MILLIMAN REPORT

Complexities in forecasting eligible cases and associated costs of cell and gene therapy

Beyond epidemiology, clinical trial criteria, and the science

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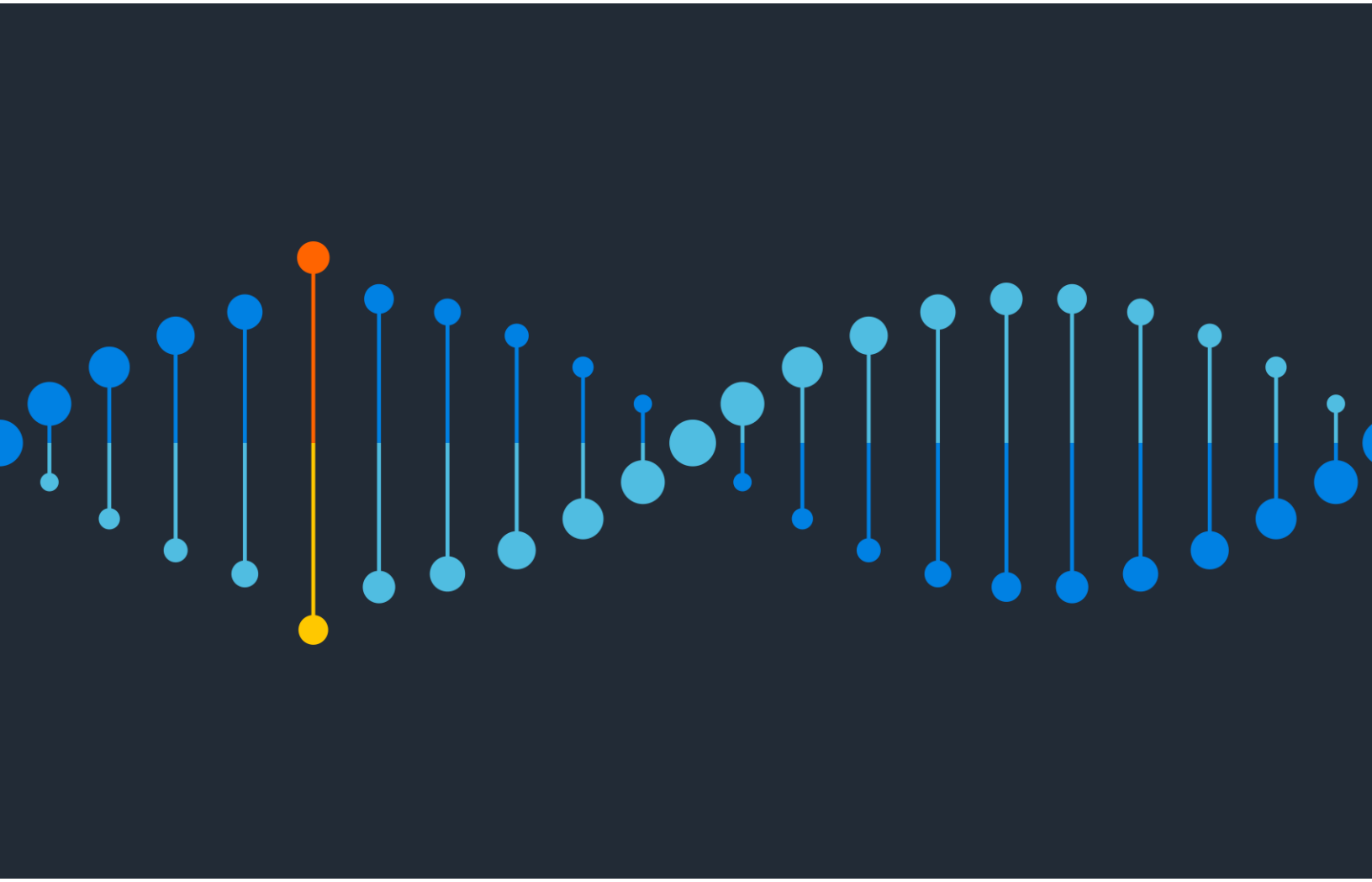
Brenda Cordell, MBA



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Cell and gene therapies (CGT) are a recurring topic for discussions on emerging risks and opportunities in the U.S. healthcare sector. These novel therapies represent incredible scientific advancements, offering hope for people suffering from rare diseases. CGT also bring considerable uncertainty to health plan and other payers' financial forecasts.

This material aims to share our experience in gathering evidence to help inform key components necessary for any financial forecast. Our perspective is limited to CGT dosed via a single episode for the treatment of rare diseases. These therapies present some of the greatest challenges with respect to forecasting. In most situations, a payer cannot confidently anticipate that a case for a given rare disease is coming in the next plan year; and, once the case has occurred, there will be no ongoing utilization of the CGT that can be used to build a trend forward. In short, a payer is perpetually in the same situation of being unable to rely on claims history to predict future exposure because of the rarity of these diseases, as most payers do not have a group large enough for a reliable prediction to be possible.

This material is arranged into five sections that can be read in any order:

Introduction to CGT: This section provides a brief overview of the science and a snapshot of the currently approved therapies for the most commonly used methods under the CGT umbrella: gene addition, gene editing, and gene-modified cell therapy.[1, 2, 3]

The remaining sections dive deep into 4 categories of complexities that make forecasting the potential number of cases, rate of treatment, and associated costs of CGT a challenge.

CGT pipeline identification: Identifying a complete and up-to-date list of all CGT in the market or with the potential to come to market is not trivial.

CGT approval timing and cost: Informing the anticipated timing of market entrance and the potential launch price of CGT that are not yet approved by the U.S. Food and Drug Administration (FDA) is a necessary component of the forecasting process.

CGT treatment-eligible population: Estimating the number of people in a population who may be eligible for treatment with a CGT is a necessary input to forecasting the number of potential cases.

CGT rate of treatment: Developing an expectation for the rate at which eligible patients will receive CGT in the first and subsequent years after FDA approval is critical to producing realistic forecasts of CGT financial exposure.

Introduction to CGT

This section provides a brief explanation of the three most commonly used methods associated with single-episode CGT: gene addition, gene editing, and gene-modified cell therapy.

Gene addition adds a working gene where the patient has a defective gene and/or defective copies of that gene.[4] The product may be administered *in vivo* or *ex vivo*, depending on the characteristics of the product. Roctavian™, approved for the treatment of hemophilia A, is an example of a gene therapy that is administered *in vivo*. *In vivo* administration means that the genetic material is delivered directly into the patient, via intravenous infusion (IV).[5] Although the manufacturer has provided evidence that Roctavian is disease-modifying, it is not known whether it is also curative. Only time will tell if the therapeutic benefit lasts for an extended number of years or a given patient's whole life. Lyfgenia™, approved for sickle cell disease (SCD), is an example of a gene therapy that is administered *ex vivo*. In this case the patient's own blood stem cells are extracted through apheresis, then these cells are genetically modified in a manufacturing process to produce a therapeutic factor, and then administered *ex vivo*, or transplanted, back into the patient.[6] A complete list of FDA-approved gene addition therapies is provided in the table in Figure 1.

