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**Review Article**

# Gene Therapy: A Revolutionary Approach in Modern Medicine – A Review

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## ABSTRACT

The main aim of gene therapy is to introduce specific genes into cells to correct genetic defects or add new functions, aiming to improve health at the cellular level. Genes can be delivered using viral vectors, which are highly effective but may trigger immune reactions, or non-viral systems, which are safer but less efficient. Common viral vectors include retroviruses, lentiviruses, adenoviruses, and adeno-associated viruses, while non-viral delivery can involve plasmids, nanocarriers, and other synthetic systems. Advances in molecular biology and nanotechnology have improved the design of these delivery vehicles, enhancing the safety and efficiency of gene therapy. Gene therapy is being explored for a wide range of conditions, including genetic disorders, cancer, neurodegenerative diseases like Parkinson's and Alzheimer's, and viral infections such as HIV. Despite notable progress and several approved therapies, challenges remain in achieving safe, targeted, and long-lasting gene delivery. Continued research is focused on developing better vectors, improving delivery methods, and ensuring ethical and clinical safety. This review summarizes the history, key methods, current applications, and future prospects of gene therapy, highlighting its potential to transform the treatment of genetic diseases.

## INTRODUCTION

Gene therapy is one of the most innovative and promising approaches in modern biomedical science, aiming to treat, prevent, or potentially cure diseases by addressing their underlying genetic causes. Unlike conventional drug-based therapies that primarily alleviate symptoms, gene therapy focuses on correcting, replacing, silencing, or modifying defective genes responsible for disease development. This strategy offers a fundamentally different therapeutic paradigm, particularly for inherited genetic disorders, cancers, and certain acquired diseases. The concept of gene therapy emerged in the late 20th century with advances in molecular biology and recombinant DNA technology. Early

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developments laid the foundation for understanding gene regulation, gene transfer mechanisms, and the role of genetic mutations in disease pathogenesis. Over the past few decades, significant progress has been made in vector development, gene delivery systems, and genome manipulation techniques, enabling safer and more efficient transfer of therapeutic genes into target cells.

Gene therapy strategies can be broadly classified into in vivo, and ex vivo approaches. In in vivo gene therapy, therapeutic genes are directly delivered into the patient's body, whereas ex vivo therapy involves genetic modification of cells outside the body followed by reinfusion into the patient. Viral vectors such as adenoviruses, adeno-associated viruses (AAV), and lentiviruses have been widely used due to their high transduction efficiency, while non-viral vectors offer advantages in terms of safety and reduced immunogenicity.

In recent years, the field has witnessed remarkable clinical success, leading to regulatory approval of several gene therapy products for conditions such as inherited retinal disorders, spinal muscular atrophy, and certain haematological diseases. These approvals mark a major milestone, demonstrating the clinical feasibility and therapeutic potential of gene-based interventions.

Despite these advancements, gene therapy remains a complex and evolving field, facing challenges related to delivery efficiency, immune responses, long-term safety, and ethical considerations. Continued research and technological innovation are essential to overcome these limitations and expand the applicability of gene therapy across a broader range of diseases [1,2,3,4,5]

## 2. History of Gene Therapy.

The concept of gene therapy emerged in the mid-1960s, when scientists proposed that genetic diseases could be treated by introducing functional DNA into a patient's cells. At the time, this idea remained largely theoretical due to the lack of reliable molecular tools. Subsequent advances in molecular biology and recombinant DNA technology during the following decades gradually enabled the practical exploration of this approach [1,3]

One of the earliest attempts at human gene transfer was carried out by Martin Cline in 1980, who introduced foreign DNA into bone marrow cells of patients with thalassemia. Although controversial and clinically unsuccessful, this effort demonstrated the technical feasibility of gene transfer in humans. A breakthrough occurred in 1989 with the first demonstration of stable gene transfer in human cells, leading to the first approved clinical gene therapy trial in 1990 led by Dr. W. French Anderson.

This landmark trial involved a child with adenosine deaminase (ADA) deficiency–related severe combined immunodeficiency (SCID). Autologous T lymphocytes were genetically modified ex vivo using a replication-defective retroviral vector carrying a functional ADA gene and reinfused into the patient. The treatment resulted in partial immune restoration and is regarded as the first clear clinical success of gene therapy.

