IQVIA INSTITUTE FOR HUMAN DATA SCIENCE

Strengthening Pathways for Cell and Gene Therapies

CURRENT STATE AND FUTURE SCENARIOS

MARCH
2024

Introduction

Cell and gene therapies can provide transformative benefits to patients who are often left with no other treatment options. Recent years have seen record funding, clinical research, and new launches in this sector. Despite the increasing activity, the health system infrastructure needs and the complexities of the journey often required by patients to receive these therapies pose significant barriers to the future success and sustainability of these treatment modalities. Significant uncertainty remains about the future trajectory of the sector, highlighting the need for a deep understanding of the current state and potential evolutionary paths over the coming years.

Cell and gene therapies are a broad group of medicines, including cell-based immunotherapies, cell therapies, gene therapies, and tissue-engineered products but do not include RNA therapeutics. In this report, we characterize the current state of these therapies across the product lifecycle, beginning with pre-commercial activities such as funding and clinical research. We also detail the hurdles to commercialization, including infrastructure needs, reimbursement, and patient access.

Reflecting on the current state of the end-to-end environment for cell and gene therapies, we provide potential future scenarios across eight indicators that can be monitored to understand the evolution of the sector through 2035 and beyond. We intend for this report to provide a foundation for meaningful discussions about the future of the sector and the role cell and gene therapies will play in healthcare.

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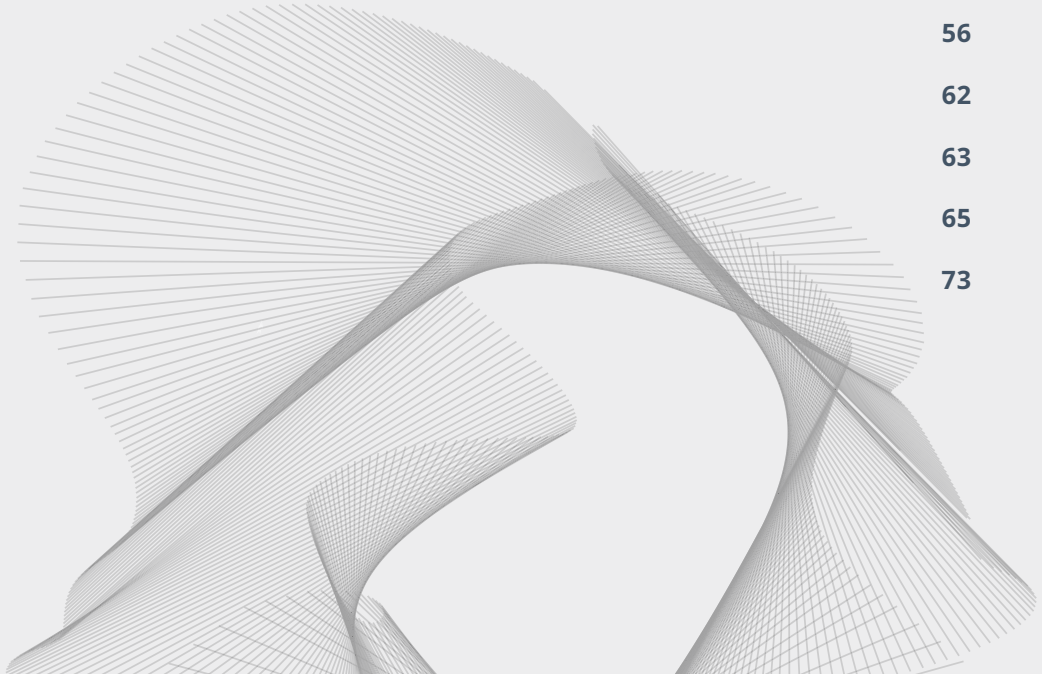


Overview

Over the last few decades, as technology has advanced and knowledge about disease mechanisms has progressed, novel modalities — including the rise of cell and gene therapies — are changing the way diseases are treated and providing hope to patients with few options. Cell and gene therapies encompass a broad group of medicines, including cell-based immunotherapies, cell therapies, gene therapies, and tissue-engineered products, which often follow complex paths from research to patient treatment. Although cell and gene therapies follow the traditional pathway for medicines from discovery and preclinical research to commercialization and patient treatment, additional complexities exist for these products across the lifecycle compared to other medicines. This research seeks to highlight the complexities faced by stakeholders involved in this lifecycle and to characterize the current state of the cell and gene therapy industry, as well as the factors that may impact the industry's future potential.

VENTURE FUNDING FLOWS AND DEAL ACTIVITY

The flow of funding into companies active in cell and gene therapies and subsequent level of deal activity involving these entities is an indicator of investor interest, commitment, and support for this sector. The number of cell and gene therapy deals are up 48% from a decade ago, although deals declined in 2022 and 2023 from the peak years of 2020 and 2021. Additionally, cell and gene therapies represent a larger share of all life sciences deal activity, as the industry increasingly focuses on these novel medicines. Deals for manufacturing account for a growing share of cell and gene therapy deals as developers seek to acquire the skills and capacity to bring their products to market. Emerging biopharma companies are involved in nearly all deal activity, reflecting the high degree of research in the space originating from start-up companies, often the result of academic work. Venture capital activity has accelerated in the past three years and reached $3.4Bn in 2023, up 70% from 2022 although down 43% from the record funding in 2021.

Growing interest in the sector has resulted in increased funding and clinical activity. Venture capital funding reached $3.4Bn in 2023, and a record number 406 industry-sponsored clinical trials started in 2023.

CLINICAL RESEARCH

Many early-stage research funding and collaborative initiatives have been established around the world to coordinate and advance cell and gene therapy research. Industry-sponsored cell and gene therapy trials have more than tripled over the last decade, while non-industry trials — typically led by academic researchers or government agencies — have grown 5%, largely driven by growing interest in CAR T-cell therapies. Oncology accounts for the largest share of cell and gene therapy research, although the disease focus varies by modality. Academic institutions and emerging biopharma companies are driving overall clinical research, while large pharma companies focus on gene therapies and later-stage research. China has seen growing representation in cell and gene therapy trials, with 42% of industry-sponsored trials that started in 2023 having sites in China compared to 14% a decade ago. However, nearly all trials taking place in China are only being conducted with domestic sites and therapies may require additional multi-country trials to reach global markets.

REGULATORY REVIEW, APPROVAL, AND NEW LAUNCHES

As of the end of 2023, 76 cell and gene therapies have been launched globally, more than double the number of therapies that had been launched by 2013. Access to cell and gene therapies across geographies is not uniform and is primarily limited to developed markets, with gene therapies and cell-based immunotherapies having the greatest acceptance across markets. Eight new cell and gene therapies were launched globally in 2023, including the first cell therapy for diabetes, the first gene therapy for Duchenne muscular dystrophy (DMD), and the first topical gene therapy. Regulatory agencies across geographies classify cell and gene therapies differently and have varying frameworks for regulatory review, leading to fragmented and sometimes inconsistent regulatory activity. Efforts to improve harmonization are underway, and new regulations and refined frameworks are expected to improve regulatory efficiency in the coming years.

MANUFACTURING AND DELIVERY INFRASTRUCTURE

Manufacturing methods and needs depend on the type of therapy and cell source, with varying complexity across cell and gene therapies. Companies have built various types of manufacturing networks to suit the needs of their products and operations are predominantly located in the U.S., with products being shipped globally. This requires extensive logistics and results in long product turnaround times. Manufacturing investments in point-of-care manufacturing, automation, and other enablers can increase productivity and reduce treatment wait times for patients.

The treatment journey for patients who may be eligible for treatment with a cell and gene therapy is complex, and numerous barriers exist throughout the process.

Cell and gene therapies must be administered in specialized treatment centers to ensure patient safety throughout the treatment process. There are more than 500 accredited CAR T-cell therapy treatment centers globally for commercialized products, concentrated in developed markets. However, healthcare facilities with clinical capabilities, as demonstrated through involvement in clinical trials, have a wider distribution. Within countries, treatment centers are concentrated around urban centers and do not necessarily carry all available products, requiring patients to often travel long distances for treatment.

REIMBURSEMENT AND PAYMENT MODELS

The average ex-manufacturer price across major markets for CAR T-cell therapies is more than $350,000, and for gene therapies, it is $1.8Mn, with prices contributing to the budgetary concerns of payers. As a result, public reimbursement for cell and gene therapies varies across major markets, with many payers putting in place restrictions that go beyond the product label, potentially limiting patient access. Wealthier countries in Western Europe, which allocate more of their economic resources to healthcare, have higher reimbursement rates for cell and gene therapies, whereas Eastern European countries have more limited access. Due to the high cost of treatment, payers and manufacturers are employing a wide variety of innovative payment models to manage costs, with outcomes-based agreements being the most common.

PATIENT ACCESS AND USE

The treatment journey for patients who may be eligible for treatment with a cell and gene therapy is complex, and numerous barriers exist throughout the process, leading to some patients not receiving treatment. For CAR T-cell therapies, patient treatment rates vary across countries, from 25% of referred patients treated in Brazil to 70% in Italy. The most common reasons for patients not receiving treatment are disease progression and patient fitness for treatment, which often worsens as patients progress through the lengthy treatment journey. For gene therapies treating heritable disorders, patients often need to be identified early in life, and the limited availability of newborn screening in many countries makes patient identification challenging. Due to the complex logistics related to treatment and the affordability challenges faced throughout the patient journey, patient support services from manufacturers or patient organizations are essential to ensure that patients can access therapies.

PATIENT OUTCOMES

Post-treatment follow-up of patients after receiving treatment is longer for cell and gene therapies than for other medicines, lasting up to 15 years or potentially the patient's lifetime, based on recent regulatory concerns about long-term safety. However, even the basic task of following the patient is challenging in long-term follow-up studies, increasing the risk of patient loss to follow-up as patients move or become disengaged from the healthcare system. To adequately measure the long-term safety and efficacy of cell and gene therapies, follow-up studies must be custom designed for each therapy and consider the situational characteristics specific to that therapy and disease. While early data from these follow-up studies highlights the continued efficacy of some gene therapies, it is difficult to draw conclusions about the long-term efficacy for the sector given the variation in treatments and mechanisms being used.

SPENDING

Spending on cell and gene therapies reached $5.9Bn in 2023, up 38% from 2022, with 62% attributable to the U.S., where there is broader acceptance of these products. Despite the patient treatment costs and budgetary concerns often associated with cell and gene therapies, spending accounted for only 0.4% of the $1.6Tn spent on medicines globally in 2023. Spending is higher in the U.S., where cell and gene therapies accounted for 0.8% of manufacturer net medicine spending in 2023. The high costs of bringing products to market and small treatment populations make commercialization and return on investment difficult for cell and gene therapies, which has led to notable market exits. The commercial environment for cell and gene therapies may become more challenging as additional therapies and other modalities, such as bispecific antibodies and antibody-drug conjugates, become available.

FUTURE STATE

The future evolution of the cell and gene therapy sector is influenced by eight key elements, with a range of indicators available to track the sector's progress over time. A range of potential scenarios is possible across these elements, which will have differential impacts on the overall market. The current commercialization model may need to adapt to ensure the long-term sustainability of the sector, potentially through non-traditional approaches such as academic or non-profit involvement. The emergence of less complex treatment modalities, such as bispecific antibodies, could challenge the role of cell and gene therapies in disease treatment. Monitoring the progress of the industry across these indicators will help elucidate the cell and gene therapy sector's trajectory through 2035 and beyond and focus attention on policy or investment interventions that allow these therapies to play a sustainable role in patient care and fulfill their promise.

Framework for assessing cell and gene therapies

+ **The pharmaceutical market has evolved from a focus on treatment with small molecules and biologics to the utilization of innovative cell and gene therapies.**

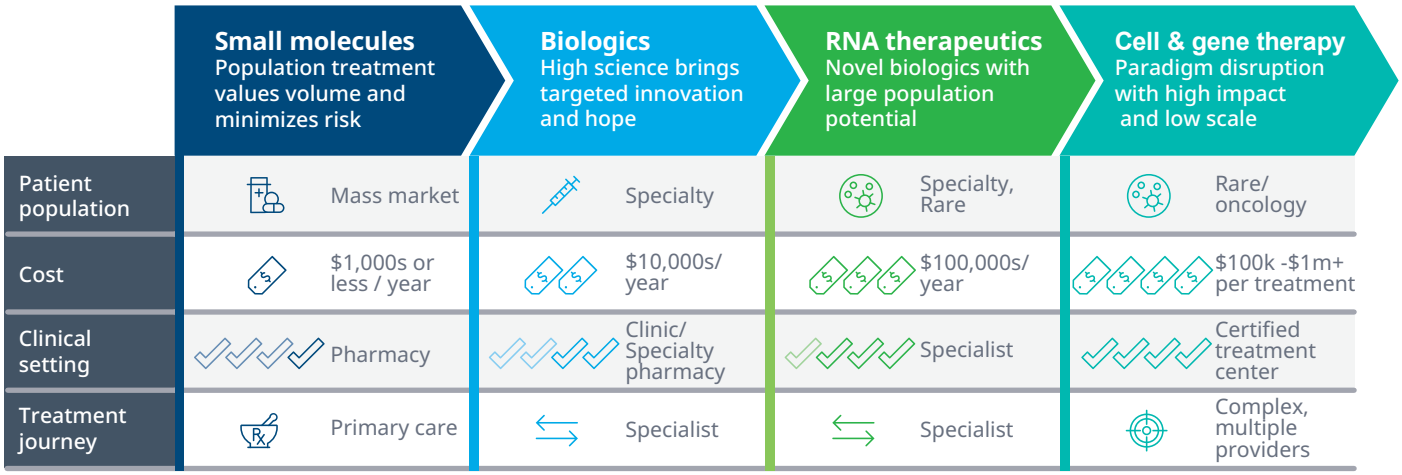
+ **Cell and gene therapies are a broad group of medicines, including cell-based immunotherapies, cell therapies, gene therapies, and tissue-engineered products.**

+ **While cell and gene therapies follow the traditional pathway from discovery to commercialization, additional complexities exist throughout their lifecycle compared to other medicines.**

Over the last few decades, as technology has advanced and knowledge about disease mechanisms has progressed, the treatment of diseases has shifted. Small molecule medicines have been used to treat patients for over a century and are widely used today to treat diseases from bacterial infections to heart disease to cancer.[1] Biologic medicines, which are derived from living organisms, have seen increasing use in healthcare since the introduction of the first monoclonal antibody in 1986.[2] Biologics have revolutionized disease treatment for patients and play an important role across various therapy areas, particularly in immunology and oncology. These medicines are typically more expensive to produce than small molecules, may treat smaller patient populations than small molecules, are usually prescribed by a specialist rather than primary care provider, and are often delivered to patients at a clinic or through a specialty pharmacy rather than a traditional pharmacy (Exhibit 1).

Biologics have continued to progress from monoclonal antibodies and vaccines to the introduction of next-generation biotherapeutics — RNA therapeutics and cell and gene therapies. RNA therapeutics began to enter the market in the 2010s and provide advances in treatment through post-transcriptional gene expression regulation to patients living with diseases such as spinal muscular atrophy and Duchenne muscular dystrophy. Cell and gene therapies are a broad group of therapies commonly referred to as regenerative medicine, which the Alliance for Regenerative Medicine defines as "gene therapies, cell therapies, and tissue-engineered products intended to augment, repair, replace or regenerate organs, tissues, cells, genes, and metabolic processes in the body."[3] Other organizations have differing definitions of the types of therapies included in the cell and gene therapy sector.

Exhibit 1: Progression of pharmaceutical technologies



Source: IQVIA Institute, Dec 2023.
Notes: Overall attributes are directional only and may vary by specific types of medicines within each category.

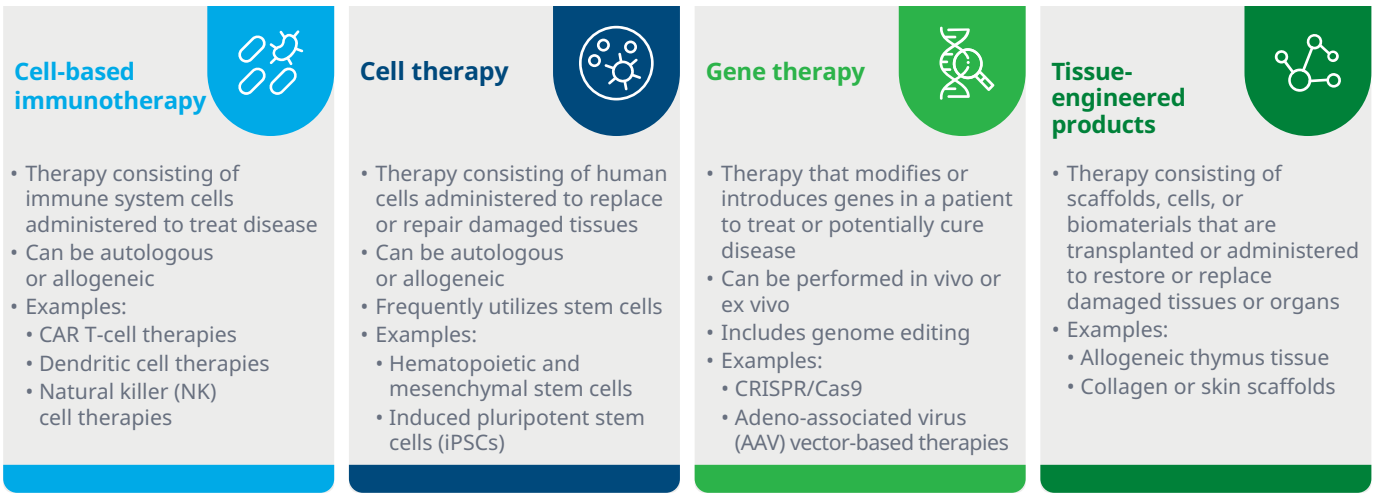
While RNA therapeutics and cell and gene therapies both represent significant advances in biotechnologies used to treat diseases, cell and gene therapies tend to involve more complex processes for testing, manufacturing, delivery, and treatment (Exhibit 1). RNA therapeutics have their own challenges and considerations that may occasionally resemble those of cell and gene therapies. Nevertheless, due to the substantial differences in these next-generation biotherapeutics, this analysis focuses on cell and gene therapies to provide meaningful insights into the often complex lifecycles of these therapies.

Cell and gene therapies entail a broad group of medicines including cell-based immunotherapies, cell therapies, gene therapies, and tissue engineered products (Exhibit 2). Cell-based immunotherapies and cell therapies are modalities that use either patient (autologous) or donor (allogeneic) cells to treat a disease. Cell-based immunotherapies employ immune system cells to treat disease. Chimeric antigen receptor (CAR) T-cell therapies are cell-based immunotherapies that utilize T-cells to target and kill cells (e.g., cancer cells) to treat disease.[4] Cell therapies are other cell-based therapies administered to repair or replace damaged tissues. These therapies often use stem and progenitor cells, derived from various tissues, which are manipulated or modified to target or enhance treatment.[5] Both cell-based immunotherapies and cell therapies can be genetically modified ex vivo, [6] as seen in CAR T-cell therapies and induced pluripotent stem cells (iPSCs). Unmodified cord blood therapies, which the Food and Drug Administration regulates as cell therapies, are not included in this analysis. They are not always similarly regulated in other countries and do not necessarily follow the same commercialization pathways as other cell therapies.

Gene therapies modify or introduce genes (extra- or intra-chromosomally) into a patient's cells to treat and potentially cure the patient's disease.[6] Gene therapies may be delivered directly in vivo or ex vivo, where the gene modification occurs in harvested cells that are transplanted back into the patient. Gene therapies can utilize viral vectors, such as adeno-associated virus (AAV) and other viral vectors, or may involve genome editing, with various platforms such as CRISPR/Cas and base editors, all currently in clinical development.

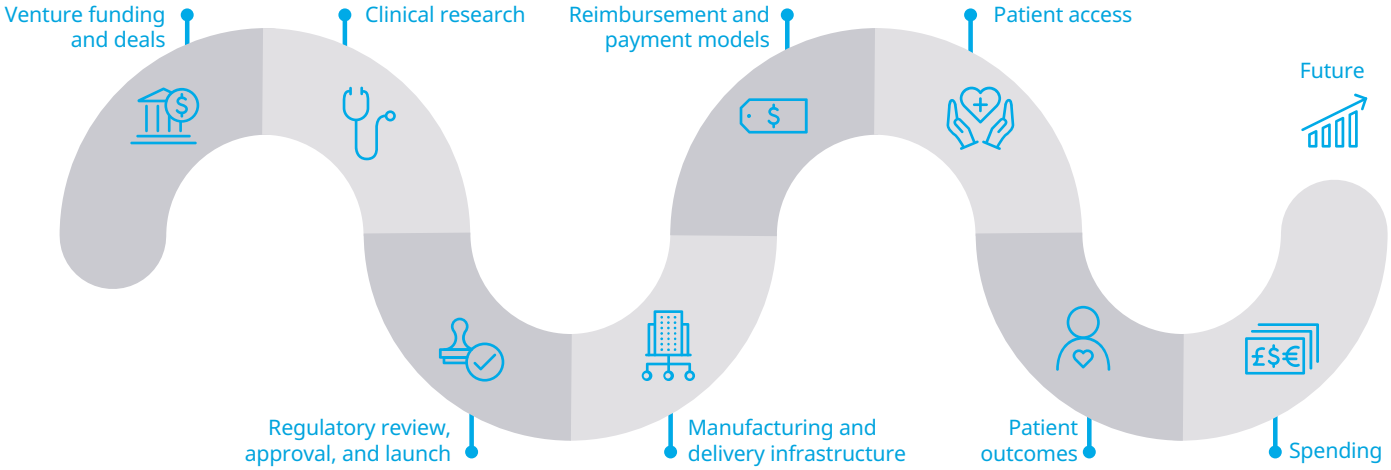
Tissue-engineered products are therapies that utilize scaffolds, tissues, cells, or other biological materials to restore or replace damaged tissues or whole organs.[7] These products typically use a cellular component (e.g., stem cells, progenitor cells, iPSC-derived differentiated cells) to create an engineered implant. This group of therapies includes a broad range of products, with currently marketed products including allogeneic thymus tissue, engineered skin grafts for wound healing, and cultured cartilage for joint repair among others.

Exhibit 2: Cell and gene therapy types



Source: Alliance for Regenerative Medicine, IQVIA Institute, Dec 2023.

Exhibit 3: Cell and gene therapy pathway from discovery to treatment



Source: IQVIA Institute, Jan 2024.

Tissue-engineered products may not follow the same processes as other cell and gene therapies, given their tendency to more closely resemble medical devices, and are included in this analysis where information is available and relevant. However, they may not be fully captured in certain analyses that focus on medicines, as devices are not included (e.g., clinical trial activity).

While cell and gene therapies follow the traditional pathway for medicines from their discovery and preclinical research to commercialization and patient treatment, additional complexities exist for these products across the lifecycle compared to other medicines (Exhibit 3). Research and development activities may involve additional steps, regulatory review and commercial launch often includes additional steps, and the manufacturing and patient treatment is often bespoke. This research seeks to highlight the complexities faced by stakeholders involved in this lifecycle and characterize the current state of the cell and gene therapy industry. Additionally, findings have been used to create future scenarios and measures that might predict success for cell and gene therapies through 2035.

As cell and gene therapies have developed, the understanding of these products has changed over time and some cell and gene therapies have been unregulated in the past (e.g., cosmetic stem cell treatments). Additionally, some cell and gene therapies for ultrarare conditions may not be commercially viable and are accessible to patients only through clinical trials, including expanded access or compassionate use programs. These products may not follow the traditional pathway of drugs, including regulatory approval and commercialization. Though an important contributor to the cell and gene therapy field and an alternative way to provide access to patients, this segment of the field is not addressed in the commercialization discussion detailed here and is not included in the characterization of the potential future scenarios due to the semi-regulated nature.

A NOTE ON DEFINITIONS

Different stakeholders within the cell and gene therapy sector have different ways of defining cell and gene therapies. Some include RNA therapeutics, given their ability to regulate gene expression. Others have more strict definitions that do not include tissue-engineered products. Some include all genetically modified cell therapies as a part of gene therapies and others do not. These disparities exist across industry, professional organizations, and even regulatory agencies (see Exhibit 21). This research does not set out to solve this issue but utilizes a single framework for defining these products to characterize the sector.

Venture funding flows and deal activity

+ **The number of cell and gene therapy deals are up 48% from a decade ago and represent a larger share of all life sciences deals, despite a decline in 2022 and 2023 from the peak years of 2020 and 2021.**

+ **Cell and gene therapy manufacturing is complex and contract manufacturing deals represent a growing share of the deal activity in this space.**

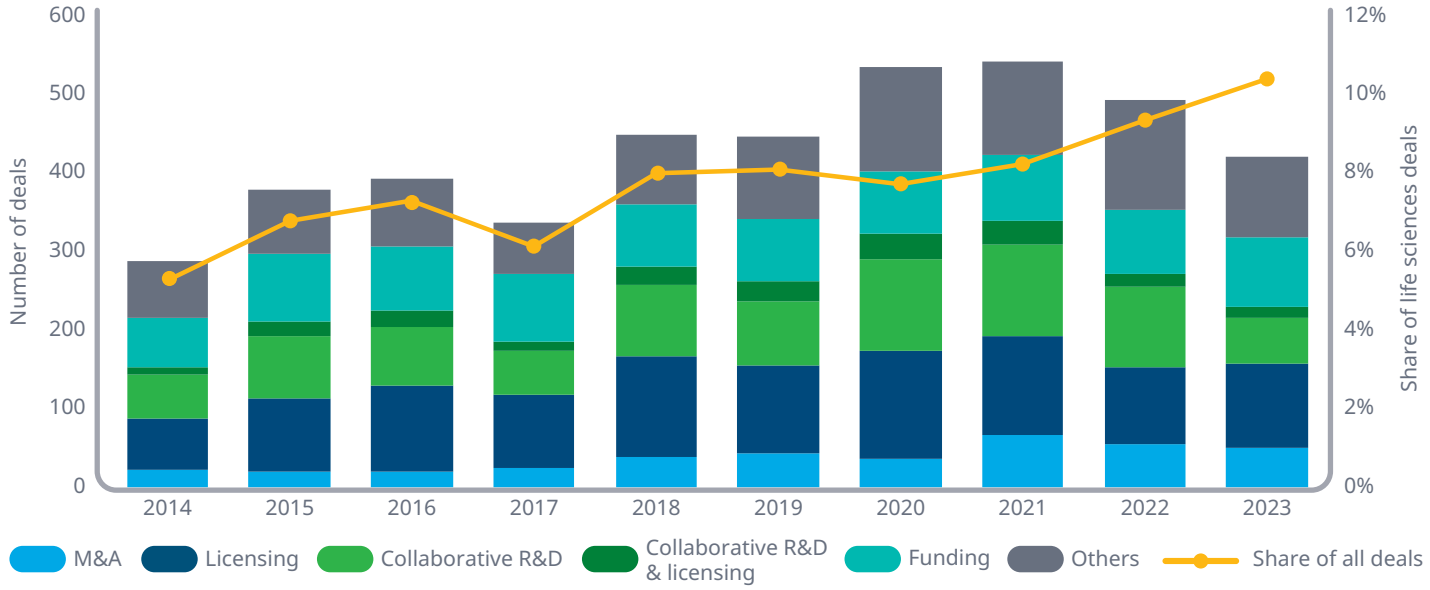
+ **More than two-thirds of deals are between emerging biopharma companies, and emerging biopharma companies are involved in nearly all deal activity, reflecting the degree of cell and gene therapy innovation and new technologies coming out of these companies.**

+ **The level of venture capital funding grew in 2023 to $3.5Bn, although still below historic levels seen in 2021.**

Early-stage advances in cell and gene therapies, along with continued clinical success, have led to increased funding for companies working in this sector. This increased funding has enabled both large pharmaceutical companies and emerging biopharma companies, including start-ups, to continue innovating in the cell and gene therapy space. Deals and funding include but are not limited to company-to-company transactions, funding from governments or non-profits, and funding provided through venture capital firms or funds.

The number of cell and gene therapy deals declined by 14% in 2023 compared to 2022, but deals are up 46% from a decade ago (Exhibit 4). The declining trend in cell and gene deal activity over the past two years follows that of deal activity across the life sciences industry.[8] However, deal-making for these advanced therapies accounts for a growing share of all life sciences deals, representing 10% of life sciences deals in 2023, up from 8% in 2021 and 5% in 2014. This highlights the growing confidence and interest in these modalities as cell and gene deal activity has not slowed as much as the rest of the industry.

Exhibit 4: Number of cell and gene therapy deals by type and share of all life sciences deals, 2014–2023



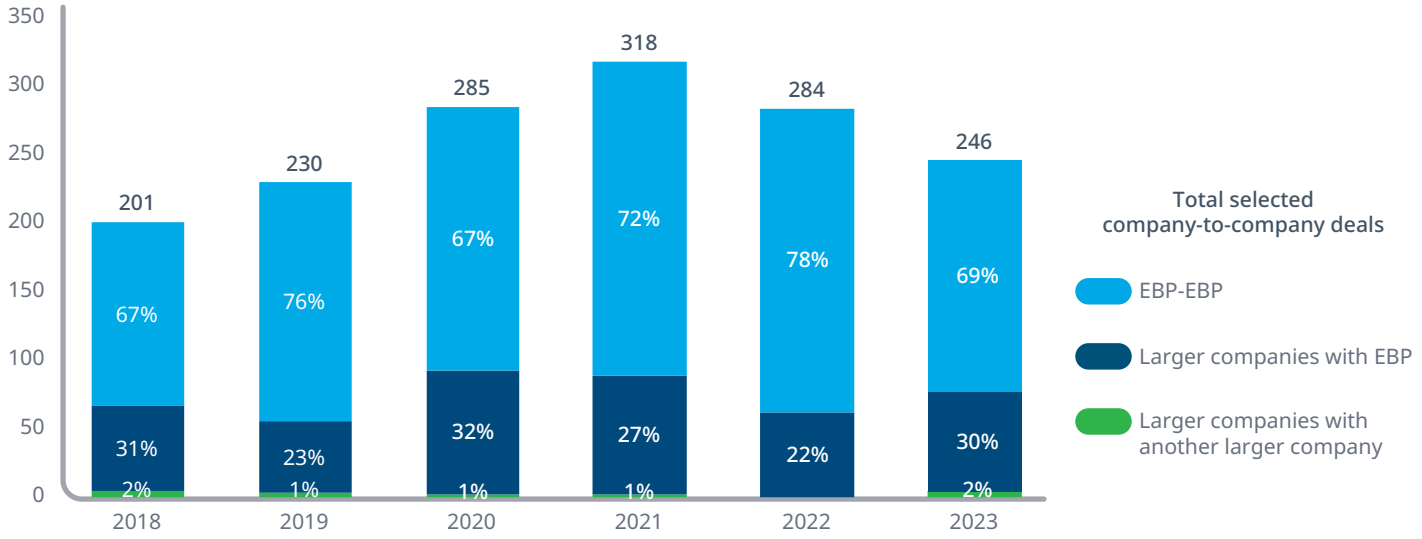
Source: IQVIA Pharma Deals, IQVIA Institute, Jan 2024.
Notes: Funding deals are those where no additional collaboration or licensing occurs and are where money is provided by an independent organization, frequently government institutions, academic institutions, or research consortium. Deals are those including cell and gene therapies but may additionally include other modalities.

Declining deal activity has not impacted all deal types equally. While mergers and acquisitions, collaborative research and development, and collaborative research and development plus licensing deals all declined in 2023, licensing deals alone grew by 13% in 2023 following a slowdown in 2022 compared to prior years. Novo Nordisk had two significant deals in 2023 for advanced therapies in diabetes, obesity, and cardiometabolic diseases. One deal for up to $1.9Bn is to leverage base editing technology from Life Edit Therapeutics to develop therapeutics to treat rare and cardiometabolic diseases;[9] the other deal for up to $2.7Bn is for licensing bioprinting technology from Aspect Biosystems to develop bio-printed tissue therapeutics to treat diabetes and obesity.[10]

Manufacturing of cell and gene therapies is complex and requires specialized facilities and experience to scale for commercialization. For this reason, many companies partner with a contract development and manufacturing organization (CDMO) to aid in the manufacturing of these therapies, particularly for the commercial market. As more of these products are reaching the market, contract manufacturing deals have been increasing. In 2023, 19% of cell and gene therapy deals involved contract manufacturing agreements compared to 8% of deals in 2018. Recent contract manufacturing deals include Vertex's agreements with both RoslinCT and Charles River to manufacture the first approved CRISPR-based gene editing therapy.[11,12] Additionally, cell and gene therapy companies and CDMOs have been bringing cell and gene therapy manufacturing capabilities in-house through acquisitions, with Sartorius' acquisition of Polyplus — a manufacturer of plasmids, viral vectors, and other components used in cell and gene therapies — for $2.6Bn representing one of the largest deals in 2023.[13]

Contract manufacturing deals accounted for 19% of deal activity in 2023, up from 8% five years ago, as companies invest more in manufacturing capacity.

Exhibit 5: Number and share of deals by company segment, 2018–2023



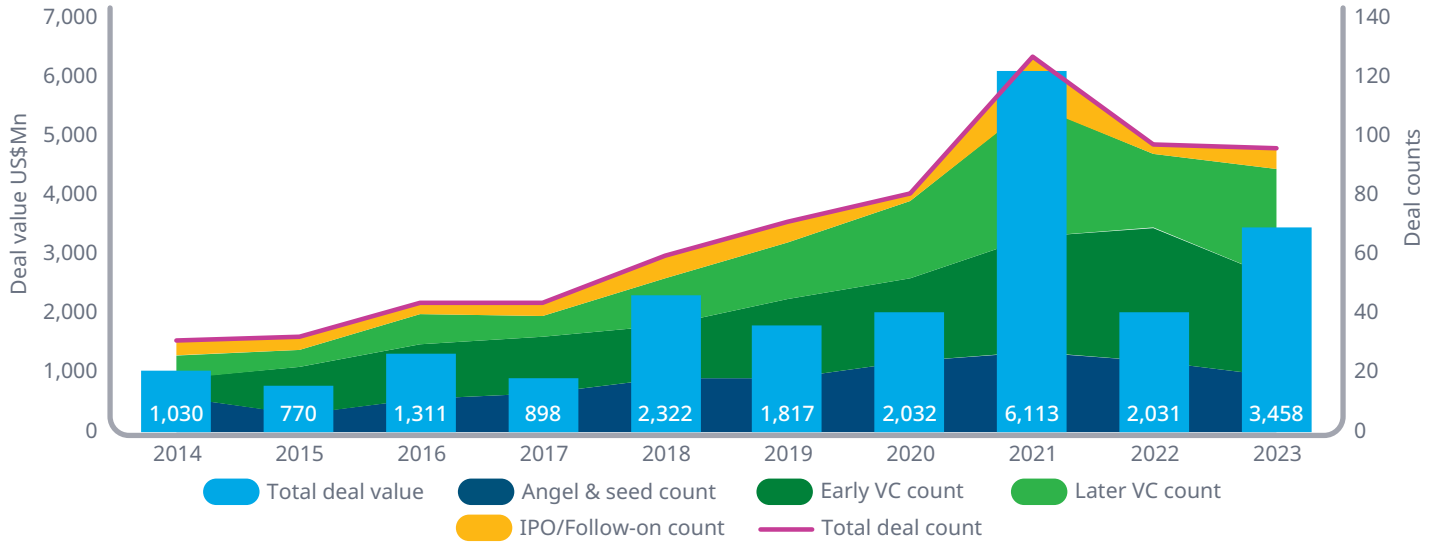
Source: IQVIA Pharma Deals, IQVIA Institute, Jan 2024.
Notes: Deals in this analysis exclude funding deals — deals that involve research grants or funding from government institutions, government bodies, universities or other academic institutions. Deals are those including cell and gene therapies but may additionally include other modalities. Excludes deals with non-commercial partners.

Emerging biopharma companies — defined as those with less than $200Mn in R&D spending and less than $500Mn per year in annual sales — have significant involvement in deals. Nearly all cell and gene therapy deals between two or more companies involve emerging biopharma companies, and more than two-thirds of deals involve only emerging biopharma companies (Exhibit 5). Large and mid-sized companies — those with more than $5Bn in global sales — are consistently involved in approximately 30% of deals, partnering with emerging biopharma companies. While larger companies partner with each other across all life sciences deal activity, cell and gene therapy deals between larger companies are rare. This reflects the significant amount of innovation and new technologies coming from emerging biopharma companies.

