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Abstract

Gene editing technology has been one of the breakthrough technologies for life science research. With the application in biomedical research, healthcare, food and agriculture field, related ethical issues are also concerned. This study summarized the research and application progress of gene editing technology involving ethical issues in recent years. Based on sorting out the international discussions, attitudes, and explorations about gene editing ethics issues, after analyzing the current status, discussions, and measures of applications of gene editing technology on human beings in China, we propose five suggestions about the ethical governance system construction of gene editing technology for China.

Keywords

gene editing technology CRISPR; ethical governance

Authors

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Ethical Governance of Gene Editing Technology

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Abstract: Gene editing technology has become one of the breakthrough technologies for life science research. With therapid development of it's applications in biomedical research, healthcare, food, and agriculture fields, gene editing-related ethical issues have drawn much attention. Here we summarize the recent progress of gene editing research and application, and gene editing-related ethical issues. We first focus on the international discussions, attitudes and explorations on the ethical governance associated with this Technology. We next analyze the current status of ethical discussions and governance on gene editing applications in China. Finally, we propose five suggestions about the system construction of ethical governance on gene editing in China. **DOI:** 10.16418/j.issn.1000-3045.20210316002-en

Keywords: gene editing technology; CRISPR; ethical governance

Gene editing technology represented by CRISPR has been one of the breakthrough technologies for life science research. However, the advancing research and application of gene editing have aroused wide ethical issues concerns, especially for the application to human beings. At the beginning of 2013, studies showed that gene editing technology can be used to edit human stem cell genes [1,2] and to modify the entire organism (zebrafish) [3], which aroused the related ethical concerns ① [4]. In 2015, the CRISPR/Cas9 technique was for the first time applied to the editing of human embryos, triggering a heated discussion on ethical and regulatory issues concerning gene editing technology. In November 2018, the birth of gene-edited babies climaxed the discussions on ethical issues and governance system construction of gene editing. This study summarized the recent progress of gene editing research and application, and gene editing-related ethical issues reviewed the international discussions and explorations on ethical governance, and provided suggestions for the ethical governance system construction of gene editing technology for China.

1 Ethical issues triggered by the research and application of gene editing technology

With the application of gene editing technology in biomedical research, healthcare, food and agriculture field, related ethical issues are also concerned.

1.1 Rapid advancement of research and application of gene editing technology

Since the advent of CRISPR technique in 2013, gene editing technology has been booming, and the related research papers have been surging. According to the data from Web of Science Core Collection, there have been nearly 30 000 papers related to gene editing technology by 2020, with an average annual growth rate over 20%.

For the research on the genetic mechanism of human development, the use of model animals has certain limitations [5], while gene editing technology shows significant advantages. The research on gene editing of human embryos focuses on the mechanism of embryogenesis by knocking out important genes and the possibility of repairing genetic loci associated with underlying genetic diseases. In gene repair of genetic diseases, therapeutic embryo gene editing has cured such diseases as cataract [6], tyrosinemia [7] and myodystrophy [8] in mouse models. However, a few studies applying gene editing technology to human embryos have provoked disputes within the academic community over the necessity of those studies and over the rationality of the risk-reward ratio, despite their compliance with related ethical codes. For example, Fan's team edited the *CCR5* gene in zygotes to explore treatment for AIDS [9]. Ma et al. [10] edited the

① Savulescu J. As a species, we have a moral obligation to enhance ourselves. (2014–02–19) [2021–10–29]. https://ideas.ted.com/theethicsof-genetically-enhanced-monkey-slaves/.

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MYBPC3 gene to seek treatment options for hypertrophic cardiomyopathy (HCM). Fogarty et al. [5] knocked out the *Oct4* (*POU5F1*) gene in zygotes to study the abnormal development of embryos.

