Proceedings of the 8th World Congress on New Technologies (NewTech'22)
Prague, Czech Republic– August 03-05, 2022
Paper No. ICBB 005
DOI: 10.11159/icbb22.005

Embryo Editing Technology and Its Effect on Conceptions of Motherhood

Tiffany Yeung[1], Sujata K. Bhatia[2]
[1]The Lawrenceville School
2500 Main Street, Lawrenceville NJ 08648
tiffanyyeung2022@gmail.com; sbhatia@g.harvard.edu[2]
Harvard University
51 Brattle St, Cambridge MA 02138

Abstract - Mothers are central figures in all societies, and motherhood is a critical experience. Revolutionary advances have been made in the ability to sequence, manipulate, amplify, and finely edit DNA, granting human beings the power to tune the genetic makeup of offspring. In particular, CRISPR-Cas9 gene editing represents a major step forward from previous technologies for genetic modification and gene therapy. Unlike prior approaches to DNA modification, CRISPR-Cas9 gene editing can perform genomic editing of both somatic and germline cells, and can be readily used to edit the genomes of embryos. The impact of embryonic gene editing on mothers and motherhood, especially societal perceptions of mothers, has not yet been thoroughly examined. The goal of this paper is to consider historical conceptions of mothers and motherhood, along with the arc of scientific discoveries and technological development for DNA and biotechnology, leading up to contemporary gene editing methods. The paper then discusses the ethical, moral, and social dilemmas presented by embryonic gene editing, including the rogue editing of two female embryos in an attempt to impart HIV immunity. Society must not only define acceptable uses of gene editing technology according to ethical and moral standards, but also contemplate the societal impacts on mothers and motherhood, and include mothers in the conversation.

***Keywords*:** CRISPR-Cas9, gene editing, gene therapy, bioethics, embryo, motherhood

Introduction

Mothers are considered by society as one of the most central figures in the improvement of our world. As Joseph Hale stated in the New York Magazine in 1795, motherhood is key in the development of children but also in the "preservation and advancement of what was good and noble in the young nation's civic and religious life" [1]. Even before 1795, the ancient Greeks celebrated Rhea while the ancient Romans celebrated Cybele, both of which were considered theGreat Mother of the Gods [2]. The role of motherhood progressed from initially being the sole purpose of women to an assumption, and then to a duty to produce heirs, and finally, a decision up to the woman herself.

Around the same time, in 1809, Jean Baptiste Lamarck proposed a doctrine that stated that physical changes during a parent's lifetime could be inherited by their offspring [3]. Lamarckism was influential in evolutionary theory for a majority of the 19th century before becoming disreputable to scientists after the 1930s. Following this theory was Charles Darwin's theory that evolution occurs by natural selection, proposing that the most advantageous traits for survival in a certain environment would triumph and persist over other traits. In one of Darwin's most notable experiments, in which he observed the beaks of different species of Galapagos finches, Darwin discovered that although the finches all lived on the Galapagos islands, they all had different beaks depending on what type of food was available to them. This helped Darwin theorize that species will adapt to their environment by inheriting the most preferable trait in order to survive [4]. At the same time, the idea of human progress and logic was central to the Enlightenment movement of the 19th century. In the middle of the 19th century, scientist Gregor Mendel explored heredity of traits by cross-pollinating garden peas, which became the basis of genetic studies [5]. Mendel discovered the laws of inheritance: the dominant allele in a heterozygote isalways expressed over the recessive allele, each parent only passes one allele to its offspring, and "the inheritance of one

pair of factors (genes) is independent of the inheritance of the other pair" [6]. In 1953, James Watson and Francis Crick discovered the double helix structure of deoxyribonucleic acid (DNA) which was revolutionary to the scientific community's understanding of the genetic code [7]. The two demonstrated that DNA carried genetic code and contained a mechanism for protein synthesis. They also found that the double helix structure assists with replication of the DNA. Crick also discovered the central dogma of molecular biology, which states that genetic information moves from DNA, to ribonucleic acid (RNA) and then to protein.

