**Section 1.1 - What is gene therapy?**

Modern medicine and the way we treat diseases are constantly changing. Gene therapy is one of these new forms of treatment that is used to stop or slow the progression of a disease or illness at the source (“What is Gene Therapy?”). This is done by changing some of the genetic makeup in a person. This can either be done by the replacing, adding, editing or through the inactivation of a **gene** (“What is Gene Therapy”). You might be asking yourself, “What even is a gene?” Well a gene is a unit that is formed out of DNA. A single human can have anywhere from about 20, 0000 to 25, 000 different genes. Genes are responsible for some of the traits that are passed down from generation to generation. When a person is born, they have a duplicate of every gene, one gene coming from their mother and the other gene coming from their father. The same form of the gene with slight variations in their DNA sequences are known as **alleles**. These slight variations are what contribute to a person’s uniqueness. Genes also can be special instructions to create proteins. Now scientists have found a way to treat diseases by actually changing the diseases. Some of the diseases that Gene Therapy can treat are cancers, diseases that are infectious and diseases that are genetic (“What is Gene Therapy?”). Although this is a new study and there are still studies being done the results from these studies are very promising.

**Section 1.2- History of Gene Therapy**

Gene Therapy is an extremely popular topic in both the medical and science community today. The potential for gene therapy was first written about in a scientific paper written by two American scientists named Theodore Friedmann and Richard Roblin in the early 1970’s. (Mitha, 2021). In their paper they discussed not only the potential for gene therapy but also some of their fears about the potential drawbacks in gene therapy (Mitha, 2021). Their reasons were mainly because of the lack of knowledge they had about gene therapy and the possible side effects that gene therapy could have on a person (Mitha, 2021). The first trial of gene therapy was done on Ashanthi De Silva who was only four years old at the time (Mitha, 2021). Ashanthi had a genetic disease where she was missing a crucial enzyme called ADA or adenosine deaminase (Mitha, 2021). This disease caused her to have an extremely weak immune system where her getting sick could potentially cost her, her life. She was treated by using an ADA copy and was introduced by using a vector (Mitha, 2021). This treatment was successful and helped her live a healthy life without constantly being afraid of getting sick (Mitha, 2021). Not only was her treatment successful but it opened up the door for many other trials to be ran to further test the potential of treatment for other diseases.

**Section 1.3- How is gene therapy done?**

Gene therapy works by inserting genetic material to make up for genes that are not normal or to help make a protein that will be helpful in slowing or curing a certain disease. When a gene is directly put into a cell the gene does not operate correctly (*How does gene Therapy Work?: MedlinePlus Genetics* 2020). In order for the inserted gene to function properly the gene is carried through a **vector** (*How does gene Therapy Work: MedlinePlus Genetics 2020)*. A vector is specifically created to deliver a gene and can be in the form of a virus which infects the cell (*How does gene Therapy Work?: MedlinePlus Genetics* 2020). You can think of a vector as the UPS or delivery driver for **DNA**. The virus is altered in a way that prevents the human that is infected from actually contracting that disease. The vector is inserted into the patient through a couple of different ways. The first way is through the injection of an IV (*How does gene Therapy Work?: MedlinePlus Genetics* 2020). The IV is injected into a particular tissue and is received by the live cells (*How does gene Therapy Work?: MedlinePlus Genetics* 2020). Another way that the **vector** can be put into the body is by taking out a section of an individual cells and inserting the cells with a virus in the medical laboratory (*How does gene Therapy Work?: MedlinePlus Genetics* 2020). After the virus is inserted into the cell, it is put back into the patient usually producing a protein that functions properly (*How does gene Therapy Work?: MedlinePlus Genetics* 2020). There are still some difficulties when it comes to the application of gene therapy as an actual treatment *(How does gene Therapy Work?: Medline Genetics 2020).* Doctors and scientists are searching for improved ways on delivering the modified genes to a cells and ways to make sure that the body is able to manage these genes (*How does gene Therapy Work?: MedlinePlus Genetics* 2020).

