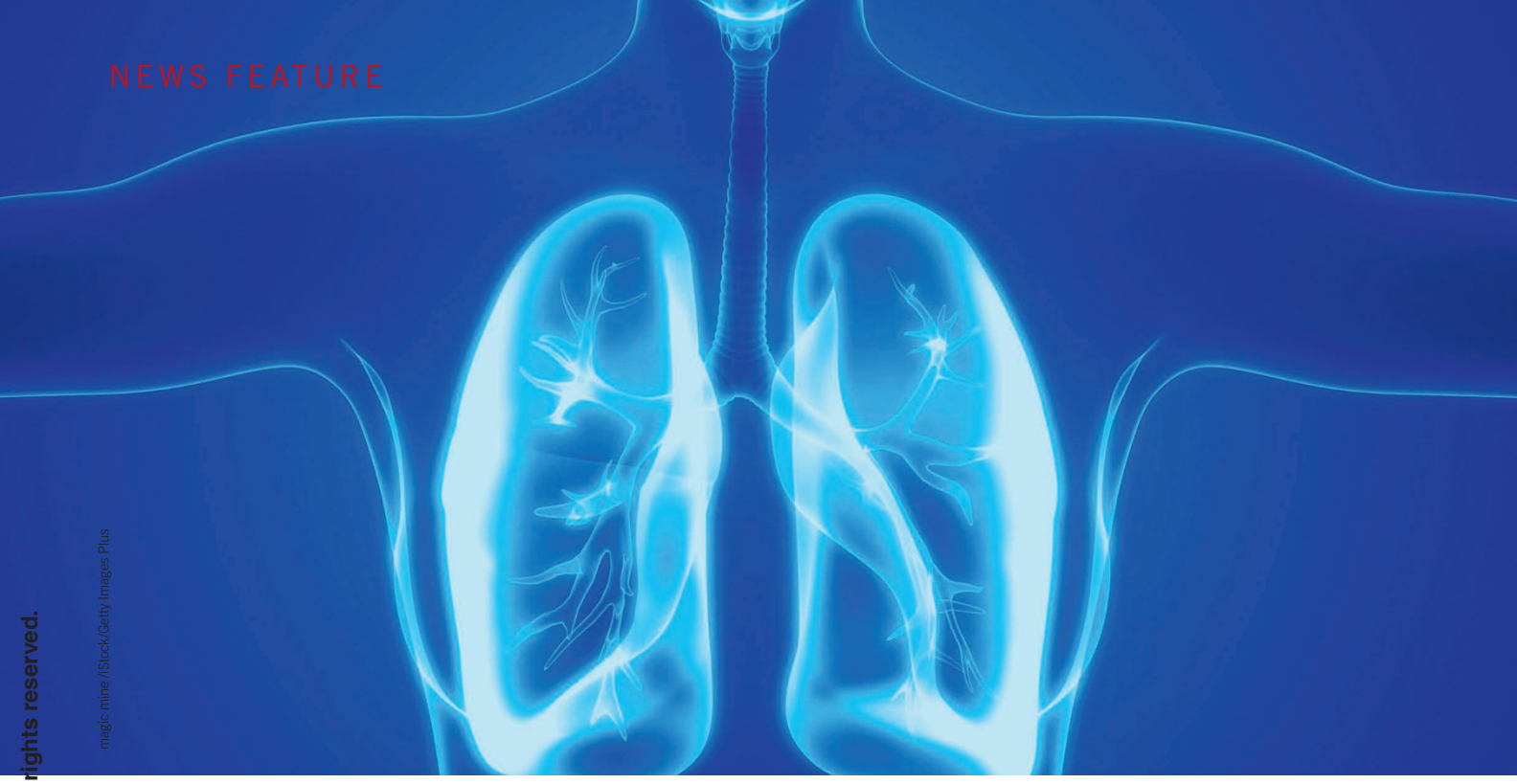

magic mine /iStock/Getty Images Plus

Beating the organ clock

Donor organ monitoring and *ex vivo* perfusion technology are transforming transplantation and offering new therapeutic opportunities. Melanie Senior reports.

