OCTAVUS∞ CONSULTING

GENE THERAPY

CONTENTS

INTRODUCTION

Gene therapy is "a novel approach to treat, cure, or ultimately prevent disease by changing the expression of a person's genes" (AMA, 2016). Gene therapies repair, deactivate or replace dysfunctional genes that cause disease, with the aim of (re)establishing normal functions. Cell and gene therapies have been serving as the forefront of medical science, promising a hopeful future for many patients suffering from a wide variety of diseases. For two decades they have been in the headlines for scientific and clinical breakthroughs, with trial results disappointing patients. Many of the therapies are novel and curative. Underwhelming outcomes and headline-grabbing adverse events have caused setbacks across the entire field.

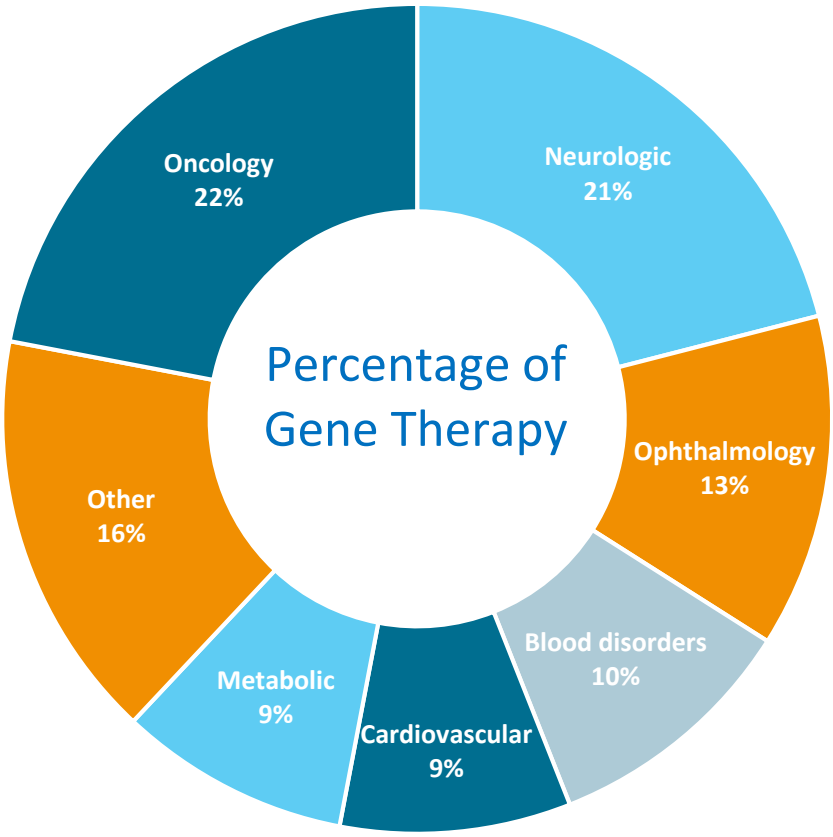
However, the first cell therapy is launched in the US and Glybera: first gene therapy approved in Europe. Consequently, the benefits of these therapies may not be limited to clinical gains; curative treatments may enable healthcare systems to make significant savings from a reduction in long-term expenditures on chronic treatments. IMS Health has identified four key challenges to succeed in cell & gene therapies that stem from their novel and unique characteristics: Valuation, Reimbursement, Commercialization, Manufacturing & Logistics. Additionally, for several cell & gene therapies targeting diseases with large populations such as HIV, angina or beta-thalassemia, payers may further struggle to reimburse them broadly.[1]

The first approved gene therapy experiment occurred on September 14, 1990 in US, when Ashanti DeSilva was treated for ADA-SCID

Pricing and budget management is required for the cost burden and the uncertainties associated with these therapies. Implementing an annuity-based reimbursement agreement will, however, be challenging with feasibility depending on country and payer sophistication.

The cell therapies are the treatments in which intact, living and human cells are injected into the patient for therapeutic benefits while their origin can be autologous or allogeneic. Many cell types are used ranging from neural stem cells to genetically engineered immune system cells.

Comparatively, gene-therapies are the treatment in which genetic material is incorporated into the cells of a patient with an intended therapeutic benefit. Most gene therapy trials involve the use of an adenovirus vector for genetic manipulation, often replacing faulty or missing genes in patients with genetic disorders. A typical example would be a gene therapy replacing the non-functioning enzyme in a patient with Sanfilippo Syndrome –
a lysosomal storage metabolic disorder.



The number of gene therapies have been increasing with increasing rates of diseases as the development and operation cost is higher in gene therapies. The gene therapies have also been awarded Breakthrough Therapy designations and fast track designations. Multiple gene-therapies are in clinical trials and is designed to move into P-III trials.

