concept of maintaining euvolemia, avoiding both overhydration as well as underhydration, remains a critical component of dialysis therapy. However, there is currently no gold-standard method for measuring extracellular volume in patients on dialysis (1). In clinical practice, nephrologists seek to define the optimal dry weight and ultrafiltration (UF) rate to balance the ischemic consequences against fluid overload complications, individualized for each patient, as there is no one-size-fits-all strategy. The initial approach to volume assessment typically involves clinical evaluation, including patient history and a physical examination. However, this method often demonstrates limited sensitivity in detecting subclinical volume overload or accurately characterizing fluid distribution (2). Consequently, technology-guided methods have emerged as valuable adjuncts to standard clinical assessment in refining dry-weight determination.

Recent technologic advancements, including bioelectrical impedance analysis (BIA), lung ultrasound (LUS), and blood volume monitoring (BVM), provide next-step approaches to confirm clinical suspicion of extracellular volume excess and offer prognostic value (1). Evidence from a recent meta-analysis by Wathanavasin et al. (3), involving 4239 patients on dialysis, revealed that implementing these instruments significantly improves cardiovascular (CV) parameters, particularly pulse-wave velocity, and reduces CV events. Of these, BIA showed the greatest promise, offering additional mortality benefits compared with the other approaches. This may be attributed to its greater objectivity relative to LUS and BVM, which are operator dependent, lack standardization, and require specialized training (4). Remarkably, most BIA devices included in this analysis were whole-body, multifrequency systems, which are considered more accurate because they incorporate fundamental physical principles into their estimations. However, hypovolemic events, particularly muscle cramps, were reported more frequently with these technologies. This finding suggests that, beyond achieving the target dry weight, gradual fluid removal during hemodialysis (HD) should be emphasized to prevent hypovolemia, especially in patients with abnormal fluid distribution or impaired plasma refilling such as those with hypoalbuminemia, sepsis, or frailty. Given the complexity and dynamic nature of volume control, it is not feasible for patients to reach their dry weight in every HD session. Therefore, clinicians should individualize fluid management strategies and ensure early detection and intervention for volume-related intradialytic complications.

Looking ahead, even with the integration of clinical and technology-guided approaches, volume-related events may still occur, as these methods provide only single time-point assessments. Although establishing an accurate volume target is essential for conceptualizing treatment goals, guiding UF, and predicting complications, future directions point toward the integration of machine-learning (ML) models. These emerging approaches hold promise for predicting volume-related complications, particularly intradialytic hypotension (IDH), and for enhancing the precision of UF rate prescriptions, allowing clinical practitioners, such as nephrologists and nursing staff, to intervene promptly to prevent these events. Lee et al. (5) applied a deep-learning approach using a recurrent neural network that integrated time-stamped data from 261,647 HD sessions along with patients' demographic characteristics, laboratory results, and medication profiles to predict the real-time risk of IDH. Their model accurately predicted IDH, defined as a systolic blood pressure drop below 90 mm Hg within 1 hour, with an area under the receiver operating characteristic curve (AUROC) of 0.94. This concept was further validated in a study by Zhang et al. (6), who used ML and

Continued on page 18 >

Figure. Evolution of volume management in patients undergoing dialysis



A comprehensive strategy integrating traditional clinical assessment with static technology-guided adjuncts (BIA, LUS, and BVM) and emerging dynamic artificial intelligence and ML predictive models for real-time risk stratification.

Technology-Guided Dry-Weight Management in Dialysis

Continued from page 17

cloud-computing infrastructure to analyze retrospective electronic health records integrated with intradialytic machine data. Their model successfully predicted IDH, generating alerts 15 to 75 minutes before an IDH event, with an AUROC of 0.89. Together, these studies highlight the importance of incorporating dynamic patient data—such as vital signs and HD parameters—that fluctuate over time and significantly influence risk of IDH. Leveraging artificial intelligence, which excels at interpreting complex and large-scale datasets, may therefore provide a powerful complement to current technology-guided clinical approaches.

In line with this vision, we propose a comprehensive approach to dry-weight adjustment and volume management in patients undergoing dialysis, as illustrated in the Figure. Future research should continue to move toward a goal-directed, personalized strategy tailored to each patient's individual risk profile, thereby further enhancing patient safety and treatment precision in this vulnerable population with high CV risk. ■

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Automation and Innovation in Home Hemodialysis Machines

By Osama El Shamy, Maria Bermudez, and Ankur Shah

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The first home hemodialysis (HHD) machine approved in the United States by the US Food and Drug Administration (FDA) was in 2005. Since then, there have been many iterations and technologic advancements in machine design and capabilities. Key design considerations include ensuring outcomes comparable with in-center HD, offering flexibility in dialysate baths and flow rates, providing an intuitive user interface to minimize errors, and streamlining dialysate production and delivery.

Exploring HHD machines

There are currently seven FDA-approved HHD machines, to our knowledge, many of which have a great deal of overlap and some of which have their own unique set of features and capabilities.

Fresenius Medical Care previously manufactured the 2008K@home (not covered in this article) and currently manufactures the NxStage System One, System One S, and VersiHD devices. Features of the NxStage machines include the ability to use either premixed dialysate bags or at-home pretreatment dialysate production using the PureFlow SL system. The PureFlow SL system—often placed underneath the dialysis machine—purifies patients' home water and mixes it with concentrate contained inside 40-, 50-, or 60-L sacs. The availability of and ability to connect to premixed dialysate bags make the NxStage machines travel-friendly. Moreover, the system relies on low-volume dialysate delivery, thereby maximizing dialysate saturation—minimizing home space needs, water consumption, and overall cost of delivery (Table). Dialysate flow rates of the company's most recent devices (System One S and VersiHD) can go as fast as 300 mL/min. A unique feature of the NxStage devices is the use of lactate buffer rather than bicarbonate, thereby reducing calcium carbonate formation in the premixed or pretreatment bags. NxStage devices are also the only ones FDA-approved for solo and nocturnal HHD; however, there are avenues to using the other HHD devices for solo nocturnal HHD (1).

Outset Medical Inc (Tablo), DEKA Research & Development Corp (HemoCare), and Quanta Dialysis Technologies (Quanta) manufacture HHD machines that operate via on-demand dialysate production, using patients' home water supply. This reduces home space needs (compared with premixed dialysate bag use) and treatment preparation time (compared with pretreatment dialysate production); however, it can limit travel options. Given the nature of on-demand dialysate, Tablo, HemoCare, and Quanta use bicarbonate-based buffers rather than lactate buffer solutions. This is an important consideration when dialyzing individuals with liver failure, given that lactate is converted to bicarbonate primarily in the liver.

Although Tablo offers dialysate flow rates that are comparable with the NxStage System One S and VersiHD (300 mL/min), both HemoCare and Quanta allow for dialysate flow rates of up to 500 mL/min, offering flexibility from the low-dialysate volume approach. To reduce potential system clotting, Tablo provides the option of automatic saline flushes, which can replace the need for heparin bolus and maintenance dosing. HemoCare has an integrated access disconnect system, leveraging electrical impedance at a sensor interface to detect needle dislodgement, stopping the machine, and sounding an alarm, thereby reducing the chances of catastrophic blood loss. Other HHD machines rely on moisture-detecting devices, such as Redsense, to identify episodes of potential blood loss at the venous cannulation site (2). While all device manufacturers provide prestrung cartridges, Quanta allows for a "hot swap": swapping a malfunctioning cartridge for a new one without repeat water testing.

All on-demand dialysis devices require similar source water requirements; incoming source water meets Environmental Protection Agency primary and secondary standards for drinking water with source water pressures of approximately 20–80 psi. Furthermore, all commercially available HHD machines provide electronic treatment log capture via a portable or cloud system that is accessible to the treatment team. The NxStage VersiHD, Tablo, HemoCare, and Quanta all have touchscreen interfaces and provide both audio and visual prompts to their users. The Nx2me Connected Health platform (NxStage), TabloHub (Tablo), CareLinQ (Quanta), and HemoCare's secure two-way cloud communications transmit prescriptions, patient monitoring data, and device status.

NxStage and Quanta systems offer a "swap-and-replace" model for technical issues, minimizing downtime. Tablo, however, requires on-site technician visits for repairs. The NxStage, Quanta, and HemoCare systems are relatively compact (32.0–34.0 kg), whereas Tablo is heavier (88.5 kg) but has wheels for easier movement.

Conclusion

Although automation and innovation in HHD machines have been moving at great pace, with multiple manufacturers in the space, HHD use in the United States remains comparably far inferior, with only 0.4% of people with incident kidney failure receiving HHD (3). Exploring barriers to HHD growth is not the topic of this piece but will be crucial in the realization of the benefits of the technologic advancements discussed in this article, with combating needle phobia being one such example in which innovation may be crucial. Involving the different stakeholders in the continued growth and innovation in HHD is critical for patients, caregivers, and their treatment teams. ■

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Table. Comparison of conventional HD with the low dialysate volume approach

Parameter	Conventional in-center HD	Low dialysate volume approach
Dialysate flow rate	500–800 mL/min	200–300 mL/min
Dialysate volume per treatment	120–200 L	25–50 L
Treatment frequency	3 Times/week	Typically 4–6 times/week
Treatment duration	3.5–4.0 Hours	2–3 Hours (short daily) or 6–8 hours (nocturnal)
Dialysate saturation	Moderate	High
Water consumption	High	Lower
Space requirements	Large (central water treatment)	Reduced (bagged or batch dialysate)
Portability	Not portable	Portable options available

Leveraging Artificial Intelligence to Optimize Anemia Management in Dialysis and Transplantation Populations

By Luca Neri, Doris Fuertinger, and Len Usvyat

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Anemia remains a pervasive and multifaceted challenge in kidney failure care. In both dialysis and transplant populations, the interplay of iron deficiency, inflammation, erythropoietin resistance, shortened red blood cell survival/lifespan, fluid shifts, and variable residual kidney function makes stable anemia management elusive. The advent of artificial intelligence (AI)-based decision support systems offers an emerging opportunity to bring consistency, personalization, and operational efficiency to anemia therapy. In this commentary, we highlight two approaches in AI-driven anemia care—in silico trial platforms and neural network-based precision dosing tools—and discuss how together they can advance anemia management across dialysis and transplantation populations.

