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A Bioethics Practitioner's Thoughts on Gene Editing in Human Embryos

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Abstract

At the 31st annual meeting of the Japan Association for Bioethics in 2019, an open public forum, entitled "A dialogue with citizens on genome editing technology of human embryos," was held. As a liaison member between experts and citizens, the author offered his opinions on the matter, dividing the matters of the expected spread of the technology and relevant issues into three sections. First, in the phase of basic medicine/preclinical studies, during which no one is born using this technology, the main issues are research integrity and assessment of the safety and accuracy of the technology. The next anticipated phase comprises clinical trials and treatment, and a genetically edited baby would be born using this technology. Ethical issues that would need to be addressed during this phase would include the protection of research participants and ensuring that fair medical practices are maintained. Discussion on the moral status of the human embryo may also need to be revisited in this phase. In the third phase, the technology goes beyond medical practice and is made more accessible. The births of many designer babies could influence human relationships, individual lives, and the community structure, in massive and complicated ways. In order for society to accept and ensure that this technology becomes widespread in the future, a multidisciplinary and collaborative approach is necessary.

Keywords

Gene editing

Human embryo

Open public forum

1. Introduction

First, it should be declared that the author is not committed to ethical considerations, regulation, policy-making, or medical research on the genome-editing technology of human embryos. The author was asked to write this article probably because he was a symposiast for the public lecture "Dialogue with the public on genome editing technology of human embryos", which was jointly organized by the Cabinet Office at the 31st Annual Conference of the Japanese Society for Bioethics held at Tohoku University in December 2019. The author would like to express his gratitude

once again to the Executive Committee of the Annual Meeting and the Editorial Board of the Journal for the valuable opportunity. The author was responsible for the presentations and discussions at the symposium, together with Dr. Osamu Ishihara of Saitama Medical University and Dr. Yuri Aono of the Mainichi Shimbun Editorial Board. These two individuals are members of the Task Force on the Review of the Basic Approach to the Handling of Human Embryos and the Specialist Committee on Bioethics of the Council for Science, Technology, and Innovation, and their presentations were from the advocacy and opposition of human embryos genome editing, respectively. The author was asked to act as a bridge between these two experts and the public. As a non-specialist and a jack-of-all-trades in bioethics, the author presented and debated from the complicated and somewhat half-hearted position of expressing his opinions to the public and experts without bias. This article is based on the content of the presentations at the symposium and does not present the latest scientific findings or in-depth discussions. It is a simple question and thought from a common perspective by a non-specialist in genome editing whose daily duties include academic research in clinical and medical ethics, education of students in general bioethics, clinical ethics support, and research ethics in the local area.

The timing of the writing of this article also coincided with the explosive spread of COVID-19 infection. The cumulative number of infected people worldwide has already exceeded 10 million, and more than 500,000 deaths have occurred. A state of emergency has been declared in Japan, and most people have been ordered or requested to reduce contact with others to prevent infection, and work and daily life have yet to return to normal. The infection raises several ethical and social issues, such as the allocation of healthcare resources, restrictions on behavior and privacy, and the protection of vulnerable people and healthcare professionals at high risk of viral exposure. The author believes that many bioethics specialists in Japan have shifted their interest to COVID-19 and have found new research topics to discuss and investigate. However, the impact of human embryo genome editing crosses not only borders but also generations, which means that its scale and scope are no less than this virus. Preparation for safe future use is necessary and is an issue that many in the bioethics field can approach.

2. Point in question

Almost five years ago, the news was reported that a Chinese research team had genetically engineered human fertilized embryos using clustered regularly interspaced short palindromic repeats (CRISPR), and in December of the same year, the Organizing Committee of the International Summit on Human Gene Editing issued a statement. There, the view was expressed that clinical medicine using germline gene editing should be regularly reviewed as scientific knowledge advances and societal views evolve. The author therefore believes that this technology will be applied to the treatment of intractable diseases and reproductive medicine in the future and that its scope will be further expanded. The following developments and expansions can be foreseen (**Table 1**). The order in which editing will be permitted in the laboratory, then in medical facilities, and then outside of medical institutions.

