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# Human Genetic Intervention: How Far Should We Go?

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Hon 49I (Senior Honors Seminar)  
Mentor: Dr. Zoia Stoytcheva

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*Since the beginning of time, man has treated illness and disease with natural remedies. With the advancement in knowledge and technology, new kinds of treatments have entered the realm of medicine—namely genetic intervention. This paper aims to help determine where we should take our development of this technology. In each branch of genetic intervention—whether it be gene therapy, prevention, remediation, or enhancement—issues of ethics, socio-economics, and religion have casted a cloud over the technology, hindering its progression. In contrary, the power to improve the quality and save the lives of individuals affected by genetic diseases does not fail to fuel the fire behind advancement in research. From successful cases like Elisabeth Hartmann and Molly Nash's to cases with undesirable outcomes like Jesse Gelsinger's and the adenosine deaminase French gene therapy trials', one thing stood out in the mix to help us determine where we should draw the line that should not be crossed—intent. Three areas of genetic intervention seem to not cross that line: gene therapy, prevention, and remediation. However, based off intent, enhancement proves to be the most controversial branch of genetic intervention and gives insight as to where exactly that line should be drawn.*

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## Genetic Intervention

When diseases occur due to missing or dysfunctional proteins, scientists look to the central dogma of biology as a means to cure these diseases. This novel approach to medicine—gene therapy—is the most common kind of genetic intervention, and seeks to remedy the etiological source of genetic disease

directly. Gene therapies traditionally involve the introduction of genetic material into cells with the aim to regulate a gene's expression and restore the levels of gene product needed for proper bodily function (1).

The idea of gene therapy was first discussed in a 1972 paper in the journal *Science* (2). Since then, the field of genetic intervention has made some significant strides, (e.g., Elisabeth Hartmann and Molly Nash) and as well as some setbacks (Jesse



This paper was written for the senior Honors Seminar instructed by Dr. Zoia Stoytcheva. As a senior studying Molecular Biosciences and Biotechnology, the ethics behind genetic intervention strategies is a topic that proves to be increasingly important. This essay aims to discuss the early stages of genetic intervention, the trials and triumphs that were faced, the impact its had on history, as well as the implications it has for the future. Writing this paper allowed me to familiarize myself with different case studies that provide the basis of many arguments for each side of this topic. This is especially important for me as I enter the first year of the Developmental and Reproductive Biology Master's program at the John A. Burns School of Medicine, working on a gene therapy project. Following the completion of my master's degree, I plan to pursue a PhD in Stem Cell Biology where I can use gene therapy techniques that I have learned and apply it to regenerative medicine.

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Gelsinger and the adenosine deaminase therapy French trials). This paper will discuss these case studies and a couple others to analyze the impact gene therapy has had on history, and its implications for the future. The goals of gene intervention can be broken up into four distinct categories; therapy, enhancement, prevention, and remediation (3).

## Therapy

Of the genetic intervention categories, gene therapy seems to be the most widely accepted among the general population and the medical field. In 1990, the first gene therapy trial was reported in the United States (4). Ashanti DeSilva was a four-year-old suffering from Severe Combined Immunodeficiency (SCID) caused by adenosine deaminase (ADA) deficiency. ADA deficiency is a monogenic disease, meaning that the deficiency is the result of the lack of function of a single gene located on the long arm of chromosome 20 in humans (5). Ashanti's treatment consisted of removing white blood cells from her body, treating the cells *ex vivo* with the functional copy of the gene, and then returning the transfected blood cells back into her body. Ashanti survived treatment and regained some immune function. However, the effectiveness of this trial was debatable because Ashanti was given enzyme replacement therapy (polyethylene glycol 273 adenosine deaminase [PEG-ADA]) simultaneously with the gene therapy (6). Similar trials that followed in France took an unexpected turn when two children who underwent the therapy developed leukemia. Doctors treated the leukemia and successfully stopped its proliferation, but the event casted a shadow on the safety of gene therapies (7).