FIGURE 1: FDA-APPROVED, SINGLE-ADMINISTRATION GENE ADDITION THERAPIES

THERAPY NAME	RARE CONDITION	FDA APPROVAL DATE	MANUFACTURER
Luxturna®[7]	Retinal Dystrophy	December 2017	Spark / Roche
Zolgensma®[8]	Spinal Muscular Atrophy (SMA)	May 2019	Novartis
Zynteglo®[9]	Beta Thalassemia	August 2022	bluebird bio
Skysona®[10]	Cerebral Adrenoleuko-dystrophy (CALD)	September 2022	bluebird bio
Hemgenix®[11]	Hemophilia B	November 2022	uniQure / BMS
Elevidys[12]	Duchenne Muscular Dystrophy (DMD)	June 2023	Sarepta Therapeutics
Roctavian™[13]	Hemophilia A	June 2023	BioMarin
Lyfgenia™[14]	Sickle Cell Disease (SCD)	December 2023	bluebird bio
Lenmeldy™[15]	Metachromatic Leukodystrophy (MLD)	March 2024	Orchard Therapeutics / Kiowa Kirin
Beqvez™[59]	Hemophilia B	April 2024	Pfizer

Note: Current as of May 31, 2024.

Gene editing involves splicing the defective gene and replacing it with a working gene. Clustered regularly interspaced short palindromic repeats (CRISPR) and CRISPR-associated protein 9 (Cas 9) are examples of this technology.[16] This type of therapy is administered *in vivo* also. These therapies are believed to have the potential to be curative.[17] As of May 2024, Casgevy™ is the only single-administration gene editing product approved by the FDA. It has been approved for two indications: SCD (December 2023) and beta thalassemia (January 2024).[18]

Gene-modified cell therapy is the most complicated of these three methods. The patient's own cells are extracted through leukapheresis, then these cells are genetically modified in a manufacturing process to produce a therapeutic factor, and then they are administered *ex vivo*, or transplanted back into the patient.[19] This requires a hospital stay for the cell extraction and the transplantation. Multiple technologies—e.g., T cell receptor natural killer (TCR-NK), chimeric antigen receptor macrophage (CAR-M), T cell antigen coupler (TAC-T)—are used to create genetically modified cell therapies, with chimeric antigen receptor-positive viable T cells (CAR-T) being the most commonly used.[20,21] Most CAR-T therapies treat liquid tumors such as leukemias, myelomas, and lymphomas.[21,22] A complete list of FDA-approved single-administration gene-modified CAR-T therapies is provided in the table in Figure 2.

FIGURE 2: FDA-APPROVED, SINGLE-ADMINISTRATION GENE-MODIFIED CAR-T THERAPIES

THERAPY NAME	RARE CONDITION	FDA APPROVAL DATE	MANUFACTURER
Kymriah®[23]	r/r Acute Lymphoblastic Leukemia (ALL)* 3L Diffuse, Large B-cell Lymphoma (DLBCL) 3L Follicular Lymphoma (FL)	August 2017 May 2018 May 2022	Novartis
Yescarta®[24]	3L DLBCL r/r FL 2L DLBCL	October 2017 March 2021 April 2022	Kite / Gilead
Tecartus®[25]	2L Mantle Cell Lymphoma (MCL) r/r ALL	July 2020 October 2021	Kite / Gilead
Breyanzi®[26]	3L DLBCL 2L DLBCL 3L+ Chronic Lymphocytic Leukemia (CLL) 3L FL 3L MCL	Feb. 2021 June 2022 March 2024 May 2024 May 2024	Juno Therapeutics / BMS
Abecma®[27]	5L Multiple Myeloma (MM) 3L MM	March 2021 April 2024	2seventy bio / BMS
Carvykti®[28]	5L MM 2L MM	February 2022 April 2024	J&J / Legend Biotech

r/r = relapsed or refractory
* Patients 25 years of age or younger.
Note: Current as of May 31, 2024.

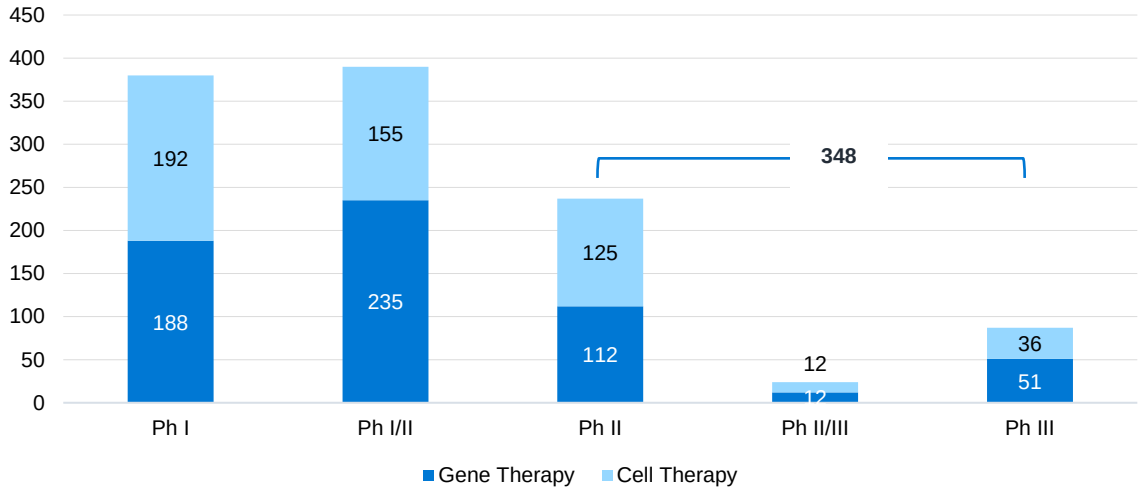
CGT pipeline identification

Identifying a complete and up-to-date list of all CGT in the market or with the potential to come to market is not trivial.

Tackling this complexity is a continuous process that begins with the identification of CGT that have the potential to reach the market in the next three to five years. Referencing publicly available sources of information that are complete, credible, reliable, and up-to-date is critical to this process. Of those necessary characteristics, "complete" is the reason it is nontrivial to create the list of CGT that have the potential to come to market. There is no source that publishes a complete list.

However, there are sources that can be utilized to compile a complete list. For example, the Alliance for Regenerative Medicine (ARM), an international advocacy organization, produces a report that can be used to set the parameter of how many CGT may need to be researched.[29] The report tracks the number of CGT by clinical trial phase (globally), with updates available on a quarterly basis, shown in Figure 3.

FIGURE 3: CGT IN CLINICAL DEVELOPMENT – BASED ON THE ALLIANCE FOR REGENERATIVE MEDICINE Q1 2024 REPORT[30]



Adapted from the Alliance from Regenerative Medicine website

According to the sources used by ARM, there are potentially 348 therapies to research and track that have the potential to come to market in the next three to five years (those shown within the bracket in Figure 3), rather than just the 87 that are in Phase III clinical trials. We need to consider CGT that are not yet in a Phase III clinical trial because, under certain circumstances, the FDA may consider the Phase II clinical trial a pivotal trial upon which an approval could be based.[31]

Other information in this same report can be used to reduce this number of CGT to reflect only those that are (1) in a pivotal trial in the United States (or another market where the FDA has agreed to evaluate the data), and (2) being investigated for a rare disease. By limiting it to those in U.S. clinical trials, there are 182 therapies in Phase II, 21 in Phase II or III, and 71 in Phase III, for a total of 274.[30] By narrowing this down to therapies targeting rare disease, the number is further reduced to 215.[30]

A wide range of stakeholders attempt to publish comprehensive lists and reports of CGT: pharmacy benefit managers (PBMs), health insurance companies, think tanks, rare disease advocacy groups, Wall Street analysts, and consultants. Although many of these lists or reports have merit and some contain valuable information about the CGT identified, there is no single source that lists all 215 CGT, nor all the data needed to evaluate each therapy. Most sources limit their list to the CGT that are likely to be approved in the next six to 12 months; and many of these lists are out of date as soon as they are published due to the rapid pace at which development of cell and gene therapies changes.

