# Innovations in Wearable and Implantable Artificial Kidneys

*Megha Salani, Shuvo Roy, and William H. Fissell IV*

More than 2 million people worldwide receive treatment for end-stage renal disease (ESRD). Current modalities of renal replacement therapy include in-center hemodialysis, peritoneal dialysis, home hemodialysis, and kidney transplantation. Patient survival has gradually increased during the past 2 decades and efforts continue to improve mortality and quality of life for patients with ESRD. Developments in sorbent technology, nanotechnology, and cell culture techniques provide promise for new innovations in ESRD management. New modalities currently in testing include wearable (WAKs) and implantable artificial kidneys (IAKs). The automated WAK (AWAK) and WAK are devices that have undergone small trials in humans. Additional study is needed before regulatory approval, coverage decisions, and widespread clinical implementation. The IAK is a biohybrid combining artificial filters and living cells currently in preclinical testing. These portable devices reduce the need for large quantities of water and continuous electrical supply. This could lower some barriers to home dialysis, making self-care renal replacement therapy more accessible and desirable. If widely successful, these devices could reduce the need to build and staff dialysis facilities, thus lowering health care costs associated with dialysis. The potential advantages and shortcomings of the AWAK, WAK, and IAK are described here.

*Complete author and article information provided before references.*

*Am J Kidney Dis. 72(5): 745-751. Published online August 23, 2018.*

*doi: 10.1053/j.ajkd.2018.06.005*



## Introduction

Although dialysis provides a way to survive in the setting of kidney failure, it is still associated with a high mortality rate, a major change in quality of life, and residual symptoms of kidney failure. More intensive dialysis has not been convincingly shown to confer a survival advantage, but may reduce pill burden, lessen dietary restrictions, and restore female fertility.[1-5] Performing dialysis overnight, whether hemodialysis (HD) or peritoneal dialysis (PD), may afford some normalization of daily routine. Patients can plan their dialysis around their activities rather than the other way around. Nocturnal dialysis therapies may permit patients to continue working. However, additional time connected to a machine and assuming the burden of care may not be an appealing option for a patient or caregiver.[6] Currently, in-center HD remains the most common modality of choice. In-center dialysis facilities have large electricity and water needs and generate a significant amount of medical waste. The construction, maintenance, and staffing of these facilities are costly and partially account for the high financial costs of end-stage renal disease (ESRD). Patients who could benefit from longer sessions with nocturnal in-center dialysis may not be able to procure transportation at those times or childcare during the night. Those who are willing and able to do home dialysis must have room for storage of their equipment and supplies. Home HD may increase utility costs and require expensive water purification systems.

Wearable (WAKs) and implantable artificial kidneys (IAKs) lower potential operational and infrastructural barriers to self-care treatment of kidney failure. The automated WAK (AWAK) and WAK are currently undergoing trials in humans and aim to change dialysis from intermittent treatments to the use of small portable machines that can be worn throughout the day.[7-9] Increased portability of therapy and associated supplies may make the AWAK and WAK attractive options for those who work or otherwise wish to travel. They may also help patients who are less mobile who do not have help to lift heavy bags of dialysate. The IAK, influenced by earlier innovations by H. David Humes at the University of Michigan, is currently undergoing preclinical studies.[10,11] Successful clinical implementation of any of these could minimize the burden of self-care and expand the option of home dialysis to those who are otherwise incapable of doing it. Costs to the health care system could be significantly decreased if it led to a reduced need for in-center facilities.

## Overview of Portable Dialysis Technologies

Each of the 3 technologies described here uses a different ensemble of strategies to overcome the most difficult barriers to the evolution of renal replacement therapy from a tethered bedside procedure to a low-impact continuous therapy similar to an insulin pump or pacemaker (Table 1). These key barriers are package size (a conventional HD filter is large, along with the machinery/equipment used with it), power (most dialyzers require energy-intensive pumps to circulate blood and dialysate), and water (a PD patient uses about 10-15 L/d of dialysate, and an HD session could easily consume 140 L of dialysate). Thus, the size of the machinery, its power requirements, and the weight of dialysate are barriers to wearable and implantable devices.