AI in dialysis-associated anemia

In the in-center hemodialysis (HD) space, computational modeling has advanced rapidly over the past 15 years. Fuertinger and colleagues at the Renal Research Institute pioneered the "virtual anemia trial" framework, generating large cohorts of patient avatars derived from real-world electronic health record (EHR) data (1). These avatars are physiologically informed models of erythropoiesis that can be subjected to in silico simulations of anemia treatment protocols over extended time horizons. Seminal work comparing 1-year avatar trajectories with outcomes in more than 79,000 patients undergoing HD demonstrated both high fidelity and strong translational potential (1).

A defining strength of this approach is its utility in protocol development, particularly in situations in which real-world data are sparse, "noisy," or logistically costly to obtain. Virtual platforms allow rapid testing of treatment strategies, exploration of subgroups prone to erythropoiesis-stimulating agents (ESAs) hypo-responsiveness, and forecasting of population-level tradeoffs. Crucially, they allow incorporation of clinic-specific operational constraints (e.g., laboratory timing, dialysis schedules, drug administration cycles, and data latency patterns) to generate optimized and operationally feasible anemia treatment protocols. This tailoring to real-world workflows is often missing in traditional guideline development but is essential for implementation success.

Parallel to this, the artificial neural network-based decision-support tool known as the Anemia Control Model (ACM) has achieved real-world implementation. Developed by Dr. Carlo Barbieri and colleagues, ACM uses historical patient data to predict individual hemoglobin (Hgb) trajectories, simulate various ESA/iron-dosing scenarios, and recommend the optimal dose with a utility-based reward function (2). In a large-scale retrospective HD cohort (2013–2019, >50,000 patients, 1.5 million patient-months), use of ACM was associated with improved Hgb target achievement, reduced ESA dosage, and reduced hospitalization risk (2, 3). More recently, a health economic evaluation showed that ACM was cost-effective compared with standard of care (4).

Whereas virtual avatar simulation provides population-level optimization and protocol development, precision-dosing engines expand this framework to the individual patient—but only in settings in which timely access to rich EHR data is feasible. In silico trials can generate robust, clinic-tailored anemia treatment protocols that integrate global best practices with operational realities, such as lab schedules, medication administration workflows, and data latency constraints. When real-time or near–real-time clinical data streams are available, neural network dosing engines can be used to continuously adjust recommendations to each patient's evolving physiology. Together, these two tools create a unified AI ecosystem that supports both strategic, population-level protocol design and individualized, real-time execution of anemia therapy (Figure).

Extending AI-driven anemia optimization to the transplant population

Anemia following kidney transplantation remains common, under-recognized, and undertreated. Between 20% and 50% of transplant recipients experience anemia both early and late after transplantation, with strong associations to increased mortality, graft loss, and reduced kidney function (5). Guidelines from Kidney Disease: Improving Global Outcomes (KDIGO) for chronic kidney disease include transplant recipients, yet transplant-specific dosing algorithms and AI frameworks remain limited (6).

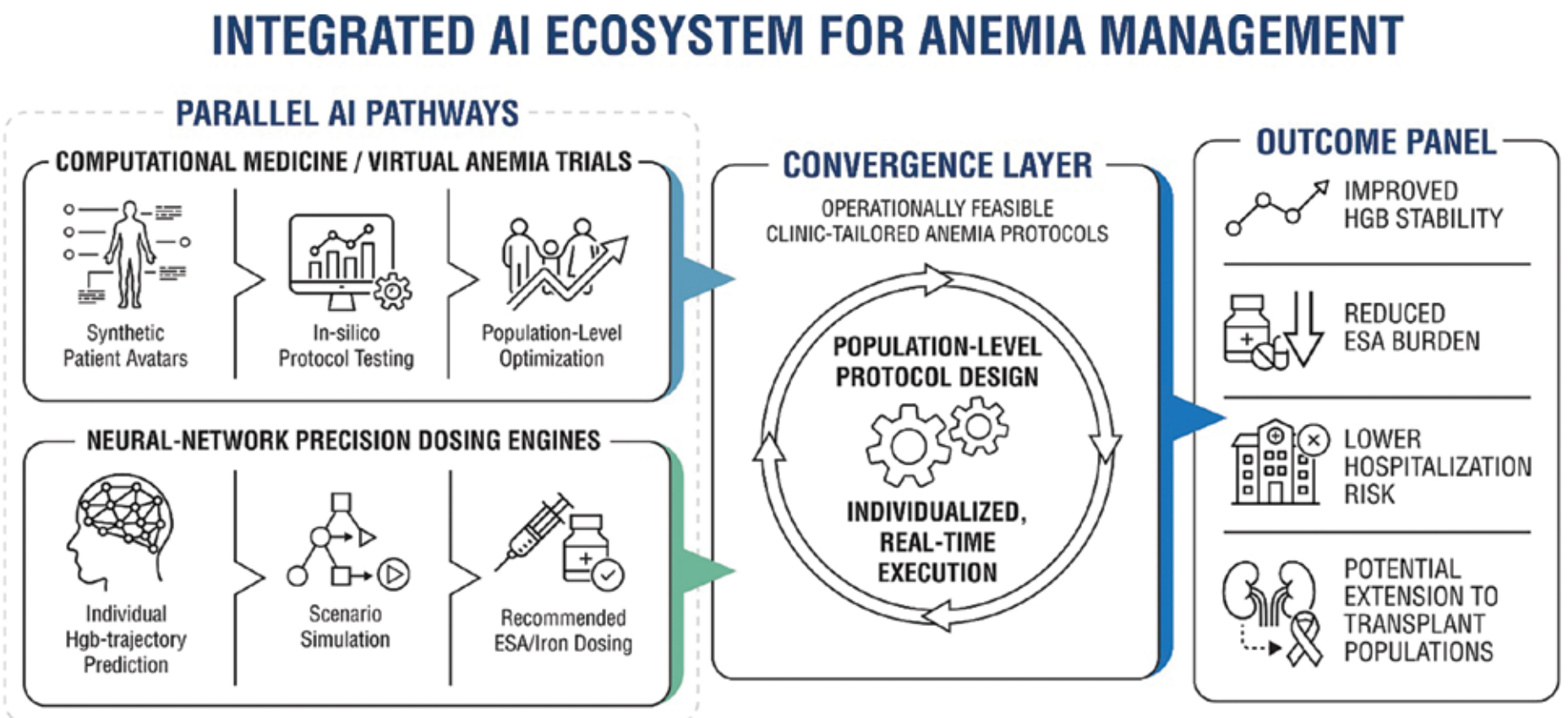
The modeling and AI ecosystem developed in the dialysis setting provides an opportunity to change this. Avatar-based in silico trials could be adapted to simulate post-transplant erythropoiesis, iron kinetics under immunosuppressive regimens, dynamic graft function, and responsiveness to ESA and iron therapies. These simulations could explore how anemia protocols might differ among early postoperative, stable long-term, and late graft-decline phases. They could also test strategies without exposing patients at risk to experimental regimens—an especially valuable feature in the transplant population.

Similarly, ACM-like neural network decision engines could be retrained for transplant-specific cohorts to support individualized dosing in this complex population. Such AI-augmented models could bridge the gap between guideline-based anemia care and personalized precision management in the transplant setting.

Practical considerations and implementation

Successful translation of both computational medicine and AI approaches requires more than algorithmic accuracy. Key operational considerations include:

Figure. Unified AI ecosystem supporting strategic protocols and individualized execution of anemia therapy



- Data integration: merging dialysis EHRs, transplant registries, and medication records to ensure timely model inputs
- Clinic-specific protocol tailoring: ensuring virtual trial-derived protocols respect realities such as lab frequency, administration timing, and data latency constraints
- Change management: building clinician trust through interpretability, over-ride tracking, and performance monitoring
- Regulatory and quality frameworks: treating AI tools as evolving medical devices, with ongoing validation and safety checks
- Outcome measurement: monitoring Hgb stability, ESA dose burden, transfusion avoidance, and cost savings

Real-world experience from more than 100 clinics using ACM suggests feasibility in large dialysis networks.

Conclusion

As nephrology evolves in the era of big data and advanced analytics, AI-driven tools offer a new frontier for anemia management. In dialysis populations, the convergence of virtual avatars and neural network dosing engines has already demonstrated improved Hgb control, reduced ESA use, and cost-effectiveness. Extending this paradigm into the transplant population—in which anemia is common, harmful, yet often neglected—represents a timely opportunity. Furthermore, with advancements in real-time data processing, incorporating real-time machine-based observations of hematocrit levels may also offer further improvements in Hgb management. By embracing AI-driven decision support, clinicians can move from reactive anemia control toward proactive, precision-guided anemia optimization, ultimately improving patient outcomes across the kidney disease spectrum. ■

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The authors report no conflicts of interest.