Venture capital activity and public transactions for cell and gene therapies have accelerated in the past three years (Exhibit 6). Following historic funding levels in 2021 and a retraction in 2022, nearly 100 deals and $3.4Bn of deal value occurred in 2023. The total number of deals peaked at 127 in 2021 — 57% higher than in 2020 — dropped 24% in 2022 to 97 deals, and remained flat in 2023 at 96 deals, although still up 19% from 2020. Later-stage venture capital deals, which typically bring in more dollars, grew in 2023 while earlier-stage deals declined; however, all remain above levels seen five years ago. Initial public offerings (IPOs), which have been muted in the past two years with only three in total, are showing signs of rebounding early in 2024. Several cell and gene therapy companies have announced plans for IPOs, including Fractyl Health, an obesity gene therapy developer;[14] Metagenomi, a preclinical gene-editing company;[15] and Kyverna Therapeutics, a CD19 CAR T-cell developer. [16]

Venture capital funding reached $3.4Bn in 2023 with a 5-year CAGR of 8%.

Exhibit 6: Cell and gene therapy venture capital and public funding deal value in US$Mn and number of deals by type, 2014–2023



Source: PitchBook, IQVIA Institute, Jan 2024.

Notes: Excludes funding for companies only engaged in RNA therapeutics. VC = Venture Capital. Deals involve companies defined as life sciences which includes a range of biopharma, healthcare delivery and distribution, and other types of companies.

PATIENT ORGANIZATION FUNDING LEADS TO LIFE-SAVING GENE THERAPY

Patient organizations have played an important role in bringing attention to rare diseases, with many partnering with or supporting life sciences companies in developing therapies to treat often debilitating diseases.[17] One example of the role of patient organizations in supporting research for cell and gene therapies is the development of Zolgensma, a gene therapy treatment for spinal muscular atrophy (SMA).

Early preclinical studies in mice of a potential gene therapy for SMA, completed in 2010 at Nationwide Children's Hospital, were supported by the Miracle for Madison and Friends Fund, a fund set up in honor of Madison Reed — a patient living with SMA.[18] The patient organization Cure SMA provided additional grants to Nationwide Children's Hospital, including an award of $750,000 in 2012 to the Kaspar Laboratory. This partnership between the patient organization and the academic research center expanded when a $3.8Mn cooperative agreement was awarded by the National Institute of Neurological Disorders and Stroke (NINDS) to further the collaboration between Nationwide Children's Hospital, Cure SMA, and the federal government to develop a potential cure for SMA.[19]

As the development of a gene therapy candidate continued to progress, additional partnerships provided support in furthering research. Sophia's Cure Foundation donated $650,000 in 2012 to support clinical research, in addition to funds already raised to support the Kaspar Laboratory.[20] Cure SMA provided additional funding in 2015 for further clinical development.[21] Following this close partnership between patient organizations and Nationwide Children's Hospital, AveXis was founded by Dr. Kaspar and licensed the gene therapy candidate from Nationwide Children's Hospital. A Phase I trial funded by Sophia's Cure Foundation, Nationwide Children's Hospital, and AveXis began in 2014 at Nationwide Children's Hospital.[22]

Following the success of the gene therapy candidate in clinical trials, Novartis acquired AveXis in 2018 for $8.7Bn.[23] Shortly after the acquisition, the Biologics License Application (BLA) for Zolgensma was accepted by the FDA and Zolgensma was approved in 2019. Deal-making activity continued to support the launch of Zolgensma, with AveXis, now a Novartis subsidiary, acquiring a manufacturing facility from AstraZeneca to add to the existing gene therapy manufacturing capacity.[24] In 2020, AveXis was renamed Novartis Gene Therapies, and as of March 2023, more than 3,000 children living with SMA had been treated with Zolgensma.[25] Madison Reed turned 27 in February 2024, even though when she was diagnosed with SMA in 1997, she was not expected to live past the age of two.[26] She continues to advocate for other people living with SMA, highlighting the important role that patients and patient organizations play in developing life-saving treatments.

Clinical research

+ **Many early-stage research funding and collaborative initiatives have been established around the world to coordinate and progress cell and gene therapy research.**

+ **More than 3,200 trials have been started in the last five years, of which a growing share are industry-sponsored; industry-sponsored trials have grown 34% since 2018 and now represent 64% of total starts.**

+ **Oncology accounts for the largest share of cell and gene therapy research, although disease focus varies by modality, and 50% of trial activity is sponsored by emerging biopharma companies, with another 41% of trials run by academic institutions.**

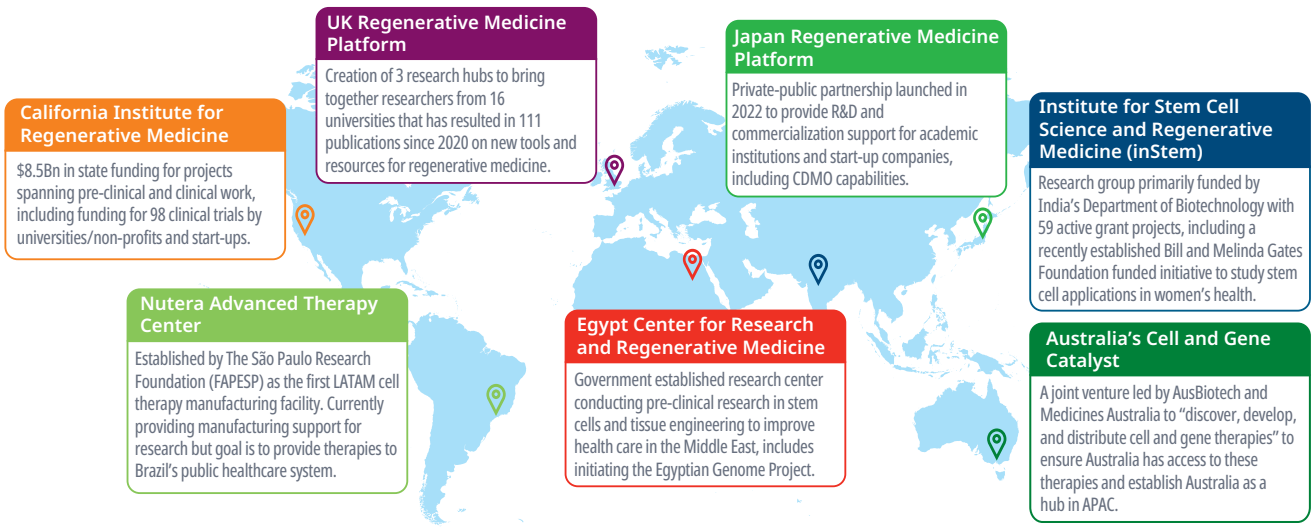
+ **China has had growing representation in cell and gene therapy trials, although most China-based trials are domestic only and Chinese companies may require additional effort or multinational partners to bring new therapies to global markets**

EARLY-STAGE RESEARCH INITIATIVES

Research centers and initiatives are important tools for fostering collaborative research environments and knowledge sharing to advance medical science. These initiatives are frequently established through government investment but can be established through or evolve into public-private partnerships between government, academic institutions, and industry. Initiatives provide funding for research projects to de-risk early research into new technologies, create a knowledge network of researchers, and provide other resources and support to academics and start-up companies engaged in early-stage research with emerging technologies. These collaborative efforts have contributed and will continue to contribute significantly to the advancement of the cell and gene therapy field. Research centers can be found globally with variations in structure and focus to prioritize the needs of the region (Exhibit 7).

One of the earliest examples is the California Institute for Regenerative Medicine (CIRM), established in 2004 by the California state government to invest in promising

Exhibit 7: Select cell and gene therapy research centers and initiatives



Source: IQVIA Institute, Dec 2023.
Notes: Research initiatives and centers presented are not meant to be representative of all research centers/initiatives globally.

treatments and advance the field of regenerative medicine. CIRM has received $8.5Bn in state funding in its history and funds preclinical, translational, and clinical research, with over 200 active awards at universities, non-profits, and start-up companies.[27] CIRM has provided nearly $900Mn to support 98 clinical trials testing new advanced therapies, with 79% of these trials being either Phase I or Phase I/II.[28] This financial support provides research labs and start-up companies with the resources to test novel technologies that might not otherwise make it into clinical research.

Another research hub in the U.S. is the Bespoke Gene Therapy Consortium (BGTC), managed by the Foundation for the National Institutes of Health. The BGTC is a public-private partnership focused on addressing some of the obstacles in developing gene therapies for rare diseases. The consortium aims to accelerate the time to patient access for AAV vector gene therapies by further understanding the basic biology of AAV vectors, streamlining the path from preclinical to clinical research, developing manufacturing efficiencies, and expediting the regulatory process.[29] Additionally in North America, the Centre for Commercialization of Regenerative Medicine (CCRM) — a Canadian non-profit organization funded by the government, academic, and industry partners — provides funding, manufacturing support, and other expertise to assist academics and start-ups in bringing new therapies to patients.[30]

Funding is not the only mechanism used in research centers. For example, the UK Regenerative Medicine Platform does not provide funding but has established three hubs to connect researchers across universities, creating a centralized organization for tools and resources. The platform has led to more than 100 peer-reviewed publications in the last four years, focusing on pluripotent stem cells and tissue engineering.[31] Additionally in the UK, the Cell and Gene Therapy Catapult has created a network collaborating with researchers across academia, industry, and healthcare. The CGT Catapult collaborates with groups both in the UK and internationally to advance the cell and gene therapy field across all aspects of the lifecycle, including manufacturing improvements and workforce development.[32]

Research centers in other geographies have focused on increasing access to cell and gene therapies where access is currently limited. In Brazil, the Nutera Advanced Therapy Center — Latin America's first cell therapy manufacturing plant — was created with support from The São Paulo Research Foundation (FAPESP). It is providing manufacturing support for clinical research, but the long-term goal is to manufacture cell and gene therapies for Brazil's public healthcare system and to become a leader in advanced therapies in the region.[33] Similarly, the Egypt Center for Research and Regenerative Medicine is a government-established research unit with the vision of being a leader in cell and gene therapies in the Middle East. In 2021, the Egyptian Genome Project was established to advance precision medicine and gene therapy in Egypt and to become a leading hub in Africa and the Middle East.[34] Both of these efforts could help bring cell and gene therapies to regions that have lagged the U.S. and Europe in patient access.

Several collaborative research efforts exist in the Asia-Pacific region. The Chinese National Stem Cell Resource Center provides a repository of stem cells available for research and treatment purposes and serves as a technical resource to researchers.[35] They also initiated the China Stem Cell and Regenerative Medicine Collaborative Innovation Platform to standardize management of stem cells across the country and promote knowledge sharing.[36]

Research centers and initiatives can be found globally to provide funding, knowledge-sharing, and resources in early-stage cell and gene therapy research.

Japan's Regenerative Medicine Platform and Australia's Cell and Gene Catalyst are both private-public partnerships looking to further cell and gene therapy efforts in those countries and the larger Asia-Pacific region. The Institute for Stem Cell Science and Regenerative Medicine (inStem) in India is a government-backed research group with an emphasis on advancing stem cell research for patients in India, a country that has often been overlooked in cell and gene therapies.[37]

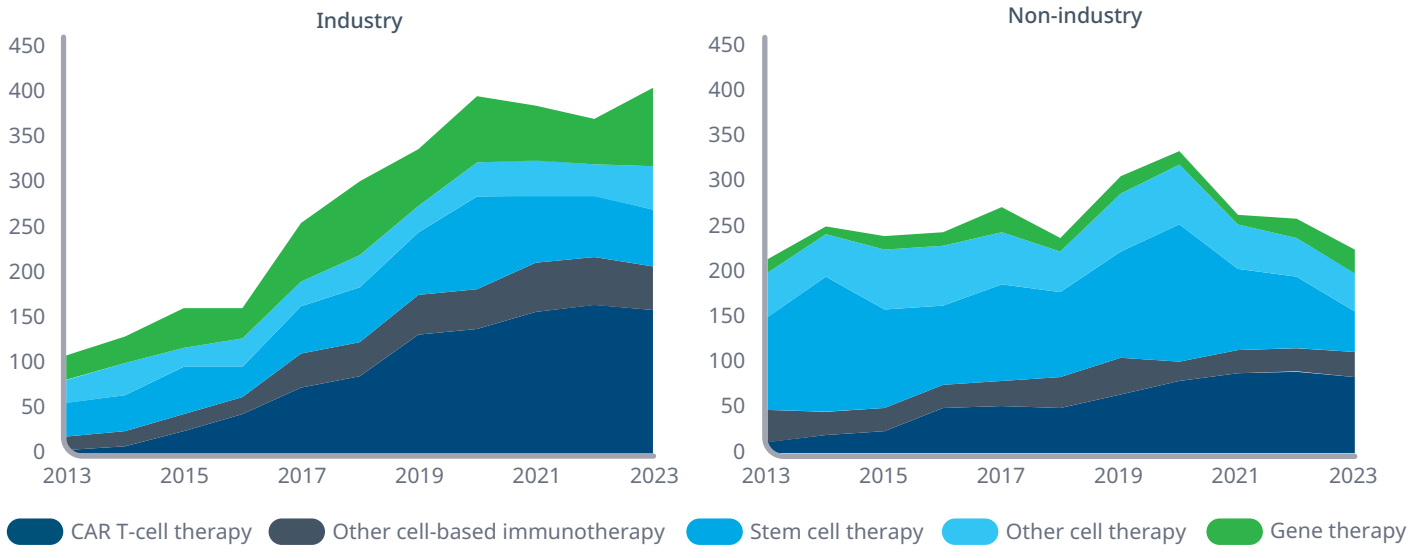
Other cell and gene efforts globally include the Novo Nordisk Foundation Center for Stem Cell Medicine, which is a collaboration across universities in Denmark, the Netherlands, and Australia,[38] and the European Consortium for Communicating Gene and Cell Therapy Information (EuroGCT), which is focused on distilling and communicating information about cell and gene therapies to patients, healthcare professionals, and other researchers.[39] Many other research centers are operating around the world, and new efforts are starting as interest in cell and gene therapy research continues to grow.

A record number 406 industry-sponsored clinical trials started in 2023 with a 5-year CAGR of 6%.

CLINICAL TRIAL ACTIVITY

Cell and gene therapies developed by academic and research institutions and biopharma companies have gradually progressed from preclinical research to being evaluated in patients in clinical settings. Over the last five years 3,285 trials were started to evaluate cell and gene therapies in patients across all sponsor types, including 631 in 2023 (Exhibit 8). Non-industry trials, which include those sponsored by academic institutions, non-profits, and governments with no biopharma involvement, represented 36% of trial starts in 2023, while industry-sponsored trials (with or without non-industry involvement) accounted for the other 64%. While non-industry trials have remained relatively flat

Exhibit 8: Cell and gene therapy clinical trial starts by type, 2013–2023



Source: Citeline Trialtrove, Dec 2023; IQVIA Institute, Jan 2024.
Notes: Includes phase I, II, and III. Terminated trials are included to track the activity still involved with their initiation, partial execution and termination. Trials are interventional trials. Trials are categorized by type based on disclosed information. Other cell-based immunotherapies includes T-cell receptor, tumor-infiltrating lymphocyte, natural killer, and dendritic cell therapies.

over the last decade, industry-sponsored trials have increased 276% from 2013 and 34% from five years ago. Much of this increase can be attributed to the growing research on CAR T-cell therapies in the clinic, which had just four industry-sponsored trials started in 2013 and has grown to more than 150 starts in the last three years. A shift occurred in 2023 as the share of industry-sponsored trials that were CAR T dropped to 39% from 44% in 2022, while the share that was gene therapy increased to 22% from 14%.

Differences exist in the types of cell and gene therapies investigated by industry and non-industry sponsors. Both have had a growing focus on CAR T-cell therapies, with 39% of industry and 38% of non-industry trials started in 2023 evaluating CAR Ts. Other cell-based immunotherapies such as natural killer (NK), T-cell receptor (TCR), and tumor-infiltrating lymphocyte (TIL) cell therapies accounted for 12% of all trials in 2023. Stem cell therapies, which used to account for a larger share of non-industry trials (38% in 2019), have seen waning interest, and 20% of trials in 2023 were for stem cell therapies, more closely aligning with the share of industry trials (16% in 2023). The largest difference in research focus across industry and non-industry is in gene therapies, with 88 gene therapy trials (22%) started by industry in 2023 compared to just 26 (12%) by non-industry.

Cell and gene therapies are being investigated for a range of diseases by various types of sponsors and companies. Over the last five years, trial activity has shown notable differences in focus between modality and therapy area, as well as between modality and sponsor size/type (Exhibit 9). Cell-based immunotherapies, including CAR T, are predominantly being researched for cancer treatment. These therapies have been successful in treating hematological cancers, with several CAR T-cell therapies now approved by regulators and commercially available. They may also prove effective in treating solid tumors. Although only 2% of cell-based immunotherapy trials in the past five years have targeted autoimmune diseases, recent preliminary results are promising for the application of CAR T beyond oncology. In one study, all patients were able to discontinue other immunosuppressive drugs following CAR T treatment.[40]

Stem cell and other cell therapies are being clinically investigated for a wider range of diseases. Immunology, neurology, and metabolic/endocrinology diseases represent a combined 53% of stem cell therapy clinical trials. Numerous therapies have been explored for treating severe cases of COVID-19 and its complications. Since 2020, 205 COVID-19 cell and gene therapy trials have started, with a focus on stem cell and other cell therapies. Gene therapies target a variety of diseases, with 35% of trials evaluating their use in solid tumors. Neurological, metabolic, endocrine, cardiovascular, and ophthalmic diseases are all significant areas of focus in gene therapy trials. Gene therapies often target inherited diseases, offering hope to patients with lifelong or debilitating conditions. One recent success story is the restoration of hearing in children with gene-mediated hearing loss, as demonstrated in various studies in the U.S. and China.[41] Women's health constitutes a small but important portion of cell and gene therapy research, with 34 trials started in the past five years primarily focused on treating infertility.

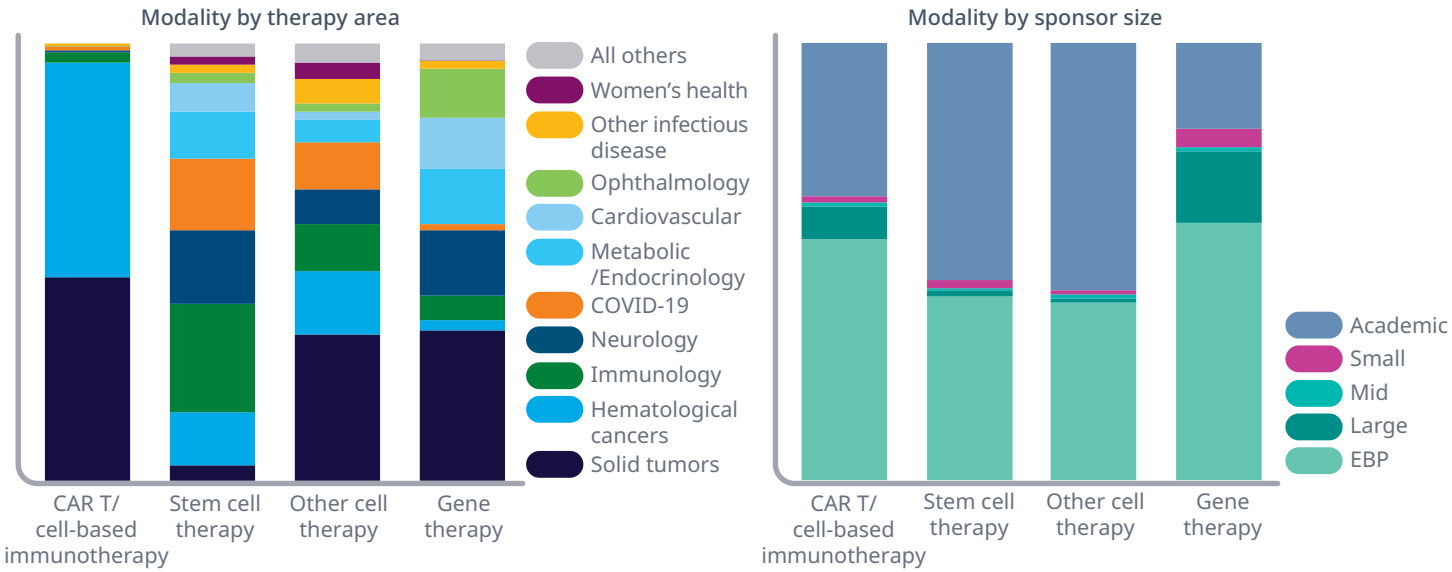
Emerging biopharma companies account for 50% of all trial activity and academic institutions account for an additional 41%.

More than 90% of cell and gene therapy trials are run by emerging biopharma companies and academic institutions, with variation in sponsors across modalities (Exhibit 9).

- Emerging biopharma companies account for 50% of all trial activity, representing larger shares of cell-based immunotherapy and gene therapy trials.
- Academic institutions — without the involvement of a pharma company — account for 41% of all trial activity over the last five years, representing the majority of stem cell and other cell therapy research.
- Large pharma companies represent only 6% of cell and gene therapy activity, with nearly all focus in cell-based immunotherapies and gene therapies. Large pharma companies are more likely to be involved in later-stage activity, likely the result of partnerships with emerging biopharma and acquisitions of programs that have had success in early-stage research.
- In the last five years, 18 of 21 large pharma companies and more than 650 smaller companies have sponsored cell and gene therapy trials.

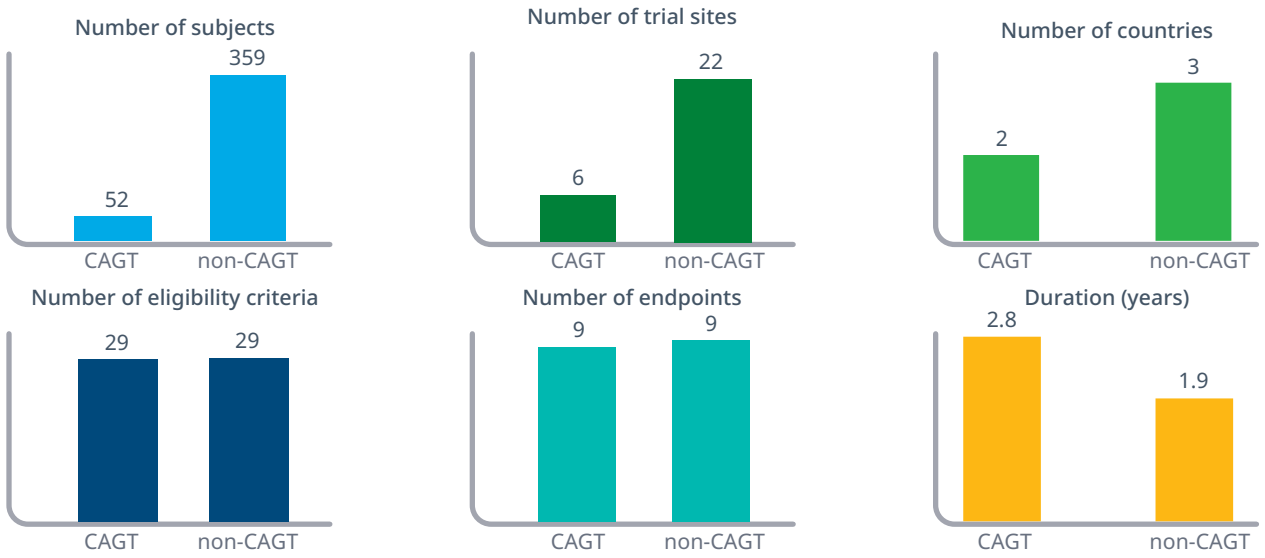
The effort required to perform a clinical trial is an important contributor to clinical development productivity and can be measured by trial complexity. The number of subjects, sites, countries, eligibility criteria, and endpoints can be used to understand the complexity of trials. On average, cell and gene therapy trials have 85% fewer subjects than trials for other medicines, as cell and gene therapies tend to target rare diseases (Exhibit 10). Due to the complexity of manufacturing, distributing, treating, and following patients, cell and gene therapy trials have fewer trial sites and, on average, are being evaluated across two countries. The use of inclusion and exclusion criteria and the breadth of primary and secondary endpoints being evaluated is consistent across cell and gene therapy and other trials. Driven by the extended evaluation period following treatment, cell and gene therapy trials take approximately one year longer, on average, than trials for other medicines. Despite the increased complexity of cell and gene trials and the extended time needed, cell and gene therapies in clinical development are 2 to 3.5 times more likely than other medicines to be successful and reach the market.[42]

Exhibit 9: Cell and gene therapy trial starts by therapy area and company size, 2019–2023



Source: Citeline Trialtrove, Dec 2023; IQVIA Institute, Jan 2024.
Notes: Includes phase I, II, and III. Terminated trials are included to track the activity still involved with their initiation, partial execution and termination. Trials are interventional trials. Trials are categorized by type based on disclosed information. Company segment when two or more companies are involved is determined by the larger sales segment. Emerging biopharma companies (EBP) are those with R&D spend less than $200Mn and global sales less than $500Mn per year. Small companies have global sales between $500 million and $5Bn per year; mid-sized companies between $5Bn and $10Bn per year; and large companies exceeding $10Bn per year.

Exhibit 10: Average cell and gene therapy clinical trial characteristics vs. other trials, 2019–2023

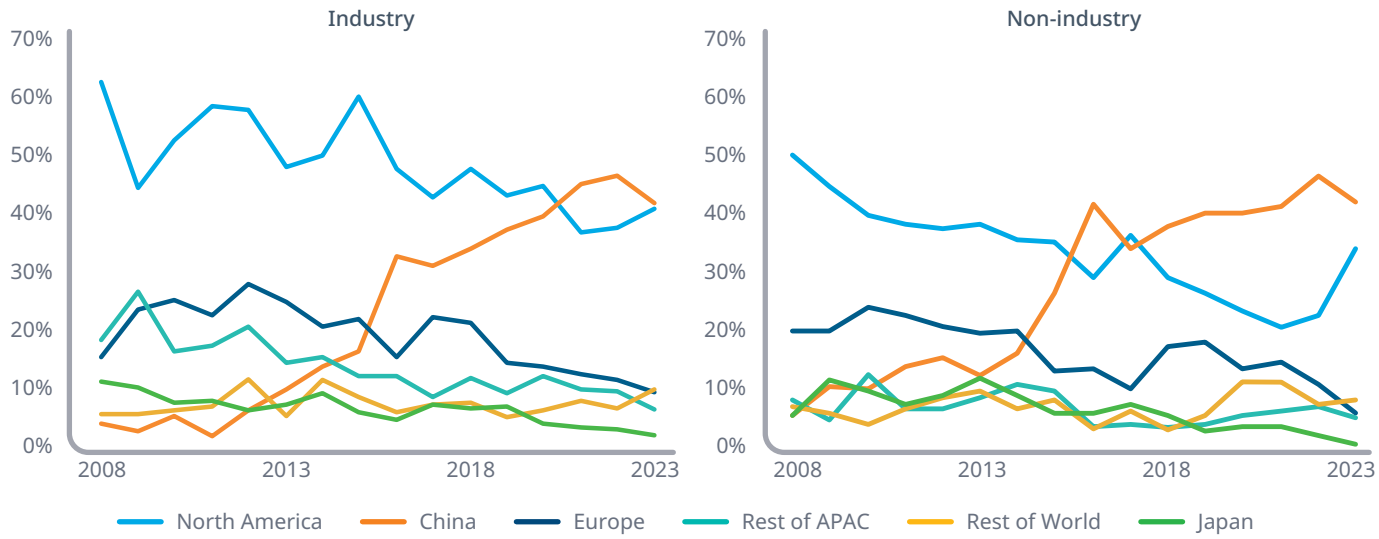


Source: Citeline Trialtrove, Dec 2023; IQVIA Institute, Jan 2024.
Notes: Includes phase I, II, and III. Terminated and withdrawn trials were excluded from the analysis. Trials were industry sponsored and interventional. Trial duration is calculated as the time between trial start and the completion of the primary endpoints even as some trial activity may continue after this.

GEOGRAPHIC SHIFTS

The location of clinical trial sites has important implications for the effort required to complete the trial and can impact regulatory approval due to the representativeness of the trial population to the intended treatment population. The geographies where cell and gene therapy trials have been conducted have shifted over the last 15 years (Exhibit 11). In 2008, most trials started had sites in North America, including both industry and non-industry trials. However, North America's representation in clinical trials has decreased over the years, with 41% of industry and 35% of non-industry trials started in 2023 having sites in North America.

Exhibit 11: Share of cell and gene therapy trial starts with sites by geography, 2008–2023



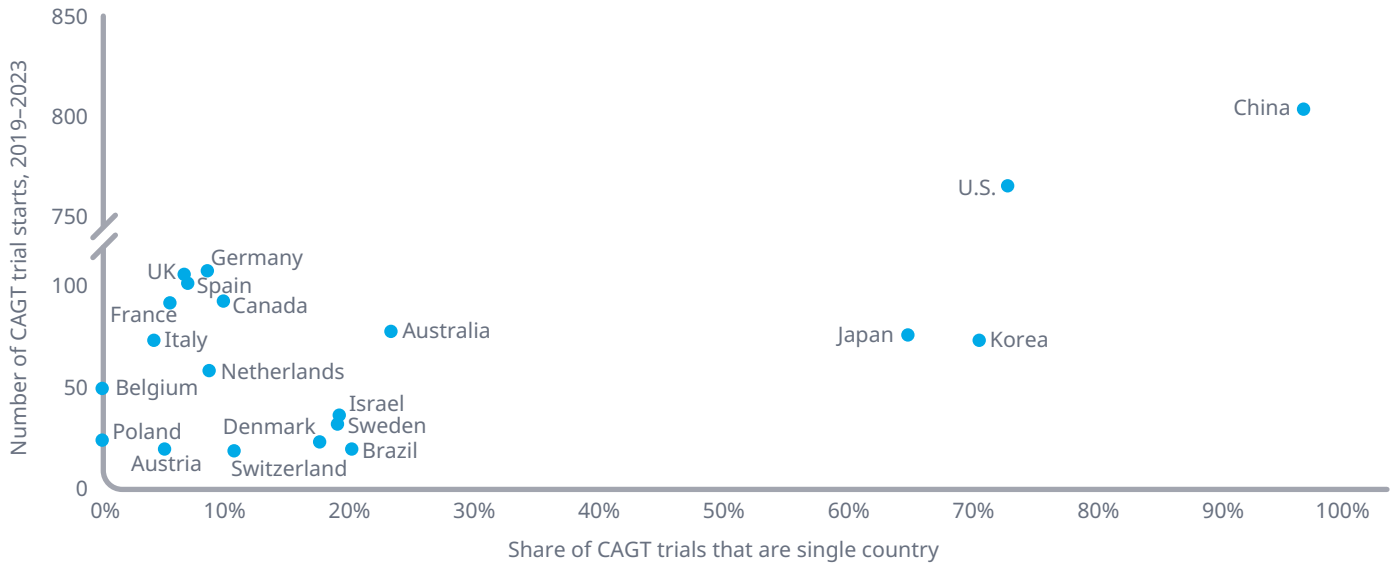
Source: Citeline Trialtrove, Dec 2023; IQVIA Institute, Jan 2024.
Notes: Includes phase I, II, and III. Terminated trials are included to track the activity still involved with their initiation, partial execution and termination. Trials are interventional trials. Trial geographies are based on disclosed information and trials may have sites across multiple geographies.

Despite a declining share, trials with sites in North America have more than doubled over the last decade, with 167 started in North America in 2023. Europe had 39 trials started in 2023 with sites there, up from 27 in 2014. Like North America, Europe has also seen a decline in the share of cell and gene therapy trials, with only 10% of industry and 7% of non-industry trials started in 2023 taking place in Europe, down from 25% and 20% in 2013, respectively.

A smaller proportion of cell and gene therapy trials are being conducted in North America and Europe as more trials are run in China. In 2008, only 4% of industry and 6% of non-industry trials had clinical sites in China, with only 12 trials started across all sponsor types. By 2018, this had increased to 34% of industry and 39% of non-industry trials treating patients in China as the number of trials started grew to 195. For non-industry trials, the share of trials with sites in China surpassed the share in North America in 2016, while for industry trials, this shift did not occur until 2021. This reflects the significant contribution of academic and other non-industry sponsors to Chinese biotech. By 2023, the number of trials started in China grew to 267 across industry and non-industry sponsors, up 37% from 2018. In 2023, North America saw an increase in the share of trials, while China experienced a slight decline. This could be a single-year anomaly or indicate a potential shift back to North American trials, as U.S. regulators have indicated that clinical trial data from single foreign countries may not be applicable to the U.S. population.[43,44]

Cell and gene therapy trials tend to have small geographic footprints in only a few countries due to the complex infrastructure and treatment involved in these therapies (see Exhibit 10). Certain geographies have more trials taking place within a single country rather than being multinational (Exhibit 12). Despite China's growing representation in clinical trial activity with 804 trials started in the last five years, 96% of these trials are taking place only in China. This stands in stark contrast to other countries, which are more likely to have multinational trials. The U.S. has the second-highest number of trials at 765, with 73% of these trials having trial sites only in the U.S. Despite a smaller number of trials, Korea and Japan have similar

Exhibit 12: Number of cell and gene trial starts within top 20 geographies and share that are single-country, 2019–2023



Source: Citeline Trialtrove, Dec 2023; IQVIA Institute, Jan 2024.
Notes: Includes phase I, II, and III. Trials are industry-sponsored, interventional trials. Trial geographies are based on disclosed information and trials may have sites across multiple countries.

proportions of single-country trials to the U.S. at 70% and 64%, respectively. Rounding out the top 20 are Australia, Brazil, Israel, and Western European countries, where trials being conducted there are more frequently multinational studies.

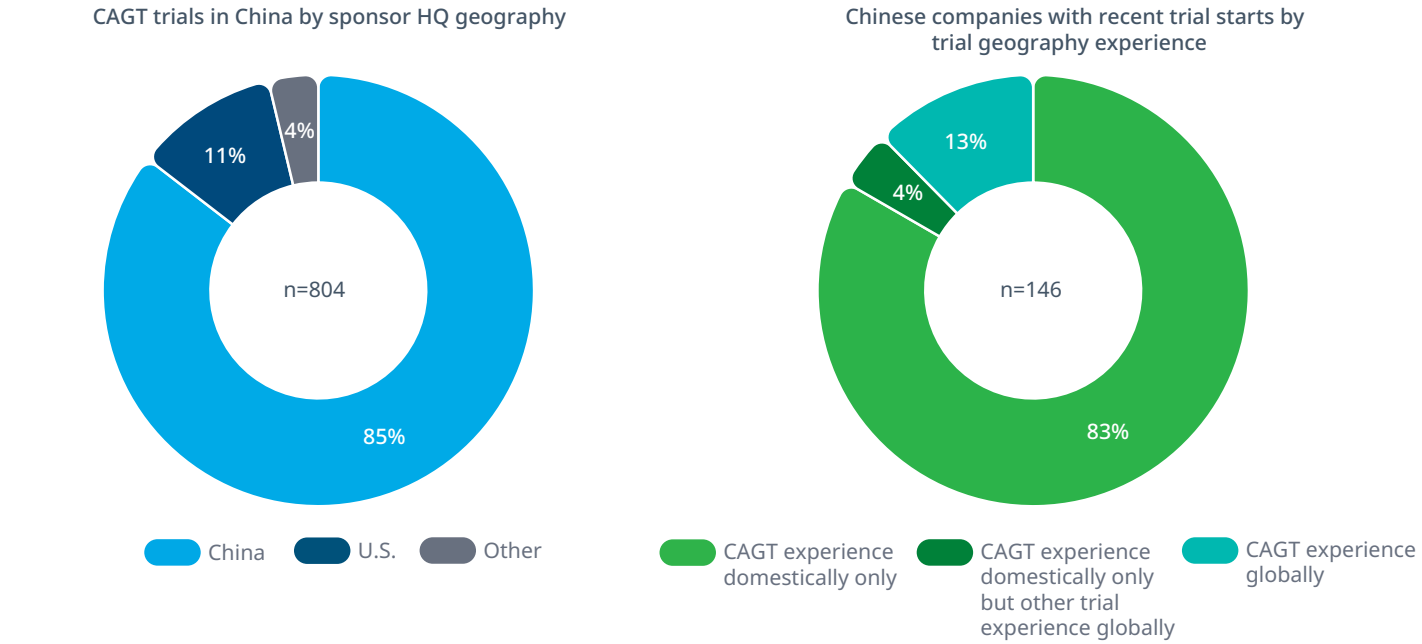
Given the increasing contribution of China to cell and gene therapy clinical research and the self-contained nature of the current activity, it is important to understand the potential future global impact of research originating from China. Of the 804 cell and gene therapy trials started in the last five years that have sites in China, 85% are sponsored by China-headquartered companies (Exhibit 13). U.S.-based companies account for 11% of Chinese trial activity, and the remainder of the trials are sponsored by multinational partnerships or companies from other geographies.

