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Gene Editing – Ethical Pathways to Connect Science & Society

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Abstract: Effective translation of scientific advancement for health benefits needs integration of ethical values which can guide better outcomes and help to connect with the society to reap the fruits of knowledge. As gene editing procedures are evolving with a promise to offer a cure for innumerable diseases, the time is right to put in place a suitable governance framework which integrates the ethical and moral values to enable an appropriate use of the proposed technological advancements. The paper discusses the need to include ethical considerations, improved communications, ensure transparency and accountability, accessibility and affordability, building capacity, collaborations, and defined regulatory processes in order to have a better uptake as well as to build public trust in the technology.

Keywords: gene editing, molecular scissors, governance framework, new technology, integrate ethics, ethical values, build public trust.

Introduction

In the year 2020 The Nobel Prize for Chemistry was awarded to two women scientists for their research work involving development of method for genome editing. This was a huge encouragement for the emerging role that this promising technology may play in improving human health in the near future[1]. The power of CRISPR-Cas9 technology and other similar molecular scissors used for editing the gene may allow scientists to make major strides in tackling serious debilitating diseases which otherwise have no cure. There is a potential to treat more than 10000 monogenic genetic conditions as well as complex polygenic disorders. These technologies offer huge hope, though it's still a long way to go. It is important to start planning for a suitable governance framework that would enable appropriate use of the proposed technological advancements. The ethical and moral considerations must get integrated in this evolving governance framework right from inception.

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This framework would guide the researchers as well as policy makers in the development and implementation of this new technology and thereby help the society to reap the full benefits.

During the last decade, bioethicists and researchers from across the world have debated and have pointed out a number of concerns regarding ethical and societal issues that may arise due to use of gene editing technology (Brokowski and Adli. 2019; Fani et al, 2018). Thus, the time is ripe for India to discuss scientific and ethical concerns, propose a regulatory and governance framework, identify ways of tackling biosafety issues related to the use of the novel technology. On one hand there is need to support basic science research and on the other hand identify and define what would be socially relevant research for betterment of mankind. In view of the large size and population which is multilingual, multicultural, socio economically diverse, having different religious beliefs, enormous efforts are needed to rightfully reach out to the stakeholders and explain about the technology and its pros and cons. Steps have to be initiated to facilitate improved understanding and create opportunity for autonomous decision making based on actual facts rather than false beliefs. A lot of efforts have to go hand in hand to engage, educate, improve dialogue and understanding the societal concerns. Since this is a new technology, that is still evolving but has an untapped enormous potential, all stakeholders need to work together to explore newer avenues to fulfil the promise towards unprecedented improvements in human health.

Somatic and Germline Editing

The capability to make precise changes to the human genome whether somatic or germline raises all kinds of difficult questions about how far we should go ahead with it for it to be used in a manner that is accepted by the society. This is also the time to discuss and understand the basic differences related to the fact that the changes could be heritable in case of germline gene editing and therefore there are some questions whether genome editing be used to avoid genetic diseases or can it be justified for genetics enhancement for serious disorders. It's time to think where does one draw a line about what can or cannot be allowed. Should germline gene editing be allowed for some conditions? What kind of heritable changes can be allowed to be inherited? What can be the long term effects of these

changes and is there a worry related to changing the gene pool? Can they create mosaics? Are there possible effects on the future generations? There is dilemma if the germline gene editing would qualify as a boon or bane for mankind (Krishan *et al*, 2018). Somatic cell gene editing may require very similar treatment to other research since the changes are not a heritable and will not go to the next generation. It has a therapeutic potential and may eradicate disease promising a better life. However, there is need for abundant caution since in the present state of our knowledge, gene editing may present issues that are still unresolved.

An international moratorium was announced on clinical use of human germline editing which does not allow creation of genetically modified children and allows time to debate about the moral, ethical, scientific, societal, legal issues and to establish regulatory frameworks that would govern the technology[2] (NAS, 2015). There is a gradual move to open up but there have been a few scandals such as the birth of the twins in China with the gene edited for HIV which was looked down upon by the world. Even though considered a scientific advancement, it was determined to be ethically and morally unacceptable. It was criticized and outrightly rejected by the scientific communities since investigators had faulted on many accounts such as safety assessments, ethics review, informed consent etc (Regalado, 2019; Kleiderman and Ogbogu, 2019). This example clearly highlights the importance of having a governance and monitoring framework and ensuring that scientific research is carried out in a manner that is socio-culturally acceptable and relevant to serve societal values and customs. There is an added responsibility to allay fears, such as those, that may be related to irreversible changes in germline, inaccurate gene editing, off target mutations, deleterious mutations, unknown affects, implications for future generations, interaction with other genetics variations or even environment the high chances of being misused for prenatal testing, damaging further sex ratio, unmonitored and unreported fetal manipulations, ethics of creating designer children, eugenic manipulations, enhancement, commodification and possibilities of exploitation of sorts (NAS, 2017).