The clinical application of human somatic cell gene editing has made it possible to treat diseases with no other effective therapies. The phase I clinical trial of CRISPR gene-edited T cells in patients with cancer, conducted by Lu et al. [11] in West China Hospital of Sichuan University, has demonstrated the feasibility of the clinical application of this technology. Editas Medicine and Allergan have completed the dosing of the first patient ② in phase I/II clinical trial of the CRISPR medicine AGN-151587 (EDT-101) for treating the genetic eye disease Leber congenital amaurosis (LCA10). Intellia Therapeutics and Regeneron Pharmaceuticals are the first companies in the world to have completed the dosing of the first patient with transthyretin amyloidosis (ATTR) in phase I clinical trial of the gene editing therapeutic agent NTLA-2001, showing good interim results [12]. In October 2021, Intellia Therapeutics received U.S. Food and Drug Administration (FDA) orphan drug designation for the therapy ③. Additionally, β-thalassemia and sickle cell anemia have been cured by the gene editing therapy co-developed by CRISPR Therapeutics and Vertex Pharmaceuticals [13]. We can see that gene editing technology shows great potential in the treatment of diseases. Meanwhile, some researchers have pointed out that caution is needed in the direct use of CRISPR/Cas9 technology *in vivo* considering the technical shortcomings and safety risks.

The application of gene editing technology in such fields as crop breeding and food improvement develops faster than that in human body. The United States Department of Agriculture (USDA) will no longer impose additional regulations on gene-edited crops. By the end of 2020, the USDA has approved more than 70 gene-edited crops. In December 2020, the Ministry of Health, Labour and Welfare of Japan approved the application for the sale of gene-edited tomatoes containing more γ-aminobutyric acid (GABA), which are expected to be available on the market as early as 2022 ④.

1.2 Ethnical issues related to gene editing

With the rapid development of gene editing technology, the research on related ethical issues is also underway. The ethical issues related to gene editing can be discussed at the technical, social and ecological levels.

(1) At the technical level, the ethical issues related to gene editing mainly concern the uncertainties in the application due to the unsound technology. The risks of gene editing technology mainly include off-target effect (edits in the wrong place) [14], mosaicism (some cells carry the edit but others do not due to the insufficient editing) [15], immune response caused by the entry of the CRISPR/Cas9 system into human body [16], and unpredictable side effects caused by the editing of specific functional genes [17,18]. Alanis-Lobato et al. [19] have detected a large number of mutations around *POU5F1* in 22% of cells, including DNA rearrangement and deletion of thousands of bases. After Zuccaro et al. [20] corrected *EYS2* mutations with CRISPR/Cas9, about half of embryos lost a large number of chromosome segments, some even lost the whole chromosome. Liang et al. [21] discovered that although gene conversion can be used for gene correction, the conversion tracks may expand beyond the target region, leading to an extensive loss of heterozygosity (LOH), which presents a serious safety risk. These risks and their possible consequences are still uncertain, and it is difficult to make clear the risk-reward of this technology.

(2) At the social level, the application of gene editing technology may affect social equity and justice, causing alienation of human dignity and thus raising ethical issues concerning social development. Sociologists and ethicists have discussed the ethical issues about gene editing technology from three aspects. ① Possible negative effects produced by gene selection. In view of the unclear boundaries of the clinical application of gene editing technology, parents may select certain human traits through prenatal testing and gene editing, thereby worsening prejudice and insularity which already exist in the society. ② The impact on family values and common interests. Parents are the most appropriate surrogate medical decision maker before their children gain independence and are able to make decisions by themselves. However, on a large time scale, there are so many uncertainties between parents and children over the consistency of their values and common interests, which may involve family relationships, the autonomy of children and other social issues. ③ Social justice and equal access to technology. The clinical application of gene editing technology is affected by such factors as region, race, public health service coverage, scientific and technological development, and socioeconomic status, and thus is difficult to be widely accessible to the masses.

