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A Review on Advancements of Gene Therapy for Genetic Disorders

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ABSTRACT: Gene therapy has evolved significantly, offering permanent solutions for a range of genetic ailments, from blood disorders to cancer. This groundbreaking technology has two primary approaches: germ-line gene therapy, aiming to alter inherited genes in future generations, and somatic cell gene therapy, targeting genes in the patient but not passed to offspring. Advantages of gene therapy include the potential to treat diseases like HIV, heart disease, and cancer, as well as hereditary conditions. However, disadvantages include the novelty of the techniques and the potential for an immune response. Various viral and non-viral vectors are employed to deliver therapeutic genes. Recent advances, such as CRISPR-Cas9 technology, AAV and lentiviral vectors, and personalized gene therapy, offer hope for treating previously incurable diseases and promoting precision medicine. Regulatory approvals are also streamlining the path to gene therapy implementation.

KEYWORDS: Gene Therapy, Genetic Disorder, Advance technologies

I. INTRODUCTION

[1]. Ailments that previously only received temporary therapies now have permanent remedies because to gene therapy. Gene therapy failed for a very long time; nevertheless, in recent years, successful and long-lasting treated instances have been documented. Promising results have been reached for a wide range of genetic ailments, including blood abnormalities, immunological inadequacies, eyesight problems, nerve cell regeneration, metabolic disorders, and several cancer kinds.

[2]. Unprecedented advances in gene therapy, which involves changing a person's genetic makeup to replace or correct damaged genes, have the potential to change the way that many different genetic illnesses are treated. Gene therapy is proving to be a source of hope for a variety of diseases, from complex polygenic illnesses like cardiovascular disorders and diabetes to monogenic afflictions like cystic fibrosis and sickle cell anaemia. The promise for highly targeted, precision medicine, which was long thought to be science fiction but is now becoming reality, has been unleashed with the advent of the genomic era.

[3]. Medical professionals, researchers, and those affected by genetic disorders—a broad and frequently fatal collection of medical conditions—have long faced enormous difficulties. However, a number of ground-breaking scientific developments in the area of gene therapy have recently led to a significant change in how we view, identify, and treat these conditions. The therapeutic potential of gene therapy is changing the field of genetic medicine and giving those who have faced seemingly insurmountable challenges in the past fresh hope(Fig. 01).

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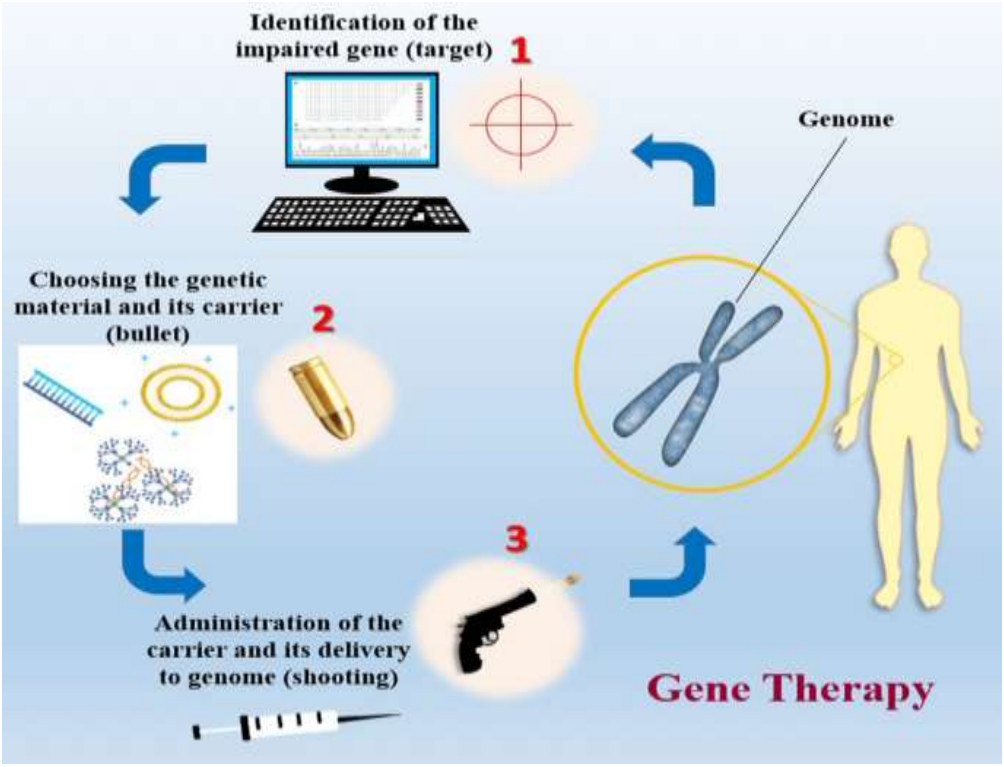

