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Gene Therapy for Rare Genetic Disorders: Recent Breakthroughs

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ABSTRACT

Gene therapy has become an exciting new way to treat rare genetic diseases, with the possibility of long-lasting or even curing solutions. Recent improvements in gene therapy have made it much safer and more effective, making it a possible way to treat genetic diseases that couldn't be cured before. Researchers have made a lot of progress in the last few years in learning how genetic diseases work at the molecular level and how gene-based treatments can be used to treat them. Better and more accurate treatments have been made because of this, especially for rare genetic diseases like spinal muscular atrophy (SMA), cystic fibrosis (CF), haemophilia, and some inherited eye diseases. The FDA's approval of the first gene treatment for spinal muscular atrophy, a serious neurological disease that affects babies, is one of the most important steps forward in gene therapy. This treatment has been shown to stop the disease from getting worse and make movement skills much better, showing how gene therapy can change things. Also, improvements in viral vector technology, like adeno-associated viruses (AAV), have made it easier to get restorative genes to the cells that need them. Now, these vectors are being tweaked to make them more specific, lower defensive reactions, and make transport more effective overall. The creation of CRISPR-Cas9 gene-editing technology has also changed the field by making it possible to fix genetic changes at the DNA level. It looks like CRISPR could help treat a number of rare genetic diseases, such as sickle cell anaemia and β-thalassemia. These cutting-edge technologies have made gene therapy easier to get and more successful. They have also made it possible to precisely change genes. Even with these improvements, gene therapy for rare genetic diseases still has some problems. Some of these are worries about the long-term effects of changing genes, the high cost of treatments, and the lack of good delivery methods. Even so, these problems are still being worked on in continuing research and clinical studies, which brings gene therapy closer to becoming a common way to treat odd genetic diseases. Gene therapy has a bright future ahead of it. It could change the field of genetic medicine and give people with diseases that couldn't be treated before hope.

Keywords: Gene therapy, Rare genetic disorders, CRISPR-Cas9, Spinal muscular atrophy, Genetic medicine

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INTRODUCTION

Gene therapy has become one of the most hopeful ways to treat genetic diseases, especially rare ones that were thought to be impossible to treat in the past. Gene therapy includes adding or changing genetic material inside of a patient's cells to fix or change genes that aren't working properly and cause diseases. Gene therapy has gone from being an idea for experiments to a real treatment choice in the last few decades, thanks to progress in molecular biology, genetic engineering, and transport methods. Because of recent progress in this area, gene therapy is starting to show that it might be able to cure odd genetic diseases that have been ignored by standard medicine for a long time. A small part of the population has rare genetic diseases. These disorders are usually passed down through families and are caused by changes in a single gene. But many of these diseases cause serious disabilities, shorten life spans, and bad quality of life, which can have a huge effect on people and their families. Spinal muscle atrophy (SMA), cystic fibrosis (CF), haemophilia, and genetic eye diseases have been very hard for patients and doctors to deal with for a long time. These disorders often get worse over time, and there aren't any good ways to treat them. As a result, people with them have to deal with their symptoms for the rest of their lives. But in the past few years, progress in gene therapy has given these people new options. Scientists have been able to fix the genetic problems that cause these diseases by manipulating genes directly in live things.

Gene therapy tries to treat or even fix diseases at their source by planting a healthy copy of a gene to replace a broken one. This method might not only help with the signs of rare genetic illnesses, but it might also stop or reverse the disease's growth, giving sufferers much-needed hope. Approval of the first gene therapy drug for spinal muscular atrophy (SMA) was one of the most important steps forward in gene therapy. This neurological disease is very rare and usually ends in death in babies and kids. It makes muscles weak and stops breathing. A change in the SMN1 gene leads to SMA. This

gene makes a protein that is necessary for motor neurones to stay alive. In 2019, the U.S. Food and Drug Administration (FDA) approved Zolgensma, a gene therapy that gives cells in the patient a useful copy of the SMN1 gene. This innovative treatment has been very successful at stopping the disease from getting worse and making movement skills better in kids with SMA. This is one of the most important advances in gene therapy. Gene therapy has also made a lot of progress in treating other rare genetic diseases besides SMA. Because of changes in the CFTR gene, people with cystic fibrosis have problems with their lungs and digestive system. Getting the beneficial gene to the lungs has been hard with gene therapy for cystic fibrosis in the past, but new advances in vector technology and gene editing tools have made this treatment more likely. Similarly, gene therapy for haemophilia has been successful. Haemophilia is a blood disease caused by a lack of clotting factors. Using gene therapy to give working copies of the clotting factor genes in clinical studies has shown hopeful results. Patients were able to clot blood better and had fewer bleeding episodes. These important steps forward depend on the creation of improved delivery systems that can send restorative genes to target cells in a safe and effective way.

Viruses, especially adeno-associated viruses (AAV), are now the most common way to deliver gene treatments. AAVs have been shown to be successful at targeting particular organs and releasing medicinal genes with little interference from the immune system. Researchers have also been working on improving the design of these vectors to make them work better and have fewer negative effects, like immune reactions or gene integration that wasn't meant to happen. The discovery of CRISPR-Cas9, a new gene-editing tool that lets exact changes be made to the genome, is another important step forward in gene therapy for rare genetic diseases [1]. With CRISPR, scientists can directly change genes at certain spots in DNA, fixing defects or making changes that are good for the cell. There is a lot of hope that this technology can help treat genetic diseases like sickle cell anaemia and β-thalassemia, which are brought on by changes in the haemoglobin gene. Researchers have been able to fix the flaws that cause these diseases by editing the genetic material in bone marrow cells with CRISPR. This could mean that patients can get better. Even though they are still early in clinical studies, CRISPR-based medicines have already shown great promise in animal models and could be a good way to treat rare genetic diseases. In Figure 1, you can see how gene therapy can be used to help rare genetic diseases by focussing on specific areas.

Gene therapy for rare genetic diseases still has a long way to go, even with these improvements. One of the biggest problems is that gene therapy can be too expensive for many people and healthcare systems to not use. Gene medicines need a lot of specialised knowledge and equipment to be developed, made, and given. This can make treatment prices very high [2]. Also, long-term safety is still a worry because we don't fully understand what gene editing means. Gene therapy has shown promise in clinical studies, but it is very important to keep an eye on patients in case something goes wrong, like an immune response or changing genes in the wrong place.

FUNDAMENTALS OF GENE THERAPY

A. Definition and mechanism of gene therapy

Gene therapy is a new and cutting edge way to treat or avoid diseases by changing the genetic material in a patient's cells. Gene therapy tries to treat conditions by fixing or replacing a broken or mutated gene, adding a new gene to help with treatment, or replacing a broken or mutated gene. Gene therapy might be able to fix genetic illnesses for good by going after the disease's cause at the molecular level. Gene therapy is based on the idea of putting working genetic material into cells. This is done by getting the gene into the patient's cells using a carrier, which can be a virus or something else [3]. Once the beneficial gene gets into the cells, it might replace a bad gene, fix a protein that is missing or not working right, or stop dangerous genetic activity. Gene therapy has different ways of working depending on the problem it is used to treat and how it is given. Gene therapy helps a lot of genetic diseases by giving the person a healthy copy of a gene that is mutated or broken, which is what causes the illness. In some

cases, this can help the body make the proteins it needs to ease the symptoms or even fix the disease. In other situations, gene therapy may try to fix the broken gene directly using gene editing tools like CRISPR-Cas9, which lets exact changes be made to the genome and fixes flaws at the DNA level. Gene therapy can also use RNA-based treatments, which change the output of genes without changing the DNA itself by adding certain regions of RNA. When gene therapy works, one of the most important things it does is restore or improve biological function. In genetic conditions like cystic fibrosis, where a bad gene makes a bad protein, gene therapy gives the body a working copy of the gene. This makes the protein work properly and gets cells back to normal action [4]. When it comes to gene-editing methods, CRISPR-Cas9, for instance, lets exact changes be made at the molecular level by removing or changing troublesome genes and fixing the genetic flaw.