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Incremental and Hybrid Dialysis: Treatment Plans With Individualized Care

By Mariana Murea and Masanori Abe

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Most commonly, dialysis—whether extracorporeal, such as hemodialysis (HD) or hemodiafiltration (HDF), or intracorporeal, such as peritoneal dialysis (PD)—is prescribed in-center thrice-weekly (for HD or HDF) or home daily (for PD), each as a stand-alone modality. Although these treatment plans are adequate for many patients, some people present with lower or higher metabolic or volume management demands. Two treatment plans address this variability: 1) incremental dialysis, in which HD, HDF, or PD begins at lower frequency for patients with residual kidney function (RKF) and clinical stability and then escalates in frequency in parallel with evolving clinical needs, and 2) hybrid dialysis, which combines PD with supplemental HD or HDF when a fully optimized PD prescription no longer meets physiologic demands. Both approaches—illustrated in the Figure and summarized in the Table—accommodate patient-specific clinical heterogeneity and preferences.

Incremental extracorporeal dialysis

Thrice-weekly HD or HDF, delivered at single pool Kt/V ≥1.20 and validated in patients with minimal RKF (urine volume <200 mL/day), is not always necessary at dialysis initiation. For patients with appreciable RKF, an initial less-frequent treatment—often twice weekly—can maintain stability, supported with diuretics; sodium restriction; and monitoring of volume status (e.g., interdialytic weight gain, respiratory signs), blood pressure, and biochemical parameters. In these patients, combined (kidney and HD) weekly Kt/V is equal or superior to weekly Kt/V of patients without RKF treated thrice-weekly with HD or HDF.

Frameworks for implementing and prescribing in-center incremental extracorporeal dialysis have been published (1, 2). Importantly, reduced frequency is temporary. Dialysis frequency must increase as clinical requirements change, or residual function declines, driven by factors such as volume status, metabolic demand, comorbidities, and dietary intake. Timing of escalation, from less frequent to conventional thrice-weekly, varies by individual, and it requires ongoing patient education and clinical assessment. By extension, when conventional thrice-weekly HD or HDF fails to meet metabolic or volume management demands, escalation to four or more sessions per week should be used.

Evidence supports this approach: A systematic review of 24 observational studies and 2 pilot trials found no difference in all-cause mortality with incremental twice- to thrice-weekly HD versus conventional thrice-weekly HD (3). A recent randomized clinical trial (RCT) showed that incremental HDF is as safe and effective as conventional HDF, with similar outcomes and potential short-term quality-of-life and resource benefits (4). Data on incremental home HD are limited, but the same principles apply when clinically appropriate.

Incremental intracorporeal dialysis

Incremental PD follows the same clinical rationale. Patients with appreciable RKF on a daily PD treatment plan often achieve combined (kidney and PD) Kt/V >2.30. For these patients, a less-intensive regimen—such as PD, 5 to 6 days per week—can often provide adequate metabolic and volume control (5).

Globally, approximately 37% of incident patients undergoing PD begin with an incremental prescription. Evidence supports its safety: A systematic review found no differences in mortality, technique failure, or peritonitis versus standard PD (6), and Peritoneal Dialysis Outcomes and Practice Patterns Study (PDOPPS) data confirm similar rates of hospitalization, infection, and modality transfer (7).

Inherent in the concept of "incremental" and consistent with incremental extracorporeal dialysis, incremental PD is dynamic. Intensification—adding exchanges or increasing treatment days—must occur as clinical needs evolve, or RKF declines. As with incremental extracorporeal dialysis, timing of dialysis intensification varies by individual, influenced by volume status, metabolic demands, comorbidities, and dietary intake.

Hybrid dialysis (combined intracorporeal and extracorporeal therapy)

Hybrid dialysis is considered when PD, optimized at its highest feasible intensity for a given patient, no longer achieves clearance or volume targets—typically in those with negligible RKF and altered peritoneal transport. At this stage, the treatment plan often switches to conventional HD or HDF. However, some patients prefer to maintain home-based therapy for autonomy or logistical barriers to in-center dialysis. In such cases, adding once-weekly in-center HD or HDF or a once-weekly home HD session to ongoing PD (5–6 days/week) can restore adequacy and sometimes serves as a bridge to conventional extracorporeal therapy.

Evidence supports its feasibility and safety: In the Japan PDOPPS, hybrid therapy accounts for one-third of PD transitions and a transfer rate to hybrid therapy of 5.5 per 100 patient-years, with an approximate 80% initiated for inadequate clearance, with results of similar all-cause mortality to thrice-weekly HD and lower infection-related mortality versus continued PD alone (8, 9). Limited North American experience confirms practicality; in a Canadian cohort, 33% transitioned to home HD or transplantation (10).

Hybrid therapy requires monitoring of clearance, volume, and biochemical parameters, with escalation of extracorporeal dialysis and reduction of PD—or full conversion to conventional extracorporeal dialysis—as clinically indicated and aligned with patient preference.

Conclusion

Incremental and hybrid dialysis represents treatment plans guided by physiologic reserves and evolving clinical needs. These treatment plans complement, and often converge with, conventional treatment plans. ■

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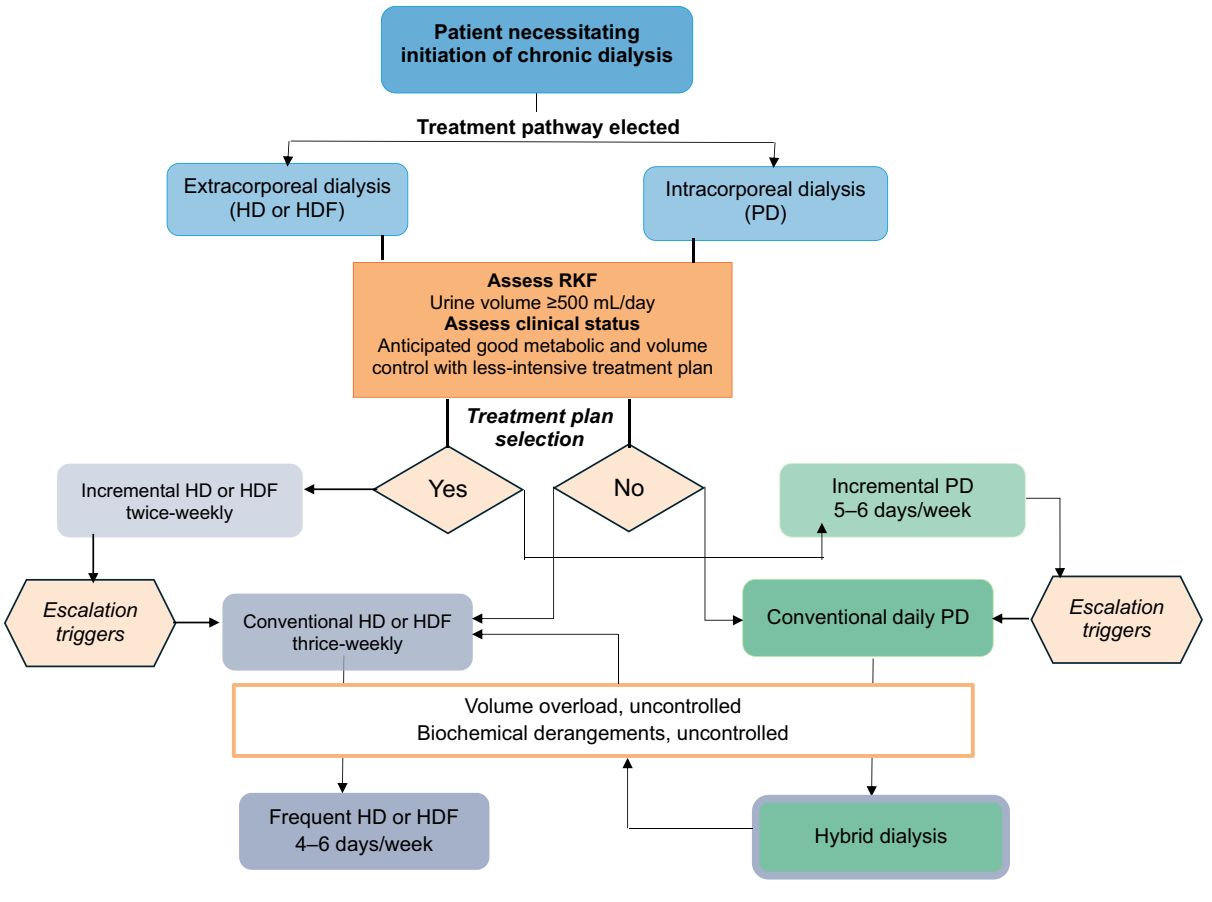
Figure. Dialysis treatment pathways and plans



Incremental and hybrid dialysis allows individualized treatment for patients with residual kidney function and evolving clinical needs. These approaches often intersect with conventional prescriptions. Escalation triggers represent clinical or biochemical indicators that necessitate intensifying dialysis therapy, such as uncontrolled interdialytic weight gain, respiratory compromise (orthopnea, dyspnea), uncontrolled hypertension, decline in RKF, or persistent biochemical derangements. When conventional thrice-weekly HD or HDF no longer achieves metabolic or volume stability, escalation to four or more sessions per week may be required. Similarly, when optimized PD fails to maintain adequacy, hybrid therapy combining PD with HD or HDF can serve as an intermediate step or alternative to conversion to conventional extracorporeal dialysis.