Over the next few decades, many scientists made revolutionary discoveries about genetic technology–how to replicate DNA, read its sequence, and more. In 1972, Herbert W. Boyer, Stanley N. Cohen, and Paul Berg, created recombinant-DNA (rDNA) technology, which provides a way to artificially insert genetic information from one organism into the genome of another organism. The host organism with the foreign genetic material inserted from the donor organism would then be able to replicate and express the foreign DNA [8]. This technology allowed the production of virtually any protein from any species in a host organism. Years later, in October 1990, the Human Genome Project (HGP) was initiated, a project designed to research more about the pattern of our genes, where genes are located on all chromosomes, and a way to track inheritance of genes through generations. The HGP sparked some controversy due to the massive amount of money it would take away from conventional biomedical research; many were against the project.

However, with help from the United States Department of Energy and the National Institutes of Health (NIH), American geneticist Francis Collins led the HGP, which eventually resulted in uncovering the ability to read the genetic blueprint for human beings. Celera Genomics and its president and chief scientific officer, biochemist J. Craig Venter, competed against the HGP, hoping to win control over possible patents on the genome sequence. Celera Genomics eventually united with the NIH, and in June 2000, Collins and Venter had completed the rough draft of the sequence. Finally, three years later, in April 2003 on the 50th anniversary of the paper that discussed DNA's double-helical structure, the HGP was finally completed [9]. During the timeline of the HGP, other groundbreaking discoveries about DNA were also made, and numerous events occurred that were consequential in the field of gene therapy. For example, chemist Kary B. Mullis invented the Polymerase Chain Reaction (PCR) technique, giving scientists the ability to create countless copies of DNA samples [10].

In the 1980s, gene therapy became increasingly popular. Gene therapy offered the opportunity to cure inherited diseases through the introduction of genes for needed proteins, thereby correcting deficiencies in protein or enzyme production. Traditional gene therapy relied on viral vectors for the delivery of therapeutic genes. The death of Jesse Gelsinger due to gene therapy, however, stripped gene therapy of its popularity for at least a decade. Gelsinger had ornithine transcarbamylase deficiency syndrome (OTCD), a metabolic disorder where ammonia develops to a lethal level in the blood. Most babies born with OTCD die shortly after their birth because they are homozygous for OTCD, meaning that they have two deficient copies of the ornithine transcarbamylase gene, Gelsinger was diagnosed with a milder version because he was heterozygous for OTCD, meaning that he had one normal copy of the ornithine transcarbamylase gene and one deficient copy of the gene. He managed OTCD by taking almost 50 pills a day, but eventually, when he was 17, Gelsinger did not take his pills regularly, leading to potentially fatal conditions. After hearing about a clinical trial being conducted at the University of Pennsylvania for a treatment for OTCD, Gelsinger agreed to participate. Patients in the trial were injected with an adenovirus that would help the OTC gene produce functioning enzymes that help prevent buildup of ammonia. While most patients in the trial experienced mild side effects, Gelsinger's side effects were fatal, and four days after injection of the adenovirus, Gelsinger was dead. Issues that arose about the trial included failing to inform Gelsinger that the other patients had experienced side effects (informed-consent process) and a potential conflict of interest and financial incentive for James Wilson to succeed in the clinical trial [11]. Gelsinger's case highlighted the problems with gene therapy trials and human research overall, putting the safety of it all into jeopardy. Jesse Gelsinger's case exemplifies the potential risks of gene editing and also points to some of the ethical issues of gene therapy. The risks of gene modification will always exist despite the precision of the technology, and any mistakes made during gene editing are irreversible. Those opposed to germ-line gene modification point out that there are alternative ways to avoid genetic diseases, such as preimplantation or prenatal genetic diagnosis, although these strategies are ethically problematic [12].

- Traditional gene therapy can cause leukemia, as a result of foreign genes being inserted at locations in the genome that regulate the cell cycle. (SCID trial in France; gene therapy caused leukemia in 20% in children) [13]

In 2012, a new and more powerful tool for gene editing emerged: Clustered regularly interspaced short palindromic repeats (CRISPR)-Cas9 gene editing, a tool that enables direct genomic modification at desired locations in the genome. While contemporary gene editing technology–CRISPR–provides scientists with a much more precise tool to modify genes, it also raises unprecedented ethical and moral concerns due to its ability to permanently alter the genome of individuals.