Factors Influencing Price

- The impact on patient lives
- Savings as a result of treatment
- Risk taken by the manufacturer
- Target patient population size
- How much can the payer afford?

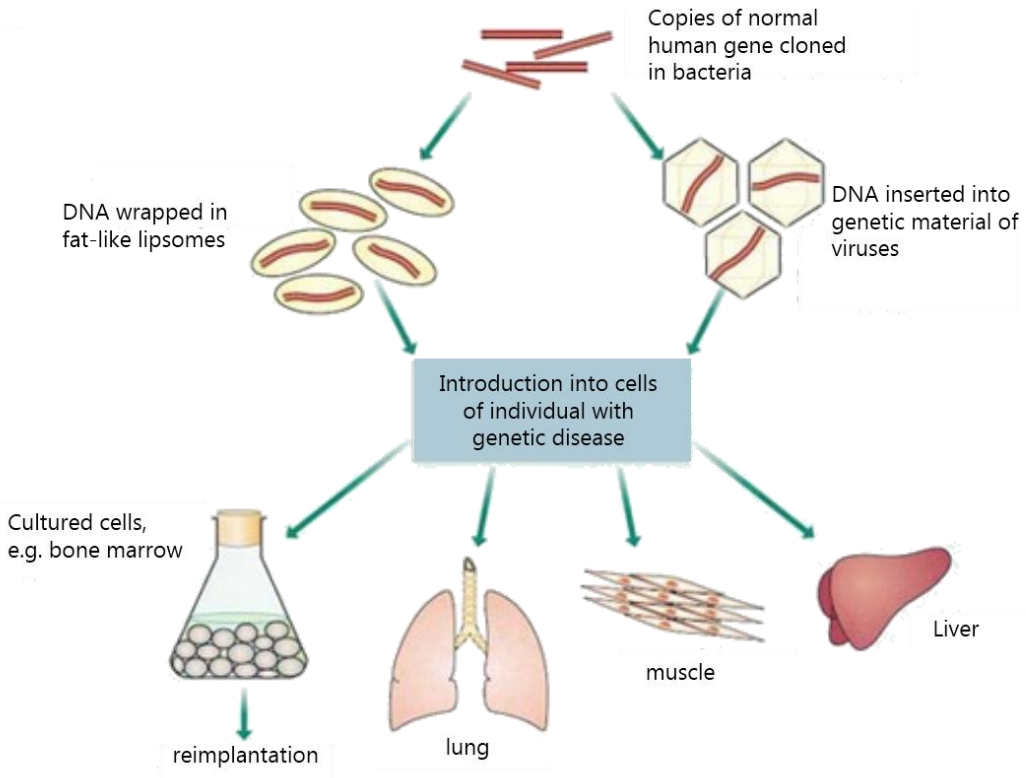
Most gene therapy trials involve the use of an adenovirus vector for genetic manipulation, often replacing faulty or missing genes in patients with genetic disorders. Gene therapy is basically divided into two major categories.

- **Somatic Cell Gene Therapy**
- **Germ Line Gene Therapy**

Somatic Cell Therapy

Somatic cells are nonreproductive cell therapy viewed as a more conservative, safer approach because it affects only the targeted cells in the patient and is not passed on to future generations.

Somatic gene therapy is the transfer of genes into the somatic cells of the patient, such as cells of the bone marrow, and hence the new DNA does not enter the eggs or sperm. Additionally, the targeted area of the bone marrow cells can be easily isolated and re-implanted. Bone marrow cells continue to divide throughout a person's life to produce blood cells, so this approach is useful only if the gene you want to deliver has a biological role in the blood.