Two of the 3 devices have adapted dialysate regeneration processes similar to that first commercialized in the REcirculating DialYsate (REDY) dialysis system.[12] Some nephrologists may not be familiar with the chemistry of sorbent-based dialysate regeneration. Briefly, spent dialysate that contains small solute wastes is directed to a

**Table 1.** Comparison of the WAKs and IAK

| | AWAK | WAK | IAK |
|---|---|---|---|
| Weight | <2 kg | <5 kg | ~500 g |
| Power requirements | Battery operated | Battery operated | None, uses cardiovascular pressure and chemical energy of cellular metabolism |
| Fluid requirements | ~2 L dialysate/treatment | 6 L dialysate/treatment | No dialysate, patients drink an electrolyte-rich fluid to keep up with losses |
| Stage of development | Trials in human | FDA clinical trials | Animal models |
| Strengths | Bloodless, easily portable, high clearances | Portable, low UF rate, electrolyte balance seen in clinical use | Low burden to patient, minimal waste generation |
| Limitations | Frequent exchange of cartridges (every 7 h) | Clotting and bleeding issues | May require repeated invasive procedures |

Abbreviations: AWAK, automated wearable artificial kidney; FDA, US Food and Drug Administration; IAK, implantable artificial kidney; UF, ultrafiltration; WAK, wearable artificial kidney.

column containing the enzyme urease. The urease hydrolyzes urea into ammonia and carbon dioxide. Hydration with water molecules provides hydrogen ions for each ammonia molecule to be protonated to ammonium and hydroxide ions for carbon dioxide to become bicarbonate and hydroxide. Ammonium accomplishes 2 things: first, it is a vehicle for removal of dietary acid; and second, it has a charge to which a cation exchange column can bind, removing nitrogen from the dialysate.

The dialysate passes sequentially over cation and anion exchange columns. The former is based on zirconium phosphate, which has a negative charge to which hydrogen and sodium ions are initially bound at the time of manufacture. The hydrogen and sodium ions are exchanged for cations in spent dialysate, such as potassium, calcium, and magnesium. As mentioned, the ammonium produced from urea cleavage is also bound by the negative charge and removed from the spent dialysate. Any failure or premature saturation of the cation exchange column could lead to ammonia breakthrough into the regenerated dialysate and thus into the patient, with potential adverse reactions such as nausea and hypotension. Moreover, the released hydrogen is free to bind carbonate from the breakdown of urea, creating bubbles of carbon dioxide gas. This gas formation might inadvertently pressurize the dialysate space, altering ultrafiltration and/or causing a mechanical fault with the system. The next layer of the sorbent column is composed of zirconium oxide and zirconium carbonate with bound bicarbonate and acetate, which exchange for negatively charged compounds including phosphate and sulfates. Organic toxins are then removed from the dialysate by a bed of activated charcoal. The dialysate is then recharged with calcium and magnesium to become fresh dialysate and returns to flow through the dialyzer again. The chemical components of REDY system dialysate regeneration and their associated function in processing of spent dialysate are listed in Table S1.

## WAK PD

The AWAK (AWAK Technologies Pte, LTD) system is a tidal PD-based artificial kidney that uses dialysate regeneration to minimize fluid requirements. The system is composed of a tubing set, disposable storage module, and system controller, all in a small-form factor system that can be worn like a purse (Fig 1). As in conventional PD, 1 to 1.5 L of dialysate (the reserve volume) is instilled into the peritoneal cavity and absorbs toxins, waste products, and fluid through the peritoneal membrane. In the AWAK system, a tidal volume of 500 mL of equilibrated dialysate is drained from the patient into the storage module and pumped through sorbents (vide supra) for toxin removal. This sterile dialysate is then filtered and degassed and supplemented with prescribed amounts of electrolytes and glucose. This regenerated dialysate is returned to the peritoneal cavity. The tidal exchange takes 7.5 minutes, so that there are 8 exchanges each hour, providing a cumulative dialysate flow of 96 L/d. The sorbent cartridge can be used for 7 hours, after which it must be replaced. The reserve volume of the regenerated dialysate is returned to the peritoneal cavity and the remaining fluid (the ultrafiltrate) is drained into the ultrafiltration bag and can be discarded with the sorbent cartridge. When the spent cartridge is replaced with a new one, the procedure begins again.

The use of a sterilized sorbent cartridge to regenerate dialysis allows for a higher cumulative flow into and out of the peritoneum, increasing clearance compared with traditional PD. One of the problems of sorbent technology, as discussed previously, is gas formation. The AWAK addresses this by including a gas removal module to degas the dialysate during the regeneration process.