Contemporary Gene Editing

CRISPR-Cas9 gene editing allows incredibly selective, site-specific deoxyribonucleic acid (DNA) modifications, and it enables scientists to edit both somatic (body cells other than sperm and egg cells) and germline cells (sperm and egg cells). The CRISPR-Cas9 system is made up of two components: a guide RNA (gRNA) that locates the target DNA to edit and the Cas9 enzyme, which has the ability to cut the DNA sequence. First, scientists find the sequence of DNA that will be edited, and then the system of the gRNA attached to the Cas9 enzymes is introduced to the target cells. The gRNA and Cas9 complex will then cut the DNA at the target spot, thus allowing scientists to edit the genome by modifying, inserting, or deleting new DNA sequences [14]. While the CRISPR-Cas9 system is a revolutionary advancement in the field of gene editing, CRISPR gene editing yields many risks and is not perfect. After editing the genome, it is possible for the genes to revert back to their original sequence, and the potential adverse effects of this reversion are not completely understood.

Furthermore, CRISPR can have off-target effects–in a few cases, unintended genomic modifications can be made at other parts of the genome other than the intended target. Notably, germline modifications made using CRISPR will permanently alter the genome of not only the patient but all offspring and descendants, signifying that if something goes awry during or after the editing of the genome, all future generations will be affected.

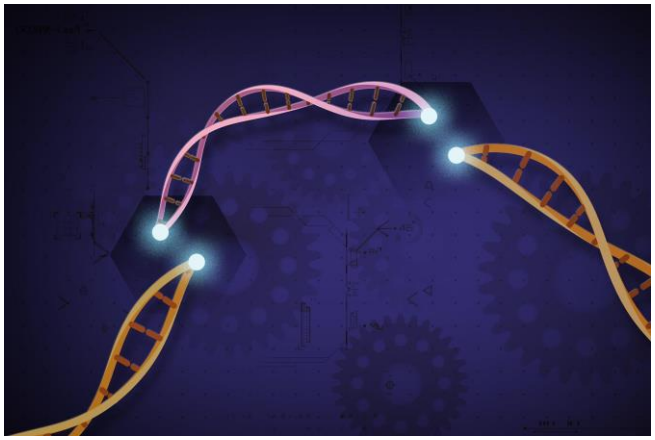

Fig. 1: Modern CRISPR-Cas9 gene-editing technology allows scientists to cut and edit DNA at a location of choice [15].

In 2020, American biochemist Jennifer Anne Doudna at the University of California, Berkeley, and French professor Emmanuelle Marie Charpentier won the Nobel Prize in Chemistry. Although scientists previously knew about the workings of the CRISPR system and how it helps prevent infections in prokaryotes using specialized enzymes, like Cas9, Charpentier discovered in 2011 that in the CRISPR system, there is also an "RNA molecule involved in recognizing phage sequences, in the bacterium Streptococcus pyogenes, bacteria that can cause disease in humans" [16]. That same year, Charpentier teamed up with Doudna, and in 2012, the pair published a paper that demonstrated how the aspects of the CRISPR-Cas9 system could be used to precisely edit parts of isolated DNA [16]. In 2013, biochemist Feng Zhang and his colleagues of the Broad Institute of Harvard University and Massachusetts Institute of Technology showed the use of CRISPR-Cas9 in mammalian and human cells. Both teams made key contributions to the new gene editing technique, and

there is an ongoing patent battle between the Broad Institute and UC Berkeley. The United States Patent and Trademark Office (USPTO) granted U.S. Patent No. 8,697,359 to the Broad Institute, MIT, and Feng Zhang in 2014 [17]. Still, thepatent dispute continues even in 2021.

