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Consequences of Unregulated Use of CRISPR/Cas9 Technology on Humans and the Need for Regulation

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ABSTRACT

The ability for human beings to artificially alter their DNA, and change themselves from birth, physically and mentally, was set to become a reality when in 2018, a Chinese research claimed that he had created the first HIV resistant human being through a technology known as Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR/Cas9).

This technology has a wide range of applications, from disarming viral vectors to pest control. However, the scope of this paper shall be limited to the application of CRISPR/Cas9 on human DNA.

One of the direct human applications is the selective targeting and deleting of harmful genes in the embryo's DNA. The result is the possibility of saving the child from a potential genetic disease. While this is a positive application of this technology, unregulated usage of this would have negative consequences. Such negative effects will be discussed. This paper is split into three parts.

Firstly, the paper discusses general concern of the possibility of creating 'designer babies'. The author proposes a restriction on the application of CRISPR/Cas9 for biological enhancement based on preference, rather than necessity would be proposed. This would be accompanied by a proposal to regulate CRISPR/Cas9 application on germline cells.

Secondly, the military application of this technology and its possible devastating effects would be discussed and regulation on the application of this in defence would be proposed.

And finally, the prematurity of the development of this technology would be acknowledged. This part focuses on the detrimental effect of the technology, such as mosaicism and high-frequency occurrences of off-target effects. Therefore, in order to avoid these effects, regulations would be proposed with the aim of restricting the procedures used to certain methods that minimize these effects. This paper would explore the various methods available that would help minimize these effects.

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I. INTRODUCTION

In 2018, a Chinese scientist had claimed that he used CRISPR/Cas9 technology and had created a baby that was resisted to HIV. The author would like to shed light on this technology before proposing regulations on its usage.

The CRISPR/Cas system is originally found in nature as a defence mechanism for the bacterium, *Streptococcus thermophilus*. It was found that the naturally occurring system provided immunity in the bacterium against foreign invasive organisms, such as bacteriophages, by using a protein to target and disable the potential damaging genetic element of the invader, thus preventing the damaging effect.[2]

How does CRISPR/Cas9 work? The idea is simple: An enzyme, called the Cas9 enzyme, has the function of cutting the DNA. This enzyme contains a guide RNA, which can identify the particular section of the DNA that requires cutting. The Cas9 enzyme then cuts the DNA at that identified sequence.

At this stage, the DNA is damaged and requires repair. This can be done in one of two ways: The first mode involves simply gluing the two pieces together imperfectly, leaving behind a leftover scar that interrupts and thus disables the targeted gene. This leads to the prevention of the negative phenotypic expression associated with that gene, usually manifesting itself in genetic diseases.[3]

In the second mode: the cut segment of the DNA is deleted and the cell can then copy a nearby segment of DNA and use that copy to fill in the missing sequence.[4]

If this function is carried out in the nucleus of a somatic (non-reproductive) cell, then this change exhibits itself in only the somatic cells of the body. Thus, the phenotypic expression is limited to that individual. However, if this technology is applied in reproductive cells (gametes), then the edit is transmitted genetically to the progeny of that person. Thus, the phenotypic expression through the entire germline will be edited, as opposed to editing the expression for a single individual.[5]

II. REGULATION ON APPLICATION

In this segment, two potential problems with the unregulated utilization of CRISPR/Cas9 would be identified and certain restrictions with the goal of preventing these manifestations

[2] Rimantas Sapranauskas et al., *The Streptococcus thermophilus CRISPR/Cas system provides immunity in Escherichia coli*, 39 NUCLEIC ACIDS RES. 21 (2011).
[3] Amber Dance, *Core Concept: CRISPR gene editing*, 112 NATIONAL ACADEMY OF SCIENCE 20 (2015).
[4] *Ibid.*
[5] Edward Lanphier, et al., *Don't edit the human germ line*, 519 NATURE 7544 (2015).

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of these problems would be proposed. It is acknowledged that the technology is premature and thus cannot be ready for human applications. However this segment is dedicated to regulations that must be considered once this technology is ready for clinical use.