Because of the information gaps in publicly available sources, our research team within Milliman was determined to find a robust method to not only identify, but also to continuously monitor reliable and verifiable sources from which to extract the data necessary to ensure this information is comprehensive. After years of conducting this research and reviewing dozens of sources, our team has narrowed down these sources to four main types of publications and websites.

- **ClinicalTrials.gov.**[32] An official website of the federal government that is run by the National Library of Medicine, National Center for Biotechnology Information.[32] It includes a web-enabled, searchable database where all FDA clinical trial information is maintained. It can be searched to find individual CGT and specific information about the clinical trials, such as clinical trial status. Clinical trial status indicates whether a clinical trial is suspended or on hold (by the manufacturer or the FDA), completed, still recruiting patients, or has been terminated. This can be used to further reduce the list of potential CGT to those actively under study. Between selected searches in this database and the source listed below, CGT that are not single-administration can also be ruled out, further decreasing the number of therapies.
- **Manufacturer websites.** Most websites divulge the manufacturer pipeline, investor presentations, and press releases. *The pipeline and investor presentations* help identify whether individual CGT observed in the clinical trial database are still actively in development by the manufacturer. It is not uncommon to see one listed in the clinical trial database that the manufacturer has stopped pursuing. *Press releases* are often a good source for the estimated or actual Biologics License Application (BLA)[33] date, which is the date the manufacturer files its clinical trial data package with the FDA for review and potential approval. Press releases are often also produced when the FDA has announced the Prescription Drug User Fee Act (PDUFA) date. The PDUFA date, set by the FDA, is the date it expects to make a decision on the data package submitted: approval, rejection, or extension—extension means the FDA requires more information.[34] Most people have become accustomed to thinking of PDUFA as the approval date, but this is not necessarily true. For example, Onpattro, a gene-silencing drug for Transthyretin Amyloid Cardiomyopathy (ATTR-CM), was rejected by the FDA at its PDUFA in October 2023.[35]

  After a review of the first two sources, the number of potential CGT is refined from 215 to 185.

> The **BLA** date is the date the manufacturer files their clinical trial data package with the FDA for review and potential approval.
>
> The **PDUFA** date, set by the FDA, is the date it expects to decide on the data package submitted: approval, rejection, or extension – extension means the FDA requires more information.

- **U.S. Securities and Exchange Commission (SEC**).[36] The Electronic Data Gathering, Analysis, and Retrieval System (EDGAR) is another federal government website that is a searchable database, referred to as "Edgar."[36] It is a very important source because manufacturers whose stock is publicly traded are required to file financial reports on a quarterly basis with the SEC. Unlike investor presentations, quarterly and annual reports of publicly traded manufacturers are regulated in terms of what they are required to disclose. Anything that is a material event must be disclosed so that shareholders are provided with adequate information to make investment decisions Although our team regularly reviews each manufacturer's pipeline and investor presentations to get an up-to-date view of the CGTs in development, we have encountered several instances over the past few years where a CGT was removed from the pipeline without any explanation provided in press releases, investor presentations, or on the company's website. The SEC-required reports typically include reasons for the CGT no longer being listed in the pipeline. The details are usually found in the notes to a financial table. An often-cited reason for discontinuation of a specific cell or gene therapy is lack of funding from a partner company or other investors; however, there can be other reasons as well.
- **Limited selection of publicly available sources.** This category includes multiple industry CGT or biopharma news sources, rare disease advocacy websites, posters and podium presentations from medical conferences, the FDA website, and peer-reviewed journal articles (about the science, the disease state and the CGT).

Once the data supporting each of the 185 cell and gene therapies (CGTs) has been gathered from the four sources, it must be validated. This involves cross-checking the information to ensure its reliability by comparing it across these four categories of sources whenever possible. This process includes reconciling any discrepancies between sources and identifying errors or omissions in the statements or articles. Ultimately, we need to verify the accuracy of the information against the manufacturer's statements. We generally begin with information provided by the manufacturer as they are the closest to the specific CGT being analyzed and often possess proprietary knowledge about the science involved (e.g., the CGT platform or the synthetic viral vector).

Based on the validated information, the number of cell and gene therapies (CGTs) that need to be monitored for FDA approval timing and the likelihood of approval is fewer than 185. For discussion purposes, we will assume this number is reduced to 145.

CGT approval timing and cost

Informing the anticipated timing of market entrance and the potential launch prices of cell and gene therapies that are not yet FDA-approved is a necessary component of the forecasting process.

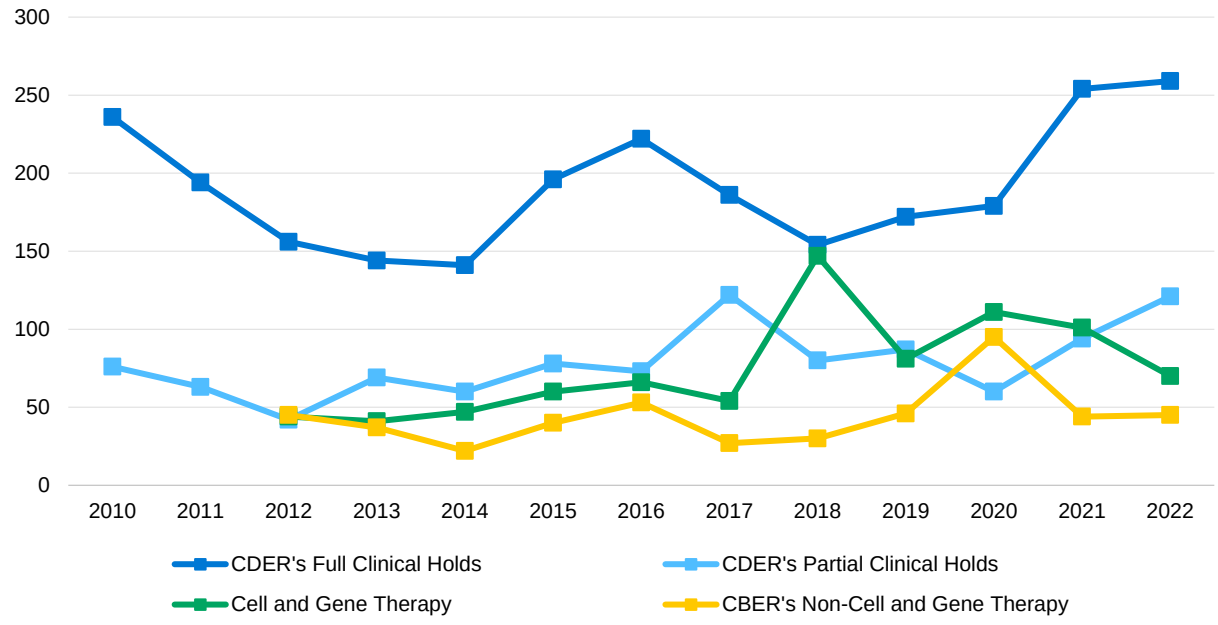
MONITORING TIMING OF FDA APPROVAL

As mentioned previously, it's important to recognize that not all 145 CGT will necessarily receive FDA approval or be brought to market by the manufacturer, due to various reasons. Similarly, the estimated timing for each of the 145 CGT to reach the market—based on BLA or PDUFA dates—should not be assumed to remain unchanged. In fact, some of the CGT we are currently monitoring might never be marketed This is exactly why tracking progress is essential. This invovles monitoring (1) clinical trial status, (2) FDA designations and expedited approval, 3) manufacturer funding, launch readiness, and BLA filing.