Fig. 01: Gene Therapy

Types of Gene Therapy:

A. Germ-line Gene Therapy (Fig. 02)

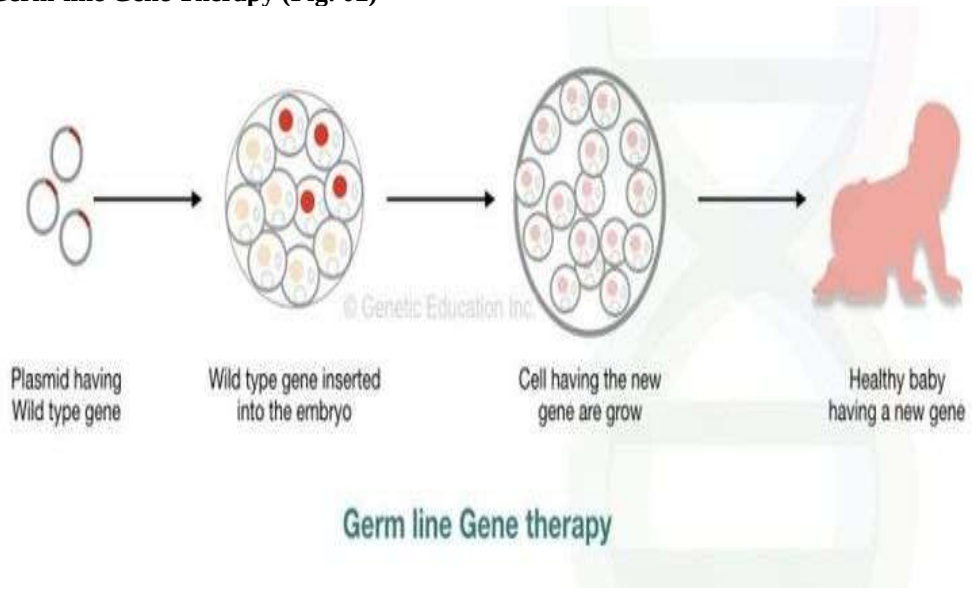

Fig. 02:Germ-line Gene Therapy

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B. Somatic Cell Gene Therapy (Fig. 03):

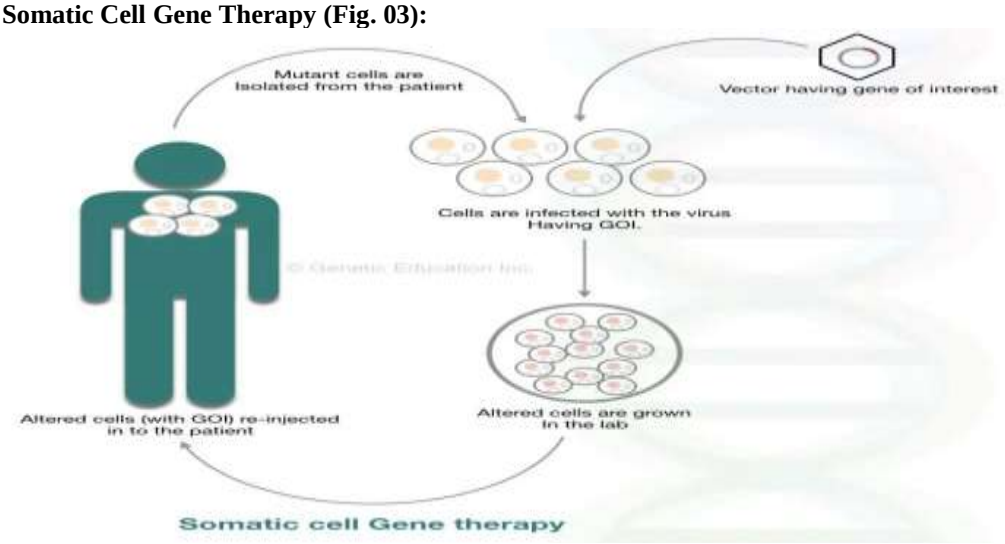

Fig. 03: Somatic cell Gene therapy

[4]. Advantages of Gene Therapy:

- Gene Silencing.
- Gene therapy has the potential to treat heart disease, AIDS, cancer, and other disorders, including the elimination and prevention of inherited conditions like cystic fibrosis.