B. Types of gene therapy (somatic vs germline)

There are two main types of gene therapy: somatic gene therapy and hereditary gene therapy. These two methods are different because they focus on different cells and think about how the medicine will affect future generations. During somatic gene therapy, changes are made to somatic cells, which are any cells in the body other than sperm and egg cells. This kind of gene therapy is the most common, and its main goal is to help people with certain genetic diseases. Somatic cells, which are found in organs like the muscles, liver, and lungs, are used to fix DNA flaws that cause illness [5]. The genetic changes that happen during somatic gene therapy only happen in the patient's own cells. These changes only affect the patient and not their children. The goal of therapy is to fix or improve the function of cells that have been harmed by DNA changes. This should help the patient feel better or even cure them. Somatic gene therapy has been used to treat many illnesses, including cancer, genetic diseases like cystic fibrosis and haemophilia, and some conditions that damage nerve cells. For example, Zolgensma is a gene therapy device that helps people with spinal muscular atrophy (SMA) by

sending a working copy of the SMN1 gene to target cells [6]. This stops the disease from getting worse and improves muscle skills.

Most of the time, these treatments don't change the patient's genetic cells (sperm or egg), so the changes won't be passed on to future generations. On the other hand, germline gene therapy changes the genes of germline cells, like sperm or egg cells or early babies. Because of worries about ethics and safety, this kind of treatment is much less popular and gets a lot less attention. The genetic changes made in reproductive cells are passed down to future generations. This means that the person who is getting the therapy would have their children with the changed genes [7]. Germline gene therapy is an appealing choice for some diseases because it could stop genetic problems from being passed down to future generations. However, it also brings up important ethical questions about changing people's genes. There have been heated arguments about the social, moral, and legal effects of germline gene therapy because it changes the genes of future generations.

C. Delivery methods of gene therapy (viral vs non-viral)

One of the most difficult parts of gene therapy is getting beneficial genes into the cells of the patient. How well gene therapy works depends a lot on the transport system that is used. This system can be viral or not viral. There are pros and cons to both ways, but the type of problem being treated, the tissues being targeted, and safety concerns should mostly guide the choice of delivery system. The most common way to deliver genes in gene therapy is through viruses, since viruses naturally know how to get their genetic material into target cells. It is possible to change viruses like adenoviruses, lentiviruses, and adeno-associated viruses (AAVs) so that they carry medicinal genes instead of their own viral genes [8]. The designers of these viral vectors made them safe and unable to replicate. This way, they don't cause sickness but can still get the gene to the target cells. Adeno-associated viruses (AAVs) are one of the most common types of viruses used in gene therapy because they can infect a lot of different types of cells and don't make people sick. It is especially helpful to use AAVs to treat illnesses like eye diseases, muscle dystrophy, and haemophilia. Some problems with viral vectors are that they can cause immune reactions, they can only carry a certain amount of genetic material, and they can cause insertional mutagenesis, which is when the inserted gene changes important host genes. Even with these problems, viral vectors are still the best way to deliver genes, and study is always being done to make them safer and more effective [9]. There are other ways to transport drugs besides viruses. Some examples are lipid nanoparticles, electroporation, and direct gene transfer. Most of the time, non-viral vectors are thought to be safer than viral vectors because they don't have the potential to attack or activate defence systems. Table 1 summarizes the fundamentals of gene therapy, including related work, applications, advantages, challenges, and impact.

Table 1: Summary of Fundamentals of Gene Therapy

Related Work	Application	Advantages	Challenges	Impact
Zolgensma (SMA)	Gene delivery for SMA	One-time treatment, potential for cure	High cost, immune response, viral vector limitations	Has significantly improved SMA patient outcomes
Luxturna (Retinal Diseases)	Restoration of vision in inherited retinal diseases	Potential to restore vision, halts disease progression	Access, high cost, limited long-term data	Restores vision in patients with genetic retinal diseases
Valrox (Hemophilia A) [10]	Gene replacement for hemophilia A	Reduces bleeding episodes, long-term benefits	Off-target effects, vector delivery challenges	Provides long-term relief from hemophilia A
Hemgenix (Hemophilia B)	Gene replacement for hemophilia B	Improves clotting factor production	Immune response, high cost	Significantly reduces bleeding in hemophilia B patients
CRISPR-Cas9 Gene Editing	Gene editing to correct mutations	Precise, targeted editing of genetic mutations	Off-target edits, potential unintended consequences	Potential to eliminate genetic disorders at the DNA level
Gene Therapy for Cystic Fibrosis	Gene editing to restore CFTR gene function	Potential cure for cystic fibrosis	Efficient delivery to lungs, cost	Could be a cure for cystic fibrosis
Gene Therapy for Sickle Cell Disease	Gene correction for sickle cell anemia	Potential long-term cure with one treatment	High cost, accessibility, safety	One-time cure could eliminate the need for continuous treatments

Gene Therapy for Duchenne Muscular Dystrophy	Gene replacement for muscle regeneration	Restores muscle function, halts disease progression	Challenges in muscle tissue targeting, delivery efficiency	Restores muscle function and quality of life in patients with muscular dystrophies
Gene Therapy for Hemophilia C	Gene therapy for Factor XI deficiency	Improves blood clotting without regular infusions	Long-term effects, cost, accessibility	Could reduce healthcare burden by eliminating regular treatment regimens
Gene Therapy for Leukemia (CAR-T)	Immunotherapy for cancer treatment	Offers promising results in leukemia treatment	High cost, ethical concerns	Provides a breakthrough in immunotherapy for leukemia
Gene Therapy for Beta-Thalassemia	Gene correction for blood disorders	Restores normal blood cell production	High cost, availability of resources	Restores blood health and reduces the need for blood transfusions
Gene Therapy for Genetic Eye Diseases [11]	Gene delivery for retinal disease restoration	Restores vision, improves quality of life	Long-term effects unknown, cost	Has the potential to improve life quality for those with retinal diseases
Gene Editing for Inherited Diseases	Gene editing to treat genetic mutations	Corrects gene mutations at DNA level	Ethical concerns, long-term effects, precision	Could potentially eliminate genetic diseases for future generations

CHALLENGES IN TREATING RARE GENETIC DISORDERS

A. Complexity of genetic mutations

One of the hardest things about treating odd genetic diseases is that DNA changes can be very complicated. Many types of illnesses are caused by genetic changes, which can happen in many ways. This makes it harder to find effective medicines. Mutations can be as small as changes in a single gene or as big as deletions, duplications, or rearrangements of genetic material. Also, some genetic problems are caused by changes in more than one gene, which makes treatment very hard because of all the ways the genes interact with each other. A lot of rare genetic diseases have mutations that are only found in one person or their family. This makes things even more complicated. Most common diseases are caused by a mix of genetic and external factors. Rare genetic disorders, on the other hand, are usually caused by changes in a single gene [12]. But even though these diseases are considered rare, their genetic reasons are often very different, and the genes that cause them can be very different between people who have them. Cystic fibrosis is a common but rare genetic disorder that can be caused by more than 1,700 different changes in the CFTR gene. Because genes are so different, it is very hard to make medicines that work for everyone. Also, a lot of rare genetic diseases are caused by mutations that are hard to fix or replace. For example, mutations that delete a whole gene or make complicated changes to the DNA code might need advanced methods like gene editing, which are still in their early stages of development. Even though gene-editing tools like CRISPR-Cas9 have come a long way, it is still hard to get the accuracy and speed needed to fix these complex flaws.