Integrating Ethical Considerations

Ethics plays an important role in improving scientific value of research and its translation to public good. Integrating the ethical principles and values

would go a long way in imparting protection to research participants and improving quality of research outcomes. The objective of an ethics review process is to look at both science and ethics to guide the researcher to better conduct of a research study which has social value, ensures safety and well-being of participants, protects their rights, involves monitoring and avoids undue harm. It must also provide an opportunity to participants for better understanding, as well as autonomous decision making (ICMR, 2017). It is therefore important that research involving gene editing be carefully reviewed by an ethics committee which is competent, updated, timely and independent in its review and decision making processes. The suggestions from an ethics committee can improve the study design conduct and its outcomes as well as impart better protection to the participants. At the present moment the promise of benefit in terms of its therapeutic potential looking at curing diseases is huge but so are the associated risks and long term outcomes mostly due to use of a novel technology. It still remains to be seen how the benefits will be balanced in a manner that the benefit risk ratio is in favour of the mankind. How can gene editing be used safely so that benefits can be assured and risks can be minimised? This is the question that needs to be answered now.

There are number of unclear risks of the technology at the moment and many of these are unknown and unproven at the present state of knowledge. Use of technology should also ensure that there is no exploitation of any person or community and appropriate counselling and consenting processes are in place to protect the people. This becomes even more important when dealing with persons who belong to the vulnerable category, which could be due to their disease, condition, age or lack of understanding due to their profile. These persons need additional protection not only for their safety as they may not be in a position to protect their own rights but also their autonomy. For all participants, the privacy and confidentiality aspects need due consideration as genetic research commonly can result in stigma and discrimination (Tavan, 2004). A small leak of information about a genetic condition, can lead to ostracisation of individuals as well as their families by their communities and also have implications related to be denied health insurance or even employment. Any identifying information of the persons has to be properly safeguarded and clinical records be filed carefully with access limited to only select authorised persons. Any collaborative research

where data sharing is needed must also take care of the concerns related to personal clinical information of the individuals who are part of this work.

Counselling and Informed Consent

An appropriately informed and understood consent is an important requirement and must be carried out in a manner that improves voluntary decision making without any undue influence or coercion to force participation. This is the basic requirement for any kind of biomedical research, however these considerations become all the more important when dealing with any new technology. The explanations should be made in a language and manner that is easily understood. Terminology used in genetics is usually not simple to understand and technical jargon that can easily be misinterpreted if not explained well. Genetic testing or interventions must always be accompanied with a pre and post counselling in a non-directed fashion to explain the available choices, limitations, probable outcomes, to facilitate good discussion, understanding and a voluntary informed consent after an opportunity has been given time to discuss with family or friends, without any undue pressure or coercion to agree to participate. There should be ample opportunity provided to decline from participating and even if agreed to once, be free to withdraw from the research at any time. It is important to share information related to possible side effects, many of which may be unknown in light of the existing knowledge. It may not be simple to explain gene editing and how it may impact life in the long run as there are many unknowns at this point of time.

However, this should be seen as an opportunity to discuss openly and allay fear or doubts and truthfully reply to any queries. The process should not be rushed and there should be ample time and opportunity in private to discuss this in detail. The engagement must be done in a culturally sensitive manner and in a language that is well understood and preferably by someone, who could even be a genetic counsellor, or a lead investigator who can devote time to patiently and correctly reply to all questions as per need. The informed consent is a process and not just signing a sheet of paper and the interaction has to continue for the duration of participation and even when the study is over. And once the results are available they need to be explained to the individual as reports stating genetic variations/ mutations/ genome sequences and gene edited or modified sequences, and

their implications would hardly be understood. Any new findings and the implications of the same on the health of the individual or the family must be explained.