The ethics of human embryo genome editing can also be described as an old and new topic. Genetic engineering technologies such as breeding and genetic modification are already in practice. We have experienced paradigm cases such as the Asilomar Conference on the Regulation of Genetic Modification Experiments in 1975 and direct discussions on genome editing in the last few years. In addition to these, the bioethics field includes debates on related key topics/categories such as the moral status of the human embryo, research ethics, and enhancement. Therefore, while we do not take an optimistic or easy view of the practical and widespread use of genome editing of human embryos, we believe we can respond reasonably well to individual research projects and practical

Table 1. Developments and expansions of human embryos gene editing

Phases and activities	Implementers and situations	Subjects of genome editing and their treatment	Main issues
Basic medical / Preclinical research	Gene editing performed by researchers in the laboratories	Human surplus embryos / new embryos are genetically edited and evaluated, then discarded	• Safety and possibility • Sound research and research misconduct prevention • The moral status of human embryos
Clinical research and care	Gene editing performed by researchers and medical professionals in medical facilities	Fetals undergo gene editing for a healthy life; individuals offered a new technology (other than gene editing)	• Subject protection • Disadvantages of treatment • Genetic linkage • Reductionist thinking • Fair access • Impact on the health insurance system • Treatment freedom
Use beyond clinical care (non-medical purposes)	Gene editing by researchers, medical professionals, or others outside of a laboratory or medical facility	Genetically edited, live fetal; individuals offered new technology (other than gene editing)	• Designer babies • Happiness disparity • Vulnerability • Slippery slope, pressure, obligation

applications with past arguments. In this paper, we raise some brief considerations and questions according to **Table 1**.

2.1. First phase: basic medical/pre-clinical research

In this phase, human embryo genome editing takes place in the laboratory. Surplus embryos that will not be used in assisted reproductive technologies are subject to gene editing, and new embryos may also be created for research purposes. The gene-edited embryos will not be implanted in utero and no individuals will develop, so stakeholders will be limited to research personnel and human embryo donors.

2.1.1. Accuracy, efficiency, potential, and safety

The first point of concern for us is the accuracy and potential for the safety of genome editing. Many of us have heard of terms such as "off-target mutations" and "mosaicism". The fact that such off-target and unanticipated effects can occur does not mean that the risks of human embryo genome editing are so great that it must be banned. There is a need to focus on improving screening and assay technologies as well as techniques to prevent and avoid unintended edits and to assess the risks as accurately as possible. In addition, not only do spontaneous/accidental mutations exist in the biological world but also in genetic modification which is already being used in several fields. The risks of human embryo genome editing should be assessed by comparison with these natural phenomena and existing technologies. We do not believe that this is the time for strong mistrust or aversion.

2.1.2. Rational research

There should be no discrediting of the scientific community as a result of research misconduct. We sincerely hope that rational research is carried out. In Japan, the Ethical Guidelines for Research Using Genetic Information Modification Techniques in Human Fertilised Embryos have already been formulated, which clearly stipulate the acquisition of informed consent, protection of personal information, ethical screening, and standards for research and donor organizations as considerations for human embryo donors. While it is natural to develop external norms such as guidelines and laws, research ethics must go deeper than this. The intrinsic morality of researchers is also important. There should be discussion and consideration of the attitudes and ideas that researchers who edit genomes should have and what kind of effective ethics education is required for them to do so. This may be one issue that bioethics should commit itself to in the future.

2.2. Second phase: clinical research and care

Genome editing has moved out of the laboratory and is now being implemented in medical facilities. One can imagine the implementation of human embryo genome editing for future patients as a treatment for intractable diseases or as a treatment for infertility. Since the genome-edited embryo is implanted in utero and the human individual is actually born, the stakeholders would include those born through genome editing and the medical community. First, clinical research would be conducted, after which the effectiveness and safety would be verified and the technology would be put into practical use as an actual therapeutic tool. It is not known how many years this will take. It would truly be gospel if an effective means of treating genetic incurable diseases and infertility had not already been established, and there should be patients/families seeking genome-edited treatments and medical practitioners willing to provide them.

