

Next-generation dialysis: implantable, wearable, and continuous modalities challenging the 3-day-a-week paradigm

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Background

Conventional thrice-weekly hemodialysis has anchored end-stage kidney disease care for over 50 years, yet delivers a fraction of native clearance and drives cardiovascular morbidity through solute and volume swings. Refinements in membranes, water purity, and vascular access have not closed the survival gap. The FDA's 2024 Breakthrough Device Designation for the Nephrodite Holly implantable continuous dialysis system has reignited debate about transcending the 3-day-a-week paradigm.

Methods

We synthesized peer-reviewed literature, regulatory filings, and trial data on three next-generation modalities: implantable continuous dialysis systems, wearable artificial kidneys, and frequent or home hemodialysis, drawing on FDA documentation with explicit caveats where peer-reviewed evidence was absent.

Results

The physiological case for transcending thrice-weekly dialysis is robust. Increased frequency improves blood pressure, left ventricular mass, and middle-molecule clearance, though randomized mortality benefit is modest and partly reversed at extended follow-up. Implantable systems (University of California San Francisco Kidney Project, Nephrodite Holly) remain preclinical, with unresolved challenges in biocompatibility, thrombogenicity, infection, and membrane durability. Wearable platforms have shown short-term human feasibility but have stalled commercially after more than 25 years. Frequent home hemodialysis, the most evidence-based alternative, serves fewer than 5% of dialysis patients.

Conclusion

Next-generation dialysis is neither imminent nor science fiction. Adoption requires regulatory pathways for continuous organ-replacement therapy, reimbursement reform beyond session-based payment, durable solutions to biofouling, and trials with validated continuous-clearance endpoints. The nephrology community must demand evidence proportional to the proposed change and resist conflating Breakthrough Device Designation with clinical readiness.

Keywords:

bioartificial kidney, breakthrough device designation, end-stage kidney disease, frequent hemodialysis, health technology assessment, hemodialysis, home hemodialysis, implantable artificial kidney, reimbursement, wearable artificial kidney

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Introduction

End-stage kidney disease (ESKD) treated by maintenance hemodialysis is one of the most consequential mismatches in modern medicine between a therapy's clinical penetration and its physiological adequacy. A native kidney delivers ~ 100–120 ml/min of glomerular filtration continuously, augmented by tubular secretion, reabsorption, and endocrine and metabolic functions that no replacement therapy attempts to recapitulate [1]. Thrice-weekly in-center hemodialysis (TWHd), at standard targets of single-pool Kt/V more than or equal to 1.4 per-session, restores a time-averaged equivalent clearance closer to 10–15 ml/min – perhaps 10–15% of healthy kidney function – and delivers it in three intermittent bursts separated by 44- and 68-h gaps during which uremic solutes and fluid accumulate [1,2] (Fig. 1). The figure

depicts precisely this intermittent-versus-continuous clearance profile.

The clinical consequences of this rhythm are well documented. Mortality in US dialysis cohorts is consistently elevated on Mondays and Tuesdays, the days following the long interdialytic interval; in the analysis by Foley *et al.* [3], the rate of all-cause death and cardiovascular events on the day after the long interval was higher than on any other day of the week. Sudden cardiac death is the single largest cause of death in this population [4,5]. Repeated ultrafiltration cycles produce regional myocardial stunning detectable

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on intradialytic echocardiography, which over time correlates with fixed myocardial fibrosis and reduced left ventricular function [6,7]. Brain perfusion falls during routine dialysis sessions in older patients, and white matter abnormalities accumulate over months of conventional therapy [8,9]. Beta-2 microglobulin and other middle molecules accrue between sessions because their distribution kinetics outpace the diffusive removal capacity of intermittent therapy [10–12]. Patients on TWHHD live substantially longer than untreated patients with ESKD, but they live substantially shorter than age-matched peers. That gap has not narrowed materially over two decades of refinement to membrane flux, dialysate purity, and vascular access [1,13,14].

Three families of next-generation modalities have emerged as candidate responses. Implantable continuous dialysis systems aim to deliver low-flow filtration around the clock from a device implanted within the body, ideally without an extracorporeal circuit and with reduced or absent anticoagulation. Wearable artificial kidneys aim to deliver portable, ambulatory therapy through sorbent-based dialysate regeneration. Frequent, home, or nocturnal hemodialysis aims to extract better outcomes from existing technology by changing the schedule rather than the hardware. The October 2024 FDA grant of Breakthrough Device Designation to Nephrodite Inc.'s Holly implantable continuous dialysis system has focused attention on the first category and prompted renewed scrutiny of the entire next-generation pipeline [15].

This review pursues three objectives. First, to characterize the physiological case against TWHHD with sufficient rigor that any candidate replacement can be measured against it. Second, to appraise the published evidence and the regulatory positioning of each class of next-generation modality, distinguishing engineering feasibility from clinical readiness. Third, to identify the structural barriers – biological, regulatory, economic, and global – that any of these technologies will have to overcome before they alter the experience of living with kidney failure for more than a small minority of patients. The Breakthrough Device Designation for Holly is taken not as evidence of efficacy but as a procedural prompt for the kind of scrutiny the field owes any technology proposing to displace a 50-year standard of care.

Methods of literature synthesis

We searched MEDLINE (PubMed), EMBASE, and the Cochrane Central Register of Controlled Trials from inception to October 2025 using combinations

of the terms hemodialysis, peritoneal dialysis, ESKD, wearable artificial kidney, implantable artificial kidney, bioartificial kidney, frequent hemodialysis, and nocturnal hemodialysis, supplemented by hand-searching of references from key reviews and from the websites of the Frequent Hemodialysis Network (FHN), the Kidney Project, Automated Wearable Artificial Kidney (AWAK) Technologies, and Nephrodite Inc. We searched ClinicalTrials.gov and the EU Clinical Trials Register for ongoing or completed studies of next-generation modalities. We retrieved FDA documentation, including Breakthrough Device Designation summaries and 510(k) and PMA listings where available, and Centers for Medicare and Medicaid Services rulemaking on the ESKD Prospective Payment System.

We included peer-reviewed studies, regulatory documents, registry analyses, and society guidelines. We excluded conference abstracts unless they reported data not available in indexed publications, in which case we cited them with explicit caveats. We weighted the synthesis toward randomized trials and systematic reviews where available; for technologies at preclinical or early feasibility stages, we drew on case series and developer disclosures, and labeled these accordingly. Evidence was appraised against established critical appraisal standards, including AMSTAR-2 for systematic reviews, GRADE for certainty of evidence, and AGREE II for guideline appraisal. This is a narrative review and does not aim for the systematic completeness of a PRISMA-compliant synthesis.