1. Clinical trial status

Figure 4 is illustrative of one of the factors that can affect when or if a therapy comes to market: the FDA has the authority to suspend a clinical trial, either temporarily or permanently. Overall, 40% of all FDA clinical holds in recent years have involved CGT clinical trials, although these therapies constitute a much smaller portion (likely around 8%) of all drugs in development.[37]

FIGURE 4: COMPARISON OF CGT CLINICAL TRIAL HOLDS VS. NON-CGT THERAPY, 2010 - 2022[38]



Data source: FDA

The yellow line in Figure 4 represents biologic therapies and the green line represents CGT. One of the viral vectors that has been associated with many CGT suspensions of is the lentivirus, which is used in both cell and gene therapy.[39] Bluebird bio has had three lentivirus-based therapies (Zynteglo, Skysona, and Lyfgenia) put on clinical hold as a result of at least one patient in each trial developing myelodysplastic syndrome (MDS).[40,41,42] In each case the trial resumed and each product was eventually approved by the FDA, but with a substantial delay.

2. FDA designations and expedited approval

The FDA created multiple designations to incentivize the development of drugs, in particular those for rare diseases with high unmet need.[43] Some have tax incentives for the manufacturer, such as the orphan drug designation, while others can impact the timing of the drug development and review process.[44] Figure 5 includes the four that can affect FDA approval timing: fast track, breakthrough therapy, accelerated approval, and priority review. Although all CGT that have come to market have had some special designation, not all affect timing.

Manufacturers, the FDA, and rare disease advocacy groups typically issue press releases when the FDA has awarded a designation. It should be noted that these designations are specific to not only the CGT, but also the indication. Several CAR-T therapies are FDA-approved for multiple indications, but the indications did not always share the same designations and therefore have followed different timing with respect to the speed of FDA approval and market entrance.

The FDA has also instituted a new office called the Office of Pediatric Therapeutics (OPT), which is 75% to 80% staffed as of early 2024.[45,46] It seeks to enable more therapies for pediatric rare diseases to come to market in expedited fashion, while at the same time allowing the time needed for safety reviews and interactions between the FDA and the CGT manufacturers. One of the goals of OPT is to reduce the number of therapies on clinical hold. In addition, Peter Marks, director of the FDA's Center for Biologics Evaluation and Research (CBER), publicly stated that the FDA intends to rely more heavily on the accelerated approval pathway for CGT, via a new pilot program called Support for Clinical Trials Advancing Rare Disease Therapeutics (START).[47]

FIGURE 5: FDA DESIGNATIONS WITH POTENTIAL IMPACT ON SPEED AND TIMING OF FDA APPROVAL

Fast track	>	Fast track is a process designed to facilitate the development and expedite the review of drugs to treat serious conditions and fill an unmet medical need.
Breakthrough therapy	>	A process designed to expedite the development and review of drugs which may demonstrate substantial improvement over available therapy.
Accelerated approval	>	These regulations allowed drugs for serious conditions that filled an unmet medical need to be approved based on a surrogate endpoint.
Priority review	>	A Priority Review designation means FDA's goal is to take action on an application within 6 months.

Source: FDA

3. Manufacturer funding, launch readiness and BLA filing

Timing of FDA approval extends beyond success of the pivotal clinical trial. Additional uncertainty arises from other factors such as funding that allows the manufacturer to build capacity and the capability to produce an adequate volume of product that meets the FDA's current good manufacturing practice (CGMP) regulations.[48] Lack of information about these elements can impair the accuracy of predicting the timing of the potential FDA approval date (PDUFA), as well as when the first patient is likely to receive therapy after approval (discussed in more detail in another section of this paper). In fact, it may even jeopardize the therapy coming to market at all.

As stated above, we have observed that several therapies over the past four to five years, in Phase II clinical trials that appeared promising in investor presentations, disappeared with no mention at all in a succeeding quarter's presentation. Although an investor presentation or press release may mention that development is contingent on funding from an investor or partner, the SEC reports provide more detail regarding the degree of reliance on that funding for a therapy to continue in its clinical development. The SEC reports also contain more specifics regarding reliance on outside funding for building manufacturing capabilities, ramping up capacity for real-world demand, and the development of qualified treatment centers (QTCs) where patients will be treated. When a manufacturer lists this contingency in their investor presentations, it helps us more accurately inform the likelihood and timing of continuation through FDA submission and approval and through production after approval.

The manufacturer may suggest the month, quarter, or half of the year that it is targeting for filing its BLA with the FDA. Typically, this information is found in investor presentations and/or press releases. Combining this data with an understanding of the FDA designations the CGT has received can help estimate the projected PDUFA date before the FDA officially assigns it. The other factors mentioned above can help us further inform the post-PDUFA timing as to when we expect the CGT to be available in the market for patients.

POTENTIAL LAUNCH PRICE AND ASSOCIATED COSTS

One of the most sought-after pieces of information is the launch price estimate for a new CGT, particularly when there is no existing treatment for the rare disease in question and no claims data to reference. Prior to the advent of CGT, manufacturers rarely signaled list price in advance of FDA approval. However, many of the CGT manufacturers have begun to signal a potential price range months in advance of launch. They do this, in their words, to provide context for the value of the therapy they are bringing to market.[49] However, even when they engage in signaling, it can be misleading. Four case studies bear this out.

CASE STUDY 1: PRICE MAY DIFFER GREATLY ACROSS CGT FOR A RARE DISEASE

BioMarin was expected to launch the first gene therapy for hemophilia A (Valrox) in 2020 and made a price announcement several months in advance that it expected to price Valrox between $2 millin and $3 million.[50] The FDA, however, did not approve it on the 2020 PDUFA date, and instead asked BioMarin for two more years of data in order to validate the durability of the therapy. That delay allowed another manufacturer (CSL Behring) the opportunity to launch the first gene therapy for hemophilia. Hemgenix was approved in the United States in November 2022 for hemophilia B, launching at a price of $3.5 million, $500,000 higher than the top of BioMarin's announced price range. When BioMarin finally gained FDA approval in June 2023, it launched Roctavian (formerly Valrox) at $2.9 million, staying within the price range it had signaled to the market back in 2000, even though CSL Behring had launched at $500,000 higher.

