SELL'N GENE THERAPIES

A LANDSCAPE ASSESSMENT OF CELL AND GENE THERAPY REIMBURSEMENT

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A Landscape Assessment of Cell and Gene Therapy Reimbursement

Cell and gene therapies hold great life-saving potential, with the ability to treat disease states with significant morbidity, mortality, or treatment-related complications. Kymriah became the first CAR-T cell therapy to bring transformative efficacy to B-cell acute lymphoblastic leukemia in children and young adults in August 2017. Luxturna—the first-ever treatment for a rare form of hereditary blindness—also became the first in vivo gene therapy approved in the US in December 2017. By some estimates, as many as 40 or more cell and gene therapies will launch in the next five to seven years.[1] In addition to bringing substantial benefits to patients, many of these new therapies will bring steep price tags. While payers acknowledge the clinical value of cell and gene therapies, they are anxious about their associated costs and the ability of the US healthcare system to afford them.

Table 1 | Cell and Gene Therapies on the Horizon

Drug	Indication	Company	Status
Zolgensma	Spinal muscular atrophy	Novartis/ AveXis	Expected FDA decision in H1 2019[2]
LentiGlobin	Transfusion-dependent ß-thalassemia; severe sickle cell disease	bluebird bio	TDT: In Phase 2/3; for EU approval and first launch in 2019; US approval and launch in 2020[3] SCD: In Phase 2/3; US and EU filing and approvals in 2022[3]
Lenti-D	Cerebral adrenoleukodystrophy	bluebird bio	In Phase 2/3; US/EU approval in 2020[3]
bb2121	Relapsed/refractory multiple myeloma	Celgene/ bluebird bio	In Phase 2/3; approval in R/R expected in 2020
Fidanacogene elaparvovec (SPK-9001)	Hemophilia B	Pfizer/Spark Therapeutics	Phase 3
AMT-061	Hemophilia B	uniQure	Phase 2b

The novel financial challenges created by cell and gene therapies must be understood and addressed by all healthcare stakeholders, including payers, providers, patients, and the manufacturers of those therapies. This article will detail the two main challenges posed by cell and gene therapies. We also will examine some potential solutions to meeting these challenges, including our thinking around how to enable broader access to cell and gene therapies through the utilization of shared payment pools.

Two Key Challenges

Payers often have a positive view of the clinical value that cell and gene therapies offer, based on the clinical results these therapies have shown. However, payers would prefer to await long-term, real-world evidence before committing to a reimbursement strategy for cell and gene therapies. Meanwhile, the high cost of these treatments is a growing concern, particularly in the treatment of rare diseases such as hemophilia, spinal muscular atrophy, sickle disease, and cancers.[4]

The challenges posed by cell and gene therapies consist of two elements: (1) the temporal gap between payment and benefit, and (2) the risk of a cell and gene therapy patient becoming a significant cost to plans.

CHALLENGE 1: TEMPORAL GAP BETWEEN PAYMENT AND BENEFIT

Manufacturers have promised durability of clinical benefits—extending for many years or even a typical patient lifetime—as a defining feature of cell and gene therapies.[4,5] These clinical benefits translate into value for a plan that can be quantified on an annual basis; that value can come from efficacy improvements or from treatment offsets. Based on the annual value and one-time cost of a cell or gene therapy, health plans can calculate a break-even point for recouping an investment in administration of a cell or gene therapy. The period over which an individual health plan can accrue benefits from a durable therapy is limited by how long the patient stays with that health plan. The sooner a patient is expected to switch insurance providers, the shorter the time to the break-even point must be for coverage of a durable therapy to present a positive financial case to the plan. This dynamic, referred to by payers as the issue of patient "portability," is common to any treatment or program that offers long-term efficacy or prophylaxis, but it is amplified for cell and gene therapies based on their anticipated high cost and their relatively unproven track record.

Some payers note that expensive procedures such as organ transplants already require large up-front payments while providing long-term benefits, and payer organizations have managed the financial burden. Currently, the volume of transplantation procedures dwarfs the incidence of rare disease patients receiving cell and gene therapies. However, as more cell and gene therapies are approved for a broader range of rare diseases, the financial impact of this drug category will grow.