In 1999, the worst-case scenario for gene therapy came to a realization. Jesse Gelsinger suffered from a rare metabolic disorder called ornithine transcarbamylase (OTC) deficiency. OTC deficiency occurs when a person lacks the gene encoding for a liver enzyme responsible for the removal of excess nitrogen from amino acids and proteins (5, 6, 8). Despite the disorder, Jesse could survive without gene therapy. His deficiency was under control with a low protein diet mixed with oral medication of 32 pills a day. Jesse was told that the study he would enter at the University of Pennsylvania would not benefit him, but was for testing the safety for treatment of babies with a fatal form of his disorder. Jesse, however, saw it as hope that he may one day stray away from the bothersome medication reminders, indulge in a less restrictive diet, and help the babies along the way. Jesse's treatment consisted of an adenovirus injection containing the corrected gene. Previous tests of this same therapy at the same dosage were done on mice, monkeys, baboons, and one human patient. Side effects included flu-like symptoms and, less prevalently, mild liver infections, which cleared up without treatment. Jesse, however, suffered a severe immune response that resulted in multiple organ failures: lung failure, abnormal blood clotting, kidney

failure, and brain death (9). Jesse's death was the first recognized and recorded death due to gene therapy.

Despite Jesse's tragic death, gene therapy has continued to progress in safety and effectiveness. In 2015, the United Kingdom approved a gene therapy for mitochondrial diseases, metabolic disorders caused by defective mitochondrial genes. Because all children inherit their mitochondrial DNA from their mothers, a single case of mitochondrial disease can propagate throughout a family and affect future generations. (10). Mitochondrial donation is the process of transferring a nucleus from a fertilized egg into an enucleated egg, resulting in a chimeric embryo comprised of genomic DNA from two parents and mitochondrial DNA from a third. This process replaces the defective mitochondrial DNA with functional copies from the donor (11), which is a different kind of gene therapy because it deals with therapeutics targeting germline cells rather than somatic cells (12).

In 2015, two gene therapy trials occurred in which the 44-year old CEO of a biotech startup, BioVida, underwent gene therapy to reverse aging. Elizabeth Parrish stated that she underwent two gene therapies in Colombia to bypass the regulations set by the U.S. Food and Drug Administration. One therapy introduced follistatin, an inhibitor of myostatin, which has shown to increase muscle mass in animal studies. The other was an intravenous dose of modified viruses to introduce genetic material to code for telomerase, an enzyme known to increase telomere lengths. Her goals were to increase her muscle mass and telomere lengths in her cells to reverse aging (13). Six months after undergoing the procedure, Parrish had reported that the procedures reversed 20 years of normal telomere shortening, increased muscle mass, and decreased intramuscular fat confirmed by HEALES (HEalthy Life Extension Company) and SpectraCell (14).

## Prevention

The development of cheap and efficient genetic sequencing has paved the way for another kind of genetic intervention—prevention. Genetic testing has made it possible for individuals to better understand their risk of developing a disease or passing on a genetic disorder to their children. 23andMe is a personal genomics and biotechnology company. Companies like this make it possible for individuals to get genetic testing done to see if they are prone to, carry an allele for, or possess any hallmarks associated with a genetic disease or disorder. Individuals can get tested to see if they have alleles of genes that may increase the risk of developing cancer and take the necessary preventative measures to mitigate that risk, including routine preventative diagnostics and changes in lifestyle (15). A more powerful, and controversial, application of genomic sequencing involves sequencing the genes of in-vitro fertilized embryos and choosing desirable embryos for implantation. This was

the case for Elisabeth Hartmann's little brother. Elisabeth Hartmann, who was suffering from Fanconi anemia (a disease that prevents the production of healthy blood), desperately needed a bone marrow transplant. Luckily, Michael, her baby brother, was born just in time with no Fanconi anemia and was a close genetic match. Or was it lucky? Elisabeth and Michael's parents met with a genetic counselor and went through the process of pre-implant genetic diagnosis (PGD) (16). PGD is a process in which a single cell from an embryo is taken at the blastocyst stage and analyzed to see if the gene of interest is normal and if the child would have bone marrow suitable for transplant (17).

The Hartmann family is not the only one to benefit from PGD technology. Molly Nash was born with no thumbs, no hip sockets, two holes in her heart, and deaf in one ear. Molly suffered from the same condition as Elisabeth, Fanconi anemia; only, in Molly's case, the disease would have likely lead to bone marrow failure and leukemia. Molly was only expected to live up to 10 years. When Molly's condition took a turn for the worst and a bone marrow match could not be found, her parents took matters into their own hands. They used PGD to have an unaffected son, Adam, that was also a bone marrow match (15). Similarly, Abe and Mary Ayala decided to do the same thing when they needed help for their daughter Anissa, who was suffering from myelogenous leukemia. They had a daughter through PGD, Marissa, that was disease free (from myelogenous leukemia) and a suitable donor (16).