(3) At the ecological level, gene editing technology poses a challenge to natural evolution, which destroys the integrity

② Editas Medicine. Allergan and Editas Medicine Announces Dosing of First Patient in Landmark Phase 1/2 Clinical Trial of CRISPR Medicine AGN-151587 (EDIT-101) for the Treatment of LCA10. (2020–03–04) [2021–10–29]. https://ir.editasmedicine.com/newsreleases/news-release-details/allergan-and-editas-medicine-announce-dosing-first-patient.

③ Intellia Therapeutics. Intellia Therapeutics Receives U.S. FDA Orphan Drug Designation for NTLA-2001, an Investigational CRISPR Therapy for the Treatment of Transthyretin (ATTR) Amyloidosis. (2021–10–21) [2021–10–29]. https://ir.intelliatx.com/news-releases/news-release-details/intellia-therapeutics-receives-us-fda-orphan-drug-designation.

④ Xinhua News Agency. Japan approved the sale of gene-edited tomato in 2022. (2020–12–12) [2021–03–03]. http://news.sciencenet.cn/htmlnews/2020/12/450087.shtm.

and evolution of human genes and alters the entire human gene pool, leading to uncontrollable risks and consequences. First, it is difficult to evaluate the multi-generation effect brought about by the edited genetic inheritance. Germline gene editing will not only exert unexpected effects on the individual but also have an unpredictable impact on the offspring, which may increase the risk of catching genetic diseases. Second, gene editing may damage the natural ecology. Targeted gene selection by people may decrease the diversity of human genes. In addition, in a broad sense, the possible eco-environmental problems caused by plants with heterologous genes, safety and regulation relating to gene-edited food, and indirectly induced legal regulations, can also be included in the ethical issues of gene editing.

2 International research on ethical issues and governance of gene editing technology

After the CRISPR technique was firstly used for gene editing in human embryos, scientists from different countries reached a consensus at the International Summit on Human Genome Editing. That is, the basic research on gene editing is allowed to be carried out in human embryos, but it would be irresponsible to put the technology into clinical use at the present stage. This is the first international redline for gene editing research. Hereafter, related ethical issues are studied and discussed continuously. Particularly, after the birth of gene-edited babies, countries in the world further clarified boundaries and regulatory measures, and called for an international consensus and a sound governance system.

2.1 Countries around the world are actively improving laws and regulations related to gene editing technology

At present, about 30 countries in the world have introduced legislation directly or indirectly banning the clinical use of gene editing technology [22]. Australia, Canada and some other countries have brought in legislation banning gene editing in human embryos (or germ cells) and somatic cell nuclear transfer, violation of which is often punished by hefty fines or criminal sanction. The United Kingdom stipulates that a risk assessment by certain professional organizations is a prerequisite to authorized human gene editing.

In addition, more explicit measures have been introduced on the use of gene editing technology in agriculture. The United States has revised and interpreted its existing laws and regulations related to GM technology to exempt gene-edited crops from strict GM regulation. Japan, Finland, Sweden, Russia, Brazil and Argentina have also managed gene-edited plant products as non-GM products. On the contrary, many European countries have regulated gene-edited crops as GM crops.

2.2 International organizations issue consensus reports to prohibit germline gene editing at present

International organizations, governments, research institutions, academic groups and other agencies have published research reports on research and application of human germline gene editing. Most agree that basic research on human germline gene editing can be carried out, but the clinical application should be avoided in the short term. Certain criteria must be met before the clinical application of gene editing, which involves the overcoming of security and technical barriers, a social consensus on the application boundary, and an appropriate and transparent regulatory mechanism (Table 1).

After the birth of gene-edited babies, countries in the world further issued statements opposing using gene editing technology for reproductive purposes. According to the Organizing Committee of the Second International Summit on Human Genome Editing, to put human germline cell gene editing into clinical use is highly irresponsible, since the results of the clinical practice are highly uncertain and risky [28]. In 2019, the World Health Organization (WHO) established the Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing. The Committee is responsible for examining the scientific, ethical, social and legal challenges associated with gene editing of human somatic cells and germline cells (including early embryos), advising and establishing a registration system, providing a transparent and structured mechanism for future research (including clinical trials) on collecting and managing germline and somatic gene editing and on-progress research details, and so on ⑤⑥. In July 2021, the Committee issued the Human Genome Editing: A Framework for Governance and Human Genome Editing: Recommendations, aiming to help countries around the world apply human gene editing technology safely, effectively and ethically [26,27].

