REGULATION OF GENOME-EDITING TECHNOLOGY IN INDIA

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ABSTRACT

The advent of technological advances will soon lead us to an era where data of an individual's genetic information will contribute to the development of personalized medicines. At such scientific revolution, genome editing denotes an addition, removal or alteration of genetic materials at the targeted locations in gene sequences, enabling scientists to change an organism's DNA. This can be done through a plethora of technological choices that need to be protected. Out of them, CRISPR-Cas9 became the main system of preference due to its efficiency and ease-of-use. Taking into consideration the scientific evidence, media coverage and secondary literature, this essay explores the legal and ethical obligations of genome editing technology in India. It questions the legality of CRISPR-Cas9 in editing somatic and germline cells. Furthermore, it analyses the need for having strict genome editing norms in India. This has been backed by a comparative study of global measures taken for regulating genome editing norms in different countries which are pioneering this technology. In conclusion, the essay looks into certain unanswered questions of the guidelines set by Indian Medical Council for Research (IMCR) and the current Indian legislation regarding gene-modification, suggesting ways of achieving transparency, and how the regulations of World Health Organization (WHO) has a persuasive effect in influencing the future of genome-editing laws in India. As India is framing its data protection bill, debates have flared up all over the country on the subject of genome editing technologies and the protection of the individual's right to privacy.

Keywords: CRISPR, Genome, gene-editing, gene technology, regulations, norms

INTRODUCTION

Gene technology has been defined as the application of gene technique called genetic engineering, including self-cloning, deletion and hybridization.[i] Similarly, Genetic Engineering is such a technique through which genetic material that does not occur naturally, generated outside the organism, or the cell is inserted into the said cell.[ii] It implies the creation of a new gene, by the addition, deletion or alteration of an existing genome (host cell), where they occur naturally (self-cloning) as well as modification. These scientific peaks have been reached in a world where an average lab with averagely trained technicians can use them to alter the human genome. This is both terrifying and exhilarating. This two-edged sword can either lead to eugenics, the dream of Hitler's Nazi regime or an array of genetic disorders throughout the lineage. CRISPR, thus, came as both a boon and a bane and regulations for the same are much needed.

DEVELOPMENT OF CRISPR AS A GENE-EDITING TECHNOLOGY

The first time CRISPR was mentioned was in 1987 by the researchers of Osaka University in Japan. The acronym CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) was first used by Francisco Mojica and Ruud Jansen in 2001. Later, Mojica widely came to be regarded for the discovery of CRISPR.

Cas9, also known as CRISPR associated protein 9 is a protein which can protect the DNA against viruses and plasmids. The highlighting function of Cas9 has been its ability to cut DNA and therefore alter it. This has made it essential for the process of gene editing. In 2015 paper by Chinese scientists P. Liang and Y. Xu mentioned it in detail for the first time. In the same year, a research group, from Sun Yat-sen University in Guangzhou, China, led by Junjiu Huang, carried out the first attempt at genetically modifying a human embryo. A year later, a group from Guangzhou Medical University, also in China, led by Yong Fan, carried out the genetic editing of human embryos, to introduce a modification that makes a person resistant to infection by the HIV virus. In August of 2017, the media presented the first North American team destined to carry out genetic editing in human embryos.

In 2018, gene editing and CRISPR-Cas9 gained a lot of mainstream attention after Prof He Jiankui sent shockwaves to the world after he genetically altered the twins to give them protection against HIV. His move started a new debate about whether gene editing is legal and ethical. The parents of the twins were HIV positive. He worked at the Southern University of Science and Technology in Shenzhen, China and also worked for those who were suffering from infertility. On 25 November 2018 when MIT Technology Review exposed the story about the human experiment being conducted secretly in that university led by He Jiankui. Widespread criticism started flowing from the medical community around the world. Rattled by the given situation, He Jiankui came up with a documentary-like video on YouTube, explaining and defending his work. He further announced the birth of the twin babies. He named them Lulu and Nana and they were born in October 2018.

Later in December 2019, a court in Shenzhen found that He and two collaborators forged ethical review documents and misled doctors into unknowingly implanting gene-edited embryos into two women, according to Xinhua, China's state-run press agency. One of the mothers gave birth to twin girls in November 2018. The court gave the verdict that the defending party had knowingly violated national regulations on biomedical research and medical ethics, and harshly applied gene-editing technology to human reproductive medicine.[iii] He was sentenced to three years in jail.

The Hu Jiankui affair kick started a whole new discussion and debate on gene editing. Several countries have already started looking at the problems of not regulating these technologies.