Table. Characteristics of incremental and hybrid dialysis

Characteristic	Incremental extracorporeal dialysis (HD or HDF)	Incremental intracorporeal (PD)	Hybrid dialysis (PD and HD or HDF)
Population	Patients initiating chronic dialysis with ongoing RKF (e.g., urea clearance ≥2.0 mL/min and urine output ≥500 mL/day)		Established patients undergoing PD experiencing modality failure (inadequate metabolic or volume control)
Additional criteria	Ability to maintain volume status and metabolic control with reduced dialysis frequency		Patient preference to continue PD or logistical barriers to in-center HD/HDF
Typical prescription	One to two HD/HDF sessions/ week, increasing frequency and/or session duration as RKF declines or symptoms develop	Two to three CAPD exchanges/ day or 5–6 APD days/week, with or without dry days, increasing intensity as RKF declines or symptoms develop	5–6 PD days/week plus one HD/ HDF session weekly
Utilization rate	Approximately 30% of incident dialysis population, with variable adoption[a]	Approximately 40% of incident dialysis population, with variable adoption[a]	Approximately 25% to 30% of PD transfers in Japan; rare in North America[a]
Evidence base	Observational studies, three pilot trials, one RCT, and three meta-analyses; ongoing multicenter RCTs	Systematic review, observational studies, and PDOPPS data; ongoing multicenter RCTs	Japanese registry data; no RCTs
Mortality	Data from experienced centers, with HD/HDF prescribed incrementally at increasing intensity (e.g., increasing frequency per week and/or session duration); patient survival comparable with conventional HD/HDF	Data from experienced centers, with PD prescribed incrementally at increasing intensity (e.g., adding daytime dwell, increasing frequency per week); patient survival comparable with conventional PD	Data from experienced centers, mostly in Japan and Canada; patient survival comparable with thrice-weekly HD
Key monitoring	Increase dialysis frequency in parallel with clinical status needs, or decline in RKF for volume management and biochemical parameters; consider diuretics while ongoing RKF; consider bicarbonate supplementation when necessary based on biochemical profile.		Assess the need for transitioning to conventional HD/HDF based on overall clinical status, volume control, and biochemical indicators; assess combined PD and HD/HDF stdKt/V for a total ≥1.70.
	Assess combined stdKt/V: HD\HDF stdKt/V + kidney stdKt/V ≥2.10.	Assess combined stdKt/V: PD stdKt/V + kidney stdKt/V ≥1.70.	

APD, automated PD; CAPD, continuous ambulatory PD; stdKt/V, standardized Kt/V (a measure of dialysis adequacy accounting for treatment frequency and urea clearance).

[a]Adoption varies based on physician and dialysis personnel practice patterns, experience with incremental dialysis, and propensity to implement incremental or hybrid dialysis.

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Online Hemodiafiltration in the Era of Digital Dialysis

By Yuri Battaglia, Björn Meijers, and Carlo Basile

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Online hemodiafiltration (HDF) has long been regarded a promising evolution of conventional hemodialysis (HD), offering higher middle molecule clearance and a survival advantage. Several randomized controlled trials (RCTs), meta-analyses, and individual patient data (IPD) analyses have reported a beneficial effect of HDF compared with high-flux HD (1). However, these studies are limited by heterogeneous inclusion criteria and important methodologic shortcomings, including informational selection bias and the exclusion of patients who performed poorly from the HDF arm after randomization (1). The robustness of data of individual RCTs and related IPD analyses has been challenged using the fragility index (FI) and fragility quotient (FQ), which assess how easily statistically significant results for dichotomous outcomes can be influenced by small changes in event status. The FI is the minimum number of patients whose status would need to change from "event" to "nonevent" (or vice versa) to transform a significant result into a nonsignificant one, whereas the FQ (the FI divided by sample size) adjusts for study size. Although there is no accepted threshold, empirical data suggest that an FQ of 0.03 or less raises concerns about robustness (2, 3).

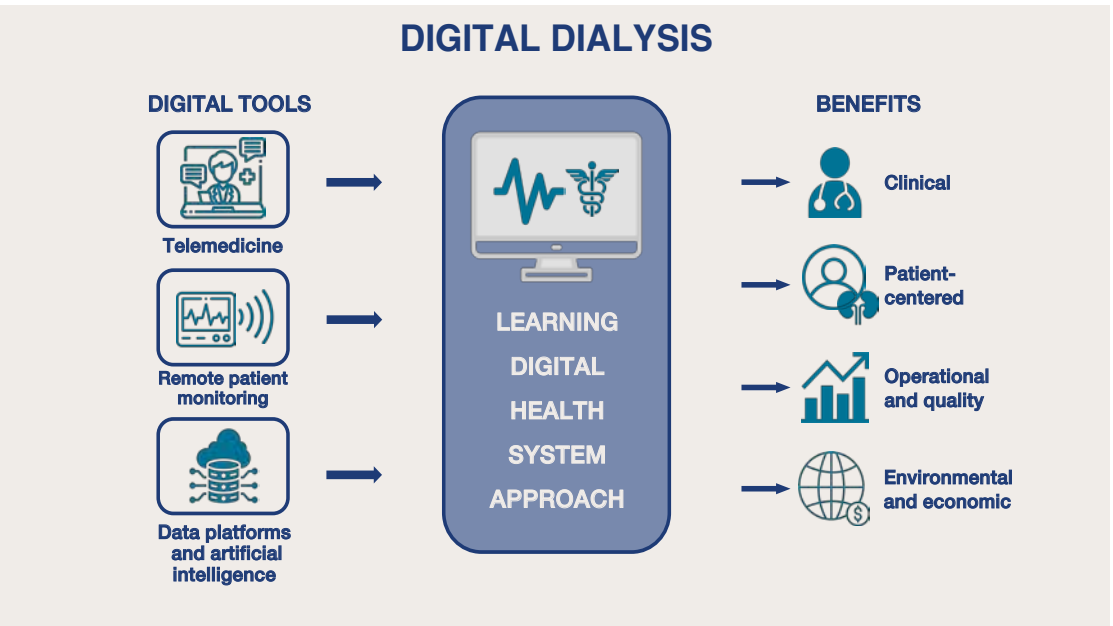
For the two pivotal RCTs, ESHOL (NCT00694031) and CONVINCE (NTR7138), changing the outcome status of just 3 to 13 participants is sufficient to lose statistical significance for all-cause mortality, with FQ values less than 0.03 (3). When the same method is applied to pooled IPD meta-analyses including more than 4000 patients on HD, the overall survival benefit also disappears after reassignment of outcomes in only 28 patients (2). These findings do not imply that online HDF is ineffective; rather, they indicate that the current evidence base is statistically fragile and more vulnerable to random variation than conventional p values alone might suggest.

A consensus statement on HDF

A recent consensus statement on HDF from the European Dialysis (EuDial) Working Group of the European Renal Association provided a more nuanced and pragmatic interpretation of the available evidence to support clinical decision-making (1). It identified 22 key points by integrating meta-analytic data, clinical experience, and expert opinion on postdilution online HDF versus high-flux HD, with a focus on survival, health-related quality of life, and biochemical outcomes (1).

The EuDial consensus statement concluded that online HDF is associated with improved all-cause and cardiovascular survival when high convection volumes are consistently achieved, with a commonly recommended target of more than 23 L per session. However, this survival benefit is mainly observed in patients with good vascular access and favorable general health, rather than being determined solely by age, diabetes, or pre-existing cardiovascular disease (1). Overall, the EuDial consensus statement did not recommend online HDF as a universal standard of care, also considering its higher environmental impact and costs compared with high-flux HD. Rather, it recommended online HDF as a component of a personalized dialysis strategy, in which the potential benefit is closely linked to the achieved convection volume and the patient's general condition (1).

Figure 1. Main components and impacts of "digital dialysis"



Perspectives in HDF: From static prescription to data-driven care

Dialysis care is undergoing a transformation thanks to digital health tools, including telemedicine, remote patient monitoring (RPM), integrated data platforms, and artificial intelligence (AI)-based decision support (Figure 1). Telemedicine-based dialysis assessments can increase the frequency of doctor-patient contact, improve patient experience, and streamline multidisciplinary care, whereas RPM systems transmit treatment and vital-sign data from HD units in near real-time (4, 5).

