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GENE THERAPY- ETHICAL AND LEGISLATIVE RESPONSE

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***Abstract*-- Nature has endowed man with different abilities. Man has no role in deciding what traits he is born with and perhaps rightly so. While earlier man bore a fatalistic attitude towards the abilities and disabilities he was born with, the story today is quite different. The rapid advancement in the field of genetics has made it very clear that gene is the basic physical and functional unit of heredity. Genetic revolution has however added much astuteness in human beings that they are not powerless against their genes. With the power of gene therapy, it is now possible to correct genetic disorders that a person is born with the help of somatic cell and germ-line engineering. Among the two, Germ- line Interventions has been surrounded by controversy due to the fact that the alterations made in the DNA of the zygote are inheritable and will affect the future generations of the recipient. Since it is germ-line engineering that is the subject of much controversy, this research will confine itself to studying the promises and pitfalls of this technology along with their ethical and legal dimension.**

Keywords: Gene therapy, Somatic Cell, Germ-Line Engineering, DNA, Ethical

INTRODUCTION

Man is one of the million species that has inhabited this planet. Yet, man is different from all the other species because he has realized the immense power that he holds over nature. He has realized that not only can he interfere with nature but also influence it. Reproduction is one of the areas where man has time again tried to control the outcome for various reasons. After successfully manipulating reproduction in plants and animals, his attention has now moved on to himself. The idea of eugenics or selective mating has been around for centuries. It was Plato who first wrote about it in his work The Republic, when he stated that "the best men must have intercourse with the best women as frequently as possible, and the opposite is true of the very inferior."[1] This idea of selective mating to produce the highest quality offspring was put into practice by Hitler who persecuted millions of innocents to achieve his own twisted ends. Today, in light of advanced research in bio- technology we have been confronted with the concept of gene therapy which on one hand offers the chance of eliminating debilitating weaknesses in the human constitution but on the other remind us of the same horrors that the Nazis had inflicted upon the world in their desire to achieve a 'superior' race.

Meaning : Gene Therapy is the process by which genetic material is introduced into human beings for the purpose of altering the expression of particular genes. These alterations are done with the aim of curing, treating or preventing some disease or disability. Gene Therapy involves two strategies:

1. Gene addition
2. Removal of harmful gene by antisense nucleotide or ribozymes[2]

The genetic interventions are of two types. They are distinguished on the basis of the type of cells that they target. They can either somatic (body) cells or germ (egg and sperm) cells. In somatic engineering, only the somatic cells are targeted and the alterations so made remain confined to the recipient and are not

1. Randy Moore, *Evolution* 144 (2006)
2. Meiligan R,"The basic science of Gene Therapy" 260 *Science* 926-32

passed on to the future generations. Ashanti De Silva was the first person to be successfully cured of severe combined immune deficiency (SCID) by way of somatic gene engineering.

In the second type of genetic engineering, it is the germ cells that are altered hence it is called as germ-line engineering. Germ –line engineering has been surrounded by controversy due to the fact that the alterations made in the DNA of the zygote are inheritable and will affect the future generations of the recipient. It is important to state here that germ-line engineering in humans is still in stages of infancy. Gene Therapy has been used successfully to breed large animals capable of producing therapeutic proteins in their milk, such as insulin or those that fight cancer.[3] It is also important to distinguish here between Gene Therapy and gene enhancement. If genetic engineering is done to cure or prevent a medically unacceptable condition, then it is called therapy, while if the aim is to enhance a function or property of the body then it is labeled as enhancement.[4] Somatic cell engineering has been more acceptable due to the fact that it aids in improving the quality of life of the people who are suffering from genetic disorders and is limited to the recipient.

GERM-LINE ENGINEERING: POSSIBILITIES AND CHALLENGES

Germ-line Gene Therapy is far more technically difficult than somatic cell therapy. Since the beginning of the Human Genome Project, there have been concerns regarding the pitfalls of gene therapy. Interactions between genes and their genetic repressors and activators are complex, depending in part on their precise location within a particular chromosome.[5]

Until recently, Germ-line engineering seemed like a distant possibility. However, rapid developments in the field of biotechnology, particularly the invention of CRISPR/Cas9 (Clustered Regularly Interspaced Short Palindromic Repeats)have made the alteration of genetic material not only possible but also relatively easy. It is interesting to note that one of the inventors of CRISPR is active in advocating *against* the technology's use for human germline editing.[6] Dr. Jennifer Doudna has been leading the crusade against widespread use of the technology she helped develop and demands a temporary halt on carrying out human germ-line editing. She is not the only one and opposition has come from all quarters. It becomes necessary to make an in depth study of the advantages and disadvantages of this technology from an ethical perspective.