Opposing Forces

Three factors have the potential to reduce some of the challenges of the high cost of cell and gene therapies.

1 | Price Controls

The Trump administration released a proposal in October 2018 in which Medicare would set payments for some drugs in Part B based on an "International Pricing Index."[6] In this proposal, the US government would not be allowed to negotiate drug prices directly, but it would be able to piggyback on price negotiations in other countries. Foreign drug prices would be used as a reference to negotiate and judge prices in the United States. This proposal would likely face political resistance from drugmakers, providers, and some legislators. Regardless of the fate of this particular proposal, government action to cap the price of cell and gene therapies could change these dynamics significantly.

2 | Small Patient Populations

Payers view common chronic diseases as potential areas of concern if gene therapy becomes part of the standard of care for more prevalent diseases with larger patient populations. Yet the data suggest that the larger the patient population is, the lower the price will be. An inverse relationship exists between the cost per year for a therapy and the number of patients, with more expensive therapies being dispensed to relatively few patients (Figure 1).[7]

The widespread willingness of payers to cover transplantation is a promising sign that cell and gene therapies will eventually gain acceptance within health plans if they show the same durable medical benefits that transplantation has. This point is supported by the fact that many cell and gene therapies promise similar benefits to existing medical procedures, such as allogeneic stem cell transplantation, with fewer safety risks. Framing cell and gene therapies as an evolution of proven medical procedures may be helpful for manufacturers.

Fortunately, some mitigating factors to portability concerns exist. When a gene-therapy-treated patient leaves a plan, other gene-therapy-treated patients could join the health plan, spreading the financial and therapeutic benefits of gene therapy. Meanwhile, for some larger payers, the patient portability issue could be less of a concern because the actuarial risk and cost are spread across a larger book of business.

CHALLENGE 2: THE TYRANNY OF SMALL NUMBERS

Given the high up-front cost of treatment, each cell and gene therapy patient can become a significant cost to the plan. Because of their rarity, the number of cell and gene therapy-eligible patients in a payer's population will be volatile. In any given year, an unexpected claim for a highly priced cell or gene therapy could have a significant impact on the per-member-per-year (PMPY) cost of drugs to the plan. This effect is especially pronounced when the price of a cell or gene therapy factors in the value of offsetting recurrent medical costs from existing treatments. Shifts in the allocation and timing of costs such as these, while likely reducing the overall budget impact of rare disease, will concentrate that impact into a single year of drug spend.

These challenges are of particular importance to self-funded employers or smaller health plans. Larger payers will be better equipped to absorb the up-front cost of cell and gene therapies, and given the size of their patient population, larger payers are more confident that they will save money in the end with the equilibrium of cell and gene therapy patients leaving and entering their plans.

Opposing Forces (Continued)

Figure 1 | Annual Price vs. Projected Incidence (US)