Following this achievement, gene therapy research expanded rapidly during the 1990s, particularly for inherited immunodeficiencies. By December 2018, more than 2,900 gene therapy clinical trials had been initiated worldwide, most of them early-phase studies focused on safety. However, progress was temporarily hindered by safety concerns such as immune reactions and insertional mutagenesis, prompting improvements in vector

design, delivery strategies, and regulatory oversight [2,4].

The field entered a new phase with the approval of commercial gene therapies. In 2017, the U.S. FDA approved Luxturna® for inherited retinal dystrophy and Kymriah®, a CAR-T cell–based therapy, for B-cell acute lymphoblastic leukaemia. Additional milestones include the approval of Patisiran, the first RNA interference therapy, and Zolgensma® for spinal muscular atrophy.

Currently, most gene therapies employ viral vectors, particularly adeno-associated viruses for in vivo delivery and lentiviruses for ex vivo applications. Emerging genome-editing technologies, such as CRISPR-Cas systems, are further advancing the field toward precise and durable genetic correction [3,4].

## 3. Types of Gene Therapy

### 3.1 Gene therapy can be broadly classified based on:

1. Classification based on type on target cell.
2. Classification based on method of gene delivery.
3. Classification based on nature of genetic modification [1].

### 1. Classification Based on Type of Target Cells.

#### a. Somatic Cell Gene Therapy.

Somatic cell gene therapy involves the introduction of therapeutic genes into non-reproductive (somatic) cells, such as blood cells, muscle cells, liver cells, or epithelial cells. These changes affect only the treated individual and are not inherited by future generations, making this approach ethically acceptable and clinically safer [1,3].

Most gene therapy trials conducted so far fall under this category. Diseases such as SCID, haemophilia, cystic fibrosis, cancer, and retinal disorders are commonly targeted using somatic gene therapy [2,4].

#### b. Germ Cell Gene Therapy.

Germ cell gene therapy targets reproductive cells (sperm or ova) or early embryos. Any genetic change introduced at this level becomes heritable and can be passed on to future generations.

Due to ethical, social, and safety concerns—including unpredictable long-term effects—germ cell gene therapy is currently prohibited in humans in most countries. However, it is actively studied in animal models to understand genetic inheritance and disease prevention [1,3].

### 2. Classification Based on Gene Delivery Method.

#### a. Ex Vivo Gene Therapy

In ex vivo gene therapy, cells are removed from the patient, genetically modified outside the body, and then reintroduced after successful gene integration. This approach allows better control over gene insertion and safety testing before reinfusion.

This method is widely used in CAR-T cell therapy, haematological disorders, and immunodeficiency diseases [1,2].

#### b. In Vivo Gene Therapy.

In in vivo gene therapy, the therapeutic gene is delivered directly into the patient's body using a vector, most commonly a viral vector such as

AAV or adenovirus. The vector carries the functional gene to the target tissue.

This method is commonly used for eye disorders, muscular diseases, and metabolic disorders [2,4].

**3. Classification Based on Type of Genetic Modification.**

**a. Gene Replacement Therapy**.

Gene replacement therapy involves removing or inactivating a defective gene and replacing it with a functional one. This approach aims to restore normal gene expression permanently.

This method is particularly useful for monogenic disorders caused by a single faulty gene [1,3].

**b. Gene Addition Therapy.**

Gene addition therapy restores cellular function by introducing an additional functional copy of a gene without removing the defective one. The newly added gene compensates for the faulty gene's function.

This strategy is widely used in cancer gene therapy, where tumour suppressor genes or immune-stimulating genes are added to target cells [2,4].

**c. Gene Editing–Based Therapy** Recent advancements such as CRISPR-Cas9, TALENs, and ZFNs allow precise editing of specific DNA sequences. Unlike traditional gene addition, gene editing directly corrects mutations at their original genomic location [3,4].