[5]. Disadvantages of Gene Therapy:

- Their novelty.
- Stimulation of immune response.
- Multigene causes the development of genetic disorders.

[6]. Approaches to Gene Therapy:

- **Gene addition**

➢ Stem cells from patients are taken away and modified in a lab.

➢ Your cells can make haemoglobin A (non-sickling haemoglobin) because the stem cell receives an extra copy of a haemoglobin A gene (without the variation).(Fig. 04)

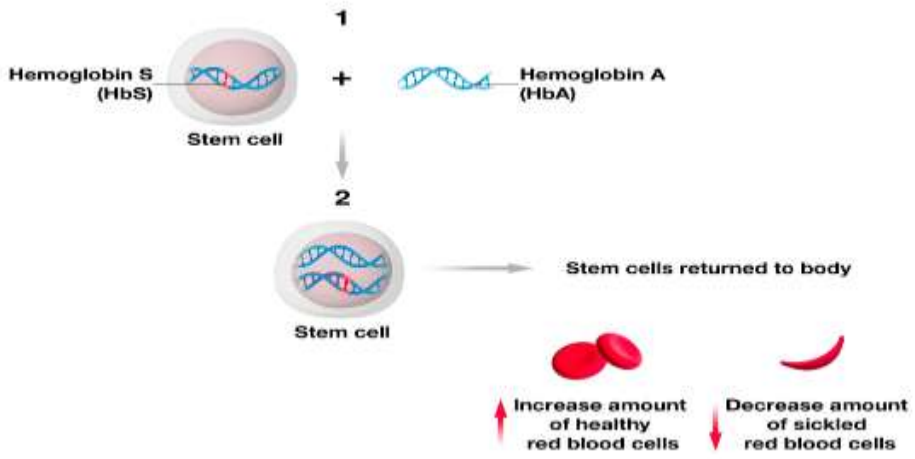

Fig. 04: Gene addition

- **Gene silencing**

➢ Stem cells from patients are taken away and modified in a lab.

➢ Haemoglobin F is rendered inactive by the BCL11A-blocking protein, which is produced by a silenced gene.

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- The gene that produces haemoglobin F can be triggered by silencing this gene, enabling your cells to manufacture haemoglobin F (non-sickling).(Fig. 05)

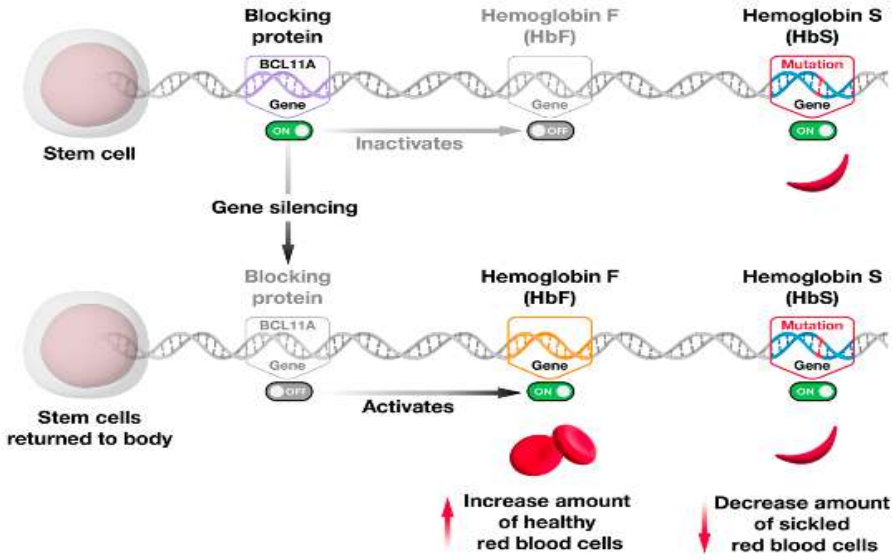

Fig. 05: Gene silencing

- **Gene correction**
- Stem cells from patients are taken away and modified in a lab.
- A non-sickling haemoglobin is produced when the sickle cell disease-causing gene mutation is fixed.(Fig. 06)