CASE STUDY 2: SCIENCE MAY NOT DEFINE THE VALUE AND THE PRICE

Casgevy (CRISPR) and Lyfgenia (gene addition) are both approved for sickle cell disease (SCD) and received FDA approval on the same date in December 2023. Casgevy is a gene editing therapy where the defective gene is spliced out and replaced with a functional gene, whereas Lyfgenia delivers a functional hemoglobin subunit beta (HBB) gene without splicing out the defective gene. Prior to FDA approval of Lyfgenia, bluebird bio stated in interviews that Lyfgenia has the potential to "reduce a lifetime of economic and societal burden."[51] Whereas Vertex, prior to FDA approval of Casgevy, stated in a press release that market research suggested that physicians had a strong preference for its approach (gene editing) versus bluebird bio's approach (other potentially curative approaches).[52] Interestingly, Vertex priced Casgevy nearly a million dollars lower, per patient, at $2.2 million relative to bluebird bio's list price for Lyfgenia ($3.1 million).[53]

CASE STUDY 3: ICER REPORTS DO NOT DICTATE LAUNCH PRICE

Six months prior to FDA approval of Lenmeldy for metachromatic leukodystrophy (MLD), the Institute for Clinical and Economic Review (ICER) made its analysis public (September 2023), suggesting that Lenmeldy would be cost-effective "across all patient subpopulations for MLD" if priced within the range of $2.3 million and $3.9 million per patient.[54] The manufacturer, Orchard Therapeutics, announced a price of $4.25 million per patient shortly after FDA approval in March 2024, going not only beyond ICER's recommended range, but giving it the notoriety of being the world's most expensive pharmaceutical therapy in history.[55]

CASE STUDY 4: PRICE OF PREVIOUS INDICATIONS MAY NOT INFORM THE PRICE OF THE NEXT

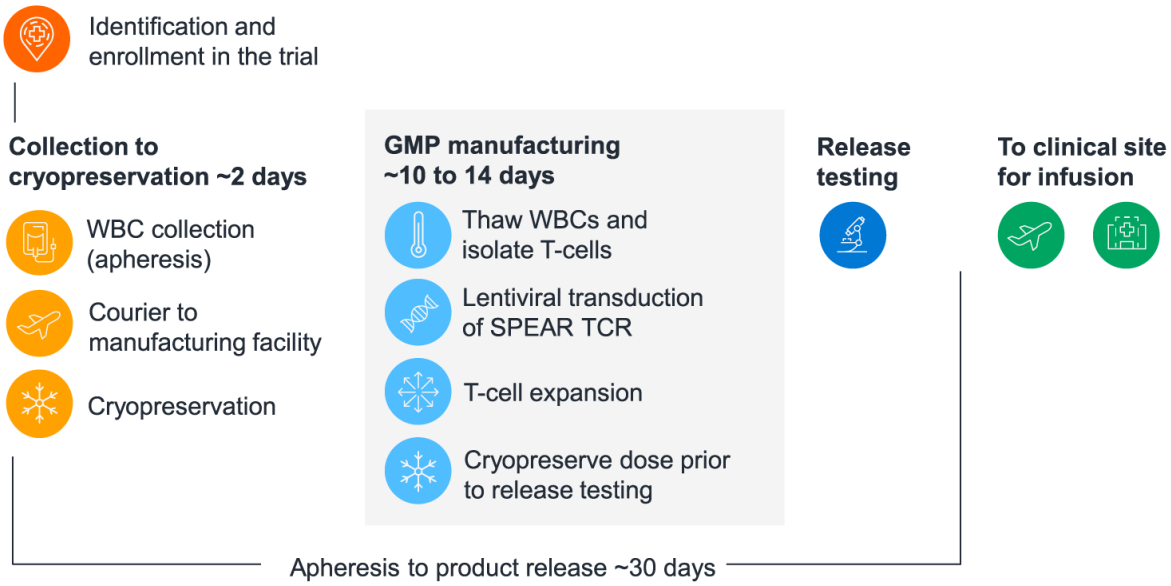
In August 2017, Novartis introduced Kymriah, the first CAR-T therapy approved in the U.S., for r/r acute lymphoblastic leukemia (ALL) in patients aged 25 or younger, priced at $475,000 per patient. In 2018, they launched Kymriah's second indication (adults with r/r diffuse, large B-cell lymphoma) at a price of $373,000 per patient, which was $102,000 less than the initial list price. This matched the price of Kite's Yescarta which had been approved by the FDA for the same indication seven months earlier. Novartis disclosed that the price of the pediatric leukemia indication reflected its assessment that Kymriah is even more valuable for the pediatric population, and they used "indication-specific" pricing to avoid overpricing Kymriah for the adult lymphoma indication.[56]

Two other aspects of cost that can be difficult to determine or predict in advance of FDA approval are (1) the cost of associated administration of the CGT, and (2) the timing and level of postlaunch price increases.

1. Cost of administration

As a general rule, the majority of the cost exposure is the cost of the therapy itself for gene therapy that is administered *in vivo*. For *ex vivo* therapies, including CAR-T or any gene therapy where apheresis is a necessary part of the process, the cost of the therapy is only one component of the cost due to the process the patient must undergo. Figure 6 is how the manufacturer of one of these therapies defines the patient journey in a prelaunch corporate presentation. As seen in the exhibit, approximately 30 days elapse between the patient preparation required before the patient's bone marrow is harvested and preparing the patient to receive the therapy.[57]

FIGURE 6: PATIENT JOURNEY EXAMPLE – SINGLE ADMINISTRATION EX VIVO CGT



Data source: Adaptimmune Corporate Presentation

Some of the elements of the patient journey shown in Figure 6 involve cost to the payer, and there are other costs the payer may be responsible for that are not shown here. Figure 7, extracted from a study published in the Journal of Managed Care Pharmacy, provides a snapshot of some of the codes and costs that may be involved for another *ex vivo* therapy.[58] Note that the products in Figure 6 and Figure 7 are not the same.

FIGURE 7: ASSOCIATED COSTS EXAMPLE – SINGLE ADMINISTRATION EX VIVO CGT

	VALUE, $	
ECONOMIC INPUT	**ACADEMIC INPATIENT HOSPITAL**	**NONACADEMIC SPECIALTY ONCOLOGY NETWORK**
Drug costs		
CAR T cell	373,000	373,000
Lymphodepletion	1578	1578
Tocilizumab	4368	4368
Dexamethasone	2.5	2.5
Filgrastim	315	315
Procedure costs (OPPS HCPCS code)		
Radiography (71045)	76	22
EEG (95812)	445	330
ECG (833531)	656	239
Lumber puncture (62272)	117	87
MRI (70552)	441	327
1-h chemotherapy administration (96413)	364	144
CAR T-cell administration (38241)	313	176
Facility costs		
ICU day	6546	6546
Inpatient day	2668	2668
Nonacademic specialty oncology network visit	NA	74

Data source: American Journal of Managed Care

2. Postlaunch price increases

Initially, none of the CGT increased their price for multiple years after their launch, unlike most other pharmaceutical products. However, most manufacturers have now taken price increases, and some have done so multiple times. Figure 8 shows the price trajectory for the CGT that were previously discussed in this paper. Three observations emerge from this analysis:

- **First**, manufacturers of CAR-Ts have consistently raised prices since Kite took the first ever price increase (for both of their products) for any CGT, in April 2021. Although this was three and a half years after the first launch, they have consistently increased prices on an annual basis since then.
- **Second**, only two gene therapy manufacturers have increased prices. Zolgensma's price increase follows the pattern established by Novartis for its CAR-T therapies—three increases since 2022, but at slightly less than half the percentage. Luxturna, the only other gene therapy that has increased price since launch, has done so only once for a net increase of one-third that of the cumulative increases for the CAR-Ts.

- **Third**, manufacturers appear to be consistent across their CGT in terms of the price increase percentage, e.g., BMS has increased the price of both Abecma and Breyanzi since launch by 18.8%. However, Kite's price increased 13.7% over the first two increases (note that the second increase is not shown in Figure 8 for Yescarta, which was 13.7% cumulatively over two increases).