A study of 20 male patients using the AWAK for 4 to 24 hours demonstrated safety and efficacy with an average urea clearance of 31.4 mL/min.[10] Middle-molecule and phosphate clearance should be higher than with conventional PD because total clearance is higher.

The AWAK can be used with a double-lumen catheter or 2 single-lumen catheters. The consequences of using a peritoneal catheter for essentially continuous fluid exchange are unknown at this time. It remains to be seen how the change in connections and how the regenerated dialysate will affect the risk for peritonitis, hyperglycemia, membrane failure, and encapsulating peritoneal sclerosis compared to traditional PD. The use of smaller dwell

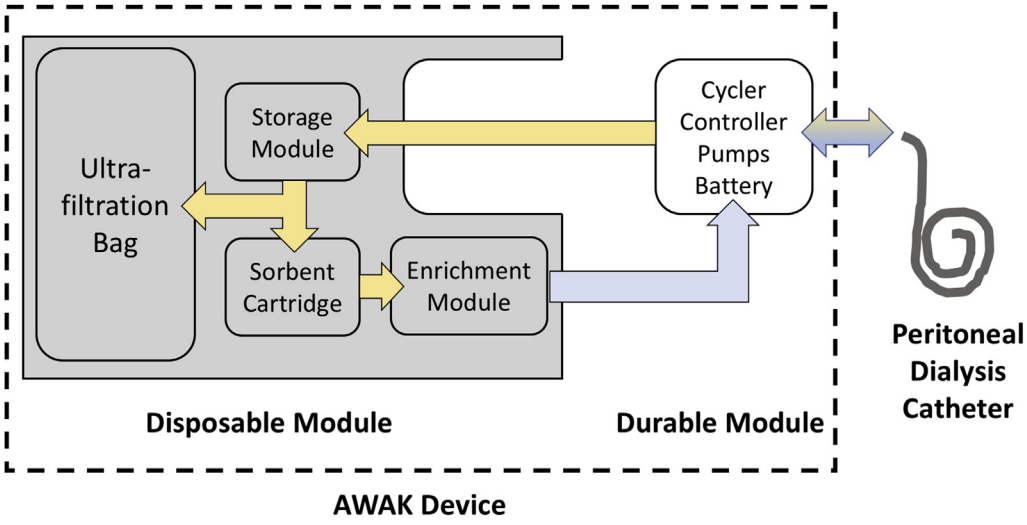


**Figure 1.** The automated wearable artificial kidney (AWAK) system: tidal exchanges are done with 500 mL of spent dialysate being drained from the peritoneal cavity to the storage module, cleaned in the sorbent cartridge, replenished with electrolytes in the enrichment module, and returned to the peritoneal cavity. Excess fluid is drained in the ultrafiltration bag to be disposed of with the disposable module shown here. Redrawn from an image supplied by AWAK Technologies, Ltd.

volumes may reduce pain from abdominal distention and the risk for hernias. It will also save on the cost of dialysate and the need to dispose of large quantities of spent dialysate at the burden of changing sorbent cartridges several times each day, even if the cartridges are small enough that a supply can be carried with the patient.

## Wearable Artificial Kidney

The WAK (Wearable Artificial Organs Inc) is a wearable blood-based renal replacement device (schematic in Fig 2). It is battery operated, weighs < 5 kg, and is presently worn like a belt or a vest. The WAK system removes barriers to home HD related to electricity and water needs. It is powered by 9-V and AA batteries and only requires 400 mL of sterile water. The system is primed with 0.45% sodium chloride solution and connected to a dual-lumen HD catheter. Blood is anticoagulated with heparin using a syringe pump and proceeds to a 2-channel pump that alternately propels blood and dialysate to a small polysulfone hollow-fiber dialyzer. The blood pump uses an unusual pulsating push-pull flow, alternating blood and dialysate pulses such that the blood compartment is at peak flow when dialysate flow is at its trough, and vice versa. The pulsatile flow generates alternating positive and negative transmembrane pressure: the dialyzer transmembrane pressure oscillates 60 to 70 times per minute. This mechanism and continuous use permit low blood flows of ~100 mL/min to produce adequate clearances.[13]

Blood exits the dialyzer and goes through a bubble detector before being returned to the patient. Blood flow is discontinued if bubbles are detected. The spent dialysate is regenerated (vide supra). An ultrafiltration pump controls fluid removal by diverting a portion of the regenerated dialysate to a waste bag, with a safety feature to stop if blood flow is halted.