**Section 1.4 - Risks of Gene Therapy**

Just like any other treatment or medication there are some possible side effects and risks to using gene therapy. These risks can be dependent on the kind of gene therapy a person is receiving, what specific vector that is being used, and the way in which the gene is inserted (“What is Gene Therapy”). Some of these potential side effects could include a damaging immune response, problems from the new gene that was inserted which can result in mutations in the **DNA**, and the unanticipated stimulation or inhibition of a gene (“What is Gene Therapy”). There can also be complications with the way gene therapy is put into the body whether that is through the IV or removal and reinsertion of the cells back into the body (“What is Gene Therapy”).

**Section 1.5- Gene Therapy Gone Bad**

Although gene therapy was successful in the case of Ashanti De Silva and many others, there were also times where gene therapy had not only negative effects on a person but were fatal. One of the first cases that made the risks of gene therapy come to light was the case of Jesse Gelsinger. In the year 1999 at the age of 18 year old, Gelsinger, was accepted into a clinical trial for a disease that was known as ornithine transcarboxylase deficiency or OTC at the University of Pennsylvania (Parker, Forester, Lister, Thi Tu, & Schneegurt). This disease can cause ammonia to be stored in the blood (Parker, Forester, Lister, Thi Tu, & Schneegurt).

This storing of ammonia is because of their body’s inability to regulate and process the ammonia (Parker, Forester, Lister, Thi Tu, & Schneegurt). Just a couple days after receiving the treatment Jesse had died due to a huge response from the immune system (Parker, Forester, Lister, Thi Tu, & Schneegurt). This response was sent to the **vector**. Before Gelsinger’s case the side effects from gene therapy and the major responses from the immune system were not really a cause of concern for scientists and doctors (Parker, Forester, Lister, Thi Tu, & Schneegurt). Even though Gelsinger was the first to die from gene therapy there were other people who had experienced negative side effects from gene therapy along with the death of a couple of monkeys that were used as testers in the trials (Parker, Forester, Lister, Thi Tu, & Schneegurt). Some of the side effects that the monkeys experienced that ended up being fatal was clotting and swelling of the liver (Parker, Forester, Lister, Thi Tu, & Schneegurt). It was found that after Jesse’s death that the scientists involved with this case were aware that this was a possibility and failed to inform Jesse or their family of this risk (Parker, Forester, Lister, Thi Tu, & Schneegurt). Gelsinger’s case not only caused this clinical trial to be put on hold but also a lot of other clinical trials that were going on during the same time to be stopped all over the country. The way trials were being ran began to be investigated and new procedures were put into place, most of which are still in place today.

**Section 1.6- Changes in Gene Therapy Clinical Trials**

Gelsinger’s case has forever changed the way clinical trials were and are ran for gene therapy. The United States Food and Drug administration immediately halted the trial Gelsinger was involved in when he died (Sibbald, 2001). Some of the concerns that were brought to the attention of the FDA was the lack of sufficient training and full disclosure of risks along with consent of the patient being tested (Sibbald, 2001). In order to further protect the patients that take part in these clinical trials a couple of new procedures were put into place shortly after Gelsinger’s death. These programs were called *Gene Therapy Clinical Trial Monitoring Plan* and the Gene *Transfer Safety Symposia* (Sibbald, 2001).

One of the issues that occurred with monitoring before the death of Gelsinger was that they made sponsors of the clinical trial be the people who were responsible for disclosing the risks to the patients (Sibbald, 2001).This of course caused a problem because it could affect whether or not an institute was allowed to use certain products and funding for the trial (Sibbald, 2001). For example, one of the directors at the institute that Gelsinger received gene therapy also owned part of a company that gave money to the institute of Pennsylvania (Sibbald, 2001). Because of this, information was not disclosed to the patient until after the trial was completely finished (Sibbald, 2001).

