HARVARD UNDERGRADUATE CBE

Gene Therapy Industry Overview

Industry Report | Fall 2020

Prepared by

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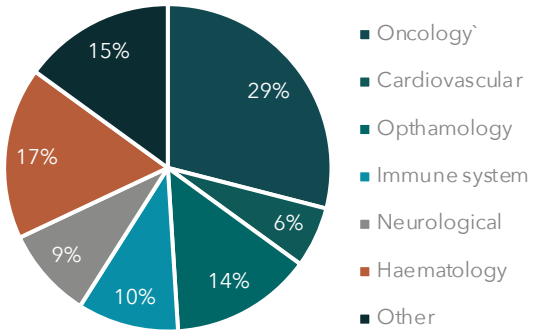
Overview of the Gene Therapy Market

Gene therapy includes all techniques using genes to treat or prevent diseases. The market is rapidly growing, with an expected shift in focus towards monogenic rare diseases.

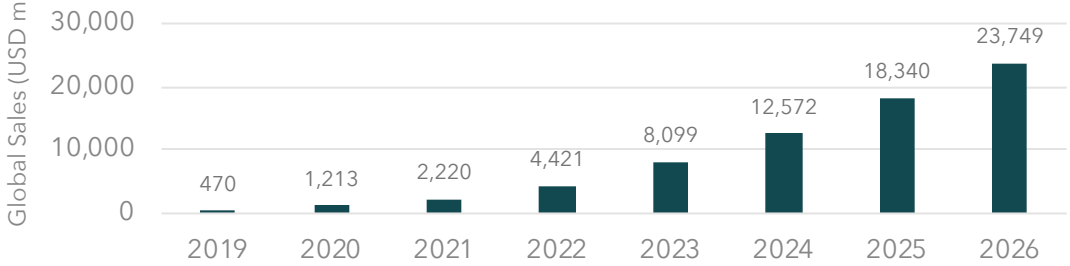
General Overview

- Total market cap of approximately 4 billion USD (2019)
- CAGR of 34.8% (2019 - 2026)
- In 2019, 939 gene therapies were in development

Gene Therapy by Sector (2019)



Total Value of Gene Therapy Market



	Then	Now
Technology	Completion of the human genome in 2001, but first FDA approval in 2017	Expected 10-20 new gene therapy approvals per year over the next 5 years
Market Drivers	Limited investment due to uncertainty of feasibility and success of these therapies	High growth due to technological advances and increased funding
Consumer Base	Difficult to get treatments since less incentives for insurance providers	Monogenic rare diseases has been an area of increased focus in recent years

Outlook

The gene therapy is rapidly growing, with the modern pharmaceutical market responding to this shift and investing heavily in gene therapy research. However, concerns still exist over existing health infrastructure and manufacturing.

Sources: Evaluate, BioPharmaDive, Your Genome, Dana Farber, Your Genome, Ciston, Grand View Research, McKinsey

Gene Therapy Treatment Targets

Most treatment targets are grouped into four broad categories, each with different methods of treatment and potentials for gene therapy application.

Immunodeficiencies

Any disease that causes failure of the immune system, leaving patients vulnerable to infection and cancers (e.g. Strimvelis for ADA-SCID)

Cancers

Broad category diseases, but generally caused by loss-of-function mutations in tumor suppressor genes or excess expression of oncogenes (e.g. Kymriah for relapsed or refractory B-cell cancers)

Monogenic Inherited Diseases

Inherited diseases not related to the immune system and limited to those caused by monogenic, loss-of-function mutations (e.g. Luxturna for congenital blindness)

Polygenic Inherited Diseases

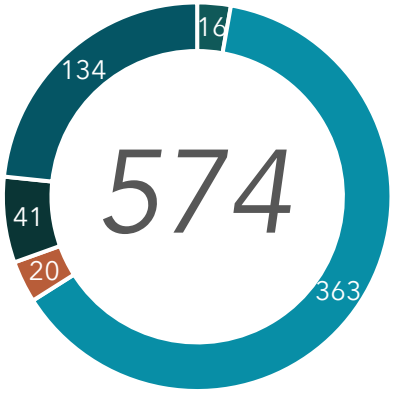
Polygenic diseases remain mostly untreatable by gene therapy (e.g. research on APOE gene is inconclusive for Alzheimer's disease)

