

CELL AND GENE THERAPY PLAYBOOK

September 2023

Supply Chain Incentives: Zolgensma

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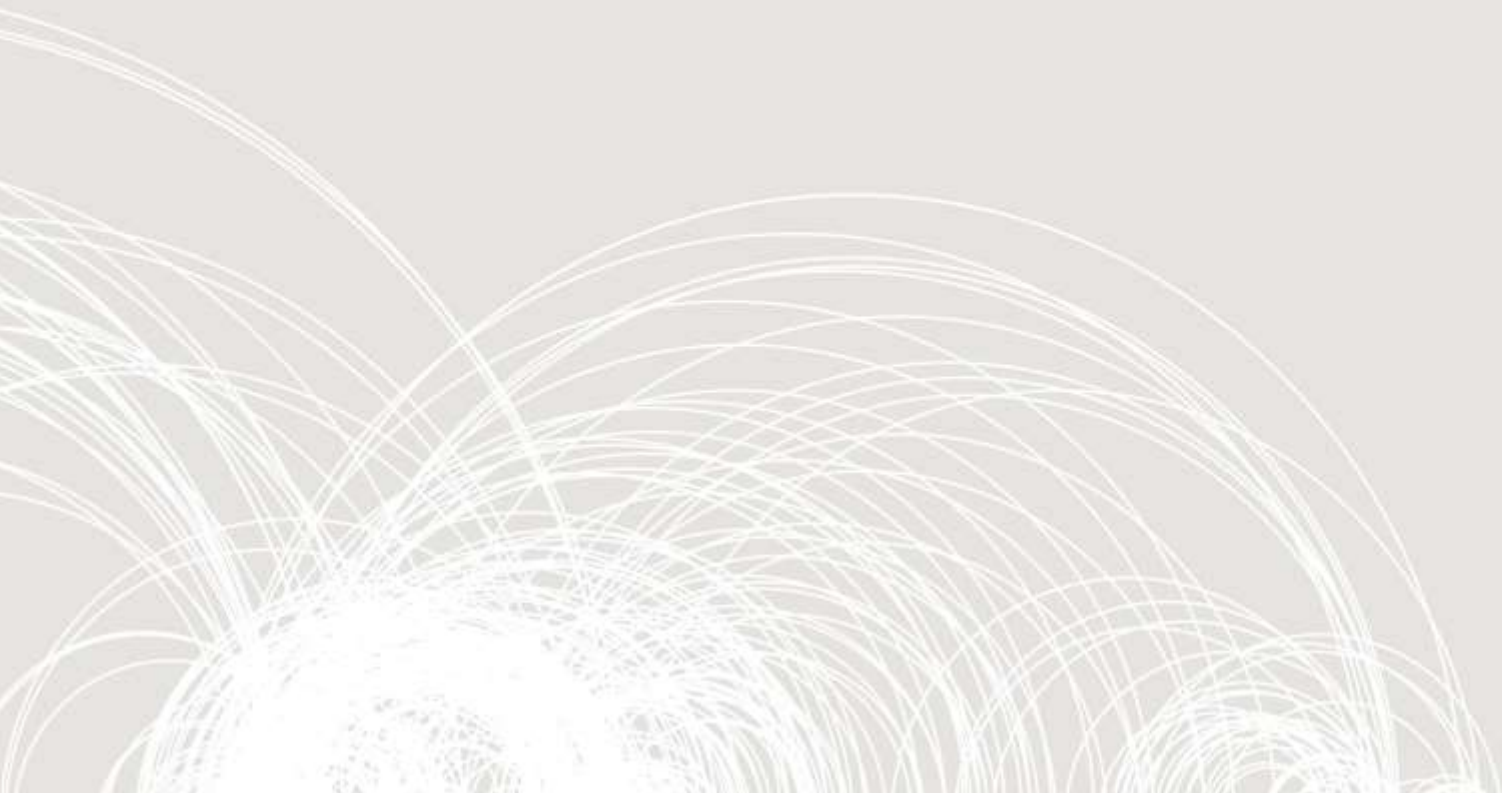


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About This Series

This paper is organized to highlight each medication or therapy in this series in three phases: production, commercialization, and access.

Within production, there are critical steps and decisions that manufacturers make regarding research and development, patenting, and manufacturing.

From there, commercialization is intended to look closely at how a product is marketed, labeled, and regulated, and the resultant impact of those decisions on the price of each featured product.