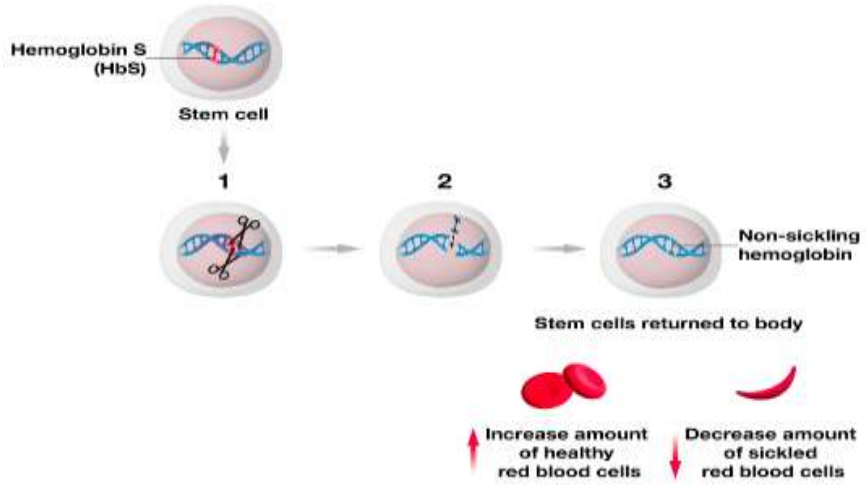

Fig. 06: Gene correction

[7, 8, 9, 10, 11]. Vectors in Gene Therapy:

- **Viral Vectors:**
- Retroviruses
- Adenoviruses
- Adeno-Associated Viruses
- Herpes Simplex Viruses
- **Non-Viral Vectors:**
- Cationic lipids
- Polymeric gene carriers

ADVANCEMENTS IN GENE THERAPY:

[12]. **A.CRISPR-Cas9 Technology**:

The CRISPR-Cas9 system is one of the most revolutionary developments in gene therapy. This gene-editing technology enables precise and targeted gene alteration, providing the opportunity

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to replace or correct defective genes that cause hereditary illnesses. Recent studies have shown that CRISPR-Cas9 is helpful in treating diseases including sickle cell disease and beta-thalassemia, opening up new possibilities for customized gene therapy. (Fig. 07)

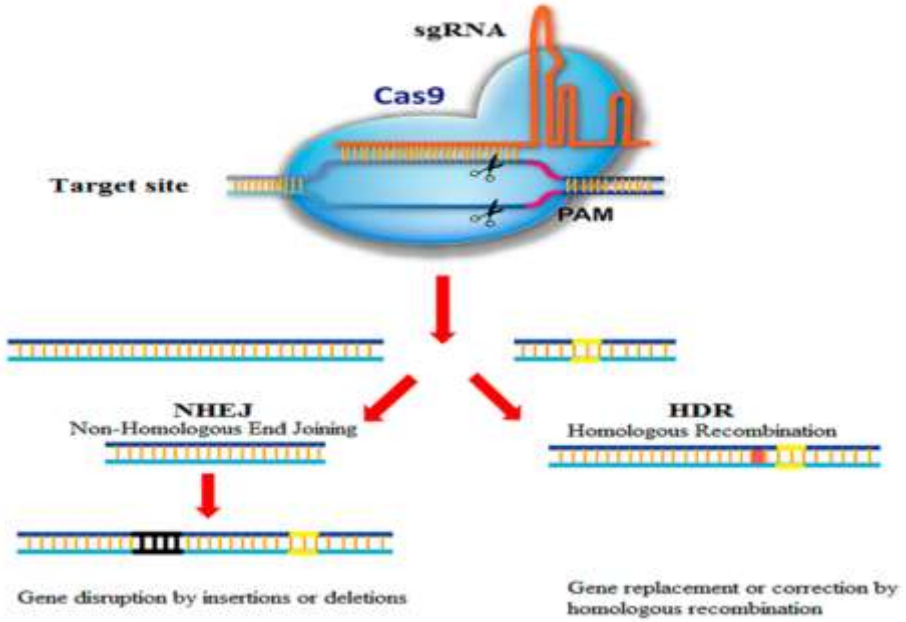

Fig. 07:CRISPR-Cas9 Technology

[13,14]. **CRISPR** dCas9–KRAB fusions can be targeted to protein- coding sequences to downregulate transcription, repressing the gene for as long as the CRISPR fusion protein is present without permanently editing DNA.

[15]. This feature is attractive for reducing expression of the voltage- gated sodium ion channel NaV1.7 (encoded by SCN9A) in the peripheral nervous system, which could reduce pain and thereby overcome the current reliance on opioids.

[16]. As developing small- molecule drugs is challenging and complete gene ablation would result in permanent undesirable pain insensitivity, CRISP-Ri is an attractive option to treat chronic pain. CRISP-Ri targeted to NaV1.7 and delivered intrathecally reduced pain sensitivity and reversed chronic pain in mouse models of carrageenan-induced inflammatory pain, paclitaxel inducedneuropathic pain and Bz-ATP- induced pain, demonstrating the therapeutic advantage of CRISP-Ri over traditional CRISPR editing in these settings.