Sources: EMBO Mol Med, American Society of Gene and Cell Therapy, CHOP, American Cancer Society, MIT Technology Review

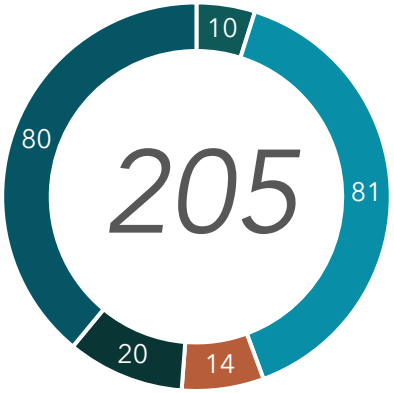
Gene Therapy Market Breakdown

Many gene therapies in early development phases are focused on oncology. Recently, there has been a shift towards focusing on monogenic rare diseases (classified as Other).

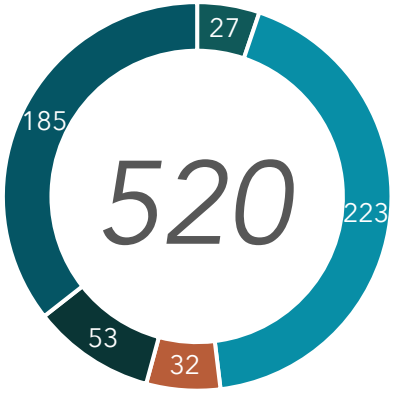
Phase 1



Phase 3



Phase 2



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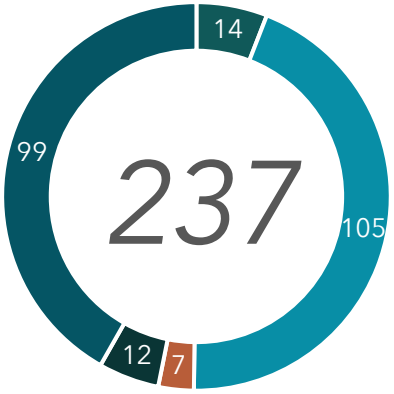
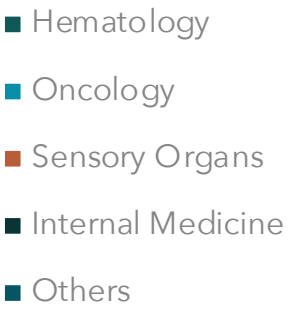
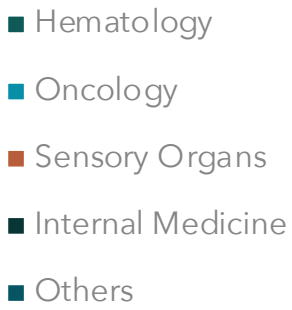
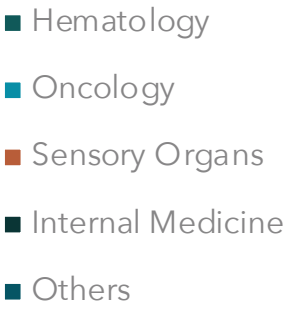
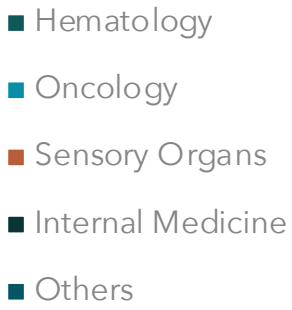