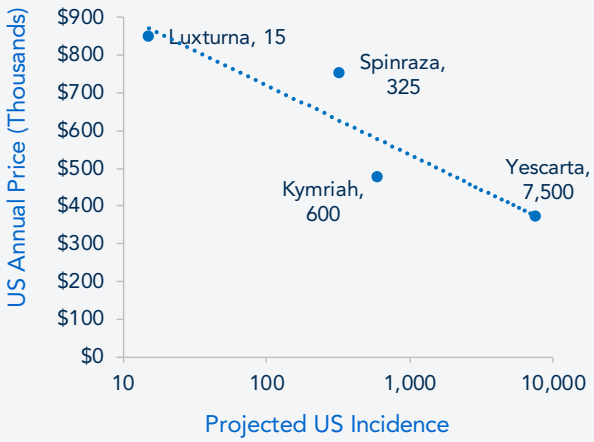


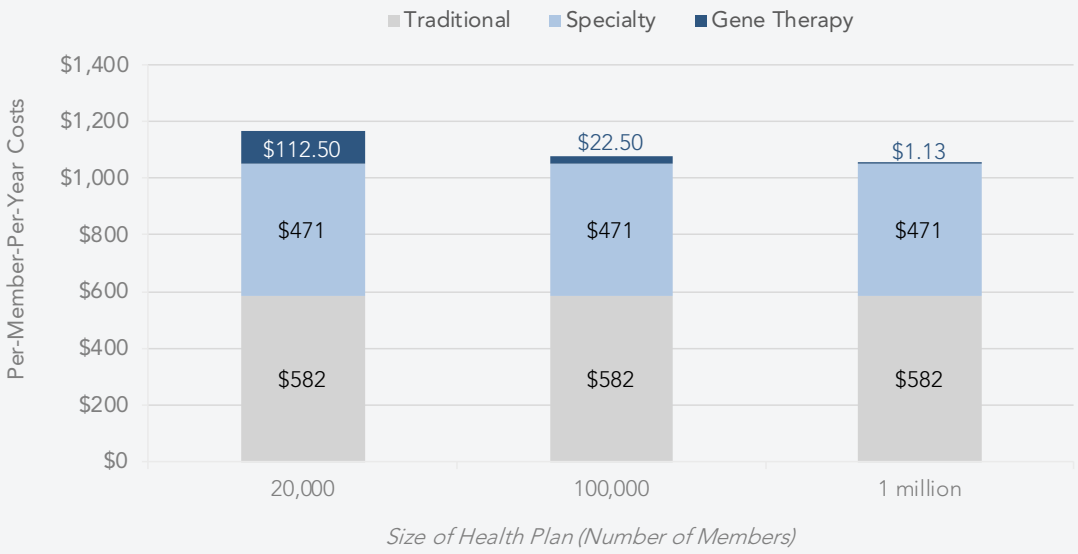
Figure 1 data sources are listed at the bottom of the References section at the end of this article.

3 | Disintermediation

Some prominent voices in the pharmaceutical industry are calling for "cutting out the middle man." Express Scripts is in talks with biotechnology companies BioMarin Pharmaceutical, bluebird bio, and Spark Therapeutics to have its specialty pharmacy business unit exclusively distribute the pharmaceutical manufacturers' new hemophilia therapies when they become available in 2019 or 2020.

Express Scripts says it saves money for payers by cutting out the markup by hospital pharmacies, which is 6% for the government Medicare program and more for commercial businesses, or at least $60,000 on a $1 million drug. Express Scripts is the sole distributor for Spark Therapeutics and is working with Novartis and Gilead to develop contracts for Kymriah and Yescarta.[8]

Figure 2 | Gene Therapy Budget Impact (Illustrative)



Assumptions: PMPY traditional and specialty drug costs estimated from 2018 ESI Drug Trend Report. Each plan is assumed to have three members receiving gene therapy at a cost of $750,000 per patient.

The impact of the challenges detailed above will vary in significance depending on the payer channel, as shown in Table 2.

Table 2 | Challenges Faced by Payer Channels

Payer Channel	Significance of Challenge ✶ Low | ✶✶ Medium | ✶✶✶ High	
	Challenge 1 *Temporal gap between payment and benefit*	Challenge 2 *Tyranny of small numbers*
Commercial health plans	✶✶✶	✶✶
Integrated delivery networks	✶✶✶	✶✶✶
Medicaid fee-for-service	✶✶✶	✶✶
Managed Medicaid	✶✶✶	✶✶✶
Medicare Part D	✶	✶
Medicare fee-for-service	✶✶	✶
Self-funded employers	✶✶✶	✶✶✶

Potential Solutions

Various solutions have been proposed by manufacturers, payers, and third-party organizations to help facilitate access to cell and gene therapies; each requires varying degrees of action and commitment from each of these parties. Four such solutions include (1) outcomes-based agreements, (2) amortization, (3) reinsurance, and (4) cell and gene therapy payment pools.

(1) OUTCOMES-BASED AGREEMENTS

Among all the potential solutions for dealing with the cost challenges of cell and gene therapies, outcomes-based contracts appear to be raised by payers and manufacturers frequently. Under such an arrangement, payers would receive a negotiated full or partial refund from the manufacturer for the cost of any treatment that proves to be ineffective for the patient.