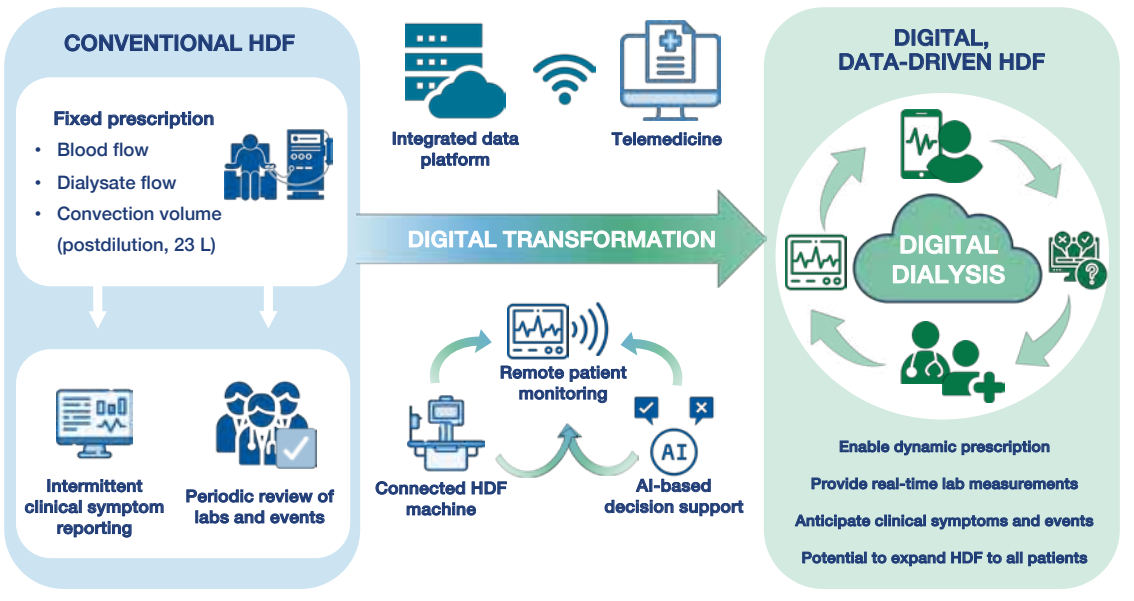
At the machine level, newer HDF platforms can automatically adjust dialysate flow, ultrafiltration, and substitution volumes based on real-time measurements of pressure, viscosity, and other parameters. These systems can facilitate high-volume HDF administration without increasing dialysate consumption compared with standard HD and simultaneously generate large, high-frequency datasets. Such data are ideal for AI-driven clinical decision support, which can help clinicians refine prescriptions, anticipate intradialytic instability, and monitor performance over time (6).

Within a digital dialysis unit, online HDF can therefore evolve from a fixed prescription ("postdilution, 23 L") to a dynamic, data-driven process. Algorithms may help identify patients most likely to achieve and tolerate high convection volumes, allowing for personalized convection doses. For instance, this could involve tailoring the target volume to body-surface area, potentially extending the benefits of HDF to a broader population. Real-time analysis can optimize blood flow, convection volume, and dialysate flow while simultaneously monitoring intradialytic hemodynamics, potentially reducing the risk of intradialytic hypotension. Environmental and economic parameters such as water consumption, energy consumption, and the use of disposables can also be monitored alongside clinical outcomes, supporting "green dialysis" principles and informing operational and policy decisions (7, 8) (Figure 2).

Although an "HDF for all" strategy is not currently justified, the integration of digital technologies points to a different path. Future studies could integrate comparisons between online HDF and high-flux HD within registry-based, digitally supported pragmatic trials that leverage data routinely collected by machines and RPMs to acquire large-scale results. One promising approach is trial emulation (or target trial emulation), which applies RCT design principles to observational data, explicitly defining eligibility criteria, treatment strategies, follow-up, and outcomes. With the increasing availability of large dialysis registries, this method may produce more reliable causal inferences about the effects of HDF, helping to inform clinical guidelines and regulatory decisions (9).

AI-based analytic tools can therefore be used to explore the heterogeneity of treatment effect, identifying which clinical phenotypes—defined by age, vascular access quality, hemodynamic profile, or comorbidity burden—benefit most from high-volume HDF. In parallel,

Figure 2. Digital transition of conventional HDF to connected, AI-supported HDF



connected infrastructures can support continuous monitoring of safety, health-related quality of life, and environmental impact (10).

In conclusion, the integration of connected dialysis machines, RPM, and AI-driven analytics (digital dialysis) offers a path to more robust, personalized, and green HDF delivery, based on concrete evidence, potentially extending the benefits of HDF to a broader population. ■

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The authors report no conflicts of interest.

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AI-Enabled Prediction and Prevention of Intradialytic Hypotension

By Hanjie Zhang

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Intradialytic hypotension (IDH) remains one of the most frequent and clinically consequential complications of maintenance hemodialysis. Despite advances in dialysis technology and clinical protocols, IDH continues to disrupt treatments, cause patient discomfort, and contribute to myocardial and cerebral hypoperfusion with long-term adverse outcomes. In routine practice, management remains largely reactive, with interventions initiated only after blood pressure has already declined. Recent advances in artificial intelligence (AI) create an opportunity to shift IDH management from reaction toward anticipation and prevention.

IDH is a complex and heterogeneous phenomenon arising from the imbalance between ultrafiltration-driven volume removal and a patient's compensatory capacity, including plasma refilling, cardiac reserve, autonomic response, and vascular tone. Early applications of AI therefore focused on identifying patients at elevated risk before dialysis treatments rather than detecting instability as it unfolds.

An important early contribution was provided by Gervasoni et al., who developed and validated machine-learning models using the XGBoost algorithm to predict the occurrence of IDH in the next dialysis session and over the subsequent month based on routinely available clinical and treatment data (1). These forward-looking models highlighted the potential of AI to improve pre-treatment risk stratification and support proactive planning, but they were not designed to guide intradialytic decision-making once treatment had begun.

Addressing this limitation, Zhang et al. (H.Z.) subsequently demonstrated that AI could be applied in real-time during dialysis. Our model continuously updated risk estimates and predicted IDH 15 to 75 minutes before onset, enabling actionable interventions within the same treatment session (2). This transition from session-level risk prediction to real-time forecasting represented a critical conceptual advance, aligning AI outputs with the temporal dynamics of IDH development.

Beyond prediction timing, recent work has emphasized the importance of interpretability and clinical usability. Yun et al. showed that explainable deep-learning models can provide real-time predictions of both intradialytic hypotension and hypertension while revealing which physiologic features drive risk estimates, supporting clinician trust and adoption (3). Similarly, Yang et al. demonstrated that AI outputs can be embedded into clinical workflows through a dashboard that integrates data from prior and current sessions to generate personalized risk estimates at the point of care (4).

Evidence is also emerging that AI-based prediction can translate into meaningful clinical impact. In a multiyear, real-world evaluation, Lin et al. reported sustained reductions in IDH after implementation of the BestShape AI system, suggesting that benefits can be maintained when prediction tools are deployed at scale and incorporated into routine practice (5). These findings underscore that implementation, not just model performance, is central to success.

Prediction alone, however, is insufficient to prevent hypotension. Effective prevention requires linking elevated risk states to timely, standardized responses. Semiautomated strategies such as blood volume-guided ultrafiltration control have shown promise by continuously adapting fluid removal to physiologic tolerance (6). More broadly, a recent systematic review highlighted persistent challenges in the field, including heterogeneous IDH definitions, limited external validation, and a lack of prospective outcome trials (7). Looking ahead, reinforcement learning approaches may further enable adaptive, patient-specific strategies that balance ultrafiltration goals against hemodynamic stability (8).

AI-enabled prediction represents a pivotal shift in IDH management. By combining forward-looking risk stratification, real-time intradialytic forecasting, and workflow-integrated prevention strategies, these tools have the potential to transform IDH from an accepted inevitability into a largely preventable complication of hemodialysis. ■

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The author reports being an inventor on several patents in the kidney space.

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Remote and Virtual Technology in Home Dialysis

By Susie Q. Lew and James A. Sloand

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Remote monitoring has become an established element of home dialysis practice and is increasingly regarded as integral to routine care by both patients and clinicians (1). Knowledge that important treatment anomalies will be flagged and addressed provides reassurance to patients considering home therapies, lowering barriers to adoption. Receipt of accurate, near real-time treatment data has provided home dialysis teams better oversight of patient issues, enabling appropriate early interventions or treatment adjustments (2).

With each iteration of peritoneal dialysis cyclers and home hemodialysis devices, patients perform fewer actions to record and share treatment data. Cloud-based, bidirectional transmission of data has reduced, if not eliminated, the need for paper records and patient involvement in ensuring the proper prescription, data collection, and data recording are communicated to patients and staff. Although patients currently still need to obtain and enter daily biometric data, future dialysis platforms coupled with wireless and Bluetooth-enabled devices could easily obviate this issue, further attenuating patient work burden while adding enhanced accuracy to data collected (Figure).

Potential and realized benefits of remote patient monitoring in home dialysis include improvement in clinical outcomes, treatment adherence, blood pressure control, and patient quality of life due to more treatment-related free time (2, 3). Additionally, remote monitoring-enabled longitudinal analytics could afford health care practitioners means for earlier identification, prevention, and treatment of psychosocial and medical issues, potentially reducing emergency department visits, hospitalizations, hospital length of stay, and technique failure—all of which would improve health-economic outcomes (4–6). Remote monitoring has also helped alleviate patient anxiety, strengthening confidence in self-care and promoting greater uptake of home dialysis therapies (7). The latter has recently been buttressed with virtual training programs that provide an immersive and interactive way to practice dialysis-related procedures. Repeatedly performing processes in a safe, virtual environment at their own pace can improve patient confidence, reduce user errors, and better enable their ability to identify potential problems prior to initiating any dialysis treatments in the home setting (8). These virtual training programs can also be accessed when a patient or staff feel that retraining would be beneficial.

While videoconferencing allows clinicians to observe the dialysis access and the presence of pedal edema in patients in the home environment, it does not substitute for an in-person performance of a physical examination. As Bluetooth-enabled technological advances emerge in the future, allowing for more accurate cardiac and pulmonary evaluations to proceed, a virtual physical examination may be a possibility, particularly when coupled with longitudinally collected analytic data.

