Rollout of high-priced cell and gene therapies forces payer rethink

The high prices of pioneering gene therapies are forcing urgent discussions around value, affordability and payment methods. The Boston-based Institute for Clinical and Economic Review (ICER) has recently had its say on the cost-effectiveness of the first two chimeric antigen receptor T-cell (CAR-T) drugs for aggressive blood cancers: Basel, Switzerland–based Novartis' Kymriah (tisagenlecleucel), priced at $475,000, and Foster City, California–based Gilead's Yescarta (axicabtagene ciloleucel), at $373,000. Its headline verdict: the CAR-T drugs are, broadly, cost-effective. But Philadelphia-based Spark Therapeutics' gene therapy Luxturna (voretigene neparvovec), which treats an inherited form of blindness (*Nat. Biotechnol.* **36**, 6, 2018), is at least twice as expensive as it should be given its clinical benefits.

The reality is far more complex than these headlines suggest. Both treatment categories are designed as one-time therapies, whose benefits may endure over years or even a lifetime. Both provide patients with options where none currently exist. These therapies are a triumph of science, and their prices should reflect that. But the lack of evidence supporting their long-term effects is putting clinicians and payers on guard. These single-use treatments also challenge current drug payment systems, designed around small molecules or biologics treatments administered every few weeks or months.

For now, cell and gene therapies' budgetary impact is limited, given the tiny populations to benefit. Kymriah is indicated for relapsed or refractory pediatric B-cell precursor acute lymphoblastic leukemia, which affects fewer than 3,000 patients in the US annually. Yescarta is approved for the estimated 6,000 US adults with relapsed or refractory diffuse large B-cell lymphoma. Luxturna, approved by the US Food and Drug Administration (FDA) in December 2017 to treat retinal dystrophy, may help restore vision for fewer than 2,000 US patients with the biallelic *RPE65* genetic mutation.

But this is just the first of a wave of similar therapies likely to reach the market over the next few years. Kymriah and Yescarta are being studied in further cancer types including solid tumors, and many other gene therapies are in the pipeline. The class will ultimately have a huge impact on health systems, which is why ICER got involved.

This independent, not-for-profit organization cannot mandate what drugs payers should fund, but has become increasingly influential in driving the drug pricing debate. On March 2, ICER convened payers, clinicians and patients to discuss its CAR-T pricing report, and how new drugs might be covered. A similar policy meeting for Luxturna was held on January 25.

Methods for determining the cost-effectiveness of drug treatments are imperfect at

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Creative new therapies need equally creative payment systems.

New drug for multidrug-resistant HIV

The US Food and Drug Administration has approved a new drug to treat patients with multidrug-resistant HIV-1, the first therapy in more than a decade with a new mechanism of action. Developed by Taipei, Taiwan–based TaiMed Biologics, Trogarzo (ibalizumab-uiyk) is a humanized monoclonal antibody that binds to the second extracellular domain of CD4 and prevents entry of HIV-1 into $CD4^+$ immune cells. Wuxi Biologics of China, its manufacturer, said that this is also the first FDA approval for a biological drug produced by a Chinese company. Trogarzo is to be used with other HIV medicines as part of an antiretroviral therapy. In August 2017, WuXi Biologics announced that the FDA had completed its pre-license inspection of its facilities in the city of Wuxi, China. Theratechnologies of Canada acquired US rights to market and distribute the drug from TaiMed. In phase 3 trials, Trogarzo used in combination with other antiretrovirals achieved a 70% viral load reduction in a week in over 80% of treatment-experienced, multidrug-resistant patients with HIV-1, and after a 24-week period the viral load of 43% of patients was undetectable. TaiMed Biologics obtained the monoclonal antibody from Genentech in 2007 (*Nat. Biotechnol.* **32**, 508–510, 2014). According to the US Centers for Disease Control and Prevention, approximately 1.1 million people in the US were living with HIV at the end of 2015. Theratechnologies says that 20,000 to 25,000 US citizens with HIV-1 are currently resistant to at least one antiretroviral therapy. Luc Tanguay, president and CEO of Theratechnologies, said in an early March press release that they hope to bring the therapy to patients in the US within 6 weeks at an annual wholesale acquisition cost of $118,000 per year.

"We need to stop investing in the third Fitbit for the 50-year-old upper-class person and start innovating for people who have common diseases and conditions, but live in communities with low access to care." Andy Slavitt, former head of the Centers for Medicare and Medicaid Services, comments on why he is investing in companies that will bring healthcare to those most in need, the oldest and sickest Americans. (*CNBC*, 4 March 2018)

"The insurers don't want to end up on the front page of the newspaper saying Little Timmy bled to death because his drug wasn't covered." Jerry Avorn, health economist at Harvard, speculates on the reasons that keep hemophilia treatment costs at an average $270,000 per year despite there being 28 drugs on the market. (*NPR*, 5 March 2018)

the best of times. They attempt to quantify the added clinical benefit of a new therapy compared with existing treatments in terms of quality-adjusted life years (QALYs). The incremental cost of the new drug is expressed as a 'cost per QALY gained', and compared with an accepted threshold range. ICER's informal, acceptable cost-per-QALY range for new drugs is $50,000–150,000. QALYs are designed to capture both quality and length of life, but they're hard to measure. "This is not simple math, and it never will be," says Steven Pearson, ICER's founder and president.