Jayan Nagendran, a cardio-thoracic surgeon in Edmonton, Alberta, recalls one Christmas Eve, when a 28-year-old woman with cystic fibrosis urgently needed a double lung transplant. Finding organs was even more challenging than usual, he says, because of the woman's small size. The only lungs available were from a woman who had died in the emergency room that evening from a pulmonary embolism. Normally, lungs from a patient with a blood clot would be discarded. "But we put them on an *ex vivo* perfusion device, perfused them with clot-busting drugs, and the machine showed the clot gradually dissolving over two hours," says Nagendran. The recipient would go on to run 5K races.

Ex vivo perfusion (EVP) keeps organs alive outside the body by pumping them with an appropriate mixture of oxygen and nutrients, providing an opportunity to repair organs in a tailored fashion, at the time of donation, enthuses Nagendran. "The hope is that every organ will eventually be placed on EVP."

But we're not there yet. Organ transplantation is one of the few areas of medicine where the standard of care, at least for the organ, remains largely the same at it was over five decades ago. Since Joseph Murray successfully transplanted the first kidney in 1954, organs have been stored and transported in an ice-box. Today, static cold storage (SCS), as the ice-box method is known, remains the gold standard for most of the estimated 130,000 organ transplants carried out annually across the globe.

But EVP promises a platform for safe and effective organ storage. It also enables more sophisticated donor-organ monitoring and restoration via therapeutic interventions. Ultimately, it could vastly expand the number of organs available for transplantation, increase times for finding the best-matched organ recipients and improve transplant outcomes.

Organs on ice

The simplicity of the SCS technique has been key to its success. But it places tight limits on how long organs can be stored before the damage they suffer from being outside of their normal, functioning environment makes them unfit for use. SCS is effectively a damage-limitation exercise, shutting down metabolism and with it harmful processes like inflammation. But ischemic injury—tissue death due to lack of oxygen— makes hearts and lungs unusable after 4–6 h, and limits livers to 12. Even if used within those tight windows of time, these organs cannot be meaningfully assessed, nor ideally matched to their recipient.

These constraints, coupled with a continued shortage of donors, help explain some sobering statistics: there are over 100,000 patients on organ waiting lists in the US, and in 2017 fewer than a third received an organ. Fewer than 2% of deaths lead to eligible organ donation. Up to 80% of donated lungs are discarded owing to damage suffered before or during death. Forty per cent of heart recipients suffer acute, if treatable, rejections within a year. One in five patients needing a liver transplant dies on the waiting list.

The need for transplants has never been greater. Rates of non-alcoholic fatty liver disease are rising due to obesity. Smoking, air pollution and infections are accelerating the incidence of chronic obstructive pulmonary disease. For both conditions, transplant is often the most effective, or the only, therapy.

Perfused with benefits

Advances in EVP technology are starting to transform organ transplantation. It is already commonly used for kidneys in some healthcare systems. Driven partly by urgent need, and partly by the continued convergence of engineering with medicine, improved generations of these machines are emerging for other organs, too, including livers, lungs and hearts.

EVP buys time to transport organs over greater distances to those most in need, and allows surgery to occur during more humane,

daylight hours with fully staffed teams. It enables organ monitoring and assessment, and better recipient matching. And by enabling suboptimal or diseased organs to be repaired, as in the case of the cystic fibrosis patient, *ex vivo* perfusion is increasing the number of usable organs from the current donor cohorts, cutting wastage and boosting the chances of those on waiting lists receiving the organ they need. Most organs, other than kidneys, are recruited from so-called 'brain dead' donors. These patients' brains have irreversibly lost all function, yet their hearts are kept going by machines, which keeps their organs viable for a while. EVP is helping expand this pool to include organs from a far larger group: patients whose hearts have stopped, and those with conditions that would normally preclude transplant.

