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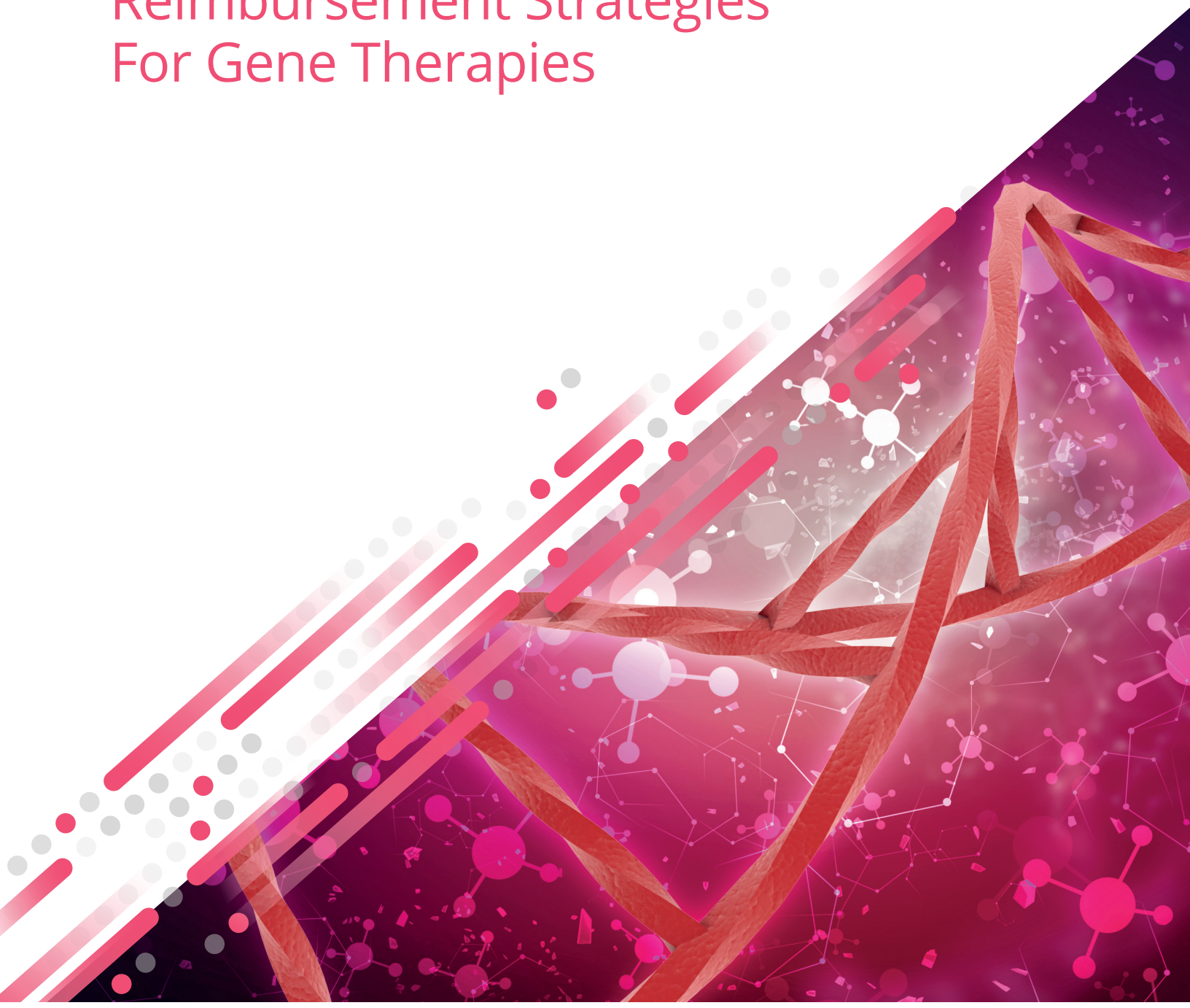
RECONCILING PRICE AND VALUE:
Reimbursement Strategies For Gene Therapies



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RECONCILING PRICE AND VALUE:
Reimbursement Strategies For Gene Therapies

If the future of medicines lies in disruptive innovation, few recent developments have been more disruptive than the market entry of cell and gene therapies. Products such as Yescarta, Kymriah, Luxturna and Zolgensma are transforming treatment paradigms for rare diseases with poor prognoses and high levels of unmet need.