[17]. The regulatory effects of CRISP-Ri can be used in many other diseases in which complete CRISPR- mediated gene knockout is not therapeutically useful. In one form of long QT syndrome (LQTS) that can be caused by a myriad of mutations in CALM2, dCas9–KRAB was used to reduce expression of the mutant gene in vitro.

[18]. This intervention overcame the disease phenotype in iPSC- derived cardiomyocytes and creates a generalizable therapeutic approach that is independent of the location of the nonsense mutation. In a mouse model of retinitis pigmentosa, dCas9–KRAB targeted to Nil rescued retinal function when delivered to postmitotic cells that normally have reduced capacity for the DNA repair mechanisms that are essential for indel formation.

[19, 20] Overexpression of DUX4 in myocytes leads to facioscapulohumeral muscular dystrophy (FSHD). DUX4 has many genomic copies that could lead to toxicity if numerous DSBs were created, and gene editing at such large repetitive regions can lead to unpredictable outcomes.CRISP-Ri has been leveraged in vitro and in vivo to reduce DUX4 expression without the risk of inducing apoptosis owing to DNA damage.

[21]. B.AAV and Lentiviral Vector Delivery Systems:

Lentiviruses and adeno-associated viruses (AAV) have grown to be common vectors for delivering therapeutic genes. These vectors make it easy and risk-free to transfer genetic material to intended cells. Recent research has shown that

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AAV-based gene therapy is exceptionally effective in curing inherited retinal disorders and muscular dystrophy, giving hope to people with ailments that were formerly thought to be incurable.

Adeno-associated viruses (AAV) and lentiviral vectors are both popular delivery systems for transferring therapeutic genes into target cells. They have revolutionized gene therapy and shown great promise in treating various genetic disorders. Below,provided a detailed overview of AAV and lentiviral vector delivery systems, their applications in gene therapy, and some recent breakthroughs.

- **Adeno-Associated Viruses (AAV): (Fig. 08)**

➢ **Introduction:** AAV is a non-pathogenic, small, single-stranded DNA virus that has gained popularity as a gene therapy vector.

➢ **Vector Structure:** A typical AAV vector consists of a small genome encapsulated in a protein coat.

➢ **Applications:** AAV-based gene therapy has been successfully used to treat various genetic disorders, including inherited retinal disorders and muscular dystrophy. For example, Luxturna, an FDA-approved AAV-based gene therapy, has been effective in restoring vision in patients with Leber congenital amaurosis, an inherited retinal disorder.

➢ **Mechanism of Action:** AAV vectors are administered to the patient, and once inside the target cells, they release their genetic cargo. The therapeutic gene integrates into the host cell's genome and corrects the genetic defect.

➢ **Advantages:**Low immunogenicity, Long-lasting expression, Safety.

➢ **Recent Advances:** AAV-based gene therapy continues to advance rapidly. Recent research has demonstrated its efficacy in treating a wide range of genetic disorders. For instance, AAV-based gene therapy has shown remarkable success in treating muscular dystrophy by delivering functional copies of the dystrophin gene.