These observations help define expectations by shedding light on what may drive the frequency and rate of increase for CGT in the future as they appear to be tied to type of therapy and the manufacturer's strategy.

FIGURE 8: COMPARISON OF LAUNCH AND CURRENT CGT PRICES

PRODUCT / MFGR.	INDICATION	FDA APPROVAL DATE	LIST PRICE AT FDA APPROVAL	DATE OF FIRST PRICE INCREASE	NEW LIST PRICE	CURRENT LIST PRICE	# OF PRICE INC. SINCE FDA APPROVAL	% INC. SINCE FDA APPROVAL
Luxturna®* / Spark	Retinal Dystrophy	Dec. 2017	$425,000	Apr. 2024	$456,875	$456,875	1	7.5%
Kymriah® / Novartis**	r/r ALL (≤ 25 years)	Aug. 2017	$475,000	Apr. 2022	$508,250	$581,895	3	22.5%
Yescarta®±¥ / Kite	3L DLBCL	Oct. 2017	$373,000	Apr. 2021	$399,000	$462,000	3	23.9%
Kymriah® / Novartis**	3L DLBCL	May 2018	$373,000	Apr. 2022	$399,110	$456,941	3	22.5%
Zolgensma® / Novartis	SMA	May 2019	$2,125,000	Nov. 2022	$2,188,750	$2,322,044	3	9.3%
Tecartus®¥ / Kite	2L MCL	Jul. 2020	$373,000	Apr. 2021	$399,000	$424,000	2	13.7%
Abecma®¥ / BMS	5L MM	Mar. 2021	$419,500	Jan. 2023	$457,255	$498,408	2	18.8%
Breyanzi®¥ / BMS	3L DLBCL	Feb. 2021	$410,300	Jan. 2023	$447,227	$487,477	2	18.8%
Carvykti®¥ / Janssen	5L MM	Feb. 2022	$465,000	Mar. 2023	$478,950	$522,055	2	12.3%
Zynteglo® / bluebird bio	Beta Thal.	Aug. 2022	$2,800,000	N/A	N/A	$2,800,000	0	N/A
Skysona® / bluebird bio	CALD	Sept. 2022	$3,000,000	N/A	N/A	$3,000,000	0	N/A
Hemgenix® / CSL Behring	Hem. B	Nov. 2022	$3,5000,00	N/A	N/A	$3,500,000	0	N/A
Elevidys / Sarepta	DMD	June 2023	$3,200,000	N/A	N/A	$3,200,000	0	N/A
Roctavian™ / BioMarin	Hem. A	June 2023	$2,900,000	N/A	N/A	$2,900,000	0	N/A
Lyfgenia™ bluebird bio	SCD	Dec. 2023	$3,100,000	N/A	N/A	$3,100,000	0	N/A
Lenmeldy™ / Orchard	MLD	Mar. 2024	$4,250,000	N/A	N/A	$4,250,000	0	N/A
Beqvez™ / Pfizer	Hem. B	Apr. 2024	$3,500,000	N/A	N/A	$3,500,000	0	N/A

Source: Milliman proprietary data.

* Price is per eye.

** Kymriah launched with indication-specific pricing. Each indication's price trajectory is tracked individually.

± Kymriah was also approved for 3L FL in May 2022, but did not price that indication differently from those already approved.

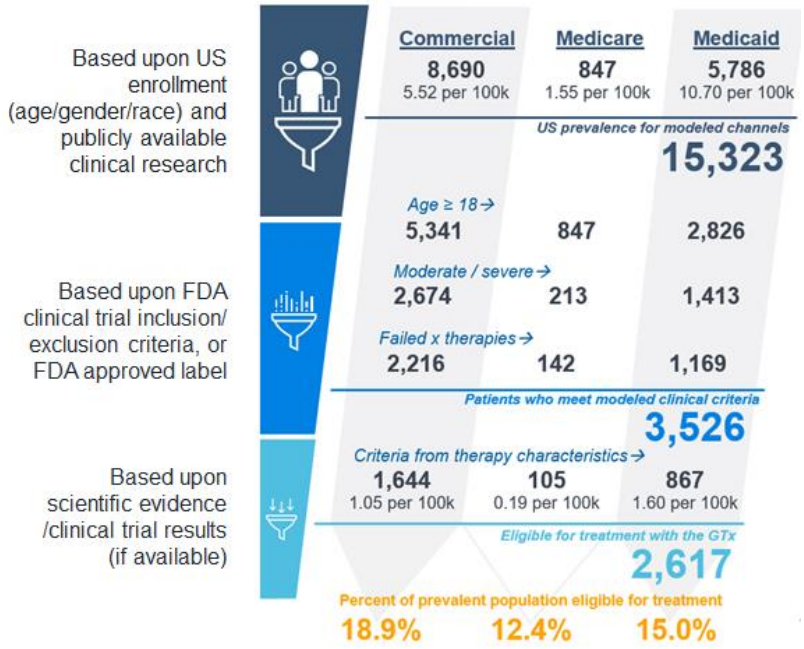
¥ The product has other indications with the same price as initially launched product.

CGT treatment-eligible population

Estimating the number of people in a population who may be eligible for CGT is a necessary input to forecasting the number of potential cases. Many rare diseases have no disease-specific ICD-10 diagnosis code, and therefore no claims data, that could provide a starting place for estimating potentially eligible patients. It is important to note that, although claims data could be available for some rare diseases (e.g., hemophilia A and B) to identify the diagnosed population, the diagnosis codes would fall short in differentiating patients based upon many other relevant criteria that refine the population to those who would be considered treatment-eligible for a particular CGT.

Given this complexity, our team established a methodology that individual CGT in the pipeline undergoes to develop initial estimates of treatment-eligible populations. Estimates resulting from this process for a hypothetical CGT are shown in Figure 9.

FIGURE 9: CGT PATIENT FUNNEL TO ESTIMATE POTENTIAL CGT TREATMENT-ELIGIBLE POPULATION



Source: Milliman DNA.

As part of this process, our research team reviews published peer-reviewed journal articles, clinical and scientific studies, and other credible sources to find the U.S.-specific prevalence and incidence of the rare disease, quantifiable clinical trial criteria, and quantifiable aspects of the CGT themselves in order to inform the treatment-eligible population by payer channel:

- **As seen in the dark blue area** at the top of the funnel in Figure 9, the estimate begins with nuances about the rare disease that the CGT would treat such as type, severity, or specific gene mutation. For example, spinal muscular atrophy (SMA) has types 0 through 4, but Zolgensma's labeled indication is to treat only types 0 and 1. The birth prevalence must be drawn down from total SMA to include only those types.