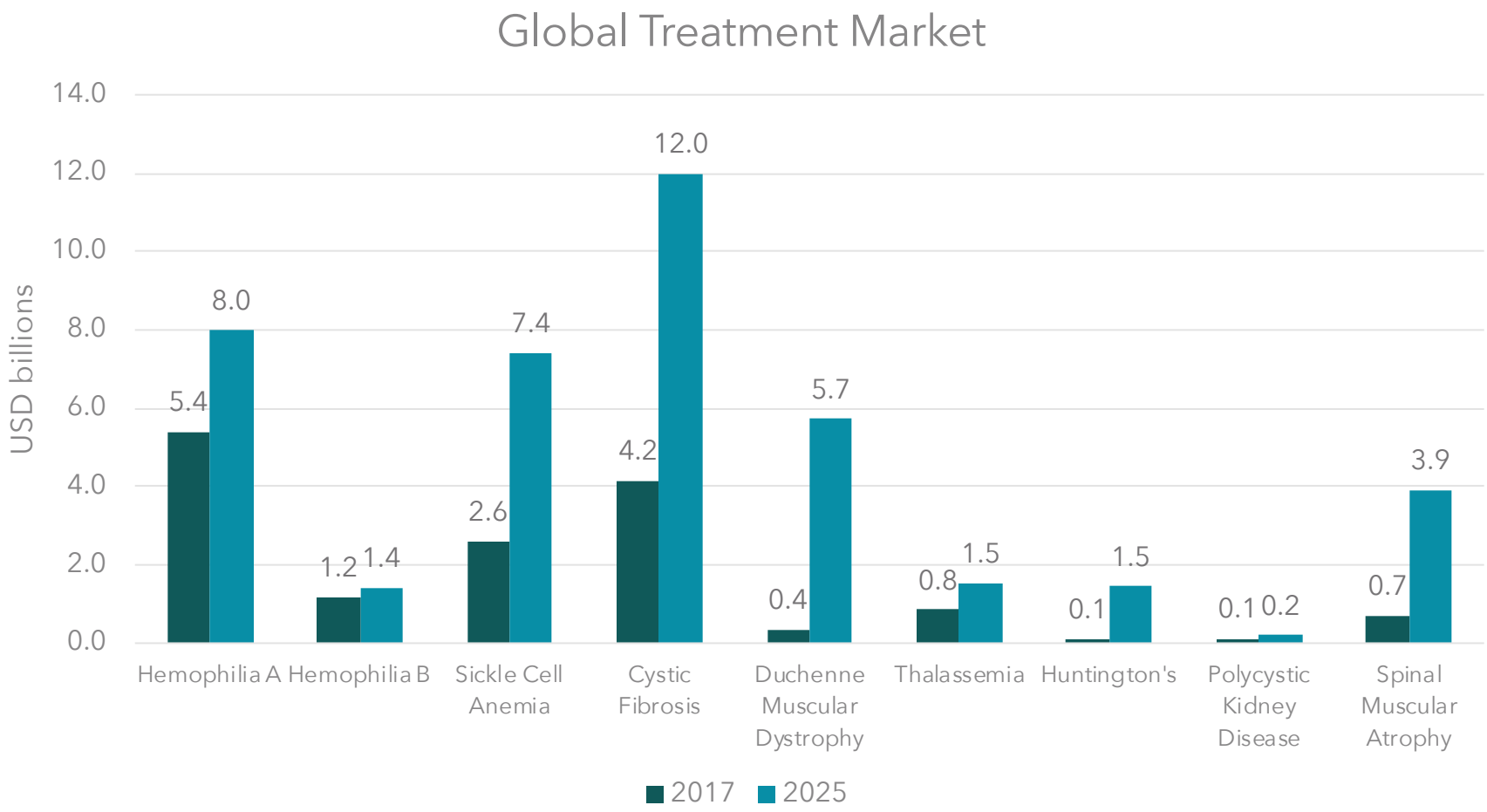




Sources: McKinsey & Company (2019)

Comparing Global Treatment Markets

In the next few years, Sickle Cell Anemia, Cystic Fibrosis, Duchenne Muscular Dystrophy, and Spinal Muscular Atrophy appear to be promising markets for gene therapy.



Sources: Statista, Market Watch, Grand View Research, Transparency Market Research

Key Competitors in the Gene Therapy Space

The pharmaceutical segment of the gene therapy space is very saturated, with players of various sizes leading the shift toward more widespread approval and use of gene therapy.

Novartis is well known for its approved therapy, Luxturna, which was licensed from Sparks Therapeutics and targets retinal disease. In March 2018, Novartis announced that it was acquiring AveXis Inc. which is using gene therapy platforms to develop treatments for eurological genetic diseases.