While there are risks to the CRISPR-Cas9 gene editing technology, there have been instances of success. In 2020, CRISPR-Cas9 gene therapy was injected for the first time ever into a human body in an attempt to cure Leber's congenital amaurosis 10 (LCA10), a rare genetic condition that causes blindness. Mark Pennesi, who specializes in inherited retinal diseases at the Oregon Health and Science University, and pharmaceutical companies Editas Medicine and Allergan of Dublin collaborated for this research trial, named the BRILLIANCE trial. During BRILLIANCE, CRISPR technology was utilized to delete a mutation in the CEP290 gene that causes LCA10. The parts of the gene-editing system were encoded in a viral genome and injected near photoreceptor cells directly in the human eye [18]. The BRILLIANCE research trial is significant as it is the first time CRISPR-Cas9 has been injected directly into the human body to treat a mutation in the genome. Before the gene-edited virus was injected into the human genome, CRISPR-Cas9 was tested in a mouse model and shown to remedy phenotypes of LCA10 by correcting a nonsense mutation in the RPE65, another gene that contributes to the disease [19].

Another notable CRISPR research trial is the sickle cell anemia trial. Earlier this 2021, at the beginning of December, the University of California San Francisco (UCSF) Benioff Children's Hospital Oakland received $17 million for a research trial grant, in which CRISPR-Cas9 will be used on patients' blood stem cells to remedy the mutated gene that causes sickle cell anemia. The trial, led by UCSF with the University of California, Los Angeles (UCLA) and UC Berkeley, is the foremost to use the gene editing technology in humans. To begin, the researchers will test the technology in up to six adults with sickle cell disease, and if successful and innocuous, the trial will extend to test three adolescents ranging from 12 to 17 years old. Using CRISPR gene editing, researchers from UCSF, the Innovative Genomics Institute (IGI), and UCLA created CRISPR_SCD001, a "patient-specific blood stem cell therapy that has been modified by a CRISPR-Cas9 nuclease to stimulate repair of the sickle mutation" [20]. On the trial, Doudna commented that her hopes for the cure are for it to not just be "safe and effective, but one that is affordable by those who need it most" [16].

Despite the groundbreaking research trials that have been or are being conducted using this gene editing technology, the ethical problems of CRISPR-Cas9 gene editing and the risks still exist. In 2018, scientists vouched for the temporary prohibition of gene editing in germline cells and embryos after He Jiankui announced that he and his team used CRISPR-Cas9 to create the first-ever gene-edited babies by editing DNA in their embryos to create resistance to human immunodeficiency virus (HIV) infection [21]. In He's experiment, the C-C Motif Chemokine Receptor 5 (CCR5) gene (a gene necessary in creating a protein HIV needs to enter cells) was immobilized [22]. Although disabling the CCR5 gene could reduce the chances of the babies contracting HIV, damaging the gene also renders the humans more susceptible to other infections. Not only were the babies not at high risk of contracting HIV, but He's methods were not completely reliable, resulting in possible off-target effects, and he completely sidestepped ethical issues of editing human embryos.

The scandal highlighted the ethical risks of CRISPR gene editing in humans and ethical issues of ensuing scientific achievement in general, and especially in embryos, as well as the outstanding consequences of irresponsible use of this technology [22].

Connecting Gene Editing Technology with Motherhood

Many legal documents and constitutions around the world have banned genetic modification, usually eliciting discussion about the conceptualization of dignity, iterating that "humans have value simply by virtue of being human and not because of their capacities, and thus cannot be treated as instruments of another's will" [23]. Editing deficiencies out of offspring and humans in general can have negative societal impacts, potentially altering social norms and the tolerance of people with disabilities or deficiencies. Some argue that being able to genetically screen and modify humans with disabilities hyperbolizes the challenges of living with a disability to the extent that avoiding the disability is a priority in health care. Similarly, studies have shown that generally, those in the health and medical field view childhood disability as primarily detrimental for children and their families even though research on the reality of life satisfaction for disabled children and their families has contrasted these views. Although it is challenging to say with certainty due to the limited

human applications and current integration of gene editing in modern society, it seems likely that using CRISPR-Cas9 gene editing to reduce the chance of disability could consequently reduce the "empathy, acceptance, or integration" of disabled people in our society [23].