The physiological case against thrice-weekly hemodialysis

The FHN Daily Trial randomized 245 prevalent hemodialysis patients to six versus three weekly in-center sessions and reported a coprimary composite of death or change in left ventricular mass that favoured frequent treatment (hazard ratio 0.61, 95% confidence interval 0.46–0.82), with a separate benefit on death or change in physical health composite of the RAND-36 (hazard ratio 0.70, 95% confidence interval 0.53–0.92) [16]. The companion Nocturnal Trial randomized 87 patients to six-times-weekly nocturnal home hemodialysis versus conventional therapy and was underpowered to detect mortality differences but showed favorable changes in phosphate control and dialysate effluent volume [17]. Long-term follow-up tempered the early enthusiasm: the FHN daily extended cohort showed attenuation of left ventricular benefit, and the nocturnal extended cohort showed a numerical excess of deaths in the frequent arm that did not reach statistical significance [18,19].

Together, these results discipline any easy claim that more dialysis is automatically better. The relationship between dose, schedule, and outcome is not linear, vascular access events accumulate with frequency, and selection bias contaminates the observational comparisons that have driven much of the enthusiasm for nocturnal therapy [20,21].

The middle-molecule clearance argument is independent of session frequency in important ways. Beta-2 microglobulin, fibroblast growth factor 23, and protein-bound toxins such as indoxyl sulfate distribute substantially in tissue compartments and rebound rapidly after dialysis; their time-averaged concentrations are dominated by total removal time rather than peak clearance [10–12]. High-flux membranes modestly improved beta-2 microglobulin removal in the HEMO and MPO trials. Still, they produced no clear survival benefit in the overall populations, with subgroup signals only in patients with longer dialysis vintage [22,23]. Online hemodiafiltration achieves greater convective clearance, and the recent CONVINCe trial reported a 23% relative reduction in all-cause mortality at a median of 30 months in patients receiving high-volume hemodiafiltration versus conventional high-flux hemodialysis [24]. Extending these observations to the implantable or wearable context is informative but not conclusive: continuous low-flow therapy is structurally different from high-volume episodic convection, and the clearance kinetics of low-flux continuous filtration have not been mapped to clinical endpoints.

Residual kidney function (RKF) appears to dominate survival in the early years of dialysis across modalities. The CANUSA reanalysis showed that each 5 l/week per 1.73 m² increment in residual GFR was associated with a 12% reduction in mortality, while peritoneal clearance contributed nothing independent of RKF [25]. NECOSAD-2 made the analogous observation in hemodialysis cohorts [26]. Any next-generation device that disrupts RKF preservation – through hemodynamic stress, repeated nephrotoxin exposure, or surgical implantation – incurs an outcome cost that must be weighed against its incremental clearance.

The hemodynamic stress model integrates these strands. Each ultrafiltration session generates intradialytic hypotension in 20–30% of treatments, regional left ventricular wall-motion abnormalities in over 60% of patients on echocardiographic assessment, and acute reductions in cerebral blood flow detectable on PET imaging [6–8,27]. Cooled dialysate ameliorates both myocardial stunning and white matter injury, providing mechanistic confirmation that the injury is hemodynamic rather than purely toxin-mediated [9,28]. The implication for next-generation design is direct:

any therapy that delivers continuous, lower-flux clearance – implantable, wearable, or simply more frequent – should reduce this cyclic injury, but only if it does so without introducing new sources of ischemia, infection, or thromboembolism.

Randomized evidence in this space remains sparse for two reasons. The patient population is heterogeneous, often frail, and the modality intervention is unblinded; trials struggle to enroll and retain participants over the durations needed to detect mortality differences. Observational comparisons of nocturnal home hemodialysis cohorts versus conventional dialysis have repeatedly favored the frequent arm but cannot disentangle treatment effect from selection [20,29]. The field has reached a point where mechanistic plausibility, intermediate physiological endpoints, and observational signals all favor more frequent or continuous therapy. Still, the trial evidence required to mandate a change in standard of care has not yet been generated.

Implantable continuous dialysis: technology, evidence, and critical appraisal

Conceptual architecture and rationale

An implantable continuous dialysis system, in its most ambitious formulation, would replace a defined fraction of native kidney function from inside the body, drawing its blood supply from the patient's own vasculature, generating filtrate that drains to the bladder or to a collection reservoir, and operating at flows orders of magnitude lower than extracorporeal hemodialysis. Two architectures dominate the design space. The first is a pure hemofilter, relying on a high-permeability membrane to generate filtrate by hydrostatic pressure across an arteriovenous gradient; this design forgoes the complex tubular processing of the native nephron and instead aims to deliver continuous, low-flux clearance approximating slow continuous ultrafiltration scaled for chronic implantation. The second adds a bioartificial component – viable renal tubule cells cultured on a scaffold downstream of the hemofilter, intended to recapitulate selective reabsorption, vitamin D activation, and immunomodulation that pure filtration cannot provide [30–32].

The conceptual gap between these two designs is substantial. A purely filtering implant cannot replicate the kidney's endocrine outputs, the regulated reabsorption that maintains volume status, or the active secretion of organic anions that handles many uremic toxins; it inherits the same continuous-clearance benefits as a wearable filter without solving the toxin

spectrum problem. A bioartificial implant addresses these gaps in principle. Still, it introduces cell sourcing, viability over years, and immunological and oncogenic concerns that have not been resolved in any sustained chronic implantation model [33–35]. These trade-offs are not incidental engineering choices; they define the clinical value proposition of each platform, and any appraisal that obscures them collapses meaningful distinctions between fundamentally different devices.

Nephrodite Holly system

Nephrodite Inc., a clinical-stage medical technology company, received FDA Breakthrough Device Designation for its Holly implantable continuous dialysis system in 2024 [15]. Publicly available descriptions characterize Holly as a fully implantable device that connects to the systemic vasculature to provide continuous hemofiltration, with filtrate routed for elimination through patient anatomy. Detailed peer-reviewed engineering characterization and clinical data have not, at the time of writing, appeared in indexed literature; available descriptions rest on the developer's communications and FDA disclosure documentation, and these claims should be treated as preliminary pending independent verification.