2.2.1. The moral status of the human embryo

According to the Council for Science and Technology Policy's "Basic Idea on the Handling of Human Embryos" and other documents, the position of the human embryo in Japan is that it is a "sprout of human life" and "different from other cells and is to be especially respected". Although this is a rough interpretation, this view makes it possible to dispose of human embryos that have undergone genetic manipulation in basic research. However, there is a question as to whether the above understanding holds true when human individuals are created through clinical research in which human embryos are subjected to genome editing. The manipulated embryo will be born outside the mother's body and live as a human being. Clinical research treats the subject as a personality as far as possible, so such an entity cannot be a " sprout of human life" all the time. It is possible to view genome editing in clinical research as an intervention on the 'research participant', the human embryo. Since the target of the editing is the potential patient, it is difficult to determine whether he or she should be treated as a human being from the embryonic stage. The question can be raised whether it is necessary to give personhood at some point from the fertilized egg to birth outside the mother's body. In the abortion debate, we have not reached a consensus on the point of becoming human. On the other hand, if human embryos are treated uniformly as personhood, without distinguishing between research and treatment of human embryo genome editing, then basic research cannot be carried out. This is because post-research disposal would be considered an act of murder. The same applies to the abandonment and disposal of pre-implantation embryos that are found to have serious abnormalities. Furthermore, as the expression "fetus as a patient" suggests, in today's medicine the fetus is already subject to treatment. As the scope of medical treatment expands, the status of the human embryo or fetus feels closer to that of a human being. Bioethics may have faced a more complex conundrum regarding the moral status of the human embryo. More profound and fundamental questions than debates about the interests of the unborn child and its right to live and grow may also need to be addressed.

2.2.2. Protection of human subjects in clinical research

The burden that research imposes on human subjects and the response to adverse events are also difficult questions. A variety of risks, from minor to serious, are likely envisaged, and research plans must include appropriate responses, such as treatment and care for such unwanted events, and be approved by an ethics review committee. For example, subjects born undergoing genome editing would undergo long-term medical examinations and tests to determine the effects of the research. The response of the researcher/medical staff should not be a mundane one, such as confidentiality or protection of personal information,

but rather the protection of the privacy of the subject in the broadest sense, who may be subject to restrictions on their life and behavior. Numerous questions are raised, such as how the individual should know that he or she has been born as a result of genome editing and whether he or she will be allowed to marry and have children in the future.

In addition, the responsibilities of researchers conducting clinical studies using human embryo genome editing may be broader and more significant. They may also need to monitor at least the next generation since the properties altered by germline gene editing are passed on to offspring. Questions such as "Will the researcher's responsibilities extend to future generations?" "When will clinical trials be completed?" "What will happen if serious complications arise in utero after the transfer of genome-edited embryos?" "If a fetal treatment is to be offered but it is not indicated or not expected to be effective, will abortion be the treatment of choice?" and "What should be done if serious health problems occur after birth?" arise. The aim would be to save lives and reintegrate society through the input of all kinds of treatment, but it is also important to alleviate the suffering of such subjects. At the risk of being scolded for such poor and unsatisfactory imaginings, it is not easy to envision future clinical trials using genome editing in concrete terms. Researchers will be following protocols and conducting research activities, but the possibility of including options such as abortion or euthanasia is unknown.