## Remediation

In addition to technology for children with genetic diseases, steps can be taken even earlier than childhood in this next category on this genetic intervention spectrum—remediation. Let's say that, through PGD, we determine an embryo would have developed into a child with less-than-normal cognitive ability or increased aggression. Steps can be taken to alter the gene responsible for an undesired phenotype to restore its normal expression and function. This was a hypothetical category described by Walters and Palmer in 1997. However, science has taken large strides since then (18). In 2014, 23andMe patented polymorphisms associated with Parkinson's Disease (19, 20). With this information, genetic testing of an embryo can indicate the risk of the child developing Parkinson's Disease later in life. Theoretically, these polymorphisms can be corrected via currently available gene editing technologies such as zinc finger nucleases (ZFN), transcription activator-like effector nucleases (TALEN), or CRISPR/Cas9 system (21, 22).

## Enhancement

Enhancement is the category of gene therapy that receives the most scrutiny because, unlike the other categories, there

is nothing wrong with the organism before the genetic intervention. Human enhancement is the process of genetically engineering an organism to have higher-than-normal levels of a beneficial gene product or ability. This category, like remediation, is a hypothetical one since technology has not been deemed safe enough yet to perform enhancement procedures (3). A primary example of human enhancement is the idea of selecting for or engineering an individual to have increased musical or athletic ability. With the rise in genetic testing and the increasing amounts of gene patents, it is only a matter of time where cognitive genes are mapped and recorded.

Paul Knoepfler wrote a book entitled, "GMO Sapiens: The Life-Changing Science of Designer Babies." In this book, Knoepfler talked about a proposition of a "Build-a-baby" tool through 23andMe that would allow genome mapping with the intention to doctor mate selection in a way to create babies with desired phenotypes (23). His proposed tool has implications for eye and hair color, height, or even metabolism—essentially designing babies. This is not so out-of-this-world as it seems to be. According to the California Cryobank main website, the required information and criteria for sperm donation is as follows: "must be at least 5'9" or taller, between 19–38 years old, attending a 4-year University or holding a Bachelor or Advanced Degree, good health" along with residency requirements (24). To a smaller extent, sperm banks are already doing what this build-a-baby tool intends to. By limiting the applicant pool, they are selecting for desired phenotypes (and genotypes) used for in vitro fertilization (IVF), like height and intelligence.

## Discussion

There are many views for and against gene therapy. The primary concern stems from the method of therapy. Viral therapies, as well as non-viral, have seemingly random insertions. This is concerning for many because a random insertion means that there is a possibility of interrupting a gene needed for survival. The only thing that could address this concern is an improvement in integration technologies. In addition to random insertion, another common fear regarding gene therapy is unexpected effects. As in the case of Jesse Gelsinger, his death was of causes not seen in previous trials, including one trial on a human. In addition to Jesse's case, the ADA gene therapy French trials also made the genetic intervention field look dangerous to the general public when patients developed leukemia following gene therapy. However, from the scientists' and doctors' points of view, this outcome may mean that more preliminary experimentation is required before they reach the clinical trial stage. In a study tracking the amount of approved gene therapy trials worldwide, results showed that the number of approved cases of gene therapy steadily rose from 1989 to 1999 and then dropped immediately following 1999 until

2003, implying stricter standards are being held when approving gene therapy trials (25).

Contrary to Jesse Gelsinger's death, many hold the stance that gene therapy can save lives. This is the case with Elisabeth Hartmann, Molly Nash, and Anissa Ayala. If it had not been for genetic intervention technology, none of these girls would be alive. From the PGD to determine the genetic fate of their unborn siblings to the bone-marrow transplants and white blood cell treatments, the power of genetic intervention seems to win over the hearts of many impacted by the tragedies associated with genetic diseases. The American Society of Clinical Oncology uses preventative measures like genetic testing to determine cancer susceptibility in patients (15).