This system has been studied in preclinical trials and trials in humans.[7,8,14,15] The goal is continuous use of the device. In one study in humans of 24-hour application of the WAK, average urea clearance was 22.7 mL/min and average creatinine clearance was 20.7 mL/min. Electrolytes and pH were stable and ammonia was not detected. The use of urease to break down urea in the sorbent cartridge resulted in the development of carbon dioxide bubbles that created problems with dialysate flow. Other complications included clotting of a dialysis catheter and needle dislodgement from a fistula. Safety mechanisms were reported to have detected the dislodgement and the issue was resolved. Patients were able to eat and drink, and some slept during the treatment. There was no evidence of hemolysis, oxygen desaturation, or arrhythmia.

Because of the risk for accidental disconnection, the WAK is likely to be used with a catheter rather than needles in a fistula. Proper aseptic technique combined with continuous use may help minimize infectious complications associated with catheter use, but the consequences of continuous catheter use are not well defined. Because the dialysate used in the WAK is sterile (dialysate in conventional dialysis is not), there may be fewer stimuli for chronic inflammation.

## Implantable Artificial Kidney

The IAK (Vanderbilt University Medical Center and University of California, San Francisco) incorporates silicon nanotechnology and tissue engineering in a device that can be surgically implanted to mimic a native kidney (Fig 3). The IAK copies the physiology of the nephron by