2.3 The academic community calls for stronger regulation on the clinical application of gene editing technology

In addition to relevant think tanks and organizations, an increasing number of scientists have called for a consensus on the clinical application of gene editing technology and the formulation of relevant laws and regulations to ensure the development of technology complies with relevant laws and regulations and will be healthy, orderly and reasonable (Table 2).

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⑤ Heritable Human Genome Editing. The Royal Society; National Academy of Sciences; National Academy of Medicine; International Commission on the Clinical Use of Human Germline Genome EditingWashington (DC): National Academies Press (US); 2020 Sep 3. (DOI: 10.17226/25665)

⑥ Xinhuanet. WHO plans to develop an international governance framework for human genome editing. (2019–03–20) [2021–03–03]. http://www.xinhuanet.com/world/2019–03/20/c_1124258632.htm.

Table 1 International consensus reports on the clinical application of gene editing technology

Year	Report	Main content	Issuing organization/institution
2017	Human Genome Editing: Science, Ethics, and Governance[23]	• Basic research of gene editing complies with existing regulatory procedures • Part of clinical trials or treatments is restricted • Research of germ cell gene editing is allowed only for the treatment of serious diseases, and should be conducted within a strict monitoring system and prescribed standards • Human enhanced gene editing is prohibited • Public participation is included in the decision-making process for human gene editing	National Academy of Sciences, National Academy of Medicine
2017	Human Germline Genome Editing[24]	Germ cell gene editing should be carried out cautiously and actively. That is, basic research should be further promoted, while gene editing should not be used for reproductive purposes	American Society of Human Genetics, British Association of Genetics Nurses and Consultants, International Genetic Epidemiology Society, Asian Professional Association of Genetic Counselors, etc.
2018	Genome Editing and Human Reproduction: Social and Ethical Issues[25]	Although the germ cell editing is ethically acceptable under existing technology, we must ensure the welfare of future babies and that the public order and good custommust be met and the discrimination and secession must be avoided	Nuffield Council on Bioethics
2020	Heritable Human Genome Editing[5]	• It points out that the heritage gene editing of human germ cells is far from safe and effective at present and cannot be used clinically • If the safety is improved to a certain extent, the technology must be only used in the prevention of serious single gene inheritance diseases such as cystic fibrosis and thalassemia, and can only be considered when there are no other options	National Academy of Sciences, The Royal Society, Chinese Academy of Sciences, etc.
2021	Human Genome Editing: A Framework for Governance[26] Human Genome Editing: Recommendations[27]	It puts forth the ethical issues that should be comprehensively considered in the application of gene editing in five fields: postnatal somatic human genome editing, prenatal (in utero) somatic human genome editing, heritable human genome editing, human epigenetics editing and gene editing that enhances certain traits	WHO Expert Advisory Committee to Develop Global Standards for Governance and Oversight of Human Genome Editing

Table 2 Expert consensus on the clinical application of gene editing technology

Year	Proposer	Main content	Source
2018	Presidents of Chinese Academy of Sciences, United States National Academy of Medicine and Unites States National Academy of Sciences	Calling on academies of sciences around the world to reach an international consensus on guidelines for the research and clinical application of gene editing	*Science*[29]
2019	Eighteen life science and bioethics experts from 7 countries, including the United States, the United Kingdom and China	● Calling for suspension of all human germline gene editing ● Setting an initial period, during which no clinical use of germline editing is allowed ● Establishing an international consensus framework	*Nature*[30]
2019	Jennifer Doudna	Strengthening relevant laws and regulations; suspension of gene editing alone may not be enough, so it is recommended that development of laws and regulations be seriously considered without suspending technique development	*Science*[31]
2020	Twenty-five scientists in such fields as management, law, bioethics and genetics	Calling for the establishment of a global assembly which consists of at least 100 non-professionals from all over the world to evaluate the ethical and social impact of gene editing technology	*Science*[32]