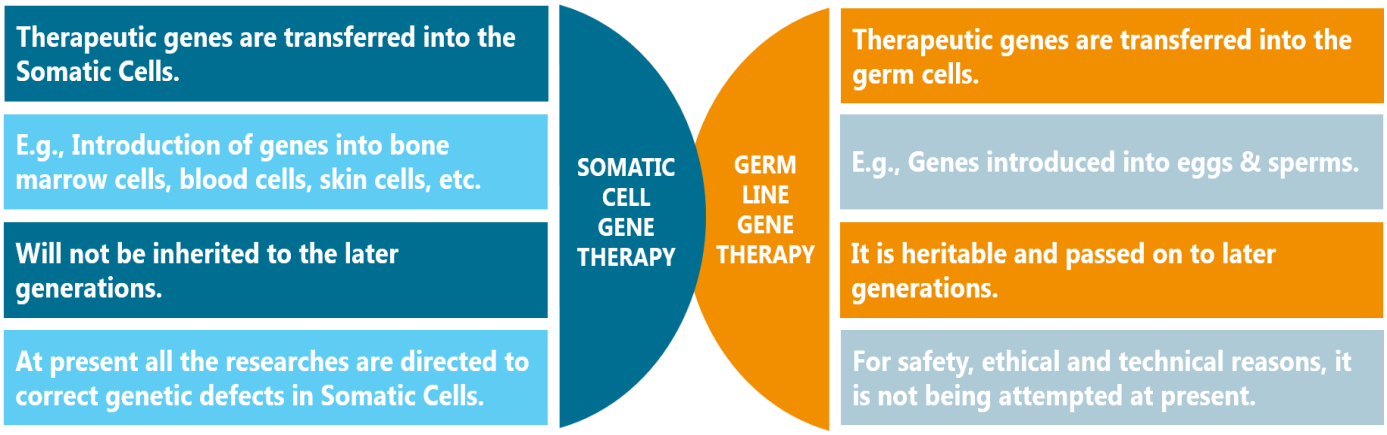


The somatic gene therapy is appropriate and most suitable for many disorders, including cystic fibrosis, muscular dystrophy, cancer, and certain infectious diseases.[1]

The somatic gene therapy is further divided into two more categories:

- **Ex vivo**
- **In vivo**

Ex-vivo gene therapy involves genetic modifications processing outside the body producing therapeutic factors and further moving their transplantation into the body. The synergy between the effect of the new cell and the additional engineered properties can often provide significant benefits to neurodegenerative changes in the brain.
In some of the clinical trials, the patient's blood cells, and bone marrow are exposed and grown in the laboratory while the cells are exposed to virus-carrying desired genes. Further, these viruses enter the cells and are further inserted into the cells' DNA. Cells grow in the laboratory and are then re-injected into the patient by injection into a vein.



Approaches in Gene Therapy

- ❖ Ex vivo gene therapy: transfer of genes to cultured cells and reinsertion
- ❖ In vivo gene therapy: direct delivery of genes into the cells of a tissue in the body

Ex vivo gene therapy

In vivo gene therapy

- Direct delivery of the therapeutic gene into the target cell of the patient's body, carried out by viral or non-viral vector systems
- In vivo gene transfer is necessary when cultured cells cannot be re-implanted in patients effectively
- It can be the only possible option in patients where individual cells cannot be cultured in vitro in large numbers (e.g., brain cells)

In its most straightforward incarnation, the goal of gene therapy for genetic diseases is long-term expression of the transferred gene at levels high enough to be therapeutic, an approach sometimes called augmentation gene therapy. The transferred gene is most frequently a normal copy of a mutated gene. One can also suppress the expression of a detrimental gene by employing RNA interference or genome editing tools. And it is theoretically possible; though not yet in clinical trials, to use genome editing techniques to correct a mutated gene in its precise genomic location through homologous recombination with a donor template or via base editing.[2]

TURNING POINT IN GENE THERAPY

The gene therapy field reached a turning point in 2017 when the FDA approved three breakthrough gene therapies.[3,4,5]

A PRIMER ON GENES

Genes hold DNA, the basic building blocks that make us who we are. Nearly every cell in the human body holds our entire set of approximately 24,000 genes. The job of most genes is to produce one or more unique proteins. A mutation in a gene's normal DNA sequence can prevent it from doing its job. A mutated gene may produce too much or too little protein, damaged protein, or none. These protein abnormalities can lead to hereditary diseases, such as sickle cell disease, a severe form of anemia caused by an inherited defect in a gene that produces hemoglobin. They can also complicate disease treatments, for example when the HER2 gene produces excess protein, which makes certain breast cancers more aggressive. These are just two examples of thousands of diseases for which gene therapy could offer safe, effective treatment and provide long-term benefits.

MIT's New Drug Development Paradigms program estimates FDA approval of three dozen new gene therapies by 2022.[6]

- Successful gene therapies have the potential to prevent years or even decades of morbidity with perhaps just one treatment. The newly approved gene therapies illustrate the substantial and unique benefits that these therapies can deliver to patients with serious illnesses and conditions who otherwise have little to no hope of meaningful improvement. Each of the new gene therapy treatments is intended to be administered just once: a single injection or infusion that can dramatically improve a patient's life. And while more study is needed, early results regarding the durability of response to these treatments is positive. Ensuring patient access to these benefits is crucial.