Harvard Pilgrim Health Care negotiated an outcomes-based contract directly with Spark Therapeutics for Luxturna. The contract provides for a reduced net cost to Harvard Pilgrim for Luxturna by tying the level of payment to measured improvements in patients at a 30-day to 90-day interval and then again at the 30-month mark. If the therapy fails to perform as agreed upon, Harvard Pilgrim would receive a rebate from Spark Therapeutics. In negotiating its contract, Harvard Pilgrim took into account clinical trial results. In addition to risk sharing, the agreement enables Harvard Pilgrim to purchase Luxturna directly from Spark, bypassing mark-up of the drug by the institution administering it.[9]

Among the challenges of implementing outcomes-based contracts, for therapies with a large Medicaid population, managing best price looms as a significant obstacle. Medicaid best price requires drug manufacturers to give Medicaid programs the lowest or "best" price (through rebates) that they negotiate with any other buyer.

For outcomes-based contracts, various structures have been proposed: (1) a per-patient refund in which payers are refunded in full when a patient does not respond to treatment; (2) a limited refund in which any money back for each non-responder is limited (e.g., to 23.1%) to minimize impact on statutory best price; and (3) a population-based refund in which outcomes are tracked for populations of patients and refunds are given for all patients based on aggregate response rate. Among these structures, the per-patient refund would most likely have the greatest implications for Medicaid best price.

Legislation Clears the Path

Legislative steps are being taken to improve the ability of health plans to develop outcomes-based contracts. The Pharmaceutical Information Exchange Act, introduced in the House of Representatives in April 2017, amends the Federal Food, Drug, and Cosmetic Act to allow information about a new investigational medication or the investigational use of a medication approved by the FDA to be provided to healthcare entities if the information is based on reliable scientific evidence.[10]

The legislation is designed to encourage sharing of clinical information between manufacturers and health plans 12 to 18 months in advance of potential approval. This will allow plans to better prepare for emerging therapies, to put programs in place, and to think about appropriate utilization management, allowing for a smoother transition when the product does become available.

(2) AMORTIZATION

Payers and manufacturers are exploring a number of options to reduce the one-year budget impact of cell and gene therapies. One approach involves spreading the financial impact of expensive therapies by entering into amortization agreements with manufacturers. The advantage for the health plan is that by spreading the payment out, the high cost of the therapy makes less of an impact on the plan's budget in the first year. Spark Therapeutics has proposed an installment-based plan to CMS for Luxturna and has engaged with CMS about the possibility of CMS waiving Medicaid "best price" requirements.[11] Spark Therapeutics may also sell directly to Express Scripts, which could then make installment-based payment arrangements on its own with payers.[9]

Amortization can be combined with outcomes-based agreements in the form of milestone-based payments. At the 2019 J.P. Morgan Healthcare conference, bluebird bio announced that the company is offering a five-year payment period that includes risk sharing based on outcomes of up to 80% of therapy cost.[3]

Judging from these early examples, payers and manufacturers are likely to set an upper limit on the duration of such milestone-based payments of around five years to ensure timely reimbursement of the full list price and to prevent long-standing liabilities for the plan. Some plans are considering a three-year amortization plan for paying the cost down, based on the assumption that most patients stay on a health plan for about three years at a time.

Some payers, in contrast, view arrangements that draw out the duration of repayment as unattractive and prefer to settle all of the payments in the year in which the charge was incurred. This view is especially apparent in light of the portability issue: under an amortization arrangement, a plan could be paying for a patient's treatment years after the patient has left the health plan!

It is possible, however, that health plans could cooperate to solve the issue of amortization portability: AveXis and Harvard Pilgrim have announced plans to pilot a joint effort among Massachusetts payers that would enable payment installments for AveXis's therapy Zolgensma to follow patients between health plans.[12] Zolgensma is a treatment for spinal muscular atrophy and is anticipated to cost up to $5 million per treatment.