Orchard Therapeutics, founded in 2015, is developing and marketing gene therapies for treating patients with rare disorders, including immune deficiency and inherited metabolic disorders. Orchard has alliances with GSK and Genethon.

Pfizer had the highest market share in the pharmaceutical industry, with 5.6%. It has the resources to commit to gene therapy treatments, investing $500 million into a gene therapy manufacturing facility in 2019.

Gilead acquired Kite Pharma and Cell Design Labs in 2017 and has licensing deals with Sangamo Therapeutics. Kite Pharma & Cell Design Labs are focused on CAR and T-cell receptor (TCR) engineered cell therapies for cancer applications.

Roche is a Swiss Multinational healthcare company that has a strong gene therapy pipeline with many products. It has recently acquired Spark Therapeutics, a company that is trying to use gene therapy to treat hemophilia.

Biogen has long been a leader in the using gene therapy efforts to tackle neurodegenerative diseases, particularly with its approved Spinraza treatment for SMA. Currently, it focuses on a variety of indications, including Alzheimer's disease, Parkinson's disease, MS, ALS, and strokes.

Sources: Brand Finance, Pfizer, Roche, BCC Research

Major Categories of Genetic Medicines

The major gene-based medicines in development or on the market fall into four categories and cover a range of both polygenic and monogenic therapeutic targets.

Gene Therapy	▪ Introduces functional genes into cells with defective genes through adeno-associated vectors (AAVs) and lentiviral vectors ▪ Commonly targets diseases like Parkinson's, Hemophilia, and Muscular Dystrophy ▪ Led by uniQure, Spark Therapeutics (acquired by Roche), BioMarin
Gene editing	▪ Directly edits the patient's DNA, research is less advanced than other areas ▪ Successful clinical trials for hemophilia and beta thalassemia, with potentially promising treatments for cystic fibrosis, cancer, heart disease, and HIV ▪ Major companies include Sangamo, CRISPR Therapeutics, Beam, and Vertex
RNA Therapy	▪ Target RNA inhibits gene expression using approaches such as RNAi, Antisense Oligonucleotides (ASO), and mRNA ▪ Major diseases are cancer, metabolic disorders and diseases, neurological disorders ▪ Leading companies are Moderna in mRNA, Alnylam in RNAi, and Ionis in ASO's
Modified Cell Therapy	▪ Genetically modified viable cells are injected into a patient, mostly Car T-cell therapy ▪ Targets cancers (approved for B-cell ALL), blood diseases, and immunodeficiencies ▪ Notable companies include Novartis, Bayer (BlueRock Therapeutics)