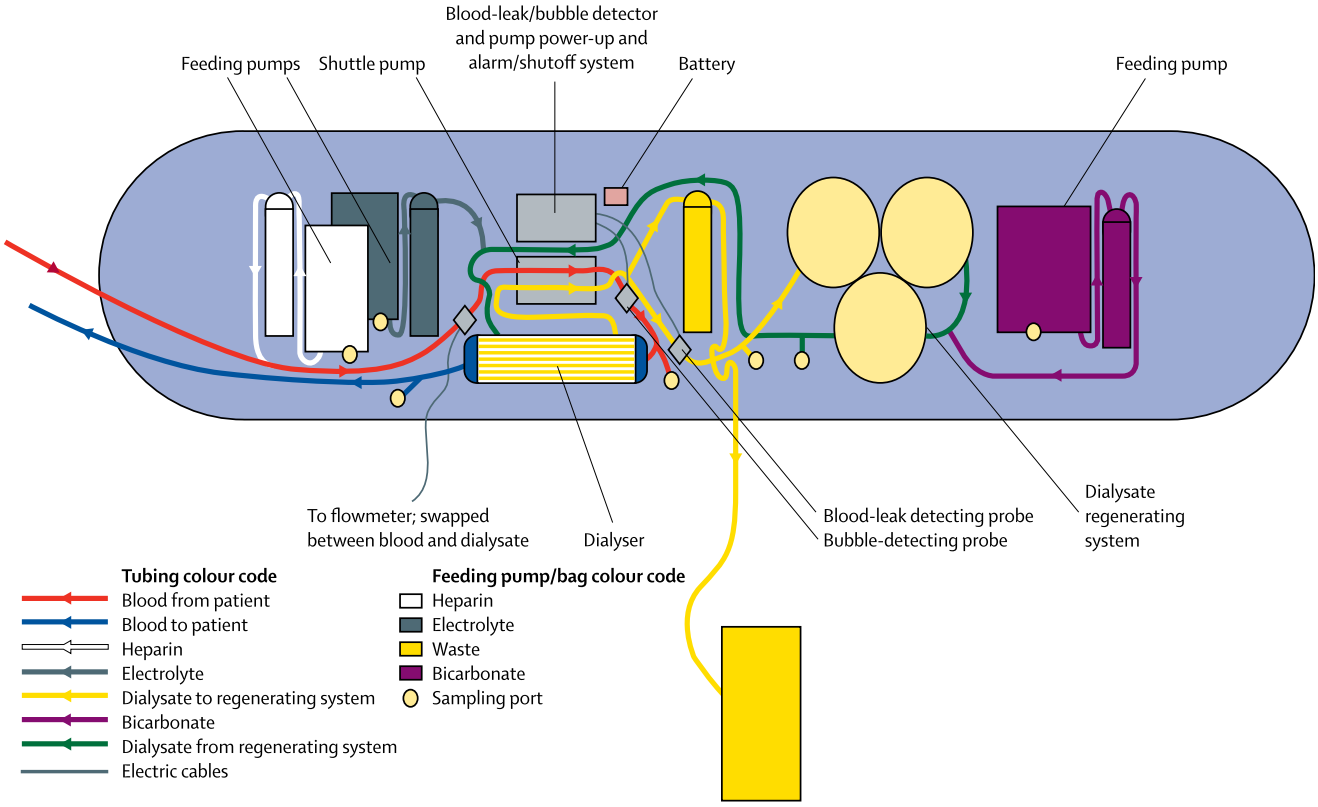


**Figure 2.** Schematic of wearable artificial kidney (WAK) system. Blood from the catheter is anticoagulated using the heparin pump. A shuttle pump pumps blood through the dialyzer. The blood is reconstituted with electrolytes and returns to the patient. The dialysate goes through the dialyzer and the spent dialysate goes to the dialysate regenerating system to be used again with any excess dialysate discarded into the ultrafiltration bag. The system has alarms in place for leaks or bubbles. Image is ©2007 Elsevier Ltd and is reproduced from Davenport et al[8] with permission of the copyright holder.

combining a high-efficiency filter (the HemoCartridge) with a bioreactor of cultured renal tubule epithelial cells (the BioCartridge). Ultrafiltrate generated in the HemoCartridge is then processed by the BioCartridge, which returns salt, water, and glucose to the blood and progressively concentrates toxins into a small volume of fluid similar to urine.

This device overcomes the need for electrical pumps because it is directly connected to arterial vasculature, allowing the patient's own blood pressure to pump blood through the filter. It also obviates the need for dialysate because reabsorption of salt and water in the BioCartridge maintains approximately neutral fluid balance while excreting concentrated wastes. The blood conduits in the IAK have been carefully engineered to protect flowing blood from stagnation and excess shear. The silicon membranes are coated with hydrated biocompatible polymers.[16-19] This combined approach has allowed prolonged anticoagulant-free preclinical implantation of fully functional HemoCartridge prototypes for up to a month in experimental animals.[20]

The HemoCartridge contains innovative filters made using silicon nanotechnology; each microchip has uniform, elongated, slit-shaped pores, reminiscent of glomerular slit diaphragms, that create a novel highly porous compact membrane.[21,22] Just as in the glomerulus, these pores retain molecules such as albumin while passing smaller wastes and electrolytes to the BioCartridge for processing.

Tubular cells from donated human cadaver kidneys rejected for transplantation have been successfully grown in cell culture to be used in the BioCartridge.[23-25] The same high-efficiency silicon membranes that form the HemoCartridge filters also can be used as the scaffold on which tubule cells are grown. The scaffold permits passage of salt and water transported by the cells while serving as a barrier between the tubule cells and the molecular and cellular effectors of the patient's innate and acquired immune system. Thus, no immunosuppressant drugs are needed. Expansion of renal epithelial progenitor cells can yield more than $10^9$ cells for each gram of harvested cortex so that each cadaveric kidney can be used to develop several IAKs.[25] The IAK may prove an early clinical application for stem cell–derived kidney cells in the future for the same purpose. Progress toward integrating the HemoCartridge and BioCartridge has not been reported in the peer-reviewed literature as of the time of writing.