The inherent difficulties in measuring cost-effectiveness are compounded by huge gaps in long-term efficacy and safety data. FDA's Breakthrough Therapy designation allowed the CAR-Ts to be approved on the basis of single-arm studies with 100 or fewer patients, with median follow-up of less than two years. Luxturna's FDA go-ahead, similarly, hung on a phase 3 study with 31 participants. "Substantial uncertainty remains around CAR-T therapies' effectiveness", concludes ICER's pricing report, as existing trials are small, uncontrolled, and have relatively short follow-up. Yet the theoretical value (and price) of these therapies are in large part predicated on their long duration of effect.

Frustration over that lack of evidence was clear during the March 2 meeting, where most panelists voted that Kymriah's value is "intermediate," and half voted that Yescarta's was "low"—despite strong enthusiasm among pediatric clinicians for what were described as "game-changing" treatments. In the final summary published at the end of March, as *Nature Biotechnology* went to press, ICER was expected to follow similar conclusions.

There are good reasons for the data shortcomings. FDA's accelerated access pathways are designed to provide early access to innovative treatments for patients with few options. The tension between having enough evidence, and the need to assess a drug's value to support coverage decisions is always present, says Pearson. "There is even more uncertainty when dealing with single treatments that promise long-term benefits."

That uncertainty is clear from the huge variability in the cost-per-QALY range ICER assigned to Kymriah and Yescarta, relative to existing chemotherapy. If their benefit lasts only a year, they will cost $1.2 million and $5.1 million more, respectively, per QALY generated than chemotherapy. If they last an average lifetime that cost per QALY shrinks to a very reasonable $57,093 per QALY for Kymriah and $145,158 for Yescarta, still within the bounds of ICER's unofficial cost-effectiveness margin.

By the same token, Luxturna may not be overpriced. Its value depends heavily on the patient's age and on whether the drug's benefits are calculated from the perspective of the healthcare system, or taking a broader, societal view (including, for instance, the benefits of returning to work and not claiming welfare support). At best—consider a three year old whose vision is restored for many years—Luxturna's price only narrowly misses the $755,633 it would need to meet a $100,000 cost-per-QALY threshold, if it takes into account a societal perspective. The report acknowledged the limitations of standard economic models and assumptions in assessing a drug like Luxturna, whose benefit clearly extends well beyond the health system.

If ICER's pricing reports raise more questions than they answer, that's the idea, says Pearson. "We're not interested in nice clean headlines. It's about trying to move us along, as a society, in our ability to have more complicated discussions."

Those tricky discussions about how much, and how, to pay for CAR-T drugs and gene therapies are already underway. Even before the ICER pricing reports, the makers of these one-time therapies with potentially lifetime benefits were exploring innovative payment structures. Spark engaged with payers prior to Luxturna's approval and has proposed ways to reduce the risk to payers should the drug fail to deliver the expected outcome. Under an already agreed to pay-for-performance deal with Wellesley, Massachusetts–based Harvard Pilgrim Health Care, for example, the company will provide rebates if the drug doesn't meet agreed outcomes after 30 days, 90 days and at 30 months. Spark is also discussing with the Centers for Medicare and Medicaid Services (CMS) ways to enable payment by installments over several years, and for deeper rebates than current price-reporting regulations allow. Jeffrey Marrazzo, Spark's CEO, claims there's "momentum" for an agreement in principle. "It's now down to the detailed logistics and modalities of how this is done," he says.

Spark wants to further help payers reduce their costs by cutting out some of the markups enjoyed by middlemen in the US drug payment labyrinth. The idea is that payers, or their affiliated specialty pharmacies, purchase Luxturna directly from Spark, rather than from treatment centers. Normally, these providers add a hefty premium for specialty drugs; in Spark's model, they would instead be reimbursed at a level "commensurate with the type of care required to deliver Luxturna," explains John Furey, Spark's COO. In exchange, payers must provide coverage consistent with FDA labelling, expedite benefits processing and cap patient co-pays.

Novartis is also trying to address Kymriah's affordability. It has proposed that CMS pay for the drug only in patients who have responded by the end of one month. Critics like Memorial Sloan Kettering Cancer Center's Peter Bach claim that this is too short a period over which to assess the benefit of a long-term treatment—and that it won't save much, given that over 80% of trial patients had responded at four weeks. But the practicalities of administering rebates over a longer period, such as one year, are considerable.

These first steps toward new payment methods are encouraging. Indeed, Spark's reimbursement strategies should be considered as "potential best practice by other manufacturers of high cost therapies for ultra-rare conditions," according to ICER's January 2018 policy roundtable on Luxturna.

Philip Reilly, venture partner at Boston-based Third Rock Ventures, adds a word of caution. He says these discussions fail to properly consider the other health system costs that Luxturna, and other forthcoming gene therapies, will help avoid, such as, for instance, the cost of liver transplants and other interventions in patients with hemophilia or other blood disorders, for which several gene therapies are in development, including at Third Rock portfolio company bluebird bio, based in Cambridge, Massachusetts.

As drug prices rise to match or exceed the cost of many surgical interventions, and as drugs like cell and gene therapies, with their complex administration, begin to look more like one-time procedures, it is appropriate to consider the value of drugs relative to the interventions they may replace. "This is an artificial debate until we enlarge it" beyond drugs, says Reilly. Fragmented health systems and siloed drug budgets will make that very difficult though.

Meanwhile, there's little question that these new therapies will have to be paid over time, in line with the durability of their effect. If these expensive therapies "are going to be seen as part of the solution, we must acknowledge the differential value as to whether they work or not," and for how long, says Harvard Pilgrim Health Care's chief medical officer, Michael Sherman. On that point, in principle, he continues, payers and manufacturers are singing from the same hymn sheet. That's a small miracle in itself. The bigger one will be figuring out how to put the principle into practice. "We're headed toward some kind of payment-by-instalment approach. But we're not there yet," concludes ICER's Pearson.

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