The Breakthrough Device Designation pathway is procedural rather than evaluative. It provides expedited interaction with FDA reviewers, prioritized review timelines, and access to presubmission feedback on study design. It does not constitute a determination of safety or efficacy, and it does not waive the requirement for adequate clinical evidence under either the *de novo* or premarket approval pathways. The FDA's Breakthrough Devices Program guidance is explicit on this point. A BDD is best understood as a regulatory acknowledgment that the device targets a serious condition with no satisfactory alternative; it is not a step toward approval that exempts a device from standard endpoints, nor does it shift the burden of evidence to the regulator.

A device with the conceptual architecture described for Holly faces five biologically grounded concerns that any clinical trial program must address. Thrombogenicity at the blood–membrane interface remains the single largest unresolved problem in chronic blood-contacting implants; long-term success has historically required either continuous systemic anticoagulation or extraordinary surface-modification engineering, neither of which has been demonstrated at the durability required for years of continuous use [35,36]. Inflammatory response and the foreign-body capsule progressively reduce membrane permeability and may abolish clinically meaningful clearance over months.

Infection risk in an implanted device with vascular anastomoses is non-trivial; rates from comparable implanted devices, including ventricular assist devices and implanted vascular grafts, provide the relevant prior, and dialysis populations carry baseline infection risks that compound this concern. Membrane biofouling – protein adsorption, platelet adhesion, and biofilm formation – is universal in chronic blood-contact applications and has no established solution at the durations required [37]. Anticoagulation management in a population already at competing hemorrhagic and thromboembolic risk is a clinical problem distinct from the engineering problem, and has caused trial failure in this space before. Press communications and a Breakthrough Device Designation are not evidence that any of these problems have been solved.

The kidney project/University of California, San Francisco bioartificial kidney

The Kidney Project, a long-running collaboration anchored at the University of California, San Francisco and Vanderbilt, has pursued an implantable bioartificial kidney combining a silicon nanopore membrane with a renal tubule cell cartridge [32–34,38]. The silicon nanopore membrane is fabricated using photolithographic processes developed in semiconductor manufacturing, achieving a narrow, uniform slit-pore geometry with selectivity profiles superior to conventional polymer hollow fibers in bench testing [33]. The hemofilter component has been demonstrated in large-animal preclinical studies to deliver clinically relevant filtrate flows for limited durations, with some configurations operating without external anticoagulation for short periods. The bioartificial reabsorption component, derived from earlier work by Humes *et al.* [30] on the renal tubule assist device for acute kidney injury, would be intended to selectively reabsorb water and solutes from filtrate before discharge [31].

Published human feasibility data for the integrated implantable device have not appeared at the time of writing; demonstration of the components has been *in vitro* or in animal models, and integrated, sustained chronic implantation has not been reported in peer-reviewed literature [32,34,35]. The Kidney Project leadership has been candid about the translational gap, including in a journal commentary that distinguishes engineering progress from clinical readiness [35]. Two decades of consistent funding and an incremental publication record provide a more reliable platform for eventual translation than newer entrants without comparable preclinical infrastructure. Still, no implantable artificial kidney has yet demonstrated months of sustained clinically relevant clearance in a

single human. That benchmark – not designation, not preclinical proof of concept – is the threshold the field should require before clinical adoption is contemplated.

Cross-cutting critical appraisal of implantable systems

Three issues cut across all implantable platforms. First, patient selection criteria are unresolved. Implantation requires vascular access surgery in an often vasculopathic population; surgical candidacy alone may exclude a substantial fraction of prevalent dialysis patients. The denominator of those for whom an implantable device is a candidate therapy is likely smaller than the prevalent dialysis population, and trial inclusion criteria will materially shape generalizability claims.

Second, regulatory classification is ambiguous when a device incorporates viable cells, generating overlapping device, biologic, and combination-product considerations that complicate both trial design and approval pathways. The cell component of a bioartificial kidney triggers the FDA Center for Biologics Evaluation and Research review framework on top of the device review, with implications for manufacturing controls,

donor screening, and tumourigenicity assessment that are absent for a purely synthetic implant.

Third, endpoint validation is genuinely difficult. Conventional dialysis adequacy metrics (Kt/V, urea reduction ratio) are session-based and do not reflect continuous clearance; surrogate endpoints (cardiovascular events, hospitalization, RKF preservation) require trial durations and sample sizes that the developer pipeline does not currently support. A registry-based, adaptive trial framework with composite endpoints, validated against an active TWHG comparator, is the realistic path forward. Still, neither regulators nor developers have committed to such a framework. Without such commitment, the field risks either underpowered approvals based on early feasibility data or indefinite delays in any pivotal trial. Table 1 summarizes the implantable platforms and their development status.

Wearable dialysis: technology, evidence, and critical appraisal

Wearable artificial kidney for hemodialysis

The wearable artificial kidney concept, advanced over

Table 1 Implantable artificial kidney platforms – technology architecture, development stage, evidence base, and unresolved challenges

Platform/developer	Technology architecture	Vascular/access interface	Development stage	Key published evidence	Primary unresolved challenges	Regulatory status
UCSF Kidney Project (UCSF/vanderbilt)	Silicon nanopore hemofilter + bioartificial renal tubule cell cartridge	Implanted vascular anastomosis (planned arteriovenous configuration)	Preclinical (component-level large-animal studies); first-in-human pending	Nanopore membrane characterization in vitro; tubule cell function in extracorporeal cartridges in animals; integrated implant data not yet in indexed peer-reviewed literature [30–35]	Long-term cell viability under chronic implantation; immune and oncogenic safety of cell component; biofouling at the membrane; integrated device durability; no human feasibility data	Pre-IDE (no active clinical trial registered at time of writing)
Nephrodite Holly (Nephrodite Inc.)	Implantable continuous hemofiltration system (developer description)	Vascular anastomosis (per developer disclosures)	Preclinical/first-in-human pending (per developer disclosures and FDA BDD documentation)	No peer-reviewed clinical or detailed engineering data identified; available description rests on developer communications and FDA BDD summary [15]	Thrombogenicity and biofouling at blood–membrane interface; infection risk at vascular anastomoses; clearance durability; anticoagulation strategy; independent verification of architecture and performance	FDA Breakthrough Device Designation granted 2024 (procedural; not approval)
Renal Tubule Assist Device/RAD (Humes; Innovative BioTherapies)	Extracorporeal cartridge of cultured human renal tubule cells in series with a conventional CRRT circuit	Extracorporeal (not implantable in current form)	Phase 2 trials in acute kidney injury	Phase 2 RCT in critically ill AKI showed a mortality signal (n=58); chronic ESKD development was not pursued [31]	Cell sourcing and viability for chronic use; not currently developed for implantation	Not in active development for ESKD
Human Nephron Filter (Nissenson <i>et al.</i>)	Continuous filtration concept without sorbents; two-stage filter design	Wearable extracorporeal in concept	Conceptual/early prototype	Concept paper; no sustained human data identified [39]	Engineering is not advanced past the concept stage	None