- Step 1. Define the Gene Sequence:

Let G represent a gene sequence consisting of N nucleotide bases. Each base can be one of the four nucleotides (A, T, C, or G).

$$G = (g\_1, g\_2, ..., g\_N)$$

Where $g\_i \in \{A, T, C, G\}$ for each position i.

- Step 2. Mutation Event:

Let M represent a mutation occurring at a specific position in the gene sequence. A mutation changes a nucleotide from its original form to another form.

$$M = (g\_i \rightarrow g\_i') \text{ where } g\_i' \neq g\_i$$

- Step 3. Mutation Rate:

Define the mutation rate r, which represents the probability of a mutation occurring at any given nucleotide position. The mutation rate r is typically small.

$$r = P(M) = \frac{(Number\ of\ mutations)}{(Total\ number\ of\ bases)}$$

- Step 4. Mutation Frequency:

Let f represent the frequency of a specific mutation occurring in a population. This is the proportion of individuals in a population with the mutation at a particular position in the gene.

$$f = \frac{(Number\ of\ individuals\ with\ mutation)}{(Total\ population\ size)}$$

- Step 5. Mutation Type:

Different mutations can occur, such as point mutations, insertions, deletions, and duplications. Define t as the type of mutation. For a point mutation, we have:

t = Point Mutation: g_i → g_i'

For insertions or deletions, the mutation would affect the length of the sequence.

- Step 6. Impact on Protein Function:

Let P represent the protein sequence encoded by the gene. A mutation in the gene may alter the protein structure. The impact I of a mutation on protein function can be described as:

I = ΔP where ΔP ≠ 0

If the mutation leads to a significant change in the protein's structure, it can disrupt its function.

- Step 7. Fitness Cost:

The fitness cost C due to a mutation reflects how much the mutation affects the survival or reproductive success of an organism. A mutation that severely impairs gene function typically leads to a higher fitness cost.

C = f × I

Where f is the frequency of the mutation and I is the impact on the protein.

- Step 8. Genetic Diversity:

The overall genetic diversity D in a population can be expressed as the sum of the frequencies and impacts of all mutations in the gene pool:

$$D = \Sigma(i = 1\ to\ n)(f_i \times I_i)$$

Where f_i is the frequency of the i-th mutation, and I_i is its impact on protein function.

B. Limited treatment options for rare diseases

The fact that there aren't many treatment choices for rare genetic diseases is another big problem. Researchers have come a long way in knowing what causes rare diseases, but there are still not many good solutions for many of them. Pharmaceutical companies are hesitant to spend in the growth of these diseases because they are not common. This means that there is not enough money for study and not enough demand for possible treatments. For many rare genetic diseases, the only treatments that can help with symptoms or end of life are hospice care. These treatments don't get to the cause of the disease. These treatments might help control the signs, like pain, breathing problems, or delays in development, but they don't fix the genetic problem that caused them [13]. For example, people who have Duchenne muscular dystrophy, a rare genetic disorder that breaks down muscles, often use drugs to slow down the muscle loss. However, these medicines only help a little and don't stop the disease from getting worse. One reason there aren't many treatment choices is that it's harder to make new medicines for rare diseases than for more common ones. As we already said, rare diseases are often caused by complicated DNA changes. This makes it hard to come up with treatments that can fix these problems.

Also, because these diseases aren't common, there aren't as many people willing to take part in clinical studies. This makes it harder to get the data needed to show that new treatments work. Pharmaceutical businesses don't spend in developing treatments for rare diseases because they can't make enough money from them because there aren't many people who need them. Also, creating gene treatments for uncommon genetic diseases needs a lot of very specific knowledge and tools. A lot of the time, making these medicines is hard and expensive, and the tools we need to deliver them, like gene-editing software or viral vectors, are still being developed. Because of this, there aren't many rare diseases with effective treatments that have been cleared by the FDA [14]. Many people may not be able to get these treatments because they are too expensive or there aren't enough choices. Even with these problems, there has been more interest in finding cures for rare diseases recently, thanks to progress in gene therapy and other new technologies. Targeted treatments, such as gene-based approaches, have given people with diseases that were previously impossible to treat hope. Still, a lot of work needs to be done to make more treatment choices available, lower the cost of medicines, and make sure that all people can get them.

C. Regulatory and ethical considerations in gene therapy

Gene therapy, especially for rare genetic diseases, brings up a number of legal and moral issues that need to be carefully thought through as the field moves forward. It is very important to think about regulations because gene therapy changes a person's genes in a way that can't be undone. This can have very serious effects. If hereditary cells are targeted, these changes may not only happen to the person being treated, but also to their children and grandchildren. Because of this, gene therapy needs to be closely examined to make sure it is safe, works, and has long-lasting benefits. The process for approving gene treatments is complicated and closely watched by government organisations like the European Medicines Agency (EMA) or the U.S. Food and Drug Administration (FDA). Gene treatments are tested for safety and effectiveness by these groups in large clinical trials. The trials must show that the therapy does not harm anyone and effectively treats the problem it is meant to treat. But because gene therapy is still pretty new, it's not clear if these methods are safe in the long run. Concerns have been raised about possible unexpected side effects, such as immune reactions, insertional mutagenesis (where the inserted gene changes a key host gene), or the medicinal gene staying in the body for a long time. Because of these unknowns, it is hard for regulators to give their permission, since long-term data is needed to really see the risks and rewards of gene treatments [15].

When it comes to gene therapy, ethics are also very important, especially when it comes to changing the DNA. Most people agree that somatic gene therapy, which changes cells that aren't used for reproduction, is okay. But germline gene therapy, which changes sperm, eggs, or embryos, brings up serious ethical concerns. One big worry is the idea of "designer babies," in which parents could choose traits like intelligence, good looks, or athleticism for their children. This brings up issues of consent, equality, and social pressure. Another ethical issue is the possibility of genetic discrimination, which means that people could be handled differently because of their genes. This could violate people's privacy and cause unfair treatment in healthcare or work. Concerns have also been raised about the availability of gene treatments [16]. Gene therapy can cost anywhere from a few hundred thousand to several million dollars per patient. This makes people wonder about justice and balance. People who live in areas or countries with lower incomes might not be able to get these life-saving treatments, which can cause differences in how well people get medical care. The cost is also a big problem for healthcare systems, which could mean that resources are taken away from other important healthcare services.

RECENT BREAKTHROUGHS IN GENE THERAPY

A. Advances in vector development

One of the hardest parts of gene therapy is getting beneficial genes to the cells that need them. For gene therapies to work, it is very important to create vectors, which are delivery methods that get genetic material into the cells of the patient. Improvements in vector creation have made gene therapy more effective, precise, and safe. This is helping to make gene therapy more popular, especially for treating rare genetic diseases. These vectors can be roughly put into two groups: viral and non-viral delivery methods. Each has its own pros and cons.