THE NEED FOR REGULATING HUMAN GERMLINE EDITING

Germline edits are done to genes that are within sperm cells, eggs or embryos. The DNAs that are morphed in these germ cells are passed on to children, and in doing so, may alter the human lineage.

However, in contrast, gene modification in non-germline, somatic cells will only alter the treated individual and are much less controversial than germline editing. Ethically, the idea of somatic cell modification is acceptable by communities and the State. In the US, the

government has allowed experimental trials exploring such changes in somatic cells through CAR-T cell therapies. The FDA too has approved the modification of T cells in immune systems for cancer treatment. Strict regulations that are methodical and cautious in nature are required to be implemented in germline editing for multiple concerns it raises:

- Germline modifications may produce toxic proteins capable of altering the human lineage
- CRISPR technology can deliver accidental alterations in unintended locations of the genome. The chances of such off-target edits are required to be minimalized as much as possible
- A formation of mosaic embryo leads to another set of problems where a genetic modification is applied to one cell, but the alteration does not reach to all the cells in the developing embryo. This results in an unpredictable outcome of an unevenly altered embryo
- If these scientific innovations are left unregulated, various groups will certainly pursue germline edits that target lifestyle enhancement or alterations. It gives way to eugenics and exclusivity of gene-editing domains defining beauty.

REGULATION OF GENETICALLY MODIFIED ORGANISMS IN INDIA

Rules, 1989

In accordance to the Indian laws, the Genetically Modified Organisms (GMOs) and its resultant products are governed by the "Rules for the manufacture, use, import, export & storage of hazardous microorganisms, genetically engineered organisms or cells, 1989" (hereby referred to as Rules, 1989)[iv]. Notified under the Environment (protection) Act, 1986, the regulations under Rules, 1989 are implemented by the Ministry of Environment, Forest and Climate Change (MoEFCC) with due diligence to the powers conferred by Sections 8 and 25 of Environment (Protection) Act, 1986.The rules, as such, are broadly defined for GMOs and its products thereby, covering an entire array of such gene-edited specimens. Under the Rules, 1989, composition of six component authorities is notified into three broad functions: Advisory, Regulation and Monitoring.[v]

- Advisory Committee(s): Recombinant DNA Advisory Committee (RDAC) takes notes of developments in biotechnology at national and international levels, giving recommendations on the laws governing GMO and its products
- Regulating Committee(s): International Biosafety Committee (IBSC) has to be essentially constituted by every institution willing to conduct research on GMOs and Genetic engineering. The Review Committee on Genetic Manipulation (RCGM) monitors the safety related aspects of the on-going research conducted by institutions on GMOs. However, the Apex committee of regulation is Genetic Engineering Appraisal Committee (GEAC) which approves or disapproves researches that involve large-scale hazardous microorganisms and recombinant products that have a detrimental effect to the environmental factor
- Monitoring Committee(s): The State Biotechnology Coordination Committee (SBCC) is constituted in every state to monitor research conducted for GMOs. Similar applicability of functions is laid on the District-Level Committee (DLC), which oversees the safety regulations in installation and usage of microorganisms and its application in the environment, public health, pollution control etc.

Approvals and Prohibitions

Section 7 of the Rules, 1989 elaborates the approval and prohibitions, safeguarding the usage and implementation of GMOs. Accordingly, without the approval of the GEAC, no person can "import, export, transport, manufacture, process, use or sell any GMOs, substances or cells".[vi] The above statement attempts to highlight certain essential dimensions:

- Trade of GMOs;
- Their manufacturing and processing;
- Buying and selling of such substances or cells

The use of pathogenic organisms or GMOs or cells for research purposes shall only be allowed in laboratories or inside laboratory areas informed for this purpose under the EPA, 1986.[vii] The scientific experiments involving GMOs for educational purposes can be undertaken with the oversight of IBSCs.[viii] This implies that deliberate, or even, inadvertent release of GMOs are not allowed.[ix] GEAC shall also have the powers to revoke approvals in case[x]:

- Any new information regarding the harmful effects of GMOs
- The damage caused by these substances or cells could not be foreseen when the approval for it was claimed
- Non-compliance of any conditions specified by GEAC

Supervision and Penalties

The GEAC supervises the implementation of all the terms and conditions laid down in coherence to the approval granted by it. The Committed does its job of supervision through the state-level or district level committees or with the approval of any authorized person. As far as penal consequences are concerned, the District or State-level Committees can take all the necessary steps against the person who is responsible for the damage to "environment, nature or health"[xi] The Rules of 1989 provide for an overarching law for all the GMOs – whether crop or animal, somatic or germline. This persists a problem of not having into effect a streamlined legislation to focus on individual products or organisms, human gene-edited organisms per se. A prevalence of ambiguity can be seen as to whether newer technologies of genome editing, such as CRISPR-Cas9, are covered in the definition of 'genetic engineering' in the Rules which refers to a modification of gene through "gene technique".[xii] The competent authorities established under the rules, may also, review the experiences of other countries or organizations in the global perspective, while dealing with such emerging technologies.