Statements drawn from regulatory or developer documentation are flagged in the text and table; independent peer-reviewed verification is pending where indicated. BDD, Breakthrough Device Designation; CRRT, continuous kidney replacement therapy; ESKD, end-stage kidney disease; FDA, US Food and Drug Administration; IDE, Investigational Device Exemption; RCT, randomized controlled trial; UCSF, University of California, San Francisco.

two decades by Gura *et al.* [40], attempts to deliver continuous or near-continuous extracorporeal therapy from a device that the patient wears on a belt, with sorbent-based regeneration of small-volume dialysate replacing the high-volume single-pass dialysate of conventional hemodialysis. The 2007 Lancet pilot reported on eight prevalent hemodialysis patients undergoing 4–8 h sessions with the belt-worn device, demonstrating the engineering feasibility of continuous low-flow blood and dialysate circuits delivering urea and creatinine clearance comparable to a fraction of conventional therapy in that timeframe [41]. A subsequent FDA-supervised feasibility study reported on seven patients receiving up to 24 h of WAK therapy and identified key technical limitations: variable blood and dialysate flows, intermittent CO₂ bubble formation in the circuit, and one episode of dialysate leakage requiring removal [42].

Sorbent cartridge capacity, urease-mediated ammonium production, and the management of phosphate and potassium in a regenerated low-volume dialysate remain unresolved at the durations required for sustained chronic use [40,42]. The Human Nephron Filter concept extended the wearable framework to a continuous-flow design without sorbents; it has not progressed to human trials [39]. No wearable hemodialysis device has progressed to pivotal trial enrollment or commercialization at the time of writing, despite a research timeline now exceeding 25 years. The gap between feasibility – hours to days of operation under controlled study conditions – and the clinical use case of months to years of ambulatory continuous therapy is the central unresolved problem in wearable hemodialysis, not the absence of an immediate engineering solution to any single component.

Automated Wearable Artificial Kidney for peritoneal dialysis (AWAK PD)

The Automated Wearable Artificial Kidney for peritoneal dialysis (AWAK PD), developed in Singapore, uses sorbent regeneration in the peritoneal dialysis circuit, allowing continuous flow exchange of a small volume of regenerated dialysate through the peritoneal cavity rather than the cyclical intermittent fill-dwell-drain of automated peritoneal dialysis [43]. The published feasibility study in incident PD patients demonstrated 7-day continuous wear, achievable solute clearances and an acceptable adverse event profile in a small cohort, supporting progression to larger trials [43].

The peritoneal route avoids vascular access constraints and exploits the patient's own peritoneal membrane as a biocompatible interface – a meaningful advantage given the difficulty of engineering a synthetic

blood-contacting surface for chronic use. The unresolved questions for AWAK and similar devices include sorbent capacity for sustained ammonium and phosphate handling, peritonitis risk over months of continuous wear, peritoneal membrane preservation under continuous exposure to regenerated dialysate, and a reimbursement architecture that does not currently distinguish a wearable continuous PD device from cyclical-based automated PD. The PD route may prove the most pragmatic near-term pathway to genuinely portable, continuous dialysis for selected patients, though the evidence base remains early-stage.

NxStage and Tablo: enabling platforms for frequent home hemodialysis

The NxStage System One and the Outset Medical Tablo platforms fall into different categories. Neither is wearable, but each lowers the infrastructure threshold for home or self-care hemodialysis by reducing water purification requirements (NxStage uses pre-packaged dialysate sachets; Tablo uses a smaller integrated water purification footprint), shortening setup times, and simplifying patient training [44]. Their relevance to the next-generation conversation is that they enable more frequent or extended home hemodialysis without any new dialytic principle.

Outcome data for home hemodialysis with these platforms, drawn from observational cohorts and registries rather than randomized trials, suggest blood pressure control, left ventricular mass regression, and quality-of-life benefits broadly consistent with the FHN findings [44–46]. These platforms do not solve the wearable or implantable problem; they make the existing schedule-based intervention practically deliverable for patients with appropriate caregiver support and home infrastructure. In settings where home hemodialysis accounts for fewer than 5% of the prevalent dialysis population, the most consequential near-term intervention may be removing the practical barriers to using these platforms rather than awaiting a fundamentally novel device.

Critical appraisal of wearable platforms

The wearable device literature is dominated by feasibility demonstrations measured in hours to days, not the months to years that constitute the clinical use case. Quality-of-life evidence under sustained ambulatory continuous therapy is essentially absent; the demands on a patient wearing a belt-mounted device 24 h a day for years have not been characterized in a durable form. Vascular and peritoneal access durability under continuous use, distinct from intermittent use, has not been systematically studied. Reimbursement structures designed around session-based therapy do not naturally

accommodate continuous wearable therapy and have impeded the commercialization of two generations of WAK devices. Table 2 summarizes wearable platforms and their stage of development.

Frequent, home, and nocturnal hemodialysis: the evidence base and its limits

The FHN Daily and Nocturnal trials remain the largest randomized assessments of more frequent dialysis. The Daily Trial, randomizing 245 patients to six versus three weekly sessions of in-center hemodialysis, reported significant improvements in left ventricular mass and self-reported physical health on its coprimary composite endpoints, with reductions in predialysis blood pressure and improved phosphate control [16]. The Nocturnal Trial, randomizing 87 patients to six-times-weekly nocturnal home hemodialysis versus conventional therapy, did not meet either coprimary endpoint with statistical significance. However, directional changes were consistent with the daily trial [17].