The final step in the process is access, how product acquisition (moving from manufacturer, through wholesalers, and on to pharmacies) and distribution (PBMs, payers, and providers) shapes patient access, which is so often impacted by cost.

Introduction

In the last decade, new therapeutic advancements such as cell and gene therapies (CGT) have garnered significant attention due as much to their potential for life-changing impact as their pricing. CGT refers to three distinct types of treatment that use “living cells” to heal and replace damaged tissues or organs which cause disease (Exhibit 1). Many of these therapies are potentially curative and others significantly halt the progression of a disease, targeting life-threatening conditions like cancer and genetic abnormalities. These innovations provide hope for those with debilitating rare diseases that previously faced significantly shortened lives or severely life-limiting conditions.

There is substantial variation within CGTs when it comes to therapeutic mechanism, distribution channel, and applicable patient population. There is also significant variability in the price of these medications, ranging from tens of thousands to multiple millions per course of treatment. For those treatments that tip the higher end of the pricing scale, there are vastly different incentives and access points than most small molecule and biologic products. As a result, there is a need for different risk-sharing and payment mechanisms for these ultra-high priced CGTs, which are explored in this playbook.

Exhibit 1: Key Differences between Types of Cell and Gene Therapies and Examples

	Cell Therapy	Gene Therapy	Cell-Based Gene Therapy
Treatment Mechanism	Transfer of stem cells either the patient’s own cells (autologous) or a healthy donor’s (allogenic). Cells are infused with a functioning protein.	Transfer of a functioning gene via a viral vector into the patient.	Stem cells are extracted from a patient, genetically modified to address underlying issue, and reinfused.
Therapeutic Response	Enhances immune response.	Addresses underlying cause of disease and may restore lost function.	Addresses underlying cause of disease and may restore lost function. Most often used to treat cancer with CAR T-cell therapy.
FDA Approved Examples	Provenge AlloCord	Zolgensma Luxturna	Kymriah Yescarta

Source: FDA^{1,2}

As an example of the incentives and dynamics at play with the highest cost CGTs, this playbook focuses on Zolgensma, a gene therapy used to treat spinal muscular atrophy (SMA). SMA is a hereditary disease in which motor neurons, cells that control essential activities such as breathing,

¹ U.S. Food And Drug Administration. (2018, July 25). *What is Gene Therapy?* <https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/what-gene-therapy>

² U.S. Food And Drug Administration. (2023, June 30). *Approved Cellular and Gene Therapy Products.* <https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products>

walking, speaking, and swallowing, are progressively destroyed.³ There are four forms of SMA classified by the age of onset, but all are caused by inheriting a mutated gene. Genetic screening is used to determine if an individual carries the mutated gene and is at high risk of passing the genetic disorder to their offspring through pregnancy. Genetic screening during pregnancy and in newborns is also used to diagnose SMA and has shown to be successful in allowing infants to be treated before disease progression, resulting in improved clinical outcomes.⁴ In most cases, the symptoms of SMA will present in children by 18 months of age, but children with the most severe form of SMA (SMA type I) will exhibit reduced movements even in utero. Individuals with SMA type IV may not develop symptoms until after 21 years of age. Because the disease is progressive, earlier diagnosis and treatment improves quality of life. Currently there is no cure for SMA, but Zolgensma, which was approved by the FDA in 2019, prevents further complications from the disease and has demonstrated the ability to significantly improve quality of life.^{5,6,7} Zolgensma is a one-time treatment that is currently indicated only for children under the age of two. It should be noted that although Zolgensma is often referred to as a “one and done” treatment, even children who have received Zolgensma may require further disease modifying treatments.⁸

The list price of a one-time dose of Zolgensma was announced at \$2.1 million in 2019 and has stayed above \$2 million since.⁹ While Novartis, Zolgensma’s manufacturer, went to great lengths in the initial announcement of the drug to demonstrate that this is well below the estimated lifetime cost of treating SMA, the extraordinarily high price caught national media attention, shining a light on a new societal challenge—how to support scientific advancements such as Zolgensma while ensuring that individuals have access to and can afford these important treatments. There are no direct competitors to Zolgensma, however there are alternative treatments for SMA, including Spinraza and Evrysdi, which are not CGTs; instead, these treatments are used to slow motor neuron degeneration. Both can be used in patients older than two years of age. In 2021, Novartis reported more than \$1.3 billion in annual sales

³ National Institute of Neurological Disorders and Stroke. (n.d.). *Spinal Muscular Atrophy*. [https://www.ninds.nih.gov/health-information/disorders/spinal-muscular-atrophy#:~:text=Spinal%20muscular%20atrophy%20\(SMA\)%20is,to%20muscle%20weakness%20and%20atrophy](https://www.ninds.nih.gov/health-information/disorders/spinal-muscular-atrophy#:~:text=Spinal%20muscular%20atrophy%20(SMA)%20is,to%20muscle%20weakness%20and%20atrophy).

