GENE THERAPY

Must Sky-High Prices 'Come on Down' Before the Price Is Right?

It is finally starting to happen. The first gene therapy to treat an inherited disease is out of the gate. But my, that price tag: $850,000. Many more gene therapies are on their way. How can they be priced to hit the sweet spot of affordability, access, and innovation? Outcomes-based pricing doesn't really do the trick.

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A $1 million drug. Per treatment.

That's the generous ceiling analysts set when Spark Therapeutics received FDA approval last year for the first gene therapy to treat an inherited disease, a form of congenital blindness. But Spark came in lower, setting the price at $850,000, or $425,000 per eye, and then promptly announced an agreement with Harvard Pilgrim Health Care, which became the first health plan to cover the treatment.

Even minus whatever discounts and rebates the two sides negotiated, and even for a one-time treatment that can save a child from a lifetime of blindness, the price is steep. The rare form of blindness the drug Luxturna treats, known as biallelic RPE65 mutation-associated retinal dystrophy, affects fewer than 2,000 children in the United States, so it's a safe bet that only a very few (if any) of the three million lives Harvard Pilgrim covers will need the treatment. With $3 billion in revenue last year, it would seem the health plan could absorb the cost of a handful of people getting the treatment, even though the plan posted operating losses of $28.3 million last year and $91.3 million the year before that.

The outcomes-based contract pays Spark full freight only if the drug works after 30 months, with an interim payment made upon a "look-in" period at 30 to 90 days. Spark is also on the hook for rebates if the drug fails. The agreement also sidesteps the typical charges hospitals add on for medically administered therapies. To get the drug, patients must submit to genetic testing to confirm the gene mutations, and they must also have enough viable retinal cells to restore or preserve vision.

To cover drugs like Luxturna, payers, providers, and drugmakers are facing hard math. A potentially curative therapy can zero out other long-term costs to justify the expense over time, but the drugmakers want to get paid as much as they can up front. Drugs like Luxturna for rare diseases do not always offset existing costs because there is no existing treatment. The benefits are individual and societal; they don't necessarily show up in anybody's bottom line.

Today three, tomorrow hundreds?

Luxturna isn't the first FDA-approved gene therapy. It was preceded by Novartis' Kymriah for B-cell acute lymphoblastic leukemia (ALL) and Gilead Sciences' Yescarta for treatment of large B-cell lymphoma, a form of non-Hodgkin lymphoma. Kymriah costs $475,000; Yescarta, $373,000. Neither is a first-line therapy. Kymriah is indicated in children and young adults for ALL that has defied treatment or has relapsed at least twice. Fewer than 10% of children with ALL survive five years. The National Cancer Institute estimates that approximately 3,100 people age 20 and younger are diagnosed with ALL each year. Yescarta is indicated for

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adults whose disease has relapsed or defies treatment after at least two or more lines of systemic therapy. About 24,000 new cases are diagnosed each year. The current treatments for these diseases involve multiple rounds of chemotherapy, radiation, targeted therapy, and stem cell transplant.

The pipeline for gene therapies is flush. ClinicalTrials.gov lists 721 gene therapy trials. Last year, the FDA received 106 new drug applications for gene therapies, up 34% from 2016.

There is no shortage of diseases for gene therapies to target. The National Organization for Rare Diseases lists 1,194 rare diseases on its website and estimates that 30 million Americans have some form of rare disease. Even if those people with rare diseases are uninsured at the rate of the general population, 12.2%, that leaves about 26.3 million covered lives. Say only 5% of them received an $850,000 therapy. The bill before any discounts would be $1.227 trillion, which is almost four times the nation's total prescription drug bill of $328.6 billion in 2016.

Crafting the Spark agreement

In negotiating its outcomes-based contract for Luxturna, Harvard Pilgrim took into account clinical trial results. Patients on Luxturna had a more than 100-fold increase in sensing white light at a year and maintained that at three years. They also were able to navigate mobility testing at three years and sustained improvement in visual acuity—measured by how many letters a person reads on an eye chart—by being able to read eight more letters on the chart than they could before treatment. Spark emphasizes the drug improves functional vision—a person's ability to perform daily tasks—more so than visual acuity. In its report on Luxturna, the Institute for Clinical and Economic Review (ICER), the cost-effectiveness think tank in Boston, noted, "Further, individuals who had received the treatment cited increased mobility, self-confidence, and independence as potentially important benefits."

