Cell and gene therapies: Informing the uncertainties using research and retrospective claims analysis

Navigating cell and gene therapy (CGT) complexities

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Accurately estimating CGT cost exposure requires a nuanced approach integrating clinical research, market monitoring, and claims analysis.

Introduction

The advent of single-administration cell and gene therapies (CGTs) has the potential to change the landscape of modern medicine. However, these therapies are accompanied by significant costs and other uncertainties that complicate risk assessment and forecasting for healthcare payers and plan sponsors. This white paper aims to:

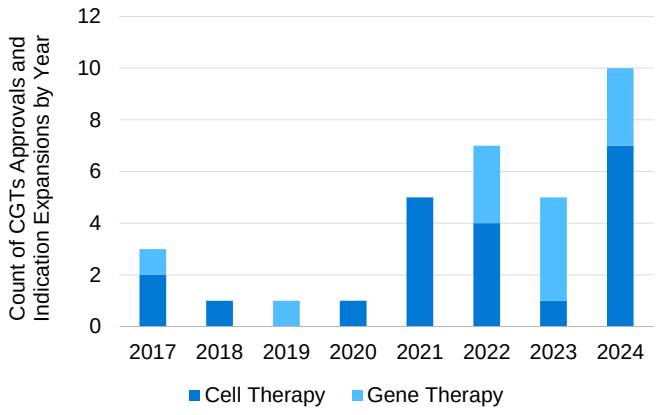
- Explore the factors that drive unpredictability in CGT utilization and costs and outline a practical approach to estimating CGT case and cost exposure
- Present findings associated with episodic costs from a commercial claims analysis of CGTs

Current landscape of single-administration CGTs

The landscape of CGTs is rapidly evolving. As of September 2024, there are 21 single-administration CGTs that have been approved by the U.S. Food and Drug Administration (FDA), representing 33 initial approvals or indication expansions. This includes 21 cell therapy approvals or indication expansions and 12 gene therapy approvals or indication expansions.[1]

There have been numerous FDA approvals of gene therapy over the past two years, but only one (Elevidys) of the 10 gene therapies approved since mid-2022 has had notable demand.[2] Additionally, there are nearly 60 more single-administration CGTs in the three-year outlook that Milliman DNA Gene and Cell Therapy Forecasting is monitoring, suggesting a continuation of increasing approvals.[3]

FIGURE 1: FDA-APPROVED SINGLE-ADMINISTRATION CGTS THROUGH SEPTEMBER 2024



Note: Approval counts in the graph include original approvals and indication expansions.

Source: Milliman DNA Gene and Cell Therapy Forecasting; v3.3.0, September 2024 release. Gene therapies include gene therapies and gene editing technology, cell therapies include CAR-T, and one tissue therapy.

1. Milliman DNA Gene and Cell Therapy Forecasting; v3.3.0, September 2024 release.
2. Based on a review of public reports and manufacturer press releases, investor reports, and financial filings by the U.S. Securities and Exchange Commission (SEC).
3. Milliman DNA Gene and Cell Therapy Forecasting, v3.3.0, op cit.

Key factors driving unpredictability in CGT utilization and costs

RARE DISEASES

The currently approved conditions targeted by CGTs are for rare or ultra-rare diseases and cancers, resulting in cases that are likely to occur sporadically, rather than trend toward an average, even for the largest payers. The low prevalence rates complicate the process of identifying eligible patients within a population. For example, in the case of ultra-rare conditions, the prevalence might be so low that traditional statistical methods become less effective in predicting the number of eligible patients. As a result, a more nuanced approach to data collection and analysis should be employed for these conditions, leveraging multiple data sources to build a comprehensive picture of the patient population.

It is probable that CGTs could be available to treat larger patient populations in the upcoming years. There are CGTs in clinical trials for higher prevalence conditions, including refractory angina[4] and ischemic stroke.[5]

CLINICAL ELIGIBILITY CRITERIA

Clinical eligibility for CGTs is not only determined by the presence of a specific diagnosis but also by a range of other factors, including age, severity of disease, specific genetic markers, or failure on multiple other therapies. Often, many of these clinical criteria are not observable in claims data, making it more difficult to identify specifically eligible patients within a covered membership. The specific clinical criteria, and estimated portion of the population who meet those specifications, are important to capture in order to narrow the number of potentially eligible patients, adding complexity to the forecasting process.