The 647 trials being run in China by Chinese companies are spread across 146 companies (Exhibit 13). These companies have a range of experience in performing clinical research both within China and globally.

This could be an indicator of the potential reach of cell and gene therapies coming out of China, as Chinese companies with global experience may more easily be able to take their products to international markets. Of the Chinese companies with recent trial activity in China, only 35 (17%) have experience conducting trials outside of China, with 26 of these companies having conducted cell and gene therapy trials globally. The remaining 83% of Chinese companies only have domestic experience and may require additional resources or partnerships with multinational companies to bring their therapies to the global market.

China has played a growing role in cell and gene therapy trial activity with 804 trials started in the last five years and 96% of these trials taking place only in China.

Exhibit 13: Characterization of industry-sponsored cell and gene therapy trial starts in China by sponsor geography and trial experience, 2019–2023



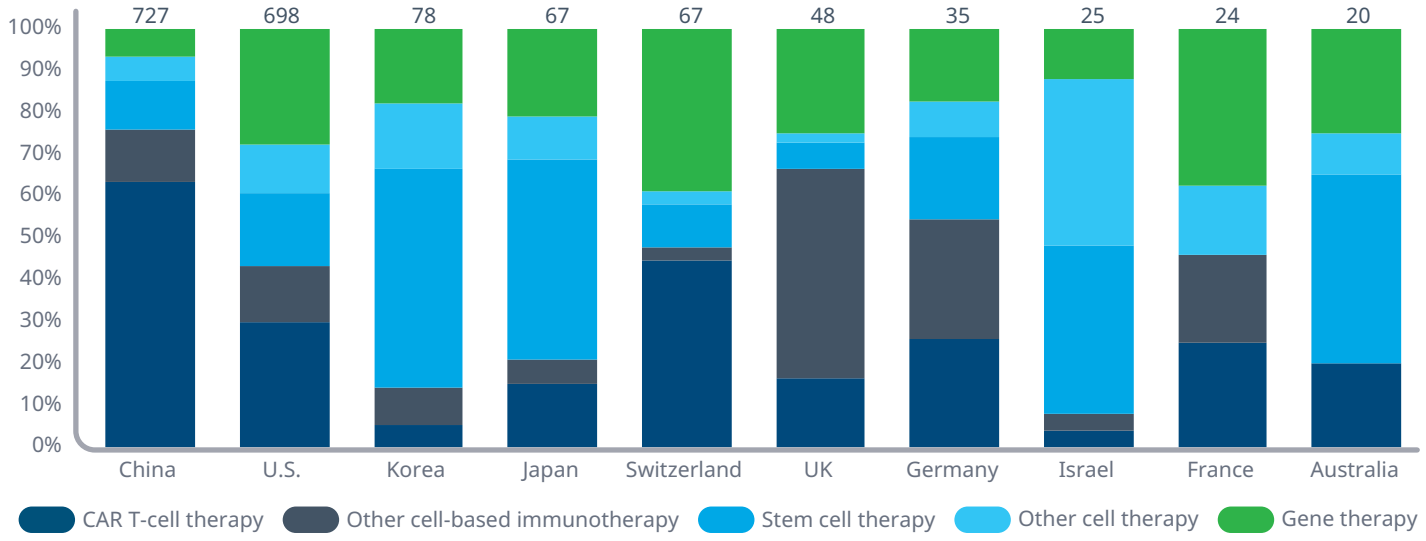
Source: Citeline Trialtrove, Dec 2023; IQVIA Institute, Jan 2024.
Notes: Includes phase I, II, and III. Trials are interventional trials. Trials that include sponsors from multiple geographies are included in Other. Trial experience is based on disclosed trial site locations. Sponsor names could change through mergers and acquisitions, which are not accounted for.

One example of a multinational partnership is that between Legend Biotech and Janssen, whose collaboration to develop and commercialize Carvykti has led to the approval and launch of the product in several major markets.[45] A potential limiter of growth in cell and gene therapy activity in China is the government's restriction on foreign investment in "the development and application of human stem cell, genetic diagnosis, and treatment technologies."[46]

Trial geographic footprint is not the only difference in cell and gene therapy companies across different geographies; the modalities most frequently researched also vary with company headquarters location. Chinese companies have a significant focus on CAR T and other cell-based immunotherapies, which account for 76% of Chinese companies' trial activity in the last five years (Exhibit 14).

U.S.-based companies have a more diverse portfolio, with 43% of activity in cell-based immunotherapies, 29% in stem cells and other cell therapies, and 28% in gene therapies. Swiss companies have the largest focus on gene therapies, at 39% of trials, largely driven by Novartis. Japanese and Korean companies have a strong focus on stem cell therapies; induced pluripotent stem cells (iPSCs) have long been a cornerstone of advanced therapy research in Japan.[47] UK-based companies have 50% of their recent clinical activity in cell-based immunotherapies outside of CAR T, including T-cell receptor (TCR) and tumor-infiltrating lymphocyte (TIL) cell therapies.

Exhibit 14: Share of industry-sponsored cell and gene therapy trial starts by sponsor headquarter geography and type, 2019–2023



Source: Citeline Trialtrove, Dec 2023; IQVIA Institute, Jan 2024.
Notes: Includes phase I, II, and III. Terminated trials are included to track the activity still involved with their initiation, partial execution and termination. Trials are industry-sponsored, interventional trials. Trials may involve multiple sponsors and are included in geographies of all involved sponsors. Other cell-based immunotherapies includes T-cell receptor, tumor-infiltrating lymphocyte, natural killer, and dendritic cell therapies.

Regulatory review, approvals, and new launches

+ **As of the end of 2023, a total of 76 cell and gene therapies have launched globally — more than double the number of therapies that had been launched through 2013 — including 20 launched in the last three years.**

+ **Access to cell and gene therapies across geographies is not uniform and primarily limited to developed markets, with gene therapies and cell-based immunotherapies having the greatest acceptance across markets.**

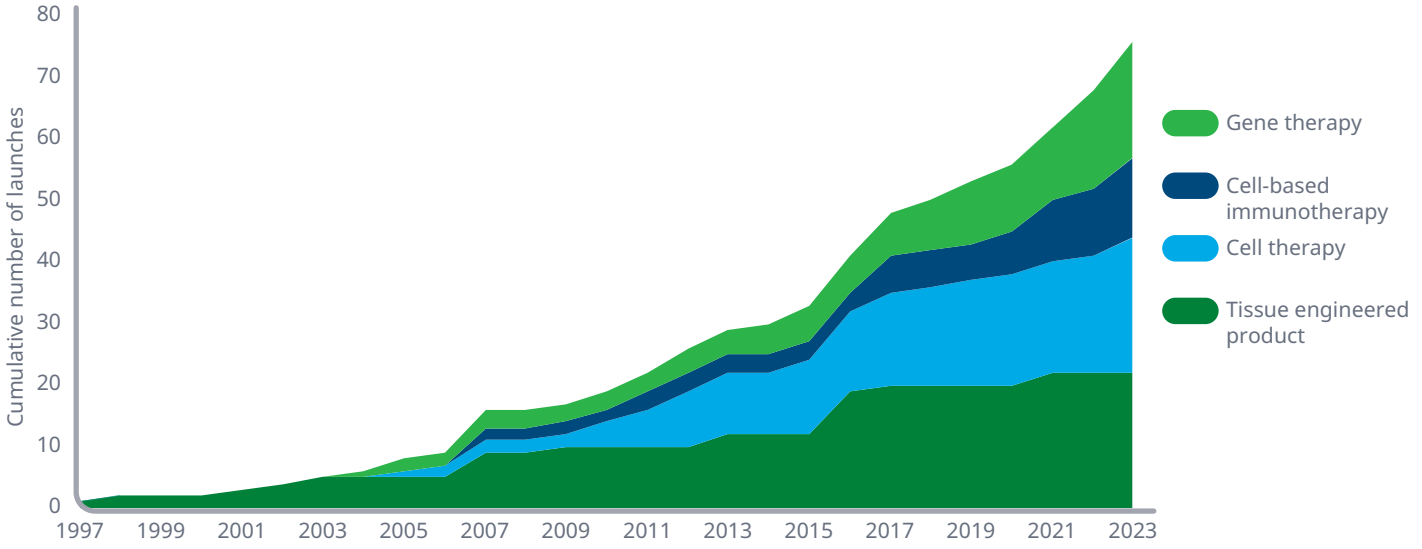
+ **Eight cell and gene therapies launched globally in 2023 with a median time from first clinical trial to launch of 10 years, as expedited development and review programs shorten time to treatments being available to patients.**

+ **Regulatory review is not harmonized globally with varying requirements across geographies and regulators, although efforts to improve harmonization are underway.**

NEW LAUNCHES

Cell and gene therapies include cell-based immunotherapies, cell therapies, gene therapies, and tissue-engineered products. The first of these therapies to receive regulatory approval and launch commercially was Transcyte, a tissue-engineered skin substitute for the treatment of epidermolysis bullosa, which launched in the U.S. in 1997 (Exhibit 15). Other early advanced therapies included tissue-engineered products, primarily skin substitutes and cartilage repair products. The first gene therapy, Gendicine, was launched in China in 2004 for the treatment of head and neck cancer. The number of cell and gene therapies available globally increased significantly in 2017 as the first CAR T-cell therapies reached the market. As of the end of 2023, 76 therapies have been launched globally, more than double the number of therapies that had been launched by 2013. However, not all these therapies are still available; for example, Glybera was withdrawn from the market largely due to lackluster commercial performance.[48]

Exhibit 15: Global cumulative cell and gene therapy launches by type



Source: Alliance for Regenerative Medicine, Sep 2023; IQVIA Institute, Oct 2023.
Notes: Includes products with regulatory approval and launch determined based on desk research. Evidence of launch includes sales data, company statements, or availability of patient support websites. When launch evidence is not available, products are assumed launched at approval unless otherwise stated publicly. Year of launch determined by earliest global launch. Includes products which launched and were subsequently withdrawn from the market.

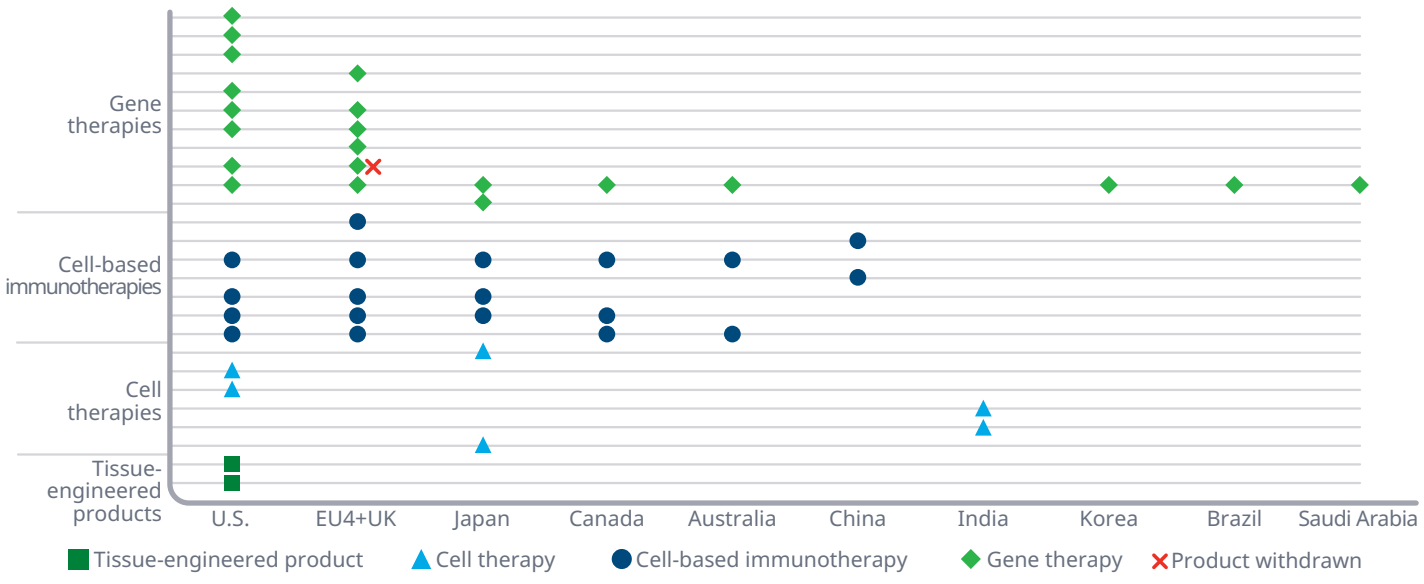
Currently, 58 companies have commercially available cell and gene therapies of which five are large pharma companies — those with greater than $10Bn in annual pharmaceutical sales.

Of the 76 therapies launched to date, 29% are tissue-engineered products primarily used for wound healing, but others include treatments for cardiovascular defects or congenital athymia. Cell therapies, not including cell-based immunotherapies, account for 30% of the available products, with a range of treatments for fistulas, burns, and type 1 diabetes, among others. Cell-based immunotherapies have seen significant growth over the last decade but still represent the smallest share of therapies (16%), with 12 therapies launched globally, all for cancer treatment. Nineteen gene therapies have been launched globally, predominantly for inherited diseases such as inherited retinal dystrophies and SMA.

Access to cell and gene therapies across geographies is not uniform, and thus far, these products are primarily available only in major markets (Exhibit 16). In the last five years, 26 new therapies have been launched globally, with 16 of these launching in the U.S. and 11 in major European markets (France, Germany, Italy, Spain, and the UK). However, one has since been withdrawn from Europe by the company (Zynteglo). All nine new tissue-engineered products and cell therapies have launched in only a single geography. This reflects the longer-term trend where these products often are not available globally. Cell-based immunotherapies have seen wide acceptance across geographies, with four of the six launched in the last five years available in three or more countries; however, they remain mostly in developed markets. Gene therapies, which have more than doubled in the past five years (Exhibit 15), are primarily limited to the U.S. and major European markets. Nevertheless, Zolgensma for the treatment of SMA has launched widely, is approved in over 50 countries,[49] and available across both developed and developing cell and gene markets, such as Brazil and Saudi Arabia. However, it is not available in China or India.

Despite the significant amount of clinical research in China (Exhibit 11), few products have made it to the market to date. Five cell and gene therapies have received regulatory approval and launched in China to date: two gene therapies and three CAR T-cell therapies.

Exhibit 16: Availability across select markets of cell and gene therapies launched globally 2019–2023



Source: Alliance for Regenerative Medicine, Dec 2023; IQVIA Institute, Jan 2024.
Notes: Each line represents a single therapy and symbols represent availability in that geography. Products available by country reliant on company announcements and publicly available information as of December 31, 2023. Products sorted within type by launch year (earliest on bottom).

In the last five years, two CAR T-cell therapies have launched in China. One, Carteyva, was developed by JW Therapeutics using the same CAR construct as Juno Therapeutics' (Bristol Myers Squibb) Breyanzi,[50] which also launched in the last five years and is available in the U.S., Europe, and Japan. Fucaso, a BCMA-directed CAR T-cell therapy, launched in China in 2023 and has also received orphan drug, regenerative medicine advanced therapy (RMAT), and fast track designations from the U.S. FDA, indicating potential future expansion into the U.S.[51]

Although China has seen few advanced therapy launches thus far, it could serve as an important market in the region with medical tourism. Cell and gene therapy companies with approved products in China have indicated an interest in attracting foreign patients who either don't have access to treatment or the cost of treatment in China is much lower than that of similar products in their home country.[52,53] China's Hainan Province also has the Boao Lecheng International Medical Tourism Pilot Zone, where treatments not approved by the National Medical Products

Exhibit 17a: 2023 global cell and gene therapy launches

Cell therapy

donislecel (Lantidra) – U.S.

Price >$300,000

Indication: Adults with Type 1 diabetes unable to achieve target HbA1c despite prior therapy		**Mechanism:** Allogeneic pancreatic islet cellular therapy
Other available treatments/prior LoT: Insulin		**Patient population:** Affects 0.3% of insulin-dependent diabetes patients
Originator: University of Illinois at Chicago (Academic)	**Marketer:** CellTransInc. (EBP)	**Timeline earliest clinical trial to launch:** 2004 18.7yrs 2023

Cell therapy

neltependocel (Vyznova) – Japan

Price not yet set

Indication: Bullous keratopathy of the cornea		**Mechanism:** Allogeneic, fully differentiated corneal endothelial cells (CECs)
Other available treatments/prior LoT: Corneal transplant		**Patient population:** Affects 4% of adults aged 40+
Originator: Kyoto Prefectural University of Medicine (Academic)	**Marketer:** Aurion Biotech (EBP)	**Timeline earliest clinical trial to launch:** 2015 7.6yrs 2023

Cell therapy

omidubicel (Omisirge) – U.S.

Price $338,000

Indication: Patients 12 years and older with hematologic malignancies planned for cord blood transplant to reduce the time to neutrophil recovery and the incidence of infection		**Mechanism:** Nicotinamide modified allogeneic hematopoietic progenitor cell therapy
Other available treatments/prior LoT: Unmanipulated cord blood		**Patient population:** ~350 cord blood derived allogeneic hematopoietic cell transplants in 2021
Originator: Gamida-Cell (EBP)	**Marketer:** Gamida-Cell (EBP)	**Timeline earliest clinical trial to launch:** 2010 12.5yrs 2023

Cell-based immunotherapy

equecabtagene autoleucel (Fucaso) – China

Price not disclosed

Indication: Relapsed or refractory multiple myeloma with at least three prior lines of therapy		**Mechanism:** Autologous BCMA-directed CAR T-cell therapy
Other available treatments/prior LoT: Proteasome inhibitors (e.g., bortezomib), immunomodulators (e.g., lenalidomide), and anti-CD38 monoclonal antibodies (e.g., daratumumab)		**Patient population:** 5.68 per 100,000 people (prevalence of multiple myeloma in China)
Originator: Innovent/ IASO Bio (EBP)	**Marketer:** Innovent/ IASO Bio (EBP)	**Timeline earliest clinical trial to launch:** 2018 4.8yrs 2023

Continued on the next page...

Exhibit 17b: 2023 global cell and gene therapy launches *continued*

Cell-based immunotherapy — **tabelecleucel (Ebvallo) – EU** — **Price not disclosed**

Indication: Relapsed or refractory Epstein-Barr virus positive post-transplant lymphoproliferative disease (EBV+ PTLD) with at least one prior therapy		**Mechanism:** Allogeneic, EBV-specific T-cell immunotherapy
Other available treatments/prior LoT: rituximab +/-reduction in immunosuppression		**Patient population:** Affects 2–20% of patients depending on transplant type, more common in solid organ transplants than hematopoietic cell transplants
Originator: Memorial Sloan Kettering Cancer Center (Academic)	**Marketer:** AtaraBiotherapeutics / Pierre Fabre (EBP)	**Timeline earliest clinical trial to launch:** 1995 — 28.2yrs — 2023

Gene therapy — **beremagene geperpavec (Vyjuvek) – U.S.** — **Price $631,000 per year**

Indication: Treatment of wounds in patients with dystrophic epidermolysis bullosa with mutations in the COL7A1 gene		**Mechanism:** Topical herpes-simplex virus type 1 (HSV-1) vector-based gene therapy delivering functional copies of the human COL7A1 gene to keratinocytes and fibroblasts
Other available treatments/prior LoT: Symptom care including bandaging and pain management		**Patient population:** 1 to 9 cases per 1,000,000 people
Originator: Krystal Biotech (EBP)	**Marketer:** Krystal Biotech (EBP)	**Timeline earliest clinical trial to launch:** 2018 — 5.2yrs — 2023

Gene therapy — **delandistrogene moxeparvove (Elevidys) – U.S.** — **Price $3.2Mn**

Indication: Children aged 4 through 5 years old with Duchenne muscular dystrophy (DMD) who have a confirmed mutation in the dystrophin gene		**Mechanism:** AAV vector-based gene therapy carrying a transgene encoding a micro-dystrophin protein
Other available treatments/prior LoT: Corticosteroids, antisense oligonucleotides		**Patient population:** affects 1 in 3,500 male births
Originator: Nationwide Children's Hospital (Academic)	**Marketer:** Sarepta Therapeutics (EBP)	**Timeline earliest clinical trial to launch:** 2018 — 5.6yrs — 2023

Gene therapy — **nadofaragene firadenovec (Adstiladrin) – U.S.** — **Price $240,000 per year**

Indication: treatment of adult patients with high-risk, Bacillus Calmette-Guérin (BCG)-unresponsive non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS)		**Mechanism:** Non-replicating adenoviral vector-based gene therapy delivering a copy of a gene encoding a human interferon-alfa 2b (IFNα2b) to the bladder urothelium
Other available treatments/prior LoT: Bacillus Calmette-Guérin (BCG), bladder removal surgery, pembrolizumab		**Patient population:** More than 80,000 estimated new cases of bladder cancer in U.S. in 2023, 75-80% of new cases are NMIBC and 70% of patients will respond to BCG therapy
Originator: Schering-Plough (Large)	**Marketer:** Ferring Pharmaceuticals (Small)	**Timeline earliest clinical trial to launch:** 2011 — 12.5yrs — 2023

Notes: Originator is based on the company which filed the first patent, and the company segmentation is applied based on revenue or R&D spend at the time of the patent filing. Marketer is the company granted marketing authorization by the relevant regulatory body in the country of first launch. Other available treatments represent current alternative treatment options or prior lines of therapy for conditions where no other therapy is available. Patient populations are estimates based on desk research and available epidemiology data. Price is publicly available list price in first launch country.
Source: IQVIA Institute, Dec 2023.

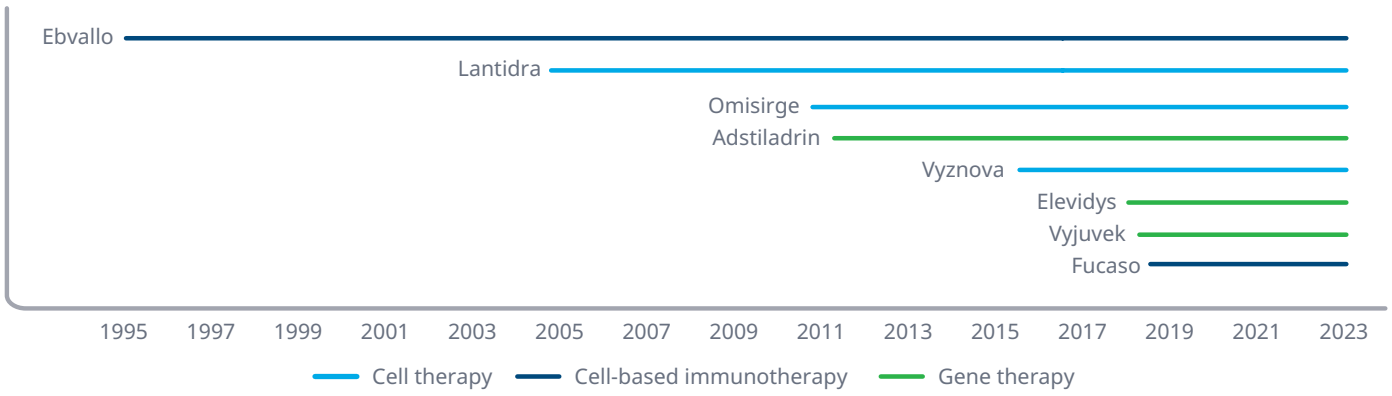
Administration (NMPA) but approved elsewhere globally can be imported and used to treat patients within the Pilot Zone. This provides limited access to some of these therapies to both Chinese and international patients.[54]

In 2023, eight new cell and gene therapies were launched globally, many of which represent significant advances in how patients are treated (Exhibit 17). These include the first cell and gene therapy available for the treatment of diabetes, alternatives to traditional corneal and cord blood transplants, a topical gene therapy, and the first gene therapy for the treatment of Duchenne muscular dystrophy (DMD). Five of the eight new launches occurred in the U.S., and they may reach other markets in the future. China had one new cell and gene therapy launch in 2023, with the approval and launch of Fucaso, a BCMA-directed CAR T-cell therapy for the treatment of multiple myeloma, marking the first advanced therapy for multiple myeloma in China. The prices for these new therapies, where information is available, range from $240,000 per year to $3.2Mn.

Both Adstiladrin and Vyjuvek are on the lower end of the pricing range for gene therapies (Exhibit 30), given the potential for multiple doses, compared to Elevidys which has a much higher price but is intended to be a one-time treatment.

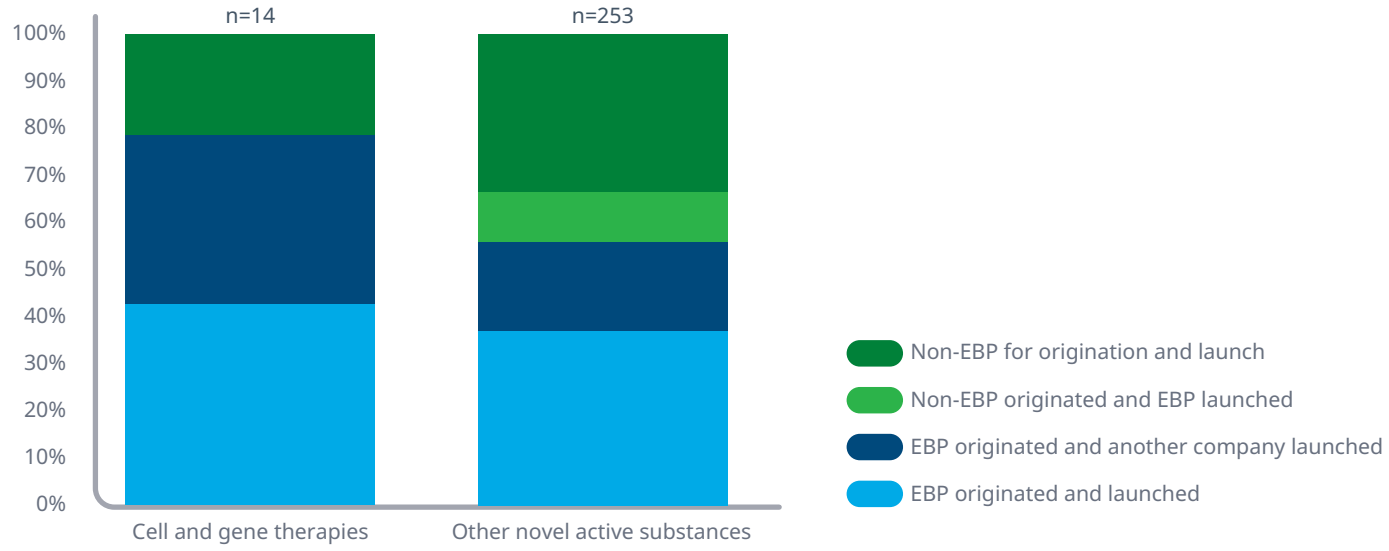
The time it takes for these therapies to reach the market varies, with the 2023 launches taking anywhere from 28 years to 5 years from the start of clinical trials to commercial launch. The median time it took for therapies launched in 2023 to reach the commercial market was 10 years (Exhibit 18). The speed at which patients gain commercial access to these treatments can be accelerated through regulatory development and review programs (Exhibit 21).

Exhibit 18: Timeline of start of first clinical trial to global launch for 2023 new cell and gene therapies



Source: IQVIA Institute, Dec 2023.
Notes: Time is counted from the start of the first known human trial to the first launch globally (not approval).

Exhibit 19: Companies originating and filing cell and gene therapies vs. other novel active substances launched in U.S., 2019–2023



Source: IQVIA Institute, Jan 2024.
Notes: Includes novel active substances launched in the United States 2019-2023 regardless of the timing of FDA approval. Does not include tissue-engineered products. Originator segment is based on the company which filed the first patent, and the company segmentation is applied based on revenue or R&D spend at the time of the patent filing. Launch company segmentation has been assessed based on the company granted marketing authorization by the FDA. EBP includes academic institutions.

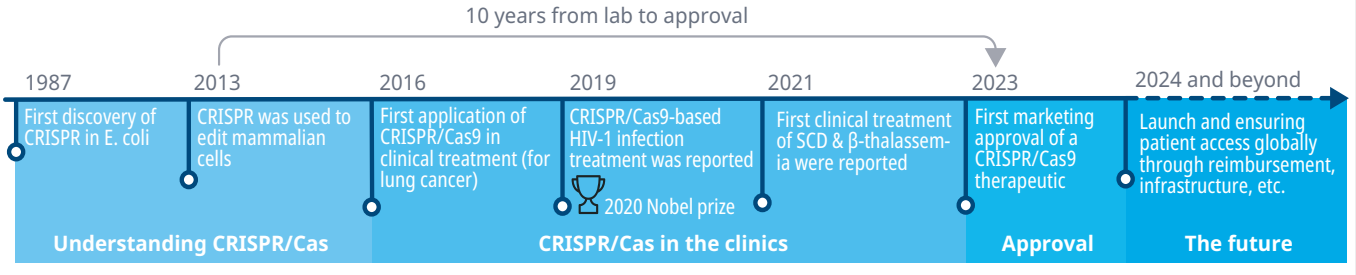
The majority of cell and gene therapies are originated from emerging biopharma companies, including academic institutions (Exhibit 19). In the last five years, 79% of cell and gene therapy launches were originated by emerging biopharma companies, compared to 56% for other novel medicines. However, nearly half of these cell and gene therapies are then acquired and launched by a larger company. This contrasts with other novel medicines where only one-third of emerging biopharma originated medicines are launched by a larger company and reflects the increased complexity of bringing these products to market compared to other modalities.

FIRST GENE EDITING TECHNOLOGY GRANTED REGULATORY APPROVAL

Gene therapies marketed to date have focused on adding genes to patients' cells to address genetic defects that are the cause of diseases. The field of cell and gene therapy took a significant leap forward in 2023 with the first approval of a gene-editing therapeutic, exagamglogene autotemcel or Casgevy. Casgevy is an ex vivo CRISPR/Cas9 genome-editing therapy, first approved globally for patients with sickle cell disease and beta thalassemia in November 2023.[55] This approval represents the first for a CRISPR-based gene-editing therapy and a move for cell and gene therapies into larger population diseases.

CRISPR can be used to insert or delete nucleotides, causing gene disruption, or to insert genes into a DNA strand. Other gene-editing technologies are in the pipeline, with CRISPR-based therapeutics using both Cas9 and other nucleases, and zinc finger technologies accounting for the bulk of researched therapeutics.[56] CRISPR was first discovered in 1987 and was first used in preclinical tests for gene editing in cells in 2013.[57] Just three years after CRISPR/Cas9 entered clinical research and 10 years after initial lab tests, the first CRISPR/Cas9 therapeutic received regulatory approval. This is a rapid evolution for a complex technology, although the journey to patient access has just begun, as reimbursement, infrastructure, and other barriers must be overcome to ensure equitable patient access to treatment (Exhibit 20).

Exhibit 20: Brief history of CRISPR development



Source: Lutzmayer S, Wright A. Rewriting the Code: Gene-editing Therapeutics. IQVIA. 2023 Jul 6. Available from: https://www.iqvia.com/blogs/2023/07/rewriting-the-code-gene-editing-therapeutics

The approval of Casgevy and another gene therapy for sickle cell disease, Lyfgenia, also signifies a shift in advanced therapies toward diseases with larger patient populations. An estimated 25,000 patients will be eligible for treatment in the U.S. and the European Union. This contrasts with gene therapies currently on the market, which have a combined patient population of less than 34,000.[58] As more advanced therapies are developed, it is likely that they will reach larger patient populations as the focus of disease treatment shifts from rare diseases to those affecting larger populations. However, in some cases these treatments may struggle to reach the patients who need them most, as the prevalence of certain diseases, such as sickle cell disease, can be highest in low- and middle-income countries where access is likely to be limited. A crucial test for the future of gene editing therapies, and the cell and gene therapy sector overall, entering larger disease markets, will be the ability of Casgevy to overcome global access and uptake barriers.

REGULATORY FRAMEWORKS

As the cell and gene therapy space has expanded over the last decade, regulators have worked to keep up with the increasing demands for the review of development programs and marketing applications. Countries with longer histories of working with these therapies, such as the U.S. and EU, have more established frameworks for regulation. In contrast, emerging economies, such as Vietnam and Indonesia, which have little experience with these products, lack a framework for assessment (Exhibit 21). However, even in established markets, regulatory definitions, pathways, and requirements can vary and the patchwork implementation of regulatory frameworks has led to differences across geographies.

Countries differ in how they classify cell and gene therapies, which can lead to different regulatory controls and pathways. In the EU, the European Medicines Agency (EMA) has developed a separate pathway for cell and gene therapies and regulates them as advanced therapy medicinal products (ATMPs). ATMPs are classified into one of four major groups: gene therapy medicines, somatic-cell therapy medicines, tissue-engineered medicines, or combined ATMPs.[59] In the U.S., cell and gene therapies

Regulatory review is fragmented and sometimes inconsistent, however efforts are underway to improve harmonization which is expected to improve regulatory efficiency in the coming years.

Exhibit 21: Cell and gene therapy regulatory framework in select countries

Country and regulator	U.S. (FDA)	EU (EMA)	JAPAN (PMDA)	AUSTRALIA (TGA)	SINGAPORE (HSA)	MALAYSIA (NPRA)	VIETNAM (DAV)
Regulatory category	Biologics	Advanced Therapy Medicinal Products (ATMPs)	Regenerative medicine	Biologics or biological medicines	Cell, tissue, and gene therapy products (CTGTPs)	Cell and Gene Therapy Products (CGTPs)	Biologics
Regulatory classification and controls (for non-minimally manipulated products)	Can be regulated as: • Biologic • Device • Human cell, tissue, and cellular and tissue-based product (HCT/P) • Combination product Premarket approval is required	Can be regulated as: • Gene therapy • Somatic cell therapy • Tissue-engineered medicines • Combined ATMPs Products that are non-homologous and non-minimally manipulated require premarket approval	Cell therapies (CTs) that are non-minimally manipulated fall under Class I (high risk) and Class II (medium risk) products Ex-vivo gene therapies (GTs) are handled like Class I CTs and follow CT procedures All Class I and II CTs and ex vivo/in vivo GTs are subject to regulatory review and approval	Fall under Class III (medium risk) and Class IV (high risk) products All cell and gene therapies, regardless of class, must apply for approval to get included in the Australian Register of Therapeutic Goods (ARTG). Class III and IV products require close-to-full and full regulation respectively	Class II products, require premarket approval from HSA	Class II products, require premarket approval from Drug Control Authority (DCA)	No regulatory classification, administered the same controls as conventional pharmaceutical products
Approval pathways	• Accelerated approval • Breakthrough therapy • Fast track • Orphan • Priority review • Regenerative Medicine Advanced Therapy (RMAT)	• Accelerated assessment • Conditional Marketing Authorisation • PRIME • Orphan	• Priority review, orphan • Conditional and time-limited approval • SAKIGAKE	• Orphan • Provisional approval • Priority review	• Abridged route that has been approved by at least one of HSA's comparable overseas regulator (COR)	• Conditional approval • Priority review	• Absence of cell and gene therapy specific or priority pathways in general • Follows the same approval pathways as other drugs

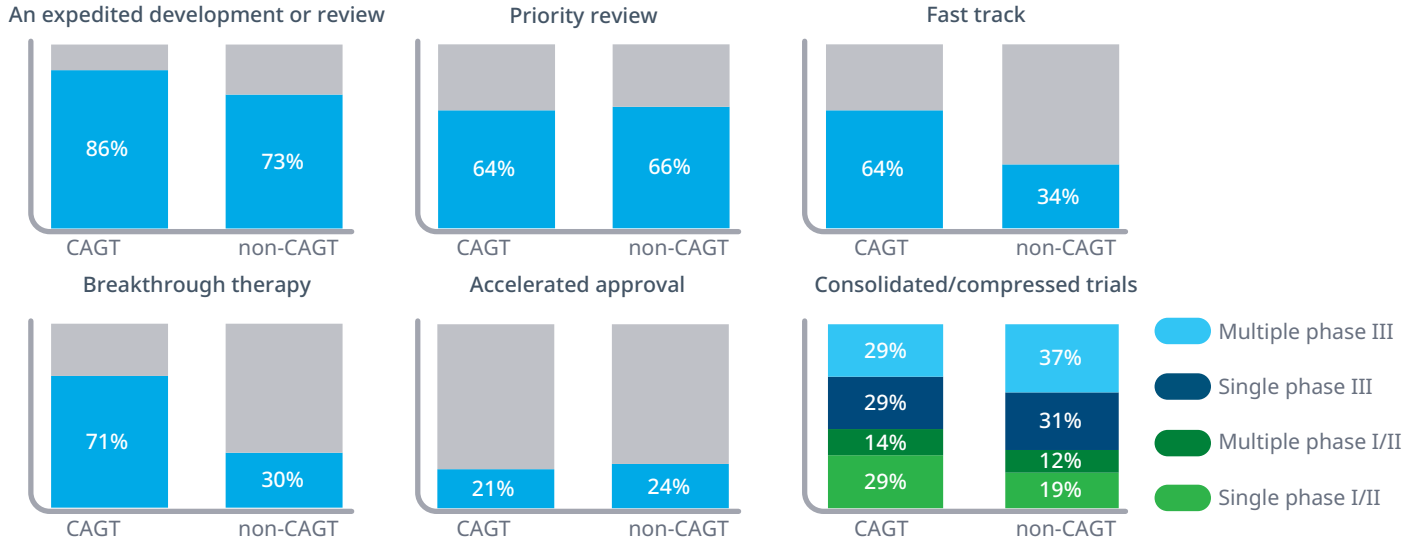
Source: Navigating the Diverse Cell, Tissue, and Gene Therapy Landscape in Japan and Asia Pacific (JAPAC), IQVIA, Aug 2022.
Available from: https://www.iqvia.com/locations/asia-pacific/blogs/2022/08/navigating-the-diverse-cell-tissue-and-gene-therapy-landscape-in-japan-and-asia-pacific

are regulated as biologics through the Center for Biologics Evaluation and Research (CBER), with specific guidelines in place for these therapies.[60] Other countries, such as Japan and Singapore, regulate these products based on risk classifications, with minimally manipulated cell therapies being the lowest risk and gene-modifying therapies the highest risk. These differences in regulatory processes can create challenges for cell and gene therapy developers seeking regulatory approval across multiple geographies.