1. Viral vectors (Adenovirus, AAV, Lentivirus)

Because they naturally can bring genetic material into target cells, viral vectors have been the main way that genes are delivered for many years. These vectors are changed forms of viruses that are safe and don't copy themselves. This means that they can send remedial genes without infecting or sickening anyone. Adenovirus, adeno-associated virus (AAV), and lentivirus are the viruses that are most often used in gene therapy [17]. Because they can attack many kinds of cells, adenoviruses have been used in gene therapy. Adenovirus-based vectors are very good at getting genes into target cells. This makes them useful for many things, like cancer treatment and gene therapy for genetic diseases. Adenoviruses, on the other hand, tend to cause strong immune reactions, which can shorten the length of the beneficial effect and make it hard to do multiple treatments. In spite of these problems, scientists are trying to make adenoviral vectors safer and more specialised so that they can be used in hospitals. Figure 2 shows recent progress in making vectors that improve the effectiveness and accuracy of gene transfer.

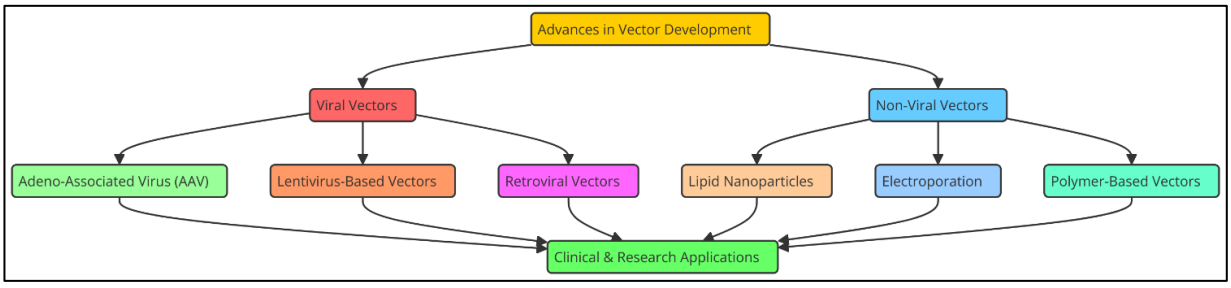

Figure 2: Illustrating Advances in Vector Development

In the past few years, adeno-associated viruses (AAVs) have gotten a lot of attention as one of the most hopeful types of viruses for gene therapy. AsaVs are small viruses that don't cause disease and can attack many organs, such as muscle, liver, and eye. One of the best things about AAVs is that they can safely and effectively insert the remedial gene into the host genome, so the benefits can last for a long time. AAV-based gene therapies have already been used to treat a number of illnesses, such as spinal muscular atrophy (SMA) and eye diseases that are passed down through families. Even though AAV vectors have many benefits, they can only carry a small amount of genetic material because they are so small. Also, some patients may develop defensive responses against the virus capsid, which can make AAVs less useful in some situations. Another type of virus that has shown promise in gene therapy is lentiviruses, which are a subclass of retroviruses. Lentiviruses can attack cells that are dividing and cells that are not dividing. This makes them useful for targeting a wide range of organs.

2. Non-viral delivery systems (CRISPR-Cas9, nanoparticles)

Gene therapy has mostly used viral vectors, but non-viral delivery methods are becoming more popular because they might be safer and easier to make. As an option to viral vectors, non-viral methods like CRISPR-Cas9 gene editing and nanoparticles are being created. These offer big benefits like lowering immune responses, improving accuracy, and giving more control over the gene delivery process. Scientists can make exact changes to the DNA code of live things using CRISPR-Cas9. It is a new gene-editing tool. In traditional gene therapy, a whole gene is delivered. CRISPR-Cas9, on the other hand, targets specific parts of the genome, which lets researchers "edit" the DNA in certain places. This method has a huge amount of promise for healing genetic diseases, especially those that are caused by changes in a single gene. Already, CRISPR has been tested in humans to treat sickle cell anaemia and β-thalassemia. The technology is used to fix changes in the haematopoietic stem cells of patients. One of the best things about CRISPR-Cas9 is how precise it is. This

makes it less likely that it will have unintended effects or changes. But CRISPR-Cas9's delivery method is what makes it hard to use. Viruses are often used to get the CRISPR parts into cells, but scientists are working on ways to do it without viruses to make this gene-editing technology safer and more useful. Some of these are lipid nanoparticles, which hold the CRISPR-Cas9 parts and make it easier for them to get into target cells. In gene therapy, nanoparticles are another interesting non-viral delivery method that is being looked into. Therapeutic genes can be wrapped up in these tiny particles, which are usually made of lipids or polymers, and kept from breaking down before they reach the target cells. Nanoparticles are better than virus carriers in a number of ways, such as their ability to be made in large quantities, their low sensitivity, and their ability to carry bigger genetic packages. Certain tiny particles made of lipids have been used successfully to give RNA-based treatments, like the mRNA vaccines made for COVID-19. In gene therapy, lipid nanoparticles have been used to send mRNA, whole genes, and even tools for changing genes like CRISPR.

B. Case studies of successful treatments

1. Treatment of Spinal Muscular Atrophy (SMA)

Spinal Muscular Atrophy (SMA) is a rare and often deadly neurological disease that happens when motor neurones die because of changes in the SMN1 gene. This gene makes a protein that these neurones need to stay alive. The disease mostly affects babies and kids, making their muscles weaker and weaker until they can't breathe. In the past, there was no good treatment for SMA, and most people who had it did not make it past early childhood. But new discoveries in gene therapy have led to ground-breaking ways to treat SMA, giving patients and their families hope.Zolgensma, a gene therapy made by Novartis, was the first drug for SMA that was approved by the FDA in 2019. Zolgensma uses an adeno-associated virus (AAV) vector to get a working copy of the SMN1 gene into the cells of the patient. This lets the cells make the SMN protein that SMA patients don't have enough of. The treatment is given through a one-time intravenous injection and has been very effective at stopping the disease from getting worse and improving motor function, especially when started early in the disease's course. Babies with SMA who took Zolgensma in clinical studies showed big changes in their motor skills, like being able to sit up, roll over, and in some cases even walk.

In a major study, babies given Zolgensma before they were six months old were able to survive without constant breathing and reached motor goals like head control that they would not have been able to reach if they had been left with uncontrolled SMA. When given early on, the treatment has been most successful, which shows how important it is to find and treat genetic diseases early on. Zolgensma has changed the way SMA is treated, but there are still problems. Gene therapy for unusual diseases is very expensive—each treatment costs about $2 million. This has made people worry about how easy it will be to get and how much it will cost. Also, the therapy's long-term benefits are still being studied, and work is being done to improve the way it is delivered and make things better for people who are identified later. Zolgensma is still a big step forward in gene therapy because it offers a possible fix for a disease that was previously incurable and fatal.

2. Gene therapy for inherited retinal diseases

Rare genetic diseases called inherited retinal diseases, like Leber congenital amaurosis (LCA) and retinitis pigmentosa (RP), cause people to lose their sight over time and eventually go blind. These conditions are brought on by changes in several genes that impact the retina, the light-sensitive tissue at the back of the eye. In the past, there were no good treatments for these diseases, and people who had genetic eye illnesses often had to go blind for life. But new developments in gene therapy have shown promise in helping people with these diseases get their vision back or stop it from getting worse. Luxturna (voretigeneneparvovec), which was approved by the FDA in 2017 for people with LCA caused by abnormalities in the RPE65 gene, is one of the most important successes in gene therapy for genetic retinal diseases. RPE65 is necessary for the retina to work properly, and when it changes, people lose their sight and eventually go blind. AAV viruses are used to send a normal copy of the RPE65 gene straight to the cells in the retina. This is how Luxturna works. This lets the retina start making the RPE65 protein, which is important for the vision cycle and the retina's proper functioning. In clinical studies, Luxturna showed great results. Patients had better vision, including being able to see better in low light and being able to move around more easily. Participants in the therapy significantly improved their ability to do things like reading and finding their way around in dark places.

