TURBOCHARGING

From the start, Mat Risher swore that dialysis wouldn't upend his life. He had been working at a software company, conducting research on a car-racing simulator, when kidney damage from lupus forced him to start the blood-filtering treatments three times a week.

Five years have slipped by, and the sessions have sapped his resolve. The 33-year-old now works part-time. On good days, he enjoys trying out new recipes. On bad days, his lupus flares up and the strain of incessant dialysis leaves him drained. "The times in between [dialysis days], I have no social life, no dating life," says Risher, who lives just outside Seattle, Washington. "I have become a recluse in my room."

Risher is relatively fortunate; he has access to treatment, whereas up to seven million people could die each year without getting such care[1]. But Risher, a member of a patient advisory board at Seattle's Center for Dialysis Innovation (CDI), is impatient for a more liveable option than dialysis — which has remained largely the same for 50 years.

Walk into any facility, says CDI co-director Buddy Ratner, and you'll find a big machine at the bedside of every person undergoing dialysis. "These days it's going to have LCD screens and modern controls," he says. "But look at the pictures in the 1960s of those machines. They look rather similar to what we're doing today." Survival has increased, but still, just 42% of US patients receiving the most common form of treatment, known as haemodialysis, live even for five years — shorter than for many cancers.

Ratner is among an international cadre of physicians, bioengineers and entrepreneurs who are working to revolutionize treatment for kidney failure, designing devices that are portable enough to carry into work or strap around the waist. Some are even developing artificial kidneys that could be surgically implanted.

The complexities remain daunting. Dialysis poorly mimics the sophistication of the human kidney, and improved and more portable versions will need miniaturized components and a substantial reduction in the amount of water required. Any approaches that make use of biological materials will face steep regulatory hurdles, too.

But a new wave of funding is helping to reverse the years of stagnation. Last year, US President Donald Trump issued an executive order on kidney health, including strategies to reduce the shortage of kidneys available for transplantation, encourage more dialysis at home and incentivize research into artificial kidneys through a partnership called KidneyX. The partnership is led by the US government and the American Society of Nephrology and plans to raise US$250 million over the next five years. Last year, it awarded a total of $1.1 million to 15 US-based research teams tackling various pieces of the dialysis puzzle, including groups pursuing wearable dialysis devices and bioengineered kidney grafts.

Around the world, clinical trials of portable devices are advancing, and researchers are finalizing a low-tech approach that they hope will reach regions of the world where clean water is unreliable and dialysis is scarce.

All these efforts are a drop in the ocean compared with the hefty bill to treat people living with end-stage kidney disease — at least US$35 billion annually in the United States alone. But the field is bullish. John Sedor, a nephrologist at the Cleveland Clinic in Ohio, who chairs the KidneyX steering committee, predicts that a much more portable device will be available in the next five years, and the first wearable device in the next decade. "I think this is a remarkable time and we're at a tipping point in our field," he says.

That innovation is long overdue, says Valerie Luyckx, a nephrologist at Graubünden Cantonal Hospital in Switzerland who researches the global burden of kidney disease. Dialysis "is a multibillion-dollar industry, with multiple billions in profits since the early 1960s", she says. "And nobody has bothered to try to innovate until all of the sudden there is research and grant funding for it."

A smart organ

The kidneys are complex and resilient organs, each roughly the size of a fist. They filter some 140 litres of blood each day, leaving behind a litre or two of water and waste in the form of urine.

Each kidney features a latticework of roughly one million tiny filtering units, called nephrons. Blood entering a nephron passes through a cluster of tiny vessels called the glomerulus. The thin walls of the glomerulus enable waste, water and other small molecules to pass through, while blocking larger ones such as proteins and blood cells. From there, the filtered fluid

flows into kidney tubules, where the balance of minerals, water, salts and glucose is calibrated and molecules necessary for bodily functions are reabsorbed into the bloodstream.

But many medical conditions can strain the kidneys, including diabetes, obesity and high blood pressure. And those conditions are becoming more common. By 2030, it's projected that 5.4 million people worldwide will be getting dialysis or a transplant, and many more will die without[1].

For haemodialysis, patients usually need to travel to a clinic, where they are connected to a machine weighing more than 100 kilograms that filters the patient's blood through a semi-permeable membrane, designed to replicate the function of the glomerulus. Then a water-based dialysis solution is used to

MOHAMMED HUWAIS/AFP/GETTY

IG DIALYSIS

After decades of slow progress, researchers are starting to test better treatments for people with failing kidneys.
By Charlotte Huff

Kidney dialysis is inefficient and exhausting for patients such as this person in Yemen.

rebalance the blood's components and carry the toxins down the drain. Haemodialysis is much better at replicating the filtering than at achieving the subtle recalibration provided by the kidney tubules, says Jonathan Himmelfarb, the other co-director of the CDI. Healthy kidneys make subtle adjustments around the clock, whereas patients get just 12 hours of dialysis across 3 sessions each week, he says. Rebalancing the blood so abruptly can be a shock to the body and take hours to recover from. This is dubbed dialysis washout. Risher, who takes a shuttle to dialysis, often falls asleep on the way home.