The issue of ethics, however, arises when PGD comes into play. Could genetic testing result in the government stealing our genetic information? Can we trust that they or private companies are handling our genetic material responsibly? Is it ethical to have a child for the sole reason of saving another? Could this affect the identity of the child? One argument is that the PGD child may feel that their sole purpose of existence was to save the life of their sibling instead of leading a life of their own. They may feel that if their sibling were not sick, they would not exist. In contrast, others argue that this gives them a unique bond between the siblings and that the PGD child born can be happy to know that they saved their siblings life. This is true in the case of Marissa Ayala. In an interview for Press-Telegram, Marissa responds to the question of what she has planned after college graduation at 23 years old:

Well, what now is, I'm graduating from Cal State Long Beach. I couldn't be happier, and I'm making my own goals and setting my own aspirations. And, yes, even though I saved my sister's life and I'm so happy that she's here with us today, I have a separate life besides this story. (26)

There is also the religious point of view: gene therapy or genetic intervention is "playing God" or tampering with God's work (27). More contemporary members of religious groups argue that God gave us the knowledge to understand our genetic makeup, and therefore we have a right to intervene. Essentially, God helps those who help themselves. In the Ten Commandments, it states, "Thou shalt not kill." Members of religious groups argue that you are committing a mortal sin by killing embryos. Opposing arguments state that an embryo is not a human being yet, and therefore it is okay for them to be sacrificed (24).

The economy has a tremendous play on this topic, more specifically socio-economic standing. Arguments against genetic intervention state that technologies such as gene therapy and preventative technology can only be available to members of higher classes. Due to expensive procedures and lifelong medications and therapies, some argue that the wealthy mem-

bers of society can be healthier and have access to the technology. This would cause an even more massive socio-economic rift in society. Opposing arguments state that the genetic intervention field can be helpful to the economy. Drug sales and therapies, in addition to an increased job opportunity, could be a good economic boost.

There are social views that are associated with the genetic intervention, specifically regarding the types of cells are being treated. Many of the case studies introduced in this paper are of genetic intervention technologies targeting somatic cells (i.e., blood cells, bone marrow). In the case of the UK approving mitochondrial donation procedures, genetic intervention has taken a giant step in moving in the direction of germline cell intervention. Is this a good thing, however? Some argue that it is not right to change genetic information in cells that will impact the next generations (28). However, many agree with the UK and their choice in approving the technology to cure an otherwise fatal and incurable mitochondrial disease (29).

With this technology to make humans better from a diseased state, one question remains to be answered: *Where does better stop?* Human enhancement is the last genetic intervention on our list and serves to be a category well disputed against. In opposition to enhancement, the unethicity of enhancement lies in its intent. Human enhancement aims to better an organism beyond its normal, healthy state, while gene therapy aims to fix something that has malfunctioned. With how expensive this kind of technology would be, the socio-economic issue arises again. The problem of class standing and availability is a prevalent fear among the public.

Supporters of human enhancement state that it has been around longer than we think—it just has not been genetic. For example, plastic surgery procedures increased to 17.1 million cosmetic procedures in 2016, a 3% increase from the year prior (30), which hints at the increasing acceptance of plastic surgery in the US. Another example is fertility treatments for couples wanting to undergo IVF (31). Furthermore, office workers drinking caffeine or the use of meditation, fish oil, or exercise for mood can also be seen as an enhancement (32). So where do we draw the line?

## Conclusion

The field of genetic intervention is filled with cases that prove both the practicality of the field as well as the dangers. From cases like the Hartmann's, Nash's, and Ayala's to cases like the Gelsinger's and the French trials, genetic intervention technology has shown the power it holds to impact the lives of people who are affected by genetic diseases. With all the ethical, economic, and social stances associated with the technology, I think that one thing remains the most important—intent. I believe that genetic interventions like gene therapy, genetic prevention, and remediation, ethically, should have the most

attention paid to in current research. The intent to better the life of an individual who is impacted by a genetic disease proves to surpass the ethical dilemmas associated with religion and social views. The danger of gene therapy trials is concerning, however stricter and more thorough requirements for clinical trial entry should be enforced to lessen the death count on the genetic intervention reputation. In time, research will further our understanding of the human anatomy and our genetic origin, which will open the doors to human enhancement. While ethical reasons stand in the way of the development of enhancement, I believe that research should still be conducted to define that line that should not be crossed so that we know how far we should go.

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