Additionally, characteristics of the therapy itself can result in a portion of the otherwise eligible patients to be excluded from the treatable population. For example, Roctavian, a gene therapy for hemophilia A, requires patients to be tested for neutralizing antibodies prior to treatment.[6] According to a published study, 27% of people with hemophilia A may have resistance to adeno-associated virus (AAV) 5 in the United States, making them ineligible for the therapy.[7]

Lastly, even among those who are clinically eligible for the therapy, a number of factors may affect the uptake of a CGT, such as distance to a qualified treatment center, other treatment option availability, payer coverage and prior authorization criteria, and patient or provider dynamics. These factors will further dampen the number of patients who will ultimately have access and be treated with the therapy.

SINGLE-ADMINISTRATION NATURE OF TREATMENTS

The single-administration nature of CGTs, where a patient can only be treated once with the therapy, adds another layer of complexity to forecasting. For example, in the case of gene therapies that are delivered using AAV vectors, a treated patient could develop neutralizing antibodies to the AAV vector that renders the same therapy ineffective if administered a second time.[8] These neutralizing antibodies can also extend to other AAV serotypes, meaning a patient treated with one therapy could have neutralizing antibodies that make other AAV-based therapies ineffective, even those using a different AAV serotype.

Unlike traditional drugs where there is typically a consistent base of members who remain on therapy over time, the single-event nature of CGTs, in combination with the low prevalence of the conditions they treat, means historical claims experience may not be indicative of future experience. Additionally, single-administration CGTs can have significant budget impact, particularly for smaller payers or plan sponsors, because the full cost of the treatment is typically incurred at the time the treatment is administered, even though the clinical benefit can extend for years after treatment.

COSTS ASSOCIATED WITH THE EPISODE OF CARE

CGTs may be administered in vivo or ex vivo, depending on the characteristics of the product. In vivo means the cells or genetic material is delivered directly into the patient, via intravenous infusion. Ex vivo means the patient's cells or genetic material are extracted (e.g., apheresis, leukapheresis), these genes or cells are genetically modified in a manufacturing process to produce a therapeutic factor, and then they are transplanted back into the patient.[9] In general, for in vivo therapies, the majority of the cost exposure is associated with the cost of the therapy itself rather than the administration process. For ex vivo therapies, including

4. ClinicalTrials.gov (July 19, 2022). Ad5FGF-4 In Patients With Refractory Angina Due to Myocardial Ischemia (AFFIRM): Participation Criteria. Retrieved October 24, 2024, from https://clinicaltrials.gov/study/NCT02928094?intr=GENERx&rank=1#participation-criteria.
5. ClinicalTrials.gov (February 9, 2022). MultiStem® Administration for Stroke Treatment and Enhanced Recovery Study (MASTERS-2): Participation Criteria. Retrieved October 24, 2024, from https://clinicaltrials.gov/study/NCT03545607?intr=MultiStem&rank=9#participation-criteria.
6. Roctavian package insert. See https://www.fda.gov/media/169937/download.
7. Klamroth, R. et al. (April 19, 2022). Global Seroprevalence of Preexisting Immunity Against AAV5 and Other AAV Serotypes in People With Hemophilia A. Hum Gene Ther. Retrieved October 24, 2024, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9063149/.
8. Earley, J. et al. (June 2023). Evading and Overcoming AAV Neutralization in Gene Therapy. Trends in Biotechnology. Retrieved October 24, 2024, from https://www.cell.com/trends/biotechnology/fulltext/S0167-7799(22)00303-1.
9. Cordell, B. (September 2024). Complexities in Forecasting Eligible Cases and Associated Costs of Cell and Gene Therapy. Milliman Report. Retrieved October 24, 2024, from https://www.milliman.com/-/media/milliman/pdfs/2024-articles/9-18-24_complexities-forecasting-eligible-cases-costs-cell-gene-therapy.ashx.

chimeric antigen receptor, T cells (CAR-T) and certain gene therapies, the cost of preparing the patient for treatment, administering the therapy, and monitoring the patient after administration can be a substantial portion of the total cost exposure. This process can include apheresis to extract the necessary cells, extended inpatient stays, and other procedure costs. If there are complications, there may be additional incremental costs.

Approach to estimating CGT case and cost exposure

Estimating CGT cost exposure should leverage a multi-faceted approach that integrates clinical trial data, the FDA-approved label, published literature, market monitoring, and retrospective claims analysis. A comprehensive approach enables estimates of CGT utilization and costs to be addressed with a consistent framework across all conditions treated with CGTs.