**4. Overview of Gene Therapy Approaches.**

**4.1 In Vivo and Ex Vivo Gene Therapy.**

Gene therapy strategies are broadly classified into in vivo, and ex vivo approaches based on the site of genetic modification. In vivo gene therapy involves the direct administration of genetic material into the patient, where target cells are transduced within their native tissue environment. This approach is particularly suitable for organs such as the eye, liver, muscle, and central nervous system, where localized or systemic delivery can be achieved efficiently. Approved therapies for retinal dystrophies and haemophilia exemplify the success of in vivo approaches [3,4].

Ex vivo gene therapy, in contrast, involves the isolation of patient-derived cells, genetic modification under controlled laboratory conditions, and subsequent reinfusion into the patient. This method allows precise control over gene transfer efficiency and safety testing prior to administration. Ex vivo approaches are widely used in hematopoietic stem cell therapies and chimeric antigen receptor T-cell (CAR-T) therapies for cancer treatment [1,2].

**4.2 Viral and Non-Viral Gene Delivery Systems.**

Efficient and safe delivery of genetic material remains a central challenge in gene therapy. Viral vectors, including adeno-associated viruses (AAVs), lentiviruses, retroviruses, and adenoviruses, are commonly used due to their high transduction efficiency. AAV vectors are particularly favoured for in vivo applications because of their low pathogenicity and long-term gene expression, whereas lentiviral vectors are extensively used in ex vivo therapies due to their stable genomic integration capabilities [2,4].

Non-viral delivery systems, such as lipid nanoparticles, polymer-based carriers, and physical methods, offer advantages in terms of safety and cargo capacity but often suffer from lower transfection efficiency. AI-driven interpretation of vector performance data is increasingly used to guide the selection and

optimization of both viral and non-viral delivery systems.

between computational scientists, biologists, and clinicians will be critical for realizing the full potential of AI-assisted gene therapy [2,4].

## 5. Vectors for Gene Therapy

In gene therapy, a vector is a carrier system that delivers therapeutic genetic material into target cells. Based on their origin and mechanism of delivery, gene therapy vectors are broadly classified into viral and non-viral vectors. Each category has distinct advantages and limitations that influence their clinical application [1,2].

### 5.1 Viral Vectors

Viruses naturally possess the ability to enter host cells and deliver their genetic material. In gene therapy, this property is exploited by removing disease-causing viral genes and replacing them with therapeutic DNA or RNA. Once inside the host cell, the introduced genetic material can either remain episomal or integrate into the host genome, leading to gene expression.

Retroviruses and lentiviruses integrate their genetic content into the host genome, enabling long-term gene expression. In contrast, adenoviruses and adeno-associated viruses (AAVs) generally do not integrate and instead support transient or semi-stable expression. Herpes simplex virus and vaccinia virus are mainly used for targeting neuronal and cancer cells [2,4].

#### 5.1.1 Common viral vectors.

1. Retrovirus
2. Adenovirus (types 2 and 5)
3. Adeno-associated virus (AAV)
4. Herpes simplex virus (HSV)
5. Pox virus
6. Human foamy virus (HFV)
7. Lentivirus

Viral vectors are carefully modified to improve safety and effectiveness in gene therapy, but several challenges remain:

- these vectors are engineered to prevent replication, reducing the risk of uncontrolled viral spread.
- strong immune responses can occur, leading to inflammation in the host.
- viral component expression may cause damage to surrounding tissues.
- unintended integration of genetic material can disrupt normal genes, potentially causing instability or cancer.
- many vectors have limited capacity to carry large therapeutic genes, restricting their use for certain disorder. [2,4].

#### 1. Retrovirus vector.

Retroviral vectors are derived from retroviruses, which have RNA genomes that are reverse transcribed into DNA and integrated into the host cell genome. This integration allows for stable, long-term expression of therapeutic genes in dividing cells. By removing genes required for viral replication, retroviral vectors have been made suitable for clinical use. These vectors have been historically applied in the treatment of monogenic disorders, such as X-linked severe combined immunodeficiency (X-SCID), and metabolic

diseases like hyperlipidaemia. They are also used in developing experimental cancer vaccines. In contemporary research, retroviral vectors are frequently applied in ex vivo approaches, where patient cells are modified outside the body and reintroduced, allowing precise control over gene delivery. Emerging studies are also exploring combinations of retroviral vectors with genome-editing tools like CRISPR-Cas systems to correct genetic defects at the DNA level [1,2,4].