2.4 Ethical research supports normative development of gene editing

The rapid development of gene editing technology has caused great changes in biomedical research worldwide, and the research of ethical issues concerning gene editing has received great attention as the technology develops. The searching of articles on ethical research on gene editing from the Web of Science Core Collection on October 26, 2021 obtained a total of 587 articles, which accounted for less than 2% of the total articles on gene editing. Among these articles, more than 60% (365 articles in total) were published after 2019, namely after the birth of gene-edited babies. However, gene editing technology began to be widely applied as early

as 2013, and the West China Hospital of Sichuan University carried out the first clinical trial of gene editing in the world in 2016. This shows that the speed of research on ethical issues related to gene editing and its impact on technological development are still insufficient, compared with the development of the technology.

From the perspective of geographical distribution of published articles on gene editing, the top five countries are the United States (218 articles in total), the United Kingdom (77), Germany (55), China (47) and Australia (36). The United States, as the origin country of gene editing technology, has the most publications on ethical issues related to gene editing. China ranks second in publications on gene editing technology. China has also carried out relevant ethical research and ranked fourth in the world in the number of publications on ethical issues related to gene editing.

From the perspective of content, global research on ethical issues about gene editing mainly focuses on four fields. ① Ethical issues concerning human germline cell gene editing. Human germline cell gene editing is the most controversial field of ethical research, which generally focuses on the technical risks, moral disputes, social issues, laws and regulations of various countries and the exiting consensus of international regulations in this field. Studies suggest that instead of completely suspending and banning human germline cell gene editing, it is better to establish a global research framework that balances risks and benefits as well as being open, cooperative and complying with relevant rules [33]. ② Ethical issues concerning human non-germline cell gene editing. Great importance has been attached to the medical value of somatic cell gene editing, while the security risks caused by off-target and other technical shortcomings are widely concerned. Doudna [34], one of the creators of the technology, also published an article indicating the urgency of further improving gene editing technology, to ensure that this breakthrough technology is used with responsibility in the treatment and prevention of genetic diseases. ③ Ethical issues concerning animal and plant gene editing in agriculture. The discussion of ethical issues about non-human cell gene editing mainly focuses on biosafety. Nearly all the articles recognize the great value of gene editing in agriculture. However, there are still challenges of gaining social acceptance from people against genetic modification [35]. ④ Ethical issues concerning animal and plant gene editing in ecology. Ethical research in eco-environment has focused on the feasibility of gene editing as a potential biocontrol tool (such as for killing mosquitoes [36]) and for restoring ecosystems and biodiversity. Meanwhile, ethical research in this field has also presented concerns about the impact of gene editing on the ecological chain, and called for the establishment of relevant regulatory frameworks [37].

3 Research on ethical issues related to gene editing technology and construction of ethical governance system in China

China has achieved significant progress in ethical regulation and governance of gene editing technology in recent years.

3.1 The effect of laws and regulations on gene editing technology has become stronger

There are strict legal regulations on the application of gene editing technology in human in China. The Ministry of Science and Technology and Ministry of Health (now the "National Health Commission") jointly issued the Ethical Guiding Principles for the Research of Human Embryonic Stem Cell in 2003, which prohibits any research on reproductive human cloning and specifies that human blastocysts that have been acquired and used in research should not be implanted into the reproductive system of humans or other animals. In the same year, the Ministry of Health issued the Ethical Principles for Human Assisted Reproductive Technology and Sperm Bank, specifying that patients' gametes and embryos should not be disposed of or sold without the informed consent of the patients. In 2020, the Ministry of Science and Technology issued the Administrative Measures for the Safety of Biotechnology Research and Development, categorizing the research and development activities involving human gene editing and other gene engineering with significant risks as the level of high risk and requiring strict management in research institutions at all levels.