Long-term follow-up has tempered the initial enthusiasm. The FHN Daily extended cohort

showed attenuation of left ventricular benefit, and the nocturnal extended cohort showed a numerical excess of deaths in the frequent arm that did not reach statistical significance [18,19]. The Cochrane systematic review and a subsequent meta-analysis of frequent and extended hemodialysis reported consistent improvements in blood pressure, phosphate, left ventricular mass, and quality of life across heterogeneous studies, with effect sizes generally larger in nocturnal versus short daily comparisons but mortality data remaining inconclusive [47]. The Alberta Nocturnal Hemodialysis Trial, involving 51 patients randomized to nocturnal versus conventional therapy, reported regression of left ventricular mass index by 15.3 g/m² and improvement across several quality-of-life domains [48]. Observational comparisons of nocturnal home hemodialysis cohorts versus contemporaneous transplant recipients have shown comparable survival, though selection bias materially complicates causal interpretation [20,21,29].

The persistent observation across this literature is that the physiology favors more frequent and longer treatment, the patient-reported outcomes favor it, the surrogate cardiovascular markers favor it, and yet

Table 2 Wearable dialysis platforms – comparative specifications, clinical evidence summary, and stage of development

Platform/developer	Technology architecture	Vascular/peritoneal access	Development stage	Key published evidence	Primary unresolved challenges	Regulatory status
Wearable Artificial Kidney/WAK (Gura and colleagues; Blood Purification Technologies/AWAK network)	Belt-worn hemodialysis with sorbent-based dialysate regeneration; small-volume continuous flow	Arteriovenous fistula or central venous catheter	Phase 0/1 feasibility (multiple iterations across 2007–2016)	Davenport <i>et al.</i> , Lancet 2007 (n=8, 4–8 h) [41]; Gura and colleagues, JCI Insight 2016 (n=7, up to 24 h) [42]	Variable blood and dialysate flows; CO ₂ bubble formation; sorbent capacity over days to weeks; reimbursement vacuum; no sustained-use trials	Investigational; no FDA approval at time of writing
Automated Wearable Artificial Kidney for PD/AWAK PD (AWAK Technologies, Singapore)	Wearable continuous-flow PD with sorbent-based dialysate regeneration	Tenckhoff catheter (existing PD access)	Phase 1 feasibility complete; pivotal evaluation reported as in progress (verify)	Htay and colleagues, Perit Dial Int 2022 single-arm cohort, 7-day continuous wear with safety and clearance signals [43]	Peritonitis risk under continuous wear; sorbent capacity; peritoneal membrane preservation; reimbursement classification	Investigational
NxStage System One (NxStage Medical/Fresenius)	Compact home HD machine using pre-packaged sterile dialysate sachets	Arteriovenous fistula or catheter (standard HD access)	Commercially available since 2005	FREEDOM and other observational cohorts [45]; no randomized mortality trial vs in-center HD	Not a continuous device; supports daily/nocturnal home HD; access events with frequency	FDA cleared (510(k))
Outset Tablo (Outset Medical)	Compact HD platform with integrated water purification; touchscreen-driven setup	Arteriovenous fistula or catheter	Commercially available since 2018 (acute and home indications)	Real-world evidence from observational cohorts; no head-to-head RCT against in-center HD on hard endpoints	Not continuous; setup, training, and supplies cost; same access constraints as conventional HD	FDA cleared (510(k))
Quanta SC+ (Quanta Dialysis Technologies)	Compact cartridge-based HD platform aimed at acute, in-center, and self-care use	Arteriovenous fistula or catheter	Limited commercial deployment	Limited published clinical data	Same as above; commercial scale-up	FDA cleared/CE marked

CO₂, carbon dioxide; HD, hemodialysis; PD, peritoneal dialysis; WAK, Wearable Artificial Kidney.

uptake of frequent home or nocturnal dialysis in most healthcare systems remains under 5% of the prevalent dialysis population [44,49]. Multiple structural barriers explain this gap. Patient and caregiver burden is considerable: nightly cannulation, alarm fatigue, technique training, and the conversion of the home into a clinical environment generate dropout rates that observational cohorts do not capture. Vascular access events accumulate with frequency, with FHN Daily reporting approximately twice the rate of access interventions in the frequent arm [16]. Reimbursement structures in most systems do not adequately compensate the additional supplies, training, and home support required, and dialysis providers face direct financial disincentives to support patients away from in-center treatment chairs whose throughput drives unit economics [44,46]. The Canadian experience with quotidian nocturnal hemodialysis, anchored in early single-center programs that built dedicated training and remote monitoring infrastructure, demonstrates that the modality is sustainable when health-system incentives align – but those alignments have not generalized internationally [21,29,50].

The implication for next-generation devices is sobering. Frequent nocturnal hemodialysis, which has a stronger evidence base than any implantable or wearable platform, has nonetheless failed to achieve majority adoption. Implantable and wearable systems will face the same reimbursement, training, and infrastructure barriers that have constrained frequent home HD, in addition to their own implantation, biocompatibility, and long-term durability problems. A clear-eyed assessment of next-generation modalities should therefore treat frequent home or nocturnal hemodialysis as both the most pragmatic near-term opportunity for clinical improvement and the most relevant comparator against which any novel device should eventually be evaluated.

Convergent technological challenges across modalities

Across implantable, wearable, and intensified hemodialysis, five technical bottlenecks recur with sufficient consistency to be the rate-limiting factors in the field rather than incidental engineering problems.

Membrane biofouling is the universal constraint on chronic blood-contacting devices. Within minutes of blood exposure, proteins adsorb to artificial surfaces; platelets adhere within hours; and biofilm and inflammatory cells colonize within days. Conventional hollow-fiber dialyzers, used for single

sessions and replaced thereafter, circumvent the long-term consequences of these processes; chronically implanted or chronically worn devices cannot. Surface modifications – heparin coatings, zwitterionic polymers, polyethylene glycol grafts – have improved short-term hemocompatibility but have not been demonstrated to maintain function for years of continuous use in any blood-contacting implant [36,37].

Miniaturized dialysate regeneration remains unsolved at the clinical scale. Sorbent technology, derived from the historical REDY system, can adsorb urea, creatinine, and several uremic toxins from a small recirculating dialysate volume. Still, it generates ammonium via urease-mediated urea hydrolysis, which must be subsequently captured, requires sequential sorbents for cation exchange, and exhibits exhaustion kinetics that limit cartridge life. Phosphate, potassium, and bicarbonate management in a continuous, low-volume, regenerated dialysate is more challenging than in single-pass conventional dialysate and has constrained wearable device design across multiple generations [40,42].