Sources: BCC Research, Umass Medical, NIH, CNN

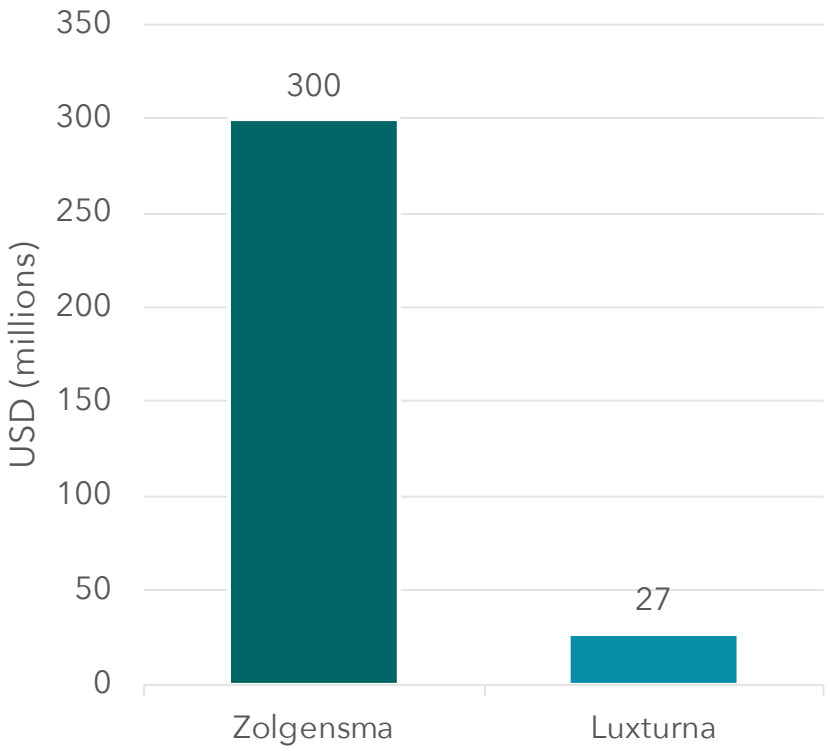
Gene Therapy: Adeno-Associated Viruses

Since Adeno-Associated Viruses (AAVs) have increased safety, stability, and ability to target specific cells, they are the preferred vector for in vivo gene therapy.

Why AAVs?

- AAVs in vivo gene therapy has been shown to be effective in clinical trials and in approved treatments
- AAVs have **low immunogenicity**, and are not linked to any known disease
- AAVs have a resilient protein coat which aids stability and allows it to target **specific cell lines**
- AAVs can cross the blood brain barrier, allowing them to target neuronal diseases
- AAVs normally include single stranded DNA, but double stranded DNA have been used to improve efficacy (e.g. Zolgensma)
- Main obstacles include **small transgene capacity and insufficient localization**

Forecasted 2019 Revenue of AAV Therapies



Sources: Drug Development, BCC Research, SMA News, Stat news, Spark Therapeutics, Fierce Pharma

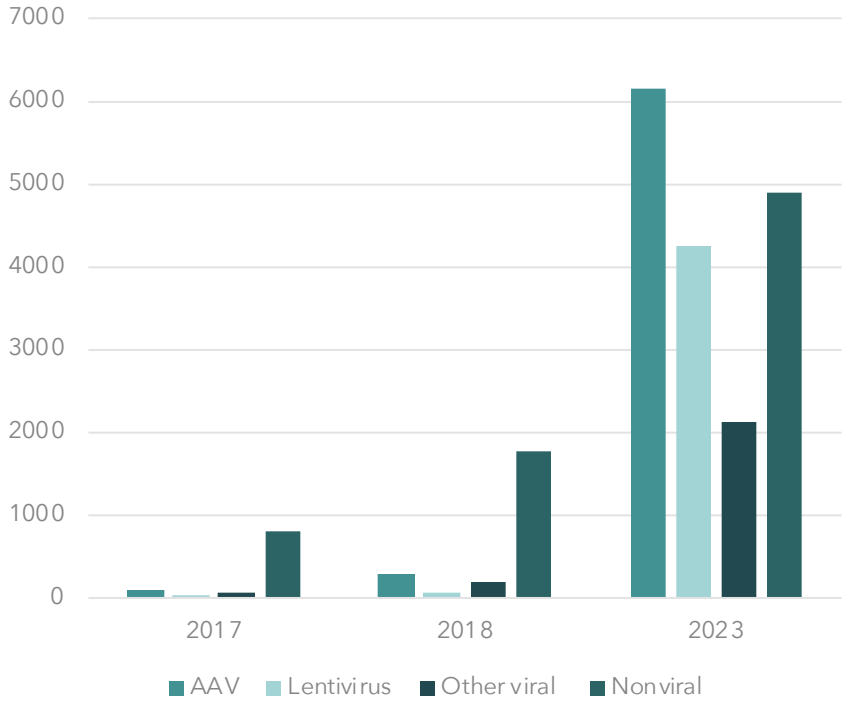
Gene Therapy: Lentivirus Vectors

While AAVs are the most popular vectors on the gene therapy market, lentiviral vectors are another promising delivery vector with some distinct advantages for ex vivo treatments.