Julian Savulescu, the Uehiro Chair in Practical Ethics at the University of Oxford, preaches the principle of Procreative Beneficence: a principle of selecting "the child, of the possible children… who is expected to have the best life," arguing that parents have a moral obligation to choose the "best" child for the "best" life, which can be by means of genetic editing [24]. This principle invokes the question of defining what the "best life" for a child is. Using gene editing to obtain the best life for a child is ambiguous, as it is inconceivable to hypothesize that enhancing or removing a certain trait in a person would result in a better life. As Ronald M. Green, professor emeritus of religion and ethics at Dartmouth College, stated in his essay, "Do We Have a Moral Obligation to Genetically Enhance our Children?", the "healthy natural human genome has enough variety in it to let any child successfully navigate the world and fulfill his or her own vision of happiness" [25]. Not only does Savulescu's defense of the moral obligation for the best child and best life affect children, but it also impacts parents and norms for what a good parent is. As Robert Sparrow, professor at Monash University, stated, in a society where parents did choose the best child, "everyone would choose the same kind of children" [26]. To provide the best life, then, for the best child, it would be necessary for parents to spend all of their income and their time on their children's upbringing, and these are impossible and unfair standards for parenting.

On the topic of parents, the ability to genetically edit an embryo seems to undermine the role of mothers. There is a part of motherhood that is conceiving the child and then another part that is raising the child. If the job of setting the genetic material for the child is placed in the hands of scientists in the case where babies are genetically modified, have we removed that fundamental aspect of motherhood (which is giving genetic material to the child)? Although there is not quite enough research to say with certainty what societal effect this new technology will have, already, in most discussions of CRISPR-Cas9 gene editing and gene therapy in general, mothers are excluded from the conversation. Rachel Adams, Professor of English and Comparative Literature at Columbia University, reflected on the He Jiankui case and the effects of the lack of a maternal presence in the conception of the genetically modified twins. While censoring the identity of the mother was in part to protect her and the parents in general from Chinese media, the invisibility of the mother in the birth of the twins suggests that she is nonexistent, even though she will become the babies' primary caregiver [27]. Because the long term effects of gene editing are unpredictable, a genetically edited baby would, in reality, place even more responsibility on mothers, making their role even more central to the health of the offspring. However, if mothers are virtually removed from the story as in the case of the twins genetically edited by He Jiankui, the significance of mothers could be diminished as well as neglecting the health of pregnant women carrying genetically modified babies. Omitting the health of mothers, who are arguably the most important and inextricable figure in the birth and upbringing of a child, presents ethical implications for women in regards to gene editing.

As much about the long term effects of gene editing on humans is still unknown, germline research requires the "involvement of women willing to gestate a modified human embryo," until an artificial uterus is created that duplicates a female's uterus carrying a baby [28]. The article, "Prioritizing Women's Health in Germline Editing Research," published in the AMA Journal of Ethics, indicates that previous data on assisted reproductive technologies, such as in vitro fertilization, insinuate that female subjects carrying genetically edited babies could face various health risks. These women would be at an increased risk for obstetric complications, such as preeclampsia, placenta previa, placental abruption, and vasa previa, all deformities that would negatively affect the health of the mother [28]. In cleavage-stage embryos (the stage during which the zygote undergoes repeated mitotic division), "The microinjection of artificial nucleases into human embryos with chromosomal instability may also increase the rate of chromosomal breakage and aneuploidy via off-target effects" [29][30]. These chromosomal abnormalities could result in miscarriage, disease, or development issues of the offspring [30]. Mitotic error during the cleave stage can also result in mosaicism at the blastocyst stage, the stage reached by the embryo five to six days after fertilization [31]. Moreover, after birth, fetal cell-free DNA (cfDNA) persists in the maternal blood for months after delivering the baby, denoting that the modified genome of cfDNA would linger in maternal blood circulation for a period of time after birth. Due to the lack of research surrounding the effects of this persisting cfDNA during the postpartum period, it would be exceedingly important to observe the effects of how the modified cfDNA could affect maternal health in the months, years, or even generations after birth [28]. Current discussions around the health implications of gene editing emphasizes the health of the genetically modified offspring, but it is just as critical to discuss the health effects on the mother. Including the mother's interests and her health in CRISPR-Cas9 gene editing research will promote the development of "scientifically and ethically justifiable safeguards that do not compromise the health of women subjects for the expected benefit of the fetus or child," and allows scientists to consider how women's roles as mothers and in general may be impacted by gene editing [28].

