Ethical Controversies and Challenges in Human Genome Editing

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ABSTRACT

Human genome editing consists of human somatic cells editing and human germ layer editing. Somatic cell editing utilizes all human cells except reproductive cells. Germ layer editing includes reproductive cells. Any changes made by germline editing is passed through generations. Arrival of CRISPR technology and its increasing utilization has also raised concern and controversies in ethical areas. Somatic cell editing enables cells causing heritable disease to be replaced by normal somatic cells and elimination of heritable disease. Further basic and clinical research for somatic cell editing have increased for therapeutic purposes, and are considered an asset for the elimination of heritable disease in the future. At present, the ethical needs in somatic cell editing are safety, risk-benefit calculation, protection of vulnerable subjects, informed consent and equity of access. The ethical concerns and controversies surrounding germline editing are: whether potential benefits outweigh the potential risks, therapeutic need, affordability and equity. The most important controversy lies in intergenerational effects and raises the question as to whether the benefits outweigh the risks of utilizing germline editing. Further, this type of research and clinical process violates fundamental values, ethical governance and societal safety. The ethics of embryo research is also in need of revision because of controversial research conducted by Dr. H.E. Jiankui. Slippery slope concerns, for example, 1. allowing basic research in human embryos with germline editing 2. risk of moving from basic research to therapeutic stage and 3. allowing basic and clinical research with genome editing of somatic cells may open the door to basic and clinical research on germline editing. Thus, safety and beyond safety concerns, with lack of good governance, pose: danger of potential harm to the child who was unable to give consent to this process, potential for any state to impose eugenic application, commodification of children, social inequality and criminal use of this technique, are still to be resolved. In spite of the benefit of resolving human illness, ethical questions, controversies and challenges remain, particularly from human germline editing.

KEY WORDS

human genome editing, ethical controversies, human germ layer editing, human somatic cell editing, basic and clinical research
Organizing Committee of the 2015 International Summit of Human Genome Editing44,45,46 and 2) The 2017 US National Academies of Science, Engineering and Medicine (NASEM)14,15. These groups along with other ethicists and researchers suggestions, places CRISPR somatic genome editing to be governed by existing ethics for gene therapy. The view of these groups and ethicists is that CRISPR somatic genome editing does not cause any concerns and challenges. Thus, the gene therapy ethical committee will be sufficient to appropriately and rigorously evaluate potential safety, harm, and benefits of somatic cell editing. NAS-NAM reports have also suggested that gene therapy committee is sufficient enough to manage somatic genome editing with a strong and rigid ethical safeguard14,15. According to this group, the gene therapy regulatory mechanism has been very successful in preventing unauthorized uses of research in the area of gene therapy research. The opposing groups23-26 indicate that CRISPR somatic genome editing is novel, unprecedented and questions whether the sufficiency of existing gene therapy regulation is able to govern efficiently for the extension of their new responsibility. The lack of capability and the lack of coordination across jurisdictions, will hamper the evaluation of safety, efficacy and utility. High variability of biological manufacturing processes for the individual focus need, protection of the vulnerable patient, informed consent, and above all stakeholders for further conversation requires separate ethical regulatory mechanism for the somatic genome editing. However, majority views are that human somatic genome editing should be allowed to treat or prevent diseases and disability, by the Food and Drug Administration’s (FDA) gene therapy mechanism. Clinical trial with CRISPR human somatic genome editing have been allowed (including by FDA) and these trials have been started23-26. The specificity of approved product regulation may limit the use and special requirements are in place to ensure that somatic genome editing may not inadvertently involve the germline genome editing studies. Expansion in future of genome editing for other purposes should be based on the inclusive stakeholders’ conversation.