Overview

- Like AAVs, Lentiviral vectors offer high efficiency infection of both dividing and non-dividing cells, long-term expression of a transgene, and low immunogenicity
- **Distinct advantages include:**
  1. a larger load size – up to 10 kb,
  2. effective *in vitro* infection
  3. Integrative rather than episomal
- Production of lentiviral vectors has a **high barrier to entry** due to consolidation of industry and difficulty of producing clinical-grade vectors
- In the gene therapy field, AAVs will likely remain dominant with lentiviruses more focused on **ex vivo treatments**

Global Market for Genetic Modification Therapies, by Delivery Technology through 2023
($ Millions)



Sources: BCC Research

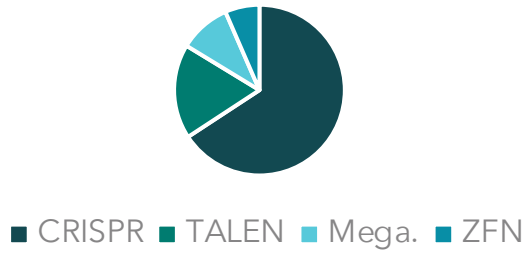
Gene Editing Overview

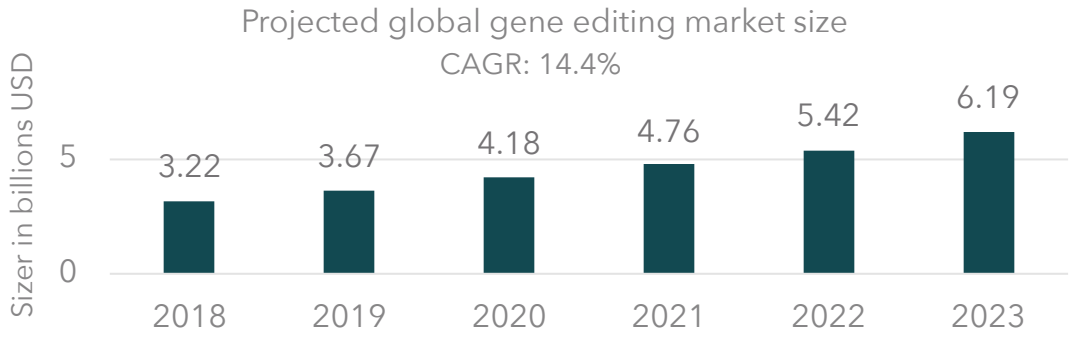
Despite less established consumers and treatments, gene editing presents a competitive opening for any company able to address its various uncertainties in the market.

Gene Editing

- **Permanent and precise modification of host genes** using molecular tools to repair or delete DNA sequence
- Can treat both **monogenic and polygenic** diseases, though current research focuses on former
- **Newest** branch of genetic modification, with accompanying consumer suspicion

Patents Filed Per Technology (2014)





Technology

ZFN (zinc finger nuclease), **TALEN** (transcription activator-like effector nuclease), **CRISPR** (clustered regularly interspaced short palindromic repeats), and **meganucleases**

History

ZFNs were first published in 1991 before being supplanted by the discovery of TALEN in the early 2000s. CRISPR was **introduced in 2012** as the latest in a developing current of research.

Current Market

No approved treatments on market yet. CRISPR Tx is close to clinical trials for beta thalassemia and sickle cell, and Sangamo is in early phases for MPS II.

Obstacles

In addition to technical issues like **off-target effects**, gene editing faces a **contradictory legal system**—with the US and EU having different regulations—and fraught **ethics**.

Key Takeaway

A company that can **increase precision** and quell consumer fears over **safety and ethics** could competitively enter the genetic modification market without being far behind competitors.