The inefficient treatment is also very costly, as much as $91,000 annually per patient in the United States. And as well as using a lot of water, the current approach consumes vast quantities of power and materials such as plastics. "We use massive amounts of water – it's not a green therapy," Sedor says.

Plus, access is patchy around the globe. No more than one-third of people in Asia get dialysis, and even fewer in Africa[1] (see 'A neglected need'). And even when patients in sub-Saharan Africa do begin the treatments, they are rarely able to sustain them for more than a few months[2].

The reason, in large part, is cost. Even when the government pays for the sessions, the patient's family often has to foot the bill for lab tests, medications and other costs, says Gloria Ashuntantang, a nephrologist at Yaounde General Hospital in Cameroon. "Most of our patients will stop the therapy halfway, after having sold all property, and the children having dropped out of school."

Still, there has been a lack of drive to improve the procedure, in part because the treatment has proved highly profitable for dialysis providers around the world, says Murray Sheldon, a physician and associate director for technology and innovation at the Center for Devices and Radiological Health at the US Food and Drug Administration (FDA). "They have a cash cow. And there's no need to do any innovation." Dialysis companies challenge that argument. Brad Puffer, a US-based spokesperson for Fresenius Medical Care in Waltham, Massachusetts, says that his company is investing in improvements, including a haemodialysis device that incorporates a material designed to reduce blood clotting, a potential side effect that today's recipients have to take medication to prevent.

Kidney in a backpack

One of the big problems with modern dialysis is that the machines require vast amounts of water: 120–180 litres for each 4-hour session, Himmelfarb says. "Obviously nobody can carry that around them because it would weigh tons." There are a few in-home models marketed as portable: Fresenius sells a device that it says gives patients more mobility. It weighs 34 kilograms and can be used with a home tap, as long as the water meets certain quality standards. But the first priority in making dialysis more convenient is to remove the need for an external water supply.

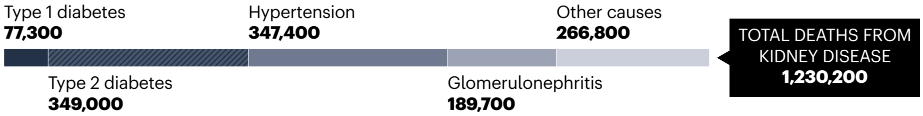
In Seattle, CDI researchers have developed a technique that pushes the used dialysis solution through a cartridge that uses light to convert urea – a key toxin targeted by dialysis – into nitrogen and carbon dioxide, so that the solution can be recycled[3]. The method can remove 15 grams of urea in 24 hours, sufficient for most people with kidney failure, and requires only 750 millilitres of solution, Himmelfarb says.

The team's standalone haemodialysis device could be made compact enough to fit inside a rolling case, Himmelfarb says, weighing no more than 9 kilograms. Ideally, patients would use it daily, he says.

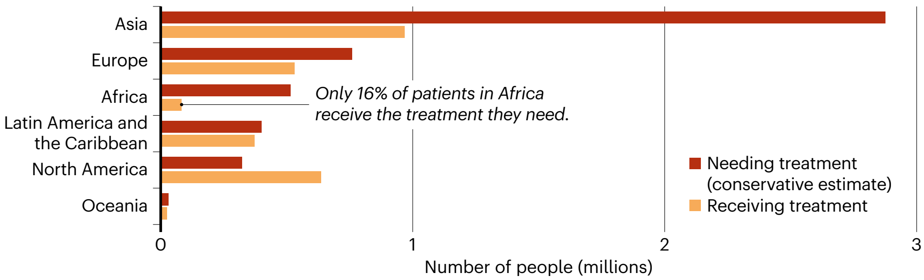
Another group trying to downsize dialysis was recently formed by the Dutch Kidney

A NEGLECTED NEED

Chronic kidney disease kills more people each year than tuberculosis or HIV. Many cases are linked to hypertension and diabetes, which can be products of obesity, and a type of kidney inflammation called glomerulonephritis.



The number of people receiving treatment for kidney failure in the form of either dialysis or a transplant varies widely around the world.



SOURCES: MORTALITY: GBD CHRONIC KIDNEY DISEASE COLLABORATION *LANCET* **395**, 709–733 (2020); TREATMENT: REF. 1

Foundation, the medical-devices firm Debiotech in Lausanne, Switzerland, and non-profit insurers. Its latest prototype, which it hopes to make available to patients by 2023, weighs about 10 kilograms and will require only 6 litres of solution, according to Ton Rabelink, a nephrologist at Leiden University Medical Center in the Netherlands who is on the medical advisory board of the company, called NextKidney. The device, which could be used at home, limits the quantity of dialysis solution needed by using an absorbent material to soak up the toxins, Rabelink says.