ARGUMENTS IN FAVOUR

Scientific freedom: One of the foremost arguments in favor of research in Gene Therapy is scientific freedom. Scientific freedom is the basic principle on which the advancement of research rests. This is because of the belief that all knowledge is good and therefore there shouldn't be any restraints on acquiring it. Dr. Zimmerman voiced his opinion well when he stated that, "the prevailing ethic of science

3. "Medicine From Milk: Gene Therapy Could Transform Goats Into Pharmaceutical Factories" *Sciencedaily,* Feb 1, 2008, *available at* https://www.sciencedaily.com/releases/2008/01/080131082224.htm (last visited on Jan 3 ,2018)
4. B. Hoose, "Gene Therapy: Where to Draw the Line" 1 *Human Gene Therapy* 299-306 (1990).
5. *Ibid*.
6. "The Ethics of Human Germline Gene Editing", *available at* https://www.scienceboard.net/content/article/the-ethics-of-human-germline-gene-editing/ (last visited on Jan 3, 2018)

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and medicine is that knowledge has intrinsic value, and that its pursuit should not be impeded except under extraordinary circumstances."[7]

Potential for eradication of diseases: The most substantial argument in favor of germ-line engineering is that it could be developed to eliminate genetic disorders permanently by editing the faulty genes in the zygote. Thus it could be more beneficial than somatic gene engineering where the benefits are limited to the treated person alone and not his/her future generations. It could also be useful in those cases where somatic Gene Therapy is ineffective. Proponents of germ-line therapy argue that in the latter case, medicine has a moral commitment to provide the best existing treatment.[8]

Improving the quality of life: Advocates of gene enhancement argue that such enhancements could make life better in many ways by promoting desirable characteristics. According to them people try to make themselves better already by dieting, exercising, using cosmetics and plastic surgery because we value traits like intelligence, beauty, strength, etc. If these socially desirable traits were found to be linked to a gene, we could enhance them.

Reproductive freedom: The argument for reproductive freedom is best viewed from the perspective of the patients. There might be a situation where both the partners are carriers of a disease and germ-line Gene Therapy would give them a chance to have healthy children. There would no need for considering abortion or other invasive procedures like somatic-cell engineering. In such cases withholding treatment would be unethical. The right to have healthy children is an extension of reproductive freedom. If it is possible for the medical community to ensure that a child is born without genetic defect, then the burden of providing this treatment is an inherent responsibility.[9]

Arguments Against Germ-Line Engineering

Irreversible nature: One of the most common arguments advanced against Gene Therapy is that it is irreversible in nature. For example once it is known that a particular mutated gene is responsible for a disease then by way of Gene Therapy this gene will be "repaired" and the individual's genome will be permanently altered as far as scientific knowledge holds good. This shall be passed on to all the future offspring indefinitely. However as research has shown, the genes which may appear to be unhealthy might have some positive effects too and by repairing it we will be losing the benefit. Sickle-cell anemia is a case in study. Even though it is a genetic disorder yet people with sickle-cell anemia are less susceptible to contracting malaria. Had it been eliminated, the resistance to malaria might never have been discovered. It is also possible that tremendous portions of the African population who are carriers of sickle-cell anemia would have been wiped out by malaria.[10]

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7. B.K Zimmerman, "Human germ-line therapy: the case for its development and use",16 *The journal of medicine and philosophy* 593-612 (1991)
8. J.C Fletcher and W.F Anderson "Germ-line Therapy : A New Stage of Debate" *Health Care Law, Medicine* 26-39 (1992)
9. Rebecca S Feinberg, "Ethical issue in Gene Therapy research: an American perspective." in Jörg Niewöhner et. al.(eds.) *Gene Therapy: Prospective Technology assessment in its societal context* 102 (2006)
10. *Ibid.*

Potential effects on gene pool: This argument is similar to the previous one. It is believed that gene pool is a joint possession of all members of human society, and should not be subjected to any intentional, artificial, perhaps arbitrary manipulation by a few individuals.[11]Experts believe that Gene Therapy will diminish the gene pool by removing the bad ones. This will affect the diversity of the gene pool even eliminating those genes which are beneficial in nature. Many believe that it is a right of the future generation to be born with the entire human genome intact. The right to be born with one's genome has been included in the report of the Parliamentary Assembly of the Council of Europe[12] Diminishing the gene pool manually is considered as unnatural and it is feared that such activities may be harmful to the future generations.