Guidelines by Indian Council of Medical Research

Indian Council of Medical Research is the supreme body for development and regulation of biomedical research. ICMR's Ethical Guidelines for Biomedical Research on Human Participants of 2006 is one of the only laid down rules for clinical research of the genome. Chapter VI of the guidelines titled Statement of Specific Principles for Human Genetics and Genomics Research has discussed DNA research. In the subsection (iii) of part III of this chapter, gene editing for enhancement of humans has been discussed. The idea of a designer baby has clearly been put down by the guidelines. The reasons given for the same is lack of information regarding the risk relating to gene therapy. It has further called gene therapy for the subject and the doctor unethical. It will also be unethical to design babies with superhuman characteristics.

One must remember that these guidelines were laid down almost a decade and half ago. The term "gene editing" is not even mentioned in these guidelines instead gene therapy and gene enhancement has been used. It was only in 2017 that the ICMR and department of biotechnology came up with the National Guidelines for Stem Cell research which talked precisely about gene editing and CRISPR-Cas9.

The three main areas of aim and scope of these guidelines are -:

1. To have a monitoring mechanism and a regulatory framework for the issues concerning clinical research and and development of products in those areas.
2. Propagating stem cells lines and to bank and distribute them. Gametes, embryo and somatic cells for derivation have to be procured.
3. Spreading awareness and informing important interested bodies, exchanging stem cells/lines by collaborating with other international organizations.

Section 8.2 of the guidelines talks about restrictive areas of research which have been defined as issues of contention which need additional monitoring. The Section 8.2.8 discusses in detail about CRISPR-Cas9. It lays down the process as to how the gene editing research is to be carried out. They are only restricted to *in vitro* studies and first it needs to reviewed by Institutional Committee for Stem Cell Research (IC-SCR), Institute Ethics Committee (IEC) and Institutional Biosafety Committee (IBSC) and finally by Review Committee on Genetic Manipulation (RCGM). The research team should have the required skills, expertise and proper resources for the research. In addition to this, the embryos, gene editing and gametes used in the research should be spare ones. Their sources should also be defined. And finally, the gene edited human embryos should not be propagated more than 14 days of fertilization of primitive streak.

So, a transition can be seen in the approach towards gene editing when comparing the 2006 guidelines to 2017 ones. The 2006's guidelines totally rejected any attempt towards gene editing, citing lack of information and unethicalness as the reason, the 2017 guidelines take a more contemporary stance at it by forming strict regulations. But even the 2017 guidelines fail at understanding the complexities involved in gene editing.

COMPARATIVE ANALYSIS OF GENOME EDITING NORMS

United States

Regarding gene editing technologies, there are no federal laws that restricts the conduct of experiments aimed at morphing human DNA or certain banning protocols on the same. However, federal control can be seen through allocation of federal funding towards research projects on gene technology, granting approval to run gene therapy clinical trials on humans and awarding FDA (Food and Drug Administration) approval in terms of gene being a marketable product. The official position of FDA, as of 2019, is that federal money can be used to conduct research on somatic cell therapy and not on germline cells. By this, the FDA has the capacity to reject human experimental trials that alter germline cells, preventing eugenics and its entry at the marketplace. However, in California, a bill that prevents companies from selling CRISPR kits was passed. This became the first American legislation overseeing the use of CRISPR.

China

After the event of CRISPR twin babies, the Chinese government issued new regulations on gene-editing technology. In the country's draft of the new civil code, a list of human genes and embryos were included as personality rights ought to be protected. It gave way for gene experiments in adults or embryos that endanger health or violate the ethical values. This, in itself, can be seen as a violation of a person's fundamental right to personal life and to live with dignity. The move of including gene editing norms in the Chinese legislation was a last-minute addition, but a welcomed one. The twin baby experiment was claimed by Jiankui to be a scientific attempt of DNA A engineering that may make the babies less susceptible to contracting HIV. Even if Jiankui's work made it less likely for the twin girls to get HIV, there lies a possibility that they, now, have the susceptibility to other infectious diseases or genetic disorders. While Jiankui remains in hiding, it is unclear as to what happened to the genetically modified twins. Perhaps, they are under the supervision of the Chinese government.