Efforts are underway globally to harmonize the regulatory review of advanced therapies. The International Council for Harmonisation (ICH), which brings together regulatory agencies globally to foster the harmonization of pharmaceutical regulatory activity, established a Cell and Gene Therapies Discussion Group in 2023 to develop "a roadmap of potential harmonization areas" for cell and gene therapies.[61] Additionally, the FDA recently announced the Collaboration on Gene Therapies Global (CoGenT Global) Pilot program to facilitate information sharing between regulatory agencies to expedite regulatory review and make the process more efficient for companies, similar to the framework used for oncology medicines under Project Orbis. The initial participants in this pilot will include the FDA, EMA, PMDA, Health Canada, and Swissmedic.[62] Regulatory harmonization could ease the burden on companies for submissions and decrease disparities in access across geographies.

Regulatory authorities provide a variety of programs to accelerate the development and review of medicines, with some specific to cell and gene therapies. For U.S. cell and gene therapy launches in the past five years, 86% had some form of expedited development or review (Exhibit 22), which is only slightly higher than the 73% of all other novel drugs that had expedited programs, reflecting the frequent use of these programs for novel medicines to expedite time to patient access. Nearly two-thirds of cell and gene therapies received priority review, cutting approximately four months off the FDA's review time.[63]

Exhibit 22: U.S. cell and gene therapy (n=14) vs. other novel active substance (n=253) launches by characteristics of approval, 2019–2023



Source: IQVIA Institute, Jan 2024.
Notes: Includes novel active substances — a new molecular or biologic entity or combination where at least one element is new — launched in the United States 2019-2023 regardless of the timing of FDA approval. Does not include tissue-engineered products. Percentages are rounded and may not add to 100%.

Fast track, provided to drugs filling an unmet need, was used nearly twice as often for cell and gene therapies as for other novel medicines. Breakthrough therapy was the most frequently utilized expedited program for cell and gene therapies, with 71% of launches having breakthrough therapy designation, compared to just 30% for other medicines. This reflects that most cell and gene therapies are being developed to treat serious or life-threatening diseases.

Accelerated approval is available similarly across all novel medicines, including cell and gene therapies, of which only three have received accelerated approval. Forty-three percent (43%) of cell and gene therapies launched in the U.S. have been approved based on Phase I and/or Phase II trials alone (including Phase I/II), as these therapies often involve small patient populations and high unmet needs where additional trials may be burdensome and significantly slow down patient access to these therapies. Additionally, more than half (57%) of cell and gene therapies have been approved based on single clinical trials (either Phase I, II, or III).

Additionally, the FDA provides the regenerative medicine advanced therapy (RMAT) designation, which was created as part of the 21st Century Cures Act, for therapies that meet regenerative medicine criteria and show potential for addressing unmet needs. The RMAT designation provides sponsors with the benefits of both the fast track and breakthrough therapy programs, including early engagement with the FDA, rolling review, and discussions to support accelerated approval.[64] Seven cell and gene therapies have been approved with the RMAT designation, including two sickle cell disease gene therapies approved in December 2023.[65]

Similar expedited programs are available across other geographies to accelerate the speed at which patients gain access to advanced therapies. These include PRIME, accelerated assessment, and conditional marketing authorization in the European Union; priority review and provisional approval in Australia; and SAKIGAKE in Japan (Exhibit 21). Another program available for cell and gene therapies in Europe is the EMA's pilot program, which provides guidance to academic and non-profit organizations developing cell and gene therapies on regulatory requirements and the review process to aid in eventual marketing authorization. The EMA has accepted three therapies/organizations into the pilot program as of February 2024 and expects initial results on the efficacy of the program by 2025.[66] Many cell and gene therapies originate and are developed by academic groups, but they often require assistance from a commercial partner to achieve regulatory approval. The EMA's program could allow more therapies from these groups to reach the market.

Expedited programs across geographies can accelerate the time to patient access; 86% of U.S. cell and gene launches in the last five years utilized expedited programs.

Manufacturing and delivery infrastructure

+ **Currently available cell and gene therapies utilize different technologies and cell types which each come with unique manufacturing and logistics needs.**

+ **Cell and gene therapy companies have built varying types of manufacturing networks to fit the needs of their products, and operations are predominantly located in the U.S. and Western Europe, with products shipped globally requiring extensive logistics and increasing product turnaround times.**

+ **Accredited CAR T-cell therapy treatment centers for commercialized products are mostly in developed markets though healthcare facilities with clinical capabilities, as demonstrated through involvement in clinical trials, have wider distribution.**

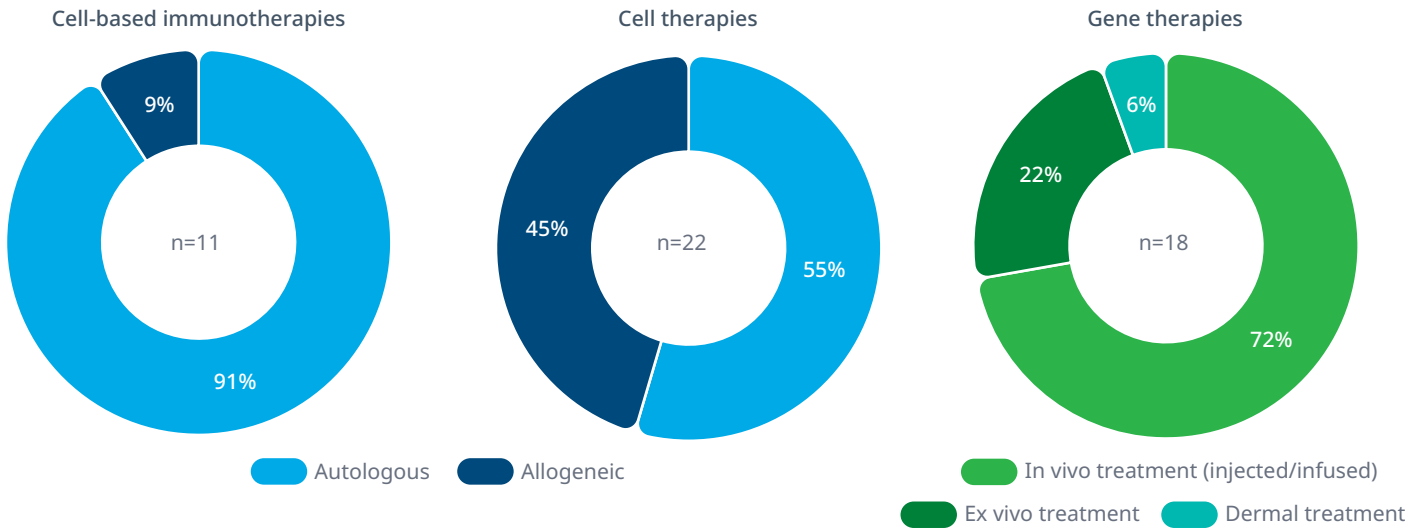
+ **Within countries, treatment center accessibility may be difficult and treatment centers do not necessarily carry all available products.**

MANUFACTURING

Cell and gene therapies have complex manufacturing processes that require a significant and early investment in technology and manufacturing components. During pre-clinical and clinical development and before launching a new cell and gene therapy, companies must work to build infrastructure, including scaling up manufacturing and certifying treatment centers to deliver these complex products to patients. Companies that already have cell and gene therapy products on the market may not require much effort to expand their existing infrastructure to add an additional product to their portfolio; however, companies just entering the market may need significant time and effort to build-out this infrastructure to get their product to patients. Those bringing cell and gene therapies to a commercial market must be prepared to scale up manufacturing and establish a dispersed network of treatment centers to ensure patient access to these therapies.

The manufacturing needs and level of complexity can vary by the type of product. Allogeneic cell therapies, or 'off-the-shelf' therapies, are pre-manufactured and ready to be delivered to the patient upon eligibility. Autologous

Exhibit 23: Cell and gene therapies by cell source and treatment method



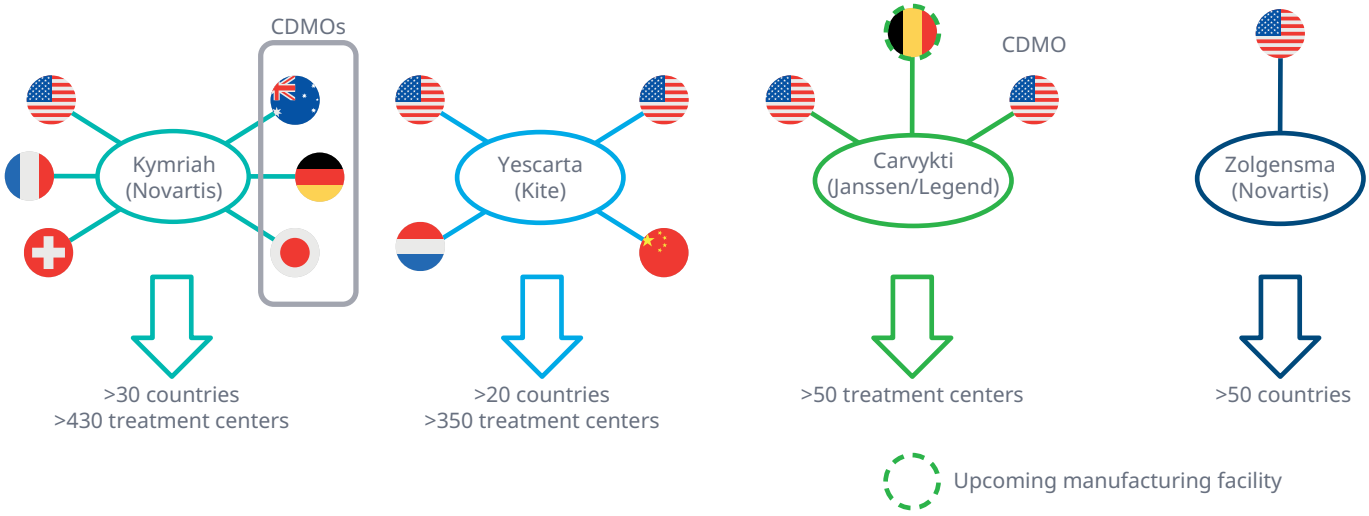
Source: IQVIA Institute, Jan 2024.

cell therapies require additional steps since each batch of the product is unique to every patient: cell collection from the patient, manufacturing and quality control, and transport back to the treatment center for patient transplant/infusion. To date, most available cell therapies and cell-based immunotherapies are autologous (55% and 91%, respectively), requiring additional logistical considerations (Exhibit 23). Additionally, gene therapies have similar distinctions with in vivo treatments available for 'off-the-shelf' injection or infusion, typically delivering copies of the gene that may be damaged or missing. In contrast, ex vivo treatments require the collection of cells from patients and manufacturing before transplant/infusion back to the patient. Unlike cell therapies, 72% of available gene therapies are available 'off-the-shelf' for injection or infusion. However, a growing number of ex-vivo gene therapies have come to market in the last few years, with three launched since 2020.

While the overall mechanisms of producing allogeneic and autologous therapies are similar in reaching the result, the system demands are quite different and can impact the resources needed to increase capacity. Autologous therapies require that cells for a single patient be processed individually; therefore, for manufacturing to scale up, additional equipment may be required to allow for multiple batches to be in production simultaneously. For allogeneic therapies, cells can be handled in larger, pooled batches, and scaling up manufacturing focuses on increasing batch sizes rather than the number of batches running simultaneously.[67] Therefore, the type of therapy has a significant impact on the manufacturing processes needed to produce the product at a scale sufficient for serving a commercial market.

For therapies where genes are modified or introduced (either cell or gene therapies), a vector must be used to introduce the new genetic material. The supply of these vectors can also limit manufacturing capacity. Commercially available CAR T-cell therapies rely on lentiviral vectors to introduce the CAR construct into the patient's T-cells. During the COVID-19 pandemic, these vectors were not immune to the supply chain issues seen across all business sectors. This shortage in viral vectors was further exacerbated by the increased demand for these vectors for COVID-19 vaccines globally, although the introduction of mRNA COVID-19 vaccines, which do not require viral vectors, relieved some of this stress

Exhibit 24: Manufacturing networks for select cell and gene therapy products



Source: Company reports, IQVIA Institute, Dec 2023.
Notes: Each flag represents a single manufacturing site based on company publicly reported information. Countries available and treatment centers are estimates based on historic company announcements. Kymriah CDMOs are: Cell Therapies Pty Ltd (Australia), Fraunhofer-Institut für Zelltherapie und Immunologie (Germany), and Foundation for Biomedical Research and Innovation at Kobe (Japan). Novartis has a deal with Cellular Biomedicine Group to manufacture Kymriah in China, however Kymriah has not yet received regulatory approval and this site is not included here. Carvykti CDMO is Novartis (U.S.).

on the system.[68] Drug manufacturers have identified vectors as a critical supply resource and have invested significant resources in manufacturing capacity.

To address these manufacturing hurdles, cell and gene therapy marketers have adopted various approaches to commercially manufacture their products (Exhibit 24). These approaches include having a mixed portfolio that utilizes both in-house manufacturing capacity and contract development and manufacturing organizations (CDMOs) to supplement manufacturing. This is the case for Kymriah, where Novartis has both in-house CAR T manufacturing facilities in the U.S. and Europe and has contracted with CDMOs in other geographies, particularly in the Asia-Pacific region, to support manufacturing in those areas. Due to manufacturing delays following the launch of Carvykti and limited in-house capacity, Janssen and Legend Biotech have contracted with Novartis to supplement their in-house manufacturing capacity.[69] Additionally, Janssen is bringing an additional manufacturing facility online in Belgium,[70] although adding more facilities for these therapies can be an extensive process given the manufacturing and regulatory requirements. These manufacturing delays for Carvykti have resulted in alternative therapies being provided to patients and are believed to have contributed to the termination of access in the UK.[71,72] For other products, in-house manufacturing alone is sufficient and CDMOs are not utilized, as in the case of Kite's (Gilead) Yescarta and Novartis' gene therapy Zolgensma.

In addition to the manufacturing of the cell or gene therapy itself, companies must consider where they will acquire the starting materials, including viral vectors. Production of these vectors can be done in-house or acquired from a CDMO. Kite opened its own viral vector manufacturing facility in 2022,[73] bringing the end-to-end CAR T manufacturing process in-house, which can be beneficial when there are strains on CDMO capacity. Additionally, Bristol Myers Squibb, which markets CAR T-cell therapies Abecma and Breyanzi, recently acquired a viral vector manufacturing facility from Novartis to increase capacity for the necessary starting materials.[74] This shift toward in-house viral vector manufacturing provides additional supply chain security for cell and gene therapy companies when CDMOs are at capacity or shortages occur. Competition for CDMO manufacturing space among gene therapy developers was a key driver for Krystal Biotech building their own in-house manufacturing facility.[75] Many companies are also evaluating the use of non-viral vectors, such as lipid-based vectors and nanoparticles.[76]

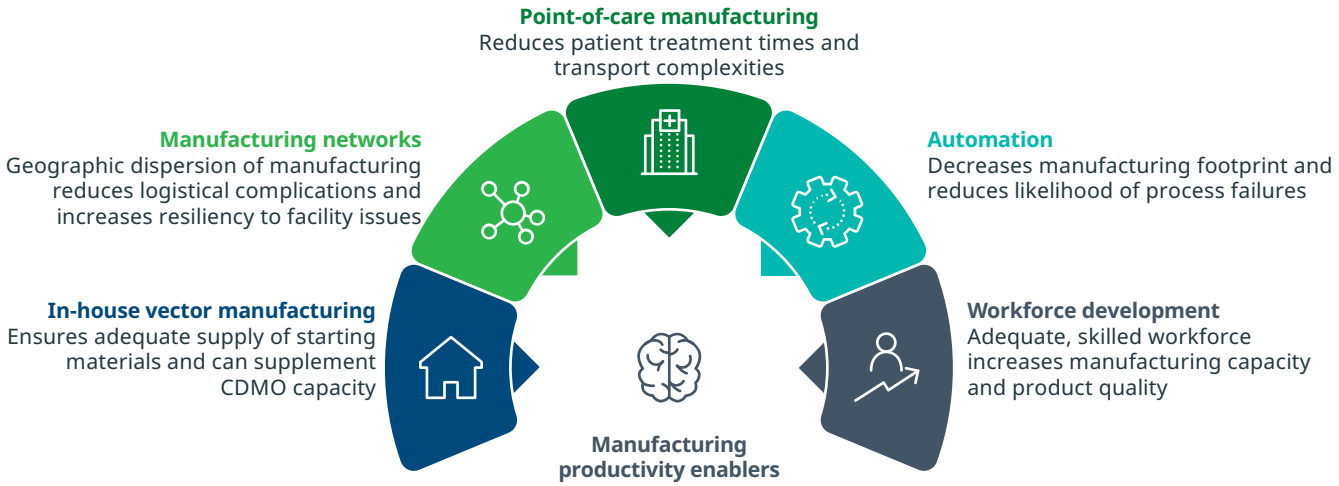
Other considerations for cell and gene therapy manufacturing include the geographic footprint of a company's manufacturing network. Therapies that have gained wide acceptance globally are available across many markets and regions, with Zolgensma approved for treatment in more than 50 countries.[49] Despite this broad dispersion of patient access, manufacturing is predominantly concentrated in the U.S., with some capacity in other major markets. For instance, based on available public information, Zolgensma's manufacturing is concentrated at a single facility worldwide. While this centralized approach to manufacturing can reduce costs related to building additional infrastructure, it can also lead to increased logistical complications in transporting these therapies globally and reduce resilience in the event of an issue at that facility. Autologous therapies require bidirectional transport, which can increase manufacturing times when these facilities are highly concentrated. Consolidated manufacturing may limit the expansion of cell and gene therapies into developing markets.

The complex manufacturing and logistics involved in cell and gene therapies prolong the time to treatment for patients, which can be detrimental given their often-advanced disease state and limited window for treatment effectiveness. Decentralized manufacturing and process improvements can increase manufacturing productivity, decrease turnaround times for these therapies, and thereby increase access (Exhibit 25). For autologous therapies, point-of-care manufacturing is being explored to bring manufacturing closer to the patient and decrease turnaround times from cell collection to infusion. A recent study showed that point-of-care manufacturing can result in reduced time to treatment, as patients in a clinical trial utilizing point-of-care manufactured CAR T-cells received treatment in a median of 7 days,[77] much quicker than the 4 to 5-week turnaround times for centralized manufacturing.

The use of automation in the cell and gene therapy manufacturing process can accelerate treatment timelines. Additionally, automated systems can decrease the space needed for manufacturing and reduce potential process failures that may result from manual manipulation, which can lead to increased costs and time to treatment.[78] Automation allows for parallel production as well, which can increase manufacturing capacity. Point-of-care manufacturing and automation can alleviate some of the logistical issues faced by cell and gene therapies, thereby increasing capacity, reducing time to treatment, and improving patient access.

The manufacturing of cell and gene therapies requires a skilled workforce to deliver these often bespoke products with high quality and rapid delivery of the finished product. As cell and gene therapies become more widely used, an increasing number of skilled workers will be needed to support production, although automating processes may alleviate some of this need.[79] Efforts are underway across many organizations to train and develop the biomanufacturing workforce, including for cell and gene therapies. Workforce development programs are offered by various organizations. One example is the UK's Cell and Gene Therapy Catapult, which provided workforce development activities for nearly 4,000 people in 2023 and has 252 people employed through the Advanced Therapies Apprenticeship Community to provide employment training in the advanced therapies sector.[80]

Exhibit 25: Manufacturing productivity enablers



Source: IQVIA Institute, Feb 2024.

Additionally, the Workforce Development in Biomanufacturing program, a joint effort between the National Science Foundation Engineering Research Center for Cell Manufacturing Technologies (CMaT) and International Society for Cell and Gene Therapy (ISCT), provides both virtual and in-person hands-on training to address labor shortages.[81]

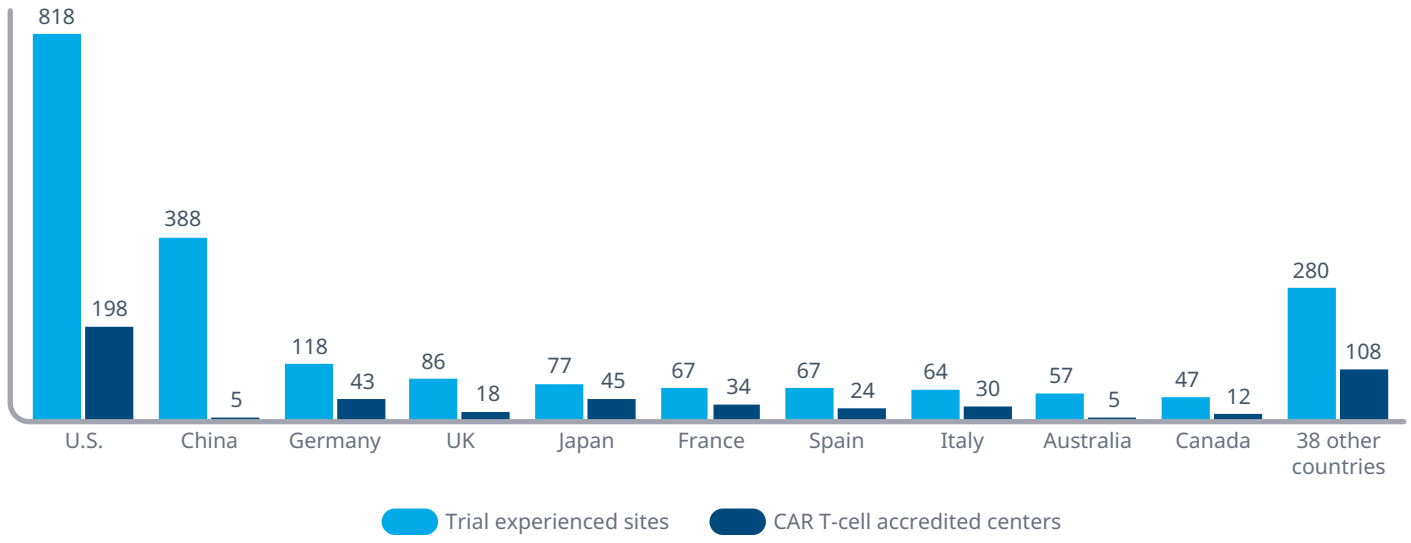
Other efforts include the Biofactory Competence Center in Switzerland, which provides hands-on manufacturing process training and opened a gene therapy facility in 2022 to address the unique skills required for gene therapy production,[82] and the Alliance for Regenerative Medicine's GROW RegenMed Internship Program, which provides paid summer internship opportunities for Black undergraduate and graduate students at cell and gene therapy companies.[83] As the cell and gene therapy sector continues to grow, additional workforce needs will arise; research centers, professional organizations, and other stakeholders play a crucial role in providing specialized skills training for producing these therapies and ensuring a diverse workforce.

TREATMENT CENTERS

In addition to building out a manufacturing network, cell and gene therapy companies must establish a network of treatment centers to deliver their products to patients in a commercial setting. All these advanced therapies involve complex administration and follow-up. To ensure patient safety, they must be administered in certified treatment centers. These centers must be equipped to handle any adverse events that may arise, typically limiting the centers to larger hospital systems where additional capacity may be available.

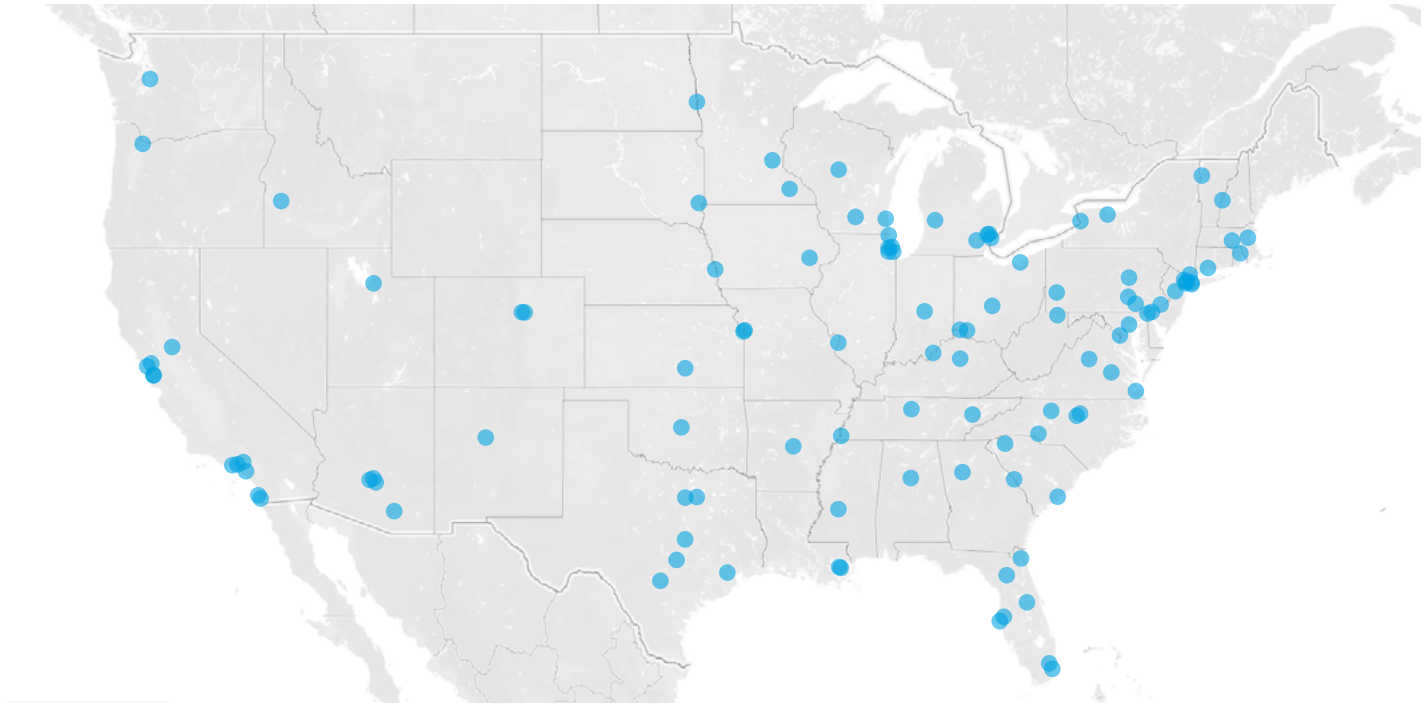
The availability of currently accredited treatment centers varies significantly by country and is concentrated in high-income countries where these therapies are more widely used (Exhibit 26). For CAR T-cell therapies, many hospitals and other clinical trial sites have experience administering these therapies to patients in a research context. In the U.S., 818 clinical trial sites have worked with patients in trials testing CAR T-cell therapies. However, only 198 treatment centers are certified to treat patients with commercially available CAR Ts.

Exhibit 26: Number of research sites or treatment centers with CAR T capabilities by country, Q3 2023



Source: Citeline Trialtrove, IQVIA CAR T-cell Monitor, IQVIA Institute, Sep 2023.
Notes: Accredited CAR T-cell centers based on company disclosure and publicly available information. Some treatment centers may not be reflected in numbers if not disclosed.

Exhibit 27: CAR T-cell treatment centers in the U.S., Dec 2023



Source: IQVIA CAR T-Cell Monitor, updated December 18, 2023.
Notes: Each dot represents one CAR T-cell treatment center. Data collection methodology removes duplicate centers; if adult and pediatric centers within the same health center have different addresses they are combined.

The much larger number of trial experienced sites reflects a potential opportunity for treatment center expansion; however, the resources needed to incorporate these sites into the commercial treatment center network may pose a barrier to broader access. China, which has seen an uptick in CAR T research in recent years (Exhibit 11), has the second-largest number of trial experienced sites but few accredited treatment centers. This is likely because there are currently only two commercially available CAR T-cell therapies in China.

Broad treatment center networks and community-based sites must be established to ensure equitable patient access, as geographic distance can be a barrier to patients accessing therapy (Exhibit 32). In the U.S., CAR T-cell treatment centers are concentrated around larger cities, leaving patients living in more rural areas with long travel distances to access these therapies (Exhibit 27). Additionally, not all centers carry all commercially available products, further complicating the logistics of getting patients treated. Of the 198 CAR T treatment centers in the U.S., 45% carry at least one product for treatment of diffuse large B-cell lymphoma, follicular lymphoma, acute lymphoblastic leukemia, and multiple myeloma; only 22% carry all available CAR T-cell therapies.

In some cases, when treating an extremely rare disorder, a single treatment center may be the only viable option for approved advanced therapies. Strimvelis, a gene therapy treatment approved in Europe for the treatment of adenosine deaminase-deficient severe combined immune deficiency (ADA-SCID), is available at a single treatment center in Milan, Italy, due to the limited shelf-life of the product.[84] However, given that an estimated 15 children are born in Europe each year with ADA-SCID,[85] an extensive treatment center network and decentralized approach would not be realistic. This highlights that each cell and gene therapy product will have specific needs for manufacturing and treatment infrastructure based on the type of therapy and the target patient population.

Reimbursement and payment models

+ **Public reimbursement of cell and gene therapies is variable across major markets with many payers putting restrictions in place that go beyond the product label, potentially limiting patient access.**

+ **Wealthier countries in Western Europe that devote more of their economic resources to healthcare have higher reimbursement rates for cell and gene therapies, while Eastern European countries have limited access.**

+ **The average price across major markets for CAR T-cell therapies is over $350,000 and $1.8Mn for gene therapies, with prices increasing the scrutiny of payers.**

+ **Payers and manufacturers are utilizing a wide variety of innovative payment models to cover the high cost of treatment, although outcomes-based agreements are most common.**

REIMBURSEMENT

Cell and gene therapies have presented challenges to payers when evaluating the cost-effectiveness of these treatments that are often priced significantly higher than other existing therapies. Many questions about the efficacy, durability, and superiority over other treatment options have been raised due to the often-limited data available. These advanced therapies have challenged traditional health technology assessments (HTAs), as clinical data at the time of evaluation is often limited to single arm studies, use of surrogate endpoints, and small patient populations.[86] Additionally, the uncertainty around long-term efficacy of these therapies makes it difficult to determine the economic value of treatment. These challenges have resulted in differing HTA evaluations and reimbursement decisions across countries.[87] Innovative models are required to understand the true value of treatment and ensure consistency across countries. While positive steps have been made in reimbursing cell and gene therapies, reimbursement can be a significant barrier to treatment and is an important step in bringing these therapies to patients.

Exhibit 28: Reimbursement of select products across major markets

tisagenlecleucel (Kymriah)	✓	◐	◐	✓	✓	✓	✓	◐	✓	✓
axicabtagene ciloleucel (Yescarta)	◐	–	◐	✓	✓	✓	✓	◐	✓	✓
ciltacabtagene autoleucel (Carvykti)	✗ [i]	–	✗ [i]	✓	✓	✗ [i]	✓ [ii]	–	–	✓
onasemnogene abeparvovec (Zolgensma)	✓	✓	◐	✓	✓	◐	✓	◐	◐	✓
voretigene neparvovec (Luxturna)	✓	◐	✓	✓	✓	✓	✓	◐	✓	✓

✓ Publicly reimbursed ◐ Limited reimbursement ✗ Not reimbursement – Not launched

Source: IQVIA HTA Accelerator, IQVIA Institute, Dec 2023.
Notes: Reimbursement is determined at a specific point in time and is current as of December 2023. Publicly reimbursed means the product is fully reimbursed through a national reimbursement system. Limited reimbursement means the product is reimbursed but with certain restrictions or conditions, which may include limitations on the indication or patient population.
[i] Carvykti is not reimbursed but currently undergoing evaluation or re-evaluation. [ii] Carvykti is available and undergoing pricing.

Many cell and gene therapies have seen launches across only a handful of countries (Exhibit 16), with CAR T-cell therapies and gene therapies having wider geographic launches. Among those products that have global reach, there are differences in reimbursement that limit access (Exhibit 28). Among CAR T-cell therapies, Kymriah, Yescarta, and more recently, Carvykti, have had launches across most major markets, as well as Zolgensma and Luxturna among gene therapies. These products have regulatory consensus on the benefits for patients; however, many payers across countries have limited views of the value these products bring to the healthcare system.

Brazil has a relatively new cell and gene therapy market, with the first launches occurring within the past few years, and reimbursement has thus far been limited. Kymriah, although widely accepted globally, was approved in Brazil in 2022 and still has limited access, and access is similar for Luxturna. Zolgensma has better access compared to other advanced therapies in Brazil, but this was only after significant negotiations between the manufacturer and health system, as well as interventions by patients and the court system. Although Zolgensma received regulatory approval in 2020, the health system set the maximum price 77% lower than the manufacturer's requested price, resulting in the manufacturer's decision not to market the product in Brazil.[88] Many families with children diagnosed with SMA sued the government for access to Zolgensma under Brazil's right to health law, and courts ordered the government to provide access to treatment in over 100 cases.[89] In 2023, Brazil included Zolgensma on the reimbursement list following the negotiation of an outcomes-based agreement with Novartis,[90,91] finally granting larger numbers of patients access to this life-saving treatment.

For all CAR T-cell therapies, Canada and Spain have more restrictive patient selection criteria for reimbursement than what is approved in the drug label, including a limitation to patients who have Eastern Cooperative Oncology Group (ECOG) scores of 0 or 1, which is a measure of the impact of a patient's cancer on their level of functioning. Although patients with higher ECOG scores generally have poorer outcomes with CAR T-cell therapy,[92] patients with intermediate scores (ECOG 2-3) who are ineligible for stem cell transplants may still benefit from CAR T treatment.[93] The decision on eligibility should be left to the healthcare provider when evaluating the patient's overall fitness. Additionally, reimbursement in Canada occurs at the provincial level, which can delay patient access and limit access, particularly in smaller provinces where the advanced infrastructure for these therapies may be limited and patient populations small. Similarly, in Australia, funding agreements must be signed with each state as funding is split 50/50 between the state and federal governments, which can extend the time to reimbursement.