In recent years, China has laid increasing emphasis on the construction of ethical regulation and governance system of emerging biotechnologies such as gene editing technology. The Plan on Establishing a National Science and Technology Ethics Committee was adopted at the Ninth Session of the Central Comprehensively Deepening Reforms Commission. At the session, it was pointed out that ethics must be valued in all science and technology activities. The purpose of establishing the Committee is to strength overall planning, guidance and coordination, and promote the establishment of a science and technology ethical governance system that covers all fields, has clear orientations, complies with relevant laws and regulations and be coordinated. The Civil Code also explicitly stipulates that people engaged in medical and scientific research activities related to human genes, human embryos and other aspects shall abide by laws, administrative regulations and national rules, and shall not endanger human health, violate ethics or morals, or damage public interests. This is the first time that medical and scientific research activities related to human genes and embryos have been explicitly stipulated at the legal level of higher rank of legal effect in China.

3.2 Meetings have called for stronger ethical regulation on gene editing technology

With the rapid development of gene editing technology, conferences and discussions over relevant ethical issues have been held continuously. In June 2016, at the Xiangshan Science Conference, which is themed by the research and application of gene editing technology, it is suggested that regulatory and ethical research on gene editing technology be deployed as quickly as possible, strict boundaries are set for gene editing which could cause great ethical and social issues, and clinical trials and applications be prohibited. In the first forum of scientific responsibility and responsible science and the symposium of ethics and responsibilities in gene editing technology, ethical issues and responsibilities related to gene editing technology were discussed heatedly. Suggestions on the legislation of gene editing technology and recommendations about improving the professionalism of researchers engaged in gene editing were put forward.

Gene editing technology has also attracted attention at the two sessions (the National People's Congress and the Chinese People's Political Consultative Conference), and calls for related legislation have been growing. In 2019, some representatives at the two sessions proposed that the government should establish the application boundaries of gene editing technology, and legislate things that can and cannot be done. They called for prohibitive and restrictive provisions on recruitment of people as human subjects for research, and on the research involving gene-edited embryos, as well as for harsher punishment for violation of the provisions to ensure strict management. Bai Chunli, President of Chinese Academy of Sciences and Secretary of the CPC Group at that time, said to reporters of *Science and Technology Daily* that clinical trials and applications of human germline gene editing should be prohibited before the technology is mature and corresponding social and ethical issues are fully discussed and resolved, while basic research can be tried. In 2021, some representatives at the two sessions suggested setting out Guidelines for Ethical Considerations for relevant research, according to which judgments can be formed in light of the original source, production process, indications and other aspects, and ethical risks can be considered comprehensively to guide clinical trials/studies. It is also suggested that bioethical norms should be enforced for the research involving advanced biotechnologies such as gene editing.

3.3 The academic community has paid increasing attention to the ethical issues about gene editing

In recent years, the Chinese academic community has paid more attention to the research on ethical issues about gene editing, and the number of related articles is growing. According to the data in CNKI by October 2021, there had been more than 500 Chinese publications related to ethical issues about gene editing. The main research institutions included the School of Humanities of Huazhong University of Science and Technology, School of Philosophy of Fudan University, School of Humanities and Social Sciences of Chinese Academy of Medical Sciences & Peking Union Medical College, School of Law of Renmin University of China, Peking University Health Science Center, Wuhan University of Technology, and so on. These articles focus on the ethical arguments, ethical reflections, moral principles, ethical review, legal regulations and other aspects related to gene editing technology involving human embryos, germline cells and so on.