Russia

The Russian Ministry of Health, being the key national regulator for germline editing in the country, published a statement announcing their consensus with the WHO regulations.

Comprehensive research, along with a global registry for clinical human experiments, is an essential towards setting global standards for the governance and regulation of human genome-editing technology[xiii].

Regulation in Other Countries

The regulations relating to gene editing in the different countries of the world are heavily inspired by the US, particularly with respect to the centrality of pre-market risk and benefit assessment. For instance, gene therapy in South Korea has a pathway consisting of a system of conditional approval for gene editing. The United Kingdom has intense pre-market risk and benefit review, similar to the United States, but it lays special emphasis on therapies involving gametes or embryos for more strict regulation. UK's biotechnology advisory system for somatic gene therapy involves inter-relation between the Gene Therapy Advisory Committee and the Health and Safety Executive Scientific Advisory Committee on Genetically Modified Organisms. The U.K. Clinical Trials Regulations lays down rules for approval from Medicines and Healthcare Products Regulatory Agency before the medical research on genes are carried out. The European Union has far stricter regulation for quality control for advanced therapy medicinal products, which includes gene therapy products. In Japan, new products are sorted prospectively by level of expected risk and are regulated accordingly. Similarly, Singapore has adopted a risk-based approach, when it comes to the question of gene editing.

CONCLUSION

The level of development in the area of gene editing has been remarkable in the 21st century. The coming up of CRISPR-Cas9 technology can be credited with the development of genome editing. The issues related to this technology have also been very concerning. What CRISPR-Cas9 seeks to achieve is something which has always fascinated the human race that is the idea of a superhuman or being which is supremely skilled. The popularity of science fiction novels and movies clearly proves this. But it has also made us anxious because of the fear of the unknown. Nobody has truly explored the potential and risks associated with this technology

and this coupled with the unaccountable governments running their own research raises some deep concerns.

In India, there is no proper structure in place for when it comes to legal framework for the technique of gene editing. The guidelines of 2006 and 2017 by the Indian Council of Medical Research are not legally binding and therefore, don't have much scope for applicability when it comes to regulating individual or even sponsored research. This lacuna of the ICMR guidelines should be addressed primarily for two reasons - to foster regulated research and to hinder quackery and malfeasance. A variety of genetic disorders as well as several diseases need a regulatory environment that results in sound gene-editing techniques. However, this is not the current scenario. The ambiguity in terms of the guidelines and paradoxical attempts to even meet the obligations already laid down in some of these guidelines. With the proliferation of illegal and dangerous activities such as caste biases, IVF centers and stem cell therapies, the problems have worsened. Biohacking kits which are popular in the US might soon be emulated by India. These guidelines deal with the technicalities of gene editing of human cells or their derivatives. Even the Rules of 1989 provides for a general legislation for all types of GMOs and because of its wider scope has left uncertainty in the ambit of terms such as 'gene technology'. Many of the ethical concerns on human experimental trials have already been addressed in the guidelines and the pertinent legislation in India. However, focus has to be given to a regulatory pathway for basic clinical research and product development, considering the objective of research and extent of acceptability of such research and scientific technique.

When looked at from the technological viewpoint, the Personal Data Protection Bill, 2019 is the most recent bill to mention the concept of genetic data. Even though the bill has not been passed, it has become a subject of deliberations and discussions. Section 3 (19) of the Bill defines genetic data as the data acquired through genetic nature of a person and comes from the analysis of biological samples of the concerned person. The bill categorizes data of such genomes as sensitive personal data, therefore, recognizing the importance and vulnerability the genes carry. Also, section 27 of the Bill discusses data fiduciary intending large scale profiling of genetic data and that such processing should not be done unless the data fiduciary has undertaken a data protection impact assessment. A separate legislation is needed for regulation of biotechnology in India. These uneven and broad mentions of medical science and research

in various legislations brings about uncertainty in the protection of genome as a data and the protection of such technology that brings about genome modification.

Among the variety of legislations prevalent in different nations governing genome editing, emphasis has to be given to the importance of a global framework for regulating and preventing irresponsible and unacceptable application of gene-editing technology. The World Health organization has set up a new advisory committee to develop global standards for regulating genome-editing norms. The committee has called for the creation of a new transparent global registry in which the details about all human experimental trials will be recorded so that clarity is maintained for the protection of genome data and its technology. India, can strive for such clarity by bringing into a persuasive effect of the guidelines set in accordance to the global perspectives. If, by doing so, an optimal level of efficient transparency is achieved, then the future implications of safeguarding human trials of gene-modification will not be as dismal as the prevalent regulations are, as of now.

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