⁴ Keinath MC, Prior DE, Prior TW. Spinal Muscular Atrophy: Mutations, Testing, and Clinical Relevance. *Appl Clin Genet*. 2021 Jan 25;14:11-25. doi: 10.2147/TACG.S239603. PMID: 33531827; PMCID: PMC7846873.

⁵ ClinicalTrials.gov. (n.d.). *Gene Transfer Clinical Trial for Spinal Muscular Atrophy Type 1 - Full Text View* - <https://clinicaltrials.gov/ct2/show/NCT02122952>

⁶ ZOLGENSMA. (n.d.). *Clinical studies results*. <https://www.zolgensma.com/clinical-studies>

⁷ Novartis. (2022, March 14). *Novartis data again demonstrate age-appropriate development when Zolgensma is used presymptotically, and post-hoc data reveal SMA Type 1 patients could speak, swallow and maintain airway protection*. <https://www.novartis.com/news/media-releases/novartis-data-again-demonstrate-age-appropriate-development-when-zolgensma-used-presymptotically-and-post-hoc-data-reveal-sma-type-1-patients-could-speak-swallow-and-maintain-airway-protection>

⁸ Milton, A. (n.d.). *“One-and-done” gene therapies*. <https://advisory.kpmg.us/content/dam/advisory/en/pdfs/2021/cell-and-gene-therapies.pdf>

⁹ Novartis. (n.d.). *AveXis Announces Innovative Zolgensma® Gene Therapy Access Programs for US Payers and Families*. <https://www.novartis.com/news/media-releases/avexis-announces-innovative-zolgensma-gene-therapy-access-programs-us-payers-and-families>

for Zolgensma, which far eclipses annual sales for Spinraza and Evrysdi at \$431 million and \$294 million, respectively.¹⁰

Impact of Incentives

Production

Research and Development

For manufacturers, pursuing the development of treatment for rare diseases and producing what are often referred to as orphan drugs is a complicated equation. While the potential patient population may be small, there are regulatory incentives aimed to encourage investment in advancing treatment options. The Orphan Drug Act, signed in 1983, is designed to stimulate the development of drugs by offering patent and financial incentives to manufacturers. From a regulatory standpoint, a rare disease is one that impacts less than 200,000 persons in the U.S., or it affects more than 200,000 people but there is no reasonable expectation that the cost of developing a targeted therapeutic will be recovered by the potential sales.¹¹ Once this designation is achieved and a treatment developed, manufacturers are afforded seven years of market exclusivity and tax credits of up to 50% of research and development costs. Since passage of the Orphan Drug Act, over 1,000 orphan drugs have made it to market.¹²

The high unmet need represented by rare diseases, such as SMA, mean that CGTs to treat them go through the Accelerated Approval Program under the U.S. Food and Drug Administration (FDA).¹³ At the time of its approval, Zolgensma had just completed a Phase 1 study consisting of only 15 participants. There is an ongoing Phase 3 trial with 21 patients, which focuses on two primary endpoints: the ability to sit without support for 30 seconds at 18 months of age and survival at 14 months of age.¹⁴ While the evidence used to support approval was promising and sufficient for the FDA's decision, the treatment has not been on the market long enough to study long-term outcomes. This has implications for the complex payment dynamics at play when parents, along with their providers and payers, are faced with the decision to pursue this treatment.

¹⁰ Pagliarulo, N. (2022, October 25). *Novartis sales of Zolgensma gene therapy slow as market shifts*. *BioPharma Dive*. <https://www.biopharmadive.com/news/novartis-zolgensma-sales-slow-newborn-screening/634896/>

¹¹ U.S. Food And Drug Administration. (2018, March 9). *Orphan Drug Act - Relevant Excerpts*. <https://www.fda.gov/industry/designating-orphan-product-drugs-and-biological-products/orphan-drug-act-relevant-excerpts>

¹² U.S. Food And Drug Administration. (2018, February 23). *The Story Behind the Orphan Drug Act*. <https://www.fda.gov/industry/fdas-rare-disease-day/story-behind-orphan-drug-act>