Enhancement and Germline Editing:

It has been stated that one of the applications of the CRISPR/Cas9 technology is to delete a disease-causing segment of the DNA, thus preventing its phenotypic expression. However, it must be noted that the potential capability of this technology is not limited to this. It is also possible to add and replace DNA segments so as to influence phenotypic expression. This could create the possibility for parents to selectively choose characteristic traits for their children, enhancing their physical and mental capabilities, thereby creating 'designer' babies.[6] While this opportunity might appear as a positive consequence of CRISPR/Cas9, it is actually one of the most popular criticisms against the unregulated use of the technology.

In order to draw the distinction between therapeutic use and enhancement, it is stated that the therapeutic treatments come under healthcare and might be owed to the people by the state, healthcare professionals or insurers as a basic social good, whereas enhancements are requested privately, purely for personal advantage.[7]

The term 'eugenics' was originally coined by Francis Galton. He defined it as the study of "the conditions under which men of a high type are produced" and as "the science which deals with all influences that improve the inborn qualities of a race".[8] In the present context, it is appropriate to characterize the enhancement function of CRISPR/Cas9 as positive eugenics (active steps taken to artificially 'improve' the gene pool), as opposed to the negative eugenics (which is done with the intent to prevent any 'deterioration' of the gene pool).

The cause for concern exists because the opportunity to enhance biological function might not be universally accessible. It is worth noting that while CRISPR/Cas9 technology is regarded as a 'cheap' way of gene editing, this measure of cost is relative since it is cheaper in comparison to other forms of gene editing. This does not mean that the technology is objectively cheap for everyone.[9] Factoring in the on-going patent dispute[10], the royalties paid to the patent-holder would increase the costs further. Therefore, there will be an existing

[6] *Supra* Note 3.
[7] Nuffield Council on Bioethics, *Genome editing and human reproduction* (2018).
[8] S Wilkinson, *"Eugenics talk" and the language of bioethics,* 34 J MED ETHICS 6 467-471 (2008).
[9] Mark Shwartz, *Target, Delete, Repair*, STANFORD MEDICINE (2018), https://stanmed.stanford.edu/2018winter/CRISPR-for-gene-editing-is-revolutionary-but-it-comes-with-risks.html.
[10] Catherine Jewell & Vijay Balakrishnan, *The battle to own the CRISPR–Cas9 gene-editing tool*, WIPO MAGAZINE (2017) , https://www.wipo.int/wipo_magazine/en/2017/02/article_0005.html.

disadvantaged group who would be deprived of the opportunity to use CRISPR/Cas9 for enhancement. Allowing the unregulated use of this function would allow those that do have such a privilege to use it and consequently, deepen the inequality. [11]

The privileged class will 'enhance' their progeny, who would be endowed with a higher intelligence, sharper focus or enhanced strength, and be able to perform better than those with natural abilities, thus creating a biological class system that would deepen the inherent inequalities between those who have access to this technology and those who do not.[12]

One might argue that such technology should be introduced in such a way that it would not have the effect of discriminating unfairly among people.[13] This could be done through state-funded universal healthcare. However, the problem with this argument is that it assumes that every state would employ this policy, failure of which would create an inequality between citizens of the state adopting the policy and those of the state without it.

Another concern that was raised was that the existence of such a technology would cause a threat to the existing diversity in humanity.[14] It would be appropriate to point out that problematic biases in society might be entrenched by the commercial availability of selective reproductive techniques.[15] An example of this is how the availability of sex-determination has entrenched the patriarchal bias against women and has led to a skewed sex ratio.[16] An example in the present context would be how the inherent bias against coloured people in the United States would lead African-American couples to genetically alter the skin colour of their child, for the sake of their safety. This would lead to a decrease in diversity.