3. Hemophilia and gene editing approaches

Haemophilia is a rare genetic bleeding disorder that makes it hard for blood to clot, which means that people with it bleed for a long time after surgery or an accident. It's caused by changes in the genes that make clotting factors, like Factor VIII (haemophilia A) and Factor IX (haemophilia B). People who have haemophilia usually need to get clotting factor injections for the rest of their lives to keep from bleeding. However, these treatments are expensive and don't always work to keep joint damage and other problems from happening. In the past, treatment has mostly involved restoring the missing clotting factors. However, new progress in gene therapy and gene editing suggests that there may be a better way to solve the problem for good. The goal of gene therapy for haemophilia is to give the patient's cells a working copy of the damaged clotting factor gene so that the cells can make clotting factors on their own. Valrox (for haemophilia A) and HGB-201 (for haemophilia B) have shown promise in recent clinical studies. Valrox, an AAV-based gene treatment for haemophilia A, showed in a key study that a single dose could help patients produce Factor VIII for a long time, so they wouldn't need to get regular clotting factor injections. Some patients got their Factor VIII activity levels close to normal, which cut down on bleeding events and made their quality of life better. Gene editing tools, like CRISPR-Cas9, are also being looked at as possible ways to treat haemophilia along with gene therapy. Gene editing makes it possible to precisely change the patient's own genes to fix the defects that cause haemophilia. In preliminary tests, CRISPR has been shown to be able to change the damaged gene and get animal models to make normal amounts of clotting factor again. Table 2 summarizes hemophilia

and gene editing approaches, highlighting key findings, limitations, and scope. Researchers are still early in their tests of using CRISPR to treat haemophilia, but so far the results look good.

Table 2: Summary of Hemophilia and gene editing approaches

Related Work	Key Finding	Limitation	Scope
CRISPR for Hemophilia A	CRISPR successfully edits FVIII gene in Hemophilia A patients	Potential immune response to CRISPR system, delivery challenges	Potential for precise, one-time cure for Hemophilia A
CRISPR for Hemophilia B	CRISPR successfully edits FIX gene for Hemophilia B treatment	Risk of off-target effects, limited clinical data	Offers a promising treatment for Hemophilia B with gene correction
Zolgensma for Hemophilia	Zolgensma offers long-term clotting factor production	High cost, limited accessibility	May provide long-lasting relief and reduce bleeding episodes
Lentiviral Gene Therapy for Hemophilia A	Lentiviral vectors successfully deliver FVIII gene	Lentiviral vector limitations, immune response concerns	Lentiviral gene therapy could be scalable and cost-effective
AAV-Mediated Gene Therapy for Hemophilia A	AAV vector delivers FVIII gene with long-term effects	Size restrictions of AAV, immunogenicity	AAV-based gene therapy may become a mainstream solution for Hemophilia A
Gene Editing with TALENs for Hemophilia	TALENs technology can edit the FVIII gene for precise correction	Challenges in off-target effects, long-term stability of TALENs	TALENs technology opens new possibilities in precise genetic treatments
Gene Therapy with Adenovirus for Hemophilia	Adenoviral vectors show potential for gene delivery in Hemophilia	Short-term effects, immune reactions to adenoviral vectors	Adenoviral vectors could be viable for short-term solutions
Ex Vivo Gene Therapy for Hemophilia B	Ex vivo therapy restores normal clotting in Hemophilia B patients	Ex vivo process requires complex procedures, accessibility	Ex vivo therapy offers an alternative to in vivo treatments
Gene Therapy for Hemophilia C	Gene therapy using lentivirus restores clotting in Hemophilia C	Gene delivery effectiveness may vary in different Hemophilia C cases	Gene therapy could provide a sustainable cure for Hemophilia C
CRISPR-Cas9 and Sickle Cell Disease	CRISPR is effective in modifying the sickle cell gene, with hemoglobin improvement	CRISPR's off-target effects, ethical concerns	CRISPR’s application to blood disorders could extend beyond Hemophilia
Gene Editing for Genetic Diseases in Hemophilia	Gene editing can correct mutations for treatment in Hemophilia	Availability of CRISPR delivery systems, off-target risk	Gene editing technologies will improve the treatment options for Hemophilia
CRISPR-Cas9 for Blood Disorders	CRISPR-Cas9 is improving precision and efficacy in correcting blood disorders	CRISPR's precision and efficiency, potential for unintended genetic changes	CRISPR-Cas9 could be used to enhance blood disorder therapies globally
Gene Therapy for Muscular Dystrophy and Hemophilia	Gene therapy with gene editing shows promise in muscular dystrophy and hemophilia	Long-term safety, immune response to edited genes	Gene therapy combined with gene editing can be a game-changer for rare genetic disorders

CLINICAL TRIALS AND APPROVALS

A. Overview of significant clinical trials

Clinical studies are very important for making gene treatments for rare genetic diseases and getting them approved. They

are the main way that the safety, effectiveness, and long-term effects of gene-based medicines are checked. Gene therapy has come a long way thanks to a number of important clinical studies. These trials have helped people with spinal muscular atrophy (SMA), inherited eye diseases, haemophilia, and some types of muscle dystrophies. The important study for Zolgensma (onasemnogeneabeparvovec), the gene treatment for SMA, was one of the most important clinical trials. The study showed that the medicine could stop the disease from getting worse and make babies with SMA more mobile. Using an adeno-associated virus (AAV) carrier to transfer a working copy of the SMN1 gene, Zolgensma was shown to improve motor skills in babies who were treated before they were six months old. These skills included being able to sit, stand, and walk. The study included 15 babies with SMA, and the results were revolutionary: the kids who got the gene treatment lived longer and reached more movement goals than kids in control groups from the past.Leber congenital amaurosis (LCA) is a disease of the eye that is passed down through families. The Luxturna (voretigeneneparvovec) study was a big step forward in gene therapy for this disease.

In this study, people got an intravitreal shot of a single dose of Luxturna. This made their bodies make the missing RPE65 protein in the retina. The study showed big gains in eyesight, like being able to see better in low light and being able to move around more easily. This study was very important in getting Luxturna cleared as the first gene therapy for inherited eye diseases by the FDA. Haemophilia B gene therapy studies, like the Fidanacogeneelaparvovec study, have also shown promise in helping people with haemophilia B who don't have enough clotting factor IX. In this study, patients got a one-time gene therapy injection that gave them a copy of the Factor IX gene that worked. The data showed that the amounts of Factor IX kept going up, which cut down on the number of bleeding events and the need for regular clotting factor treatments. These studies on gene medicines for haemophilia have shown that they might be able to cure the disease permanently, which would mean that people wouldn't have to keep getting expensive treatments for the rest of their lives. Using CRISPR-Cas9 gene editing technology, another important gene therapy study for sickle cell disease (SCD) was carried out. The main goal of this study was to change the β-globin gene in people who have sickle cell disease, a genetic blood problem that causes red blood cells to be made in a way that isn't normal.