Lack of informed consent: While the above two arguments have been made from a utilitarian perspective, this argument is made from an individual's perspective. It is a widely accepted legal and moral principle that competent adults are not to be subjected to medical treatment without their consent.[13] This principle creates a problem for germ-line genetic intervention. Since the alterations are made in early embryos, germ-line therapy essentially creates a generation of unconsenting research subjects. The germ-line Gene Therapy would be performed on the parent before the conception of the offspring and therefore it would be impossible to obtain the consent of the offspring, and it will not only affect one individual but all the future generations of the descendant. Hence the doctrine of informed consent which is central to the medical ethics will be violated.

Risk of harm: This is the strongest argument against Gene Therapy. One of the key researchers in the field, Jennifer Doudna who helped develop CRISPER-Cs9 is of the view that that the editing of the human germline for creating genome modified humans should be halted for the time being because of unknown social consequences and safety concerns. [14]

It will foster discrimination: Many fear that Gene Therapy will foster social discrimination and violate the principle of distributive justice. There is a fear that only richer population would benefit from the germ-line therapy, because it would be very expensive.[15] Those who are unable to afford it,will be discriminated at the hands of society.

Fear of enhancement and eugenics: It is feared that once germ-line interventions are allowed it will be impossible to control the consequences, including the undesirable ones. It would be a slippery slope if we start walking down the path of germ-line therapy and allow for *designer babies*. Emily Smith Beitiks, disability researcher at the University of California, San Francisco, said recently[16]:

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11. *Supra* note 2 at 7
12. Parliamentary assembly, Council of Europe, recommendation on genetic engineering 934(1982)
13. Faden and beauchamp, *A history and theory of informed consent* 241 (1986)
14. Akshat Rathi, "The pros and cons of genetically engineering your children", *available at* http://qz.com/564649/the-pros-and-cons-of-genetically-engineering-your-children/(last visited on Jan 7, 2018)
15. Emberger, G.f cahill, *Morality in the new genetics : a guide for students and health care provider*,32 (1994)
16. *Ibid.*

These proposed applications raise social justice questions and put us at risk of reviving eugenics—controlled breeding to increase the occurrence of 'desirable' heritable characteristics. Who gets to decide what diversity looks like and who is valued?

This revives the painful memories of the Nazi era. It is possible that in the future, advancements in genetic manipulation could allow parents to choose the desired eye color or IQ level or hair color, etc. If this advanced ability for genetic manipulation were attained, ethical landlines would abound in issues of distributive justice (only the rich could afford to design to their ideal child) as well as discrimination and narrowing of the gene pool. It will also create a genetic divide where people who are not genetically enhanced will be discriminated against those who are.

GENE THERAPY- LEGISLATIVE RESPONSE

The International Covenant on Civil and Political Rights indicates in Article 7 that "No one shall be subjected without his free consent to medical or scientific experimentation."

The specific response to germ-line engineering found its place in the 1997 universal declaration of Human Genome and Human Rights.[17] Many sections can be interpreted as a response to germ-line interventions. The declaration, states that "Everyone has a right to respect for their dignity and for their rights regardless of their genetic characteristics."[18] Article 12(b) of the declaration states that, "The applications of research, including applications in biology, genetics and medicine, concerning the human genome, shall seek to offer relief from suffering and improve the health of individuals and humankind as a whole."[19] Hence it implicitly excludes genetic enhancement.

Article 24 of the declaration makes a mention of germ-line interventions by stating that they could be contrary to human dignity.[20]

The Council of Europe's convention for the Protection of human rights and dignity of the human being with regard to the application of biology and medicine prohibits germ-line therapy and enhancement. Article 13 of the convention states that ''an intervention seeking to modify the human genome may only be undertaken for preventive, diagnostic or therapeutic purposes and only if its aim is not to introduce any modification in the genome of any descendants"[21] This stand was reiterated by the additional protocol to the convention[22]. European parliament also called for an absolute ban on all experiments designed to reorganize on an arbitrary basis the genetic make-up of humans.[23] This stand is reiterated by the

17. A. Res. 152, U.N. GAOR, 53d Sess., U.N. Doc. A/53/625/Add.2 (1998) (hereinafter U.N. General Assembly Resolution on the Human Genome Declaration) (adopting Universal Declaration on the Human Genome and Human Rights *available at* http:// www.unesco.org/ibc/uk/genome/ projet/index.html (visited on Jan 7, 2018).
18. *Id*., Art. 2(4).
19. *Id*., Art. 12(b)
20. *Id*., Art. 24.
21. *Id*., Art 13.
22. Council of Europe. 1998. Additional protocol to the convention for the protection of human rights and dignity of the human being with regard to the application of biology and medicine, on the prohibition of cloning human beings. *Available at* http://conventions.coe.int/treaty/en/treaties/html/ 168.htm.(visited on Jan 18,2016)
23. European Parliament, Resolution on the Ethical and Legal Aspects of Genetic Engineering, Doc. A2-327/88