In particular, Chinese scientists and ethicists have published articles in international journals to state their opinions and attitudes after the birth of gene-edited babies. Many scientists have appealed the Chinese government for a positive and open attitude towards gene editing technology in agriculture, and for the timely formulation of related policies, regulations and rules in healthcare to standardize and guide the development of gene editing technology, so as to promote the sustainable and healthy development of gene editing in China. In 2018, a team of scientists published articles on *Lancet* to elaborate on the current situation of gene editing technology, the ethics of human embryo research, and the science background of the *CCR5* gene and HIV prevention from perspectives of science ethics, science policies, and medical, scientific and technical backgrounds respectively, taking the attitude of the scientific community. Ethicists such as Lei Ruipeng, Zhai Xiaomei and Qiu Renzong called, on *Nature*, for stronger ethical regulation on medical research, taking the birth of gene-edited babies as an opportunity [38]. They recommended in-depth discussions on the rights and wrongs of human gene editing, firmly opposed practices in violation of basic ethics and urged researchers to do right things in the field of human gene editing [39].

4 Suggestions about the ethical governance system construction of gene editing technology

While promoting human progress, gene editing technology may also cause potential safety risks and ethical issues due to misuse and abuse. Thus, efforts from all levels, such as governments, institutions, the scientific community, industry associations and the public, should be made to comprehensively and systematically strengthen normative governance, so as to ensure that the technology complies with the interests of humans and realizes reasonable, orderly and healthy development.

4.1 The government should formulate a scientific and reasonable governance system

(1) A coordinated dialogue mechanism should be established. Related legislative bodies can organize inter-disciplinary and

inter-departmental collaboration to construct the governance system of emerging technologies such as gene editing technology and comprehensively evaluate the current governance systems (including the legal system, regulatory system, innovation system, and review system). By analyzing technical characteristics, conceiving technique application scenarios and predicting the development trends of the technique, the technical governance systems can be upgraded for different objects, such as humans, animals, plants and microorganisms, so as to meet the needs of the rapid development of the technology.

(2) A risk-reward evaluation system should be established. For the strategic layout of the technology, in addition to the evaluation of the scientific significance, the economic and social significance, especially such potential risks to life ethics, biosafety and biosecurity should also be comprehensively assessed before funding related research projects.

(3) The Guidelines for Medical Research on Gene Editing Technology are recommended. For research on the medical application of gene editing technology, such as therapies or drugs research and development, it is recommended to develop a technical route for preclinical research on gene editing technology, determine the methods, criteria, technologies, and tools used for the safety evaluation of the clinical application of gene editing, and further formulate related management norms on this basis.

4.2 Research institutions should assume the principal responsibility for management and supervision

Research institutions are the first subject of responsibility for the governance of emerging technologies such as gene editing technology [40]. In December 2018, the Ministry of Education of China issued the Notice on Self-inspection of Gene Editing-related Research Projects in Colleges and Universities, requiring colleges and universities to organize and conduct self-inspection of gene editing-related research projects. Charters, working systems and working procedures of ethics committees of colleges and universities should also be reported during self-inspection.

(1) The management and supervision systems in relevant research institutions should be improved. Within the framework of national laws and regulations, guidelines and systems should be developed for standardizing the scientific research in research institutions. Ethics committees be established to take effective measures to ensure that ethic review can be conducted independently.

(2) Educational and training courses should be set up for researchers and related managers. Ethic reviewers should always maintain a fair and objective attitude and possess ethical professionalism so as to create a normative research environment and governance atmosphere.

4.3 Ethical regulation should be conducted according to local conditions

Scientific research and ethics regulation are always developing cooperatively during their interactions. The research applying gene editing technology should be conducted within the existing ethical regulatory framework, while the technological progress will also cause new ethical issues. These issues, on the one hand, bring new challenges to the ethic regulation system, on the other hand, help the ethic regulation system to be more precise and well-rounded in the process of dialogues and discussions.