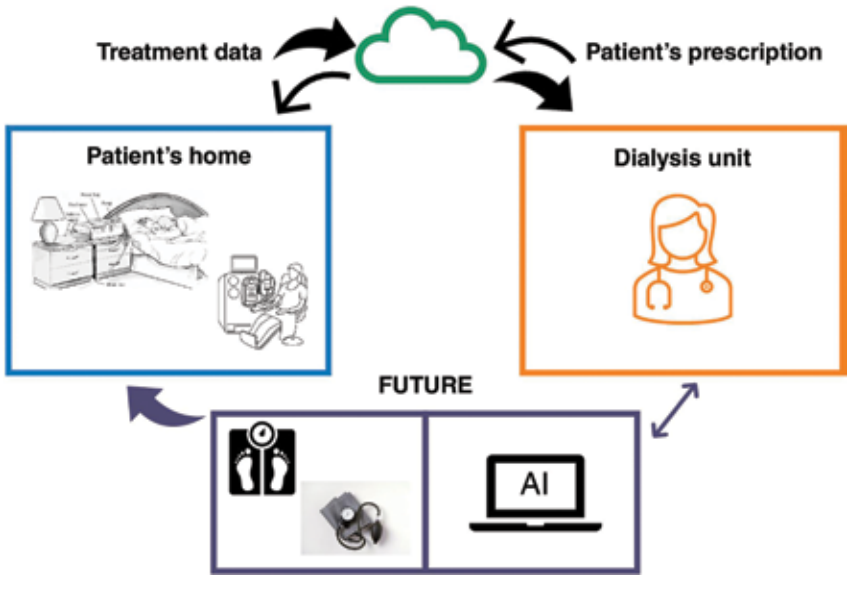
Telehealth regulation

Prior to January 1, 2019, the Centers for Medicare & Medicaid Services allowed the practice of telehealth in certain geographic locations, originating and distant sites, and among physician types in the United States. The dialysis unit and home were specifically excluded from being the originating sites.

Under the Bipartisan Budget Act of 2018, patients undergoing home dialysis could request up to two of three monthly visits per quarter to be conducted as telemedicine (audio-videoconferencing) after three monthly in-person visits were initially completed to establish a relationship (9). This regulation allows telehealth to be conducted from the patient's home as an originating site and without geographic restrictions. The physician must have a license in the state in which the patient lives, however, complicating remote care for some patients and clinicians.

During the COVID-19 pandemic, Public Health Emergency waivers resulted in reimbursement of both videoconference and telephone visits, in which new and existing patients and clinicians could be located at home and without geographic restrictions. These temporary regulations also had relaxed requirements for platforms, devices, and licensure. As a result, the pandemic spurred the use of telemedicine for the general population, as well as for the population of people with kidney failure (in-center hemodialysis and home dialysis). These flexible regulations have been extended beyond the end of the pandemic and are pending final determination by Congress (10).

Figure. Current and future state of data transmission between patient's home and dialysis unit



AI, artificial intelligence.

Impact on patients and caregivers

Telehealth eliminates traveling to the dialysis unit for both patients and practitioners. This offers particular advantages to those who live several hours from their dialysis facility (7). Pediatric patients enjoy the added benefit of not having to miss school and extracurricular activities, and parents and caregivers benefit from not having to miss work or time away from family (11). Older adults with mobility issues can avoid costly transportation and consuming caregivers' time to accompany them.

Remote monitoring and teletechnologies provide health care professionals daily and longitudinal insights into the well-being of their entire patient population undergoing home dialysis. However, this comes at the cost of changes in workflow and scheduling to accommodate daily review of remote patient monitoring data and to participate in telemedicine encounters (2). Similarly, the voluminous biometric and treatment data obtained from each patient will require an artificial intelligence approach to managing data, looking for patterns and deviations and creating predictive models (2).

In summary, remote monitoring and teletechnologies are here to stay, requiring ongoing commitment and learning by patients and care practitioners with the promise of improving health-economic outcomes. ■

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Dr. Lew reports no conflicts of interest. Dr. Sloand reports serving as a consultant for Hydrox Laboratories, Sequana Medical, and Simergent LLC.

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CREATIVE CORTEX

Kidney Transplant: A Journey of Healing

By Zahoor Ahmed

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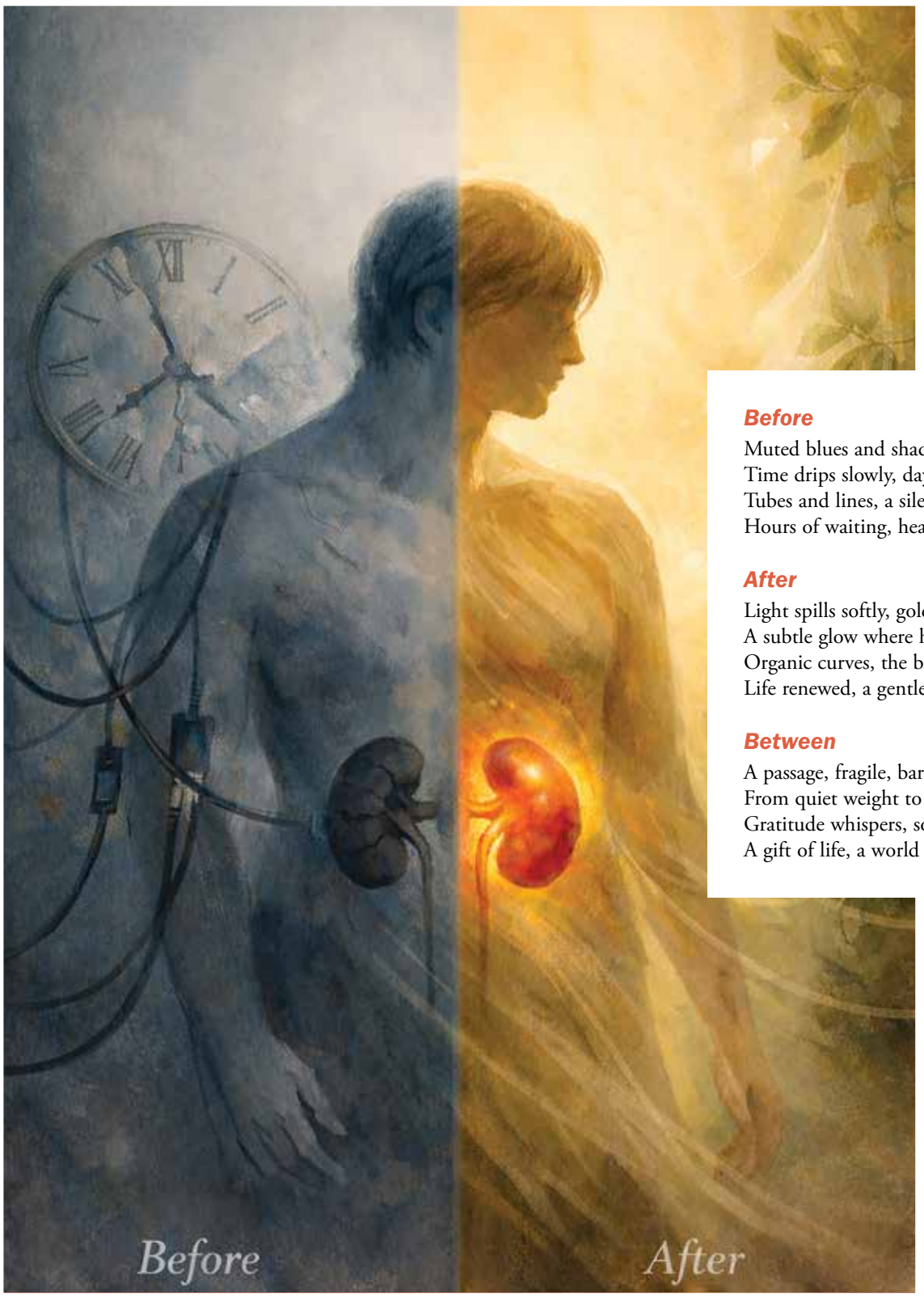

Before

Muted blues and shadowed gray,
Time drips slowly, day by day.
Tubes and lines, a silent thread,
Hours of waiting, hearts that dread.

After

Light spills softly, gold and green,
A subtle glow where hope has been.
Organic curves, the body flows,
Life renewed, a gentle glow.

Between

A passage, fragile, barely seen,
From quiet weight to vibrant sheen.
Gratitude whispers, soft and true,
A gift of life, a world made new. ■

The artist, Zahoor Ahmed, MD, is with Jefferson Einstein Philadelphia Hospital, Philadelphia, PA. This artwork is a digital mixed-media illustration, created using layered digital painting techniques that emulate watercolor and soft-brush textures. The composition intentionally contrasts muted, cool tones with warm, luminous hues to symbolize the transition from chronic dialysis dependence to renewal and restored life following kidney transplantation. As a nephrology fellow, Ahmed aims to use visual storytelling alongside clinical work to humanize the emotional and clinical journey of transplant recipients and highlight the transformative impact of kidney transplantation.