Donation after circulatory death (DCD), routinely used for kidneys, is already becoming more widespread with other organs like the liver that are naturally regenerative. EVP, by allowing organs to recover from cellular injury, may expand that further, potentially allowing demand for organs, such as livers and lungs, to be more fully met[1]. "DCD organs is the biggest untapped pool of organs we have," says Korkut Uygun, assistant professor in surgery at Harvard Medical School and Massachusetts General Hospital.

Shaf Keshavjee, surgeon in chief at the University Health Network in Toronto, and director of the Toronto Lung Transplant Program, says *ex vivo* lung perfusion (EVLP) has led to a more than 70% increase in the number of lung transplants at his center over the past five years. Lungs are now being stored well over 20 h, over three times the previous average. "We're moving toward making lung transplants more elective than emergency," he says.

On the margins, for now

Still, for organs other than kidneys, the use of EVP machines remains experimental. Most devices are being used "in a limited capacity, specifically for marginal organs," acknowledges Nagendran. Most studies to date of EVP technologies have been small, single-center trials focused on proving the safety and feasibility of the method, and on its ability to resurrect extended-criteria (suboptimal) organs to achieve similar outcomes as acceptable organs on SCS.

The pioneering 2011 Toronto EVLP trial showed that high-risk donor lungs, transplanted after four hours of EVLP with a bloodless solution of oxygen, proteins and nutrients, have similar success rates, in terms of primary graft dysfunction, as conventionally selected lungs transplanted without EVLP[2]. The EVP machine and solution were provided by Gothenburg, Sweden-based XVIVO Perfusion, whose XPS machine was the first EVP technology approved (in 2014) by the US Food and Drug Administration (FDA; **Table 1**). Marginal livers can also be resurrected with EVP to achieve the same, or even better, results than conventionally stored organs. A 2014 study of 60 patients at Columbia University Medical Center in New York showed that hypothermic machine perfusion (using a modified portable bypass system made by Medtronic) on marginal livers led to significantly fewer biliary complications, and shorter hospital stays, than appropriately matched organs undergoing SCS[3]. In 2016, a study of 20 warm-perfused livers showed similar 30-day survival rates, and significantly lower levels of mean peak aspartate aminotransferase, a marker of organ damage, than cold-stored livers[4].

Results from larger multicenter trials are emerging. In April, Oxford, UK-based OrganOx published results from a randomized study involving 220 livers, all deemed transplantable at the outset, to either SCS or warm perfusion in the company's portable normothermic EVP device, the 'metra'. The EVP livers—given a carefully prepared mixture of red blood cells, oxygen and nutrients—showed a 49.4% reduction in peak serum aspartate transaminase levels within seven days after transplant. One-year graft survival was similar across the two groups, despite the 54% longer mean preservation time for EVP livers[5].

Also in April, results were published from the INSPIRE (International Randomized Study of the TransMedics Organ Care System for Lung Preservation and Transplantation) randomized control trial of TransMedics' Organ Care System (OCS) for lungs, supporting FDA Pre-Market Approval for the device in double lung transplants. In INSPIRE, the largest-ever controlled lung preservation study, 320 patients across the US, Europe, Australia and Canada received either standard criteria organs perfused at body temperature in TransMedics' portable lung perfusion device, or standard criteria organs stored in static cold. The primary effectiveness endpoint—non-inferiority across incidence of severe (grade 3) primary graft dysfunction within 72 h of transplant, and 30-day survival—was met, though the data were just short of showing superiority on these measures. Further research is needed to establish whether reduced rates of graft dysfunction in the OCS translate into better long-term outcomes.

XVIVO Perfusion's non-randomized, open-label NOVEL (Normothermic *Ex Vivo* Lung Perfusion as an Assessment of Extended/Marginal Donor Lungs) study of the XPS warm EVLP technology aims to show non-inferior survival outcomes for patients receiving perfused marginal lungs versus those receiving acceptable organs stored conventionally. It's a tough hurdle, as the quality of the unacceptable lungs may vary. The study, which completed recruiting over 250 participants in June 2017, is the largest multicenter US warm perfusion lung trial, according to XVIVO's CFO Christoffer Rosenblad. A hypothermic (rather than normothermic) EVP (hypothermic oxygenated machine perfusion; HOPE) trial of liver allografts from extended-criteria donors after brain death at RWTH Aachen University in Germany, using the ORS LifePort Liver instrument, is due to report results later this year.