A study published in the European Journal of Human Genetics in August 2020, titled "How will new genetic technologies, such as gene editing, change reproductive decision-making? Views of high-risk couples," found that there was generally a

positive opinion on germline gene editing (which is what CRISPR-Cas9 does) for these high-risk couples. The high-risk couples were couples that were at risk of having offspring with a genetic disorder who wanted to avoid having affected children. The study illustrated that the option of gene editing would reduce instances of pregnancy termination. Still, the participants in the study reported their fears of abuse of gene-editing technology, and some regarded editing the DNA of embryos as "a bridge too far" [32]. Clearly, parents are ambivalent at best about gene editing of children; on one hand, most parents would like to save their children from a debilitating disease, on the other hand parents express discomfort with gene editing of embryos.

Discussion and Conclusion

Because there have been limited research trials on the efficacy, long-term effects, and safety of CRISPR-Cas9 gene-editing technology, gene editing on embryos is not ready for implementation. Until there is more extensive knowledge on how this modern gene-editing technology affects the human body, gene editing of embryos should not be permitted for the time being. In 2019, Feng Zhang, Emmanuelle Charpentier, amongst various other scientists called for a moratorium on human genome editing in embryos, and proposed for a period of time where no clinical germline editing would be performed [33]. The temporary suspension would allow for more time for discussions about the "technical, scientific, medical, societal, ethical and moral issues" of gene editing and permit time to develop an "international framework" [33]. This call for a global moratorium highlights that the unknown facets and effects of CRISPR-Cas9 gene editing heavily outweigh the known details of the technology. He Jiankui's experiment showcased the importance of transparency and public involvement when utilizing science as complex and consequential as CRISPR-Cas9.

While He Jiankui's embryo editing experiment represents a clear ethical transgression that must be prevented, gene editing also presents more nuanced issues, particularly in the context of motherhood. As CRISPR-Cas9 gene editing becomes more prevalent with the continuing advancement of technology, the role of mothers and the health of pregnant women must be included in the conversation of genetically editing babies. Maternal health should be given precedence in the research of modifying embryos or babies, and overall, it is important to not neglect the presence of the mother in the story of genetically modified offspring, such as in the twins in He Jiankui's experiment. This pioneering technology offers incredible possibilities and options for future generations and for parents to correct mutations and diseases, but the safety concerns of gene editing are still considerable. In considering and defining acceptable uses of gene editing technology, society must grapple not only with ethical and moral implications, but also social implications for changing the role of mothers and motherhood.

References

[1] J. Vandenberg-Daves, "Introduction," in Modern Motherhood: An American History, New Brunswick, NJ: Rutgers University Press, 2014.

[2] The Editors of Encyclopedia Britannica, "Great Mother of the Gods | ancient deity," *Encyclopædia Britannica*. Jun. 18, 2009, [Online]. Available: https://www.britannica.com/topic/Great-Mother-of-the-Gods.

[3] The Editors of Encyclopedia Britannica, "Lamarckism | Facts, Theory, & Contrast with Darwinism," Encyclopædia Britannica. Oct. 11, 2017, [Online]. Available: https://www.britannica.com/science/Lamarckism.

[4] A. J. Desmond, "Charles Darwin - On the Origin of Species," Encyclopædia Britannica. Sep. 06, 2018, [Online]. Available: https://www.britannica.com/biography/Charles-Darwin/On-the-Origin-of-Species.

[5] "The work of Mendel," Encyclopædia Britannica. [Online]. Available: https://www.britannica.com/science/genetics/The-work-of-Mendel. [Accessed: 31-Dec-2021].

[6] Lumen, "Laws of Inheritance | Boundless Biology," Lumenlearning.com, 2013. https://courses.lumenlearning.com/boundless-biology/chapter/laws-of-inheritance/.

[7] U.S National Library of Medicine, "The Discovery of the Double Helix, 1951-1953," Francis Crick - Profiles in Science. https://profiles.nlm.nih.gov/spotlight/sc/feature/doublehelix.