¹³ U.S. Food And Drug Administration. (2023, May 30). *Accelerated Approval Program*. <https://www.fda.gov/drugs/nda-and-bla-approvals/accelerated-approval-program>

¹⁴ U.S. Food And Drug Administration. (2019, May 24). *Summary Basis for Regulatory Action*. <https://www.fda.gov/media/127961/download>

Payers have expressed concerns with these therapies' performance and whether manufacturers have provided enough evidence of their efficacy to justify coverage and reimbursement given the availability of the accelerated approval pathway.¹⁵ The introduction of precision financing, which may include performance-based contracts or performance-based annuities, has been piloted as one option to offset both the high upfront cost, as well as concerns about long-term outcomes driven by the accelerated pathway.¹⁶

Commercialization and Access

Addressable Market

Once on the market, there is often little competition among CGTs to treat a particular condition and prices can stagnate at high levels. As with many rare diseases, bringing a product to market that cures or treats SMA has significant barriers. SMA is diagnosed in approximately 1 in 10,000 people¹⁷, resulting in an addressable patient population that is less than a fraction of one percent. When considering a therapy like Zolgensma, indicated for pediatric patients less than two years of age, the addressable patient population is even smaller. Since its launch in 2019, sales for Zolgensma have declined, with revenues dropping by 15% from 2021 to 2022.¹⁸ To balance the high costs of developing novel therapies for rare diseases or diseases that impact a relatively small patient population, manufacturers target high price points to achieve profitability and sustainability. At minimum, these high prices can be sustained during the seven-year market exclusivity period, keeping these medications out of reach for some patients. Manufacturers aim to be the sole product in a given class where there are no incumbents and are well positioned to monitor competitors' drug development efforts. This further creates a lack of product competition, which establishes market conditions that can keep prices high well after launch.¹⁹

Distribution

¹⁵ MIT NEWDIGS. (2021, March 25). *Payer perspectives on outcomes tracking for value-based payment arrangements (VBPs)*. newdigs.tuftsmedicalcenter.org/wp-content/uploads/2022/06/FoCUS-Research-Brief-Outcomes-Tracking-2021F203v053.pdf

¹⁶ Caffrey, M. (2019, June 18). *MIT Group Brings Together Stakeholders to Brainstorm How to Pay for Curative Therapies Over Time*. <https://www.ajmc.com/view/mit-group-brings-together-stakeholders-to-brainstorm-how-to-pay-for-curative-therapies-over-time>

¹⁷ Centers for Disease Control and Prevention. (n.d.) *Spinal Muscular Atrophy*. [https://www.cdc.gov/nceh/dls/nsmbb_sma.html#:~:text=Spinal%20Muscular%20Atrophy%20\(SMA\)%20is,being%20unable%20to%20make%20protein](https://www.cdc.gov/nceh/dls/nsmbb_sma.html#:~:text=Spinal%20Muscular%20Atrophy%20(SMA)%20is,being%20unable%20to%20make%20protein)

¹⁸ Novartis. (n.d.). *Q3 2022 Results Investor presentation*. https://www.novartis.com/sites/novartis_com/files/q3-2022-investor-presentation.pdf

¹⁹ Tribble, S. J. (2017, January 17). *Drugs For Rare Diseases Have Become Uncommonly Rich Monopolies*. <https://www.npr.org/sections/health-shots/2017/01/17/509506836/drugs-for-rare-diseases-have-become-uncommonly-rich-monopolies>

Since CGTs target a small population, their production is often limited to a small number of manufacturing plants. Zolgensma, for instance, is approved to be manufactured at only two plants—one in Libertyville, Illinois and the other in Durham, North Carolina—the latter of which was only approved in April, 2022.²⁰ Processes to produce adeno-associated virus, the vector used to carry the corrective gene in Zolgensma and many other CGTs, result in low yields, reducing efficiency and further contributing to the high price.²¹

All cell and gene therapies require strict temperature ranges for shipping and storage, close patient monitoring, involve small patient populations, and precise dosing customized to the patient. For instance, Zolgensma must be administered to a patient by intravenous infusion within 14 days of arrival at the site of administration (most often a hospital), therefore close coordination with patients is required to ensure doses aren't missed, which has implications both for the success of the treatment and the potential for significant financial loss. The complex patient journey for CGT treatments also requires more effort from manufacturers; for example, having a CGT coordinator to help with data flow from one authorized site or hospital to another site of care. Authorized treatment centers are chosen to maximize patient concentration for safety and efficiency. While each of these steps is in place to coordinate and successfully deliver the treatment to the patients in need, it adds complexity and ultimately, cost into the drug development process.²²

Patient Implications

Note: Patient scenarios are meant to be illustrative only. The goal of these scenarios is not to provide exact prices, but to demonstrate the patient experience while accessing their medications and the ways these prices are impacted by upstream incentives. Prices are based on publicly available information when possible (and cited accordingly) and based on good faith estimates when prices were not available.