Carvykti is one of the more recent CAR T launches, with the first global launch occurring in 2022 for patients with relapsed or refractory multiple myeloma. Many countries are still evaluating it for reimbursement. Australia initially declined to reimburse Carvykti but is currently re-evaluating it. Similarly, Carvykti is still undergoing the pricing and reimbursement process in Canada and Italy. Other countries have not yet seen the launch of Carvykti, notably the UK, where Janssen withdrew its reimbursement application, likely due to limited supply.[72] This underscores the time and effort required not only to launch a cell and gene therapy globally but also to ensure that it is reimbursed so patients can access the treatment.

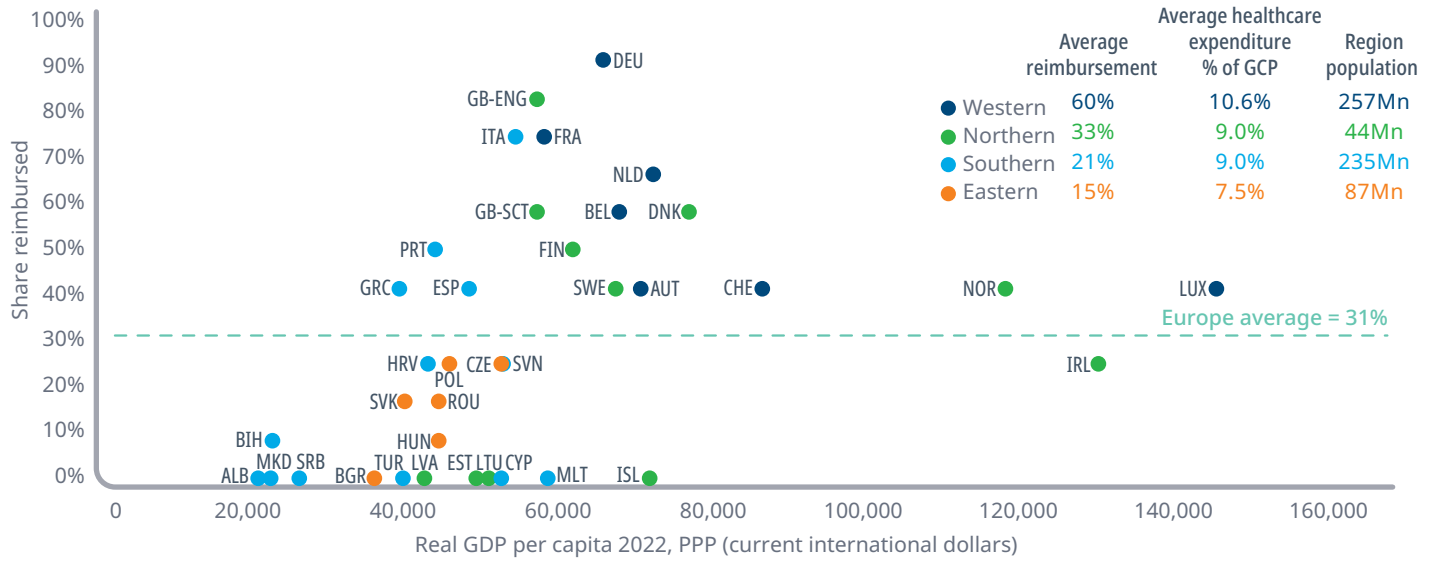
Other restrictions on reimbursement can be related to payers' views on the robustness of the clinical efficacy data, which can limit reimbursement to certain patient populations or indications. This is the case for Yescarta in Australia, where it received regulatory approval for an earlier line of therapy but received a negative reimbursement decision. A similar situation has occurred in various countries for Zolgensma, where reimbursement has been limited to specific patient populations that are more restrictive than the drug label based on populations evaluated in clinical trials. These limitations include restrictions to younger patients (less than nine or six months old) or patients under a specific weight.

The U.S. healthcare system, while attractive to many companies due to the high reimbursement rates, poses challenges due to the differences among payers. Generally, Medicare covers FDA-approved therapies in line with the indication on the approved label; however, reimbursement for hospital costs for treatment varies based on the location of administration, with higher reimbursement rates when administered in an outpatient setting versus inpatient.[71] Commercial plans generally reimburse cell and gene therapies, although prior authorization is required and restrictions may be in place that limit access. However, Medicaid plans more often have coverage policies that are more restrictive than the approved label,[94] a concerning trend given the legal requirement that Medicaid policies cover medicines as approved by the FDA. This will have important implications for the newly approved sickle-cell disease gene therapies, where an estimated 50-60% of patients are covered by Medicaid.[95]

More significant variations in reimbursement rates emerge when looking outside of major markets. In Europe, wealthier countries generally reimburse cell and gene therapies more readily (Exhibit 29). Similar correlations between access to medicines and GDP are observed for all novel medicines, not only cell and gene therapies.[96] Countries in Western Europe, which generally have the highest GDP per capita, have an average reimbursement rate of 60% for cell and gene therapies, the highest among the European regions. Within Western Europe, the wealthiest countries — Luxembourg and Switzerland — reimburse fewer therapies (42%) than Germany and France, which have lower GDP per capita but reimburse 75% or more of therapies. Germany has the highest reimbursement rate at 92% and devotes a larger share of its economic resources to healthcare,[97] reflecting a potential relationship between resource allocation to healthcare and the willingness to reimburse these high-cost therapies.

Northern Europe has an average reimbursement rate of 33%, similar to the overall European average, with high variation across countries. Ireland, which has the highest GDP per capita in the region, reimburses only 25% of therapies, compared to England, which has a GDP per capita less than half that of Ireland but reimburses

Exhibit 29: Status of cell and gene therapy reimbursement in Europe (Apr 2023) compared to GDP per capita 2022, current international dollars PPP



Source: European Medicines Agency, IQVIA EFPIA Patients W.A.I.T. Indicator 2022 Survey, Apr 2023; International Monetary Fund, Oct 2023; IQVIA Institute, Jan 2024.
Notes: Includes cell and gene therapies approved as advanced therapy medicinal products (ATMPs) by the European Medicines Agency 2014–2021 (n=12). Does not include products withdrawn from the market.

83%. Germany has the highest healthcare expenditure relative to GDP at 12.7% and reimburses 92% of cell and gene therapies approved in Europe. The Baltic states and Iceland, in Northern Europe, reimburse no therapies, which is likely driven by infrastructure needs and smaller populations in these countries but could be the result of companies not pursuing reimbursement. Even countries with similar GDP per capita have high variability in reimbursement rates. Germany and Sweden, which have similar GDP per capita, show a stark contrast in reimbursement rates; Sweden reimburses 42% of therapies compared to Germany's 92%.

Southern Europe is a mix of markets with some of the lowest GDP per capita in Europe, but it also includes wealthier countries such as Italy and Spain, with wide variation in reimbursement rates. Malta, which has the highest GDP per capita in the region, reimburses no cell and gene therapies. This is likely driven by the infrastructure needs for these therapies, which may not be viable in a small island nation like Malta and might require patients to travel elsewhere to receive treatment. Eastern Europe has historically had lower access to novel medicines than other parts of Europe.[96] This disparity is also reflected in the low reimbursement rate of cell and gene therapies, with an average reimbursement rate of 15% across the region. This region also has the lowest average healthcare expenditure relative to GDP at 7.5%, highlighting that the healthcare systems in these countries are still developing and may be behind in access to care relative to more developed countries in Western Europe.

Access to cell and gene therapies across Europe may be improved with the introduction of the centralized EU health technology assessment (HTA) process, potentially accelerating time to market access following approval and reducing the burden of HTA assessments. The centralized HTA process is still being finalized; however, the implementation of the joint assessment is expected to begin with new cancer medicines and cell and gene therapies in 2025. While this will centralize the clinical assessments, non-clinical assessments (including economic evaluations), and pricing and reimbursement decisions will still be managed at the national level.[98] Though this could reduce the time and effort for market access across the EU, if countries continue to require additional separate evaluations, this could lead to duplicative efforts that slow down market access.

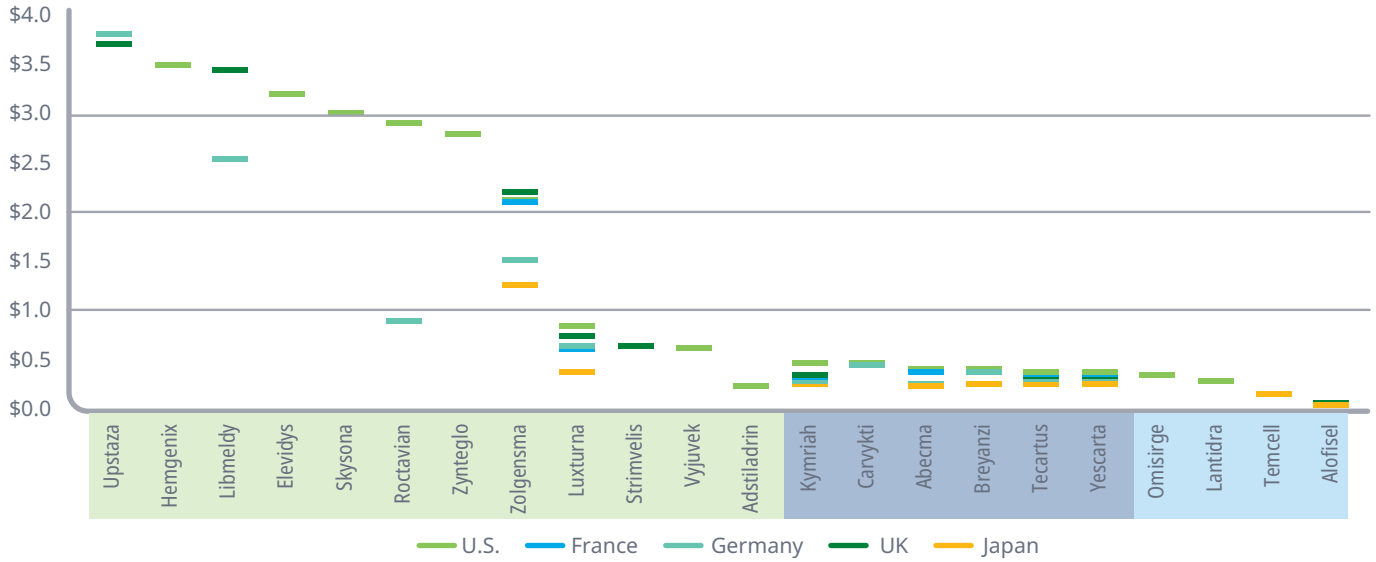
In Europe, less than one-third of therapies approved by the European Medicines Agency are on reimbursement lists, with higher rates in Western Europe and lower rates in Eastern Europe.

PRICING AND PAYMENT MODELS

Cell and gene therapies typically come with high price tags, usually more than $100,000 and often exceeding $1Mn for many gene therapies. This is significantly higher than the median annual cost for other new specialty medicines, which was nearly $30,000 in the U.S. in 2022.[99] However, most cell and gene therapies are intended for one-time use and would not incur annual costs like other medicines. The high prices for these advanced therapies are driven by the substantial research and development costs, expensive manufacturing processes, cost-effectiveness compared to the standard of care, small patient populations, and their potential curative nature.

The average gene therapy price across all geographies is $1.8Mn (Exhibit 30). Upstaza, a gene therapy for the treatment of aromatic L-amino acid decarboxylase (AADC) deficiency, carries the highest price tag among cell and gene therapies, at nearly $4Mn in Germany and the UK. However, this disease is very rare, affecting fewer than one in one million people. In the UK, fewer than 10 children are estimated to have AADC deficiency and be eligible for treatment with Upstaza.[100,101]

Exhibit 30: Ex-manufacturer price per patient of approved cell and gene therapies across select markets, US$Mn



Source: IQVIA Value & Access Strategy Consulting, IQVIA Institute, Dec 2023.
Notes: Prices converted using exchange rates as of Dec 2023. Prices based on publicly available information and do not reflect net prices paid by payers. Prices do not reflect all discounts and rebates provided by manufacturers.

CAR T-cell therapies have lower costs than gene therapies, with an average price across geographies of approximately $350,000. These prices reflect the cost of the therapy only and do not account for the additional healthcare costs that come with treatment, including hospital stays, pre-/post-treatment testing and monitoring, or treatment for adverse events.

The average ex-manufacturer price across major markets for CAR T-cell therapies is more than $350,000, and for gene therapies, it is $1.8Mn, with prices contributing to the budgetary concerns of payers.

U.S. list prices are generally higher than those in other countries, although these list prices do not reflect the negotiated prices after discounts and rebates. For CAR T-cell therapies, U.S. prices average over $400,000, which is 16% higher than those in France, the country with the second-highest prices. Japan has the lowest prices for CAR Ts, averaging 38% below U.S. prices at just $250,000. The pricing environment in the U.S. has led some cell and gene therapy developers to prioritize U.S. launches and has led to market exits from Europe, notably Bluebird Bio's withdrawal of Zynteglo.[102]

Because of the high prices of these therapies and the uncertainty around their long-term effectiveness and durability, payers and manufacturers have negotiated a range of innovative payment models. These models aim to provide access for patients while mitigating the financial burden on the health system. Examples of payment models include outcomes-based agreements, subscription models, risk pools, and installment payments.[103,104] Outcomes-based agreements are the most widely used innovative payment model for cell and gene therapies. These include pay-for-performance contracts, utilizing agreed-upon outcomes that a patient

must reach, with payments made upon achieving each milestone. They also include warranties, where the full price is paid up front and payers are refunded if the outcomes are not met.

Zolgensma has received acceptance across many countries and Novartis has negotiated several different payment agreements with payers. In the U.S., both outcomes-based agreements and installment payment options over five years have been offered.[105] Additionally, Zolgensma is one of the six gene therapies covered under the Embarc subscription program, where payers pay $0.99 per member per month to receive access to gene therapies when needed. However, reimbursement and the use of payment models in the U.S. are complicated by the frequency with which patients switch health plans, with an estimated 15-20% of insured patients changing plans or experiencing disruptions to insurance coverage each year.[106] Because of this, payers who pay the high upfront costs for these therapies may not realize the long-term value of the treatment if the patient switches payers or the patient may be difficult to follow if a payment model with multi-year follow-up is implemented.

Outside the U.S., a pay-for-performance managed entry agreement was also established for Zolgensma in Italy, with outcome milestones at 12, 24, 36, and 48 months.[107] A similar pay-for-performance agreement is used for Zolgensma in Spain. Outcomes-based rebates are being used for Zolgensma in Germany, with up to 100% of the upfront payment rebated based on performance.[108] The case of Zolgensma highlights the need for a suite of payment models to suit the needs of individual payers.

The UK and France have limited use of some of these payment models and instead rely on coverage with evidence development (CED) to adjust reimbursement and pricing over time as real-world evidence is generated. While CED can be a valuable tool for using real-world data to inform coverage and payment decisions, the frequent reassessment of therapies can be burdensome and lead to uncertainty around future access to therapies. NHS England announced as part of the 2024 voluntary scheme that it will establish two pilots to study the use of outcomes-based agreements for cell and gene therapies,[109] which could start the move away from CED in the UK.

The Centers for Medicare and Medicaid Services (CMS) in the U.S. has typically been hesitant to adopt some of these payment models in the past, although the rising number of therapies reaching the market is prompting the need for adaptation. CMS will launch the Cell and Gene Therapy Access Model in 2025 to increase access to cell and gene therapies for Medicaid patients. Under the model, CMS will negotiate outcomes-based agreements with manufacturers for cell and gene therapies, and states will have the option to opt-in to these agreements. Additionally, states will receive resources from CMS to support the execution of these agreements.[110] While the program is voluntary and it is unclear whether Medicaid plans and manufacturers will buy into the model, this is an important step as new sickle cell treatments enter the market where the majority of patients are covered under Medicaid.[95]

While current payment models may work due to the limited number of cell and gene therapies on the market, as the portfolio of treatments expands some payment models may become unmanageable. Payers and manufacturers will need to be flexible with payment for these therapies to ensure patient access while maintaining sound healthcare budgets. This includes payer recognition of the value of these treatments and industry development of new ways to capture this value. One method for doing this was recently proposed by an Italian senator, where a separate fund is established for cell and gene therapies, and the savings generated by these therapies are used to finance the fund for future payments for additional cell and gene therapies, creating a self-financing model.[111] However, this model, along with the many other models used to pay for these high-priced therapies, comes with many complexities and requires a shift in the long-established systems for how healthcare is funded.

Patient access and use

+ **The treatment journey for patients who may be eligible for treatment with a cell and gene therapy is complex and many barriers exist throughout the process, resulting in patients not being treated.**

+ **For CAR T-cell therapies, patient treatment rates vary across geographies, from 25% of referred patients treated in Brazil to 70% in Italy, with disease progression and patient fitness the primary reasons patients are not treated, which can worsen throughout the lengthy treatment process.**

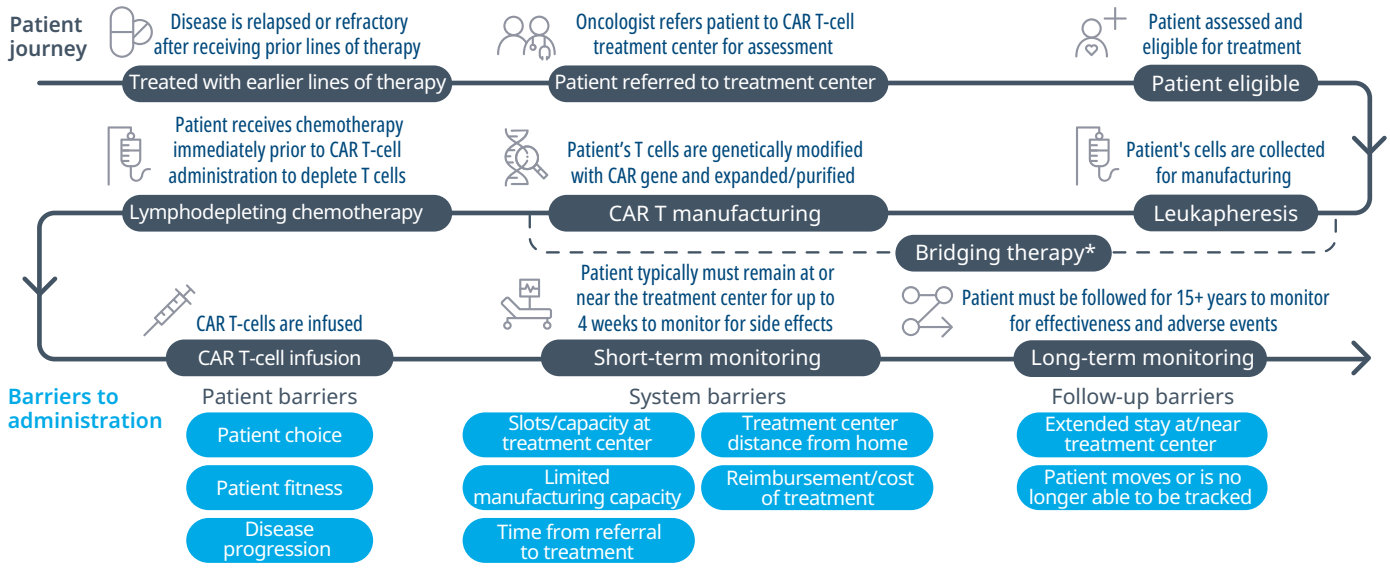
+ **The gene therapy patient journey has many similarities to cell therapies, although one important difference for gene therapies treating heritable disorders is that patients often must be identified early in life and the limited availability of newborn screening across many geographies makes patient identification challenging.**

+ **Because of the complex logistics related to treatment and affordability challenges faced across the patient journey, patient support services are essential to ensure patients can access therapies.**

Cell and gene therapies have more complex treatment pathways than other biologic and small molecule medicines (Exhibit 1). Given the requirement for these therapies to be provided in specialized treatment centers, patients depend on referrals for access to these centers. Patients receiving cell and gene therapies are often very sick and their disease has progressed after earlier treatment options or there are no alternative treatment options available. For patients to achieve the best outcomes, treatment should be received as soon as possible; however, the many steps a patient must take can cause delays, prolonging the treatment process.

The patient journey to receive CAR T-cell therapies is one of the more complex treatment pathways as cells must be collected and genetically modified before infusion.

Exhibit 31: CAR T-cell treatment patient journey and barriers



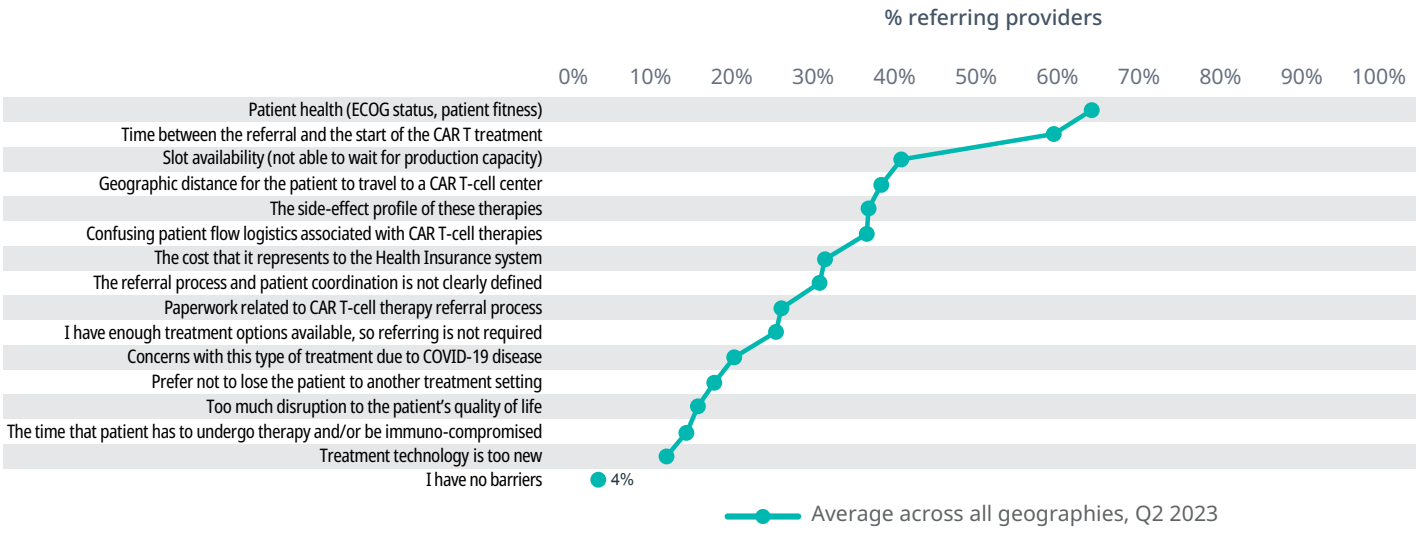
Source: IQVIA Institute, Dec 2023.
Notes: Barriers listed are those most frequently present and not comprehensive of all barriers that hamper treatment.
* Bridging therapy is provided to prevent disease progression and maintain patient health until CAR T-cell therapy can be administered.

As patients move through the process from referral to eligibility determination, to treatment and monitoring, several barriers can prevent them from reaching the end of the treatment process (Exhibit 31). CAR T-cell therapies are currently predominantly approved for later lines of therapy, and a patient's disease must have relapsed or be refractory to other less complex treatments. However, CAR Ts are shifting to earlier lines, with both Yescarta and Breyanzi approved for second-line therapy in diffuse large B-cell lymphoma (DLBCL) as CAR T has shown improved efficacy over traditional stem cell transplants.[112] Once a patient's disease has progressed after earlier failed treatment options, they typically must be referred to a treatment center. While the patient may already be seeing an oncologist who could be affiliated with a treatment center, referrals often need to be made to these more advanced clinics.

Patients may not be referred for many reasons (Exhibit 32). The majority (64%) of providers note that the patient's health is an important reason, as many patients may not be healthy enough for CAR T treatment. The time it takes for patients to make it through the treatment process is another important barrier to referral, noted by 59% of providers. The lengthy time could result in a patient's disease progressing when other therapies may be available that can be provided more quickly, such as bispecific antibodies. Other system barriers, such as slot availability, travel distance to the treatment center, and patient logistics, may not have as large of an impact but can still result in patients not being referred for CAR T treatment. Additionally, the preferences of referring providers, such as the use of other available therapies and the preference to keep the patient within the clinic, have a lesser impact but are still noted as important by 18-25% of them.

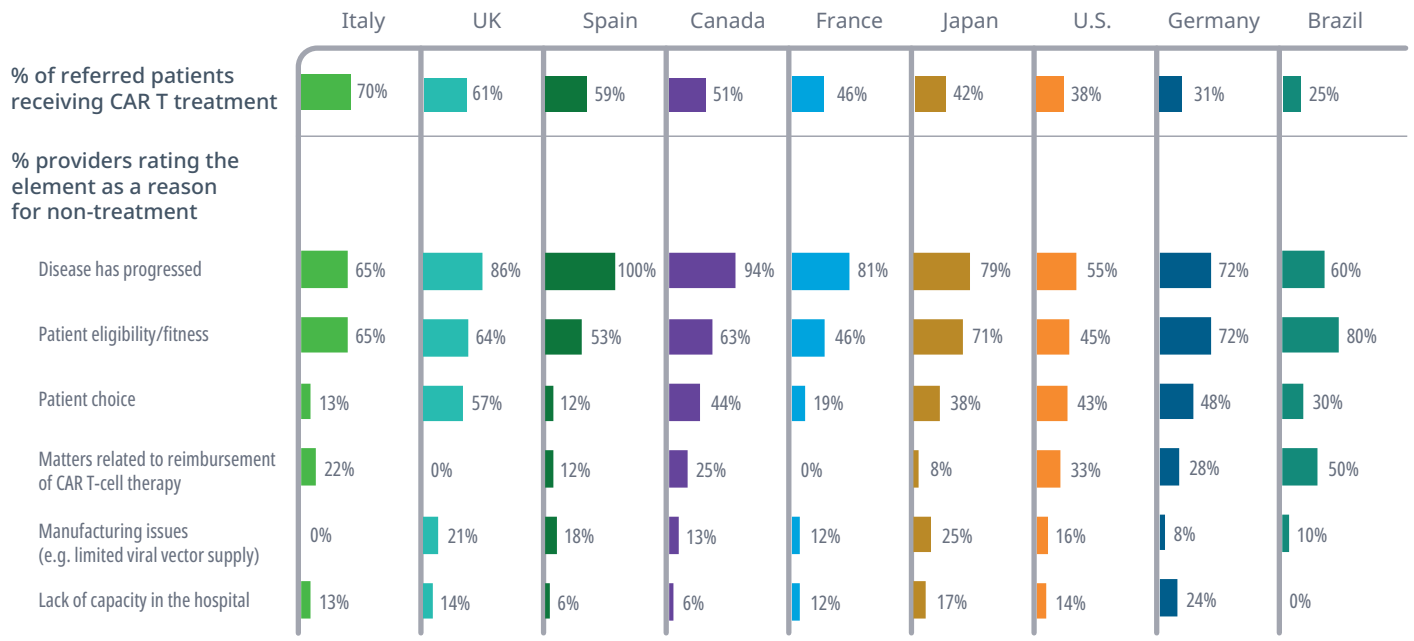
Referred patients must be evaluated for CAR T eligibility. This eligibility assessment can occur either at the referring center, at the CAR T treatment center, or with a hybrid approach between the two. For a sample of patients, the average time from referral to the decision to start treatment was 1.3 to 2.2 months across major markets, which could have implications for patient response to therapy given the often aggressive nature of their disease. Only a portion of patients referred for treatment end up receiving CAR T.

Exhibit 32: Reported barriers for referring patients to CAR T-cell treatment facilities, Q2 2023



Source: IQVIA CAR T-cell Monitor, Jun 2023.
Notes: Share represents providers who rated the barrier as "very" or "extremely" important. Includes providers from Brazil, Canada, France, Germany, Italy, Japan, Korea, Spain, and UK.

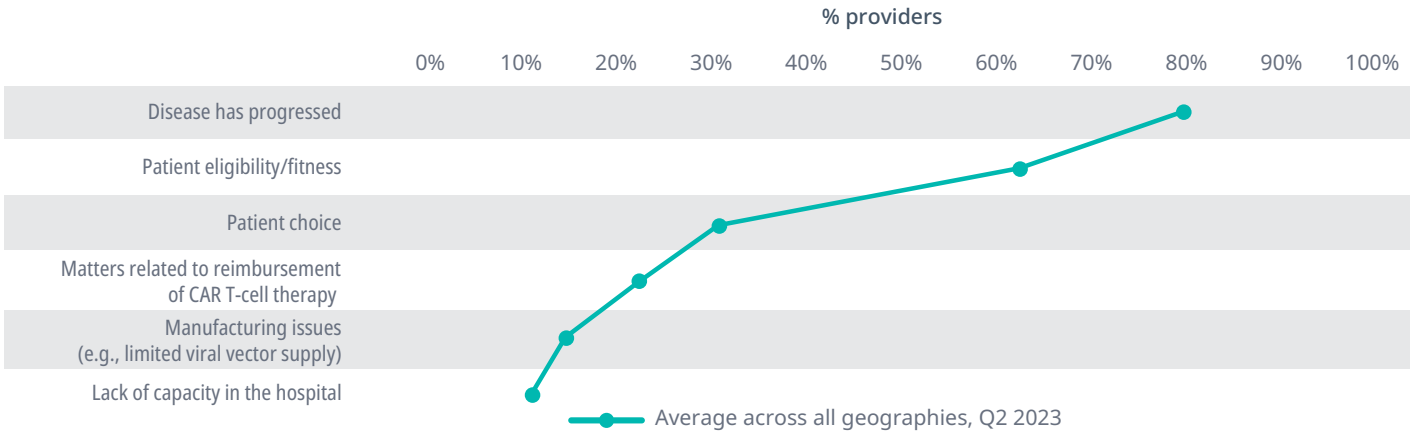
Exhibit 33: Treatment rates and reasons reported for patients not receiving treatment, Q2 2023



Source: IQVIA CAR T-cell Monitor, Jun 2023.
Notes: Treatment rates and barriers are based on surveys of oncologists providing CAR T-cell therapies and their analysis of patient records at the time of survey collection. Treatment rates reflect the average across tumors for which CAR T-cell therapies are approved. Respondents are providers directly involved in CAR T-cell treatment at accredited treatment centers.

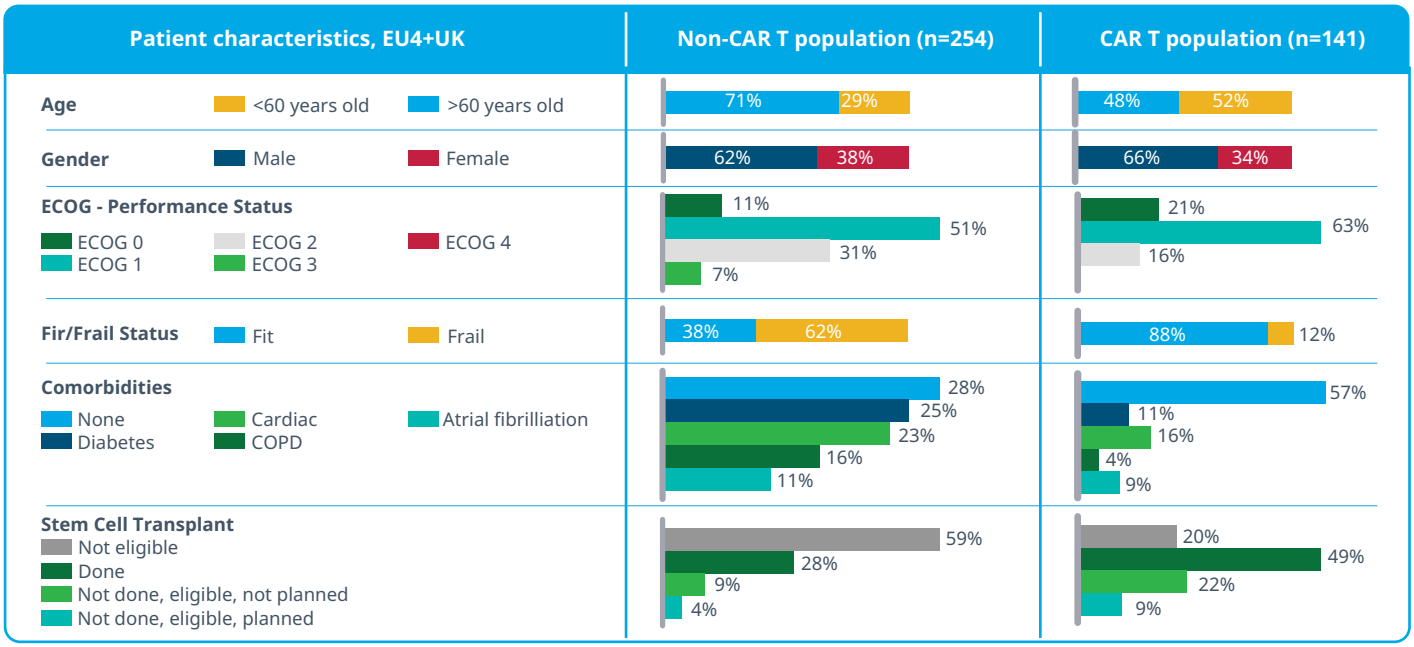
Average treatment rates for all cancers range across countries, with only 25% of referred patients being treated in Brazil compared to a high of 70% of patients in Italy (Exhibit 33). There are various reasons why patients do not receive CAR T-cell therapy in different countries, although disease progression and patient fitness are the most common across all countries. Among oncologists surveyed in all countries, 79% cited disease progression as a reason for referred patients not receiving treatment, and 62% cited patient eligibility and fitness (Exhibit 34). The need for healthy T cells from patients and the ability to undergo the demanding treatment process means that older, frailer patients typically are not eligible for treatment or have poorer outcomes from CAR T

Exhibit 34: Reasons reported by CAR T-cell centers for patients not receiving treatment, Q2 2023



Source: IQVIA CAR T-cell Monitor, Jun 2023.
Notes: Includes oncologists providing CAR T-cell therapies from Brazil, Canada, France, Germany, Italy, Japan, Korea, Spain, UK, and U.S. Multiple reasons may be given for non-treatment. Respondents are providers directly involved in CAR T-cell treatment at accredited treatment centers.

Exhibit 35: Patient profile comparison DLBCL: CAR T-cell therapy treated vs. non-CAR T-cell therapy patients



Source: Oncology Dynamics Boost DLBCL 3L+, Q2 2023.

treatment. Not surprisingly, in the five largest European markets, patients with diffuse large B-cell lymphoma treated with CAR T were younger, fitter, and less likely to have comorbidities than those treated with systemic therapy instead of CAR T (Exhibit 35).

Among patients in the U.S. who chose not to receive CAR T, concerns about safety and side effects were the most common reason (43%) for the patient's decision not to proceed with treatment. Cost concerns and logistics also contributed to patients' decisions.[114] Patient choice is a less significant factor in attrition in Italy, Spain, and France, and is more notable in the UK and Germany. When combined across countries, reimbursement was less frequently cited as a barrier to treatment (22%), as in most of these countries, CAR T-cell therapies are reimbursed through social security. However, reimbursement barriers are higher in the U.S., where residents are primarily covered through private insurance.[115] Additionally, reimbursement is a significant barrier in Brazil, which has fewer available therapies and more reimbursement restrictions than other countries (Exhibit 28).

