**STARTING THE CONVERSATION: CRISPR’S ROLE IN INDIA**

Review comments

**Reviewer 1:**

1. The article is timely because of the wide ranging international debate on the science and ethics of the easy to use CRISPR technology for gene editing or genetic engineering. It makes a forceful case for formulation and implementation of strict context / India specific regulations before making this technology available for use in the country. It also explains a few social specificities of India to be kept in mind while doing so.

However, there are the following serious shortcomings which the author must address and revise the paper accordingly:

2. The author states: “In response to these scientific advancements countries across the globe have put forth certain restrictions on gene editing”. This is one of the many sweeping statements made by the author in the article. It is important to state some basic principles used in developed countries for imposing restrictions so that readers are able to judge whether such restrictions would be equally valid in India or something more would be needed to address India’s specificities. This is also because later on in the text the author states that we just cannot confine ourselves to what the developed countries are doing as India has some different problems.

Response: We agree that it is important to paint a global picture of what gene-editing regulation look like, so that the reader can understand where on the scale of regulation India stands. We have therefore incorporated the stances of several countries into this paragraph. We decided not to detail the basic principles used to create such guidelines as we feel that this would detract from our argument, which is that morally concerning point lies not within differences in principles for gene-editing, but differences in the regulation of guidelines within each country’s infrastructure.

We have also clarified this later on in the paragraph, where we note that it is the fact that these guidelines are not translated into law, coupled with the difficulty of enforcing any restrictions, that raise the concern for potential misuse and manipulation.

3. The author states: “India has not created a framework for regulating clinical trials using CRISPR technology.” To what extent is this assertion valid and how? Clinical trials are regulated by Schedule Y of the Drugs and Cosmetics Act. The article does not say whether clinical trials with CRISPR are covered under Schedule Y, and if not, why not. And what changes are needed in it in order to cover such trials. On the other hand, it seems the author does not consider the ICMR-DBT’s 2017 “National Guidelines for stem cell research” having any relevance to the gene editing research. But the author should not ignore these guidelines because the title does not mention gene editing or genetic engineering. A simple reading of these guidelines along with the institutional mechanism for their application would show that they do cover all kind of genetic manipulation in research as well as clinical practice. In fact Section 8 provides for the list of “permissible”, “restricted” and “prohibited” areas of genetic research. These and other guidelines would clearly show to the author that the ICMR-DBT guidelines have a framework regulation, though the author is at liberty not to agree with it.

Response: This was an important recommendation by Reviewer 1, and we have now clearly explained that guidelines for gene-editing do exist, with germ line editing being prohibited.

4. Although these guidelines are still not converted into specific law, like the ICMR’s ethics guidelines for clinical research; they are not without some indirect avenues for legal regulations. Above all, they provide a regulatory framework. In the article, the author talks about India-specific issues to be kept in mind for regulating or restricting the CRISPR, but the author must explain whether those specific issues are covered in the ICMR-DBT guidelines or framework. If not, it would be useful to explain how they could be covered in such guidelines.

Response: We have called into question the legal enforceability of this framework. We explain that the fact that the guidelines have not been converted to law is concerning and we elaborate our concern about whether the existing regulatory and legal infrastructure is up to the challenge of regulating gene-editing technology efficaciously and ethically.

5. In 1970s and 80s it was believed that genetic engineering would be a game changer, and the critics felt that it would be massively misused in medical practice. None of this happened as spectacularly as was predicted. While talking about the misuse of such technology in the past and at present, the author provides no example from medicine but jumps to the application in the genetically modified – GM - crops. This is contrary to the earlier statement that advanced countries have better regulations in place because, GM crops are product of the advanced countries, patented and controlled by their corporates. The author may find it useful to explore how in the USA, the application of genetic technology on human beings is regulated in the same way as drugs, but not so well in the non-drug areas(on plants, animals etc). It is important that the article shows awareness of the nuances of the regulatory issues in the developed countries as well as in India.

Response: We have provided the medical example of stem cell technology misuse to bolster this argument, we would also like to point out that we have discussed the misuse of ultrasound for illegal sex determination and the subsequent consequences later on in the paper.

6. The article constantly emphasises the “inter-generational” effects of gene editing technology. This is only a partial story. Intergenerational issues are connected to its use on the germ line or pluripotent cells; but that is not so when gene editing is done on somatic cells. While the use on the former is opposed by many scientists (see International Summit on Human Gene Editing, 2015 demanding a moratorium), the latter, in terms of clinical applications to treat certain diseases, is not so strongly opposed.

Response: We have removed such statements from the paper.

7. The author correctly talks about the investment of resources in technology that may be used to treat only a few diseases of rich people. However, this is also a partial story. There are neglected diseases affecting the poor almost exclusively where this technology, if clinical application is discovered, could make a big difference. For example, the Sickle Cell Diseases affect mainly a large number of people from Scheduled Tribes and Castes, most of them very poor and this technology may be the only way to find cures for them.

Response: We agree that gene-editing technology can be used for medical benefit as well, but our concern is that market and social demands could result in the misuse of such technology if regulations are not in place to prevent this.

8. The author has mentioned sex determination technology, the sex ratio issue and issues related to discriminatory selection of skin colour etc in the assisted reproduction. The sex determination related aspects are covered under the India specific law, the PCPNDT Act (it is not mentioned). This law is completely different from the permissible sex selection framework used by the developed countries. Is the author arguing for similar India specific laws for gene editing? If the emphasis is not so much on the India-specific content of law and regulation but is on setting up regulatory mechanisms (the agency, governance), then what changes are needed in these mechanisms to make the regulations succeed?

Response: The emphasis is not so much on India-specific content of law, but to highlight how social forces have resulted in technology being misused to meet these unique sociocultural demands. Our point is that if past medical technology has been misused because of these social driving factors, then it gives us good reason to believe this could be the case with gene-editing technology as well.

**Reviewer 2:**

1. I enjoyed reading the article “Starting the conversation: Crisper’s role in India”, overall it covers India specific issues in the topic.
2. The major drawback in the article is that it depends heavily on newspaper articles and blogs as sources of information. These sources could have a bias because they are often written based on personal views of the authors with limited data. It would be ideal to check more peer-reviewed scientific data to support the facts.

Response: We have bolstered much of our paper with several authentic sources, such as those from *Nature Asia etc.*

1. In continuation of the above comment, statements like “Corruption within such organizations is so rampant that India’s medical administration is ranked as one of the most corrupt in the world” need authentic sources as references, rather than newspaper reports.

Response: We have reworded this to elaborate and added a more authentic source.

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