Biocompatibility and the foreign-body response differ qualitatively between intermittent extracorporeal contact and chronic implantation. Acute hemocompatibility – complement activation, contact-pathway coagulation, and leukocyte activation – is a recognized problem that is managed during single sessions through membrane chemistry and anticoagulation. Chronic implantation induces fibrous capsule formation, vascular endothelialization at anastomoses, and immunological adaptation, which have only been characterized for vascular grafts and ventricular assist devices, not for blood-filtering implants at the durations relevant to chronic ESKD therapy [36].

Power and portability constraints affect wearable and implantable platforms differently. Wearable devices currently weigh 2–5 kg, with battery life measured in hours; sustained ambulatory continuous use requires either substantial weight reduction or wireless power transfer, which has not been demonstrated for the power densities required. Implantable devices that rely on systemic arteriovenous pressure gradients for filtration can in principle operate without external power but require the patient's hemodynamics to remain compatible with stable filtration over the years. Vascular and peritoneal access remain the rate-limiting biological interfaces. Wearable devices rely on existing access; published WAK trials have used arteriovenous fistulas, which are associated with long-term complication. Implantable devices require de novo vascular anastomoses with surgical morbidity proportional to the population's general vasculopathy. Peritoneal access for AWAK and

similar PD platforms is well established but has not been characterized under continuous-wear conditions.

The clinical promise of next-generation modalities is constrained directly by these materials science and engineering bottlenecks (Fig. 2). The figure visualizes the engineering-maturity against clinical-evidence gap that this section describes. Regulatory and reimbursement reform, however necessary, will not accelerate adoption faster than the underlying technology can support clinically meaningful durability and safety.

Regulatory and reimbursement landscape

The FDA regulatory pathway for next-generation dialysis devices is shaped by three options. The de novo pathway accommodates novel low-to-moderate risk devices without a predicate, with clinical evidence typically required for safety and effectiveness at a level proportional to the risk classification. The premarket approval pathway, applied to high-risk Class III devices, requires controlled clinical evidence and has historically been the route for implantable cardiovascular devices. The Breakthrough Devices Program, established under the 21st Century Cures Act, provides expedited interaction and prioritized review for devices targeting serious conditions with no satisfactory alternative; it does not modify the safety and effectiveness threshold for approval [15]. The procedural acceleration provided by Breakthrough Device Designation is real but narrowly bounded; it does not substitute for clinical evidence, and it does not predict approval.

The Centers for Medicare and Medicaid Services reimbursement architecture for ESKD shapes the commercial pathway for any new modality more powerfully than the regulatory pathway. The ESKD Prospective Payment System, implemented in 2011, bundles dialysis services and most associated drugs into a per-treatment payment, creating direct economic incentives for in-center thrice-weekly delivery and disincentives for home modalities, intensified schedules, and devices that do not fit the per-session payment unit [51]. The Transitional Add-on Payment Adjustment for New and Innovative Equipment and Supplies (TPNIES) provides a time-limited payment supplement for new dialysis machines and supplies. Still, it does not provide a sustainable reimbursement framework for fundamentally different modalities. The ESKD Treatment Choices Model, launched in 2021, introduced incentives and disincentives intended to increase home dialysis and transplantation rates among Medicare beneficiaries; early evaluations suggest modest impact [52]. The Advancing American Kidney Health Initiative, announced in 2019, set targets

for home modality use but did not directly modify payment for novel devices.

Under the European Union's Medical Device Regulation, in force since 2021, has tightened postmarket clinical follow-up requirements and shifted notified-body capacity in ways that have affected device launches across multiple categories. CE marking under the Medical Device Regulation for an implantable continuous dialysis device would require both clinical evaluation and postmarket clinical follow-up plans calibrated to the durability claims being made.

Whether current frameworks are fit for purpose is debated. The argument for adaptation centers on the inadequacy of session-based endpoints (Kt/V, urea reduction ratio) for continuous-clearance devices; the need for surrogate endpoint validation against patient-relevant outcomes; the case for adaptive trial designs and registry-based evidence, given the small early-adopter populations; and the misalignment of bundled payment with continuous-therapy economics. The argument for caution centers on the legitimate concern that premature approval of implantable devices with inadequate long-term safety data could expose patients to harm with no exit strategy short of explantation. The international community has not reached a consensus. Both arguments have force, and the evidence to settle them has not yet been generated (Figs. 1, 2 and Table 3).

Equity, access, and global implications

The global dimension of the dialysis discussion exposes a serious mismatch between where innovation is concentrated and where the unmet need is greatest. A 2015 systematic review estimated that 2.6 million people worldwide receive kidney replacement therapy and that an additional 2.3–7.1 million die annually from untreated kidney failure, the great majority in low-income and middle-income countries [53]. The 2023 ISN Global Kidney Health Atlas documented persistent and in some regions widening, gaps in access to maintenance dialysis, with sub-Saharan Africa, South Asia, and parts of Southeast Asia having dialysis prevalence rates one to two orders of magnitude lower than high-income countries [54]. Across many regions – including parts of MENA, Latin America, and South Asia – kidney transplantation programs and peritoneal dialysis capacity remain far below what is needed to absorb prevalent ESKD populations, and conventional in-center hemodialysis itself remains rationed by cost and infrastructure [1, 55].

Next-generation dialysis devices, as currently positioned, are premium-priced products developed

Table 3 Clinical trial pipeline and recent landmark studies for next-generation dialysis modalities