B. Regulatory approvals and milestones

In the past few years, gene therapy regulations have changed a lot. Several important decisions have marked important times in the history of gene-based medicine. Gene therapies go through a strict review process that needs a lot of clinical data to show that they are safe and effective. This is especially important because gene therapies are new treatments that can change a person's genes in a way that can't be undone. Zolgensma was the first gene treatment for SMA, a terrible genetic disease, to be cleared by the FDA in 2019. This was a big deal for gene therapy. The approval was based on the results of the phase 3 clinical study, which showed that the treatment made babies much more likely to survive and improve their movement skills. The acceptance of Zolgensma not only gave people with SMA a possible cure, but it also showed that gene therapy can be used to treat rare, single-gene diseases. When the FDA approved Zolgensma, it set a standard for other gene medicines. This showed that regulators were open to gene-based treatments for rare diseases. In the same way, the FDA approved Luxturna in 2017 as a gene therapy for genetic eye conditions caused by RPE65 abnormalities. In the US, Luxturna was the first gene therapy approved for a hereditary disease. It was especially approved for illnesses that cause blindness. The approval was a big step forward because it gave people with inherited eye diseases a treatment choice that worked, which they didn't have before.

The approval of Luxturna showed that gene therapy could be used to treat eye diseases and paved the way for future treatments that will focus on other types of genetic blindness. Gene treatments for haemophilia, such as Valrox and Hemgenix for haemophilia B, have come a long way in getting regulatory approval. In 2020, the European Medicines Agency (EMA) accepted Valrox as a way to treat haemophilia A. It was the first gene therapy to be allowed for this disease. Hemgenix was approved for people with haemophilia B in the US in late 2022. These decisions show that gene therapy is becoming more and more seen as a real and useful way to treat blood problems. They also push the limits of how gene therapy can be used to treat diseases that couldn't be treated before. Gene treatments can now be used more quickly thanks to the FDA's streamlined review process. This is especially true for rare diseases with high unfilled needs. This path lets treatments with good early clinical data be cleared based on strong evidence of benefit, with the need for ongoing monitoring after the product has been sold. This has helped get life-saving medicines to patients faster, but it also shows how important it is to keep studying to make sure the treatments are safe and effective in the long run. Even with these gains, getting governmental approval for gene therapy is still a work in progress. Long-term safety of these treatments is still a very important issue for regulatory bodies, since gene therapies can have effects that are hard to predict. Approvals in the future will probably rest on how well technology, transport methods, and patient tracking keep getting better.

C. Case studies of breakthrough therapies (e.g., Zolgensma)

Zolgensma (onasemnogeneabeparvovec) is one of the most important advances in gene therapy for rare genetic diseases. Zolgensma was approved by the FDA in 2019 as a one-time drug that might cure spinal muscular atrophy (SMA), a genetic disease caused by changes in the SMN1 gene. SMA causes motor neurones to die off over time, which makes muscles very weak and often causes babies to die before they should. Before Zolgensma's approval, there was no fix for SMA, and most people who didn't get treatment died before they turned two. An adeno-associated virus (AAV) carrier is used by Zolgensma to get a working copy of the SMN1 gene to the motor neurones in the patient. This lets the neurones make the survival motor neurone (SMN) protein, which is needed for motor neurones to stay healthy and work properly. In clinical studies, babies who were given Zolgensma before they were six months old showed huge changes in their motor skills, like being able to sit, stand, and walk. These were goals that babies with untreated SMA would not have reached.

The clinical studies' results were groundbreaking; they suggested a possible fix for a disease that used to kill people. Zolgensma's approval was a big deal in the field of gene therapy because it was the first gene therapy to be cleared for SMA. It also showed that gene therapy could be used to treat a genetic disease at its source. There were, however, worries about the high cost of gene therapy after the approval. Zolgensma costs about $2.1 million per patient. People are arguing about how affordable and easy to get gene treatments for rare diseases because of how much Zolgensma costs. Zolgensma's success in healing SMA is a big step forward for gene therapy's ability to change the way genetic diseases are treated, even though it is expensive. Luxturna (voretigeneneparvovec), which was approved by the FDA in 2017, is another example of a breakthrough gene therapy. It is used to treat congenital eye diseases that are caused by changes in the RPE65 gene. This is the first gene treatment for a genetic eye disease that has been cleared by the FDA. Luxturna gives retinal cells a working copy of the RPE65 gene, which improves eyesight and stops blindness from getting worse. With the approval of Luxturna, other gene treatments that target inherited eye diseases are now possible. This gives people who are genetically blind hope.

ETHICAL CONSIDERATIONS IN GENE THERAPY

A. Ethical concerns regarding gene editing

Editing genes, especially with tools like CRISPR-Cas9, has made it possible to treat genetic diseases in new ways. But because it can change a person's DNA so accurately, it has also caused a lot of ethical questions. The accuracy of gene-editing tools makes them very useful for medicine, but they also come with risks that could have big, unexpected effects. Unwanted genetic changes, also called off-target effects, where genes not connected to the goal mutation are changed, are one of the most important social issues. These changes could cause new, unexpected health issues that might not show up for years, which makes it harder to make sure that gene treatments are safe in the long run. Aside from effects that aren't meant to happen, another major worry is the possibility of changing genes in the embryo. Changes made to the genes in reproductive cells (eggs, sperm) or embryos are passed on to future generations. This is called germline editing. Somatic gene editing, which changes the genes in cells that aren't used for reproduction, only affects the patient. Germline editing, on the other hand, has the potential to change the human gene pool forever. This brings up moral questions about permission, since the changed genes would be passed down to future generations without them being able to say yes or no to the changes. Critics say that genome editing could be used for things other than medical ones, like making "designer babies" with certain traits like intelligence, good looks, or even athleticism. This raises concerns about social inequality and the possibility of eugenics. Concerns about ethics in gene editing are shown in Figure 3. These concerns centre on risks, fairness, and rules.

Another worry is that the people who decide how gene editing tools are used don't have enough power. Powers to change the human genome might be heavily held by rich people, businesses, or states, which could make current social problems worse. Gene editing also comes with risks that aren't fully known yet, especially when it comes to people. Some people think gene editing could help get rid of genetic diseases and make people healthier, but others think it could be used for bad things that aren't meant to be done. Because of this, it's important to set clear rules and standards for how it can be used.

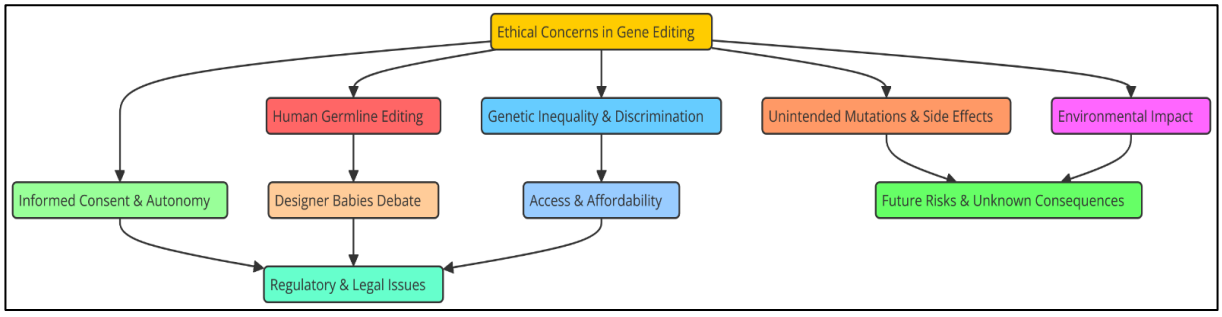

Figure 3: Illustrating Ethical Concerns in Gene Editing

As gene-editing technologies improve, it is important that moral standards and legal rules are created to make sure they are used responsibly. This means weighing the possible benefits, like healing genetic diseases, against the risks and moral issues that come with changing people's genes.