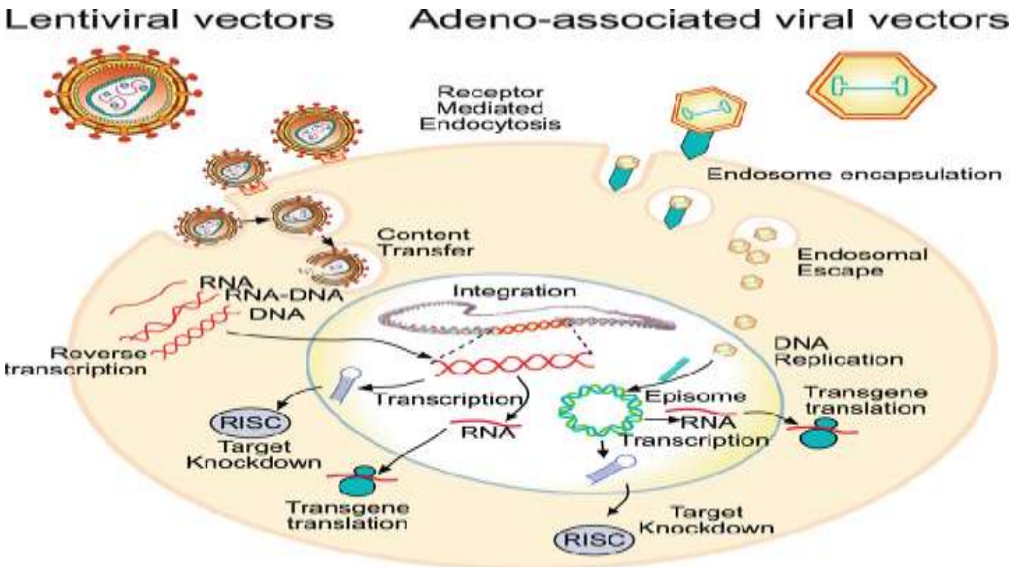

Fig. 08:AAV and Lentiviral Vector Delivery Systems

- **Lentiviral Vector Delivery Systems:**

➢ **Introduction:** Lentiviruses, a type of retrovirus, are known for their ability to integrate their genetic material into the host cell's genome.

➢ **Vector Structure:** Lentiviral vectors are derived from lentiviruses like HIV. They are engineered to be replication-defective and are modified to carry therapeutic genes.

➢ **Applications:** Lentiviral vectors have been used in gene therapy for various conditions, including blood disorders like beta-thalassemia and sickle cell disease, as well as rare genetic diseases like severe combined immunodeficiency (SCID). CAR-T cell therapies, which have shown success in treating certain cancers, also use lentiviral vectors.

➢ **Mechanism of Action:** Lentiviral vectors are typically used to modify cells outside the body (ex vivo) before reinfusing them into the patient. They integrate the therapeutic gene

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into the target cell's genome, providing long-term expression.

- **Advantages:**Efficient gene transfer, Long-term expression, Broad applicability
- **Recent Advances:** Lentiviral vector-based gene therapies have demonstrated remarkable results in clinical trials, particularly for blood disorders. For example, Lent globin, a lentiviral vector-based therapy, has shown great promise in treating beta-thalassemia and sickle cell disease.

[22,23,24,25]. C. Treatment of rare diseases:

Gene therapy's promise to treat uncommon genetic illnesses is becoming more widely acknowledged. Clinical trials have demonstrated great effectiveness in treating diseases like Leber congenital amaurosis, Duchenne muscular dystrophy, and spinal muscular atrophy (SMA).

Treatment ofrare genetic disorder with Gene Therapy:

- **Leber Congenital Amaurosis (LCA):**
- LCA is a rare inherited retinal disorder that causes severe vision impairment or blindness in children. It is caused by mutations in various genes.
- **Gene Therapy:** AAV-based gene therapy, as mentioned earlier in the previous response, has been used to treat LCA. The therapy involves introducing a functional copy of the mutated gene into the retina.
- **Effectiveness:** Clinical trials have demonstrated significant improvements in vision for patients with LCA. Notably, Luxturna, an AAV-based gene therapy for LCA, received FDA approval in 2017, marking a major milestone in gene therapy for rare genetic disorders.(Fig. 09)