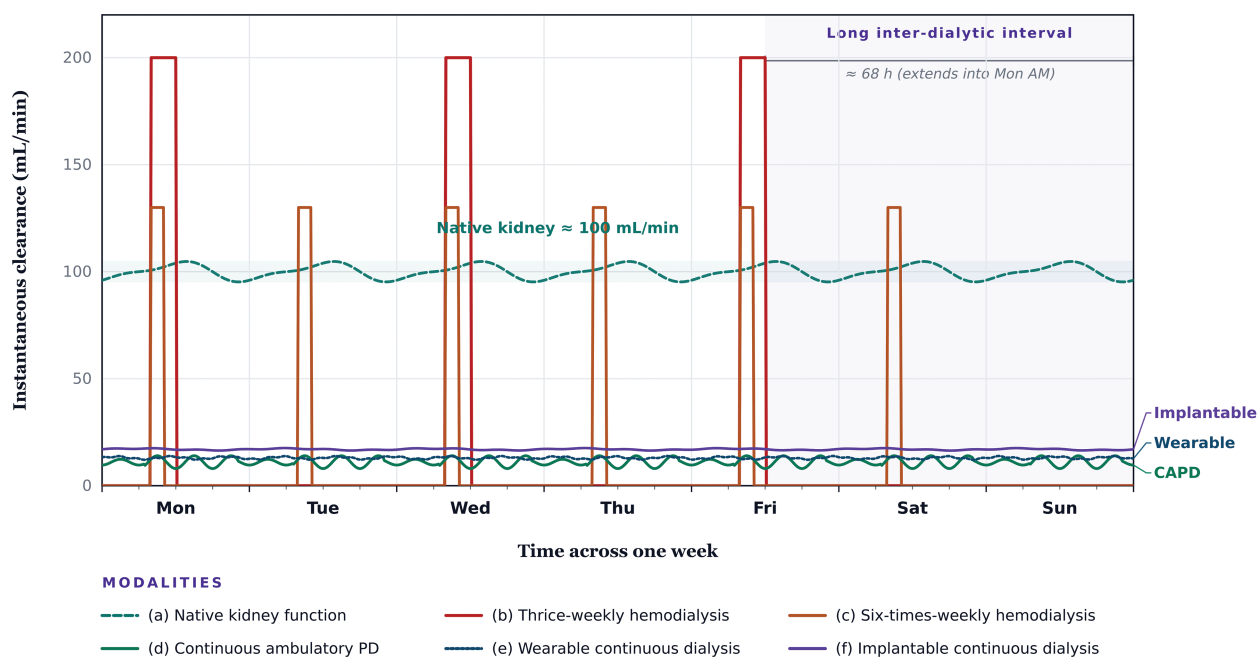
Trial/program	Modality	Phase	Primary endpoint	Target N	Status	Expected completion
AWAK PD pivotal evaluation (per developer disclosures; ClinicalTrials.gov identifier to verify)	Wearable continuous PD with sorbent regeneration	Pivotal feasibility/safety	Composite safety and dialysis adequacy	Reported as ~50–100	In planning/recruiting (verify with registry)	Not stated
UCSF Kidney Project preclinical → IND	Implantable bioartificial kidney	Preclinical	Not applicable	Not applicable	Pre-IND	Not stated
Nephrodite Holly clinical program (per FDA BDD documentation)	Implantable continuous HD	Preclinical / first-in-human pending	To be specified	Not specified	Preclinical (per BDD documentation)	Not stated
CONVINCE (Blankestijn and colleagues)	High-volume online hemodiafiltration vs conventional high-flux HD	Pragmatic multicentre RCT	All-cause mortality	1360	Completed; results published 2023	Reported[24]
FHN daily extended follow-up (Chertow and colleagues)	Frequent in-center HD vs. conventional HD	Long-term follow-up of randomized cohort	All-cause mortality and safety	245	Completed; reported 2016	Reported[18]
FHN Nocturnal extended follow-up (Rocco and colleagues)	Nocturnal home HD vs. conventional HD	Long-term follow-up of randomized cohort	All-cause mortality	87	Completed; reported 2015	Reported[19]

Identifiers and enrollment numbers reported here have been drawn from public registries and developer disclosures available at the time of writing; readers should verify current status on ClinicalTrials.gov and equivalent registries before quoting these figures. FHN, Frequent Hemodialysis Network; UCSF, University of California, San Francisco.

Figure 1

Conceptual schematic of solute clearance over time across modalities

Schematic only — not derived from a single empirical dataset; not a comparison of clinical efficacy



Conceptual profiles only. Native kidney function (a) is shown as a near-constant band at ~100 mL/min. Thrice-weekly hemodialysis (b) delivers three short, high-amplitude peaks separated by long inter-session troughs; the longest interval (~68 h) extends from the end of the Friday session into the following Monday. Frequent (six-times-weekly) hemodialysis (c) reduces peak-to-trough excursion. Continuous ambulatory peritoneal dialysis (d) shows low-amplitude cycle-related variation around a stable mean. Wearable (e) and implantable (f) continuous dialysis approach a near-flat, ambulatory low-flux profile — qualitatively closest to physiology, though at substantially lower amplitude. Intended to communicate the rationale for continuous over intermittent therapy.

Conceptual schematic of solute clearance over time across modalities.

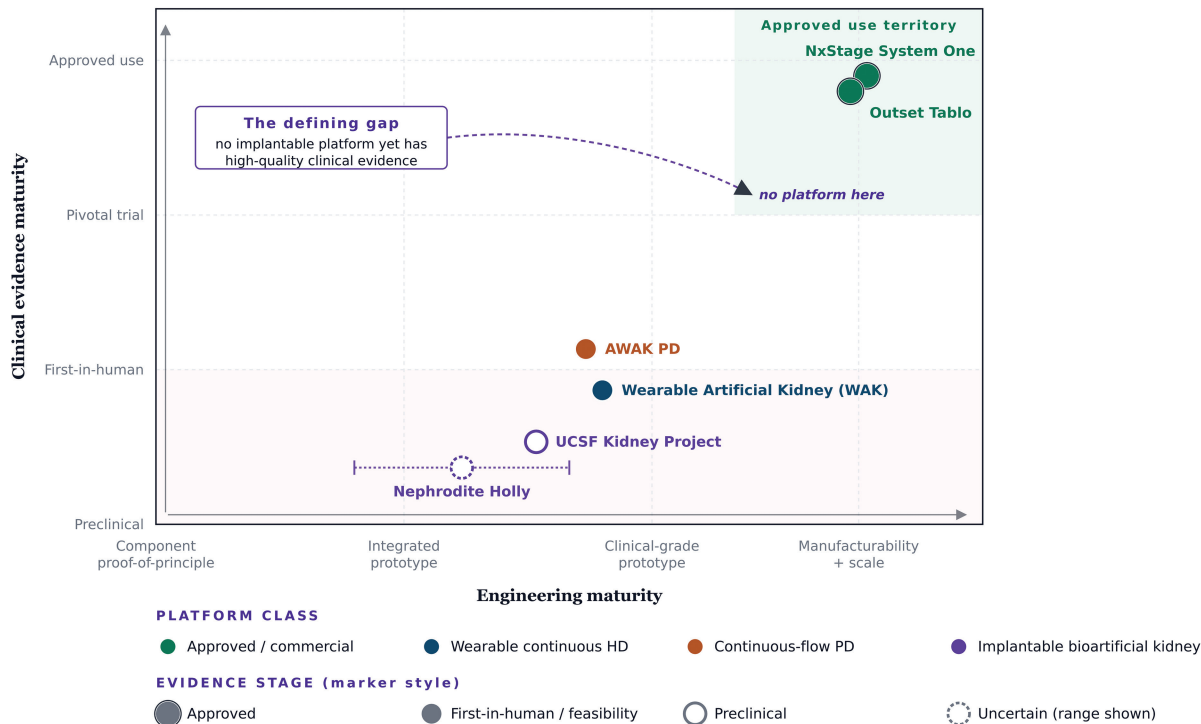
for high-income healthcare systems with established dialysis infrastructure. Their relevance to populations who cannot access conventional therapy is, in the near term, marginal. There is precedent for technological diffusion: continuous glucose monitors, originally a high-cost diabetes intervention, have followed a

cost-reduction trajectory that is bringing them within reach of middle-income systems within two decades of introduction. Whether implantable or wearable dialysis follows a similar trajectory, or whether the higher complexity and surgical infrastructure of implantation foreclose this pathway, will depend on engineering