An additional argument can be made by incorporating a reasonable extension of the expressivist objection to CRISPR/Cas9. The argument claims that the existence of a technology that makes it possible to select against the birth of a disabled child will express a hostile attitude against that disability. The general view of disability would then shift from that of an inevitable reality to an avoidable condition.[17] A reasonable extension can be made in the context of enhancement: The general view of natural human capability would shift the same way. The public would view the relatively slower performance of the unenhanced people as an avoidable condition and thus develop a hostile attitude towards them.

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[11] Carolyn Brokowsky, et al., *Cutting Eugenics Out of CRISPR-Cas9*, 6 ETHICS IN BIOLOGY, ENGINEERING & MEDICINE – AN INTERNATIONAL JOURNAL 3-4, 263-279 (2015).
[12] *Ibid.*
[13] Nuffield Council on Bioethics, *Genome editing: an ethical review* (2018).
[14] *Supra* note 9.
[15] NICHOLAS AGAR , LIBERAL EUGENICS: IN DEFENCE OF HUMAN ENHANCEMENT (Oxford-Blackwell ed., 2008).
[16] *Supra* note 9.
[17] *Ibid.*

Due to these negative consequences of the unregulated use of CRISPR/Cas9 and how enhancement could lead to inequality, it is submitted that the use of this technology must be restricted to therapeutic uses alone. This use should be allowed only after the development of the technology has reached a stage where the concerns of off-target effects and mosaicism are taken care of.

It has been mentioned that if the technology is used to edit reproductive cells, the phenotypic expression could change for the progeny of the individual. By extending the eugenics argument to germline application, it can be said that the scale of the consequential inequalities that exist would drastically increase if the procedure is conducted on germline cells since the enhancement would significantly cost less (since the procedure has to take place only once for a germline) and the inequality would then adopt a multi-generational character.[18] Referring to the argument previously made that the relatively well-off section of the population would have access to CRISPR while the rest do not, and considering that the wealth gap between the well-off and the rest also has a multi-generational character, it is submitted that germline editing would only further deeper this multi-generational gap.

There is also the concern of the power the present generation would wield over future generations in terms of the conditions of life the descendants would lead.[19] It was also argued that due to this power, the present generation must develop a sense of intergenerational justice.[20]

For the above-stated extension, it is also submitted that there must be a restriction on the application of this technology for germline editing. Many authorities concur with this position, including the Indian Council of Medical Research.[21]

Military Application

Another speculative application of CRISPR/Cas9 is in the enhancement of defence personnel, such as greater physical capabilities and the general susceptibility to conditions they may face during warfare.[22] This was also acknowledged by the National Security Strategy and Strategic Defence and Security Review that there was potential in the application of genetic

[18] *Supra* note 12.
[19] *Supra* Note 9.
[20] ROBERT GOODIN, PROTECTING THE VULNERABLE: A RE-ANALYSIS OF OUR SOCIAL RESPONSIBILITIES (University of Chicago Press, 1985).
[21] Indian Council of Medical Research, *National Ethical Guidelines for Biomedical and Health Research Involving Human Participants*, 124 (2017).
[22] *Supra* Note 14.

engineering in the field of national security.[23]

However, due to the relative accessibility and cost-effectiveness of the technology, it would be difficult to contain the technology such that it does not fall into the hands of authoritatian regimes and terrorists.[24] There is also the possibility that this technology can be used in aggression in times of escalated tensions. It is acknowledged that these risks exist with other forms of ballistic weaponry as well. However, considering the fact that this technology can have a much more damaging effect on human life coupled with its ease of accessibility, there can be catastrophic consequences if this technology is developed for military use. In fact, it was included among the six 'weapons of mass destruction and proliferation' by the US Director of National Intelligence.[25]

Due to the above stated consequences, it is argued that there must be adequate regulation in place that would either completely restrict the development of this technology for military application, or the development must be in such a way that it would not fall in the wrong hands.

III. PROCEDURAL RESTRICTIONS

Concern has been expressed regarding the prematurity of the development of CRISPR/Cas9 and the consequent negative impact this would have on embryos. The lack of development has led to the inefficiency of this technology and this manifests itself in two ways.