Harvard Pilgrim itself is no stranger to outcomes-based contracts. Last year it signed contracts with AstraZeneca to cover Brilinta for reducing the risk of heart attack and stroke and Bydureon for controlling HbA1c in diabetes, and with Amgen to cover Repatha for lowering LDL cholesterol. Harvard Pilgrim Chief Medical Officer Michael Sherman, MD, explains the rationale for the outcomes-based contracts: "It isn't the solution, but it's part of the solution for managing the drug expense and helping align our spend with the value the drugs create."

Express Scripts Chief Medical Officer Steve Miller, MD, points out other wrinkles in the Harvard Pilgrim–Spark contract besides the "look-in" period and the 30-month payout. One is that the drug can only be given at a certified center of excellence, such as Massachusetts Eye and Ear within the Harvard Pilgrim network. Harvard Pilgrim purchases the drug directly from Spark with Express Scripts acting as a distributor. This arrangement avoids the charges that hospitals typically add to cover storage and handling. "We'll send it through a distribution company, but the hospital can't mark it up; or we'll send it with a specific patient label on it right to the operating room, so the hospital has no carrying costs and no reason to mark it up," Miller says. Express Scripts is the sole distributor for Spark and is working with Novartis and Gilead to develop contracts for Kymriah and Yescarta.

Spark is pursuing other coverage agreements. A number of Blues plans have issued draft guidance "which have largely been positive," Spark corporate communications lead Kevin Giordano says. For now, many of those plans determine coverage case by case. A determination from Medicaid—a key consideration for treating rare diseases, especially in children—could be a year or so away. Among the ideas Spark is working on is installment payments over multiple years.

At a panel on gene therapy in April, Katherine High, MD, Spark president and director of research, acknowledged the obstacles in getting coverage for a therapy like Luxturna. "So, in a single intervention, the way our health care system works in the United States, you need to recover the value of this high-value, high-cost therapeutic all at once," she said. "And that does present some difficulties with the way our payer system is currently set up."

Any lessons from Europe?

While Europe may have been ahead of the United States in approving gene therapies, its track record does not provide much of a template for success.

UniQure received European approval in 2012 for Glybera, a gene therapy for lipoprotein lipase deficiency, a rare metabolic disease. The drug had little uptake, though, and UniQure pulled it off the market last October. "It wasn't just that it cost $1 million; it's that it came to market without much evidence basis that it was worth $1 million," Casey Quinn, a health economist at the MIT Center for Biomedical Innovation who specializes in European drug pricing, told *MIT Technology Review*.

GlaxoSmithKline received European approval in 2016 for Strimvelis, a treatment for a rare childhood immune deficiency. The company set the price at $665,000 but also offered a money-back guarantee. The disease, known as ADA–SCID—severe combined immunodeficiency due to adenosine deaminase deficiency—affects about 15 children a year in Europe, according to GlaxoSmithKline. The company disclosed last year that it would sell off its rare disease unit, whose portfolio includes Strimvelis. *MIT Technology Review* reported the drug had only one sale a year after its approval.

Steve Miller, MD, the chief medical officer for Express Scripts, has an idea of why these therapies may have failed: "These companies did not have the payer community behind them supporting them," he says. "And to be very frank, they weren't ideal products."

"The cost is acute while the benefit is accrued in the future," says R. John Glasspool, former head of corporate strategy at Baxalta, a biotech company that focuses on rare diseases, and who now works for a pharmaceutical think tank at MIT. "It's a reverse of what our system is used to doing."

Not really value-based

In the 1930s, Winston Churchill called Russia "a riddle wrapped in a mystery inside an enigma." The same could be said for calculating the true value of a breakthrough therapy like Luxturna, especially if the drug treats a previously untreatable disease. "Some of these drugs have a great return on investment," says Miller of some of the gene and stem cell therapies in the pipeline. He gives as an example a potentially curative gene therapy for hemophilia, which Spark, among others, have in development. Those patients spend $100,000 to $125,000 a year or more on clotting factor alone plus incur other costs to treat diseases and injuries because of their bleeding; a $1 million curative treatment might pay for itself in less than 10 years by eliminating those costs. "That's an easy one," he says.

But calculating the return on investment for a cure for congenital blindness, including Leber congenital amaurosis, is not so easy. "That is a much different economic situation because your spend is going from zero to $850,000," Miller says. While the incidence of this particular disease is so rare that a cure won't have a great impact on overall spending, the societal cost savings of a cure could be significant. Miller wonders, "In the future, are we going to have more examples of the hemophilia treatment, or more examples of Leber syndrome?"