Figure 2

Technology readiness level matrix for next-generation dialysis platforms

Schematic positioning — approximate placement based on the most recent published peer-reviewed disclosures



Engineering maturity (x-axis) progresses from component proof-of-principle through integrated prototype to clinical-grade manufacturability; clinical evidence maturity (y-axis) progresses from preclinical demonstration through first-in-human feasibility and pivotal trials to approved use. NxStage System One and Outset Tablo occupy the upper-right quadrant, though randomised mortality data remain limited. Investigational platforms cluster below the first-in-human band, with implantable concepts (UCSF Kidney Project, Nephrodite Holly) furthest from clinical maturity. The empty upper-right region for implantable platforms is the field's defining gap; closing it — translating engineering progress into pivotal-trial-grade clinical evidence — is the central problem the next decade must address.

Technology readiness level matrix for next-generation dialysis platforms.

choices, reimbursement reform, and deliberate global health planning that has not yet begun.

The more immediately scalable equity intervention remains peritoneal dialysis. PD's lower infrastructure requirements, suitability for home delivery, and consumable-driven cost structure make it more amenable to scale-up in resource-constrained settings than facility-based hemodialysis, and international initiatives have demonstrated that PD prevalence can be increased rapidly when health-system architecture supports it [49,56,57]. Romanticizing technological solutions to structural health-system deficits is a recurring failure mode in global nephrology; in the next-generation conversation, it deserves explicit guarding against.

Future research directions and clinical trial priorities

Five priorities emerge from the foregoing analysis [Table 3]. The table enumerates the completed landmark trials and the current device pipeline that motivate these priorities.

First, well-powered clinical trials with validated endpoints for continuous-clearance therapy. The session-based metrics (Kt/V , urea reduction ratio) that anchor adequacy in conventional hemodialysis do not translate to continuous therapy. Composite endpoints incorporating cardiovascular events, hospitalization, RKF preservation, and patient-reported outcomes, with sample sizes calibrated to the modest effect sizes plausible against an active TWHd comparator, will be essential. Adaptive designs and Bayesian frameworks may be required to make these trials feasible in populations of realistic size.

Second, standardized reporting of feasibility study outcomes. The wearable and implantable literature is fragmented across single-center reports with inconsistent endpoints, varying durations of observation, and incomplete adverse event reporting. A consensus reporting standard, analogs to CONSORT or STARD, for feasibility studies of continuous-clearance devices would enable cross-study comparison and evidence synthesis. Existing dialysis registries are session-based and inadequate for continuous-therapy outcome capture.

Third, biomarker development for middle-molecule accumulation as trial endpoints. Beta-2 microglobulin time-averaged concentrations, FGF-23 trajectory, indoxyl sulfate clearance, and emerging biomarkers of cardiovascular and uremic injury (high-sensitivity troponin, N-terminal pro-B-type natriuretic peptide, soluble urokinase plasminogen activator receptor) require validation as surrogate endpoints linked to patient-relevant outcomes [10–12]. Without validated surrogates, trial sizes for hard endpoints become prohibitive.

Fourth, patient-reported outcome instruments validated for continuous therapy contexts. Existing dialysis-specific instruments (KDQOL, EQ-5D-derived measures) were developed in session-based therapy populations and may not capture the burden, benefits, and lifestyle implications of continuous wearable or implantable therapy.

Fifth, an international registry infrastructure capable of capturing postmarket surveillance for implantable and wearable devices over the durations required to detect rare and long-latency adverse events. The cardiovascular community's registry models provide a precedent; nephrology has no equivalent at the international scale required.

Three unanswered questions, if resolved, would most meaningfully advance the field. Can a chronically implanted blood-contacting filter maintain clinically meaningful clearance for at least 12 months in a single human participant? What is the comparative effectiveness of frequent home hemodialysis versus continuous wearable dialysis on hard cardiovascular endpoints? And can registry-based evidence substitute, in part, for randomized data in regulatory decisions for novel modalities? Until these questions are answered, the next-generation conversation will continue to be dominated by promotional framings and inferred extrapolations rather than by evidence.

Conclusion

The physiological case for transcending conventional thrice-weekly hemodialysis is robust, supported by trial evidence on intermediate cardiovascular endpoints, by mechanistic data on hemodynamic injury, and by the persistent excess mortality of dialysis populations relative to age-matched controls. The technological ambition of next-generation modalities – implantable continuous dialysis, wearable artificial kidneys, intensified home hemodialysis – is genuine and reflects engineering progress in membrane materials, sorbent regeneration, and miniaturization. The evidentiary base for the most ambitious of these modalities, however, remains preclinical or early feasibility. Breakthrough Device Designation

granted to implantable systems should be read for what it is: regulatory acknowledgment of unmet need, not validation of safety or efficacy. Wearable hemodialysis has demonstrated short-term feasibility but has not, after more than 25 years of development, progressed to pivotal trials. Frequent home and nocturnal hemodialysis, the most evidence-anchored option, has nonetheless failed to achieve majority adoption because of structural barriers that any novel device will also encounter.

Meaningful proof of clinical readiness for next-generation dialysis would require sustained continuous clearance for months to years in human participants, demonstrated reduction in hard cardiovascular endpoints versus an active comparator, and a reimbursement framework that allows the modality to reach patients beyond a small early-adopter cohort. The international nephrology community's responsibility, in the meantime, is to demand evidence commensurate with the magnitude of the proposed clinical change, and to resist promotional framings that conflate regulatory designation with clinical readiness.

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Conflicts of interest

None declared.

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