Yet they also present fundamental challenges to health systems and the conventional pharmaceutical industry model. Not only do these products revolutionize the delivery of therapy, they also challenge physicians and health systems to learn and accommodate radical new ways of delivering care.

Perhaps the most daunting hurdle, though, is cost – how it will be financed, and by whom. Prices of other innovative medicines have sparked considerable debate about value and affordability, but they are products that manage disease over a course of treatment. Their cost to health systems or insurers is spread out in ways payers can accommodate within their routine budget planning.


David Byram, Syneos Health


Miriam Kalnicki, Syneos Health

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Gene therapies charge for the promise of, nominally, a cure, and a "one-shot" cure at that. List prices ranging from $373,000 to $2.1 million are in principle payable up front, even without the guarantee that efficacy and safety are sustainable over the long term.

This scenario would give any financial manager pause. The nearest equivalent may be the financial impact of direct-acting antivirals (DAAs) for hepatitis C, such as Gilead's Sovaldi (sofosbuvir). There, the affected populations were much larger, and the challenge was more about absorbing pent-up demand for drugs positioned as something close to a cure, especially in the first year of approval.

Alternative Models

Not surprisingly, the conversation has turned to alternative reimbursement schemes to mitigate the "sticker shock" of gene therapies. A number of options are emerging in the US and Europe, from straightforward negotiated discounts (Yescarta, Kymriah in England) to performance-based agreements (Kymriah in Italy) or novel financing mechanisms to pool risk.

In the US, manufacturers such as Novartis have offered payers outcomes-based contracts or, for Zolgensma, a five-year annual installment plan. With Luxturna, Spark Therapeutics employs a rebate-based model that tracks outcomes over 30 to 90 days and 30 months, respectively.

The long-term viability and effectiveness of these arrangements remain uncertain. The US Centers for Medicare and Medicaid Services (CMS) notably backpedalled on plans for outcomes-based reimbursement of Kymriah. Some US payers are hedging their bets by opting for coverage restrictions that take into consideration inclusion/exclusion criteria and clinical-trial patient protocols.

As Miriam Kalnicki, senior reputation and risk management strategist at Syneos Health, points out, US hospitals used to working with buy-and-bill mechanisms risk being overwhelmed by gene-therapy costs. Spark has addressed this by selling Luxturna directly to the payer's speciality pharmacy.

"It's still predominantly a fee-for-service approach," comments David Byram, a commercial advisory group director at Syneos Health. In Medicare, "that makes it really challenging for products like Yescarta, because the Severity Diagnosis Related Groups aren't adequate to cover the medication. So companies are having to pursue new technology add-on payments (NATPs), which are by no means a given."

Resources And Outcomes

CMS has now agreed to raise maximum NATPs for Yescarta and Kymriah under Medicare Part B from 50% to 65%. That still leaves a substantial gap between reimbursement and list prices of $373,000 (Yescarta) or $475,000 (Kymriah). Moreover, as Byram notes, health care facilities need to factor in significant non-reimbursable resource requirements. As an example, one hospital in California had to hire 20 additional personnel just to offer the CAR-T therapies.

Performance-based contracting for gene therapies reflects products "often so innovative that we don't have a lot of clinical data," Kalnicki observes. Value-based purchasing models for Yescarta and Kymriah in the US involve 100% payment for responsive patients. In clinical studies of Kymriah, the three-month remission rate was 83%. In this setting, though, "based on the clinical evidence, the manufacturer and clinician will typically see a therapeutic response within 30 days," Byram says.

Even if performance-based contracts can resolve some access issues for gene therapies, a number

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of gray areas remain. "One big conversation now is, what does the long-tail survival or therapeutic response look like?," Byram notes. "If we're going to invest this kind of money, presumably we would expect gene therapies to deliver a cure or a much longer response curve."

Another consideration is the potential impact of US private-sector contracts on Medicaid "best-price" requirements. If a company commits to refunding the cost of CAR-T therapy for the 17% to 18% of patients who do not achieve remission, "your best price to Medicaid is now zero," Byram points out.

Even in the private sector, value-based contracts require agreement on measurable endpoints and outcomes, which "isn't always easy," he adds. And most of these contracts are predicated on surrogate endpoints such as HbA1c levels in diabetes, rather than downstream effects such as cardiovascular risk or measurement of the medical loss ratio for the given patient population.