The following steps can aid in predicting the number of CGT cases and associated cost among an insured population over a projected time period:

1. **Research the treated condition**: Using peer-reviewed journal publications and epidemiological studies for each condition of interest, research the prevalence, incidence, demographics, treatment options, and other condition-specific characteristics. This information is used to better understand the condition, disease burden, patient population, and unmet need. For certain conditions, claims data can be used to identify the number of currently diagnosed individuals in a covered population.
2. **Refine for the approved label or clinical trial criteria**: Research should be performed to identify the inclusion/exclusion criteria from pivotal clinical trials or the FDA-approved label, as well as to capture any information indicating the portion of the population who may have neutralizing antibodies to the therapy. These characteristics will narrow the prevalent or diagnosed population down to the potentially eligible population.
3. **Inform a demand curve**: The demand curve determines the number of eligible patients estimated to receive treatment in the projection period. This metric is difficult to estimate, given the limited number of CGTs in the market and the unique dynamics associated with each therapy. The demand curve can be informed by retrospective claims data, market monitoring, manufacturer press releases or earnings reports, and other resources. The anticipated demand for a particular therapy will be influenced by a variety of factors across all stakeholders in the healthcare system, including manufacturing capacity, availability of qualified treatment centers, provider patterns in prescribing, and patient hesitancy (such as a lack of interest in CGT treatment or a wait-and-see mentality). A small number of treatment centers can make it particularly difficult for patients who are unable to travel or have socioeconomic barriers preventing them from being away from home for the longer periods of time required to prepare for treatment. Lastly, some smaller payers and self-insured employers have chosen to restrict or exclude coverage for some or all CGTs, dampening access for some patients.
4. **Estimating the costs for the episode of care**: The total costs associated with CGT treatment can be unpredictable, influenced by factors such as the process associated with preparing the patient to receive treatment, adverse events, and provider mark-up of the therapy costs. Using historical data or published information on real-world cost experience is the best resource for understanding the costs for the episode.

   Given the low number of cases associated with these therapies, there may not be enough claims history for an individual payer to use its historical data to assess the variability in episodic costs. For this reason, we performed an analysis of Milliman's proprietary commercial claims database to analyze the episodic costs associated with CGTs, as a resource for better understanding the variability in costs for these treatments. The results of this claims analysis are presented in the next section.

Episodic costs for CGTs from a commercial claims analysis

DATA AND METHODOLOGY

Using Milliman's proprietary Consolidated Health Cost Guidelines Source Database (CHSD), we assessed in-market single-administration gene and cell therapies in the commercial line of business from 2017 to 2023. Milliman's CHSD is a longitudinal administrative claims database with approximately 60 million lives per year in the commercial line of business.

We researched billing guides and other coding information associated with treatment for each CGT. The consolidated list of procedure codes was used to create an algorithm to apply to the CHSD across all data years. Treated members were identified either by Healthcare Common Procedure Coding System (HCPCS) or by International Classification of Diseases (ICD) procedure codes.

For the cell therapies, episodic/other costs are defined as those 60 days before and after treatment, plus the day-of costs, less the list price of the therapy. This time range was selected because it generally includes the period of pretreatment and post treatment procedures, monitoring, and potential adverse events associated with treatment for the cell therapies studied.

It is probable that some costs could be included in the episode window that are not related to the cell therapy and, alternately, that some treatment-related costs could fall outside the defined episode window. For the gene therapies, episodic/other costs are defined as the day-of-treatment costs less the list price of the therapy.

Costs presented are allowed costs, not billed charges; trend factors were not applied. Costs do not reflect manufacturer rebating or refunds associated with outcome-based contracts.

A few members were excluded, including those who had both ICD-10 procedure codes and HCPCS codes, and those with relevant procedure codes across multiple dates. To ensure with reasonable confidence that the claims analyzed included the cost of the CGT (e.g., not paid through a clinical trial), we also excluded members who had an appropriate procedure code but whose drug line item allowed costs were less than $300,000.

RESULTS: EPISODE AND TREATMENT COSTS

There were 17 single-administration CGTs with FDA approval through the end of our study period (December 2023).[10] However, only eight of these therapies had at least 10 cases in the 2017-2023 period. We excluded the CGTs with less than 10 cases from the study; they included CGTs for ultra-rare conditions and those with low uptake among patients.

For the eight therapies with more than 10 cases, Figure 2 displays the number of aggregate cases observed in the 2017-2023 study period for each therapy. The six cell therapies and two gene therapies we analyzed represented 12 approved indications as of December 2023.