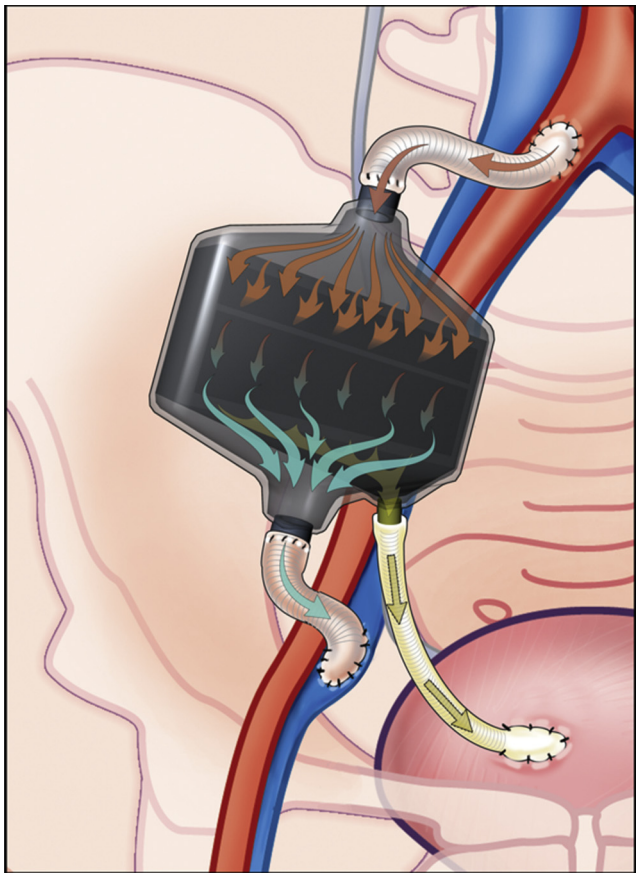

**Figure 3.** The implantable artificial kidney (IAK) is implanted into the vasculature with blood pumped using the patient's blood pressure into the HemoCartridge with membranes that mimic the slit-shaped pores of podocytes and then through the BioCartridge that contains living tubular cells, thus mimicking the glomerulus-tubule arrangement of the kidney.

The toxin-rich concentrated ultrafiltrate produced by the IAK could potentially be routed to the bladder as artificial urine. Extracellular fluid volume regulation would occur by oral intake. The IAK would excrete between 2 and 4 L of liquid waste daily. Patients would weigh themselves daily and determine the amount of fluid they need to drink to balance fluid losses. These fluids could be enhanced with electrolytes if needed. At creatinine clearance of 30 mL/min, phosphorus intake would still need to be limited. Initially, patients may need close monitoring of electrolytes, with restrictions or supplements depending on diet.

Clearly the IAK poses challenges not shared by the AWAK and WAK in that thrombus-free operation for years has been difficult to attain with vascular grafts and fistulas, which are less complex and less sensitive medical devices. Mammalian cells in culture tend to undergo slow erosion of key phenotypic features, an effect called "culture stress." Mitigation of cell culture stress during implantation or on the artificial scaffolding from which the BioCartridge is manufactured would appear to be a problem of much larger interest than kidney failure alone.

## Conclusions and Outlook

Devices presently in preclinical and clinical trials promise renal replacement therapy independent of a wired electricity source or large quantity of purified water. Each of these devices may offer improvement in some of the factors that patients receiving dialysis rate as most important: fatigue and energy, ability to travel, resilience and coping, and stress on family.[22] All devices promise significantly higher clearance than presently available with any mode of dialysis except prolonged quotidian dialysis. The increased treatment times (essentially continuous therapy) are likely to significantly improve indexes of bone mineral metabolism. The ultrafiltration-mediated hypotension and associated cardiac disease of dialysis will likely be ameliorated by the gradual ultrafiltration of continuous therapy.

To be acceptable for patients, the wearable devices will need to be lightweight and easy to use. The implantable device will need to have a long service life to minimize the need for recurrent procedures. The AWAK and WAK devices both require regular replacement of sorbent cartridges, perhaps 3 or more times daily. Both AWAK and WAK have risks that remain to be completely defined, including prolonged vascular access and increased washing of the peritoneal membranes. The IAK, unlike the AWAK and WAK, will require the patient to undergo an initial surgery and presumably additional surgeries to replace a failed device. The challenge of maintaining clot-free filtration and a stable differentiated phenotype of cultured tubule cells in the IAK is substantial, although progress is being reported. In addition to saving water and electricity, these devices may generate less waste than in-center dialysis, particularly with respect to nonbiodegradable plastics and spent dialysate. Cost information is not yet available for any of the devices, but any increase in patients choosing home dialysis should lower health care costs, as is seen with current home modalities. With wearable devices, the financial burdens to the patient doing home dialysis may be ameliorated due to decreased need for equipment and water/electricity use. The portability of these devices and continuous use, with less residual symptoms of kidney failure, may allow more patients to work and have more freedom and better quality of life.