- **Next, in the medium blue area** in the middle of the funnel in Figure 9, we assess the product's clinical trial protocol to see how patients were qualified to receive treatment and also those who were excluded from treatment. It should be noted that, after FDA approval, adjustments to these figures may be necessary because the FDA has, in the past, stipulated differentiators in the labeled indication that differed from characteristics in the clinical trial (e.g., increasing/decreasing eligible age, severity, or type). We further refine the estimate based on those criteria that are quantifiable using reliable data sources.
- **And, finally, in the light blue portion** at the bottom of the funnel in Figure 9, a percentage of patients are further ruled out if there are ineligible patients due to immunogenicity or other characteristics associated with the delivery method of the CGT or the characteristics specific to the CGT themselves that make it more likely or less likely for the therapy to work or not work. For example, scientific studies or the manufacturer's clinical trial may indicate that a certain serotype of an adeno-associated virus (AAV) may be less likely to work in a percentage of patients. When this is the case, and we have credible data, we are able to further refine the estimates. To date, however, only Roctavian and Beqvez have this included in their labeled indications. Roctavian's label states that only adults with hemophilia A who do not have preexisting antibodies to adeno-associated virus serotype 5 detected by an FDA-approved test are eligible for treatment, and the Beqvez label states that eligible patients "[d]o not have neutralizing antibodies to adeno-associated virus serotype Rh74var (AAVRh74var) capsid as detected by an FDA-approved test."[59]

CGT rate of treatment

Developing an expectation for the rate at which eligible patients will receive CGT in the first and subsequent years after FDA approval is critical to producing realistic forecasts of CGT financial exposure. Multiple factors come into play that make this a challenge. Some are a result of the characteristics of the CGT, while others are controlled by the manufacturer or the FDA, and still others are dependent upon patient and physician preferences. In addition, even when the FDA approval date is known, the date that the first eligible patient is treated with individual CGT typically lags weeks or months due to several factors. These factors can also limit the number of patients who will initially be treated after approval. The factors include: (1) CGT product characteristics, (2) availability of qualified treatment centers, (3) manufacturing readiness and capacity, and (4) patient and provider willingness to adopt CGT.

CGT PRODUCT CHARACTERISTICS

Characteristics of the CGT can impact how soon the first eligible patient receives the therapy and how many patients may be treated. Whether or not the therapy involves a process where cells are extracted from the patient (autologous) or a donor (allogenic) prior to receiving the CGT is a factor that directly influences how long it will take for an identified patient to be administered certain CGT. The therapies in the first two columns have an inherently greater chance of delay between FDA approval and when the first patient can be infused with the therapy because they require the patient to go through leukapheresis (white blood cells extraction) or apheresis (stem cells extraction) or, in the case of Omisirge, donor-derived hematopoietic stem cell extraction. In all three cases the extracted material is then combined with the cell or gene therapy before it is infused into the patient.

FIGURE 10: CELL AND GENE THERAPIES – IN MARKET OR EXPECTED TO BE APPROVED IN 2024

CAR-T THERAPY WITH LEUKAPHERESIS (EX VIVO)	GENE THERAPY/CRISPR WITH APHERESIS (EX VIVO)	GENE THERAPY WITHOUT APHERESIS (IN VIVO)
KYMRIAH[60]	ZYNTEGLO[61]	LUXTURNA[62]
TECARTUS[25]	SKYSONA[63]	ZOLGENSMA[64]
BREYANZI[65]	CASGEVY[66]	HEMGENIX[67]
YESCARTA[68]	LYFGENIA[6]	ELEVIDYS[69]
CARVYKTI[70]	LENMELDY[15]	ROCTAVIAN[71]
ABECMA[72]	KRESLADI[73]	BEQVEZ[74]
obe-cel[75]	Cell Therapy with donor apheresis (ex-vivo)	UPSTAZA[76]
	OMISIRGE[77]*	LUMEVOQ[78]

* Hematopoietic stem cells (HSCs) derived from donor cord blood.

Not only does this process take weeks or months, but it also involves significant risk, as some patients will experience adverse reactions during the leukapheresis or apheresis process and will not proceed to infusion; or other issues with the extraction or with the material extracted may prevent the stem cells or white blood cells from being combined with the CGT. Based on the information sourced from the manufacturers, it can take weeks, and sometimes months, before the patient is infused with the products in the first two columns of the list in Figure 10.

The products in the third column of Figure 10 are administered into the patient via injection, infusion, or surgically (*in vivo*) and are not subject to this more complicated manufacturing process, but some have treatment-specific requirements, beyond liver enzyme tests, that can delay the administration. Genetic testing that confirms a diagnosis is necessary before a patient receives Luxturna or Zolgensma is necessary, and Luxturna also requires confirmation of retinal viability.[79,80] Roctavian, Beqvez, and Zolgensma require that patients be tested to confirm that they do not have neutralizing antibodies to the adeno-associated virus serotype for specific CGT in order to qualify for infusion.[81,82,83] Hemgenix, Roctavian, and Beqvez all require patients to be tested for coagulation factor inhibitors.[84,85,86]

AVAILABILITY OF QUALIFIED TREATMENT CENTERS

There is variability in the approach used by manufacturers regarding the establishment of qualified treatment centers (QTCs). This variability includes geographic availability, how many will be established prior to FDA approval, and the rate at which sites will be activated (i.e., executed master services agreement between the site and the manufacturer) in the years after approval. Most manufacturers have taken a staged approach where they plan for targeted numbers of centers each year that they will activate. And, in many cases, no sites were up and running or only the clinical trial site was up and running at the time of FDA approval, which limited the number of patients who were initially treated and also delayed when the first patient was treated.

This was observed in the case of bluebird bio's three gene therapies: Skysona for an ultra-orphan neurologic condition called cerebral adrenoleukodystrophy (CALD) and two others for blood disorders, Zynteglo for transfusion dependent thalassemia (TDT)and Lyfgenia for sickle cell disease (SCD). Skysona and Zynteglo were approved one month apart in the fall of 2022 with neither having sites up and running at FDA approval. Although each had at least one site up and running within 1-2 months of FDA approval, both experienced a delay of 6-7 months before the first patient was treated.[87] Likewise, Lyfgenia experienced a delay of more than 5 months before the first patient went through cell-extraction, even though it leverages Zynteglo's centers, which were up and running at Lyfengia's FDA approval (should have Lygenia and Dunleavy).[88, 89] Bluebird and the other manufacturers requires that a prospective treatment center and any physician that will potentially administer their CGT go through the manufacturer's authorization process, so this appears to be a function of bluebird's market readiness as there was delay across all three therapies regarding time to first patient treated.

The number of activated sites and geographic penetration is not consistent across bluebird bio's products. This appears to more a function of types of rare disease being treated, as Zynteglo and Lyfgenia now have 64 sites activated across the United States, whereas there are only nine sites activated for Skysona, located in California, Dallas, Minneapolis, and New England.[90,91,92]

In contrast to bluebird bio's approach, Vertex/CRISPR had nine centers activated at the FDA approval of Casgevy, which was approved for SCD on the same day as Lyfgenia.[93] Just like Lyfgenia, the first Casgevy patient did not go through cell collection until more than five months after FDA approval. At the time of writing this report, five patients have started apheresis for Casgevy, whereas only one has started the process for Lyfgenia even though Casgevy has 18 centers activated compared to Lyfgenia's 64. Patient and provider preference may be responsible for the fivefold difference in the number of Casgevy patients versus Lyfgenia patients, given that Casgevy is nearly $1 million cheaper than Lyfgenia.

It should be noted that the neither the first FDA approved CAR-T, Kymriah (in August 2017 for r/r ALL), nor the first FDA-approved gene therapy, Luxturna (in December 2017 for inherited retinal disease due to mutation in the retinal pigment epithelium-specific 65 gene), had centers up and running at FDA approval and several months passed before the first patient was treated in either case.[94,95] One of the main differences between CAR-T and gene therapy that impacts how soon and how many patients can be treated, in general, is the number of centers that will be available in total and how far-reaching the geographic availability of the centers are. Both are significantly greater for CAR-T than for gene therapies (e.g., 172 authorized centers for Kymriah vs. 83 for Zolgensma).[96] This may be a function of CAR-Ts being indicated for treatment of cancers, while gene therapies are indicated for rare diseases that may be ultra-orphan, and therefore address significantly fewer patients. Given that each of the CAR-Ts has multiple FDA-approved or pending indications, patients for each successive indication have a jump-start on beginning the leukapheresis process as soon as the date of FDA approval because the centers are already up and running for the therapy, which may result in shorter delays in the time to first patient treated for new CAR-T indications.