In Singapore, researchers at the medical-technology company AWAK have been testing an even lighter device, one that weighs no more than 3 kilograms. It's designed for peritoneal dialysis, a technique that uses a catheter to send dialysis solution into the abdominal cavity, where a lining (the peritoneum) filters out toxins from the blood so they can drain, along with the solution, into an empty bag.

The AWAK device relies on a pump and a cartridge to absorb toxins from the used solution so that it can be recirculated. Each daily treatment would last seven to ten hours.

The company completed a safety trial involving 15 adults at Singapore General Hospital in 2018. It reported no serious adverse events, although some patients experienced abdominal discomfort or bloating. The device is one of several more-portable products in development that the FDA has agreed to expedite through its 'breakthrough devices' programme.

But testing a device in the controlled setting of a hospital is very different from using it in daily life, says Arshia Ghaffari, a researcher who directs dialysis services at the University of Southern California in Los Angeles. Furthermore, it's possible that the constant recirculation of dialysis solution could strain delicate membranes and "burn out the peritoneum faster", he says. A company spokesman discounted that concern, saying that the fluid is recirculated in small increments, just 250 millilitres at a time.

In some regions of the world, peritoneal dialysis is not an option, owing to the costs of shipping the heavy bags of solution. An international competition led by the George Institute for Global Health in Camperdown, Australia, in 2015 sought ways to improve access.

The winning technology, developed by Irish engineer Vincent Garvey, incorporates a lightweight kit that includes sterile bags containing a dry mix (dextrose and salts), along with a water distiller the size of a bread box, which sterilizes the water used to make the mix. A month's worth of supplies could be shipped in a box weighing 3 kilograms – a big improvement over a typical day's supply, which weighs 8 kilograms, says John Knight, managing director of Ellen Medical Devices in Camperdown, which was formed to develop the prototype. Knight's goal is to complete a clinical trial by the end of next year.

> **"THAT WOULD BE SO MUCH BETTER THAN ANY DEVICE, TO HAVE YOUR OWN KIDNEY FUNCTION REGENERATED."**

Recreating the kidney

Researchers at the University of California, San Francisco (UCSF), and Vanderbilt University in Nashville, Tennessee, have bypassed external devices and instead focused on developing a kidney prototype that they hope will one day be surgically implanted into a patient's body. It wouldn't require a pump because it would be attached to key arteries and powered by blood pressure, says Vanderbilt nephrologist William Fissell, who co-directs the research with UCSF's Shuvo Roy.

The device contains two key parts: a blood-filtration system and a cell-infused recalibration module. The filter is made of silicon membranes with nanometre-scale pores that are designed to mimic the glomerulus. The recalibration module uses tubule cells from discarded human kidneys to rebalance the blood's components, Fissell says.

Late last year, researchers reported at an American Society of Nephrology meeting that they had conducted the first safety test of the recalibration module in pigs, without any of the serious problems often seen with implanted devices, including an immune reaction or blood clots.

But Rabelink thinks that implantable devices will be more difficult to develop, given that they rely on a mix of engineered and biological elements, complicating the design and creating extra regulatory hurdles. In the meantime, he posits that advances in stem-cell research might surpass such efforts. "In the end, that would be so much better than any device, to have your own kidney function regenerated or prolonged," he says.

But Fissell and Roy counter that stem-cell techniques have been slow to pay off in other areas, such as diabetes treatment, so devices such as automated insulin pumps have led the way. Fissell describes the project's primary hurdle as securing sufficient funding to manufacture the device, which is roughly the size of a soft-drink can, on a larger, standardized scale so it can be evaluated by US regulators. "I've got the [device] right on my desk – it's ready to sew," he says.

Despite the confidence of some teams, Sheldon thinks that recreating the sophistication of a kidney is too complex for any single team, and will probably require a mix of engineering and biology, plus a lot more money. He proposed the idea of an international coalition at an American Society of Nephrology meeting last year, and has planned a series of meetings in Europe later this year with stakeholders and medical groups.

For Risher and other patients, access to any portable device would be liberating, providing "that freedom and flexibility to do dialysis when I want to do it", he says. As a car aficionado, he dreams of throwing his machine onto the passenger seat and steering for the open road, only the horizon before him.

Charlotte Huff is a science journalist based in Fort Worth, Texas.

1. Liyanage *et al. Lancet* **385**, 1975–1982 (2015).
2. Ashuntantang, G. *et al. Lancet Glob. Health* **5**, e408–17 (2017).
3. Shao, G., Zang, Y. & Hinds, B. *Appl. Nano Mater.* **2**, 6116–6123 (2019).