**2. Adenovirus vector.**

Adenoviral vectors are based on double-stranded DNA viruses, commonly serotypes 2 and 5, and are engineered to remove early genes to prevent replication. These vectors efficiently deliver genes to both dividing and non-dividing cells, with the delivered DNA remaining episomal, leading to transient expression. Adenoviral vectors have been widely used not only in classical gene therapy but also in vaccine development, including viral vector-based vaccines for infectious diseases such as COVID-19. They are also under investigation for cancer immunotherapy, cardiovascular gene therapy, and treatment of respiratory disorders. Due to their capacity to carry relatively large DNA sequences, adenoviral vectors are suitable for delivering complex genetic constructs, including multi-gene cassettes for therapeutic applications. Advanced generations of adenoviral vectors now incorporate modifications to reduce immune responses and improve tissue targeting, making them more versatile for clinical and experimental use [2,3,4].

**3. Adeno-Associated virus (AAV) vector.**

AAV vectors are derived from small, non-pathogenic viruses and are among the safest viral vectors currently in use. They provide long-term gene expression, particularly in non-dividing cells, and certain serotypes integrate at a specific site on chromosome 19, which reduces the risk of random insertional mutagenesis. AAV vectors have been employed in treating genetic disorders such as haemophilia B, cystic fibrosis, alpha-1 antitrypsin deficiency, and inherited retinal diseases. They are also being investigated for applications in neurological diseases, metabolic disorders, and cardiomyopathies. Innovations in AAV research include the development of tissue-specific serotypes and engineered capsids that improve delivery efficiency and reduce immune recognition. Many clinical trials now combine AAV vectors with precise gene-editing techniques, such as CRISPR, to correct disease-causing mutations in situ [2,3,4].

**4. Herp simplex virus (HSV) vector.**

HSV vectors are double-stranded DNA viruses naturally adept at infecting neurons, making them particularly valuable for nervous system applications. They can carry very large DNA fragments, up to 30 kilobases, allowing delivery of complex therapeutic genes or multiple regulatory elements simultaneously. HSV vectors, including modified versions such as Disabled Infectious Single-Cycle (DISC) vectors, enable gene delivery without generating infectious virus particles. They have been extensively studied for treating neurological disorders, brain tumours, chronic pain, and experimental neurodegenerative diseases. HSV vectors are also being explored as vehicles for oncolytic viral therapies, in which the virus selectively targets and kills cancer cells while delivering therapeutic genes to enhance immune responses [2,3,4].

**5. Lentivirus vectors.**

Lentiviral vectors, derived from lentiviruses such as HIV, can infect both dividing and non-dividing cells and stably integrate their genetic material into the host genome, ensuring long-term gene

expression. They are commonly used in ex vivo therapies, including CAR-T cell immunotherapy for cancer, and in experimental therapies for central nervous system disorders. Lentiviral vectors have been applied in preclinical and clinical studies targeting Parkinson's disease, Alzheimer's disease, Huntington's disease, spinal cord injuries, and motor neuron disorders. Modern lentiviral vectors are also combined with precise genome-editing strategies, enabling targeted gene insertion or correction with minimal off-target effects. Their ability to accommodate relatively large transgenes makes them versatile tools for complex therapeutic applications [1,2,3,4].

**5.2 Non-Viral Vectors**

Non-viral vectors deliver genetic material without using viruses and are considered safer and more flexible. These systems are easier to manufacture on a large scale and show lower immunogenicity, allowing repeated administration. However, they generally produce lower transfection efficiency and reduced gene expression compared to viral vectors [2,4].

Common non-viral delivery methods include naked DNA injection, liposomes, dendrimers, inorganic nanoparticles, electroporation, gene guns, magnetoception, and oligonucleotide-based systems. Advances in nanotechnology and cell-specific targeting strategies are gradually improving their efficiency [2] .

Modern non-viral platforms are widely used for the delivery of mRNA, siRNA, antisense oligonucleotides, and CRISPR components. Several biotechnology companies are actively developing lipid nanoparticles and polymer-based systems to overcome delivery challenges, particularly for liver-targeted therapies.

Non-viral gene delivery methods use physical or chemical method to introduce genetic material into cells without relying on viruses [2,3,4] .