MANUFACTURING READINESS AND CAPACITY

Manufacturing considerations also contribute to the uncertainty regarding how soon and how many CGT-eligible patients can be treated. The manufacturer must have adequate funding to build manufacturing facilities and to be able to ramp up production capacity to meet demand at FDA approval and after, and to meet the good manufacturing process (GMP) regulations of the FDA. This has such a substantial impact on the potential volume of patients who can be treated with specific CGT.

This uncertainty can have a material impact on uptake and is therefore it is not uncommon for manufacturers whose stock is publicly traded to share their expectations for the first few years in press releases and investor presentations in order to set market expectations. For example, Abecma (CAR-T) had been FDA-approved for fifth-line multiple myeloma in March 2021. As the manufacturers (2seventy bio and BMS) were seeking expansion into third-line, with anticipated FDA approval in 2024, they highlighted their manufacturing capacity constraints in their investor presentations and stated that, although more patients will seek Abecma treatment due to the label expansion, only a fraction of the anticipated patients will be able to be treated due to the limitation on how much product they can produce. They further indicated that, by 2025, they will still fall short even if they ramp up manufacturing capacity by 100%, with only 50% of the patients eligible for their therapy being treated.

PATIENT AND PHYSICIAN WILLINGNESS TO ADOPT CGT

The demand for given CGT also has a material impact on uptake because the willingness of patients and physicians to adopt the treatment is variable not only across rare diseases but also among CGT for the same rare disease. As mentioned above, the price of therapy is a factor that potentially drives patients and providers toward or away from particular CGT, especially when options exist (e.g., Casgevy vs. Lyfgenia, given the seven-figure cost).

Beyond cost, many of the drivers associated with the willingness to adopt CGT have to do with the rare disease itself or with the therapeutic options, some of the drivers are the following:

- Severity of the disease
- Prognosis and outcomes of the disease
- Availability of and effectiveness of existing therapeutic options
- Risk/reward of available treatment
  - Administration of therapy (e.g., frequency, pain level, degree of complexity)
  - Expected outcome (e.g., curative vs. disease modification)
  - Durability of effect (e.g., lifetime vs. years)
  - Adverse events (e.g., manageable vs. death)

Spinal muscular atrophy (SMA) provides an example where these considerations were associated with rapid adoption of Zolgensma. Even though Spinraza® (nusinersen) had been FDA-approved for SMA for two and a half years at the time the FDA approved Zolgensma, there was strong demand for Zolgensma.[97, 98] Zolgensma's clinical trial results suggested that Zolgensma-treated patients could not only survive beyond early childhood but also experience slowed progression of SMA with a one-time treatment rather than three times per year with Spinraza.[99] Additionally, Zolgensma was touted to be potentially "curative," with the lead clinical investigator in the Zolgensma clinical trial stating publicly that, "[i]t has the potential to be a cure if patients are treated early before they have manifestations of the disease."[100,101]

Beyond the rare disease and product characteristics discussed above, psychosocial considerations can also impact the patient and provider willingness to adopt CGT. A comparison of the demand for Zolgensma versus that of the gene therapies for hemophilia and SCD cannot be reduced to disease and product characteristics alone. Psychosocial factors have resulted in gene therapy hesitancy for many SCD and hemophilia patients.

With respect to SCD, bluebird bio (manufacturer of Lyfgenia) acknowledged in its investor presentation that its own market research and internal data suggest that 70% of patients may prefer gene therapy to existing treatment if recommended by a physician and 80% of physicians want access to both SCD gene therapies.[102] Although they stop short of elucidating why, a patient preference study published in the journal, Blood Advances, in December 2023 points to aspects of SCD as well as product-specific characteristics of individual CGT as reasons for this hesitancy.[103] In addition, there a significant psychosocial aspect to this hesitancy which is rooted in a lack of trust in the healthcare system, due to how SCD patients have been historically mistreated and the resulting disparities in health outcomes.[104,105,106,107]

In the case of hemophilia, not only are there effective therapies available to compare the gene therapy against, but patients can also consider the psychosocial impact of their hemophilia being potentially cured. In an article published in Hemophilia Today in early 2024, the author explained that her husband would not adopt gene therapy due to the impact of "losing part of his core identity" if his hemophilia was cured.[108] His lifelong battle with hemophilia shaped him in such a way that the resilience he has demonstrated and experiences he gained would seem like losing a part of himself that he was not comfortable doing. [108]

Specific to hemophilia, another psychosocial factor is that patients do not trust that a one-and-done therapy will truly prevent them from experiencing a break-through bleed. In primary market research we conducted, hematologists expressed frustration regarding patient hesitancy toward advanced therapies.[109] Their hemophilia patients did not even want to adopt a therapy that offered fewer weekly infusions (extended half-life coagulation factor) or once-a-month injections (Hemlibra), let alone a gene therapy.[110]

CGT product characteristics, availability of qualified treatment centers, manufacturing readiness and capacity, and patient and provider willingness to adopt CGT must be evaluated—and reevaluated—on a product-by-product basis. These factors refine the predicted number of treatment-eligible patients beyond epidemiology, clinical trial criteria, and the science. The market intelligence behind these factors ultimately enhances a forecast from one that is more academic in nature to one that provides a market-driven expectation for the number, timing, and rate at which CGT-eligible patients may be treated, from FDA approval through three to five years out from approval.

Closing thoughts

From a payer's perspective, there are a number of challenges to forecasting the number of potential CGT cases and associated costs. In our experience, it requires considerable, continuous research efforts to maintain an up-to-date repository of the current and potential CGT therapies available to treat rare diseases. For each therapy there are many assumptions that must be informed in order to understand the prevalence, cost, timing, and magnitude of the demand. However, assumptions limited to epidemiology, clinical trial criteria, and the science fall short in terms of predicting the number of patients who are treatment-eligible and likely to be treated due to a number of mitigating factors, as we identified in this research.

Payers need an accurate expectation for cost exposure in order to implement benefit solutions or risk mitigation strategies that will be effective. It may not be feasible to rely upon past experience for forecasting CGT costs. Third-party research can be a cost-effective starting point for clinicians and actuaries, in order to accelerate the development of insights rather than the development of assumptions.

About the Author

Brenda Cordell, MBA is a senior healthcare consultant in Milliman's Indianapolis Health Practice. She is a lead in the life sciences consulting group and has consulted to the developers of novel biopharma therapies for the past 16 years with a focus on market access strategy and evidence generation to support the value of novel therapies. Brenda is a co-creator of Milliman DNA Gene and Cell Therapy Forecasting, a product that provides synthesized clinical, scientific, and market intelligence research for approved and pipeline gene and cell therapies to support estimates of the costs and cases associated with these regenerative therapies. Prior to Milliman, Brenda specialized in market access and value demonstration during her eight-year tenure with two biopharma companies.

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CONTACT

Brenda Cordell
brenda.cordell@milliman.com

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