Mosaicism

Due to the inaccuracy of the CRISPR/Cas9 technology, there can be an imperfect genetic result that manifests itself as mosaicism. A mosaic embryo is one that exists when genes are edited in some of the cells of the embryo, but not all the cells.[26] This can happen when the Cas9 enzyme does not cut both copies of the gene, or when the cell starts dividing before the necessary corrections are complete.[27]

The phenotypic expression of this mosaicism could manifest itself in the form of sex syndromes. An example of a naturally occurring mosaic embryo is Down Syndrome.[28]

In the application of CRISPR/Cas9 technology, there can be an artificially induced mosaicism that would be harmful to an otherwise healthy embryo. Therefore, the priority

[23] *Ibid.*
[24] *Ibid.*
[25] James R. Clapper, *Worldwide threat assessment of the US intelligence community*, 9 (2016).
[26] Human Fertilization & Embryology Authority, *Genome Editing* (2017).
[27] *Supra* Note 7.
[28] Philip R. Reilly, *Genetic Counselling and the Law*, 12 HOUS. L. REV. 640 (1975).

must be to adopt methods that would minimize mosaicism.

One such method involved the replacement of microinjection as the method of delivery of Cas9. In a study, the method of delivery was electroporation –where an electric field is used to decrease the permeability of the cell-membrane. When this method was used to introduce Cas9 with the guide RNA into mouse zygotes, the result was found to be more efficient than microinjection. When this method was used before the first replication, it resulted in embryos that were non-mosaic and where all cells carried the same mutations.[29]

Another method involved inducing the double-stranded break at a different cell stage, which resulted in the cleaving of embryotic cells without the accompanied mosaicism. Introducing the sperm and Cas9 into the metaphase II stage in cell division of the female gamete also eliminated mosaicism.[30]

It is acknowledged that these studies were conducted on mice and the effect of the same on human zygotes is unknown. Therefore, it is submitted that research into more efficient methods of delivery must be investigated before clinical applications. It is also submitted that once the technology is ready for clinical application, the procedure employed must be restricted to those that would minimize, if not eliminate mosaicism.

Off-target effects

The biggest problem in the development of this technology for human applications is that human DNA is far more complex than that of the test analogues.[31] Thus, application of the same technology has led to many off-target effects. These effects happen when changes happen to genes other than the targeted genes.

One of the methods to reduce off-target effects is the employment of a modified Cas9 enzyme, such as a variant of Cas9 (SpCas9-HF1) to induce the Double-Strand Break. This variant, accompanied by the single-guide RNA (sgRNA), when tested in human cells rendered all or nearly all off-target events undetectable by genome-wide break capture and targeted sequencing methods.[32]

Again, it is granted that research into minimizing off-target effects is not fully developed. However, it is submitted that once such a method has been developed, the regulations must restrict the procedures to those that were designed to reduce off-target effects.

[29] *Supra* Note 27.
[30] Take stock of research ethics in human genome editing, 549 NATURE 7672 (2017).
[31] *Supra* Note 3.
[32] Benjamin P. Kleinstiver et al., *High-fidelity CRISPR-Cas9 nucleases with no detectable genome-wide off-target effects*, NATURE 529, 490-495 (2016).

IV. CONCLUSION

In conclusion, the technology behind the CRISPR/Cas9 is premature and therefore, inaccurate. This inaccuracy has potentially detrimental effects on human embryos, leading to genetic disorders, rather than curing them. It is thus submitted that clinical applications of CRISPR/Cas9 should be banned until the technology is developed to a point of high accuracy and there is no scope for inaccuracies and consequential detriments.

It must be noted, however, that the application of such technology is very wide and can have applications, the consequences of which would deepen the socio-economic problems in our society. Therefore, the application should be limited to only a certain segments, namely for therapeutic uses on non-germline cells.

It is acknowledged that by imposing such regulations, the regulatory authorities are hampering scientific progress. While it is accepted that such development would have possible applications that would fundamentally transform human society, it is necessary to point out that this technology would entail immense power and with it, immense responsibility.

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