FIGURE 2: OBSERVED COUNT OF COMMERCIAL CASES FOR CGTS

CELL THERAPIES ANALYZED	GENE THERAPIES ANALYZED
Abecma: 94 patients	**Luxturna**: 17 patients
Breyanzi: 34 patients	**Zolgensma**: 89 patients
Carvykti: 62 patients	
Kymriah: 108 patients	
Tecartus: 73 patients	
Yescarta: 413 patients	

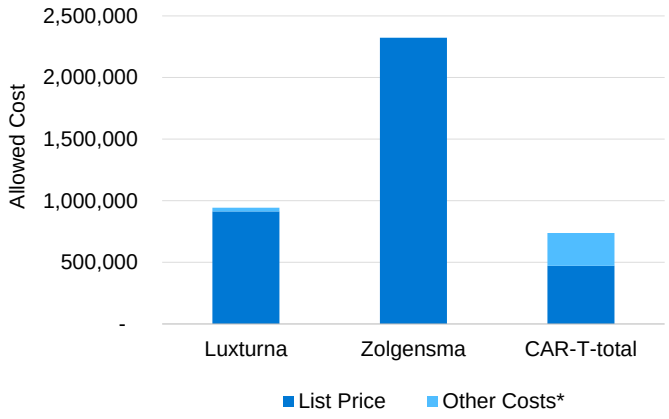
Analysis of 2017-2023 Milliman CHSD commercial claims data.

Even using a large sample of 60 million commercial lives, the treated patient counts for all the therapies were small. Yescarta and Kymriah had the largest number of cases with 413 and 108 cases, respectively. These were the first two CAR-T therapies to enter the market (both were FDA-approved in 2017) and they are currently approved for multiple indications.

Gene therapies: Zolgensma and Luxturna are both in vivo therapies and are administered in an outpatient setting. In this analysis, "other costs" are defined as the day-of allowed costs less the list price of the therapy. While Zolgensma had the highest list price among the CGTs analyzed ($2.3 million, as of September 2024), we observed that Zolgensma's other day-of costs are only $600, on average, for commercial patients. Luxturna is also an in vivo therapy, typically administered via outpatient surgery on two different days (one day for each eye). For this reason, Luxturna has higher day-of administration costs, with an average of $29,100 allowed costs in total for the two days of administration.

Cell therapies: The six CAR-T therapies analyzed are ex vivo therapies administered in an inpatient setting. In this analysis, "other costs" are defined as the 60 days before and after treatment, as well as the day-of allowed costs, less the list price of the therapy. We include 60 days before and after to capture the expected length of time associated with pretreatment preparation and post treatment monitoring associated with these therapies. On average, the list price (as of September 2024) across the CAR-T therapies was $472,000, weighted by the observed count of cases for each therapy. For a commercial population, the average total cost of a cell therapy episode—defined as 60 days before and after treatment—was $739,000. Thus, there was an average of $267,000 of other costs incurred beyond the list price. Figure 3 presents the average costs associated with the episode for the cell therapies analyzed.

FIGURE 3: AVERAGE LIST PRICE AND OTHER* ALLOWED COSTS FOR CGT THERAPIES (2017-2023)



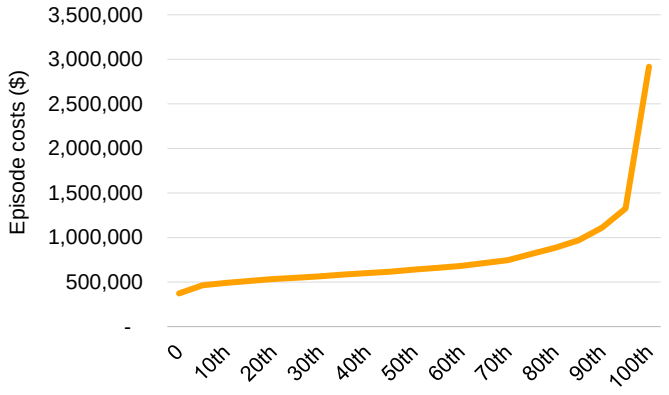
Analysis of 2017-2023 Milliman CHSD commercial claims data; Milliman DNA Gene and Cell Therapy Forecasting. List price as of September 2024.

* For Zolgensma and Luxturna, "other costs" includes costs from the day of treatment, less the list price. For CAR-T-total, "other costs" includes other medical allowed costs 60 days before and after treatment, including day-of costs above the list price.

10. Milliman DNA Gene and Cell Therapy Forecasting, op cit.

Figure 4 displays the total episode costs for the CAR-T therapies as percentiles. The total episode costs include other medical allowed costs 60 days before and after treatment, including costs of the treatment. Across all the cell therapies studied, approximately 10% of cases were above the $1 million threshold for the episode, but some cell therapies reached the $1 million threshold at the 75th percentile. The percentiles of CAR-T episode costs (including the cost of the therapy) were: 25th percentile: $549,000; 50th percentile: $640,500; 75th percentile: $817,000; 95th percentile: $1,300,000.