(3) REINSURANCE

Reinsurance and stop-loss policies are common practice among payers, and they provide protection against catastrophic or unpredictable losses. In a typical "individual" stop-loss policy, any costs incurred for a single patient in a year above a stop-loss deductible (for example $1 million) are borne by the reinsurance carrier rather than the health plan. Transplants, which can cost in excess of $1 million for complex cases, sometimes trigger a stop-loss policy.

Cell and gene therapies, which may fall in a similar price range as transplants, could be covered by reinsurance or stop-loss. According to a recent report, Novartis has proposed that public and private health plans engage with reinsurers in cases in which patients are diagnosed with a condition treatable by a cell or gene therapy.[13] Novartis and AveXis have claimed their drug Zolgensma could be cost-effective to health plans at a price point of $5 million per administration. Assuming that the drug could be covered under an individual stop-loss policy with a stop-loss deductible of $1 million, reinsurance would defray 80% of the costs in the year of administration.

Reinsurance is not a perfect solution to the budget impact of all cell and gene therapies, however, especially for those treatments with relatively more patients and lower prices. For example, Novartis's first cell therapy, Kymriah, carries a list price of $475,000 and would not trigger stop-loss for a plan with a stop-loss deductible of $1 million.

The value of reinsurance will be contingent on the number of members a given plan has on such therapies: small health plans and self-funded employers are highly likely to seek coverage of cell and gene therapies within their stop-loss policies to avoid catastrophic expenses.

(4) CELL AND GENE THERAPY PAYMENT POOLS

The payment models above will impose burdens on small health plans and gene therapies with small patient populations, even in the best circumstances. Setting up amortization or outcomes-based agreements carries a significant administrative burden for payers and manufacturers. Reinsurance and stop-loss policies are generally used as safeguards against catastrophe, not standardized mechanisms to cover entire classes of treatment. The smaller the plan or patient population, the more difficult it will be to negotiate complex contracting relationships between payers and manufacturers to enable the payment models above.

As an alternative, we propose a model wherein premiums from payer organizations would be paid into a shared pool that provides coverage of cell and gene therapies for eligible members. Participation in cell and gene therapy pools would be voluntary and could include government involvement, similar to the Federal Deposit Insurance Corporation model for banks and savings institutions. Shared pools would centralize access to cell and gene therapies and obviate the significant administrative burden posed to payers by amortization and outcomes-based payment schemes. Shared pools cater to a larger patient population than individual health plans, spreading risk and responsibility.

Analogs for this type of model already exist, such as the National Vaccine Injury Compensation Program (VICP) run by the Health Resources and Services Administration. In instances in which a vaccine causes a serious problem, such as a severe allergic reaction, VICP may provide financial compensation to individuals who are found to have been injured by a VICP-covered vaccine.[14] VICP is funded by a $0.75 excise tax on vaccines recommended by the Centers for Disease Control and Prevention for routine administration to children. Several payers interviewed by EVERSANA MANAGEMENT CONSULTING cited the VICP model as an analog for how the cell and gene therapy pools could work.

Blood banks are another analog for this model. Local community health plans will pay to fund the same blood bank. Utilization of the blood bank can be expensive, but plans recognize that when they all contribute, the cost overall is lower.

Shared pools for high-risk patients were prevalent on a state level prior to implementation of the Affordable Care Act. These pools provided basic insurance coverage for individuals with expensive pre-existing conditions who were underserved by private insurance, though each state differed as to which kinds of patients were eligible. Reactivating shared pools for high-risk patients on a state or federal level is one potential legislative option to creating cell and gene therapy payment pools.

State-level high-risk pools were phased out following the ACA, but examples of carved-out public coverage for specific indications still exist: one example is the ability for many end-stage renal disease (ESRD) patients to qualify for Medicare regardless of age or disability.[15] The purpose of ESRD coverage under Medicare is to ensure patients can obtain the dialysis or a kidney transplant they need for survival. Patients who qualify for Medicare due to ESRD are able to keep their private insurance (if they have it), and for these patients, Medicare assists with insurance premiums and any remaining out-of-pocket costs. Medicare could offer similar temporary coverage for patients eligible for cell and gene therapy following legislation to authorize and fund CMS appropriately.