Sources: MarketWatch, ResearchGate, Undark, GM Insights

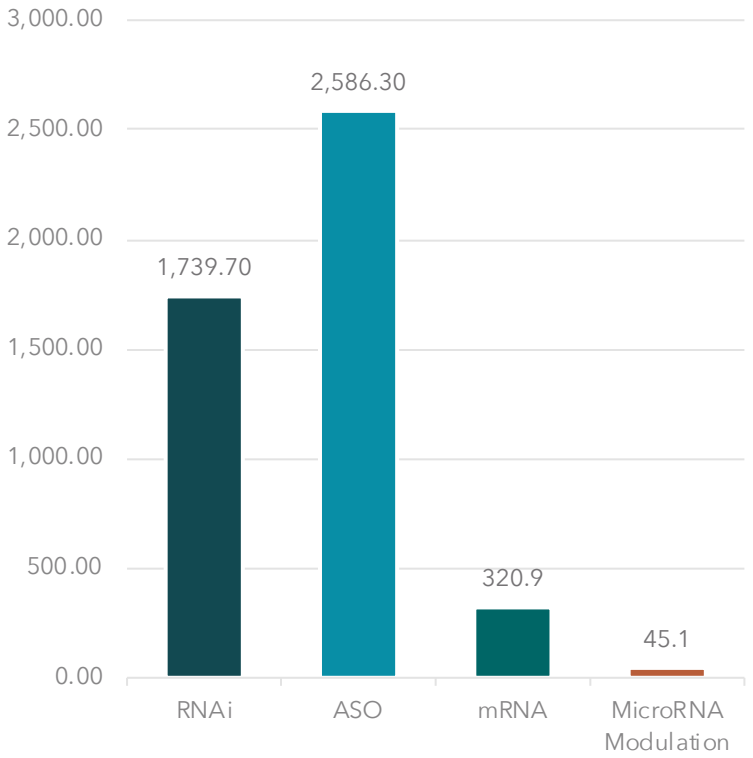
RNA Therapy Overview

The RNA therapy sector has two emerging approaches that are quickly leading the way in market approval and patient population: RNAi and Antisense Oligonucleotides (ASOs).

Overview

- RNAi involves a double-stranded DNA oligonucleotide, which **triggers the RISC (RNA-induced silencing complex) pathway** that cleaves mRNA
- **Antisense Oligonucleotides (ASOs)** are a more developed RNA-based platform that targets genetic disease caused by mutated genes
- Although ASOs have rapidly gaining FDA approval (e.g. Spinraza), they face competition from safer, more affordable treatments
- Therapeutic targets include:
  1. Cancers (especially those caused by mutated growth factors or transcription factors)
  2. Autoimmune diseases
  3. Dominant genetic disorders
  4. Viral infections

RNAi Market Share of Global RNA-based Platforms Market in 2023
($ Millions)



Sources: BCC Research, NIH, News Medical, American Cancer Society

Cell Therapy: Adoptive Cell Therapy

Adoptive Cell Therapy (ACT) is a newly emerging branch of ex vivo gene therapy in which T cells are given to a patient to help the body combat cancer.

Chimeric Antigen Receptor

CAR

Synthetic Receptor

- CAR gene is inserted into T cells so they can find and destroy cancer
- **Most clinically developed** adoptive cell therapy, with two FDA approved drugs: **Yescarta** and **Kymriah**
- 74 active (not recruiting) trials

T Cell Receptor

TCR

Natural Receptor

- TCRs **naturally recognize antigen-MHC complexes** on cancer cells
- TCR gene specific to certain antigen may be inserted into other T cells
- Successful in small trials targeting **melanoma** and **cervical cancer**

Tumor-Infiltrating Lymphocytes

TIL

Immune Cell

- TILs **naturally reside within tumors**
- TILs may be **engineered and introduced back into the body** to kill cancer
- Promising results in trials for **melanoma** and **sarcoma**

Sources: National Cancer Institute

Future Challenges and Potential Solutions

Although initial gene therapy treatments have been successful, many challenges still stand in the way of gene therapy realizing its true potential in treating patients.

	Description of Challenge	Potential Solutions	Difficulty to Overcome
Market Access	Most U.S. insurance plans are not set up for one-time payments where the benefit outlasts the patient's time with the company	Requires significant changes to health ecosystem, including exploring outcome-base or multiyear payment models	**HIGH**
Clinical Safety	Many still doubt the long-term efficacy and safety of gene therapy treatments	Requires more research to see the effects of the therapies in existence	**HIGH**
Unclear Regulation	Insufficient legal and clinical/hospital regulations complicate consumer confidence, payment, and access	Companies could respond to rare diseases' accelerated timelines with their own more stringent data collection	**MEDIUM**
Customer Depletion	Treatable populations are depleted with gene therapy cures, with few new incident rare disease patients	Target more complex diseases with larger market (e.g. heart disease) rather than focusing on rare diseases	**LOW**
Manufacturing	A time-sensitive supply chain may keep treatment costs high until production expands and yields are more stable	Allocate significant revenue into expanding own distribution channels, where yields will increase as more therapies are approved	**LOW**

Sources: Cell and Gene, BCC Research, BioPharma Dive, Cell and Gene, Research and Markets, McKinsey & Company