Another issue for US payers is that many patients only stay with a health plan for two to three years. "So if I spent a million or two million dollars to cure a patient, I presumably have only a year or two to recoup any of that investment," Byram comments. "I don't get to see the cost-avoidance offsets these therapies provide long term."

Engage Early

A key lesson from the DAAs was that manufacturers of game-changing therapies must develop a framework for health care utilization, Byram stresses. That way, payers can gauge more accurately the cost impact and offsets of therapeutic intervention, including overall patient cost and systemic benefits.

All the more reason, then, for gene-therapy companies to engage early with payers and "give them an opportunity to either set aside funding or build it into their premiums," Byram says. In the US, premiums are typically set 12 to 18 months in advance of the benefit year, "so you need to be having these conversations 18 to 24 months in advance of launch."

Early dialogue should include one-on-one meetings with the whole range of stakeholders, and in particular key opinion leaders and patient advocates, "so they understand what's gone into the therapy and the value it delivers," Kalnicki stresses. In the US this should start 12 to 18 months before the target Prescription Drug User Fee Act date for a gene-therapy approval.

Health care providers also need to know where to access the necessary training, education and tools to deliver these transformative procedures effectively and safely. "It takes a village to administer these therapies," Kalnicki comments.

Where drug communications can "go very wrong is when manufacturers don't do things like setting expectations," she notes. Moreover, communications do not stop at approval. With Zolgensma, the Novartis strategy was "brilliant" at signaling and managing expectations, including collaborative efforts to inform cost-benefit deliberations at the US Institute for Clinical and Economic Review (ICER).

Within a few months of approval, though, news articles began to emerge about lack of access to Zolgensma. "A new challenge developers must adjust to is the need also to set expectations for access," Kalnicki comments. "Contracts don't get drafted overnight. Sometimes it's a six-month lag between when you get your therapy approved and when an insurer will start to pay for it."

Real-World Data

The "translational-medicine framework" implied

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by these recommendations may seem counter-intuitive to an industry rooted in safety and effectiveness, and especially to biotech start-ups, Byram observes. Yet innovative products are now approved on the basis of more tentative data, so "that work has to be done earlier and earlier."

That might involve establishing a parallel patient registry at the start of Phase II trials to collect data on health care utilization costs, and extending the initiative into the post-approval market. "Then you begin to frame out what the true health care value of this therapy is," Byram says.

Extracting meaningful data from a limited pool of patients does present challenges, but companies must "begin with the end in sight," he adds. Switching between health plans is another obstacle, although evidence does suggest that rare- or severe-disease patients are less inclined to do this, Kalnicki notes.

Hubs that collect data on patient adherence or other treatment parameters can be critical tools in supporting outcomes-based contracts, she suggests. Here also, all relevant stakeholders must be made aware of these services at an early stage, "so that patients know they have the support and continue to engage with the hubs over time."

Innovative Thinking

With many more cell and gene therapies poised to enter the market, it is clear that ensuring patient access to treatment calls for new thinking from payers and manufacturers alike. This is likely to involve a range of strategies, depending on whether the therapy is curative or disease-modifying, what it is indicated for, and the value of that indication, Byram suggests.

Moreover, companies need to take a country-by-country approach, Kalnicki notes. EU member states, for example, apply health technology assessments similar to ICER's, but with a direct influence on drug reimbursement.

Spreading risk through reinsurance may be one option to protect payers from the cataclysmic impact of gene-therapy costs. But it does raise the question of how reinsurers spread that risk over time themselves, Byram says. Moreover, in markets without a single-payer system, it requires broad consensus on a concept never before applied to pharmaceuticals.

Another approach currently under consideration by both the US Administration and the US Congress is reference pricing tied to price levels in the EU5 markets. However, that would likely not have the intended effect on US pricing strategies. It would also have unintended consequences for Europe and the rest of the world, in terms of access to innovation.

There are also a number of regulatory and administrative issues to consider when establishing payment mechanisms for gene therapies. Traditional reimbursement tools such as diagnosis-related groups "take a retrospective view" of costs associated with therapeutic intervention, Byram points out.

Ultimately, gene-therapy reimbursement has to be grounded in value and evidence, he insists. Then health systems and societies need to determine just how important that value is to them. "At some point we have to decide how much value we are willing to take on, and how much affordability we are willing to address. Nothing's for free."

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