The *Gene Therapy Clinical Trial Monitoring Plan* was an attempt to avoid things like this from happening again. This plan forces researchers to fully inform the patient of all of the possible risks before the clinical trial start (Sibbald, 2001). It also gave the researchers a specific list of things that need to be reported to the FDA if they occurred during the trial (Sibbald, 2001). This plan also banned researchers and people that were involved in the trial from owning or being a part of companies that had a part in funding the clinical trial (Sibbald, 2001). This would hopefully help prevent conflicts of interests from happening in these situations.

The *Gene Transfer Safety Symposia* was created to help scientists and researchers come together and share information about some of the short comings and risks that they discovered in their trials (Sibbald, 2001). The problem with this program was that most of the time scientists and researchers are hesitant to give out negative information about their trials because it could impact their future rights and allow another trial to be successful and market a money-making product (Sibbald, 2001). Geslinger’s father and lawyer for the case argued that this program was not enough and did not protect the patients involved in these clinical (Sibbald, 2001). They wanted to have an independent group separate from the clinical trials whose only job was to watch over clinical trials and will specifically look for any issues or rule violations in these clinical trials (Sibbald, 2001).

Currently there are three organizations that are in charge of overseeing these clinical trials. These three comittees are the Recombinant DNA Advisory Committee or RAC, the FDA, and the Office of Human Research Protection or OHRP (Parker, Forester, Lister, Thi Tu, & Schneegurt). The local and federal agencies communicate with each other and the board of review to make sure that the proper procedures are being followed although these protocols are enforced locally (Parker, Forester, Lister, Thi Tu, & Schneegurt). Gene therapy is now one of the most heavily reviewed and protocol enforced therapies especially in comparison to other therapies that are being tested (Parker, Forester, Lister, Thi Tu, & Schneegurt). Even though the safety and well-being of the patient is definitely the main priority some people think that some of these regulations and protocols for gene therapy are too strict and prevent gene therapy research from moving forward (Parker, Forester, Lister, Thi Tu, & Schneegurt).

**Section 1.7- Morality Concerns**

Gene therapy not only raises concern with the risks and side effects but also raises concerns in regards to morality. One of the moral concerns is changing the genetic make-up of a person and the possibility of doctors and scientists not only using gene therapy for genetic disorders but also using it as in elective form of “therapy” to get rid of certain traits that some people might think unpleasant (Parker, Forester, Lister, Thi Tu, & Schneegurt). An example of this could possibly be done in an unborn child if an “unwanted” genetic trait is found in a fetus before they are born (Parker, Forester, Lister, Thi Tu, & Schneegurt). As you can predict, this can cause a lot of conflict within a person’s moral compass and brings up another issue of consent. Some of the other important questions that people have asked are who should be in control of regulating these protocols? How much should it cost? and should gene therapy be used as an elective procedure (Parker, Forester, Lister, Thi Tu, & Schneegurt)? There are also concerns of unexpected and negative results are responses that can be accidentally passed on to another generation (Parker, Forester, Lister, Thi Tu, & Schneegurt).

**Conclusion**

Although the results and research that have been done in the field of gene therapy for the treatment of genetic disorders so far has been very encouraging and promising for the future it still poses a lot of possible risks. These risks have caused a lot of regulations and clinical trial oversight at both the local and federal level. Further research and trials need to be done in order to make this therapy safer for the patient and more efficient. The questions raised by moral concerns also need to be discussed and answered before gene therapy is more widely used.

**Vocabulary**

1. **Gene**- a unit made up of DNA that is responsible for carrying traits from generation to generation
2. **Allele**- the other form of a gene that is slightly different and is found in the same location on a chromosome
3. **Vector**- a transporter in DNA that carries genetic material

1. **DNA**- a material that constantly replicates in almost all living things, stores and carries materials for the gene

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