2.2.3. Clinical care: access, equity, impact on health insurance schemes, free medical care, and commercialization

Furthermore, there are several questions about what happens when the research phase ends and genome editing of human embryos becomes routine clinical care. The first concerns the healthcare system and access. In terms of access equity, many would hope that the healthcare system would be such that all patients with the same disease title, i.e. genetic disposition, and with the same level of medical condition would receive the same genome editing. In contrast, there is a possibility leading to a situation where certain genetic carriers would not be able to join certain health and medical insurance schemes, or if they could, they may be charged higher premiums than other members. There is also concern that it will encourage the commercialization of medical care, i.e. free and mixed treatment. If human embryo genome editing is not covered by insurance, only the rich will be able to benefit from it. The financial wealth of individuals will increase medical and health inequalities. On the other hand, if clinics and hospitals offering genome editing as free medical treatment are opened, there is a possibility that biased information will be disclosed to those seeking genome editing for business reasons, such as profit, and that treatment will be carried out without legitimate informed consent. Alternatively, genome editing without sufficient verification of efficacy and safety may be provided as a service.

2.2.4. Transformation of medicine and healthcare: reductionism and decontextualization

This is not medical ethics, but our understanding of the future of medicine and medical science is also difficult to predict. It is unknown whether there will come a time when diseases, treatments, and medical education will need to be restructured, but it has long been said that the future of medicine and medical treatment will be the age of the gene. If genome editing becomes widespread as an effective treatment, and if it proves more effective than existing therapies, the genetic reductionist trend of medicine will lead to the possible intensifying of gene testing and editing. Our long-established and systematized understanding of medicine and medical treatment will be drastically altered, and if we focus only on gene testing and genome editing, some of us will neglect conventional health behaviors such as daily exercise, lifestyle improvements such as avoiding stress and overeating, medication, health check-ups

and regular visits to medical institutions. The future will continue to see a rise in the number of people who are not aware of the environment and attitudes towards their lives. The context of our environment and attitudes towards life will continue to be a factor in health for a long time to come. We should pursue a medical and healthcare system in which people are not blind to genetic testing and genome editing but have a reasonable level of literacy about genetics in addition to their existing knowledge.

2.2.5. Scope of responsibility of medical practitioners and goals of medicine

As mentioned above, the next generation will also be affected by the effects and consequences of human embryo genome editing, but the extent of medical practitioners be held responsible if several generations are affected by medical illnesses such as side effects and adverse events of genome editing is yet to be known. The protection of future generations is one of the key ethical principles, but it is difficult to know in advance the interests of each individual who has not yet been born and will be affected by unknown or unexpected factors. However, medicine using genome editing of human embryos will require imagination and insight from medical practitioners on every occasion. This style of medicine is different from conventional medicine, which pursues only the interests of the patient receiving it. Instead of vague expressions such as the responsibility to future generations, it would be good to set specific and clear goals for medical practitioners to prioritize or protect as a collective and common human value.

2.3. Third phase: use beyond clinical care (non-medical purposes)

One of the concerns about genome editing using CRISPR is the "do it yourself" problem. While it is unlikely that anyone will be able to go to a home improvement shop and edit genes at will, the accumulation of research and medicine will improve the effectiveness and safety, and easy gene-editing techniques will be available. Non-researchers and non-medical personnel may be able to carry out editing operations, and human embryo genome editing may be carried out in many places. One can imagine a situation where the scope of use is expanded and access is facilitated. The use would go beyond the scope of research and medicine, an unparalleled number of people would become direct or indirect stakeholders, and gene editing could have a very significant impact on human life and social structures. This is an inaccurate prediction by the author and it is not certain that a similar situation will come about. However, it is not unnecessary to imagine and prepare for future applications. If we view this phase as an extra-medical use of genome editing, we can apply the topics of desirable children and parental aspirations, the interests of the child, human imperfection, and eugenics, among many other issues of the past enhancement debate, to the discussion.