Transparency and Accountability

New Technologies come with an inherent challenge, in view of lack of complete understanding as well as fear of their long term implications. There is need to clarify who will be accountable in case of an unforeseen untoward event, what happens after. As a good ethical practice, it is important to understand and implement responsible use of gene editing technology and to have provisions in place to safeguard, provide medical management and compensation for any research related harm. All procedures and processes followed for gene editing processes should be as per approved protocols, and efforts should be there to ensure transparency and accountability. Before implementing, all protocols must undergo thorough scientific and ethics review, peer review process to ensure latest understanding and to the extent possible, this information should be available in public domain. All involved stakeholders have the joint responsibility to ensure that the safety and well-being of participants is ensured and risks are minimised. The research results once available must be quickly published in science journals whether the results are positive or negative and also be available on public databases such as Clinical Trial Registry of India (CTRI)[3]. Efforts must also be made to disseminate results and facilitate translation of these outcomes for the benefit of others. This can only be built and improved over a period of time. As science moves forward, there is a need for an ethical framework that facilitates socially relevant research and open dialogue, transparent processes, accountability and good communication amongst various stakeholders regarding use of genome editing technology seeking solutions towards improvement in human health (Mathur, 2018).

Communicating Science and Building Public Trust

The connection between science and society is of paramount importance and unless this societal connection is made, even the best of science would not be able to deliver and to bring about a change to betterment. The ethical issues related to gene editing have to be handled upfront to reap the full benefit and communication has to be improved and to be carried out in a

manner that it is easily understood by masses. Communicating science effectively required skills, interest and initiative to unfold its complexity (Fischhoff, 2019). The issues related to gene editing require a detailed discussion between researchers, clinicians, bioethicists, philosophers, ethics committees, legal experts, religious leaders, social scientists, civil society, patient representatives, members from press, agencies, sponsors, policy makers and others. Therefore, to make this work, as we evolve and learn to apply this technology for human betterment, efforts have to be in place to understand, connect, rightfully communicate, engage with the society and have a public discourse so that all pros and cons can be debated upon. This needs fair, honest and open discussions and utilising available platforms for advocacy. The need of the hour is to understand the local traditions, customs, or religious beliefs that may influence public opinion. An open dialogue will help to improve understanding, allay fears, clear doubts and eventually help to build trust in the technology. Usually, scientists develop technologies in the lab, publish their findings and then there is a disconnect with the society since these results are only available to a small audience who reads science journals and not available to the public at large. Efforts have to be made to connect with the masses, by translating these findings in simple form or manner so that they are useful for a much larger audience. All stakeholders must come together to find ways of engaging with the public and this has to begin right at inception of the project. They must discuss upfront details of plan, expected results, possible limitations, ways of sharing results and long term plans for translating outcomes to public health benefits. In addition, a discussion on ways of tackling mistrust, dispelling unnecessary fear and building positivity must be undertaken. An important consideration is also the fact that public trust cannot be built overnight and the engagement is a process which depends on how often and how well the scientists communicate, respond to and engage with public in a language and manner that is understood. Some of the approaches that are helpful are; having open public debates at regional level, wider consultations with stakeholders, developing advocacy material in simple language, engaging with print as well as social media, through newspaper articles, or the TV channels etc. Considerable amount of effort is needed to really do a good communication which helps to build public trust for both science as well as research community at large.

Ensuring Access to Technology

Another important consideration is to identify plans to make sure that the gene editing technology would be accessible to people who need it. At present one doesn't know well, if this is going to be a very expensive technology and be available to the very select few who may reap the advantage (Mittal, 2019). Would it really be ethical if the technology has limited access to few privileged by their position and the general population is largely unaware and with limited resources to access this. It is important to discuss what uses of technology can be permitted and for whom? How will people be able to access these? What are the pathways to ensure equitable access? For it to be ethical, the powerful techniques should not only be available to the most powerful but to the common man. The issues related to access should not lead to further widening of the gap between those who can or cannot afford to have it. On one hand is the challenge to make technology acceptable and to remove the unwarranted scare and on the other to ensure that the technology is used for betterment of many and not just the elite. Investments are needed to facilitate development of technologies that will not only be accessible but also be available at affordable costs to those who need them. In India a lot of support is expected from the government agencies as well as other sponsors for research so that science can evolve in the labs and in parallel efforts can be initiated to educate, train and develop advocacy methods to create better understanding which will eventually help in improving its acceptability.

It is also important to see that India progresses ahead and will be in a position to cater to the needs of the country when the fruits of research have ripened. There is an angle of commercialisation and profiteering from the technology as most of the genetic workup comes at huge costs and is not easily available but at very few specialised centers. Even though the technology in itself may not be expensive however, there is enormous interest amongst private players due to its commercial potential towards treatment of variety of serious genetic ailments, cancers and other polygenic diseases. As science moves on to offering personalised medicine to human beings, the technology runs the risk of being used for only those who can afford this. All of these issues need discussion on a wider platform to safeguard ethics, equity and access to novel methods to improve human health.