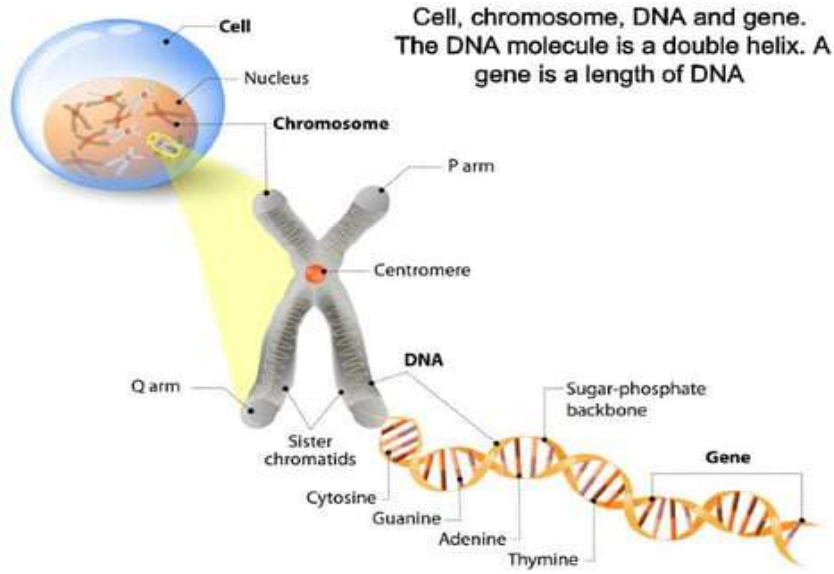

Fig. 09: Luxturna, an AAV-based gene therapy for LCA

- **Duchenne Muscular Dystrophy (DMD):**
- DMD is a rare genetic disorder characterized by progressive muscle weakness and degeneration due to mutations in the dystrophin gene.
- **Gene Therapy:** Various gene therapy approaches, including AAV and CRISPR/Cas9, have been explored to address DMD. These therapies aim to introduce a functional dystrophin gene or correct the existing mutation.
- **Effectiveness:** While gene therapy for DMD is still in the experimental stage, promising results have been seen in preclinical studies and early-phase clinical trials. These therapies hold potential for slowing or halting the progression of the disease.
- **Spinal Muscular Atrophy (SMA):**
- SMA is a rare genetic disorder characterized by the loss of motor neurons, leading to muscle weakness and atrophy. It's primarily caused by mutations in the SMN1 gene.

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- **Gene Therapy:** The FDA approved Spin Raza, an antisense oligonucleotide therapy, to treat SMA in 2016. Additionally, Zolgensma, an AAV-based gene therapy, was approved in 2019.
- **Effectiveness:**Zolgensma, in particular, has shown impressive results in infants with SMA, often achieving significant motor function improvements and halting disease progression.(Fig. 10)

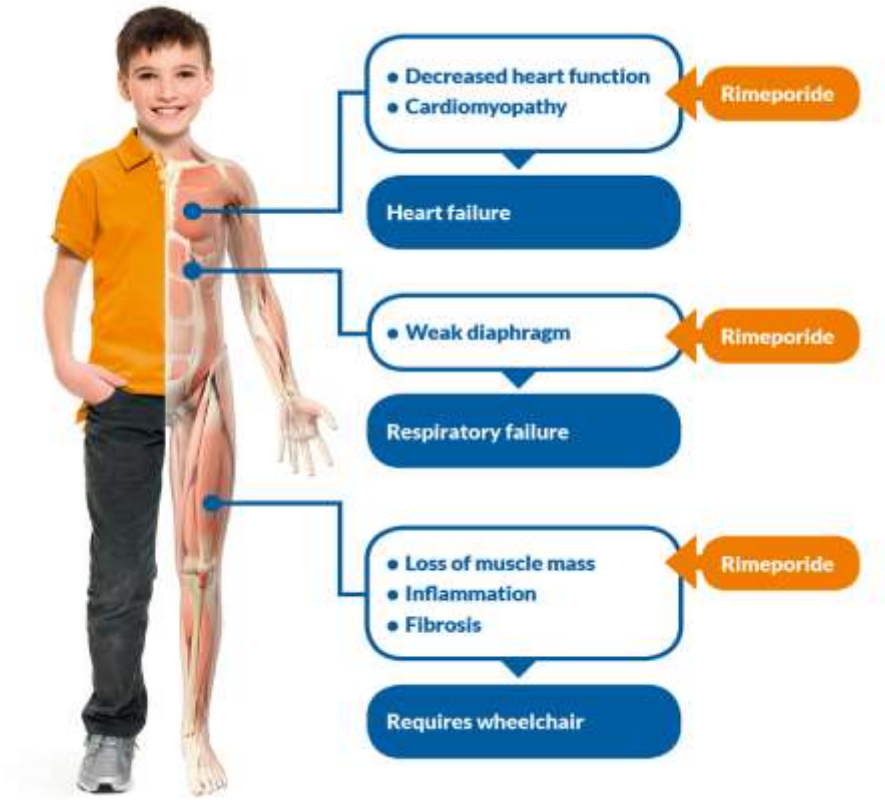

Fig. 10: **Spinal Muscular Atrophy (SMA):**

- **Fresh Hope for Patients and Families:**
- The success of gene therapy in treating these rare genetic illnesses has provided fresh hope to patients and their families. Many of these conditions were once considered untreatable, and families faced a grim prognosis for their loved ones.
- Gene therapy has the potential to significantly improve the quality of life for individuals with these conditions, offering the possibility of increased independence and reduced suffering.

D. Personalized Gene Therapy:

Today's therapies can be tailored to a person's particular genetic profile, leading to more focused, effective treatments with fewer side effects. This method has special promise for polygenic conditions including diabetes and cardiovascular disease.

Personalized Gene Therapy for Polygenic Conditions:

Personalized gene therapy is a groundbreaking approach that tailors' treatments to an individual's unique genetic profile. With the advancement of gene therapy, this approach has gained popularity, offering the potential to revolutionize the treatment of complex, polygenic conditions such as diabetes and cardiovascular disease.

- **Diabetes:**
- **Personalized Gene Therapy:** Personalized gene therapy for diabetes involves identifying an individual's genetic variants that contribute to their diabetes risk. This information is then

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used to design a therapy that targets the specific genetic factors involved.