[8] Science History Institute, "Herbert W. Boyer and Stanley N. Cohen," Science History Institute, Dec. 11, 2017. https://www.sciencehistory.org/historical-profile/herbert-w-boyer-and-stanley-n-cohen.

[9] J. L. Fridovich-Keil, "Human Genome Project | History, Timeline, & Facts," Encyclopædia Britannica. Apr. 25, 2018, [Online]. Available: https://www.britannica.com/event/Human-Genome-Project.

[10] "The History of PCR (RU 9577)," Si.edu, 2019. http://siarchives.si.edu/research/videohistory_catalog9577.html.

[11] M. Rinde, "The Death of Jesse Gelsinger, 20 Years Later," Science History Institute, Jun. 04, 2019. https://www.sciencehistory.org/distillations/the-death-of-jesse-gelsinger-20-years-later.

[12] N. Wivel and L. Walters, "Germ-Line Gene Modification and Disease Prevention: Some Medical and Ethical Perspectives," Science, vol. 262, no. 5133, pp. 533–538, Oct. 1993, doi: 10.1126/science.8211180.

[13] A. Fischer and S. Hacein-Bey-Abina, "Gene therapy for severe combined immunodeficiencies and beyond," The Journal

of Experimental Medicine, vol. 217, no. 2, Dec. 2019, doi: 10.1084/jem.20190607.
[14] Mayo Clinic, "CRISPR Explained," YouTube. Jul. 24, 2018, [Online]. Available: https://www.youtube.com/watch?v=UKbrwPL3wXE.
[15] NIH Gallery from Bethesda, Maryland, USA, "CRISPR-Cas9 is a customizable tool that lets scientists cut and insert small pieces of DNA at precise areas along a DNA strand. This lets scientists study our genes in a specific, targeted way.," Wikimedia Commons, May 10, 2018. https://commons.wikimedia.org/wiki/File:CRISPR_Cas9_(41124064215).jpg.
[16] H. Ledford and E. Callaway, "Pioneers of revolutionary CRISPR gene editing win chemistry Nobel," Nature, vol. 586, Oct. 2020, doi: 10.1038/d41586-020-02765-9.
[17] Broad Communications, "Statements and background on CRISPR patent process," Broad Institute, Feb. 15, 2017. https://www.broadinstitute.org/crispr/journalists-statement-and-background-crispr-patent-process#:~:text=In%20April%2C%202014%2C%20the%20USPTO (accessed Jan. 07, 2022).
[18] H. Ledford, "CRISPR treatment inserted directly into the body for first time," Nature, vol. 579, no. 185, Mar. 2020, doi: 10.1038/d41586-020-00655-8.
[19] D. H. Jo., "CRISPR-Cas9–mediated therapeutic editing of Rpe65 ameliorates the disease phenotypes in a mouse model of Leber congenital amaurosis," Science Advances, vol. 5, no. 10, Oct. 2019, doi: 10.1126/sciadv.aax1210.
[20] L. Fernandes, "Sickle Cell Clinical Trial Aims to Cure Disease by Correcting Patient's Mutated Gene | UC San Francisco," University of California San Diego, Dec. 01, 2021. https://www.ucsf.edu/news/2021/12/421901/sickle-cell-clinical-trial-aims-cure-disease-correcting-patients-mutated-ge ne.
[21] D. Cyranoski, "What CRISPR-baby prison sentences mean for research," Nature, vol. 577, no. 7789, pp. 154–155, Jan. 2020, doi: 10.1038/d41586-020-00001-y.
[22] S.-L. Wee, "Chinese Scientist Who Genetically Edited Babies Gets 3 Years in Prison," The New York Times, Dec. 30, 2019.
[23] National Academy of Sciences and National Academy of Medicine, Human Genome Editing: Science, Ethics, and Governance. Washington, D.C.: National Academies Press, 2017.
[24] J. Savulescu, "Procreative Beneficence: Why We Should Select the Best Children," Bioethics, vol. 15, no. 5–6, pp. 413–426, Oct. 2001, doi: 10.1111/1467-8519.00251.
[25] R. M. Green, "Do We Have a Moral Obligation to Genetically Enhance our Children? - The Hastings Center," TheHastings Center, Oct. 31, 2017. https://www.thehastingscenter.org/moral-obligation-genetically-enhance-children/.
[26] R. Sparrow, "Procreative Beneficence, Obligation, and Eugenics," Genomics, Society and Policy, vol. 3, no. 3, Dec. 2007, doi: 10.1186/1746-5354-3-3-43.