"It's an exciting period for organ perfusion. But this is matched by the fact that we don't yet have clear clinical trial evidence to answer questions about value for money, when and when not to use perfusion, and at which temperature ranges," says Barry Fuller, professor of surgical sciences in the Division of Surgery & Interventional Science at the Royal Free Hospital in London.

Hot, cold or a bit of both?

One somewhat controversial aspect of EVP is selection of the optimal temperature for perfusion. Hypothermic perfusion—at about 4 °C—has shown benefits relative to static storage, in studies of livers, lungs and kidneys. But newer research hints that warm perfusion, at physiological temperatures, may bring even greater benefits to some organs. Whether those benefits are sufficient to offset the practical and financial hurdles associated with keeping organs warm is less clear. The temperature debate is entangled with the question of whether machines need to be portable—not only available at the donor hospital but also transportable to the recipient, maintaining the organ at a constant, physiological temperature.

Growing commercial interest across the area means the multiple studies underway are being done with different protocols and machines, typically comparing a proprietary combination with SCS, rather than with each other. "A lot of research is now driven by business-related motives, rather than scientific endeavor," cautions Nagendran, who also has skin in the game as vice president and director of clinical investigation at Edmonton, Alberta-based startup Tevosol, which is developing a portable, warm perfusion technology platform for lungs, hearts, livers and kidneys.

Devices offering low-temperature machine preservation—one step beyond the ice-box—have gained the most commercial traction. Chicago-based Organ Recovery Systems' LifePort Kidney Transporter is a hypothermic machine preservation technology that

Table 1 Selected EVP companies

Company name	Production description	Stage of development
XVIVO Perfusion	XPS normothermic EVP machine for lungs, non-portable	CE-marked and FDA approved for initially unacceptable donated lungs
Organ Assist	KidneyAssist, LiverAssist, LungAssist: variable-temperature devices, mobile (on wheels) but non-portable	CE-marked
Organ Recovery Systems	LifePort Kidney Transporter, LifePort Liver Transporter; hypothermic machine preservation technology, portable	Kidney Transporter FDA approved (2003) and CE-marked (2004), globally commercialized; Liver Transporter pending approval
TransMedics	Organ Care System (OCS): normothermic, portable devices for lung and hearts	CE-marked and used in transplant centers in Europe, Canada and Australia. Lung system received FDA premarket approval in April 2018 for standard double-lung transplants. Liver system initiating trials.
Lung Biotechnology (United Therapeutics)	Lung repair centers (Silver Spring, Maryland) and planned for Jacksonville, Florida	Repair centers involved in a clinical trial where organs are sent in on ice, perfused using Toronto EVLP system for up to six hours, and recooled for shipment to the recipient.
OrganOx	The metra: portable, normothermic *ex vivo* perfusion device for livers	CE-marked; US/Canada trials ongoing
Tevosol	Portable, warm perfusion technology for lungs, hearts, livers and kidneys	Early development
XOR Labs	Standardized and scalable EVP machines for use at any temperature	Early development

has been used in over 100,000 transplant procedures across 37 national markets since being approved by the US FDA for clinical use in 2003, according to founder and CEO David Kravitz. In most transplant centers, LifePort is used for extended-criteria kidneys—those that wouldn't normally be selected for transplant, due to donor age or health and concerns over organ quality. Transplant programs in France and Switzerland have adopted LifePort nationwide for such purposes. Many transplant centers also routinely use LifePort for preserving standard-criteria kidneys, especially when longer *ex vivo* cold preservation times are anticipated, according to Kravitz.