- **Effectiveness:** Personalized gene therapy for diabetes aims to improve blood sugar control and reduce the risk of complications. By targeting the patient's specific genetic factors, it can lead to better outcomes compared to conventional treatments.

- **Cardiovascular disease:**
- **Personalized Gene Therapy:** Personalized gene therapy for cardiovascular disease is based on identifying an individual's genetic predisposition to CVD. Genetic testing helps in understanding which genes are involved and how they contribute to the disease.
- **Tailored Approaches:** For patients at risk of CVD, personalized gene therapy can involve:
  - Targeting lipid metabolism
  - Enhancing heart function
  - Reducing inflammation
- **Effectiveness:** By tailoring treatment to a person's genetic profile, personalized gene therapy for cardiovascular disease aims to reduce the risk of heart attacks, strokes, and other CVD-related events.

- **Benefits of Personalized Gene Therapy:**
- Precision Treatment
- Reduced Side Effects
- Improved Outcomes
- Optimized MedicationReference
- Regulatory Approvals

[26, 27]. Regulatory Approvals and Advancements in Gene Therapy:

The approval process for gene therapies has evolved significantly in recent years, with regulatory organizations such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) actively collaborating with researchers to expedite the development and approval of these groundbreaking treatments.

- **Luxturna for Hereditary Retinal Illness:**
- **Background:** Luxturna, developed by Spark Therapeutics, is an adeno-associated virus (AAV)-based gene therapy designed to treat Leber congenital amaurosis (LCA), a rare and severe inherited retinal disorder that leads to blindness in childhood.
- **Collaboration:** The FDA played a pivotal role in the accelerated development and approval of Luxturna. It was granted both the Orphan Drug Designation and the Breakthrough Therapy Designation, expediting its evaluation.
- **Approval:** In 2017, Luxturna became the first FDA-approved gene therapy for a genetic disease. This approval represented a significant milestone in the field of gene therapy, showcasing the FDA's commitment to streamlining the regulatory process for innovative therapies.
- **Effectiveness:** Clinical trials demonstrated substantial improvements in vision among patients with LCA. Luxturna's approval has provided hope to individuals with other genetic retinal disorders.

- **Zolgensma for Spinal Muscular Atrophy (SMA):**
- **Background:**Zolgensma, developed by Novartis subsidiary AveXis, is a gene therapy for the treatment of SMA, a severe neuromuscular disorder caused by mutations in the SMN1 gene.
- **Collaboration:** The development and approval of Zolgensma were expedited through close collaboration between researchers, regulatory agencies, and advocacy groups. The FDA granted Zolgensma the Breakthrough Therapy Designation and Priority Review.
- **Approval:** In 2019, Zolgensma received FDA approval for the treatment of paediatric patients with SMA. This gene therapy provides a functional copy of the SMN1 gene to compensate for the genetic mutation causing the disease.
- **Effectiveness:**Zolgensma has shown remarkable effectiveness in halting disease progression and improving motor function in infants with SMA. It represents a major advancement in SMA treatment.

- **Benefits of Regulatory Collaboration:**
- **Faster Approvals:** Collaborative efforts between regulators and researchers have led to more efficient clinical trial designs and accelerated reviews, reducing the time it takes to bring gene therapies to patients.
- **Priority Designations:** Regulatory agencies have introduced designations like Breakthrough Therapy and Priority Review, which facilitate the development and approval of gene therapies for rare and life-threatening diseases.
- **Increased Investment:** Streamlined regulatory pathways have attracted increased investment in gene therapy research and development, leading to a growing pipeline of potential treatments.

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- **Patient Access:** Rapid approvals of gene therapies enable patients with rare genetic diseases to access potentially life-changing treatments earlier.[26,27]

II. CONCLUSION:

In conclusion, the field of gene therapy has undergone remarkable advancements, transforming the treatment landscape for a spectrum of genetic disorders. Recent successes, particularly with CRISPR-Cas9 technology, AAV, and lentiviral vectors, showcase the potential for precise and personalized medicine. These breakthroughs offer hope for treating conditions ranging from cardiovascular disorders to rare genetic diseases. Despite the notable advantages, challenges such as immune responses and ethical considerations persist. The ability to edit, silence, or correct genes opens new avenues for treating previously incurable diseases. As regulatory bodies collaborate with researchers, gene therapy is increasingly gaining approval for clinical applications, marking a paradigm shift in genetic medicine and providing renewed optimism for individuals facing once insurmountable health challenges.

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