The barriers to market entry are formidable for any new device, whether backed by a startup company or a major medical device and solutions manufacturer.[26] Therefore, predictions of when the AWAK, WAK, or IAK will be commercially available to patients in the United States are purely speculative. The technical challenges have been mentioned briefly here and in the peer-reviewed literature, but regulatory and reimbursement challenges exist as well. In the United States, the Food and Drug Administration (FDA) is charged with assuring the public of the safety and efficacy of medical devices through a process of premarketing approvals. In other jurisdictions, greater or lesser emphasis may be placed on the conformity of the device

with its intended performance instead of patient outcomes. After a series of safety and efficacy clinical trials, the FDA may grant marketing authorization to the manufacturer. Separate from that process is obtaining a coverage determination from the Centers for Medicare & Medicaid Services (CMS). Medicare is the single largest purchaser of ESRD products and services in the United States. If a device such as AWAK allows a provider to satisfy the Medicare ESRD Program conditions for coverage, a separate coverage determination may not be necessary. An implanted device such as the IAK may not fit perfectly into an existing reimbursement model and may require a coverage determination from CMS. Uncertainty associated with regulation and reimbursement diminishes the appetite for investment from the risk capital community. Further, the time that elapses from completed device to reimbursement may be longer than investors are willing to wait to harvest returns, a second deterrent to investment at the stage of development of each these devices.

In response to this challenge, the FDA's Center for Devices and Radiologic Health (CDRH) instituted a competitive program to encourage new entrants to the ESRD field and transform an adversarial regulatory model to a collaborative effort. The WAK and IAK both participated in the Innovation Pathway 2.0 at CDRH and continue to work with the FDA today. Similarly, the FDA and the American Society of Nephrology's public-private partnership, called the Kidney Health Initiative (KHI), has worked to secure funding for innovation in ESRD care. Recently, the KHI and the US Department of Health and Human Services announced KidneyX (the Kidney Innovation Accelerator) to fund new technologies for ESRD.

## Supplementary Material

**Table S1:** Dialysate regeneration using sorbent technology.

## Article Information

**Authors' Full Names and Academic Degrees:** Megha Salani, MD, Shuvo Roy, PhD, and William H. Fissell IV, MD.

**Authors' Affiliations:** Nephrology and Hypertension, Vanderbilt University Medical Center, Nashville, TN (MS, WHF); and Bioengineering and Therapeutic Sciences, University of California, San Francisco, CA (SR).

**Address for Correspondence:** William H. Fissell IV, MD, 1161 21st Ave S, MCN Rm/Ste S3223, Nashville, TN 37232. E-mail: william.fissell@vanderbilt.edu

**Acknowledgements:** The authors thank Dr Stephen R. Ash for advice.

**Support:** Drs Fissell and Roy are supported by National Institutes of Health 1U01EB021214.

**Financial Disclosure:** Drs Fissell and Roy have financial interests in the IAK.

**Peer Review:** Received July 17, 2017, in response to an invitation from the journal. Evaluated by 3 external peer reviewers, with direct editorial input from an Associate Editor and a Deputy Editor. Accepted in revised form June 4, 2018.