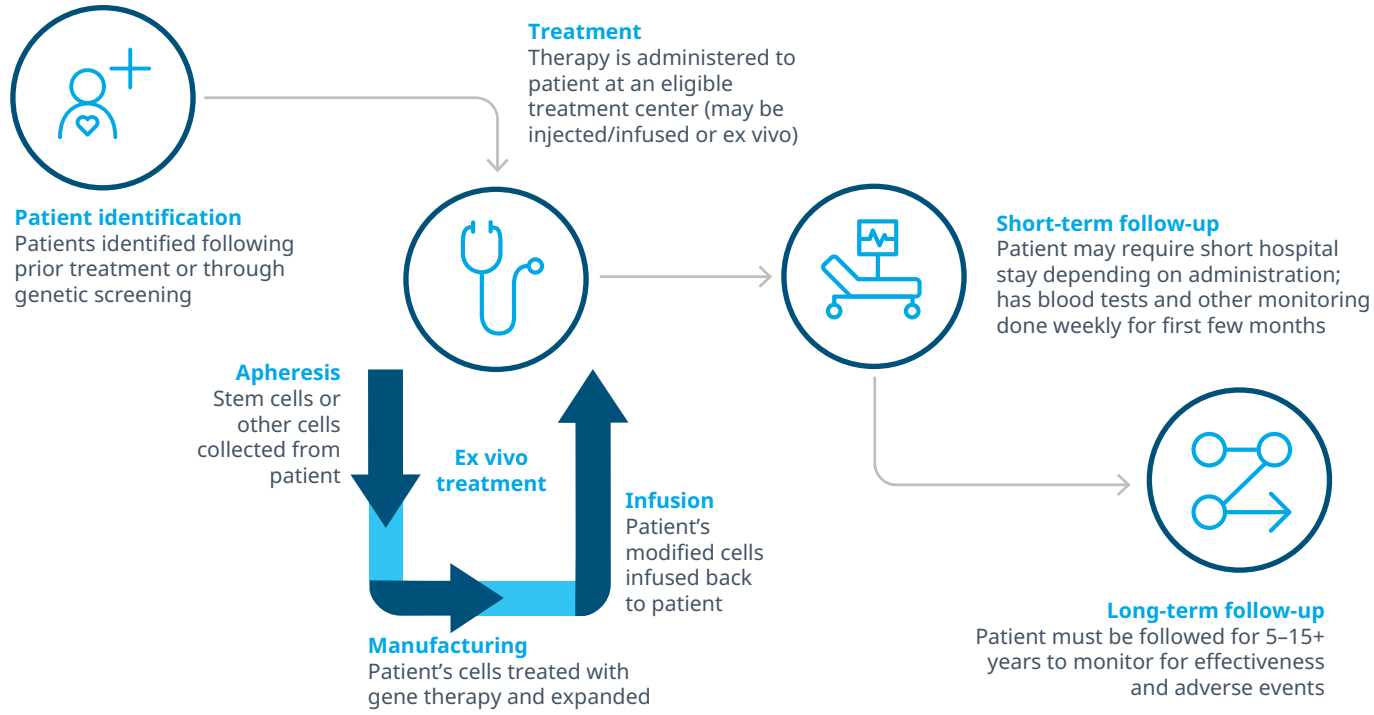
Patients who are deemed eligible for treatment must undergo leukapheresis to collect T cells, which are then modified with a CAR construct, expanded, and purified. To proceed through the treatment process there must be sufficient hospital and manufacturing capacity. Patients may be added to a waitlist until a slot becomes available. Although manufacturing and hospital capacity are not commonly cited as barriers to treatment, their impact can vary across countries, and wait times for slots can range from four to six months.[116] The manufacturing time for CAR T-cell therapies ranged from 13 to 26 days in follicular lymphoma patients, with a total vein-to-vein turnaround time — the time from leukapheresis to infusion — of 15 to 38 days.[113] As CAR Ts continue to mature and the processes become more established, turnaround times are beginning to shorten. In multiple myeloma, where CAR T-cell therapies are newer and companies have had issues meeting supply demands, longer manufacturing times have led treatment centers to provide patients with the first available option (Abecma or Carvykti) or alternative off-the-shelf therapies (e.g., bispecific antibodies).[71,116]

Due to the lengthy time from referral to treatment, patients are typically given bridging therapy to prevent disease progression, which could result in the patient becoming ineligible for treatment during the treatment journey. Once a patient's cells have been manufactured, the patient returns to the treatment center to receive multi-day lymphodepleting chemotherapy to deplete their circulating T cells prior to the infusion of the CAR T-cells. The patient's CAR-modified T-cells are then infused at the treatment center, and the patient will remain at the center for up to four weeks to be monitored for side effects. The most common short-term side effects following CAR T treatment are cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), both of which are life-threatening if not treated immediately. Patients dealing with these short-term side effects are immunocompromised, so they must be isolated from the general hospital population. After completing treatment and once their immune system returns to normal, they are often monitored by their referring oncologists for long-term side effects. However, communication with the CAR T treatment center continues in case safety issues arise. Due to the rare occurrence of secondary malignancies, the current FDA guidance is that these patients be monitored for the remainder of their lives.[117]

For CAR T-cell therapies, on average across major markets only 47% of referred patients end up receiving treatment.

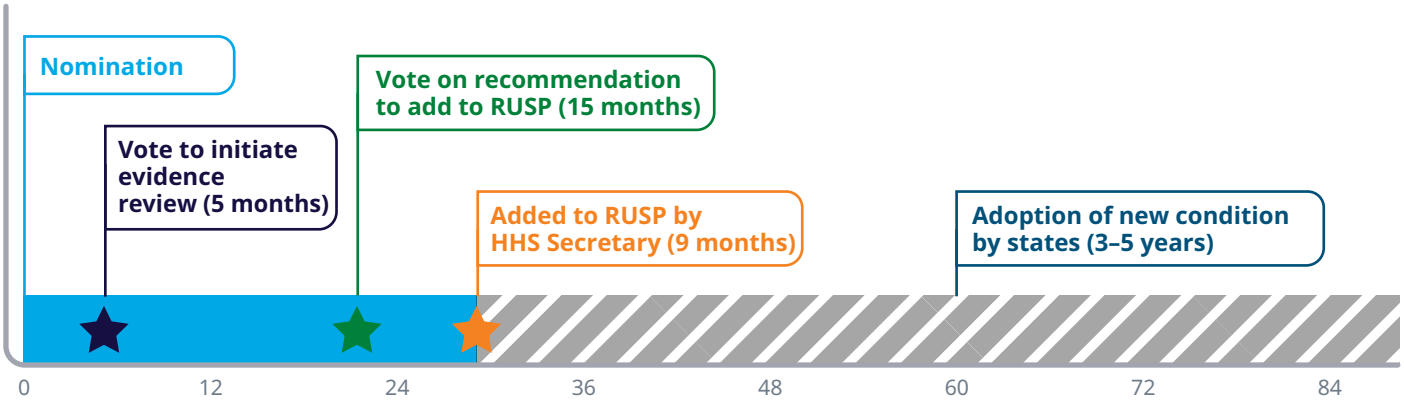
Patients receiving other cell and gene therapies follow a similar patient journey, although the steps vary based on the type of therapy. For example, the treatment journey for patients receiving gene therapy differs based on whether the therapy is administered in vivo or ex vivo (Exhibit 36). In vivo treatments, which are injected, infused, or otherwise administered to the patient in

Exhibit 36: Illustrative gene therapy patient journey



Source: IQVIA Institute, Jan 2024

Exhibit 37: U.S. timeline for addition of diseases to newborn screening panels



Notes: Time reflects the average amount of time for each step based on historic timelines for disease additions.
Source: Xu, Ganapathy & Morain, Jan 2018; Advisory Committee on Heritable Disorders in Newborns and Children, IQVIA Institute, Jan 2024.

a specialized treatment center without the need for collection and external manipulation of the patient's cells, allow for a more streamlined treatment journey. Therapies are pre-manufactured and readily available upon eligibility determination. Allogeneic cell therapies provide a similar streamlined treatment process.

An important limiting step for gene therapies is identifying eligible patients, which can prevent patients from even starting the treatment process. Gene therapies are increasingly being developed to address inherited disorders that require treatment soon after birth and necessitate early identification of patients, often before symptoms appear. Newborn screening programs vary globally, with 63 diseases screened in the U.S., 27 in Australia, and only 9 in the UK.[118] Only approximately 28% of children born globally each year undergo newborn screening, with significant gaps particularly in low- and middle-income countries.[119]

Even in the U.S., which has an advanced newborn screening program, the system is fragmented, and few of the diseases screened for involve genetic testing. This could limit the potential to screen for diseases that may not show signs until later in childhood. Newborn screening programs in the U.S. are managed at the state level, with recommendations made at the federal level by the Advisory Committee on Heritable Disorders in Newborns and Children for disorder additions to the Recommended Uniform Screening Panel (RUSP). The process for incorporating a new genetic disorder into newborn screening is lengthy, and the average time for previous conditions from nomination to implementation across all states has been five to seven years (Exhibit 37). For example, SMA was only incorporated into screening panels across all 50 states in January 2024,[120] despite being added to the RUSP in July 2018 and Zolgensma being available in the U.S. since 2019. This delay results in children who could benefit from gene therapy not being identified early enough for treatment.

Only approximately 28% of children born globally each year undergo newborn screening, with significant gaps particularly in low- and middle-income countries.

In other regions of the world, newborn screening programs are often less advanced than that in the U.S. There is variability across Europe in newborn screening programs. For example, for SMA screening, Italy and Germany have national programs, but France, Spain, and the UK only have regional pilot programs and lack broad national access to SMA screening. Additionally, access to newborn screening in Eastern Europe can be limited, with Hungary and Romania screening only 5-17% of newborns for SMA as of 2021, and Greece not including SMA in newborn screening.[121] Access to newborn screening in developing countries is even more limited, with many countries in Southeast Asia having no or very limited screening programs.[122] As more gene therapies addressing heritable conditions become available, newborn screening programs will need to be improved globally to ensure access to these therapies soon after birth. Furthermore, the inclusion of additional targeted genetic tests or next-generation sequencing should be assessed as technology advances to help identify conditions as early as possible.

The journey that patients must navigate before, during, and after cell and gene therapy treatment is long, complex, and can add additional stress to the patient and their caregiver during an already difficult time. Many cell and gene therapy companies and patient organizations have established programs and services to provide support for patients and their caregivers throughout the treatment process. These support services address many different needs that may arise, including financial assistance such as copay assistance for commercially insured patients in the U.S. for portions of treatment that may not be fully covered by insurance. Additionally, programs like Cell Therapy 360, a Bristol Myers Squibb program, connect patients and caregivers with someone who can help them navigate the treatment process.

In addition to Bristol Myers Squibb, other manufacturers have established programs to ensure patients have the support they need before, during, and after treatment. These include Novartis' OneGene Program and Kymriah Cares, Janssen's MyCarvykti Patient Support Program, and Bluebird Bio's My Bluebird Support. Some patient support programs may offer assistance for travel and lodging or connect patients with independent foundations and patient organizations that may be able to assist with these needs. The CAR-T Away from Home Service, operated by Leukaemia Care, a charity organization, provides hotel accommodations and financial assistance for eligible patients and their families in the UK who are receiving CAR T treatment.[123]

For Strimvelis, Fondazione Telethon, an Italian non-profit charity that helped develop the gene therapy, established the Just Like Home program. Treatment with Strimvelis requires a stay of three to four months near the treatment center in Milan, and patients may travel from all over the EU. While treatment costs are covered through EU Social Security Regulations, the costs for travel and extended stay in Milan are frequently not covered, with the exception of the UK which reimburses for travel and accommodation.[84] The Just Like Home program provides patient support both before the patient arrives in Milan and throughout the extensive treatment journey. This includes logistical support (e.g., finding accommodations, visa assistance), psychological support (e.g., access to psychologists and teachers), and language support, given the differing cultural backgrounds of patients.[124]

Though little data is available on the number of patients treated globally with cell and gene therapies, it is thought that those treated to date represent a small share of those who may be eligible for treatment. To improve this, cell and gene therapy companies must work with regulators, healthcare systems, patient organizations, and other stakeholders to remove the barriers preventing patients from accessing these therapies. Additionally, efforts should be made to make the treatment journey less burdensome for patients to ensure better outcomes from treatment and improve patients' quality of life.

Patient outcomes

+ **Long-term follow-up of patients after receiving treatment is longer for cell and gene therapies than for other medicines, lasting up to 15 years or potentially the patient's lifetime.**

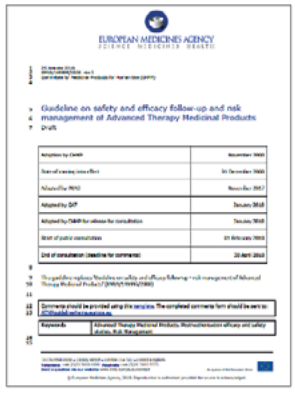
+ **Even the basic task of following the patient is a challenge in long-term follow-up studies, increasing the risk of patient loss to follow-up.**

+ **Designing long-term follow-up studies is custom to each therapy and must consider the situational characteristics specific to that disease and therapy.**

Many cell and gene therapies involve the introduction or modification of genetic material, which can result in significant off-target effects if not properly managed. Because of the potential for severe delayed adverse events from these therapies, patients treated both in clinical trials and commercial settings must be followed up on after receiving treatment. Additionally, many questions exist around the long-term durability and efficacy of cell and gene therapies, and observing patient outcomes over time can aid in providing long-term efficacy data.

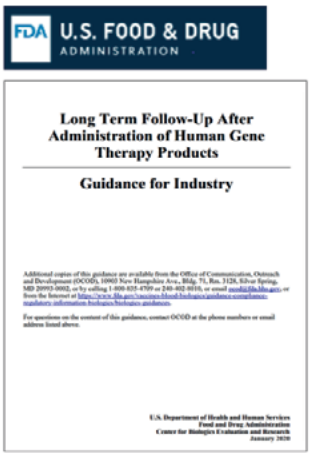
Both the FDA and EMA have developed guidance on long-term follow-up to aid cell and gene therapy developers in determining appropriate follow-up timelines. Generally, for gene therapies using integrating vectors or for genome editing therapies, patients must be followed for up to 15 years after administration (Exhibit 38). This is not only to monitor for any delayed adverse events but also to collect additional efficacy data that may not be available at the time of regulatory approval, for example, long-term durability and the curative nature of the therapy. Regulators additionally include product specific follow-up requirements as part of the regulatory approval and product label. This includes guidance on minimizing risk, which might entail provider and patient education. Additionally, many payer decisions on reimbursement are tied to the long-term efficacy of these products, and therefore long-term follow-up studies can address many needs throughout the cell and gene therapy lifecycle.

Exhibit 38: Current regulatory agency guidance for long-term follow-up



Guideline on safety and efficacy follow-up and risk management of Advanced Therapy Medicinal Product (2018 – revision 1)

- **Up to 15 years safety follow-up** expected for products with integrating vectors or vectors with potential for latency followed by reactivation
- AAV, **min 5y safety follow-up**
- Clinical trial patients to be followed up for the same length of time
- Post-authorization efficacy evaluation might be required



Long Term Follow-Up After Administration of Human Gene Therapy Products (Jan 2020)

Assessing risks of delayed adverse events as well as long term risks for vector persistence, integration, and reactivation and genome modification

- **15 years** for integrating vectors such as gammaretro-viral and lentiviral vectors and transposon elements
- **Up to 15 years** for genome editing products
- **Up to 5 years** for AAV vectors

Source: European Medicines Agency, Food and Drug Administration, Dec 2023.

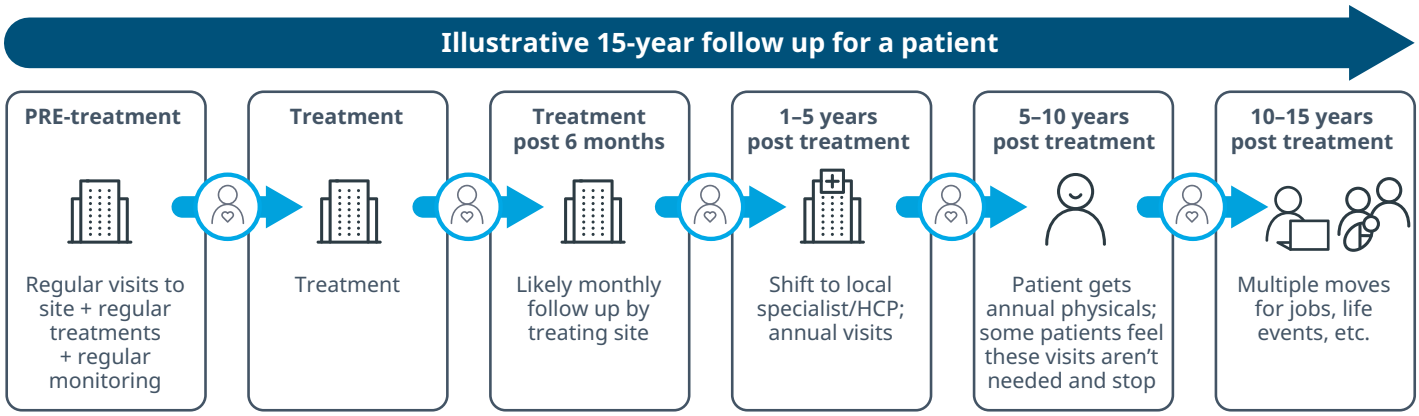
The task of following patients for up to 15 years is long and burdensome, and patients who receive a one-time therapy may be reluctant to maintain regular contact with the healthcare system. For example, early post-treatment follow-up might include monthly visits to the treatment site for bloodwork and other tests to monitor for adverse events and treatment efficacy (Exhibit 39). In the first couple of years following treatment, annual monitoring is likely to take place with a specialist or primary care provider located near the patient, reducing the burden on patients. Five to ten years after treatment, monitoring may be performed at the patient's annual physical, and if the patient is doing well, they may deem these visits unnecessary. In the later years of long-term follow-up, patients have likely moved, changed doctors and insurance, and experienced other major life events that make tracking the patient difficult. Patients with the best treatment outcomes might be more likely to disengage from the healthcare system and are therefore more likely to be lost to follow-up, which could result in a bias toward patients with poorer outcomes.

The task of following patients for up to 15 years is long and burdensome, and patients who receive a one-time therapy may be reluctant to maintain regular contact with the healthcare system as they move and experience other major life events.

Characteristics of the therapy itself, the disease, and the operating environment must be considered when designing long-term follow-up studies (Exhibit 40). The patient journey, expected outcomes, and the method of treatment can significantly impact follow-up. Traditional site-based patient monitoring, where patients must return to the treatment site, is likely not feasible for managing long-term follow-up as more patients are treated with cell and gene therapies. Additionally, each cell and gene therapy treatment has differing characteristics requiring adaptations to safety and efficacy monitoring.

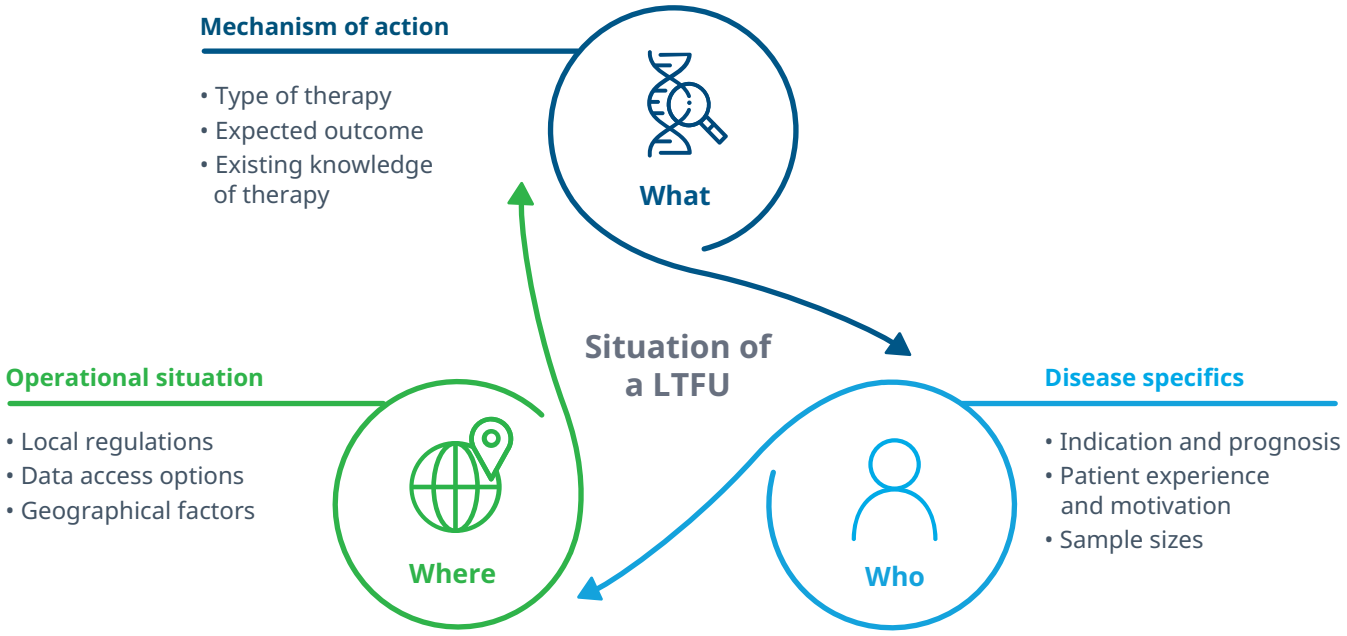
Long-term follow-up can vary based on the unique characteristics of the cell or gene therapy. Cell therapies that have not been genetically modified may require minimal long-term monitoring, as the largest concerns would likely be around treatment rejection and would

Exhibit 39: Illustrative cell and gene therapy long-term follow-up



Source: IQVIA Real World Solutions, Dec 2023.

Exhibit 40: Elements to consider in long-term follow-up study design



Source: IQVIA Real World Solutions, Dec 2023.

manifest soon after treatment. However, genetically modified therapies require additional monitoring, with those therapies where the genome is modified, or the vector used may integrate into the genome, requiring the most extensive follow-up. Additionally, the mechanism of action of the therapy and the expected treatment outcome will drive the type of monitoring required (e.g., bloodwork vs. imaging).[125] Prior knowledge of the modality, including the vector, can provide insight into the type of monitoring needed and can help refine follow-up based on real-world use.

Elements of the disease being treated also need to be taken into consideration for long-term follow-up. Some diseases targeted by cell and gene therapies occur early in life, and treatment effects may be expected to last for decades or even a lifetime. Other diseases, such as multiple myeloma, have poorer prognoses, and even with effective treatment, life expectancy may not be as long due to the later onset and severity of the disease. Patient motivation can be a key driver of study design, as long-term monitoring requires patients to remain engaged with the healthcare system.

Traditional site-based patient monitoring, where patients must return to the treatment site, is likely not feasible for managing long-term follow-up as more patients are treated with cell and gene therapies.

Additionally, the patient journey and where patients engage will be important, as it is unlikely that patients will be able or want to return to the treatment center for monitoring activities. Instead, these activities would be better integrated into their standard of care at the patient's local primary care provider or specialist. Further development and use of remote and digital tools that can collect patient data and keep patients engaged throughout the long monitoring period can improve long-term follow-up studies.[126]

Patient registries can be used to aid in data collection for long-term follow-up and can harmonize efforts across developers and products.[125] Additionally, the pooling of patient data provides additional insights into the safety and efficacy of cell and gene therapy products that may not be accessible through a siloed approach. The Center for International Blood and Marrow Transplant Research (CIBMTR), the European Society for Blood and Marrow Transplantation (EBMT), and the Japan Data Center for Hematopoietic Cell Transplantation (JDCHCT) have worked to harmonize outcome data collection for CAR T-cell therapies. The Cellular Therapy Registry, launched in 2016, has been used for the safety and efficacy monitoring of patients following CAR T treatment.[127] Another example is the World Federation of Hemophilia Gene Therapy Registry, which collects data on patients with hemophilia who have received any gene therapy product. The registry allows for the global pooling and analysis of patient data for safety signals and the evaluation of treatment durability.[128]

Long-term follow-up is critical for cell and gene therapies, given the remaining uncertainty around their long-term safety and efficacy. Long-term outcomes data from existing cell and gene therapies provide important context for the safety and efficacy of these therapies as a class. Notably, commercially available CAR T-cell therapies in the U.S. recently received boxed warnings for secondary T-cell malignancies that may occur following treatment.[129] While these types of adverse events are concerning, they are also quite rare, with only 22 cases of post-treatment T-cell cancers reported in the U.S. out of more than 27,000 patients treated. Due to the continued uncertainty around the long-term safety of these therapies, the FDA recommends that patients be monitored for the rest of their lives for secondary malignancies.[117] Advances in gene insertion and gene editing technologies that allow for more targeted approaches to gene modifications could alleviate the potential for off-target effects and these adverse events.[130]

Many of the therapies on the market have limited long-term efficacy data available; however, data from patients treated in early clinical trials have begun to emerge as these therapies mature. CAR T-cell therapies have shown positive long-term outcomes, with many patients with B-cell malignancies treated with CAR Ts experiencing complete remissions for more than three years, and some patients still in remission nine years post-treatment.[131] To date, the benefits of CAR T treatment continue to outweigh the risks, and clinicians remain confident in CAR T-cell therapies.[132] Some of the first children with SMA treated in clinical trials with Zolgensma are up to 7.5 years out from treatment and have not experienced disease progression, with no serious adverse events related to treatment. Some patients have received add-on therapy following Zolgensma treatment, including antisense oligonucleotide therapy.[25]

Other outcomes data for gene therapies include sickle cell disease patients treated in clinical trials with the recently approved Lyfgenia; early follow-up data indicate that 88% of patients had no pain events over a median of three years of follow-up and up to five years.[133] While this early data coming from long-term follow-up studies highlights the continued efficacy of these gene therapies, it is difficult to draw conclusions about the long-term efficacy of cell and gene therapies overall given the variation in treatments and mechanisms being used.

Spending

+ **Spending on cell and gene therapies reached $5.9Bn in 2023, up 38% from 2022 and 62% attributable to the U.S., where there is broader acceptance of these products.**

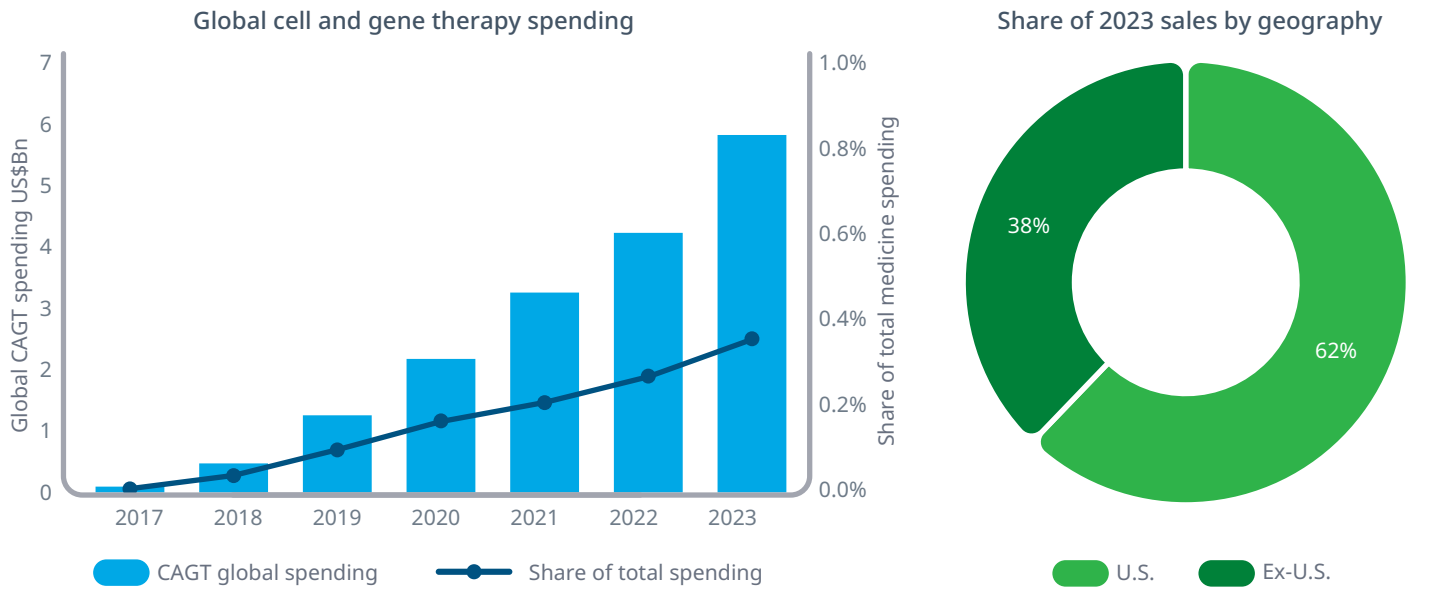
+ **Despite the high price tags and budgetary concerns often associated with cell and gene therapies, spending accounted for only 0.4% of the $1.6Tn spent on medicines globally in 2023 and represents 0.8% of spending in the U.S.**

+ **The high costs of bringing products to market and small patient populations make commercialization and return on investment difficult for cell and gene therapies, which has led to some notable market exits.**

The high cost per patient for cell and gene therapies has driven concern over spending on these products. Global spending on these therapies reached $5.9Bn in 2023 (Exhibit 41). Spending grew by 38% in 2023 from the prior year, and spending has averaged 65% annual growth over the last five years as more products are reaching the market. A majority (62%) of this spending is attributable to U.S. sales, compared to just 38% coming from other geographies. This could reflect the frequently higher prices (Exhibit 30) seen in the U.S., though net prices — the amount paid to manufacturers after all discounts and rebates — in the U.S. may be more comparable to prices in other countries. Higher spending in the U.S. likely reflects the broader acceptance of these therapies and a likely higher uptake, as more cell and gene therapies are available in the U.S. than in other countries.

One of the largest concerns for payers with cell and gene therapies is the high cost presented by these products and the impact that this will have on their healthcare budgets. Despite the growing spending on these therapies, it represents only 0.4% of the $1.6Tn spent on medicines globally in 2023. Cell and gene therapy spending accounts for 0.8% of net medicine spending in the U.S., where more therapies are available and prices are often higher. While these therapies may have high

Exhibit 41: Global cell and gene therapy spending and share by geography



Source: Company Financials; IQVIA Institute, Dec 2023.
Notes: Spending estimates based on company reported sales. Sales by geography based on company reported regional sales.

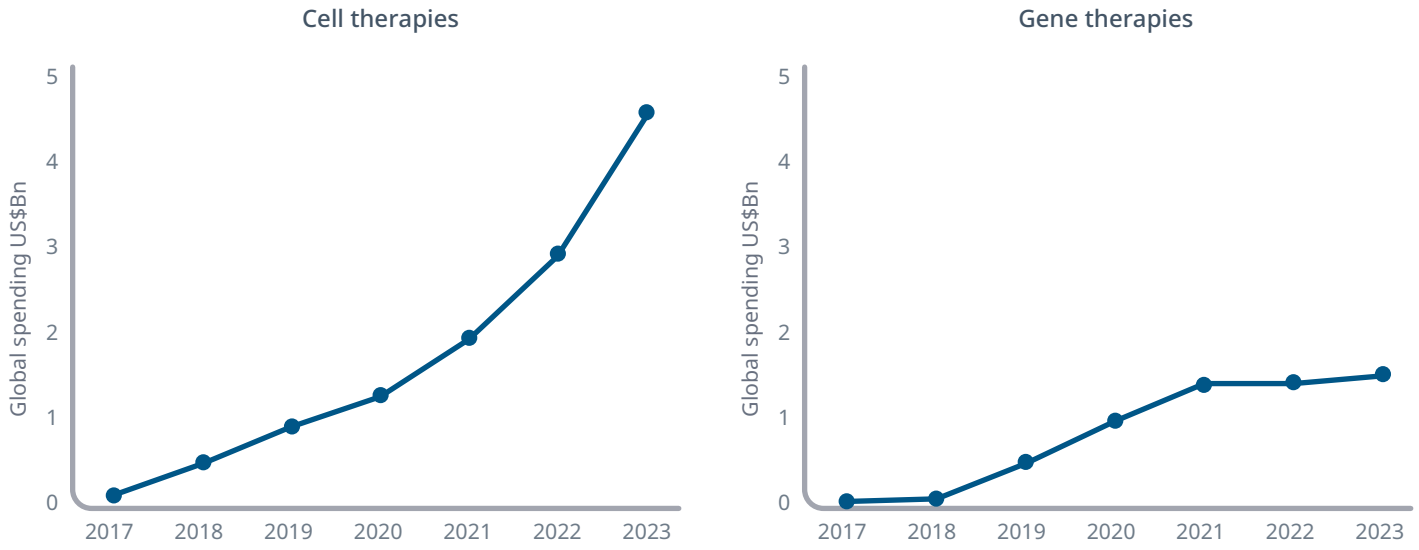
price tags, relatively few patients receive these therapies due to their placement in later lines of therapy and barriers to treatment. The $5.9Bn in spending does not reflect the additional healthcare costs that come with treatment, including hospital stays, pre-/post-treatment testing and monitoring, or treatment for adverse events. Several studies have estimated these additional healthcare costs for CAR T-cell treatment in the U.S., with estimates ranging from nearly $24,000 to more than $180,000 per patient. The cost can vary depending on the care setting (inpatient versus outpatient), level of adverse event management, and use of bridging therapy, as well as other factors that may arise during treatment.[134]

Current spending on cell and gene therapies is primarily driven by cell therapies, where sales have more than tripled over the last three years, reaching $4.5Bn in 2023 (Exhibit 42). This increase is primarily due to CAR T-cell products, which have gained broad acceptance globally for the treatment of late-stage cancer. Nearly $3.7Bn was spent globally on CAR T-cell products in 2023. However, this amount is relatively small compared to spending on other novel cancer treatments, such as PD-1/PD-L1 inhibitors, which were projected to have spending of over $46Bn in 2023.[135] The vast differences in spending can be attributed to the larger patient populations for PD-1/PD-L1 inhibitors and their relative ease of administration compared to CAR T-cell therapies.

Spending on cell and gene therapies is increasing rapidly, and reached $5.9Bn in 2023, up 38% from 2022.

Gene therapies have experienced slower growth, reaching $1.4Bn in 2023, primarily due to the widely accessible Zolgensma. Most other cell and gene therapy products have limited patient populations and have been launched in only a few countries (Exhibit 16), and therefore have not contributed significantly to overall cell and gene therapy spending. Most of these products, for which company reported sales data is available, have recorded less than $200Mn in sales since being introduced to the market. While many of these products

Exhibit 42: Global cell and gene therapy spending



Source: Company Financials; IQVIA Institute, Dec 2023.
Notes: Spending estimates based on company reported sales.

have been commercialized for less than five years, some have matured and continue to see modest sales. The modest level of sales that a company can recognize from these products raises questions about the commercial viability of products that serve small patient populations but incur significant manufacturing and research and development costs prior to commercialization.

Two examples of the difficult commercial environment for cell and gene therapies are Holoclar and Strimvelis. Chiesi Farmaceutici received approval for Holoclar from the EMA in 2015, a stem cell therapy for patients with corneal damage manufactured by Holostem Advanced Therapies.[136] In 2020, Chiesi transferred the marketing authorization to Holostem, which had earlier spun out of the University of Modena and Reggio Emilia, to focus on other priorities.[137] In 2022, Holostem announced it would transition to a non-profit foundation with financial backing from the holding company that owns a majority stake in Chiesi; however, later that year, Holostem announced it would liquidate,[138] a blow for patients receiving Holoclar and other investigational products the company was pursuing. Nearly a year after this announcement and nearing the completion of the liquidation, the Italian government announced it would step in and acquire Holostem through the Enea Tech and Biomedical Foundation, an investment fund managed by the Italian Ministry of Economic Development.[139]

Strimvelis has had a similarly turbulent history as the treatment for ADA-SCID, an extremely rare condition affecting approximately 15 children in Europe each year.[85] Strimvelis became financially unsustainable for the marketing company. It was approved in the European Union in 2016, with GSK marketing the product developed by the San Raffaele Telethon Institute for Gene Therapy.[85] Due to the small patient population and specialized care needed for treatment, Strimvelis is offered at a single treatment center, Ospedale San Raffaele in Milan, Italy. Orchard Therapeutics acquired Strimvelis and other investigational rare disease gene therapies from GSK in 2018;[140] as of 2020, only 16 patients had been treated with Strimvelis in the four years since its approval.[141] Orchard additionally received EMA approval for the gene therapy Libmeldy and announced in 2022 that in order to focus on the commercialization of this product and research on other similar gene therapies, it would discontinue investment in Strimvelis.[142] To ensure patients could continue to receive Strimvelis, Fondazione Telethon — a non-profit that was involved in the initial development of Strimvelis — took over the marketing authorization in 2023.

The modest level of sales that a company can recognize from these products raises questions about the commercial viability of products that serve small patient populations but incur significant costs.