"Our view was that evolutionary improvement in cold preservation is a better bet than taking on a revolutionary method such as warm preservation," says Kravitz. It's a pragmatic approach: organ procurement organizations and transplant surgeons are already engaged in high-risk, life-saving work. The transplant community has almost 50 years' experience using cold preservation as a safe and effective standard of care, and is wary of embracing additional clinical risks. "During our market research, we learned that surgeons were especially concerned about the hazards of contamination and machine failure," says Kravitz. If the cold machine breaks down, the organ reverts to SCS. If a normothermic machine fails, the organ is likely to be lost or compromised. In many countries, surgeons are scored on transplant outcomes. Persuading them to adopt a new technology may prove challenging.

Experience and evidence is accumulating to suggest that normothermic perfusion provides chances of a transplant where none existed before, however. "Unequivocally, normothermic perfusion from the moment of donation has the greatest potential to improve the quality of the organ prior to transplant," declares Nagendran.

Warm perfusion certainly allows more accurate organ assessment because the organ is functioning at its normal metabolic rate. "You can't truly assess an organ's viability, or treat it" in hypothermic storage, argues OrganOx CEO Craig Marshall. OrganOx's CE-marked 'metra' device has already shown safe organ preservation up to 24 hours—twice as long as hypothermic storage would allow. The company claims there have been no machine failures, after approximately 300 transplants—although the metra is fitted with early-warning systems including a Wi-Fi-connected monitor, just in case.

It is reasonable to assume that an organ kept at its normal, physiological temperature, provided with all or most of what it usually receives, is going to fare better than those pumped with cold perfusate (though all organs, after extraction, are flushed through with cool solution to clear out blood, damaged cells and inflammatory substances). And indeed, for some organs—like the heart—"the consensus is as much normothermic as possible," says Joren Madsen, director of the Massachusetts General Hospital Transplant Center in Boston.

Yet lower temperatures may help protect cells against reperfusion injury[6]—the damage incurred when oxygen-starved cells are resupplied with warm blood. Recent studies suggest that cold may help recondition and refuel mitochondria, thereby reducing levels of reactive oxygen species, which trigger inflammatory cascades[7]. Lower temperatures are also key to longer-term preservation, says Sebastian Giwa, co-founder and chairman of the Organ Preservation Alliance, a network of advisors and volunteers supporting a wide range of interdisciplinary approaches to organ preservation, including cryopreservation and vitrification (a special kind of freezing which prevents the formation of ice crystals that damage cell structures)[8]. "Chemistry is a function of temperature. Each reduction of 10 degrees halves the speed of chemical reactions, so extending preservation," he says. Giwa is also co-founder and chairman of Sylvatica Biotech, which is taking inspiration from hibernating and freeze-tolerant squirrels and frogs found in nature to develop cold-based organ preservation techniques[8].

Scientists at Massachusetts General Hospital, and others at University Hospital in Essen, Germany, are investigating room-temperature (sub-normo) thermic preservation at about 21 °C. This subjects cells to a less extreme jump in temperature from cold storage. It could, therefore, be "a sweet spot where repair mechanisms are active, but damage rates [are] reduced," Giwa suggests. "Science has to be married with practical and logistical constraints," he says.

The optimal, most practicable EVP solution for the real world of organ transplantation may lie in capturing the advantages of both warm and cold perfusion. "When extracting an organ, cold gives you that protection, just as it does when you put it back in. The intervening part is where people are, wrongly, saying 'warm is good and cold is bad', or vice versa. They are not thinking about the right temperature for the right organ at the right time," says the University of Toronto's Keshavjee.

He sees a future transplantation world wherein temperature, along with several other variables, can be matched to the specific organ in question. "We're interested in alternating

between normothermia, during which you can assess, treat and rev up recovery, and hypothermia, where the organ can rest and some negative processes can be switched off," he says. Keshavjee is CSO at Toronto-based startup XOR Labs, which is building a "standardized and scalable," simplified-use EVP machine that can operate at any temperature. Groningen, Netherlands-based Organ Assist's devices for kidneys, livers and lungs, already CE-marked, also operate at any temperature. "We wanted to be as flexible as possible, because the debate [between warm and cold] is still ongoing," says Arjan van der Plaats, chief technology officer.