## References

1. Pauly RP, Asad RA, Hanley JA, et al. Long-term clinical outcomes of nocturnal hemodialysis patients compared with conventional hemodialysis patients post-renal transplantation. *Clin Transplant*. 2009;23(1):47-55.
2. Barua M, Hladunewich M, Keunen J, et al. Successful pregnancies on nocturnal home hemodialysis [see comment]. *Clin J Am Soc Nephrol*. 2008;3(2):392-396.
3. Chan CT. Cardiovascular effects of home intensive hemodialysis. *Adv Chronic Kidney Dis*. 2009;16(3):173-178.
4. Chan CT, Floras JS, Miller JA, et al. Regression of left ventricular hypertrophy after conversion to nocturnal hemodialysis. *Kidney Int*. 2002;61(6):2235-2239.
5. Chan CT, Notarius CF, Merlocco AC, et al. Improvement in exercise duration and capacity after conversion to nocturnal home haemodialysis [see comment]. *Nephrol Dial Transplant*. 2007;22(11):3285-3291.
6. Cafazzo JA, Leonard K, Easty AC, et al. Patient-perceived barriers to the adoption of nocturnal home hemodialysis [see comment]. *Clin J Am Soc Nephrol*. 2009;4(4):784-789.
7. Gura V, Beizai M, Ezon C, Polaschegg H-D. Continuous renal replacement therapy for end-stage renal disease. The wearable artificial kidney (WAK). *Contrib Nephrol*. 2005;149:325-333.
8. Davenport A, Gura V, Ronco C, et al. A wearable haemodialysis device for patients with end-stage renal failure: a pilot study [see comment]. *Lancet*. 2007;370(9604):2005-2010.
9. Lee DB, Roberts M, Lee DBN, Roberts M. A peritoneal-based automated wearable artificial kidney. *Clin Exp Nephrol*. 2008;12(3):171-180.
10. Tumlin J, Wali R, Williams W, et al. Efficacy and safety of renal tubule cell therapy for acute renal failure. *J Am Soc Nephrol*. 2008;19(5):1034-1040.
11. Humes HD, Weitzel WF, Bartlett RH, et al. Initial clinical results of the bioartificial kidney containing human cells in ICU patients with acute renal failure. *Kidney Int*. 2004;66(4):1578-1588.
12. Lewin AJ, Greenbaum MA, Gordon A, Maxwell MH. Current status of the clinical application of the Redy R dialysate delivery system. *Proc Clin Dial Transplant Forum*. 1972;2:52-56.
13. Gura V, Macy AS, Beizai M, Ezon C, Golper TA. Technical breakthroughs in the wearable artificial kidney (WAK). *Clin J Am Soc Nephrol*. 2009;4(9):1441-1448.
14. Gura V, Davenport A, Beizai M, Ezon C, Ronco C. Beta2-microglobulin and phosphate clearances using a wearable artificial kidney: a pilot study. *Am J Kidney Dis*. 2009;54(1):104-111.
15. Gura V, Rivara MB, Bieber S, et al. A wearable artificial kidney for patients with end-stage renal disease. *JCI Insight*. 2016;1(8):e86397. https://doi.org/10.1172/jci.insight.86397.
16. Li L, Marchant RE, Dubnisheva A, Roy S, Fissell WH. Anti-biofouling sulfobetaine polymer thin films on silicon and silicon nanopore membranes. *J Biomat Sci Polym Ed*. 2011;22(1-3):91-106.
17. Melvin ME, Fissell WH, Roy S, Brown DL. Silicon induces minimal thromboinflammatory response during 28-day intravascular implant testing. *ASAIO J*. 2010;56(4):344-348.
18. Iqbal Z, Moses W, Kim S, Kim EJ, Fissell WH, Roy S. Sterilization effects on ultrathin film polymer coatings for silicon-based implantable medical devices [published online ahead of print 2017]. *J Biomed Materials Res B Appl Biomat*. 2017; https://doi.org/10.1002/jbm.b.34039.
19. Muthusubramaniam L, Lowe R, Fissell W, et al. Hemocompatibility of silicon-based substrates for biomedical implant applications. *Ann Biomed Eng*. 2011;39(4):1296-1305.

20. Kensinger C, Karp S, Kant R, et al. first implantation of silicon nanopore membrane hemofilters. *ASAIO J*. 2016;62(4):491-495.
21. Fissell WH, Dubnisheva A, Eldridge AN, Fleischman AJ, Zydney AL, Roy S. High-performance silicon nanopore hemofiltration membranes. *J Membr Sci*. 2009;326(1):58-63.
22. Kanani DM, Fissell WH, Roy S, Dubnisheva A, Fleischman A, Zydney AL. Permeability-selectivity analysis for ultrafiltration: effect of pore geometry. *J Membr Sci*. 2010;349(1-2):405-410.
23. Fissell WH, Manley S, Dubnisheva A, et al. Ficoll is not a rigid sphere. *Am J Physiol Ren Physiol*. 2007;293(4):F1209-F1213.
24. Humes HD, Mackay SM, Funke AJ, Buffington DA. Tissue engineering of a bioartificial renal tubule assist device: in vitro transport and metabolic characteristics. *Kidney Int*. 1999;55(6):2502-2514.
25. Westover AJ, Buffington DA, Humes HD. Enhanced propagation of adult human renal epithelial progenitor cells to improve cell sourcing for tissue-engineered therapeutic devices for renal diseases. *J Tissue Eng Regen Med*. 2012;6(8):589-597.
26. Agar J. An Obituary for Baxter's Vivia Home HD Machine. *Home Dialysis Central*. 2018. https://homedialysis.org/news-and-research/blog/168-an-obituary-for-baxter-s-vivia-home-hd-machine. Medical Education Institute, Inc, Madison, Wisconsin; 2016. Accessed June 4, 2018.