**1. Physical method.**

include electroporation, where brief electrical pulses create temporary pores in cell membranes, allowing DNA to enter; this method has shown potential in wound healing and tissue engineering, although its effectiveness can be limited by tissue accessibility. Another technique, the gene gun or ballistic DNA transfer, delivers DNA-coated particles made of gold, tungsten, or silver directly into target cells by physical propulsion, enabling gene transfer into tissues that are difficult to reach by conventional methods. Sonoporation employs ultrasound waves to generate transient defects in cell membranes through acoustic cavitation, with gene delivery efficiency influenced by the intensity and duration of the ultrasound, as well as the concentration of genetic material [2,4].

**A. Physical Methods for Enhancing DNA Delivery.**

**a. Electroporation**

Electroporation is a widely used technique for introducing DNA into cells through the application of brief, high-voltage electrical pulses. These pulses temporarily disrupt the cell membrane, creating nanoscale pores that allow nucleic acids to pass into the cytoplasm. This method can be applied to a wide range of cell types, including mammalian cells, bacterial cells, and primary cells. Despite its versatility, electroporation often causes significant cell stress or death, which has limited its use in clinical applications. Optimizing pulse duration, voltage intensity, and cell density is crucial to improve efficiency while minimizing cytotoxicity. Electroporation is frequently employed in research settings for gene editing,

transfection of stem cells, and delivery of therapeutic genes [1,2,4].

**b. Gene Gun (Particle Bombardment)**

The gene gun, also known as particle bombardment, is a physical DNA delivery method in which DNA molecules are attached to microscopic metal particles, typically gold or tungsten. These DNA-coated particles are accelerated using a high-pressure device, allowing them to penetrate cell membranes and deliver genetic material directly into the nucleus. While effective, careful control is required to avoid off-target insertion of DNA, which could potentially disrupt essential genes such as tumour suppressors. Gene gun technology has been applied in experimental gene therapy, including treatments for X-linked severe combined immunodeficiency (X-SCID). In clinical studies, hematopoietic stem cells (HSCs) treated with retrovirus-mediated gene delivery showed successful correction of T-cell defects in several patients. This approach is particularly useful for targeting cells that are difficult to transfect with conventional methods [1,3,4].

**c. Sonoporation**

Sonoporation utilizes ultrasound waves to transiently increase cell membrane permeability, allowing DNA and other macromolecules to enter the cell. The mechanism involves acoustic cavitation, where the formation and collapse of microbubbles create localized mechanical forces that disrupt the cell membrane. This approach has shown potential in both in vitro and in vivo applications, including gene delivery to tumour cells and vascular tissues. Key parameters, such as ultrasound frequency, intensity, and exposure duration, play a critical role in balancing transfection efficiency and cell viability. Sonoporation is often combined with microbubble contrast agents to improve gene uptake and precision targeting in tissues [4].

**d. Magnetofection.**

Magnetofection is a technique that couples nucleic acids with magnetic nanoparticles to achieve targeted gene delivery. In this method, DNA or RNA is complexed with superparamagnetic particles, and a magnetic field is applied to guide the complexes toward specific cells in culture. This enhances the local concentration of genetic material at the target site, increasing uptake and transfection efficiency. In laboratory studies, magnetofection has been successfully used for primary cells, stem cells, and other hard-to-transfect cell types. For in vivo applications, the DNA-magnetic particle complexes are administered systemically, and external magnets are used to direct them toward the target tissue. Once the complex reaches the desired location, the genetic material can be released from the nanoparticles through enzymatic cleavage, charge interactions, or degradation of the carrier matrix. This method offers precision delivery while minimizing exposure of non-target tissues to the gene construct [2,4].

**2. Chemical methods**

for non-viral delivery rely on molecules that can form complexes with DNA to facilitate cellular uptake. Cationic lipids, used in lipofection, create positively charged complexes with DNA that can fuse with cell membranes, promoting entry into the cell. Similarly, cationic polymers assemble into nanosized complexes called polyplexes, which offer enhanced stability and protection of DNA compared to lipid-based systems. Inorganic nanoparticles, composed of metals, metal oxides, or ceramics, can be coated to bind DNA efficiently, improving both cellular uptake and the expression of delivered genes. These physical and

chemical non-viral strategies are increasingly applied in experimental gene therapies, tissue regeneration, and precision medicine, offering alternatives to viral vectors with lower immunogenicity and greater flexibility for repeated administration [2,4].