[27] R. Adams, "Gene-edited babies don't grow in test tubes – mothers' roles shouldn't be erased," The Conversation, May 29, 2019.
https://theconversation.com/gene-edited-babies-dont-grow-in-test-tubes-mothers-roles-shouldnt-be-erased-117070.
[28] R. M. Farrell, M. Michie, C. T. Scott, R. Flyckt, and M. LaPlante, "Prioritizing Women's Health in Germline Editing Research," AMA Journal of Ethics, vol. 21, no. 12, Dec. 2019, doi: 10.1001/amajethics.2019.1071.
[29]University of Michigan Medical School, "First Week (Days 1-7)," www.med.umich.edu, Jan. 06, 2000. https://www.med.umich.edu/lrc/coursepages/m1/embryology/embryo/03firstweek.htm.
[30] T. Ishii, "Reproductive medicine involving genome editing: clinical uncertainties and embryological needs," Reproductive Biomedicine Online, vol. 34, no. 1, Jan. 2017, doi: 10.1016/j.rbmo.2016.09.009.
[31] "Blastocyst Culture | Factsheet," Life Fertility Clinic. https://www.lifefertility.com.au/resources/factsheets/blastocyst-culture/#:~:text=The%20word%20%27blastocyst%27%20refers%20to (accessed Jan. 07, 2022).
[32] I. van Dijke, P. Lakeman, I. B. Mathijssen, M. Goddijn, M. C. Cornel, and L. Henneman, "How will new genetic technologies, such as gene editing, change reproductive decision-making? Views of high-risk couples," European Journal of Human Genetics, vol. 29, no. 1, pp. 1–12, Aug. 2020, doi: 10.1038/s41431-020-00706-8.
[33] E. S. Lander., "Adopt a moratorium on heritable genome editing," Nature, vol. 567, no. 7747, pp. 165–168, Mar. 2019, doi: 10.1038/d41586-019-00726-5.

The IEEE citation format is used. Books and book chapters should be referenced as [1] and [2] respectively. Patents are referenced based on [3] and a thesis can be referenced as [4]. Finally, conference presentations/papers and journal papers need to be reference based on [5] and [6] respectively.

With the increasing availability of useful information that can be found on the internet, website references must also be reported based on [7]. Meanwhile, due to the dynamic nature of web pages and the fact that in most cases the information is not peer-reviewed, the use of published resources are very much preferred and advised over online references.

The reference section at the end of the paper should be edited based on the following:

[1] B. Klaus and P. Horn, *Robot Vision*. Cambridge, MA: MIT Press, 1986.
[2] L. Stein, "Random patterns," in *Computers and You*, J. S. Brake, Ed. New York: Wiley, 1994, pp. 55-70.
[3] J. P. Wilkinson, "Nonlinear resonant circuit devices," U.S. Patent 3 624 125, July 16, 1990.
[4] J. O. Williams, "Narrow-band analyzer," Ph.D. dissertation, Dept. Elect. Eng., Harvard Univ., Cambridge, MA.
[5] U. V. Koc and K. R. Liu, "Discrete-cosine/sine-transform based motion estimation," in *Proceedings of the IEEE International Conference on Image Processing*, Austin, TX, 1994, vol. 3, pp. 771-775.
[6] R. E. Kalman, "New results in linear filtering and prediction theory," *J. Basic Eng*., vol. 83, no. 4, pp. 95-108, 1961.
[7] K. Author. (2015, May 10). Facility Greenhouse Gas Reporting (2nd ed.) [Online]. Available:http://www.ec.gc.ca/ges-ghg/default.asp?lang=En&n=040E378D-1