Guarding the Gift of Giving

By Paul E. Hanna, Rima Patel, Alok Arora, Ginseng Vang, and Beje Thomas

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For people living with kidney failure, the ultimate treatment is to receive a living kidney donation. Yet, living kidney donation, while selfless and altruistic, may come at a high and unexpected cost to the donors, particularly in the context of rising metabolic syndrome and obesity rates. Obesity is now considered an independent risk factor for developing chronic kidney disease, mostly driven by hyperfiltration injury, especially if accompanied by diabetes, hypertension, and cardiovascular disease (1, 2). This directly impacts short-term surgical complications after kidney donation because wound-healing and delayed overall recovery are often in donors with obesity compared with their counterparts without obesity (3). Notably, more than 25% of living donors today meet obesity criteria compared with less than 8% in the 1970s (4). Fortunately, obesity is a modifiable risk factor, but prekidney donation counseling alone hardly achieves sustained results and weight loss (5). Based on two sets of single-center data, after being counseled on weight loss and being declined for donation, very few potential donors are successful in weight loss (4, 6). Equally concerning, a majority of these donors gained the weight back at 15 years' follow-up (6). Given these findings, structured metabolic care before, during, and after donation is essential. We need to move beyond episodic and fragmented counseling and toward a longitudinal model that safeguards kidney donors' health.

Why kidney donors' metabolic clinic models matter

Today's donor evaluations mainly address surgical safety and short-term outcomes as they pertain to kidney donation. The absence of a dedicated metabolic care pathway leaves donors vulnerable to long-term cardiometabolic risks (7). There are data to suggest that donors with obesity are more likely to develop kidney failure, diabetes, and hypertension (8–10). Donors are proceeding through the process altruistically, and striving for the best possible long-term outcomes for them is essential. A formal clinic model run by an interdisciplinary transplant team (i.e., an experienced transplant nephrologist, transplant pharmacist, nutrition team, and transplant surgeon) can address this gap by integrating lifestyle interventions, pharmacologic strategies, and psychosocial support throughout the donation process. In practice, this model should focus on prioritizing three phases as follows: pre-donation risk optimization, perioperative risk mitigation, and post-donation close surveillance. Each phase offers clinicians specific ways to reduce complications in kidney donors and preserve their kidney function (Figure).

Phase 1: Before donation and reducing metabolic risk

Pre-donation evaluation already includes a comprehensive program that extends beyond basic screening, including lifestyle and dietary habits, biochemical markers such as glycohemoglobin and lipid profile, medication review, and psychosocial readiness (11). Counseling typically addresses modifiable risks such as weight reduction, sodium restriction, and nephrolithiasis prevention, for instance. However, donors with severe obesity are often referred to weight-loss programs or endocrinology for further management. This can be limited by clinic availability and can lead to delays in intervention for potential donors. For these individuals, transplant nephrologists could discuss bariatric interventions and medical therapies while addressing their own risks such as gallstones, oxalate nephropathy, and vitamin deficiencies (1, 12). It is critical that donors understand the perioperative complications and the uncertainty surrounding long-term outcomes with a solitary kidney (13). Clear and early counseling helps donors share responsibility with their multidisciplinary care team and better understand their long-term risks and works toward mitigating these risks with weight loss.

Phase 2: Hospital stay and preventing complications

During hospitalization, metabolic syndrome biomarkers are often overlooked because surgical teams prioritize surgical needs and immediate postoperative issues that arise. However, using simple yet effective strategies, such as ensuring proper hydration, promoting early movement, and applying stress-reduction techniques, can greatly reduce the chance of postoperative complications like venous thrombosis and kidney stones (3). Additionally, 24-hour blood pressure trends using current new technology, rather than isolated clinic readings, provide better and meaningful insight. These data would then inform early interventions and aid in discharge planning and clinic follow-up (14).

Phase 3: After donation and long-term surveillance

Post-donation follow-up should be individualized based on risk factors that were previously identified during an initial evaluation. A structured surveillance plan typically at 1, 3, 6, and 12 months after donation, followed by annual assessments, allows clinicians to monitor trends in blood pressure, body mass index, kidney indices such as estimated glomerular filtration rate (eGFR) and albuminuria, metabolic parameters, and overall psychosocial well-being (11). Home-based monitoring and telemedicine can keep donors engage and allow early intervention.

For instance, for individuals with increased cardiovascular risk, timely therapy would be beneficial. Agents like sodium-glucose cotransporter-2 inhibitors or glucagon-like peptide-1 receptor agonists have demonstrated benefit in this population, particularly when glycated hemoglobin levels rise above 6.5%. If weight-loss medications are used to help with weight loss before donation, it is important to have continued access for these medications for kidney donors due to risk of weight gain upon discontinuation (15). Ongoing education about lifelong avoidance of nephrotoxins, especially nonsteroidal anti-inflammatory drugs (NSAIDs), is critical in donor care (1). Another key step is regular and consistent use of urine testing to detect early proteinuria, coupled with prompt initiation of renin-angiotensin system blockers such as angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in individuals with prediabetes or prehypertension. These proactive measures, based on Kidney Disease: Improving Global Outcomes (KDIGO) recommendations, can meaningfully reduce long-term kidney and cardiovascular risk (11).

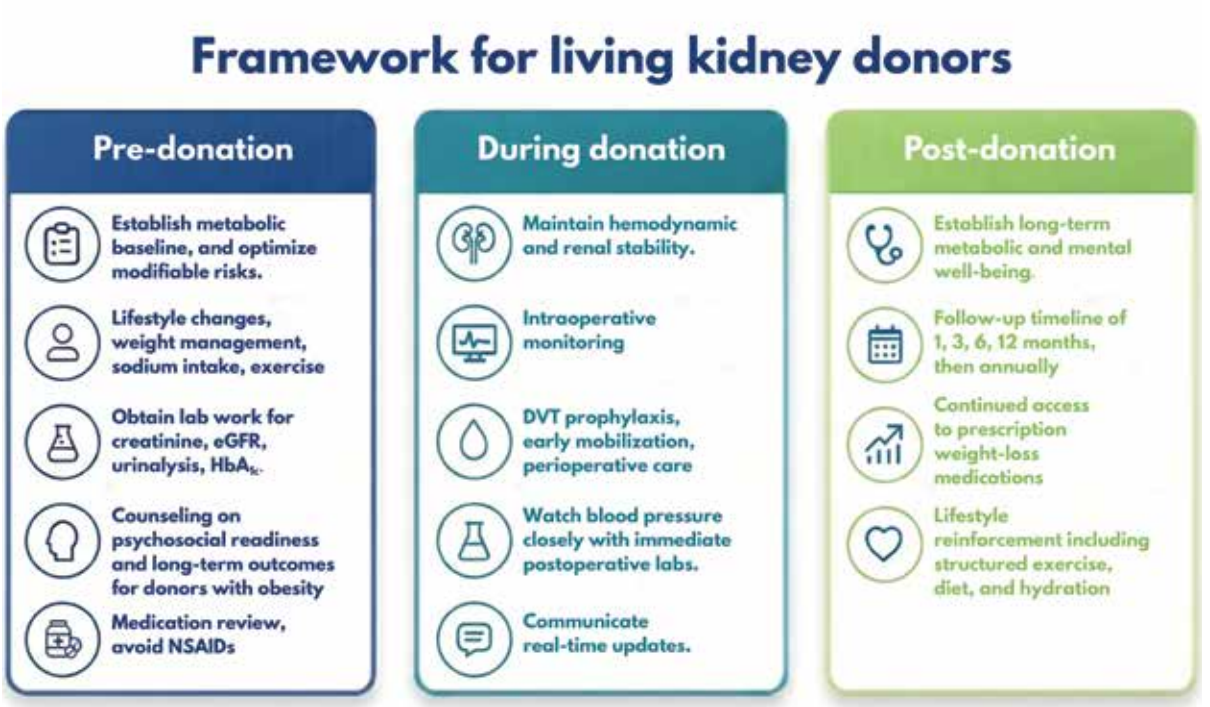
Quality improvement and risk management

Establishing a donor metabolic clinic could reduce long-term complications such as hypertension and chronic kidney disease, but its true impact depends on a sustained commitment to recognizing where the gaps are and addressing them. Clinic success should be measured using clear, evidence-based metrics such as maintaining blood pressure less than 130/80 mm Hg, tracking kidney function trajectories, and ensuring consistent follow-up at regular intervals such as 1, 3, and 5 years after donation. Prompt referral to appropriate specialists, including mental health professionals, ensures that both physical and psychologic aspects of donor health are addressed (7). Additionally, donor-reported measures like self-reported quality of life, satisfaction with care, and emotional well-being may offer essential insight into the program's overall effectiveness (16). Using telehealth can make follow-up easier for donors, which can enhance accessibility and adherence, particularly for donors who require ongoing monitoring because some donors travel a great distance to donate. Ultimately, success depends on meeting clinical targets while ensuring that donors feel supported.

Next steps

As living kidney donors make an unparalleled contribution, the duty of care toward them extends far beyond the operating room. Ensuring their long-term well-being demands an intentional and structured approach to metabolic

Figure. Comprehensive metabolic care in kidney donors



DVT, deep venous thrombosis; HbA_{1c}, hemoglobin A_{1c}.

management. Establishing dedicated metabolic clinics that strengthen interdisciplinary collaboration among transplant nephrology, transplant pharmacy, transplant surgery, primary care, behavioral health teams, and donors is pivotal. These steps protect donor health; ensure consistent, high-quality follow-up; and preserve the gift of giving. ■

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The authors report no conflicts of interest.

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Findings

Complement Factor B Inhibitor Shows Promise in IgA Nephropathy

https://doi.org/10.62716/kn.002882026

The novel antisense oligonucleotide complement factor B inhibitor sefaxersen shows evidence of clinical benefit in patients with immunoglobulin A nephropathy (IgAN), reports a preliminary study in *Kidney International*.