## Chemical Methods for Enhancing DNA Delivery

### a. Oligonucleotides.

Synthetic oligonucleotides are commonly employed in gene therapy to specifically target and silence disease-related genes. Antisense oligonucleotides bind to complementary sequences of defective mRNA, preventing its transcription and subsequent protein production. Small interfering RNAs (siRNAs) represent another approach, where they guide the cellular machinery to degrade specific mRNA sequences, effectively halting the expression of harmful genes. These strategies allow precise regulation of gene activity and have been explored in therapies for genetic disorders, cancer, and viral infections [2,4].

### b. Lipoplexes and Polyplexes.

Polyplexes are formed when DNA is complexed with cationic polymers, which help condense the DNA into nanoparticles suitable for cellular uptake. The positively charged surface enhances interaction with negatively charged cell membranes, improving entry into cells. Similarly, lipoplexes are structures created by combining DNA with liposomes—vesicles made of lipid bilayers. Neutral or anionic liposomes can protect the DNA from enzymatic degradation while facilitating its delivery into cells. Both polyplexes and lipoplexes serve as synthetic, non-viral vectors for gene transfer and are often optimized to enhance transfection efficiency, stability, and biocompatibility [2].

### c. Hybrid method

No single gene delivery method is perfect, so hybrid techniques have been developed to combine the strengths of multiple approaches. Virosomes, for example, merge liposomes with inactive viral particles such as HIV or influenza viruses. This combination allows efficient gene delivery into target cells, such as respiratory epithelial cells, surpassing the effectiveness of either viral or liposomal vectors alone. Hybrid strategies often involve combining viral vectors with cationic liposomes or modifying viral particles to reduce immunogenicity while maintaining high transfection efficiency. These approaches expand the toolbox for gene therapy, enabling the delivery of complex therapeutic constructs to a variety of tissues with improved safety and precision [1,3,4].

## 6. Gene Therapy Products.

| Product | Disease/ indications | Target gene | Company | Vector/ Technology | Delivery | Status | Ref |
|---|---|---|---|---|---|---|---|
| Patisiran | Familial amyloid polyneuropathy | TTR | Alnylam | Lipid nanoparticle (siRNA) | In vivo | Approved | [6,7] |
| Luxturna | Inherited retinal dystrophy | RPE65 | Spark Therapeutics | AAV | In vivo | Approved (USA) | [6,8] |
| Spinraza | Spinal muscular atrophy | SMN2 | Biogen & Ionis | ASO | In vivo | Approved | [6,7] |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Givosiran | Acute hepatic porphyria | ALAS1 | Alnylam | siRNA | In vivo | Approved | [6,7] |
| Golodirsen | Duchenne muscular dystrophy | Dystrophin | Sarepta Therapeutics | ASO | In vivo | Approved | [6] |
| Yescarta | B-cell lymphoma | CD19 | Kite Pharma | Lentivirus (CAR-T) | Ex vivo | Approved (USA) | [6,9] |
| Kynamro | Familial hyper-cholesterolemia | ApoB-100 | Sanofi & Ionis | ASO | In vivo | Approved | [6,7] |
| RXI-109 | Subretinal fibrosis | CTGF | RXi Pharma | RNAi | In vivo | Phase I/II | [10] |
| OLX-10010 | Hypertrophic scars | CTGF | Olix | RNAi | In vivo | Phase I | [10] |
| STP705 | Hypertrophic scars | TGF-β, COX-2 | Sirnaomics | siRNA | In vivo | Phase I | [10] |
| SYL1001 | Ocular pain | TRPV1 | Sylentis | siRNA | In vivo | Phase II | [10] |
| NCT03166878 | B-cell lymphoma | CD19 | Clinical trial | CAR-T | Ex vivo | Phase II/III | [10] |
| Zolgensma | Spinal muscular atrophy | SMN1 | AveXis/ Novartis | AAV | In vivo | Approved (USA) | [6,8] |
| Kymriah | B-cell lymphoma | CD19 | Novartis | Lentivirus (CAR-T) | Ex vivo | Approved (USA) | [6,9] |
| Zynteglo | Thalassemia | β-globin | Bluebird Bio | Lentivirus | Ex vivo | Approved (Europe) | [8,11] |
| Collategene | Critical limb ischemia | HGF | AnGes | Plasmid | In vivo | Approved (Japan) | [11] |
| Liso-cel | B-cell lymphoma | CD19 | Bristol-Myers Squibb | Lentivirus | Ex vivo | FDA review | [6,10] |
| OTL-200 | Metachromatic leukodystrophy | ARSA | Orchard Therapeutics | Lentivirus | Ex vivo | EMA review | [8,10] |
| Valrox | Hemophilia A | Factor VIII | BioMarin | AAV | In vivo | Regulatory review | [8,10] |