Other EVP companies are hedging their bets on temperature. Cold-focused ORS is working in, and has assembled intellectual property around, warm perfusion. OrganOx ran a study where organs were cold-stored for four to 4–6 hours, then preserved for 6–12 hours at normothermia before transplantation, and found that most of the benefits of warm perfusion were maintained, according to co-founder Constantin Coussios. However, he cautions against cooling organs down again before transplant. "You lose the benefits of the warm," he says, citing preclinical data.

Organ repair centers

A combined cold-warm protocol would remove the need for all donor sites to have a warm *ex vivo* perfusion machine at hand—favoring companies like XVIVO Perfusion, whose technology is not transportable and is simply placed at recipient centers. And by expanding storage times from hours to potentially a day or more, it underpins a vision of centralized organ reconditioning and repair hospitals, where cooled organs are sent in from across the nation, warmed, assessed and repaired by teams of experts, before being dispatched to appropriately matched recipients.

The vision is becoming a reality. When Toronto General Hospital opened the first organ repair center in 2008, it caught the attention of Martine Rothblatt, founder and chairwoman of United Therapeutics (UT), which develops treatments for lung disease. "Martine called me up and said she wanted to build a lung repair hospital," says Keshavjee, who consults for UT. A year later, the center was up, run by UT subsidiary Lung Biotechnology. The first case study of remote EVLP, published in 2012, involved a 54-year old man, in Chicago, whose acute respiratory distress syndrome was rapidly proving fatal[9]. The only set of organs available at the time were poorly oxygenated, with edema and infiltrate (blood, pus or other proteins) filling part of the right lower lobe. The lungs were sent by air, under standard cold-flush preservation, from the donor hospital to Toronto General Hospital for four hours of EVLP. Then they were flown, cold, to Chicago and transplanted. The second period of cold ischemia seemed to have no adverse effect, according to the study's authors.

The Maryland center has since been involved in up to 80 lung transplants, as part of a clinical trial, according to Keshavjee. The lungs, perfused at normothermia, have been cooled and returned to hospitals, including the Cleveland Clinic, the Mayo Clinic, Duke University Medical Center and the University of Maryland.

Plans to build a third organ repair center on the Mayo Clinic site in Jacksonville, Florida, have been delayed, but remain in play, according to Andrew Fisher, United Therapeutics' chief strategy officer and deputy general counsel. "It's not sustainable to expect surgeons [in all transplant hospitals] to perform both the transplant, and monitor perfusion, and potentially fix the organ," says Keshavjee. "The future will involve organ perfusion specialists doing that work, and e-mailing reports to indicate whether and when the organ is ready."

The doctor will see your organ now

There will be plenty for these perfusion specialists to do. By providing a platform for safe, effective organ storage, perfusion opens the way for more accurate diagnosis, plus a wide range of novel therapeutic interventions, including airway-administered drugs to cure existing disease and, potentially, reduce post-transplant immunological responses.

Organs are currently assessed for transplant according to a mix of donor-related criteria (age, health status, therapy regimens, blood type, human leukocyte antigen (HLA)-typing), as well as basic visual, olfactory (smell) and tactile methods (e.g., for the liver, color and stiffness, which can indicate fattiness/steatosis). Assessment is somewhat subjective. The criteria vary between hospitals, and even among individual physicians. Perfusion—especially warm perfusion—enables more accurate physical and biochemical diagnoses. For livers, these measurements include blood flow and perfusion pressure, bile production and acidity, lactate clearance and other biochemical factors. For lungs, partial pressure of oxygen (PO_2), vascular resistance, dynamic compliance and peak inspiratory pressure are monitored, as well as other damage signals like levels of inflammatory cytokines.

Harvard's Uygun has developed a viability index for livers based on energy charge—a compound score of levels of ATP and its derivatives, ADP and AMP. "We found [in a study of 19 patients] that energy charge increase is predictive of early allograft function," he says, highlighting the speed and simplicity of the test, which can be done in less than 30 minutes. His next project, not yet in human trials, is a more sophisticated algorithm to predict liver function over time, based on multiple data points.