2.3.1. Designer babies, the ego, and the parent-child relationship

Designer babies are a leading concern regarding human embryo genome editing, often seen in newspapers and on the internet. Many parents want their unborn child to be healthy as well as fit and successful in society. Several measures will be used to support this, such as providing a good living environment and learning opportunities, but it is unsure whether human embryo genome editing can be an effective tool. The embryo to be edited cannot give consent to the genetic modification. If one is born with genome editing and is successful in the future, the child may appreciate such parental consideration. However, another may be restricted in his or her freedom of choice and way of life, may be distressed, and may have to struggle even more in the formation of his or her identity and ego. The parent-child relationship can take many forms, and some may be happy to remain strongly dependent on their parents. However, some children may not be

satisfied with genome editing even if the parents wish for the well-being of their unborn child. It is possible to imagine situations where genome editing deprives children of the opportunity to take proactive control of their lives.

2.3.2. Genetic linkages, diversity, tolerance, and eugenics

We might also reconsider the implications of our genetic connection. Currently, the annual number of *in vitro* fertilization (IVF) cases far exceeds that of adoptions. The desire to have a genetically linked child could be one reason for this. On the other hand, human embryo genome editing may be manipulated to retain characteristics that the parents consider desirable and not pass on to the child any characteristics that may be considered disadvantageous. Everyone has shortcomings and faults, not all of which can be resolved or overcome as desired. It is unknown whether society can easily accept the attitude of parents who try to pass on only favorable traits to their children in order to prevent them from facing such difficulties and also the extent of the genetic link, which the author finds contraindicating. Accepting one's limitations and weaknesses as part of one's personality and, along with this, striving to adapt well to society would be an important wisdom to live by. It would also be important to raise children with careful attention to their living environment and growth process after birth, without relying for a large part of their lives on the gene editing that takes place at/before the beginning of life.

It is unclear if there is a trend toward designer babies in terms of the appearance, intelligence, and physical fitness of the unborn child. If the content of genome editing becomes defined according to the prevailing values of the period in which it is carried out, children born at the same time may be similar in appearance and content. Those who fall outside such a range or who are unique may feel lonely and uncomfortable in life. This is the opposite of today's attitude of respect for diversity and individuality, and one can imagine a world where people feel pressured or obliged to undergo genome editing in order to live well, or that it is the norm. Children born from genome-edited children, whose aim is perfection, should have excellent looks, physical strength, academic ability, and character, with no defects. They are beings who can be left alone, with little stress on their parents, as there is little burden of parenting or teaching them to learn, and little worry about illness. A world made up entirely of such people would be wonderful, and some may consider it an ideal world to aspire to, but it is easy to argue against eugenic thought of whether genome editing has the potential to promote eugenics and set standards such as qualified, preferred, or superior. It is human history that some people have been subjected to cruel treatment, such as persecution and human rights violations, based on judgments of inadequacy and inferiority. This is not a simple matter of the aforementioned wear and tear of individuality and diversity. A spirit of solidarity is also human wisdom, and it is necessary to accept the vulnerability of others and be generous enough to help each other.

4. Summary

As stated at the outset, this paper is a written version of an oral presentation to the general public at the 31st Annual Public Lecture. It is a layman's understanding and imagination that roughly summarises past direct and related discussions on human embryo genome editing, and experts who are familiar with the situation may have noticed some of the author's inadequacies. From the content of the international summit and domestic conferences, it can be inferred at this point that research into human embryo genome editing will progress toward future applications. On the other hand, we cannot overlook the situation where patients with diseases for which there is no effective treatment, or couples and women who want to have children do not have the opportunity to do so, and medical research and treatment should meet the expectations of patients and the public. At least at present, there

is no reason to stop basic research that does not involve human subjects. In addition, the academic community, including the members of our bioethics society, has already considered the issue from the fields of philosophy, ethics, sociology, medicine, biology, and genetics, and has presented many views. There is also still much to be clarified about the possibilities and risks of human embryo genome editing. New knowledge should continue to be acquired through research and discussion. We feel that we can overcome the problems of Trans Science or ELSI one by one, avoiding a slippery slope, and realizing the acceptance and dissemination of human embryo genome editing through territorial, temporal and spatial 'solidarity'.

Disclosure statement

The author declares no conflict of interest.

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