## 7. Application of gene therapy

Gene therapy has shown promising results in treating Parkinson's disease (PD), a neurodegenerative disorder caused by progressive loss of dopaminergic neurons. One strategy increases gamma-aminobutyric acid (GABA), which is reduced in PD, by delivering genes encoding glutamic acid decarboxylase (GAD) via viral vectors into movement-controlling brain regions. In a clinical trial of 45 advanced PD patients, those receiving gene therapy showed about twice the motor function improvement after six months compared to a saline-treated control group [1,2]. Recent research also indicates that PD progression involves toxic protein aggregate spread and immune-mediated neuronal damage, highlighting the need for therapies capable of crossing the blood–brain barrier to target affected neurons. However, experimental studies, including work with LRRK2 inhibitors in animal models, suggest long-term genetic modulation may carry risks, emphasizing the need for precise and carefully designed therapeutic approaches [4].

### 1. Alzheimer's disease (AD)

Alzheimer's disease is the leading cause of dementia worldwide and lacks definitive treatment. AD, along with several frontotemporal dementias, is characterized by abnormal tau protein accumulation, which destabilizes neuronal microtubules. Gene therapy using recombinant adeno-associated viruses (rAAVs) has opened new possibilities for addressing such neurodegenerative disorders [3].

Clinical trials have explored delivering nerve growth factor (NGF) genes to the brains of AD patients to determine whether deteriorating neurons can still respond to neurotrophic support. NGF gene therapy successfully stimulated axonal growth and neuronal signalling without adverse effects. Some studies have also explored silencing disease-related genes, such as BACE1, using exosome-mediated delivery systems in animal models. Exosomes can cross the blood-brain barrier and deliver therapeutic genes to specific neurons, offering a promising approach for future human applications. Neurotrophic factors such as glial cell-derived neurotrophic factor (GDNF) have shown protective effects on dopamine-producing neurons in Parkinson's disease models, highlighting their potential in neurodegenerative disease therapy [1].

## 2. Cystic Fibrosis (CF)

Cystic fibrosis is a genetic disease that primarily affects the lungs, causing repeated infections, inflammation, and tissue damage. Gene therapy for CF aims to deliver functional cystic fibrosis transmembrane conductance regulator (CFTR) genes to airway epithelial cells. Initial attempts in the early 1990s involved modified viruses as vectors to introduce normal

CFTR genes. Subsequent research explored alternative delivery methods, including lipid-based carriers, synthetic vectors, nasal sprays, and nebulizers [3].

Effective CF gene therapy requires identifying the affected lung cells, understanding the source of CFTR-producing cells, and determining optimal dosing frequency. Animal models have been critical for preclinical studies, with pig models demonstrating human-like lung disease. Both lentiviral and adeno-associated viral vectors (AAV2) have been tested in pigs, offering either permanent integration or long-term gene expression, respectively. Advances in viral engineering have improved tissue-specific targeting and infection efficiency, making CF gene therapy increasingly feasible [1,4].

## 3. Diabetic Neuropathy

Gene therapy has been investigated for treating diabetic polyneuropathy, a common complication of diabetes that damages nerves in the limbs. Intramuscular injection of genes encoding vascular endothelial growth factor (VEGF) in affected legs has shown potential in improving pain, strength, and balance in patients [1,3]. This approach delivers the gene directly without using viral packaging, reducing the risk of immune responses. While initial studies are promising, larger trials are necessary to validate safety and efficacy [2].