Similarly, Keshavjee's team at Toronto is progressing toward a 30-minute, nanochip-based test to diagnose a series of genes expressed in lung tissue that may predict transplant success. These include genes encoding inflammatory cytokines like interleukin (IL)-1 beta, IL-6 and IL-8, which are upregulated in transplanted organs, and more that he isn't disclosing. "Ultimately, we hope to have a score to determine which lungs to transplant," says Keshavjee.

Inflammation is a key part of the recipient immune response that causes many organ transplants to fail. Even in successful cases, recipients must take immune suppressants for the rest of their lives. Perfusion technology may reduce or even eliminate this need, by better preparing the organ immunologically. Keshavjee and his University of Toronto colleague Marcelo Cypel, associate professor of thoracic surgery and developer of the Toronto EVLP protocol, are exploring the use of gene therapy to program cells to continue to express IL-10, an anti-inflammatory cytokine. They're also adding recipients' regulatory T cells to the perfusate to 'acclimatize' the new organ. Another approach is mechanical 'immune cloaking': covering the endothelial surface of

Box 1 Perfused organs as models for research

Although EVP companies' main focus is on optimizing organ quality for transplantation, many organs continue to be unfit for use in a clinical setting. This is opening up a business opportunity to create *in vitro* organ systems that can be addressed to research questions. For example, working, warm-perfused livers can serve as useful tools for drug discovery. Liver function tests remain the core hurdle for new drugs as they enter human testing, yet mouse models only poorly predict the pharmacokinetics of many newer drug classes, such as antibodies, viruses, polymeric compounds and gold-based nano-medicines, according to Coussios. Using *ex vivo*-perfused human livers that are unsuitable for transplant offers a way to detect problems earlier, more cheaply and without putting patients at risk. Similarly, rejected livers that contain cancerous tumors offer "the best model for cancer available," says Coussios. Enabling drug discovery "is an important direction for OrganOx," he says.

the organ's vessels with nano-biolayers that prevent recipient cells from migrating into the tissue and triggering an immune response. Animal studies have shown that the technique prevented organ rejection for a month, without immune-suppressive drugs.

Normothermic perfusion allows many forms of obvious organ damage to be treated using relatively simple therapeutic strategies—and there are indications that normothermic perfusion alone and in itself can reverse damage. In the liver, preclinical work suggests that warm perfusion may reduce hepatic steatosis without any pharmacological intervention, says OrganOx's Coussios. (Cold perfusion wouldn't work in this setting as low temperatures cause fat cells to expand and they don't recover.) In lungs, protective enzymes, such as alpha-1-anti-trypsin, can be added to the perfusate to reduce or prevent damage; surfactant can be replaced, too. Existing pulmonary edema and clots, pneumonia and other infections can be cleared up using thrombolytics and antibiotics, says Cypel. Furthermore, higher, potentially more effective doses of these therapies may be safely applied to organs than would be possible if they were connected to the rest of the body.

That opens the door to an even wider range of therapeutic approaches, including where organs aren't transplanted at all. For example, aggressive chemotherapy may be applied to tumor-filled lungs while the organs remain *in vivo*, but isolated, via cannulae, from the systemic circulation. Keshavjee and Cypel have dose-tested this approach on two patients, with a third scheduled. EVP also allows protective effects of otherwise toxic substances, such as carbon monoxide, to be harnessed. Cypel is also involved in trials to clear the hepatitis C virus from donated livers to allow them to be safely transplanted.

For organs that prove to be unfit for transplantation, EVP companies are starting to explore possible research applications (**Box 1**).