The complex commercialization journeys of Holoclar and Strimvelis, as well as the final acquisitions by non-profit or government organizations, highlight the difficulty in commercializing cell and gene therapies for ultra-rare diseases. Other early cell and gene therapies have ceased to be marketed entirely for commercial reasons, for example Glybera. Cell and gene therapies will face competition as more therapies are launched, including other cell and gene therapies and alternative modalities. For multiple myeloma, there are now two BCMA-targeted CAR T-cell therapies and a bispecific antibody competing commercially. Additionally, there are other CAR Ts, bispecifics, and antibody-drug conjugates in the pipeline.[143] This increased competition will incentivize improving infrastructure and reducing barriers to patient access. As more therapies become available, health systems will require new approaches and investments for these novel modalities to ensure the value to patients of these potentially curative therapies is realized.

Future state

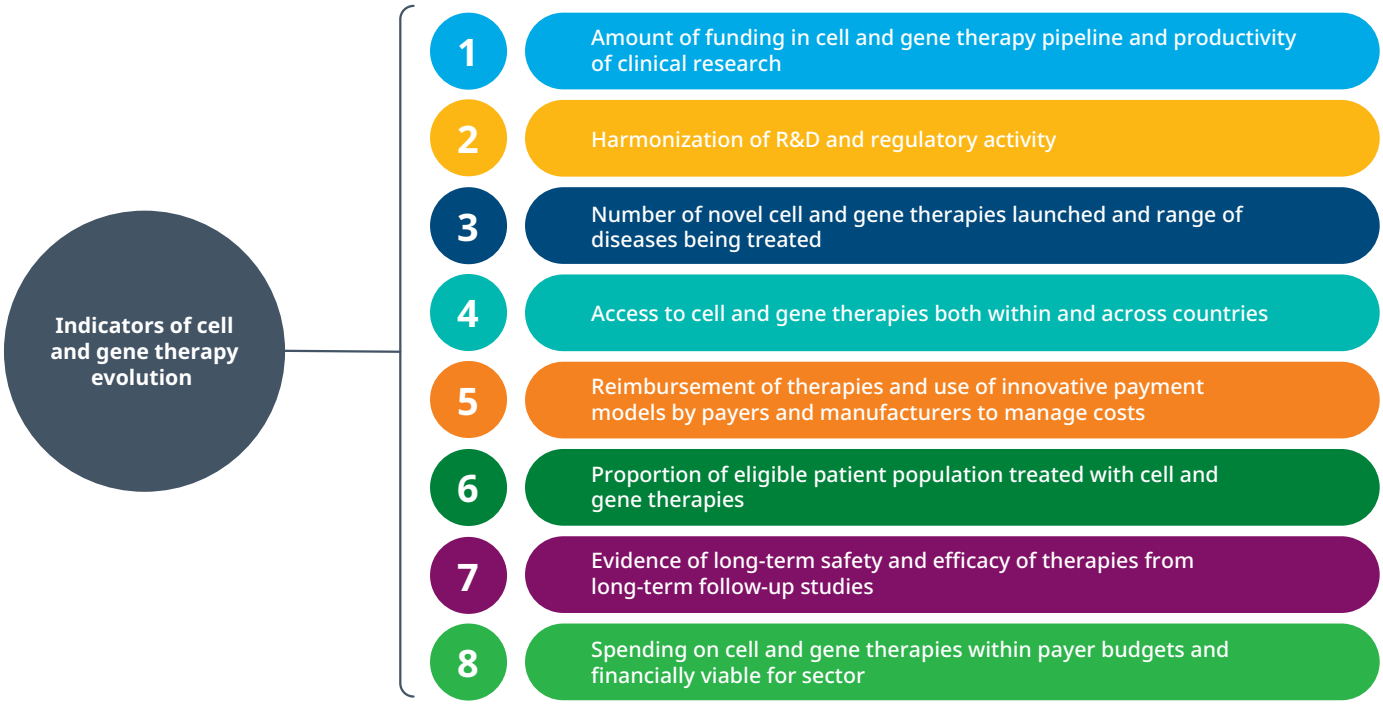
+ **A range of indicators can be used by healthcare stakeholders to track the future evolution of the cell and gene therapy market, ranging from early-stage research activity to patient access.**

+ **Each indicator can evolve across a range of potential scenarios, with varying combinations of these scenarios having differential impacts on the direction, growth, and sustainability of the overall market.**

+ **As the cell and gene therapy sector is less mature than other modalities, significant uncertainty remains about the future trajectory and tracking the evolution periodically will provide a better understanding of the long-term potential of this sector to provide improved outcomes for patients.**

The future of the cell and gene therapy market will depend on the progress of the industry across a range of indicators (Exhibit 43). These indicators measure the status of the sector at key points throughout the end-to-end lifecycle of these therapies. Although the future of cell and gene therapies remains uncertain, the evolution across these indicators of the market from the current state established in this research can provide insight into the trajectory through 2035 that can be useful for all stakeholders.

Exhibit 43: Indicators of cell and gene therapy evolution



Source: IQVIA Institute, Feb 2024.

Funding and clinical research productivity

The amount of funding flowing into the cell and gene therapy space can reflect the degree of ongoing research and the ability to engage in new research. In 2023, venture capital funding reached $3.5Bn with a 5-year CAGR of 8%. Additionally, the level of new clinical research will be important to track and the success of this research in providing benefits over current treatment options, including other cell and gene therapies. More than 400 industry-sponsored clinical trials started in 2023 and this number has been growing at a 5-year CAGR of 6%.

The potential future scenarios for funding and clinical research are:

- **Limited:** Less than 4% annual growth in venture capital funding and industry-sponsored clinical trial starts resulting in funding and clinical activity levels remaining relatively flat.
- **Moderate:** Similar growth in the future as compared to recent years with 4-7% annual growth in venture capital funding and industry-sponsored clinical trial starts.
- **Expanded:** Success of cell and gene therapies results in higher interest in the cell and gene therapy sector and greater than 7% annual growth in venture capital funding and industry-sponsored clinical trial starts.

Harmonization across geographies

Research activity and regulatory review are fragmented across geographies. China and the U.S., which have the highest amounts of clinical trial activity, also have the highest degree of single country clinical trials with 96% and 73%, respectively. This reflects a low degree of multi-country activity. Additionally, regulatory review varies significantly across geographies placing additional burden on sponsors for multi-country submissions.

The potential future scenarios for harmonization of research and regulatory activity are:

- **Limited:** Regulatory and research activity continues to be fragmented across geographies with divergent regulatory frameworks. Countries with high clinical activity have greater than 70% of trials with domestic-only sites and limited multi-country research studies.
- **Moderate:** Regulatory harmonization has reached ICH standing members only (U.S., EU, Japan, Canada, and Switzerland). Countries with high clinical activity have greater than 50% of trials with domestic-only sites and multi-country research studies occurring less than half the time.
- **Expanded:** Regulatory harmonization has occurred across all major markets, including China, and coordinated reviews are frequently utilized. Countries with high clinical activity have less than 50% of trials with domestic-only sites and multi-country research studies occurring more than half the time.

Novel therapy launches

The number of novel cell and gene therapies launched reflects the growing availability of these therapies, in addition, the range of diseases addressed by cell and gene therapies is an important indicator of the expansion of these therapies outside ultrarare diseases and oncology. A record eight novel cell and gene therapies launched globally in 2023 with half for oncology, and available therapies target patient populations in the 100s and 1,000s.

The potential future scenarios for novel launches are:

- **Limited:** The pace of launches slows with fewer than eight global novel cell and gene therapies launches annually, primarily for ultrarare diseases and oncology.
- **Moderate:** The pace of launches remains consistent at 8 to 12 global novel cell and gene therapies launches annually and more than one-third of therapies addressing non-oncology and larger population diseases in the 10,000s.
- **Expanded:** The pace of launches accelerates as regulatory review becomes streamlined and acceptance of cell and gene therapies outside of oncology grows. More than 12 global novel cell and gene launch annually and more than half of therapies address non-oncology and larger population diseases in the 10,000s.

Access to therapies within and across geographies

While cell and gene therapy launches are growing, access remains limited to major markets and treatment centers are highly concentrated around metropolitan areas. Of the 26 novel launches in the last five years, 69% have launched in a single geography. The U.S. has the largest number of certified CAR T-cell treatment centers, however treatment centers are highly concentrated around metropolitan areas and do not carry all approved products.

The potential future scenarios for access both within and across geographies are:

- **Limited:** Cell and gene therapy launches remain fragmented, with less than 50% of novel therapies available in multiple countries and concentrated in developed countries. Treatment centers remain concentrated near metropolitan centers and few or none in low- and middle-income countries.
- **Moderate:** Cell and gene therapy launches have higher dispersion, with 50-75% of novel therapies available in multiple countries, including both developing and high-income countries. Treatment centers are expanding outside of metropolitan centers but few in low- and middle-income countries.
- **Expanded:** Cell and gene therapy launches have high dispersion, with more than 75% of novel therapies available in multiple countries, including low-, middle-, and high-income countries. Treatment centers have expanded outside of metropolitan centers and are available in low- and middle-income countries as improvements in infrastructure take place, including point-of-care manufacturing and outpatient treatment.

Reimbursement and payment models

Reimbursement is a critical factor in ensuring patient access to these high price therapies, and the use of innovative payment models can alleviate payer concerns and manage costs. Among five therapies with wide launches, no therapy is fully reimbursed across 10 major markets. In Europe, the average reimbursement rate for these therapies is 31%, with higher rates in Western Europe and lower rates in Eastern Europe.

The potential future scenarios for reimbursement and payment models are:

- **Limited:** Reimbursement of cell and gene therapies is low as payers continue to have concerns about efficacy and budget impacts. Developed countries reimburse less than 25% of therapies and acceptance of innovative payment models is limited.
- **Moderate:** Reimbursement of cell and gene therapies is moderate as payer concerns about efficacy and budget impacts are addressed for some therapies. Developed countries reimburse 25-50% of therapies and low- and middle-income countries begin to reimburse on a limited basis. Innovative payment models are used more frequently to manage costs.
- **Expanded:** Reimbursement of cell and gene therapies is high as payers concerns about efficacy and budget impacts are largely alleviated due to enhanced long-term efficacy data and the use of payment models to manage costs. Developed countries reimburse more than 50% of therapies and low- and middle-income countries reimburse some therapies.

Patient access to treatment

Despite growing numbers of available therapies, many barriers prevent patients from receiving treatments. For CAR T-cell therapies, on average across major markets only 47% of referred patients end up receiving treatment. This does not consider patients who do not get referred or who do not have access to healthcare to begin with and the overall share of the patient population treated is likely lower.

The potential future scenarios for patient access to treatment:

- **Limited:** Treatment capacity becomes more limited and time to patients receiving treatment extends as more products reach the market resulting in low patient access with less than 30% of eligible patient population treated.
- **Moderate:** Existing barriers, such as capacity limitations and treatment timelines, remain consistent and patient access is moderate with 30-60% of eligible patient population treated.
- **Expanded:** Barriers around capacity are addressed through expanded infrastructure, point-of-care manufacturing, or shifts to outpatient treatment reducing the time to patients receiving treatment and allowing for more patient access as more than 60% of the eligible patient population is treated.

Long-term follow-up

Cell and gene therapies are still in their infancy with minimal long-term follow-up data which could highlight the long-term safety and efficacy of these therapies. Additionally, long-term follow-up studies are difficult to perform as patients move around and may be lost to follow-up over 15 years or longer post-treatment.

The potential future scenarios for long-term follow-up are:

- **Limited:** Traditional site-based follow-up is maintained resulting in burdensome follow-up for both providers and patients. Real-world use over longer periods shows degradation of safety and durability of treatment compared with pivotal trials.
- **Moderate:** Minimal advances in long-term follow-up mechanisms allowing for some patient flexibility but retaining a level of burdensome site-based follow-up. Real-world use over longer periods confirms safety and durability of treatment in line with that seen in pivotal trials.
- **Expanded:** Long-term follow-up has shifted to innovative models requiring minimal effort from providers and patients. Real-world use over longer periods extends safety and efficacy profile consistent with label and pivotal trials.

Spending and financial viability

The high price tags of cell and gene therapies often spark concerns over uncontrolled spending on these therapies, which limit patient access. However, spending on these therapies accounted for only 0.4% of pharmaceutical spending in 2023, much lower than other novel modalities. More than 650 companies have recently been involved in clinical research and 58 companies have commercialized products, including five large pharma companies.

The potential future scenarios for spending and financial viability are:

- **Limited:** Global spending on cell and gene therapies remains less than 0.5% of pharmaceutical spending as new launches are low and remain in small patient populations. Revenue generation is low as questions remain around efficacy and costs remain high resulting in fewer companies (<50 companies) with commercialized products in the sector and minimal large pharma involvement (<5 companies). Fewer than 500 companies will be actively involved in clinical research as funding and interest in the sector wanes.
- **Moderate:** Global spending on cell and gene therapies accounts for 0.5-2% of pharmaceutical spending as the trend in new launches remains consistent and commercially available therapies expand into slightly larger patient populations. Revenue generation remains modest for most therapies resulting in a similar level of companies with commercialized products in the sector (50-70 companies) and more involvement of large pharma (5-10 companies). Between 500 and 800 companies will be actively involved in clinical research as funding and interesting in the sector remains consistent.
- **Expanded:** Global spending on cell and gene therapies accounts for 2-5% of pharmaceutical spending as the number of new launches accelerated and available therapies expand into large patient populations. Revenue generation is high as costs come down and acceptance of therapies is high resulting in more companies with commercialized products in the sector (>70 companies) and more involvement of large pharma (>10 companies). More than 800 companies will be actively involved in clinical research as funding and interesting in the sector grows.

The long-term viability of the cell and gene therapy sector may depend on the use of mixed models of commercialization that do not follow the traditional pharmaceutical commercialization framework. The current commercialization of these therapies, which resembles the model of traditional medicines, is not necessarily sustainable for therapies that treat very small patient populations, as evidenced by the notable past withdrawals in the sector for financial reasons. To address this issue, the cell and gene therapy sector may evolve the way these medicines are commercialized to ensure benefits for patient populations of all sizes. This may entail academic or non-profit marketing of cell and gene therapies and the support of foundations and patient organizations.

The introduction of other novel modalities outside of cell and gene therapies will have significant impacts on the market. As bi- or trispecific antibodies and antibody-drug conjugates continue to show success in treating diseases, particularly cancer, these novel modalities may supplant the position of those cell and gene therapies in treatment paradigms that are often more complex. Stakeholders in the cell and gene therapy sector will need to determine the appropriate role that cell and gene therapies play in disease treatment when less complex treatment technologies are available.

Significant uncertainty still exists about the future of the cell and gene therapy sector, with a range of future scenarios possible. These indicators and the potential future evolution of these metrics can be used to track the progress of the sector (Exhibit 44). Tracking the long-term viability of the sector will be important as continued interest in the space grows. This research provides a baseline understanding of the sector across these indicators as of 2023. Reflecting on the evolution of the sector across these indicators every two years will give a better understanding of the future trajectory of cell and gene therapies through 2035 and beyond.

Exhibit 44: Future scenarios for the cell and gene therapy sector

INDICATOR	Limited	Moderate	Expanded
Amount of funding in cell and gene therapy pipeline and productivity of clinical research	• <4% annual growth	• 4-7% annual growth	• >7% annual growth
Harmonization of R&D and regulatory activity	• >70% of trials single country	• 50-70% of trials single country	• <50% of trials single country
Number of novel cell and gene therapies launched and range of diseases being treated	• <8 novel launches annually	• 8-12 novel launches annually	• >12 novel launches annually
Access to cell and gene therapies both within and across countries	• <50% of therapies available in multiple countries	• 50-75% of therapies available in multiple countries	• >75% of therapies available in multiple countries
Therapy reimbursement and use of innovative payment models to manage costs	• <25% of therapies reimbursed	• 25-50% of therapies reimbursed	• >50% of therapies reimbursed
Proportion of eligible patient population treated with cell and gene therapies	• <30% of eligible patients treated	• 30-60% of eligible patients treated	• >60% of eligible patients treated
Evidence of long-term safety and efficacy from follow-up studies	• Degradation of safety and efficacy compared to pivotal trials	• Safety and efficacy in line with pivotal trials	• Safety and efficacy extended compared to pivotal trials
Spending on cell and gene therapies and financial viability of sector	• <0.5% of pharmaceutical spending • <50 companies with commercial products (<5 large pharma) • <500 companies engaged in clinical research	• 0.5-2% of pharmaceutical spending • 50-70 companies with commercial products (5-10 large pharma) • 500-800 companies engaged in clinical research	• 2-5% of pharmaceutical spending • >70 companies with commercial products (>10 large pharma) • >800 companies engaged in clinical research

Source: IQVIA Institute, Feb 2024.

Notes on sources

THIS REPORT IS BASED ON THE IQVIA SERVICES DETAILED BELOW

ONCOLOGY DYNAMICS is a syndicated cross-sectional survey that collects patient-level data from a representative panel of physicians and provides quick access to real-world data to unravel dynamics in subpopulations and treatment patterns. Oncology Dynamics has geographic coverage across 17 countries including key European, Middle Eastern, Asian, and Latin American markets and covers more than 180,000 cases per year and over 4,000 specialists.

IQVIA™ HTA ACCELERATOR provides strategic insights into payer decision-making based on 25,000+ health technology assessments from 100 agencies and 40 countries. With additional clinical, regulatory and price information it sets the foundation for evidence-based insight generation.

IQVIA™ PHARMA DEALS is a comprehensive life science deals and alliances database that leverages worldwide information sources to deliver the latest intelligence in deals and alliances.

CAR T-CELL MONITOR provides insights on the patient journey from the referring oncologists to the advanced treatment centers that administer these therapies. This global syndicated study provides quantitative data and qualitative insights on key touchpoints along this continuum (e.g., referral rates, barriers to treatment, drivers of patient success, treatment share, line-of-therapy).

THIRD-PARTY INFORMATION

CITELINE'S TRIALTROVE provides intelligence about the drug development pipeline and information on clinical trials globally. Citeline reports that Trialtrove uses over 60,000 sources including ones in the public domain and is supported by experienced industry analysts. The database includes extracted information including protocol details, as well as additional industry-relevant search terms such as its proprietary patient segments, trial outcomes and biomarker tags. It includes information on trial design, eligibility criteria, endpoints, sites, sponsors as well as anticipated and actual start and end dates as available. For more information on Trialtrove see https://www.citeline.com/en/products-services/clinical/trialtrove

Appendix

Launched cell and gene therapy products include those with regulatory approval and launch determined based on desk research. Much of the information for these products is derived from the Alliance for Regenerative Medicine's list of available products (https://alliancerm.org/available-products/). Evidence of launch includes sales data, company statements, or availability of patient support websites. When launch evidence is not available, products are assumed launched at approval unless otherwise stated publicly. The year of launch is determined by the earliest launch anywhere in the world.

Exhibit 45a: List of launched cell and gene therapies

GLOBAL LAUNCH YEAR	TYPE	PRODUCT NAME	INDICATION
1997	Tissue-engineered product	Transcyte	treatment of wounds
1998	Tissue-engineered product	Apligraf	treatment of chronic venous leg ulcers and diabetic foot ulcer
2001	Tissue-engineered product	Dermagraft	treatment of chronic diabetic foot ulcers
2002	Tissue-engineered product	Holoderm	treatment of 2nd and 3rd degree burns
2003	Tissue-engineered product	Novocart 3D	articular cartilage repair
2004	Gene therapy	Gendicine	head and neck cancer
2005	Cell therapy	Kaloderm	treatment of burns and diabetic foot ulcers
	Gene therapy	Oncorine	head and neck cancer, nasopharyngeal cancer
2006	Cell therapy	KeraHeal	treatment of 2nd and 3rd degree burns
2007	Cell-based immunotherapy	CreaVax RCC	metastatic renal cell carcinoma
	Cell-based immunotherapy	Immuncell-LC	hepatocellular carcinoma
	Gene therapy	Rexin-G	metastatic solid tumors
	Tissue-engineered product	Aurix	treatment of wounds
	Tissue-engineered product	Epicel	deep dermal or full thickness burns
	Tissue-engineered product	Hyalograft 3D	treatment of diabetic foot ulcers
	Tissue-engineered product	JACE	Deep dermal and full-thickness burns and giant congenital melanocytic nevus
2009	Tissue-engineered product	Ossron	treatment of bone defects
2010	Cell therapy	CureSkin	treatment of depressed acne scars
	Cell therapy	Queencell	treatment of connective tissue disorders
2011	Cell-based immunotherapy	Provenge	metastatic castration-resistant prostate cancer
	Cell therapy	Cellgram-AMI	acute myocardial infarction
	Cell therapy	LaViv	moderate to severe nasolabial fold wrinkles
2012	Cell therapy	Cartistem	knee cartilage defects as a result of degenerative osteoarthritis or repeated trauma
	Cell therapy	Cupistem	Crohn's fistula
	Cell therapy	Temcell	acute graft-versus-host disease
	Gene therapy	Neovasculgen	peripheral artery disease
2013	Cell therapy	Neuronata-R	amyotrophic lateral sclerosis (ALS)
	Tissue-engineered product	CardioCel	treatment of cardiovascular abnormalities
	Tissue-engineered product	JACC	traumatic cartilage defect or osteochondritis dissecans of the knee
2014	Gene therapy	Glybera*	familial lipoprotein lipase deficiency (LPLD)
2015	Cell therapy	Holoclar	moderate to severe limbal stem cell deficiency due to ocular burns
	Cell therapy	KerHeal-Allo	treatment of 2nd and 3rd degree burns
	Gene therapy	Imlygic	Unresectable cutaneous, subcutaneous, and nodal lesions in patients with recurrent melanoma

Continued on the next page...

Appendix

Exhibit 45b: List of launched cell and gene therapies

GLOBAL LAUNCH YEAR	TYPE	PRODUCT NAME	INDICATION
2016	Cell therapy	Zalmoxis*	adjunctive treatment in stem cell transplant of patients with high-risk hematological malignancies
	Tissue-engineered product	Heart Sheet	severe heart failure caused by chronic ischemic heart disease
	Tissue-engineered product	MACI	treatment of cartilage defects of the knee
	Tissue-engineered product	Omnigraft	treatment of diabetic foot ulcers
	Tissue-engineered product	ReGenerCel	treatment of ulcers
	Tissue-engineered product	ReNovaCell	treatment of skin discoloration
	Tissue-engineered product	Vergenix FG	treatment of chronic and acute wounds
	Tissue-engineered product	Vergenix-STR	treatment of connective tissue disorders
2017	Cell-based immunotherapy	APCeden	prostate cancer, ovarian cancer, colorectal cancer, and non-small cell lung cancer
	Cell-based immunotherapy	Kymriah	r/r large B-cell lymphoma, r/r follicular lymphoma, r/r acute lymphoblastic leukemia
	Cell-based immunotherapy	Yescarta	r/r large B-cell lymphoma, r/r follicular lymphoma
	Cell therapy	Rosmir	wrinkle correction of nasojugal grooves
	Cell therapy	Spherox	articular cartilage defects
	Gene therapy	Strimvelis	adenosine deaminase-deficient severe combined immune deficiency (ADA-SCID)
	Tissue-engineered product	Ortho-ACI	treatment of articular cartilage defects in the knee and ankle
2018	Cell therapy	Alofisel	complex perianal fistulas in patients with Crohn's disease
	Gene therapy	Luxturna	RPE65 mutation-associated retinal dystrophy
2019	Cell therapy	Stemirac	traumatic spinal cord injury
	Gene therapy	Collategene	critical limb ischemia
	Gene therapy	Zolgensma	spinal muscular atrophy (SMA)
2020	Cell-based immunotherapy	Tecartus	r/r mantle cell lymphoma, r/r acute lymphoblastic leukemia
	Cell therapy	Stempeucel	critical limb ischemia
	Gene therapy	Zynteglo	ß-thalassemia
2021	Cell-based immunotherapy	Abecma	r/r multiple myeloma
	Cell-based immunotherapy	Breyanzi	r/r large B-cell lymphoma, r/r follicular lymphoma
	Cell-based immunotherapy	Carteyva	r/r large B-cell lymphoma, r/r follicular lymphoma
	Gene therapy	Libmeldy	metachromatic leukodystrophy (MLD)
	Tissue-engineered product	Rethymic	congenital athymia
	Tissue-engineered product	Stratagraft	treatment of thermal burns
2022	Cell-based immunotherapy	Carvykti	r/r multiple myeloma
	Cell therapy	StemOne	knee osteoarthritis
	Gene therapy	Hemgenix	hemophilia B
	Gene therapy	Roctavian	hemophilia A
	Gene therapy	Skysona	active cerebral adrenoleukodystrophy (CALD)
	Gene therapy	Upstaza	aromatic L-amino acid decarboxylase (AADC) deficiency
2023	Cell-based immunotherapy	Ebvallo	r/r Epstein-Barr virus positive post-transplant lymphoproliferative disease (EBV+ PTLD)
	Cell-based immunotherapy	Fucaso	r/r multiple myeloma
	Cell therapy	Lantidra	adults with Type 1 diabetes unable to achieve target HbA1c
	Cell therapy	Omisirge	patients with hematologic malignancies planned for cord blood transplant
	Cell therapy	Vyznova	bullous keratopathy of the cornea
	Gene therapy	Adstiladrin	high-risk, Bacillus Calmette-Guérin (BCG)-unresponsive non-muscle-invasive bladder cancer (NMIBC) with carcinoma in situ
	Gene therapy	Elevidys	Duchenne muscular dystrophy (DMD)
	Gene therapy	Vyjuvek	dystrophic epidermolysis bullosa

Source: Alliance for Regenerative Medicine, IQVIA Institute, Dec 2023.
Notes: *indicates the product has been withdrawn from the market. r/r = relapsed or refractory.

References

1. Jones AW. Early drug discovery and the rise of pharmaceutical chemistry. Drug Test Anal. 2011 Jun;3(6):337–44. Available from: https://analyticalsciencejournals.onlinelibrary.wiley.com/doi/10.1002/dta.301.
2. Liu JKH. The history of monoclonal antibody development – progress, remaining challenges and future innovations. Ann Med Surg (Lond). 2014 Sep 11;3(4):113–6. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4284445/.
3. Alliance for Regenerative Medicine. Technologies [Internet]. [cited 2024 Jan 18]. Available from: https://alliancerm.org/technologies/
4. National Cancer Institute. CAR T cells: engineering patients' immune cells to treat their cancers [Internet]. Updated 2022 Mar 10 [cited 2024 Jan 18]. Available from: https://www.cancer.gov/about-cancer/treatment/research/car-t-cells
5. Alliance for Regenerative Medicine. Cell therapy [Internet]. [cited 2024 Jan 18]. Available from: https://alliancerm.org/technologies/cell-therapy/
6. Alliance for Regenerative Medicine. Gene-based medicine [Internet]. [cited 2024 Jan 18]. Available from: https://alliancerm.org/technologies/gene-based-medicine/
7. Alliance for Regenerative Medicine. Tissue-engineered products & biomaterials [Internet]. [cited 2024 Jan 18]. Available from: https://alliancerm.org/technologies/tissue-engineered-products-biomaterials/
8. IQVIA Institute for Human Data Science. Global trends in R&D 2024: activity, productivity, and enablers. 2024 Feb. Available from: https://www.iqvia.com/insights/the-iqvia-institute/reports-and-publications/reports/global-trends-in-r-and-d-2024-activity-productivity-and-enablers
9. Novo Nordisk. Novo Nordisk and Life Edit Therapeutics establish multi-target collaboration to discover and develop gene editing therapies for rare and cardiometabolic diseases [Internet]. 2023 May 24 [cited 2024 Jan 18]. Available from: https://www.novonordisk.com/content/nncorp/global/en/news-and-media/news-and-ir-materials/news-details.html?id=166111
10. Aspect Biosystems. Aspect Biosystems and Novo Nordisk enter partnership to develop bioprinted tissue therapeutics for diabetes and obesity [Internet]. 2023 Apr 12 [cited 2024 Jan 18]. Available from: https://www.aspectbiosystems.com/news-resources/novo-nordisk-partnership-to-develop-bioprinted-tissue-therapeutics-for-diabetes-and-obesity
11. RoslinCT. RoslinCT to manufacture exagamglogene autotemcel (exa-cel) for Vertex Pharmaceuticals Inc following an extensive development collaboration [Internet]. 2023 Nov 28 [cited 2024 Jan 18]. Available from: https://www.roslinct.com/insights/roslinct-to-manufacture-exagamglogene-autotemcel-exa-cel-for-vertex-pharmaceuticals-inc-following-an-extensive-development-collaboration/
12. Charles River Laboratories International, Inc. Charles River and Vertex Pharmaceuticals reach important milestone in cell therapy manufacturing collaboration [Internet]. 2023 Dec 18 [cited 2024 Jan 18]. Available from: https://ir.criver.com/news-releases/news-release-details/charles-river-and-vertex-pharmaceuticals-reach-important/
13. Sartorius. Sartorius Stedim Biotech completes acquisition of Polyplus [Internet]. 2023 Jul 18 [cited 2024 Jan 18]. Available from: https://www.sartorius.com/en/company/newsroom/corporate-news/sartorius-stedim-biotech-completes-acquisition-of-polyplus-1452176
14. Fractyl Health, Inc. Form S-1. 2023 Dec 14 [cited 2024 Jan 18]. Available from: https://www.sec.gov/Archives/edgar/data/1572616/000119312523295433/d519724ds1.htm
15. Metagenomi Technologies, LLC. Form S-1. 2024 Jan 5 [cited 2024 Jan 18]. Available from: https://www.sec.gov/Archives/edgar/data/1785279/000119312524003477/d425213ds1.htm
16. Kyverna Therapeutics, Inc. Form S-1. 2024 Jan 16 [cited 2024 Jan 18]. Available from: https://www.sec.gov/Archives/edgar/data/1994702/000119312524008614/d530411ds1.htm
17. IQVIA Institute for Human Data Science. Supporting patients through research collaboration: interactions between patients organizations and life sciences companies. 2023 Oct. Available from: https://www.iqvia.com/insights/the-iqvia-institute/reports-and-publications/reports/supporting-patients-through-research-collaboration
18. Nationwide Children's Hospital. New gene therapy study reverses effects of lethal childhood muscle disorder in mice [Internet]. 2010 Mar 1 [cited 2024 Jan 18]. Available from: https://www.nationwidechildrens.org/newsroom/news-releases/2010/03/new-gene-therapy-study-reverses-effects-of-lethal-childhood-muscle-disorder-in-mice
19. Nationwide Children's Hospital. Families of SMA and Nationwide Childrens Hospital announce multi-million dollar award from NINDS to advance CNS-directed gene therapy for spinal muscular atrophy [Internet]. 2013 Mar 13 [cited 2024 Jan 18]. Available from: https://www.nationwidechildrens.org/newsroom/news-releases/2013/03/families-of-sma-and-nationwide-childrens-hospital-announce-multi-million-dollar-award-from-ninds-to

20. Nationwide Children's Hospital. Sophias Cure Foundation donates $650,000 in 2012 to Nationwide Childrens Hospital [Internet]. 2013 Jan 31 [cited 2024 Jan 18]. Available from: https://www.nationwidechildrens.org/newsroom/news-releases/2013/01/sophias-cure-foundation-donates-650000-in-2012-to-nationwide-childrens-hospital

21. Nationwide Children's Hospital. Cure SMA provides additional funding for promising spinal muscular atrophy research at Nationwide Childrens Hospital [Internet]. 2015 May 7 [cited 2024 Jan 18]. Available from: https://www.nationwidechildrens.org/newsroom/news-releases/2015/05/cure-sma-provides-additional-funding-for-promising-spinal-muscular-atrophy-research-at-nationwide

22. Nationwide Children's Hospital. Phase 1 study shows encouraging data for gene replacement therapy for spinal muscular atrophy type 1 [Internet]. 2017 Nov 1 [cited 2024 Jan 18]. Available from: https://www.nationwidechildrens.org/newsroom/news-releases/2017/11/phase-1-study-shows-encouraging-data-for-gene-replacement-therapy-for-spinal-muscular-atrophy-type-1

23. Novartis. Novartis enters agreement to acquire AveXis Inc. for USD 8.7 bn to transform care in SMA and expand position as a gene therapy and neuroscience leader [Internet]. 2018 Apr 9 [cited 2024 Jan 18]. Available from: https://www.novartis.com/news/media-releases/novartis-enters-agreement-acquire-avexis-inc-usd-87-bn-transform-care-sma-and-expand-position-gene-therapy-and-neuroscience-leader

24. Novartis. AveXis expands world-leading gene therapy manufacturing capacity with purchase of advanced biologics therapy manufacturing campus in Longmont, Colorado [Internet]. 2019 Apr 1 [cited 2024 Jan 18]. Available from: https://www.novartis.com/news/media-releases/avexis-expands-world-leading-gene-therapy-manufacturing-capacity-purchase-advanced-biologics-therapy-manufacturing-campus-longmont-colorado

25. Novartis. Novartis shares Zolgensma long-term data demonstrating sustained durability up to 7.5 years post-dosing; 100% achievement of all assessed milestones in children treated prior to SMA symptom onset [Internet]. 2023 Mar 20 [cited 2024 Feb 6]. Available from: https://www.novartis.com/news/media-releases/novartis-shares-zolgensma-long-term-data-demonstrating-sustained-durability-75-years-post-dosing-100-achievement-all-assessed-milestones-children-treated-prior-sma-symptom-onset

26. Miracle for Madison & Friends. My story by Madison Rose Reed [Internet]. [cited 2024 Jan 18]. Available from: http://www.miracleformadison.org/journey.htm

27. California Institute for Regenerative Medicine (CIRM). Active awards portfolio dashboard [Internet]. [cited 2024 Feb 5]. Available from: https://www.cirm.ca.gov/active-awards-portfolio/

28. California Institute for Regenerative Medicine (CIRM). Funding clinical trials [Internet]. [cited 2024 Feb 5]. Available from: https://www.cirm.ca.gov/clinical-trials/

29. National Institutes of Health. Bespoke Gene Therapy Consortium [Internet]. Updated 2023 Jun 13 [cited 2024 Feb 5].. Available from: https://www.nih.gov/research-training/accelerating-medicines-partnership-amp/bespoke-gene-therapy-consortium

30. Centre for Commercialization of Regenerative Medicine. About us [Internet]. [cited 2024 Feb 23]. Available from: https://www.ccrm.ca/about-us-regenerative-medicine-cell-gene-therapy/

31. UK Regenerative Medicine Platform. Hub publications [Internet]. [cited 2024 Jan 26]. Available from: https://www.ukrmp.org.uk/resource/reports-and-papers/

32. Cell and Gene Therapy Catapult. About Us [Internet]. [cited 2024 Jan 26]. Available from: https://ct.catapult.org.uk/about

33. Agência FAPESP. Nutera Advanced Therapy Center will produce CAR T-cells for use in clinical trial of cancer treatment [Internet]. 2023 Oct 18 [cited 2024 Jan 26]. Available from: https://agencia.fapesp.br/nutera-advanced-therapy-center-will-produce-car-t-cells-for-use-in-clinical-trial-of-cancer-treatment/49987

34. Egypt Genome Project [Internet]. [cited 2024 Jan 26]. Available from: https://egp.sci.eg/

35. Wang L, Ding J, Stacey GN, Hao J. The Chinese National Stem Cell Resource Center. Stem Cell Res. 2021 Jan;50:101985. Available from: https://doi.org/10.1016/j.scr.2020.101985.