The single-arm, open-label trial enrolled 23 patients with biopsy-confirmed IgAN. All had kidney C3 deposits with hematuria, proteinuria greater than 1.5 g/day, and an estimated glomerular filtration rate (eGFR) less than 40.0 mL/min/1.73 m^2 despite maximal renin-angiotensin-aldosterone system blocker therapy. Most patients were male and of Asian race; the mean age was 44 years, and the geometric mean proteinuria was 2.5 g/day.

All patients received sefaxersen (RO7434656), 70 mg subcutaneously monthly for 24 weeks, with an option to extend treatment. The change in 24-hour urinary protein excretion from baseline to 29 weeks was assessed along with secondary outcomes.

Sefaxersen was associated with selective reductions in plasma complement factor B and Bb, urinary factor Ba, and serum complement alternative pathway activity, with no change in classical pathway activity. At 29 weeks, mean urinary protein excretion was 1.4 g/day, a reduction of 43%, decreasing by at least 0.5 g/day in three-fourths of the patients and by at least 1.0 g/day in one-half of the patients. There was no significant change in eGFR, which remained stable from 70.4 mL/min/1.73 m^2 at baseline to 73.2 mL/min/1.73 m^2 through week 29.

Seven patients received extended treatment with sefaxersen; all showed a sustained reduction of proteinuria. Three patients had sharp but reversible elevations of alanine amino transferase, with no change in bilirubin.

Complement pathway activation seems to play a central role in local inflammation and kidney damage in IgAN. The new findings suggest that sefaxersen, which directly targets the complement system, reduces proteinuria and preserves stable eGFR, with good safety and tolerability. The multinational, phase 3 IMAGINATION trial (NCT05797610) will further evaluate sefaxersen as a new therapy for IgAN [Barbour SJ, et al. A single-arm phase 2 trial of an investigational RNA therapeutic to complement factor B sefaxersen for treatment of IgA nephropathy. *Kidney Int,* published online December 22, 2025. doi: 10.1016/j.kint.2025.11.017]. ■

Data on PROs Improve Mortality Prediction at Start of Dialysis

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A prognostic model incorporating data on patient-reported outcomes (PROs) improves prediction of 2-year mortality risk in patients initiating dialysis, according to an article in *Kidney International*.

The study used data from two European prospective follow-up studies: the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD) and the more recent European Quality (EQUAL) study. The researchers evaluated the impact of adding selected PROs—mental and physical component scores, general health perception, depressive symptoms, symptom burden, number of symptoms, fatigue, and pain—to standard demographic and clinical variables in a base prognostic model.

Initial and extended models were developed using data on 1956 patients from NECOSAD, including a subcohort of 862 patients aged 65 years or older. The analyses were then replicated using data on 415 patients from the EQUAL study, which enrolled patients aged 65 years or older. Multiple methods were used to assess the predictive value added by incorporating PRO data.

Two-year mortality was 22.9% in NECOSAD, 24.3% in EQUAL, and 37.1% in the NECOSAD 65-plus cohort. Models including PROs "consistently outperformed" base models. In all three cohorts, more patients were correctly reclassified than incorrectly reclassified when PROs were added. On decision curve analysis, the extended model had a higher net benefit at most risk thresholds.

Analysis of different predictor groups found that the PROs on their own were moderate predictors of mortality, outperforming demographic and laboratory variables. Across cohorts, "summarizing" PROs, such as physical and mental component score and symptom burden, showed the most consistent performance.

Prognostic models for patients initiating incident dialysis generally rely on demographic and clinical variables such as age, comorbid conditions, and laboratory results. Studies in patients with other conditions suggest that PROs can serve as useful predictors of survival.

The recent analysis suggests that PRO data "notably improves predictive performance" in patients initiating dialysis. "These findings suggest that patients have a strong intuitive understanding of their current health status," the researchers write. They add: "Looking ahead, the integration of PROs into prognostic models could help us develop more accurate, and potentially more simplified risk stratification strategies" [Milders J, et al.; EQUAL study investigators. A predictor finding study found patient-reported outcomes improve the prediction of mortality of incident dialysis patients. *Kidney Int,* published online January 21, 2026. doi: 10.1016/j.kint.2025.07.033]. ■

Aprocitentan Lowers BP in People With CKD and Resistant Hypertension

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Added to background therapy, the dual endothelin receptor antagonist aprocitentan is an efficient treatment for resistant hypertension (RHT) in people with chronic kidney disease (CKD), according to a clinical trial report in *Hypertension*.

The authors performed a post hoc analysis of patients from the Parallel-Group, Phase 3 Study With Aprocitentan in Subjects With Resistant Hypertension (PRECISION) study. Of 730 participants, 147 had high-risk or very high-risk CKD, based on Kidney Disease: Improving Global Outcomes (KDIGO) criteria. In a three-part study design, patients were randomly assigned to treatment with aprocitentan 12.5 mg or 25.0 mg or placebo, added to standardized background antihypertensive therapy. Effects on blood pressure (BP) and the urine albumin-to-creatinine ratio (UACR) were assessed, along with safety outcomes.

In the first 4 weeks, office systolic BP decreased by –13.5 mm Hg with aprocitentan 12.5 mg and –16.6 mm Hg with aprocitentan 25.0 mg compared with –4.4 mm Hg with placebo. Through 36 weeks, the reductions in BP were well maintained with aprocitentan 25.0 mg. Aprocitentan also produced a greater reduction in night-time ambulatory BP at 4 weeks: –9.6 mm Hg at the 12.5-mg dose and –13.8 mm Hg at the 25.0-mg dose versus –2.5 mm Hg with placebo.

Patients assigned to aprocitentan also had greater reductions in UACR: –47.1% at the 12.5-mg dose and –59.6% at the 25.0-mg dose compared with –2.4% with placebo. The reduction in UACR was maintained through 36 weeks at the 25.0-mg dose. Aprocitentan was well tolerated, with no adverse effects on potassium level or estimated glomerular filtration rate (eGFR).

Findings suggest that aprocitentan efficiently lowers BP, particularly night-time ambulatory BP, in people with CKD and RHT. Treatment also reduces UACR without reducing eGFR, suggesting a "considerable, clinically meaningful cardiovascular and kidney-protective benefit in these [patients who are difficult to treat]." The investigators conclude: "Aprocitentan may represent the preferred choice in patients with uncontrolled hypertension and advanced CKD to improve BP control and reduce proteinuria if present" [Rossignol P, et al. Aprocitentan in patients with chronic kidney disease and resistant hypertension. *Hypertension* 2026; 83:e25563. doi: 10.1161/HYPERTENSIONAHA.125.25563]. ■

Faster Sodium Correction Reduces Adverse Outcomes in Severe Hyponatremia

https://doi.org/10.62716/kn.003062026

In patients with severe hyponatremia, faster sodium correction rates are associated with lower risk of death or delayed neurologic events compared with the current guideline-recommended slow correction strategy, reports a study in *Annals of Internal Medicine*.

The retrospective analysis included data on 13,988 patients with severe hyponatremia (serum sodium ≤120 mEq/L) treated at 21 Kaiser Permanente Northern California hospitals between 2008 and 2023. Based on a maximum 24-hour serum sodium increase, the sodium correction rate was classified as slow (<8 mEq/L), medium (8–12 mEq/L), or fast (>12 mEq/L). Groups were compared on a primary composite outcome of death or delayed neurologic events (new demyelination, paralysis, epilepsy, or altered consciousness) within 90 days.

The median age was 74 years; 63% of patients were women. Congestive heart failure was the most frequent comorbid condition, followed by liver disease, alcohol dependence, and metastatic cancer. A primary outcome event occurred in 21% of patients: death in 18% and delayed neurologic events in 4%.

Faster sodium correction rates were associated with a lower risk of primary outcome events: 18% with medium and 11% with fast correction compared with 28% with slow correction. Mortality was 14% among medium, 8% with fast, and 24% with slow corrections. Although the risk differences were greater for patients at higher predicted risk, associated risk ratios were similar across groups. The benefit of faster correction was apparent in subgroup analyses and differing analytic methods.

Current clinical practice guidelines for severe hyponatremia call for slow, controlled correction of sodium levels—reflecting fears of potentially devastating osmotic demyelination syndrome. This large retrospective cohort study adds new evidence that faster correction of severe hyponatremia is associated with a lower risk of death or delayed neurologic events within 90 days. The researchers write, "treatment guidelines for severe hyponatremia should be reexamined to allow for faster sodium correction, regardless of presumed risk factors" [Mark DG, et al.; Kaiser Permanente CREST Network Investigators. Sodium correction rates and associated outcomes among patients with severe hyponatremia: A retrospective cohort study. *Ann Intern Med,* published online January 27, 2026. doi: 10.7326/ANNALS-25-03676]. ■

Correction

Correction to "CKM Syndrome, a New Superspecialty, and the Love Your Kidneys! Campaign" (February 2026)

https://doi.org/10.62716/kn.003032026

The ASN Executive Vice President's Update, "CKM Syndrome, a New Superspecialty, and the Love Your Kidneys! Campaign" by Tod Ibrahim, published in the February 2026 issue of *Kidney News* (1), was amended after print publication to clarify details related to the American Heart Association's Cardiovascular-Kidney-Metabolic Health Initiative. The updated version was published online on February 6, 2026.

Reference

1. Ibrahim T. CKM syndrome, a new superspecialty, and the Love Your Kidneys! campaign. *Kidney News*, February 2026; 18(2):6–7. doi: 10.62716/kn.002922026

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