In the scenarios below, genetic screening for SMA allows for diagnosis of SMA type 1 in a newborn, when treatment options may be most effective. In one scenario, the newborn is covered by the state's Medicaid program where Zolgensma treatment is covered through a value-based payment arrangement with the manufacturer. The second scenario shows the impact if the patient were covered by another health insurance where treatment is not covered due to differences in coverage policies.

²⁰ Fierce Pharma. (2022, April 5). *Novartis gets FDA nod to begin making Zolgensma in North Carolina*. <https://www.fiercepharma.com/manufacturing/novartis-gets-fda-nod-begin-making-zolgensma-north-carolina>

²¹ McKinsey & Company. (2019, October 2). *Gene therapy coming of age: Opportunities and challenges to getting ahead*. <https://www.mckinsey.com/industries/life-sciences/our-insights/gene-therapy-coming-of-age-opportunities-and-challenges-to-getting-ahead>

²² De Luca, M., & Cossu, G. (2023, February 6). *Cost and availability of novel cell and gene therapies*. <https://doi.org/10.15252/embr.202256661>

These scenarios differ primarily on variation in coverage policies. This variation will determine the patient's ability to access Zolgensma and, if inaccessible, their need to seek out alternative therapies.

Scenario 1

We consider the example of a newborn who is covered by Massachusetts Medicaid (MassHealth). During a routine newborn genetic screening, the infant tests positive for the SMA gene mutation and is subsequently diagnosed with SMA type 1. Upon further evaluation, the physician prescribes Zolgensma. Zolgensma is covered by MassHealth, under a value-based payment arrangement with Novartis, that involves financial risk-sharing based on clinical outcomes measures. Due to favorable coverage policy, the patient has access to and can receive a one-time dose of Zolgensma via intravenous (IV) infusion.

Scenario 2

In an alternate scenario, the patient is covered by a health insurance plan with different coverage policies and therefore coverage of Zolgensma is not guaranteed even with an early screening diagnosis. Coverage decisions and guidance for how to determine which patients are eligible for SMA treatments vary considerably by state and by payer, significantly impacting patient access.²³ In this scenario, the physician prescribes Zolgensma, but the patient's health insurance denies coverage. As a result of the Zolgensma denial, the patient's family instead turns to Spinraza. The patient begins Spinraza treatment, which involves multiple spinal injections.

Scenario 1	Scenario 2
During routine newborn genetic screening, infant tests positive for the SMA gene mutation and is subsequently diagnosed with SMA type 1.	
Newborn is covered by MassHealth. Upon diagnosis, physician prescribes Zolgensma, which is covered by MassHealth. Newborn has access to and begins treatment with Zolgensma.	Newborn is covered by a different health insurance plan. Upon diagnosis, physician prescribes Zolgensma, but the patients health insurance plan denies coverage. Patient's family instead begins treatment with Spinraza.
Newborn receives a one-time IV dose of Zolgensma.	Newborn begins Spinraza treatment, involving multiple spinal injections.

²³ Ballreich, J., Ezebilu, I., Khalifa, B. a. A., Choe, J. A., & Anderson, G. F. (2022). *Coverage of genetic therapies for spinal muscular atrophy across fee-for-service Medicaid programs*. <https://doi.org/10.18553/jmcp.2022.28.1.39>

Conclusion

The market for high-cost CGTs is nascent and each time a new therapy or innovation is approved, there is more to learn about what the market can bear about demand for these treatments given their medical advancement and high price tags. These treatments often target rare and life-threatening conditions, putting exceptional pressure on payers and patients to devise strategies that make them accessible without threatening the financial solvency of interested parties. The number of CGTs is expected to rise in the coming years and there will be an increasing need to solve for this issue. Precision financing may be one solution. Regulatory changes may be another. Whatever the solution, more attention and focus need to be on the unique conditions of this landscape to develop a greater understanding of the incentive changes that need to occur to increase access to these therapies.

Acknowledgements

This research was made possible with support from Arnold Ventures.

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