36. National Stem Cell Resource Center. The China Stem Cell and Regenerative Medicine Collaborative Innovation Platform initiated by the National Stem Cell Resource Bank has added new members and released a platform sharing information system [Internet]. 2023 Sep 28 [cited 2024 Feb 28]. Available from: http://www.bjscb.cn/dms/xbkydt/367.jhtml

37. Institute for Stem Cell Science and Regenerative Medicine. inStem annual report 2022-2023 [Internet]. 2023 [cited 2024 Jan 26]. Available from: https://www.instem.res.in/annual-report

38. Novo Nordisk Foundation Center for Stem Cell Medicine (reNEW). About reNEW [Internet]. [cited 2024 Jan 26]. Available from: https://renew.science/about/

39. European Consortium for Communicating Gene and Cell Therapy Information (EuroGCT). About EuroGCT [Internet]. 2022 [cited 2024 Jan 26]. Available from: https://www.eurogct.org/about-eurogct

40. Mueller F, Taubmann J, Voelkl S, Bucci L, Bergmann C, Aigner M, et al. CD19-targeted CAR-T cells in refractory systemic autoimmune diseases: a monocentric experience from the first fifteen patients [abstract]. Presented at: 65th American Society of Hematology Annual Meeting & Exposition; 2023 Dec 9-12; San Diego, CA. Available from: https://ash.confex.com/ash/2023/webprogram/Paper180547.html

41. Ungar L. Experimental gene therapy allows kids with inherited deafness to hear. The Associated Press [Internet]. 2024 Jan 24 [cited 2024 Jan 19]. Available from: https://apnews.com/article/gene-therapy-deafness-hearing-6f38a9123a9cf7a0fd44d7e8402c9951

42. NEWDIGS at Tufts Medical Center. Are Cell and Gene Therapy programs a better bet? 2023 Oct 9. Available from: https://newdigs.tuftsmedicalcenter.org/are-cell-and-gene-therapy-programs-a-better-bet/

43. Liu A. Eli Lilly, Innovent hit with FDA rejection for China-developed lung cancer drug after tough review. Fierce Pharma [Internet]. 2022 Mar 24 [cited 2024 Feb 20]. Available from: https://www.fiercepharma.com/pharma/lilly-innovent-hit-fda-no-go-discounted-pd-1-immunotherapys-lung-cancer-bid-after-bleak

44. Beaver JA, Pazdur R. The wild west of checkpoint inhibitor development. N Engl J Med. 2022 Apr 7;386:1297-1301. Available from: https://www.nejm.org/doi/10.1056/NEJMp2116863

45. Legend Biotech. Legend Biotech achieves milestone under collaboration agreement with Janssen Biotech, Inc. for BCMA CAR-T [Internet]. 2022 Apr 21 [cited 2024 Jan 19]. Available from: https://investors.legendbiotech.com/news-releases/news-release-details/legend-biotech-achieves-milestone-under-collaboration-agreement/

46. Hawksford. China's 'Negative List' for foreign investment access [Internet]. [cited 2024 Feb 8]. Available from: https://www.hawksford.com/insights-and-guides/china-business-guides/china-negative-list-for-foreign-investment-access

47. Ilic D. iPSC in the past decade: the Japanese dominance. Regen Med. 2016 Dec;11(8):747–9. Available from: https://www.futuremedicine.com/doi/10.2217/rme-2016-0153

48. Senior M. After Glybera's withdrawal, what's next for gene therapy? Nat Biotechnol. 2017 Jun 7;35(6):491–2. Available from: https://www.nature.com/articles/nbt0617-491

49. Novartis AG. From 20-F. 2024 Jan 31 [cited 2024 Feb 23]. Available from: https://www.novartis.com/investors/financial-data/annual-results

50. JW Therapeutics. Pipeline [Internet]. [cited 2024 Jan 21]. Available from: https://www.jwtherapeutics.com/en/r-d-and-manufacturing/pipeline/

51. Innovent Biologics. Innovent and IASO Bio announce the NMPA approval of FUCASO®, the first fully-human BCMA CAR-T therapy, for the treatment of relapsed or refractory multiple myeloma [Internet]. 2023 Jul 3 [cited 2024 Jan 21]. Available from: https://www.innoventbio.com/InvestorsAndMedia/PressReleaseDetail?key=399

52. Fangqing W. Medical tourism? Chinese novel treatment developers explore alternative opportunities for profits. The Pharma Letter [Internet]. 2023 Apr 24 [cited 2024 Jan 21]. Available from: https://www.thepharmaletter.com/article/medical-tourism-chinese-novel-treatment-developers-explore-alternative-opportunities-for-profits

53. IASO Bio. IASO Bio establishes international CAR-T diagnostic and treatment center in China to serve MM patients worldwide [Internet]. Business Wire. 2023 Nov 20 [cited 2024 Jan 21]. Available from: https://www.businesswire.com/news/home/20231115683764/en/IASO-Bio-Establishes-International-CAR-T-Diagnostic-and-Treatment-Center-in-China-to-Serve-MM-Patients-Worldwide

54. The People's Government of Hainan Province. [Notice of the Hainan Provincial People's Government on issuing the management regulations for clinically urgent imported drugs and medical devices in the Hainan Free Trade Port Boao Lecheng International Medical Tourism Pilot Zone]. 2023 Mar 28. Chinese. Available from: https://www.hainan.gov.cn/hainan/flfgxzgfxwj/202303/8211027e3ba147b9ad7350af6f9a3fa3.shtml

55. CRISPR Therapeutics. Vertex and CRISPR Therapeutics announce authorization of the first CRISPR/Cas9 gene-edited therapy, CASGEVYTM (exagamglogene autotemcel), by the United Kingdom MHRA for the treatment of sickle cell disease and transfusion-dependent beta thalassemia [Internet]. 2023 Nov 16 [cited 2024 Jan 21]. Available from: https://ir.crisprtx.com/news-releases/news-release-details/vertex-and-crispr-therapeutics-announce-authorization-first/

56. Lutzmayer S, Wright A. Rewriting the code: gene-editing therapeutics [Internet]. IQVIA. 2023 Jul 6 [cited 2024 Jan 21]. Available from: https://www.iqvia.com/blogs/2023/07/rewriting-the-code-gene-editing-therapeutics

57. Guo N, Liu JB, Li W, Ma YS, Fu D. The power and the promise of CRISPR/Cas9 genome editing for clinical application with gene therapy. J Adv Res. 2022 Sep;40:135–52. Available from: https://doi.org/10.1016/j.jare.2021.11.018

58. Alliance for Regenerative Medicine. Sector snapshot: December 2023 [Internet]. 2023 Dec [cited 2024 Jan 21]. Available from: https://alliancerm.org/sector-snapshot-december-2023/

59. European Medicines Agency. Advanced therapy medicinal products: overview [Internet]. Updated 2024 Feb 8 [cited 2024 Feb 12].. Available from: https://www.ema.europa.eu/en/human-regulatory-overview/advanced-therapy-medicinal-products-overview

60. Gomes KLG, da Silva RE, da Silva Junior JB, Novaes MRCG. Comparison of new Brazilian legislation for the approval of advanced therapy medicinal products with existing systems in the USA, European Union and Japan. Cytotherapy. 2022 May;24(5):557–66. Available from: https://doi.org/10.1016/j.jcyt.2021.10.008

61. International Council for Harmonisation. Press release: ICH assembly meeting, Vancouver, Canada, June 2023 [Internet]. 2023 Jun 20 [cited 2024 Feb 12]. Available from: https://www.ich.org/pressrelease/press-release-ich-assembly-meeting-vancouver-canada-june-2023

62. Marks P. Expediting the development of cell and gene therapy. Presented at: Alliance for Regenerative Medicine's 2024 Cell & Gene State of the Industry Briefing; 2024 Jan 8; San Francisco, CA. Available from: https://alliancerm.org/arm-event/sotibriefing/

63. U.S. Food and Drug Administration. Priority review [Internet]. 2018 Jan 4 [cited 2024 Jan 21]. Available from: https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/priority-review

64. U.S. Food and Drug Administration. Expedited programs for regenerative medicine therapies for serious conditions: guidance for industry. 2019 Feb. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/expedited-programs-regenerative-medicine-therapies-serious-conditions

65. U.S. Food and Drug Administration. CBER regenerative medicine advanced therapy (RMAT) approvals [Internet]. Updated 2024 Jan 25 [cited 2024 Feb 12]. Available from: https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/cber-regenerative-medicine-advanced-therapy-rmat-approvals

66. European Medicines Agency. Progress update on pilot for academic and non-profit developers of advanced therapy medicines [Internet]. 2024 Feb 8 [cited 2024 Feb 12]. Available from: https://www.ema.europa.eu/en/news/progress-update-pilot-academic-non-profit-developers-advanced-therapy-medicines

67. Todorov G. Cell and ex vivo gene therapies: a manufacturing odyssey. The Medicine Maker [Internet]. 2022 Dec 5 [cited 2024 Jan 29]. Available from: https://themedicinemaker.com/manufacture/cell-and-ex-vivo-gene-therapies-a-manufacturing-odyssey

68. Zamecnik A. A perfect storm: Covid-19 viral vector manufacturing adds further burden to CAR-T development. Pharmaceutical Technology [Internet]. 2022 Mar 16 [cited 2024 Jan 29]. Available from: https://www.pharmaceutical-technology.com/features/a-perfect-storm-covid-19-viral-vector-manufacturing-adds-further-burden-to-car-t-development/

69. Legend Biotech. Form 6-K. 2023 Apr 14 [cited 2024 Jan 29]. Available from: https://investors.legendbiotech.com/node/7936/html

70. Kansteiner F. After launch limitations, Johnson & Johnson exec touts manufacturing progress on CAR-T drug Carvykti. Fierce Pharma [Internet]. 2023 Oct 18 [cited 2024 Jan 29]. Available from: https://www.fiercepharma.com/pharma/johnson-johnson-exec-touts-carvykti-manufacturing-progress

71. IQVIA CAR T-Cell Monitor. CAR T-cell program directors insights: strategic insights for CAR T-cell products and related technologies. 2023 Oct.

72. Pellegrini E. Pharmaceutical company halts access to CAR-T cell treatment for UK myeloma patients [Internet]. Myeloma UK. 2023 Mar [cited 2024 Jan 29]. Available from: https://www.myeloma.org.uk/news/pharmaceutical-company-halts-access-to-car-t-cell-treatment-for-uk-myeloma-patients/

73. Pharmaceutical Technology. Kite Pharma's viral vector manufacturing facility, California, U.S. [Internet]. 2019 Jul [cited 2024 Jan 29]. Available from: https://www.pharmaceutical-technology.com/projects/kite-pharmas-viral-vector-manufacturing-facility-california/

74. Dunleavy K. Bristol Myers boosts CAR-T manufacturing footprint, taking over former Novartis site in Illinois. Fierce Pharma [Internet]. 2023 Apr 26 [cited 2024 Jan 29]. Available from: https://www.fiercepharma.com/manufacturing/bristol-myers-boosts-car-t-manufacturing-taking-over-novartis-site-illinois

75. Stanton D. 'Lack of good CDMOs' factor for Krystal's $90m gene therapy plant. BioProcess International [Internet]. 2020 Jan 29 [cited 2024 Jan 29]. Available from: https://bioprocessintl.com/bioprocess-insider/facilities-capacity/lack-of-good-cdmos-factor-for-krystals-90m-gene-therapy-plant/

76. CRB. Horizons: life sciences 2023 report [Internet]. 2023 Sep 26 [cited 2024 Feb 22]. Available from: https://go.crbgroup.com/2023-horizons-life-sciences-report

77. Delgado J. Initial clinical results of Euplagia-1, a phase 1/2 trial of point-of-care manufactured GLPG5201 in R/R CLL/SLL with or without Richter's transformation. Poster presented at: European Hematology Association Congress 2023; 2023 Jun 8-15; Frankfurt, Germany. Available from: https://library.ehaweb.org/eha/2023/eha2023-congress/385847/julio.delgado.initia

78. Tomtishen J. The role of automation in meeting the growing demand for CAR T-cell therapies. Evidence-Based Oncology. 2023 Jun 19;29(5):SP427–8. Available from: https://www.ajmc.com/view/the-role-of-automation-in-meeting-the-growing-demand-for-car-t-cell-therapies

79. Vives J, Sánchez-Guijo F, Gnecchi M, Zwaginga JJ. Cell and gene therapy workforce development: the role of the International Society for Cell & Gene Therapy (ISCT) in the creation of a sustainable and skilled workforce in Europe. Cytotherapy. 2023 Oct;25(10):1033–6. Available from: https://doi.org/10.1016/j.jcyt.2023.06.006

80. Cell and Gene Therapy Catapult. Annual review 2023: accelerating growth in the advanced therapies industry [Internet]. 2023 [cited 2024 Jan 29]. Available from: https://ct.catapult.org.uk/about/annual-review/2023

81. International Society for Cell and Gene Therapy. ISCT and CMaT to roll out additional training programs following successful global launch of 'Workforce Development in Biomanufacturing' course [Internet]. 2022 Aug 30 [cited 2024 Feb 23]. Available from: https://www.isctglobal.org/telegrafthub/blogs/lauren-reville/2022/08/29/isct-cmat-to-roll-out-additional-training-programs

82. Biofactory Competence Center. News [Internet]. 2023 [cited 2024 Jan 29]. Available from: https://www.bcc.ch/en/News.htm

83. Alliance for Regenerative Medicine. GROW RegenMed Internship Program [Internet]. [cited 2024 Feb 23]. Available from: https://alliancerm.org/actionforequality/

84. International Consortium for Personalised Medicine. Cross-border access to personalized treatment: the example of Strimvelis [Internet]. 2022 [cited 2024 Jan 29]. Available from: https://www.icpermed.eu/en/strimvelis.php

85. GlaxoSmithKline. StrimvelisTM receives European marketing authorisation to treat very rare disease, ADA-SCID [Internet]. 2016 May 27 [cited 2024 Jan 29]. Available from: https://www.gsk.com/en-gb/media/press-releases/strimvelistm-receives-european-marketing-authorisation-to-treat-very-rare-disease-ada-scid/

86. Drummond M, Ciani O, Fornaro G, Jommi C, Dietrich ES, Espin J, et al. How are health technology assessment bodies responding to the assessment challenges posed by cell and gene therapy? BMC Health Serv Res. 2023 May 13;23:484. Available from: https://doi.org/10.1186/s12913-023-09494-5

87. Gozzo L, Romano GL, Romano F, Brancati S, Longo L, Vitale DC, et al. Health technology assessment of advanced therapy medicinal products: comparison among 3 European countries. Front Pharmacol. 2021 Oct 7;12:755052. Available from: https://doi.org/10.3389/fphar.2021.755052

88. Ivama-Brummell AM, Wagner AK, Pepe VLE, Naci H. Ultraexpensive gene therapies, industry interests and the right to health: the case of onasemnogene abeparvovec in Brazil. BMJ Glob Health. 2022 Mar 11;7(3):e008637. Available from: https://doi.org/10.1136/bmjgh-2022-008637

89. Robbins R, Nolen S. A dilemma for governments: how to pay for million-dollar therapies. The New York Times [Internet]. 2023 Jan 24 [cited 2024 Jan 31]. Available from: https://www.nytimes.com/2023/01/24/health/gene-therapies-cost-zolgensma.html

90. Agência Nacional de Saúde Suplementar. ANS inclui medicamento para atrofia muscular espinhal no rol de coberturas obrigatórias [ANS includes medication for spinal muscular atrophy in the list of mandatory coverage] [Internet]. 2023 Feb 6 [cited 2024 Jan 31]. Available from: https://www.gov.br/ans/pt-br/assuntos/noticias/sobre-ans/ans-inclui-medicamento-para-atrofia-muscular-espinhal-no-rol-de-coberturas-obrigatorias

91. Eversana. Brazilian health system and Novartis agree to innovative payment model to cover cost of Zolgensma. NAVLIN Daily [Internet]. 2022 Dec 22 [cited 2024 Jan 31]. Available from: https://www.navlindaily.com/article/15217/brazilian-health-system-and-novartis-agree-to-innovative-payment-model-to-cover-cost-of-zolgensma

92. Nastoupil LJ, Jain MD, Feng L, Spiegel JY, Ghobadi A, Lin Y, et al. Standard-of-care axicabtagene ciloleucel for relapsed or refractory large B-cell lymphoma: results from the U.S. Lymphoma CAR T Consortium. J Clin Oncol. 2020 Sep 20;38(27):3119–28. Available from: https://doi.org/10.1200/JCO.19.02104

93. Vic S, Lemoine J, Armand P, Lemonnier F, Houot R. Transplant-ineligible but chimeric antigen receptor T-cells eligible: a real and relevant population. Eur J Cancer. 2022 Nov;175:246–53. Available from: https://doi.org/10.1016/j.ejca.2022.08.019

94. Beinfeld MT, Rucker JA, Jenkins NB, de Breed LA, Chambers JD. Variation in Medicaid and commercial coverage of cell and gene therapies. Health Policy Open. 2023 Dec 15;5:100103. Available from: https://doi.org/10.1016/j.hpopen.2023.100103

95. U.S. Centers for Medicare and Medicaid Services. Biden-Harris administration announces action to increase access to sickle cell disease treatments [Internet]. 2024 Jan 30 [cited 2024 Jan 31]. Available from: https://www.cms.gov/newsroom/press-releases/biden-harris-administration-announces-action-increase-access-sickle-cell-disease-treatments

96. IQVIA Institute for Human Data Science. Defining essential innovative medicines and measuring their use in Europe. 2022 Sep. Available from: https://www.iqvia.com/insights/the-iqvia-institute/reports-and-publications/reports/defining-essential-innovative-medicines-and-measuring-their-use-in-europe

97. Organisation for Economic Co-operation and Development. Health expenditure and financing [Internet]. 2023 Oct [cited 2024 Jan 31]. Available from: https://stats.oecd.org/

98. European Commission. Implementing the EU health technology assessment regulation. [Internet]. 2023 [cited 2024 Jan 31]. Available from: https://data.europa.eu/doi/10.2875/246730

99. IQVIA Institute for Human Data Science. The use of medicines in the U.S. 2023: usage and spending trends and outlook to 2027. 2023 May. Available from: https://www.iqvia.com/insights/the-iqvia-institute/reports-and-publications/reports/the-use-of-medicines-in-the-us-2023

100. Orphanet. Aromatic L amino acid decarboxylase deficiency [Internet]. 2024 [cited 2024 Jan 31]. Available from: https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=GB&Expert=35708

101. National Institute for Health and Care Excellence. NICE recommends life-changing gene therapy for children with ultra-rare genetic disorder in final draft guidance [Internet]. 2023 Mar 23 [cited 2024 Jan 31]. Available from: https://www.nice.org.uk/news/article/nice-recommends-life-changing-gene-therapy-for-children-with-ultra-rare-genetic-disorder-in-final-draft-guidance

102. bluebird bio. bluebird bio reports second quarter financial results and provides operational update [Internet]. Business Wire. 2021 Aug 9 [cited 2024 Feb 3]. Available from: https://www.businesswire.com/news/home/20210809005334/en/bluebird-bio-Reports-Second-Quarter-Financial-Results-and-Provides-Operational-Update

103. Horrow C, Kesselheim AS. Confronting high costs and clinical uncertainty: innovative payment models for gene therapies. Health Aff. 2023 Nov;42(11):1532–40. Available from: https://doi.org/10.1377/hlthaff.2023.00527

104. NEWDIGS at Tufts Medical Center. Precision financing solutions [Internet]. [cited 2024 Jan 31]. Available from: https://newdigs.tuftsmedicalcenter.org/payingforcures/financing-therapies/precision-financing-solutions/

105. Novartis. AveXis announces innovative Zolgensma® gene therapy access programs for U.S. payers and families [Internet]. 2019 May 24 [cited 2024 Jan 31]. Available from: https://www.novartis.com/news/media-releases/avexis-announces-innovative-zolgensma-gene-therapy-access-programs-us-payers-and-families

106. Fang H, Frean M, Sylwestrzak G, Ukert B. Trends in disenrollment and reenrollment within U.S. commercial health insurance plans, 2006-2018. JAMA Netw Open. 2022 Feb 24;5(2):e220320. Available from: https://doi.org/10.1001/jamanetworkopen.2022.0320

107. Eversana. Italy reimburses Zolgensma through “payment at result” model, priced at EUR 2.155 M [Internet]. 2021 Mar 18 [cited 2024 Jan 31]. Available from: https://www.eversana.com/2021/03/18/italy-reimburses-zolgensma-through-payment-at-result-model-priced-at-eur-2-155-m/

108. Jørgensen J, Kefalas P. The use of innovative payment mechanisms for gene therapies in Europe and the USA. Regen Med. 2021 Apr 13;16(4):405–22. Available from: https://doi.org/10.2217/rme-2020-0169

109. UK Department of Health and Social Care. 2024 voluntary scheme for branded medicines pricing, access and growth: summary of the heads of agreement [Internet]. 2023 Nov 20 [cited 2024 Jan 31]. Available from: https://www.gov.uk/government/publications/2024-voluntary-scheme-for-branded-medicines-pricing-access-and-growth-summary-of-the-heads-of-agreement/

110. U.S. Centers for Medicare and Medicaid Services. Cell and Gene Therapy (CGT) Access Model [Internet]. 2024 Jan 30 [cited 2024 Jan 31]. Available from: https://www.cms.gov/priorities/innovation/innovation-models/cgt

111. Galbraith R. Italy looking to set up fund for advanced therapies to be financed by savings they generate. APM Health Europe [Internet]. 2023 Dec 18 [cited 2024 Jan 31]; Available from: https://www.apmhealtheurope.com/nostory.php?objet=86982

112. Goodman A. High-dose chemotherapy and stem cell transplant vs CAR T-cell therapy for resistant DLBCL. The ASCO Post [Internet]. 2022 Nov 10 [cited 2024 Feb 14]. Available from: https://ascopost.com/issues/november-10-2022/high-dose-chemotherapy-and-stem-cell-transplant-vs-car-t-cell-therapy-for-resistant-dlbcl/

113. Larghero J, Ricarte C, Bonevski V. CAR T-cell therapies market outlook and future challenges [Webinar]. 2023 Dec 12 [cited 2024 Jan 30]. Available from: https://www.iqvia.com/events/2023/11/car-t-cell-therapies-market-outlook-and-future-challenges

114. IQVIA CAR T-cell Monitor. Center insights. 2023 Jun.

115. United States Census Bureau. Health insurance coverage in the United States: 2022 [Internet]. 2023 Sep 12 [cited 2024 Feb 8]. Available from: https://www.census.gov/library/publications/2023/demo/p60-281.html

116. Kourelis T, Bansal R, Berdeja J, Siegel D, Patel K, Mailankody S, et al. Ethical challenges with multiple myeloma BCMA chimeric antigen receptor T cell slot allocation: a multi-institution experience. Transplant Cell Ther. 2023 Apr;29(4):255–8. Available from: https://doi.org/10.1016/j.jtct.2023.01.012

117. Verdun N, Marks P. Secondary cancers after chimeric antigen receptor T-cell therapy. N Engl J Med. 2024 Feb 15;390(7):584-6. Available from: https://doi.org/10.1056/NEJMp2400209

118. Genomic newborn screening: current concerns and challenges. Lancet. 2023 Jul 22;402(10398):265. Available from: https://doi.org/10.1016/S0140-6736(23)01513-1

119. Padgett Powers M. Advocates work to expand newborn screening worldwide. Association of Public Health Laboratories Blog [Internet]. 2023 Nov 8 [cited 2024 Feb 2]. Available from: https://www.aphlblog.org/advocates-work-to-expand-newborn-screening-worldwide/

120. Cure SMA. 100% of states now screening newborns for SMA [Internet]. 2024 Jan 3 [cited 2024 Feb 2]. Available from: https://www.curesma.org/100-of-states-now-screening-newborns-for-sma/

121. European Alliance for Newborn Screening in Spinal Muscular Atrophy. Newborn screening status [Internet]. [cited 2024 Feb 2]. Available from: https://www.sma-screening-alliance.org/map

122. Wiley V, Webster D, Loeber G. Screening pathways through China, the Asia Pacific region, the world. Int J Neonatal Screen. 2019 Aug 22;5(3):26. Available from: https://doi.org/10.3390/ijns5030026

123. Leukaemia Care. CAR-T Away from Home service [Internet]. [cited 2024 Feb 2]. Available from: https://www.leukaemiacare.org.uk/support-and-information/support-for-you/car-t-information-hub/car-t-away-from-home-service/

124. Fondazione Telethon. Just like home [Internet]. [cited 2024 Feb 7]. Available from: https://www.telethon.it/en/what-we-do/supporting-research-and-patients/supporting-patients/just-like-home/

125. Arone B. Overcoming the challenges of long-term follow-up studies for cell and gene therapy [Internet]. IQVIA. 2023 Oct 31 [cited 2024 Feb 6]. Available from: https://www.iqvia.com/blogs/2023/10/overcoming-the-challenges-of-long-term-follow-up-studies-for-cell-and-gene-therapy

126. IQVIA Biotech. Long-term follow-up for gene therapies – innovative, patient-centered approaches. 2021 Nov 1. Available from: https://www.iqviabiotech.com/library/white-papers/long-term-follow-up-for-gene-therapies

127. Center for International Blood and Marrow Transplant Research. Current uses of CAR T-cell therapies in the U.S.: 2021 cellular therapy summary slides [Internet]. 2021 [cited 2024 Feb 6]. Available from: https://cibmtr.org/CIBMTR/Resources/Summary-Slides-Reports

128. World Federation of Hemophilia. Gene therapy registry [Internet]. [cited 2024 Feb 5]. Available from: https://wfh.org/research-and-data-collection/gene-therapy-registry/

129. U.S. Food and Drug Administration. 2024 safety and availability communications [Internet]. Updated 2024 Jan 24 [cited 2024 Feb 6]. Available from: https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/2024-safety-and-availability-communications

130. Dimitri A, Herbst F, Fraietta JA. Engineering the next-generation of CAR T-cells with CRISPR-Cas9 gene editing. Mol Cancer. 2022 Mar 18;21:78. Available from: https://doi.org/10.1186/s12943-022-01559-z

131. Cappell KM, Sherry RM, Yang JC, Goff SL, Vanasse DA, McIntyre L, et al. Long-term follow-up of anti-CD19 chimeric antigen receptor T-cell therapy. J Clin Oncol. 2020 Nov;38(32):3805–15. Available from: https://doi.org/10.1200/JCO.20.01467

132. DuFeudis N. Clinicians say benefits of CAR-T continue to outweigh risk of T-cell malignancies. Endpoints News [Internet]. 2023 Nov 29 [cited 2024 Feb 6]; Available from: https://endpts.com/clinicians-say-benefits-of-car-t-continue-to-outweigh-risk-of-t-cell-malignancies/

133. bluebird bio. Long-term follow-up data from bluebird's gene therapy program in sickle cell disease support durable, potentially curative benefits through stable production of anti-sickling adult hemoglobin and resolution of vaso-occlusive events [Internet]. 2023 Dec 9 [cited 2024 Feb 6]. Available from: https://investor.bluebirdbio.com/news-releases/news-release-details/long-term-follow-data-bluebirds-gene-therapy-program-sickle-cell

134. Jagannath S, Joseph N, Crivera C, Kharat A, Jackson CC, Valluri S, et al. Component costs of CAR-T therapy in addition to treatment acquisition costs in patients with multiple myeloma. Oncol Ther. 2023 Jun;11(2):263–275. Available from: https://doi.org/10.1007/s40487-023-00228-5

135. IQVIA Institute for Human Data Science. Global oncology trends 2023: outlook to 2027. 2023 May. Available from: https://www.iqvia.com/insights/the-iqvia-institute/reports-and-publications/reports/global-oncology-trends-2023

136. Chiesi. Europe approves Holoclar®, the first stem cell-based medicinal product [Internet]. 2015 Feb 20 [cited 2024 Feb 7]. Available from: https://www.chiesi.com/en/europe-approves-holoclar®-the-first-stem-cell — based-medicinal-product-

137. Holostem S.r.l. Chiesi Group and Holostem Terapie Avanzate announce transfer of Holoclar® from the Chiesi Group to Holostem [Internet]. 2020 Jun 16 [cited 2024 Feb 7]. Available from: https://www.holostem.com/2020/06/16/chiesi-group-and-holostem-terapie-avanzate-announce-transfer-of-holoclar-from-the-chiesi-group-to-holostem/?lang=en

138. Paterlini M. Italy's stem-cell pioneer at risk. Nature Italy [Internet]. 2022 Dec 8 [cited 2024 Feb 7]; Available from: https://www.nature.com/articles/d43978-022-00167-1

139. Paterlini M. Stem-cell therapy company saved by public funds. Nature Italy [Internet]. 2023 Dec 7 [cited 2024 Feb 7]; Available from: https://www.nature.com/articles/d43978-023-00183-9

140. GSK. GSK signs strategic agreement to transfer rare disease gene therapy portfolio to Orchard Therapeutics [Internet]. 2018 Apr 12 [cited 2024 Feb 7]. Available from: https://www.gsk.com/en-gb/media/press-releases/gsk-signs-strategic-agreement-to-transfer-rare-disease-gene-therapy-portfolio-to-orchard-therapeutics/

141. Orchard Therapeutics. Orchard statement on Strimvelis®, a gammaretroviral vector-based gene therapy for ADA-SCID [Internet]. 2020 Oct 30 [cited 2024 Feb 7]. Available from: https://ir.orchard-tx.com/news-releases/news-release-details/orchard-statement-strimvelisr-gammaretroviral-vector-based-gene/

142. Orchard Therapeutics. Orchard Therapeutics extends runway into 2024, focusing HSC gene therapy platform exclusively on severe neurometabolic diseases and research platform [Internet]. 2022 Mar 30 [cited 2024 Feb 7]. Available from: https://ir.orchard-tx.com/news-releases/news-release-details/orchard-therapeutics-extends-runway-2024-focusing-hsc-gene/

143. Sammartano V, Franceschini M, Fredducci S, Caroni F, Ciofini S, Pacelli P, et al. Anti-BCMA novel therapies for multiple myeloma. Cancer Drug Resist. 2023 Mar;6(1):169–181. Available from: https://doi.org/10.20517/cdr.2022.138

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Murray Aitken is Executive Director, IQVIA Institute for Human Data Science, which provides policy setters and decisionmakers in the global health sector with objective insights into healthcare dynamics. He led the IMS Institute for Healthcare Informatics, now the IQVIA Institute, since its inception in January 2011. Murray previously was Senior Vice President, Healthcare Insight, leading IMS Health's thought leadership initiatives worldwide. Before that, he served as Senior Vice President, Corporate Strategy, from 2004 to 2007. Murray joined IMS Health in 2001 with responsibility for developing the company's consulting and services businesses. Prior to IMS Health, Murray had a 14-year career with McKinsey & Company, where he was a leader in the Pharmaceutical and Medical Products practice from 1997 to 2001. Murray writes and speaks regularly on the challenges facing the healthcare industry. He is editor of Health IQ, a publication focused on the value of information in advancing evidence-based healthcare, and also serves on the editorial advisory board of Pharmaceutical Executive. Murray holds a Master of Commerce degree from the University of Auckland in New Zealand, and received an M.B.A. degree with distinction from Harvard University.

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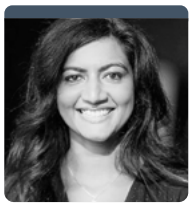

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Amritha is the Executive Director of the Cell and Gene Therapy (CGT) Center and Head of CGT Lifecycle Strategy at IQVIA. In this role she is responsible for driving an integrated and collaborative end-to-end CGT strategy to accelerate the development and commercialization of cell and gene therapies for companies, research institutes and patients worldwide. She brings a holistic view of the industry and drives transformation throughout the cell and gene therapy product lifecycle, through disruptive innovation, strategic partnerships, and other growth initiatives. Amritha has over 19 years of expertise in cell therapy programs across various academic, non-profit, government, and industry roles spanning R&D, program/policy, products/services and investments. She is a frequent speaker at industry events and serves on numerous advisory boards. She has a PhD in Genetics, MSc in Molecular Genetics, BSc in Zoology and scientific training at NINDS, NIH and the Lieber Institute/Johns Hopkins University School of Medicine.

About the Institute

The IQVIA Institute for Human Data Science contributes to the advancement of human health globally through timely research, insightful analysis and scientific expertise applied to granular non-identified patient-level data.

Fulfilling an essential need within healthcare, the Institute delivers objective, relevant insights and research that accelerate understanding and innovation critical to sound decision making and improved human outcomes. With access to IQVIA's institutional knowledge, advanced analytics, technology and unparalleled data the Institute works in tandem with a broad set of healthcare stakeholders to drive a research agenda focused on Human Data Science including government agencies, academic institutions, the life sciences industry, and payers.

Research agenda

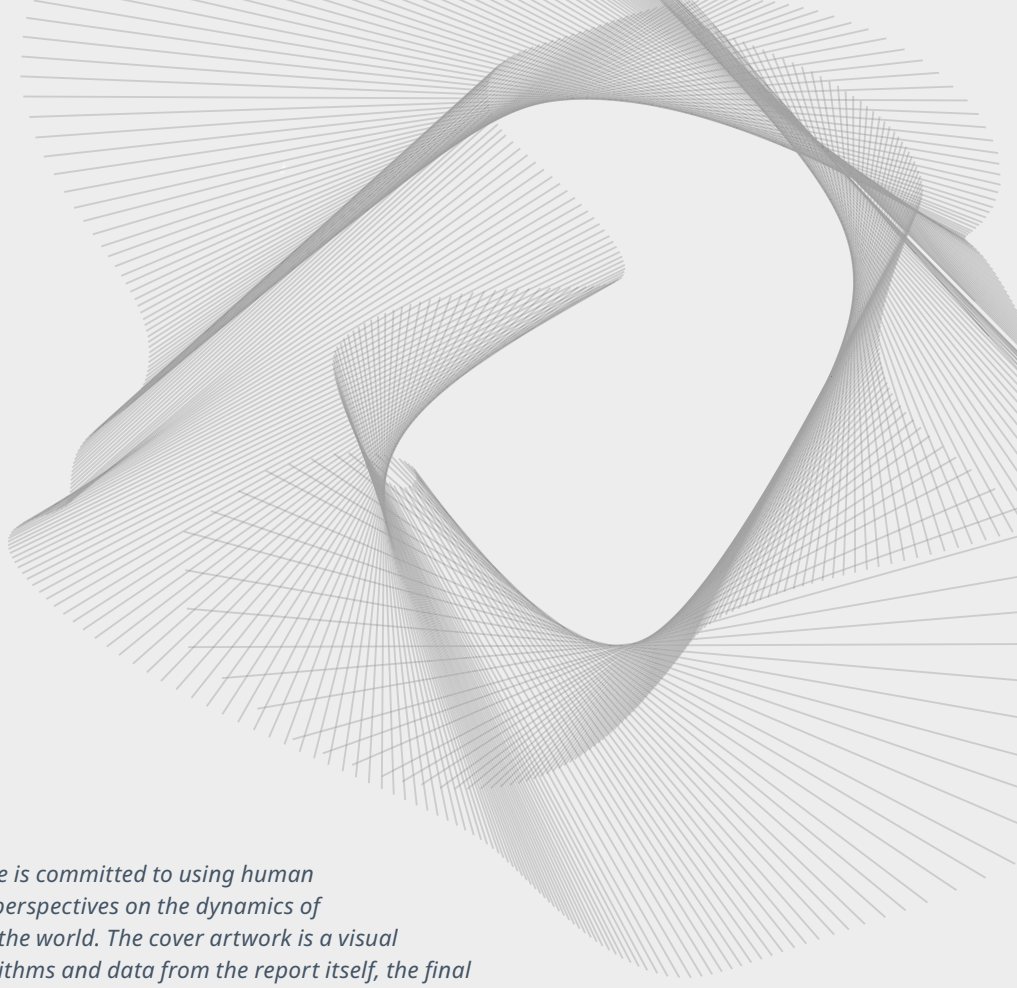
The research agenda for the Institute centers on five areas considered vital to contributing to the advancement of human health globally:

- Improving decision-making across health systems through the effective use of advanced analytics and methodologies applied to timely, relevant data.
- Addressing opportunities to improve clinical development productivity focused on innovative treatments that advance healthcare globally.
- Optimizing the performance of health systems by focusing on patient centricity, precision medicine and better understanding disease causes, treatment consequences and measures to improve quality and cost of healthcare delivered to patients.
- Understanding the future role for biopharmaceuticals in human health, market dynamics, and implications for manufacturers, public and private payers, providers, patients, pharmacists and distributors.
- Researching the role of technology in health system products, processes and delivery systems and the business and policy systems that drive innovation.

Guiding principles

The Institute operates from a set of guiding principles:

- Healthcare solutions of the future require fact based scientific evidence, expert analysis of information, technology, ingenuity and a focus on individuals.
- Rigorous analysis must be applied to vast amounts of timely, high quality and relevant data to provide value and move healthcare forward.
- Collaboration across all stakeholders in the public and private sectors is critical to advancing healthcare solutions.
- Insights gained from information and analysis should be made widely available to healthcare stakeholders.
- Protecting individual privacy is essential, so research will be based on the use of non-identified patient information and provider information will be aggregated.
- Information will be used responsibly to advance research, inform discourse, achieve better healthcare and improve the health of all people.



The IQVIA Institute for Human Data Science is committed to using human data science to provide timely, fact-based perspectives on the dynamics of health systems and human health around the world. The cover artwork is a visual representation of this mission. Using algorithms and data from the report itself, the final image presents a new perspective on the complexity, beauty and mathematics of human data science and the insights within the pages.

This algorithmic art is based on cell and gene therapy trials starts 2014–2023 by sponsor type, geography, and modality.

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