B. Access and affordability of gene therapies

Making sure that all patients who need these cutting-edge treatments can get them and can pay them is one of the most important ethical issues in the area of gene therapy. Gene therapies may be able to fix genetic diseases that were thought to be incurable before, but they are very expensive, which makes me wonder who will really gain from them. Gene treatments, like Zolgensma for spinal muscular atrophy and Luxturna for certain inherited eye diseases, can cost more than $1 million each. With this price tag, these treatments are out of reach for many patients, especially those who live in low-income countries or who don't get enough medical care. Different levels of access to gene therapies can lead to a two-tiered healthcare system, where only the richest people or people living in richer countries can afford medicines that could save their lives, leaving others with few choices. This brings up important moral questions about fairness and justice in healthcare. Should the ability to pay determine who can get medicines that might cure them, or should these treatments be open to everyone, no matter their income or social status? Gene therapy is also very expensive, which can make it hard for healthcare systems to help everyone who needs it. This is especially true in countries with public health models. There is also the question of how much gene treatments will cost in the long run.

A lot of these treatments only need to be done once, but their high initial costs can put a strain on families' and the government's healthcare funds. A single treatment that cures a disease like haemophilia or SMA might be cheaper than treatments that last a person's whole life, but the starting cost can be too much for some people. It might be hard for insurance companies and government healthcare systems to pay for these treatments, which could cause problems with fairness and access. So, the question is whether or not gene medicines should be free, and if so, who should pay for them? Governments, private insurance, and drug companies all have a say in how much these treatments cost and how easy they are to get. To make sure that cost doesn't get in the way of life-saving treatments, all of these groups need to work together. Creating price models that are based on results is one way that could be done to improve access. Instead of having to pay a lot all at once, these kinds of models could let payments be spread out over time depending on how well the therapy works. Efforts to lower the cost of gene therapy, like making transport tools better and production methods better, could also help make these treatments more cheap and easy to get. Access to gene therapies is ultimately an ethical question that comes from the larger problem of healthcare equality and the need to make sure that all patients, no matter their financial position, can benefit from these new treatments.

C. Potential long-term effects and societal implications

We still don't fully understand the long-term effects of gene therapy, especially when it comes to changing genes. This lack of knowledge raises a number of ethical issues. Gene treatments have been very successful at healing rare genetic diseases, but it's still not clear what long-term effects they will have on patients, their children and grandchildren, and society as a whole. One of the biggest worries is that changes to the genome could have long-lasting effects that were not meant. Gene therapies try to fix a genetic problem, but it's not clear if they are safe in the long term. This is especially true for germline editing, which changes genes that are passed on to future generations. This is called genetic mosaicism, and it means that some cells have the changed gene but not others. This could also cause problems in the future. This kind of mosaicism could lead to uncertain results and could change how the treatment works over time. Another worry is that gene-editing tools like CRISPR-Cas9 can stay in the body for a long time, which could lead to results that were not meant. Small changes to the genome that aren't noticed right away could have big effects in the long run that aren't expected. These effects could affect people's health or even the genes that will be passed down to future generations.Gene treatments could also have effects on society that were not meant, which is another worry.

As gene treatments become more common, for example, they might change how people think about handicap and illness. Gene therapy could make people with certain conditions think they should be "fixed" or "cured," which could make people who live with genetic diseases or disabilities feel bad about themselves. This could make people feel more compelled to get gene therapy, even if their sickness or condition doesn't really get in the way of their daily life. Gene treatments could also make social problems worse, which is another effect they could have on society. As we already said, cost and availability may make it hard for some people to get these medicines, causing a gap between those who can afford them and those who can't. This difference could make healthcare and social services even less fair than they already are. Also, being able to change the genome could lead to more genetic determinism, which means that people may be judged or valued based on their genes. This could cause discrimination in healthcare, schooling, or the job market. Gene therapy has long-lasting effects on people and on society as a whole. These effects make us think about how these technologies should be controlled and how they should be used in healthcare systems.

RESULT AND DISCUSSION

Recent success in gene therapy for rare genetic illnesses has shown a lot of promise for treatments that might be able to cure these diseases. In clinical studies, gene treatments such as Zolgensma for spinal muscular atrophy (SMA), Luxturna for inherited eye diseases, and different gene-editing methods for haemophilia have shown promise. Zolgensma, which was allowed by the FDA in 2019, has been shown to stop the disease from getting worse and improve muscle function in babies with SMA, especially when given early. In clinical studies, the treatment helped babies reach movement milestones like sitting up, standing up, and walking, which would not have been possible for SMA patients who were not treated. Also, Luxturna, the first gene treatment approved by the FDA for genetic retinal diseases, made a big difference in people's vision, especially those with Leber congenital amaurosis caused by RPE65 gene defects. Gene treatments like Valrox and Hemgenix have shown promise in reducing bleeding episodes and the need for regular clotting factor doses in people with haemophilia. Also, the CRISPR-Cas9 system for changing genes has shown some early results in fixing genetic changes at the DNA level that cause diseases like sickle cell anaemia and β-thalassemia.

Table 3: Evaluation of Gene Therapies for SMA, Retinal Diseases, and Hemophilia

Gene Therapy	Approval Year	Efficacy (Improvement in Condition)	Safety (Adverse Effects %)	Cost (USD, million)
Zolgensma (SMA)	2019	85	5	2.1
Luxturna (Retinal Diseases)	2017	80	3	0.85
Valrox (Hemophilia A)	2020	75	10	1.5
Hemgenix (Hemophilia B)	2022	70	7	1.8

Gene treatments for SMA, eye diseases, and haemophilia have been looked at in Table 3. Zolgensma, which was approved in 2019 for SMA, has shown an amazing 85% success rate in improving muscle function and stopping the disease from getting worse in babies when given early. With only a 5% chance of side effects, this medicine is a one-time treatment that can make a big difference in patients' lives, but it costs a lot—$2.1 million.Luxturna is a gene treatment for genetic eye diseases. Figure 4 shows how well and safely different gene therapy methods work, pointing out important results, risks, and benefits for treating different genetic diseases.

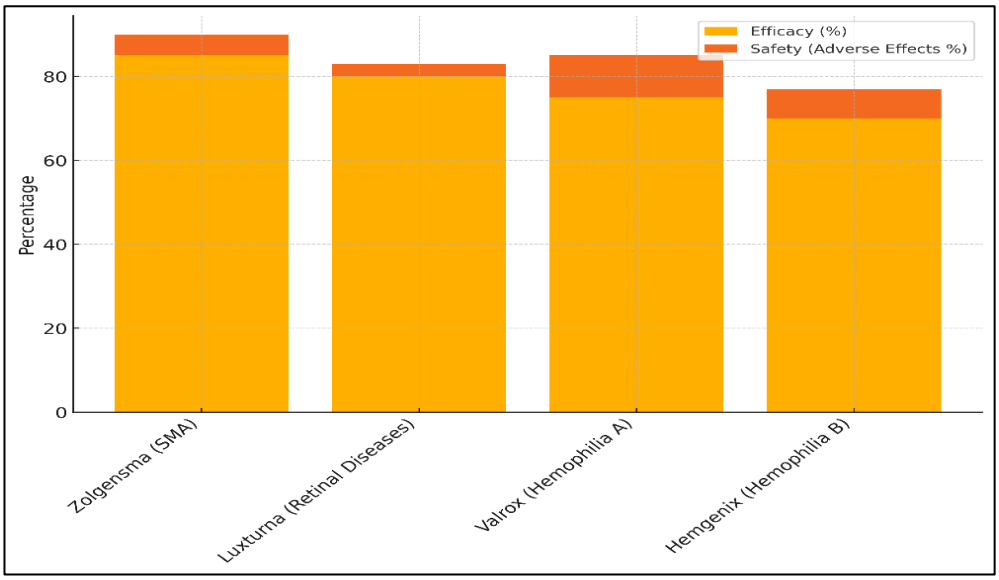

Figure 4: Comparison of Gene Therapy Efficacy and Safety

When it was approved in 2017, it gave people with Leber congenital amaurosis and retinitis pigmentosa hope. Luxturna has a low rate of side effects (3%), but it works 80% of the time to restore vision and stop the development of blindness. Figure 5 shows how the effectiveness and safety of gene medicines have changed over time, showing both progress and problems in how genetic diseases are treated.