GGE ETHICAL CONTROVERSIES, CONCERNS AND CHALLENGES

In 2015, heightened concern and controversies arose after a study by a Chinese scientist was published describing the use of CRISPR-Cas9 for modifying the DNA of a non viable human embryo. In 2018, by a Chinese scientist was published describing the use of CRISPR-Cas9 for modifying the DNA of a non viable human embryo 6) . In 2018, by a Chinese scientist was published describing the use of CRISPR-Cas9 germline genome editing, when other similar technologies cannot provide, is to consider GGE. This research magnified the concern of ethicists and scientists throughout the world. Further, they also argue that PGD and IVF can also provide serious illness or disabilities 3. enhance human function6) and 4. use of GGE justified because it can improve clinical use of IVF and also shed light on causes of early miscarriage.

BASIC RESEARCH WITH GGE

GGE deals with: 1. the importance of increased knowledge 2. research activities involving human embryo, and 3. questions about oocyte donation and increased new information. Thus, basic research with GGE on human embryo will bring: a) increased efficiency and precision which may help to understand differences between human and animal developmental biology12,20,21 and b) the preliminary data obtained from research will help in improving somatic genome editing, thereby improving the understanding and knowledge of genetic disease and mechanism of early human development12,20. Information obtained from research will also improve the therapeutic benefit of IVF by reducing incident of early miscarriage12.

RESEARCH INVOLVING HUMAN EMBRYOS

Research activities require destruction of human embryo which is opposed by many ethicists and clinicians alike13,18,19,20. Scientists also have brought another important issue of extending the statutory limit of research beyond 14 days limit to 16 or 17 days38-40 and will also help to understand the mechanism of gastrulation which takes place on 16th-17th day after fertilization39. This research news magnified the concern of ethicists and scientists throughout the world. Before considering any ethical issues and heightened concern, the important question is to find whether there is need for humans to utilize the CRISPR-Cas9 germline genome editing, when other similar technologies are available. Scientists and researchers in favour of using GGE point out the need of harmful mutation in embryos and gametes responsible for monogenetical disorders, for preventing harmful genetic disorders. Most scientists in favour also argue the medical need for GGE is so compelling that GGE is a moral imperative and using it will lighten the burden of human existence46. IVF and preimplantation genetic diagnosis (PGD) can also provide similar help. However, supporting groups in favour of GGE point out that by GGE, the risk of passing genetic disorder is eliminated for future generations. Further, they also argue that PGD and IVF are similar technologies, and are approved for research and clinical use, hence, GGE should also be allowed. Use of GGE means to have genetically related children for couples affected by disorders for which PGD is ineffective, particularly in cases where no unaffected embryo can be created. A more vital question for these couples who want genetically related children, but that present technologies cannot provide, is to consider GGE. This is a normative consideration for allowing one in favour of GGE. There are many cases (several hundred) worldwide where GGE would be the only option to create unaffected embryo. Thus, GGE has the potential to: 1. prevent the transmission of genetic variants known to be associated with serious illness and conditions6,46 2. lessen the chances of developing serious illness or disabilities 3. enhance human function6) and 4. use of GGE justified because it can improve clinical use of IVF and also shed light on causes of early miscarriage.

SAFETY OF CRISPR TECHNOLOGY

The safety of CRISPR technology is a very important part of the ethical debate. In spite of being described as a very safe and novel technique, this technique still has several limitations like other technologies for genome editing. The limitations are: a) limited on-target efficiency b) incomplete editing may result in mosaicism and c) inaccurate both on-target and off-target editing. Intergenerational long-term effects on future generations39 and moving from pre-clinical to clinical research areas, are two vital considerations for ethical issues42,43. Pre-clinical research activities can give a great deal of direction towards safety but still many scientists and ethicists believe that even safety based on scientific pre-clinical research is not safe enough. In other words, particularly knowing the benefit of technology and “how safe is safe enough”, that acceptance will become real44. Another debated issue is “violation of future generations’ (children) capacity to live as autonomous agents when their makeup are designated genetically without their consent44,45. Harris in his article13 has rejected the above views. UNESCO panel experts have raised related issues and suggested GGE threatens “equal and inherent dignity of all human beings”46 whereas a famous legal expert46 has rejected these claims and described it as “genomic metaphysics”47,48 and essentialist vision49-50. In relation to respecting dignity by not altering the human germline, is the idea of protecting the human gene pool as a distinct collective heritage. GGE can cause social inequalities and shifting of social norms particularly if it is available in selected countries or selected people15,16. The present acceptable norm of reproductive settings can be changed by GGE and prospective parents can be under pressure and expectation to avoid conception of embryos and fetuses that carry harmful genetic mutation49-51.
Supporters of GGE suggest on the contrary, that GGE will address the natural inequalities\(^4\). An important concern about GGE is that it causes negative exacerbating views of people living with disabilities, which GGE will correct\(^5\). Nuffield Council\(^6\) in 2018 reported and suggested that adopting the principle of “social justice and solidarity” will prevent GGE creating the above concern.