## 4. Cancer Therapy

Advances in human genomics have revealed that many cancers arise from genetic alterations in somatic cells, paving the way for gene therapy-based treatments [1,2]. Cancer gene therapy can involve viral or non-viral vectors to deliver therapeutic genes, stimulate immune responses, reduce tumour growth, or enhance antigen presentation for immune recognition. Oncolytic viruses, which selectively infect and destroy

cancer cells, represent a particularly promising approach [3,4].

In pancreatic cancer, gene therapy targets include the P53 tumour suppressor gene, mutated K-RAS oncogene, VEGFR anti-angiogenic genes, suicide genes like HSV-TK, cytosine deaminase, cytochrome P450, and cytokine genes. Oncolytic viruses can spread within tumours, allowing direct injection to treat localized or spreading malignancies. Despite challenges in delivery, viral vectors remain the most efficient method for gene transfer, ensuring long-term expression and targeting cancer cells effectively [4].

For breast cancer, gene therapy approaches include correcting mutations, inducing apoptosis, inhibiting angiogenesis, enhancing immune responses, and modulating drug resistance. Clinical trials primarily focus on the p53 tumour suppressor gene, often delivered using adenoviral vectors. While results indicate minimal toxicity, low clinical response rates and high transgene expression variability suggest the need for optimized vectors and hybrid therapies combining gene therapy with surgery, chemotherapy, or radiotherapy [1,4].

**Advantages of Gene Therapy.**

- Gene Silencing and Control: Gene therapy allows precise silencing of harmful genes. For instance, in patients infected with HIV, gene silencing can reduce viral activity, potentially prevent disease progression and minimize related complications. This approach provides an early protective strategy against the development of severe symptoms [1,2].

- Treatment of Genetic Disorders: Gene therapy holds promise in correcting inherited diseases by delivering functional genes to replace or repair defective ones. Conditions such as cystic fibrosis, muscular dystrophies, and haemophilia are prime examples where gene therapy could offer long-term or permanent solutions [1,3,4].

- Potential in Chronic and Complex Diseases: Beyond inherited disorders, gene therapy is being explored for its ability to treat major diseases, including cardiovascular conditions, cancer, and viral infections like AIDS. By targeting disease pathways at the genetic level, it can offer more specific and effective interventions than conventional treatments [2,4].

- Preventive Applications: In addition to treatment, gene therapy has the potential to prevent certain diseases by modifying genes before disease onset or by equipping cells with enhanced resistance against pathogens [1,4].

**Limitations of Gene Therapy.**

- Novelty and Experimental Nature: Many gene therapy techniques are still relatively new and under investigation, limiting their availability and understanding. Long-term effects and outcomes in humans are not fully known [1,3].

- Immune System Activation: Viral vectors used in gene therapy can trigger immune responses. The immune system may recognize the viral vector as foreign, causing inflammation or reducing the therapy's effectiveness. In rare cases, the viral vector itself may regain pathogenic potential, increasing safety concerns [2,4].

- Unintended Genetic Effects: There is a risk that transferred genetic material may not reach the intended target cells or may integrate in unintended locations within the genome. This

can potentially disrupt normal genes or regulatory regions, leading to unexpected genetic abnormalities [1,3].

- Complexity in Multi-Gene Diseases: For conditions involving multiple genes, gene therapy may require precise coordination of several genetic modifications, making treatment design and delivery more challenging [2,4].

## CONCLUSION

In the many years, gene therapy has made a lot of progress and has been used to treat many diseases like cystic fibrosis, diabetes, Alzheimer's, Parkinson's, and different types of cancer. Scientists have used different ways to deliver genes into the body, especially using lentivirus and adeno-associated virus (AAV) vectors, and new methods are being developed to make gene therapy safer and more effective. The experiences from past studies help improve how gene therapy is used in patients. In the future, gene therapy could treat more diseases, including rare and difficult ones, especially with new tools like gene editing. Although some conditions, like muscular dystrophy and certain brain or storage diseases, are still hard to treat, ongoing research is helping to create better treatments that are safer, more accurate, and more widely available.

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