A private version of a shared pool could be implemented, analogous to existing "carve-out" programs offered by major insurance carriers to self-funded groups.[16] Carve-outs provide "first-dollar" coverage of qualified expenses, such as costs associated with organ transplantation or cancer, in contrast to reinsurance policies that only cover expenses above a stop-loss deductible (e.g., above $1 million in a year). The benefit of a carve-out model is that it reduces the actuarial risk to smaller health plans, trading the risk of an expensive organ transplant episode (sometimes costing upwards of $1 million) for monthly premiums of about $10 per employee per month.[12] It remains to be seen whether large health insurers will begin offering carve-outs for cell and gene therapy, but the parallels to transplantation suggest it may be on the horizon.

Table 3 | Summary of Proposed Solutions

1. Outcomes-Based Agreements *Description: Pay for performance*	
Status/Examples	The Harvard Pilgrim/Spark Therapeutics agreement provides for a reduced net cost to Harvard Pilgrim for Luxturna by tying level of payment to measured improvements in patients at a 30-day to 90-day interval and then again at a 30-month mark. If the therapy fails to perform as agreed upon, Harvard Pilgrim receives a rebate from Spark Therapeutics.[9]
Challenges	▪ Potential risks posed by Medicaid Best Price ▪ Requires coordination across manufacturers, payers, and providers
Implications for Pharma	▪ Clinical trials should be designed to complement agreements. ▪ Implementation capabilities need to be built internally or outsourced.
2. Amortization *Description: Manufacturer offers an installment payment option*	
Status/Examples	bluebird bio announced a five-year payment period that includes risk-sharing based on outcomes of up to 80% of therapy cost.[3]
Challenges	▪ Patient departure from health plan before installments are paid off ▪ Need to develop infrastructure to monitor performance
Implications for Pharma	▪ Full compensation for each patient may take several years. ▪ Accounting for revenue may be challenging.
3. Reinsurance *Description: Payers purchase reinsurance to reduce financial risk*	
Status/Examples	Payers and hospitals have stop-loss policies for catastrophic events (e.g., expensive transplants).
Challenges	▪ High entry point (e.g., $1M+) for reinsurance policies ▪ Unknown whether current reinsurance policies cover cell and gene therapy
Implications for Pharma	▪ A class of reinsurers specializing in cell and gene therapy may emerge as an important stakeholder for market access.
4. Cell and Gene Therapy Payment Pools *Description: Funded by premiums payer organizations pay for insurance coverage for cell and gene therapies*	
Status/Examples	While there are no existing examples for cell and gene therapy, the National Vaccine Injury Compensation Program (VICP) has similarities.
Challenges	▪ Requires a sufficient number of initial health plans paying into the system ▪ Could be accelerated by legislative support
Implications for Pharma	▪ Government stakeholders might become more important for market access.

Conclusion

The temporal dynamic of up-front cost and delayed clinical benefit of cell and gene therapy poses challenges. These challenges are amplified in the US, where a healthcare system characterized by multiple private insurers and government-funded insurance creates an environment where patient portability is an issue. We have presented a number of payment mechanisms that have the potential to address these problems and make cell and gene therapy commercially viable.

Payer appetite for novel payment mechanisms is increasing: more than 32 value-based contracts were publicly announced between 2015 and 2018, more than double the number that had been announced in the previous two decades. And in a 2018 survey of 59 commercial health plans in the United States, representing more than 76 million lives, 32% of payers ranked reimbursement based on outcomes or value as one of the three most likely strategies to be implemented in the coming year.[17]

Now is the right time to start focusing on implementation, as all stakeholders—including payers and manufacturers—have a vested interest in increasing access to highly effective, innovative therapies that address patients' unmet medical needs.

EVERSANA MANAGEMENT CONSULTING can assist pharma and biotech organizations with developing appropriate solutions, including implementation of value-based contracts, payer segmentation, scenario planning, and policy advisory strategies. Our position within EVERSANA—the leading independent provider of global services to the life science industry—gives us unparalleled insights into the opportunities and challenges associated with launching innovative therapeutics and maximizing performance.

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Figure 2 (2018 ESI Drug Trend Report)

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