In calculating the value of the outcome, the input factor—the upfront price of the drug—must be realistic and reasonable. Instead, the early experience of gene and stem cell therapies finds these prices are often influenced by analysts' expectations. While other barriers exist for drug companies to enter into outcomes-based contracts—namely concerns about Medicaid best-price regulations, federal antikickback statutes, and off-label use regulations—the value variable is crucial in any payment model to cover these treatments.

What happens when a patient changes health plans and the gene therapy stops working two years later? asks Roger Longman of Real Endpoints. Who pays for what?

"If we think a fair market value for a drug is $100,000 and the drug company is charging $300,000 but giving a 20% rebate if it doesn't work, then, yes, we have an outcomes-based agreement, but we certainly don't have good value at the end of the day," says Sherman

at Harvard Pilgrim. "The drug companies set the list price and we're negotiating off of that price."

Anna Kaltenboeck, program director at the Center for Health Policy and Outcomes at Memorial Sloan Kettering Cancer Center, says it is important to make the distinction between value-based pricing and outcomes-based contracting rather than seeing outcomes-based contracting as a type of value-based pricing. "An outcomes-based contract in and of itself has nothing to do with value if the price is not set to a value-based price to begin with," she says.

Typically, key factors for determining a new drug's benefit came from results of large, randomized clinical trials. But therapies for rare diseases that get FDA fast track or orphan drug designation are approved based on the results of much smaller trials that may not even be randomized. "The concern for entities like Harvard Pilgrim and other payers is that when FDA approves drugs for rare diseases where there is an unmet need—in many cases, understandably, with limited evidence—it creates almost blank-check expectations on the part of physicians and patients," says Sherman.

Spark conducted "good trials," says ICER President Steven D. Pearson, MD, although more data on post-treatment quality of life would've made ICER's analysis of Luxturna less challenging.

Tools to define value

As payers and drug companies try to calculate the value of these niche but costly therapies, ICER may become their oracle. An ICER report of Luxturna concludes that at $850,000, the drug is overpriced. The explanation reads like a word problem. The analysis looked at a hypothetical 15-year-old who would derive a benefit of 10 to 20 years from the treatment. When considering only health system costs, the drug would need to be discounted by 75% to 82%, or between $153,000 and $217,000, for it to be priced correctly, according to ICER. Even adding in societal benefits, the drug would need to be discounted 50% to 57%, says ICER.

"Even when assuming an as-yet unproven lifetime benefit for the therapy, the cost remains well above commonly accepted thresholds," the report concluded. The treated patient would have to be three years old for Luxturna to meet standard cost-effectiveness thresholds, the report states.

On the other hand, a separate ICER analysis of the CAR-T therapies Kymriah and Yescarta found their pricing to be more in line with cost-effectiveness thresholds. That report has an almost prophetic conclusion: "With many other potentially transformative therapies in the pipeline, stakeholders must collaborate now to develop payment and delivery systems that can ensure timely patient access, manage short-term affordability for expensive one-time treatments, and continue to reward the innovation that brings these new treatments to market."

But even ICER finds the math is hard. "In our reports, we wrestle with this issue: You can't disentangle easily the idea of what a fair launch price is from how you're going to pay for it," says Pearson. "If you decouple those, it could be a mistake." This applies even to models like the Harvard Pilgrim–Spark outcomes-based contract that defers payment and offers refunds if the drug doesn't work. "The price could just start higher and you give a little bit more back later, and it's still not really well aligned with the benefit to patients," Pearson says.

Bringing those factors into alignment is proving to be the hardest part of this equation. MC

Beyond outcomes-based contracts

Besides outcomes-based contracting, Express Scripts is developing a menu of options for health plans to provide coverage of high-cost gene and stem cell therapies. They include risk pools, lump-sum payments, amortized payments, value-based contracting, and indications-based reimbursement.

Express Scripts Chief Medical Officer Steve Miller, MD, points out that one advantage of amortizing the cost is titrating the out-year payments to the drug company if the product does not deliver as promised.

But even amortization comes with a catch for commercial health plans, as Roger Longman, CEO of Real Endpoints, notes. "Patients do not stay in the same plan forever," he says. "What happens if an insurance company pays for the therapy, and two years later that patient has moved onto a different insurer and the drug fails to work or stops working? They'll have to figure out how to either reimburse the original plan or some other kind of economic solution."

Express Scripts is also working on a reinsurance model to cover these costly treatments. "So far, there's been a tremendous amount of interest, but very little uptake," Miller says. The reason: cost. "People right now are reluctant to enter into the risk pools because they feel like they're at risk to be on the losing side more than they are to be on the winning side," he says.

"We on the payer side have got to be just as innovative as the scientists have been on the discovery side," Miller adds.