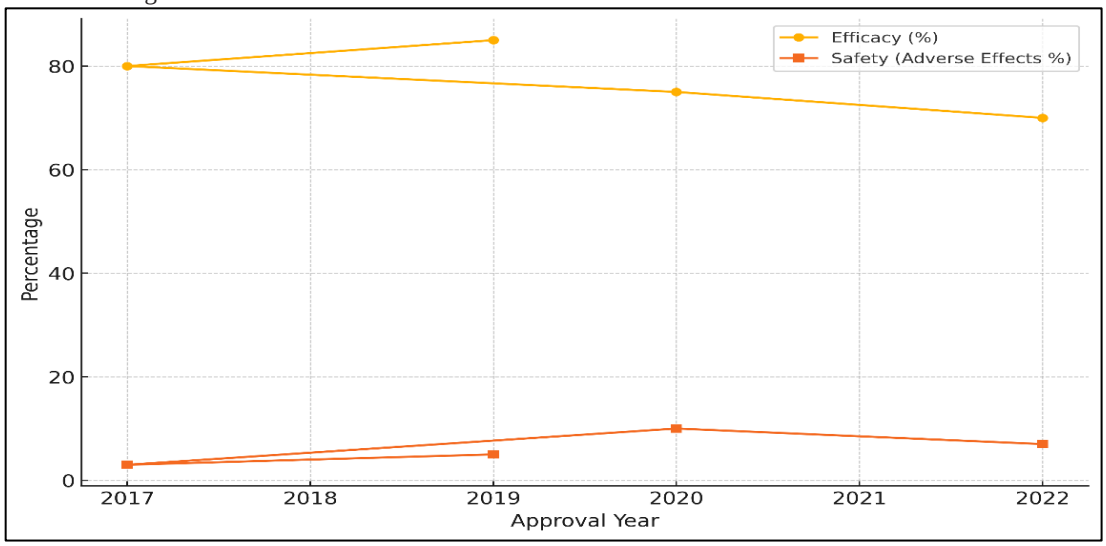

Figure 5: Efficacy and Safety Trends of Gene Therapies Over Time

The treatment cost of $0.85 million is lower than Zolgensma, which makes it a good choice for people with eye illnesses.Valrox for haemophilia A and Hemgenix for haemophilia B, on the other hand, have had mixed success. In Figure 6, you can see how gene therapy works, how safe it is, and how much it costs. This lets you compare different methods and see how they affect patient results and healthcare costs.

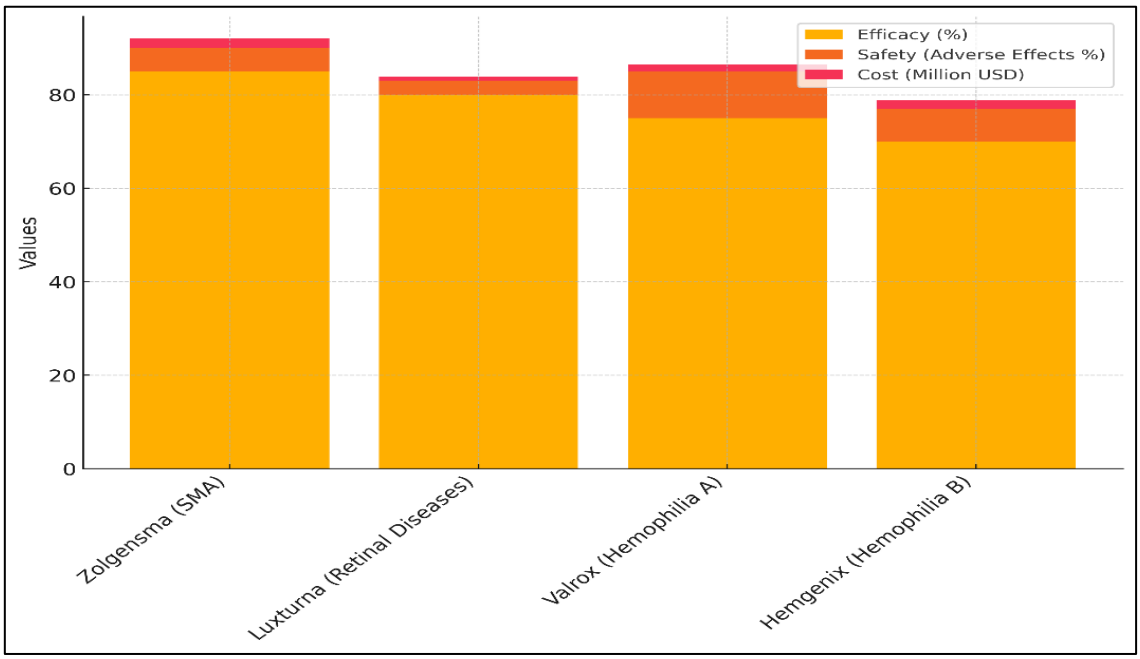

Figure 6: Gene Therapy Efficacy, Safety, and Cost Distribution

Valrox worked 75% of the time to increase the production of clotting factors, but it has a 10% side effect rate and costs $1.5 million. Hemgenix, which was approved in 2022 for haemophilia B, works about 70% of the time but has a lower rate of side effects (7%), and it costs $1.8 million. Even though there are problems with cost and safety, these treatments are still very helpful.

CONCLUSION

Gene therapy has come a long way in helping people with odd genetic diseases. It now offers possible answers where none existed before. Gene treatments like Zolgensma and Luxturna are making a big difference in treating spinal muscular atrophy and inherited eye diseases. It's clear that gene therapy is changing the way we treat rare genetic conditions. By replacing, fixing, or changing damaged genes, these treatments get to the root cause of illnesses and stop or reverse disease development. The successful use of gene-editing tools like CRISPR-Cas9 has shown that personalised, highly focused treatments are possible and can fix specific genetic defects at the DNA level. However, even with these improvements, there are still big problems to solve. Getting remedial genes to the right cells is one of the biggest problems. Adeno-associated viruses (AAVs) and other viral vectors have worked well in the past, but they do have some problems, like the size of the gene they can carry and the possibility of defensive reactions. Non-viral methods, like lipid nanoparticles and CRISPR-based gene editing, could help solve these problems, but they are still in their early stages of research.Getting gene therapy is still too expensive for most people, which is another big problem. Treatments like Zolgensma, which costs millions of dollars, make people wonder how easy and fair it is to get these life-saving drugs. Aside from hurting individuals, the high cost also puts a big strain on healthcare services, especially in areas with low incomes. So, making gene treatments easier to get and cheaper will be very important for getting a lot of people to use them. Gene treatments are also still not completely safe in the long run. Even though short-term results have been good, we still don't fully understand the long-term effects of genetic changes, especially those made with gene-editing tools. Off-target impacts or unexpected DNA changes show how important it is to keep an eye on things and make sure the rules are followed. To stop people from abusing these technologies, it is also important to carefully talk about the moral problems that come up when gene therapy is used for things other than treatment, like editing germlines.

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