FIGURE 4: CAR-T THERAPIES: PERCENTILES OF TOTAL ALLOWED COSTS, INCLUDING ALLOWED COSTS FOR THE DAY OF TREATMENT, 60 DAYS BEFORE, AND 60 DAYS POST TREATMENT



Analysis of 2017-2023 Milliman CHSD commercial claims data; Milliman DNA Gene and Cell Therapy Forecasting. Graph includes all CAR-T therapies in the study. Costs include medical allowed costs 60 days before and after treatment, including day-of costs for the therapy and administration.

LEARNINGS FROM ASSESSING CGTS WITH CLAIMS ANALYTICS

Claims data can be a powerful resource for assessing the risk of CGTs in a population. Official code maintainers—e.g., the Centers for Medicare and Medicaid Services (CMS), the Centers for Disease Control and Prevention (CDC), and the American Medical Association (AMA)—establish ICD-10-PCS codes for specific product administration, create HCPCS and Current Procedural Terminology (CPT) codes, and provide coding guidelines associated with these codes. Coding and billing guides released by manufacturers are another resource that can be used for identifying recommended diagnosis, drug, and procedure codes for a particular CGT.

However, analyzing CGTs using claims data presents several challenges:

- Some rare diseases do not have an ICD-10 diagnosis code specific to the condition[11] and, as discussed previously, there are often clinical or eligibility criteria that are not observable in claims data. These limitations mean the diagnosed population captured from data is broader than the eligible population.
- Product-specific procedure codes are often not available until 12+ months after approval, making it difficult to analyze the first year of experience for a given CGT if a medical claim is not accompanied by a National Drug Code (NDC).
- Therapies administered in an inpatient setting are identifiable using an ICD-10 procedure code. However, until 2022, most CAR-T therapies were coded with a nonspecific ICD-10 procedure code in our claims analysis, complicating the ability to analyze specific products.

Best practices for evaluating CGTs

To effectively evaluate CGTs, it is best to use a cross-disciplinary team that includes clinical, analytical, financial, and payer perspectives. Monitoring the pipeline through clinical trials, manufacturer websites, and industry news sources helps identify and validate the expected number of therapies and the timing of approvals. It is also valuable to use claims data to identify the diagnosed population and assess historical experience for CGTs.

Claims data can help identify the diagnosed population for some conditions, but additional information is needed to refine these estimates, such as clinical trial data, evidence-based guidelines, and peer-reviewed journal articles. By combining these resources, stakeholders can develop a more accurate picture of the potential patient population and their eligibility for CGTs.

The landscape of CGTs is evolving, presenting both opportunities and uncertainties. By employing a comprehensive, multifaceted approach to estimating CGT case and cost exposure, stakeholders can navigate these complexities and make more informed decisions. The approach we presented in this white paper offers a practical framework adaptable to the unique challenges posed by conditions treated by CGTs. As the field of CGTs continues to advance, it is essential for stakeholders to stay informed and adapt their strategies to the changing landscape.

11. Kuester, M.K., Naber, J.M., & Smith, C.E. (August 2022). Prevalence of Rare Disease in a Commercial Population Using ICD-10 Diagnosis Codes. Milliman Report. Retrieved October 24, 2024, from https://www.milliman.com/en/insight/prevalence-of-rare-disease-in-a-commercial-population-icd10-diagnosis.

Limitations

This white paper outlines our approach to estimating CGT cases and costs; it is not intended to be an exhaustive study of ways to approach modeling CGTs.

In performing this analysis, we relied on publicly available research, Milliman Gene and Cell Therapy Forecasting, and Milliman CHSD. We have not audited or verified this data and other information. If the underlying data or information is inaccurate or incomplete, the results of our analysis may likewise be inaccurate or incomplete. We performed a limited review of the data used directly in our analysis for reasonableness and consistency and have not found material defects in the data. If there are material defects in the data, it is possible that they would be uncovered by a detailed, systematic review and comparison of the data to search for data values that are questionable or for relationships that are materially inconsistent. Such a review was beyond the scope of our assignment.

Guidelines issued by the American Academy of Actuaries require actuaries to include their professional qualifications in all actuarial communications. Jessica Naber is a member of the American Academy of Actuaries and meets the qualification standards for authoring this report.

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