Other various criticisms of GGE include that it brings: 1. disrespect of DNA as human heritage 2. challenges of God’s role 3. lack of informed consent by children of future generations affected\(^6\) 4. negative impact on individual with disabilities 5. perception of parental negligence for deciding against GGE 6. unknown and unpredictable risks of creating novel genome mutation 7. commodification of children\(^8\) 8. danger of state imposed eugenic application and 9. potential for criminal activities\(^9\).

The complicated and tricky concern of enhancement by GGE is another important point to consider. The longstanding debate on the distinction between treatment and enhancement should be considered\(^10\) and GGE should be employed only to edit harmful mutation for the welfare of persons\(^11\).

However, on a scientific thinking basis, every treatment improves disabilities and brings a better and more successful life, but also has some degree of enhancement (for example, plastic surgery and cosmetic surgery), which are at present approved. Supporters of GGE have answered the above various criticisms but very little agreement has been reached between supporters and opposers (either side). However, one should remember genome is not static and every generation like the generation before has gone through series of mutations in one life-time. Scientists and ethicists still have time to compromise but both sides should agree to have strict, regulated, effective, and controlling governance mechanism are sufficient enough or needs further enhancement mechanism.

The majority of organizations have accepted basic research and therapeutic activities on GGE provided there is good governance of GGE, which should be based on following guidance: 1. to promote well being of human kind 2. responsible science 3. transparency in all action and steps in research or therapeutic activities 4. due care of patients participating in the research study, that is careful, deliberate, and based on sufficient scientific evidence 5. respect for patients participating, which requires recognition of dignity, integrity, acceptance of choice, and respect for individual decisions 6. transnational cooperation, support of cooperation instead to a collaborative approach, and respecting different cultural contexts 7. fairness-equitable distribution of the burden and benefit of research taking into account the risk/benefit evaluation.

GGE research should only proceed when: 1. reliable oversight mechanism exists to prevent extension to use it other than for preventing serious disease or conditions 2. there is an absence of reasonable alternatives and compelling medical rationale 3. evidence based that supports clinical use 4. maximal transparency consistent with patients privacy 5. limiting to converting such genes that has been convincingly demonstrated to cause or predispose to that disease 6. ethical justification and approval with REB and obtain informed consent 7. comprehensive plan for long-term multi-generational follow-up that also respect personal autonomy 8. credible pre-clinical or clinical data on risk and potential health benefit from GGE 9. converting genes to version that are prevalent in general population and reliable to ordinary health and benefit or no evidence of serious adverse reaction 10. doing vigorous oversight during clinical trial of GGE for safety and efficacy 11. clear and continuing public process to solicit and incorporate stakeholders’ input 12. continued reassessment health and societal benefit and risk with public participation 13. balancing individual level of benefit and societal level of risk.

**CONCLUSION**

Present analysis shows that the main concern in human somatic cell editing (genome) is whether existing research ethics of gene therapy and oversight mechanism are sufficient enough or needs further enhancement or revised ethics, and oversight mechanism. Majority of opinions agree that existing gene therapy ethics and oversight mechanism should be revisited to include the above suggestions provided by various panels, committees and experts, as described above. The oversight mechanism should have enhanced additional power and means to supervise the basic research, pre-clinical and clinical area of research activities of human somatic cell editing. There should be international agreement and that should be followed hopefully worldwide. Above should meet in balanced form of the individual benefit and societal level of risk.

**REFERENCES**


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