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Additional Protocol to the convention for the protection of human rights and dignity of the human being with regard to application of biology and medicine, on the prohibition of cloning human beings. The European Parliament has adopted a resolution providing that people have a human right to their own genetic identity (European Parliament, 1998, Article 1).[24] At the national level more than 40 countries have laws prohibiting inheritable germ-line modifications and they have already been discussed before. There also some who call for a blanket ban on germ-line engineering. Some scholars consider inheritable genetic alterations as crimes against humanity".[25] However the positive aspects of such interventions cannot be ignored. The emerging global consensus on bioethics and germ-line engineering is clearly minimalist and in addressing these sensitive issues, international instruments do not pretend to provide a precise and definitive answer to the most intricate questions posed by germ-line engineering.[26]

INDIAN POSITION

Ethical Policies on the Human Genome, Genetic Research & Services, 2000 of the Department of Biotechnology, ministry of science and technology provides that somatic cell Gene Therapy research and service may be done with appropriate safety measures. According to it, Gene Therapy may be undertaken when it is the only therapeutic option or it is indisputably considered superior to other existing options. Appropriate protocols as developed by Department of Biotechnology, Govt. of India must be followed.

It also states that considering the present state of knowledge, germ line therapy in humans shall be prohibited.

Ethical guidelines for Biomedical Research on Human subjects published by the Indian Council of Medical Research in 2000 states that the aim of the human research project is to ultimately alleviate human suffering and Gene Therapy is a logical part of this effort. According to the guidelines *Somatic cell Gene Therapy* is the only method that may be permissible for the purpose of preventing or treating a serious disease when it is the only therapeutic option. It also restricts the use of this technology to alleviation of life threatening or seriously disabling genetic disease in individual patients. Normal human traits should not be changed. The council further states that Gene Therapy trials consists of two parts. The first part is preparation of the 'gene construct' to be administered, and the second part is evaluation of the efficacy and safety of the administered 'gene (construct)'. As far as the first part is concerned, the guidelines and clearance for it is to be regulated by the National Bioethics Committee under Department of Biotechnology and for the second part clearance from the local IEC and Central Ethical Committee of the ICMR shall be obtained.

The guidelines lay stress on ensuring safety especially because gene insertion might have unpredicted consequences of gene insertion. It also stipulates that all Gene Therapy trials should have the provision for long term surveillance and no trial should be conducted without taking the informed consent of the patient especially regarding uncertainties about outcome. It permits children to be candidates for therapy, if the therapy is meant for a childhood disorder. The following practices are prohibited by the guidelines:

i) Germ Line Therapy

24. *Ibid.*
25. G. J. Annas, L. B. Andrews and R. M. Isasi, "Protecting the Endangered Human:Toward an International Treaty Prohibiting Cloning and Inheritable Alterations"28 *American Journal of Law and Medicine* 151-178 (2002).
26. P.S Jaswal , Stellina Jolly, "Germ-Line Engineering And Future Generations: An Ethical And Legal Outlook" 52:1 *Journal of the Indian Law Institute* 12 (2010)

ii) Gene Therapy for enhancement of genetic characteristics (so called designer babies) is prohibited due to limited information regarding the effects of attempts to alter/enhance the genetic machinery of humans. There is poor understanding of the influence of environmental interaction on the expression of genetic characters. The guidelines state that it would be unethical to use genetic engineering for improvement of desirable traits just as it is not safe or ethical for parents to administer growth hormones to their normal offspring so that they would become very large football or basketball players.

iii) Eugenic Genetic Engineering for selection against personality, character, formation of body organs, fertility, intelligence and physical, mental and emotional characteristics is prohibited.

The National Guidelines for Stem Cell Research (2013) too prohibit research on human germ-line therapy.

CONCLUSION

It is submitted that any discussion on germ-line therapy should be done in an objective manner. While it is true that technology has the potential of being misused, we must also bear it in mind that the benefits outweigh the cons. If the technology is perfected and such interventions can be carried out safely, it would be a boon to those affected with untreatable genetic disorders. It is also true that most technologies face opposition in the beginning but slowly become both ethically and socially accepted, in vitro fertilization being a case in point. Germ-line Gene Therapy has acquired a reputation of being a double-edged sword. On one hand it promises to find a permanent fix to diseases like Huntington's and Tay Sachs and alleviate human suffering, on the other hand it has potential to be misused for enhancement purposes. At present the scientific knowledge is insufficient to truly understand the impact it will have in the long run.