Proving cost-effectiveness

As the clinical case behind EVP gains momentum, cost and access will become the biggest challenges to more widespread use. EVP machines cost hundreds of thousands of dollars–versus just $10 or $20 for an ice-box. The UK's cost watchdog, the National Institute for Health and Care Excellence, reported a total cost of £210,000 ($237,000) for TransMedics' OCS heart console and perfusion set in a 2016 medtech innovation briefing document. The disposable component alone of TransMedics' lung machine—one of the priciest—costs close to $50,000 in the US, according to Nagendran. With the resources and training required to use and maintain the machinery, it is a prohibitive sum for most hospitals, in Nagendran's view. His company, Tevosol, aims to develop more efficient machines at a fraction of the cost. But, with just two lung EVP devices approved by the FDA to date, it will be a while before market forces push down prices. Mass General's Madsen predicts that, even if the TransMedics heart device is approved in the US (it is already CE-marked in Europe and Australia), cost concerns mean that "we'll still use the igloo" for anything other than hearts that are compromised, donated after DCD or too far away for conventional storage.

Costs may not need to fall that much. Wider use of EVP—leading to more, and more successful transplants—could help avoid some of the huge costs of long-term intensive care unit (ICU) stays, hospital readmissions and the long-term therapies required when transplants aren't available. Here, too, kidneys have shown the way: a transplant costs about $145,000. A year of dialysis and related medication costs $120,000. The spread of kidney perfusion machines reflects those numbers. Some of the trials supporting the safety of EVP have data on reduced ICU stays, and more cost-effectiveness evidence is being collected.

According to XVIVO's Rosenblad, his company sells its perfusion machines at cost and has so far sold or leased in the US 46 of its XPS EVP devices. The company's simpler LS EVP device, which uses a different protocol, has sold just under 30 units in the US, 17 in Europe and a first in China. Organ Assist, whose machine costs about €75,000 ($89,000), reports similar sales. The numbers aren't big, but not all transplant clinics have the required skills and resources for EVP (e.g., trained perfusion specialists).

OrganOx has recently signed distribution agreements in Spain, Germany, Austria and Switzerland. Marshall says most of the German health insurance funds that cover liver transplants have applied to have the company's metra device reimbursed. Switzerland has recently made perfusion of DCD livers mandatory, according to Organ Assist's van der Plaats. As healthcare payers and providers become more cost-sensitive, they are also more receptive to the cost-effectiveness data that perfusion trials are generating. And advances in gene therapy and other novel therapeutic approaches are already forcing health systems to find new ways to pay, and to capture downstream savings[10].

The future is now

EVP is just one of several multidisciplinary endeavors aiming to address organ shortages. Others include cryopreservation, sub-zero cooling, tissue-engineered grafts and xenotransplants. But most of the aforementioned approaches are still very much in the early-discovery phase.

Perfusion is already delivering compelling clinical data. The task is now to gather more human data to prove the safety and effectiveness of the various perfusion approaches in different organs and different contexts. And to demonstrate that EVP devices are capable of not only opening up a larger catchment of donor organs for transplantation via therapeutic intervention, but also delivering significant savings to healthcare systems and, most important of all, saving patients who otherwise have no treatment options. "We have already shown what is possible," says the University of Toronto's Keshavjee. "We've caught the interest of everyone, including business people. This is the future of organ transplantation."

Melanie Senior, London

1. Yeung, J.C. & Keshavjee, S. *Cold Spring Harb. Perspect. Med.* **4**, a015628 (2014).
2. Cypel, M. *et al. N. Engl. J. Med.* **364**, 1431–1440 (2011).
3. Guarrera, J.V. *et al. Am. J. Transplant.* **15**, 161–169 (2015).
4. Ravikumar, R. *et al. Am. J. Transplant.* **16**, 1779–1787 (2016).
5. Nasralla, D. *et al. Nature* **557**, 50–56 (2018).
6. Chouchani, E.T. *et al.Cell Metab.* **23**, 254–263 (2016).
7. Schlegel, A., Muller, X. & Dutkowski, P. *Curr. Opin. Organ Transplant.* **22**, 563–570 (2017).
8. Giwa, S. *et al. Nat. Biotechnol.* **35**, 530–542 (2017).
9. Wigfield, C.H. *et al. Am. J. Transplant.* **12**, 2838–2844 (2012).
10. Brennan, T.A. & Wilson, J.M. *Nat. Biotechnol.* **32**, 874–876 (2014).