Gene therapy's next installment

Sky-high-priced gene therapies face slow uptake and market failure unless healthcare payers and drug makers can find common ground in 'pay-for-performance' reimbursement.

At the end of May, Zolgensma was approved by the US Food and Drug Administration (FDA) as a gene therapy for children up to the age of two with spinal muscular atrophy (SMA). This was followed on June 3 by the European Commission's marketing authorization for Zynteglo, a gene therapy against transfusion-dependent β-thalassemia in patients 12 years or older. While patient groups hailed the news, the price of these products provoked sticker shock: Zolgensma costs $2.1 million; Zynteglo $1.8 million. They are the two most expensive medicines in the world. Finding a way for resource-constrained healthcare systems to pay for them is an ongoing conundrum. The good news is that a new type of reimbursement model—pay-for-performance milestones or installments—may offer a solution.

Zolgensma is a one-time, intravenous injection of human *survival motor neuron gene 1* (*SMN1*) under the control of chicken beta-actin promoter delivered by adeno-associated virus serotype 9 (AAV9). It was developed by Nationwide Children's Hospital's spinout Avexis, sailed through regulatory review on the back of two trials with a combined 35 patients and was ultimately being gobbled up by Novartis for $8.7 billion in 2018. Zynteglo is Bluebird Bio's single injection of autologous $CD34^+$ cells transduced ex vivo with the gene encoding $\beta^{A\text{-}T87Q}$-globin via a lentiviral vector pseudotyped with vesicular stomatitis virus glycoprotein G. It rocketed through conditional approval at the European Medicines Agency in just 150 days on the basis of three trials involving a combined total of 41 patients.

When first announced, the astronomical price of Zolgensma spurred outrage. But as Acting FDA Commissioner Ned Sharpless put it at the June conference of the Biotechnology Innovation Organization in Philadelphia, "This is a completely novel, almost magical, miracle that ends a devastating disease for lots of little kids … and the thing you care the most about is the price?"

But this is no magic. Reality has to be paid for or the miracle disappears. The first ever gene therapy, Glybera (an AAV1 lipoprotein lipase gene therapy), was approved to much fanfare in Europe in 2012, but priced at $1.2 million. Three years later, manufacturer Uniqure and its marketing partner Chiesi withdrew the product from the market, having treated just one patient. With hundreds of gene therapies in the pipeline and an estimated 10–20 products reaching the market annually by 2025, solving the reimbursement riddle is urgent.

These treatments have premium prices for several reasons: they have limited markets, targeting disorders that are rare (<200,000 US patients) or even ultra-rare (<10,000 US patients); they are one-shot, potentially curative (or at least disease-modifying) products; they are infinitely more effective than most other drug regimens or interventions; and, initially at least, they incur high development costs and manufacturing overheads.

Gene therapies are broadly promoted as long-lasting cures, but the emergent products are unconvincing on that account. In any business other than healthcare, these products would be viewed as prototypes. All seven products marketed thus far (Glybera, Strimvelis, Kymriah, Yescarta, Luxturna, Zolgensma and Zynteglo) received accelerated approval on the basis of very small numbers of patients. One of the trials testing Zolgensma, for example, studied only 15 patients, who each displayed a variety of responses: 20 months after injection, only 11 spoke, 10 exhibited head control, 10 could sit unassisted for 10 seconds, and just 2 could walk. This is not a description of a cure, but rather a treatment that may delay but does not obviate much of the care that people with SMA still need. One-time outlay on a high-priced gene therapy cure does not, therefore, save a lifetime's outlay on palliative care. Indeed, by extending the lives of people with SMA, costs of traditional care may increase, too.

Some national and state governments are exploring subscription-based (Netflix-like) contracts that pay a lump sum to drug makers in return for unlimited access for patients over a defined period. A recent study reports that Australia has saved an estimated $4.9 billion over five years using this approach to pay for hepatitis C treatments (like Sovaldi). State governments in Louisiana and Washington are now following suit. Unlike just-approved gene therapies, however, hepatitis C treatments have a proven track record of clinical effectiveness.

For gene therapy, drug maker–payer negotiations have been shifting to a different solution: pay-for-performance, risk-sharing contracts—in essence money-back guarantees in which payers track patient outcomes and reward manufacturers for maintaining patient health over a defined period. These arrangements were first conceptualized by the Massachusetts Institute of Technology's New Drug Development Paradigms (NEWDIGS) program and the Margolis Center for Health Policy at Duke University.

By the end of 2018, New England insurer Harvard Pilgrim Health Care had completed around 17 of these value-based deals, all for traditional drugs. It also made a big splash by negotiating the first agreement for a high-priced gene therapy: Spark Therapeutics' $850,000 Luxturna, which is approved for a rare inherited form of vision loss. In the deal, Harvard Pilgrim pays the sticker price for Luxturna, but gets rebates if the treatment fails to meet pre-agreed outcomes. Novartis is offering a similar installment plan for Zolgensma, with refunds if it doesn't perform as expected.

Disease-modifying capability, steep development costs, small markets and high manufacturing overheads dictate that drug makers set a premium on the price of gene therapy products. On the other hand, payers are rightly cautious about covering newly approved gene therapies that might not work as advertised in the wider population.

And until post-marketing clinical data about new gene therapies are in, consensus about these products remains unlikely. Value-based deals are a good compromise, making companies and payers meet in the middle. Compromise may not be as good as consensus, but it is better than no deal at all—as Uniqure found out with Glybera. ❐

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