- Tisagenlecleucel (Kymriah) treats patients up to 25 years old with B-cell precursor acute lymphoblastic leukemia that is resistant to other treatments or is in second or later relapse.[3] In the Kymriah clinical trial, the overall remission rate was 81 percent at 3 months (no detectable leukemia).[7]

Second Indication Approved for Kymriah

On May 1, 2018, the FDA approved Kymriah for the treatment of adult patients with certain types of relapsed or refractory (r/r) large B-cell lymphomas. Before approval of Yescarta, which also treats relapsed or refractory large B-cell lymphomas, these patients had no treatment options and a median life expectancy of approximately 6 months. In the Kymriah trial for the new indication, the overall response rate in treated patients was 50 percent and 32 percent had a complete response. The Kymriah price for treatment of r/r large B-cell lymphomas is $373,000.8

- Axicabtagene ciloleucel (Yescarta) treats aggressive forms of non-Hodgkin lymphoma in adult patients with large B-cell lymphoma that has relapsed or is resistant after two or more lines of systemic therapy.[4] In a Yescarta clinical trial, 72 percent of treated patients had an overall response (tumor shrinkage or elimination) and 51 percent had no detectable cancer (complete remission) six months following the treatment.

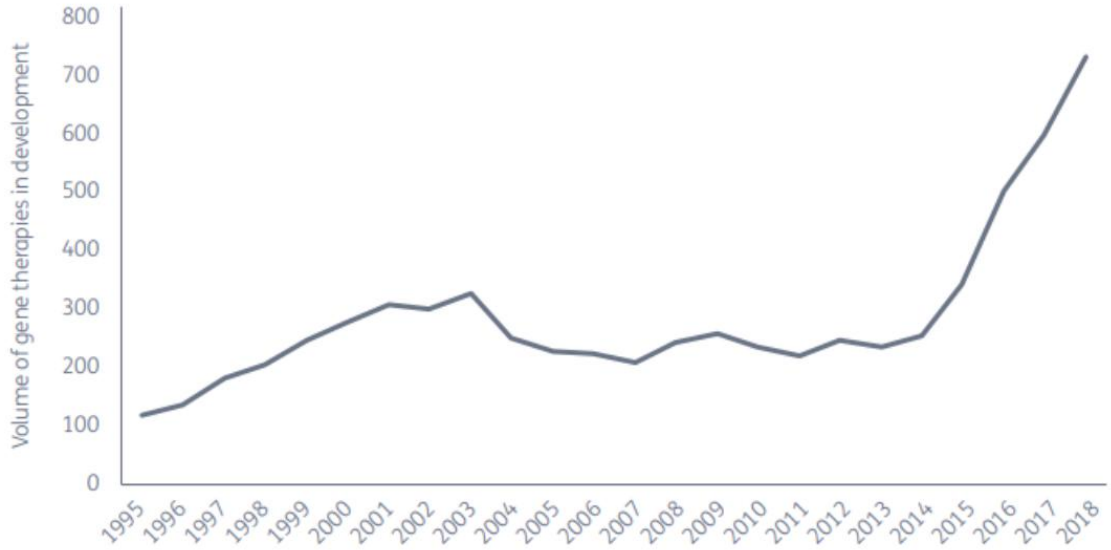
- Voretigene neparvovec-rzl (Luxturna) is the first gene therapy for patients with a hereditary disease[5]; vision loss due to mutations on both copies of a particular gene (RPE65) that nearly always progresses to complete blindness. Three-year follow-up data from the Phase III trial provides evidence of sustained results, as well as safety.[8]

The Gene Therapy Pipeline

Since then, the development of gene therapy has taken a positive turn. The safety of vectors has improved, and the strong investment from venture investors and Big Pharma, as well as mid-sized pharma and other larger pharmaceutical companies, into regenerative medicine firms pioneering work in gene therapy, has made it possible for the field to move forward. For several years, particularly during the period of 2004–14, the number of therapies being worked on remained virtually flat.

Gene therapy pipeline volume, pre-clinical through pre-registration phase, 1995-2018

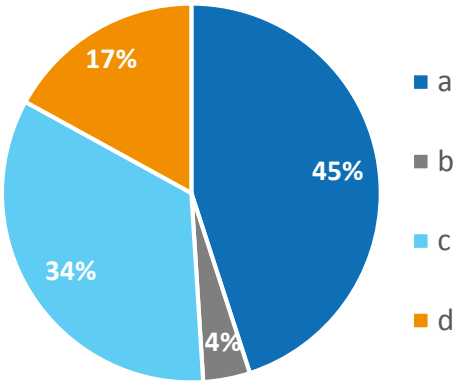
Note: Annual volume snapshots are captured in May of each year



KEY TAKEAWAYS

1. About 40 gene therapies by 2022 will likely gain regulatory approval

2. Four gene therapy archetypes were identified



- Oncology will see the most gene therapies (45%)
- Novel Breakthroughs non-oncology orphan diseases for ultra-small populations (4%).
- Orphan Disrupters for remaining non-oncology orphan conditions (34%)
- Budget Buster gene therapies in therapeutic areas such as cardiology, metabolic disorders: neurology may reach 1/5 (17%) of products

3. Precision financing that targets the specific challenges of each payer and stakeholder type in each gene therapy archetype will be needed.

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