Capacity Building & Collaboration

There are few institutions that have the infrastructure and mandate to undertake intensive research related to gene editing. Unless there are more opportunities the technology will remain limited to influential and there will be limited trained manpower available to work around novel research methodologies. The institutions need to provide a supportive backing with an environment that cultivates and nurtures cutting edge research, provides an environment for innovative work, independence to undertake scientific explorations, and infrastructure to commit to this cause. The support from institutions in terms of their policies and leadership is important to provide encouragement to undertake research, scientific and technological developments. Research may require investments for lab work and also to build in opportunities for mentoring, training, collaborations, sharing of resources, joint research programs, platforms for exchange of ideas. Collaborations between partners to have clear objectives, areas of cooperation, roles and responsibilities, sharing of data, publications, patents and other such considerations (NAS, 2017). They should also take care that any biological material and data sharing on global platforms or other observatories takes care of individual privacy issues. The country must build its capacity to work on gene editing and eventually to develop the connections for bench to bedside translation involving medical professionals. A lot of efforts are now needed to initiate dialogue, foster collaboration and trust amongst all stakeholders. Being a new area, there may be need to train more scientists and medical professionals to join hands to develop methods that can improve human health following the right regulatory and ethical procedures.

Ethical and Regulatory Governance Framework

There are several stakeholders who are connected with the governance of Gene Editing. It is not only the researchers, but ethics committees, institutions, sponsors, regulators, government agencies and all others involved in review, monitoring, funding research. The governance framework should be developed in a manner that it supports quality research, helps to translate benefits to the population, regulates, monitors and safeguards the interest of the population. There is need to initiate a discussion to understand

the type of frameworks needed to regulate the technology to promote use that serves the public interest. Even though there are no direct regulations, however, there are existing guidelines and regulations that would facilitate mechanisms to govern gene editing research and applications. The ICMR National Ethical Guidelines, 2017 have discussed the ethical aspects that need to be considered while using gene editing technology (9). All clinical trials for product development need to follow the New Drugs and Clinical Trial Rules, 2019 which have provisions that will allow for regulation of the new technology by *Central Drugs Standard Control Organisation* (*CDSCO*) and govern the conduct of clinical trials for use of any new technology on humans (CDSCO, 2019). Also ICMR and DBT have jointly brought up a new National guideline document on gene therapy, product development which provides description of requirement for the research and clinical trials (ICMR-DBT, 2019). The guidelines have also given a flow chart to explain the step wide procedures to be followed including review by the DBT committee on gene/ genetic modification and the Institutional biosafety committee which is involved in oversight. As of now the germline gene, therapeutic and gene editing for therapeutic purposes, in utero gene editing is prohibited in India and somatic cell gene editing can be pursued as a clinical trial study. The applications will need the approvals of various committees before being submitted to the CDSCO to be carried out as a clinical trial with a pre-clinical and clinical research model. The existing frameworks can be further tailored and strengthened to support research and use of gene editing technology. There is a need to develop the expertise and the capacity within the regulatory system to handle gene editing related concerns and guide against potential misuse. The government needs to make the right investments now, to support good research through grants, ensure quality outcomes and putting into action an appropriate ethical and regulatory framework for monitoring this technology.

Conclusion

In pursuing gene editing, the first step is to build bridges between science and society through pathways guided by ethical values to developed a framework. The importance of increasing awareness of various aspects of gene editing is important not only among public also but also amongst other stakeholders such as clinicians, researchers, regulators and agencies.

Being a new subject, education as well as understanding even among medical fraternity would be limited and efforts are needed to change this and promote research. This is an ever evolving field and we need to learn as the science evolves and there are new global experiences that would guide evolution of guidelines and regulatory framework. Pursuing state of the art quality research in the country can bring out safe affordable accessible reliable technology in future which can be made available to common man at affordable costs. The approaches have to be humane to serve societal interest and efforts be made to keep coming up with the advancement in technology to put it to full use through adequate engagement and communication. It is time that this topic is discussed openly so that the fruits of this technological advancement can be reaped by our population.

Endnotes

1 Genetic scissors: a tool for rewriting the code of life. 7 October 2020. The Royal Swedish Academy of Sciences Nobel Prize in Chemistry 2020 awarded to Emmanuelle Charpentier & Jennifer A. Doudna "for the development of a method for genome editing". https://www.nobelprize.org/prizes/chemistry/2020/press-release/

2 Eric Lander, Françoise Baylis, Feng Zhang, Emmanuelle Charpentier, Paul Berg and specialists from seven countries call for an international governance framework. Adopt a moratorium on heritable genome editing. 13 March 2019.

3 Clinical Trial Registry of India (CTRI). http://ctri.nic.in/Clinicaltrials/login.php

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