(1) More targeted ethics regulatory approaches should be supplemented. Opinions in different countries are divided over the boundaries of the application of gene editing technology in human embryos. Some believe that this should be completely banned, while others consider that this should be suspended on certain conditions instead of being totally banned. For new ethical challenges caused by gene editing technology, we should study the development pattern of the technology itself and the characteristics of related ethical issues, and supplement more targeted ethical regulation approaches within the existing regulatory framework.

(2) A long-term mechanism of studying and a national safeguarding ethics regulation on new technologies should be established. Complying with the relevant national laws and regulations, ethicists, scientists, sociologists and jurists should be jointly engaged in ethical governance. At the advent of emerging technologies, it is essential to launch relevant ethical research projects in time, study the ethical issues and formulate special codes of ethics based on the characteristics of new technologies, specific development patterns, application fields and scenarios, while ensuring precise and effective regulation.

4.4 The scientific community should bear in mind its mission and strengthen self-discipline

Researchers, as the source of new technological innovations such as gene editing technology, have the responsibility to avoid or reduce research risks and harm.

(1) Researchers should bear in mind the lofty mission of promoting human progress. They should conduct scientific research for the benefit of all humans, publicize truths to the mass, always protect the benefits of the public, and only do the right things.

(2) Researchers should strengthen self-discipline and actively participate in educational and training courses related to ethics. While ensuring their research complying with the overall benefits and needs of humans, they should understand and abide by related regulations, guidelines, and take safety measures. They should fully understand the possibilities of abuse and misuse of their research, identify ethical issues, master approaches to ethical analysis and making ethic-related

decisions, and regularly evaluate the biosafety risks of their research projects to timely adjust and reduce risks. In addition, they should bear their responsibility for educating and training others, and control the safety risks within their capacity. This is the social responsibility of scientists.

4.5 Other participants should jointly promote the construction of the governance ecosystem

In addition to governments, regulators, research institutions and the scientific community, other participants involved in the development of emerging technologies such as gene editing technology can also promote the normative governance of the technologies.

(1) Ethical issues can be discussed comprehensively and extensively from multiple links and levels. The supervision, management and standardization in multiple links involving the application of gene editing technology, such as funding, intellectual property management, experimental material management, paper publication, peer review, result transformation and even medical services, are also important parts of the construction of the governance ecology.

(2) A public dialogue platform can be built. In terms of science popularization, we should improve the ability of research institutions to popularize science and give full play to the role of media in guiding the public through the ethics issues concerning gene editing. While strengthening science popularization with multiple media, we should also standardize the wording of media so that the public can have a comprehensive and objective understanding of the advantages and possible risks of gene editing technology.

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References

1 Ding Q R, Regan S N, Xia Y L, et al. Enhanced efficiency of human pluripotent stem cell genome editing through replacing TALENs with CRISPRs. Cell Stem Cell, 2013, 12 (4): 393–394.

2 Musunuru K. Genome editing of human pluripotent stem cells to generate human cellular disease models. Disease Models & Mechanisms, 2013, 6 (4): 896–904.

3 Chang N N, Sun C H, Gao L, et al. Genome editing with RNA-guided Cas9 nuclease in Zebrafish embryos. Cell Research, 2013, 23 (4): 465–472.

4 Araki M, Ishii T. International regulatory landscape and integration of corrective genome editing into *in vitro* fertilization. Reproductive Biology and Endocrinology, 2014, 12: 108.

5 Fogarty N M E, McCarthy A, Snijders K E, et al. Genome editing reveals a role for *OCT4* in human embryogenesis. Nature, 2017, 550: 67–73.

6 Wu Y X, Liang D, Wang Y H, et al. Correction of a genetic disease in mouse via use of CRISPR-Cas9. Cell Stem Cell, 2013, 13 (6): 659–662.

7 Yin H, Xue W, Chen S D, et al. Genome editing with Cas9 in adult mice corrects a disease mutation and phenotype. Nature Biotechnology, 2014, 32 (6): 551–553.

8 Xu L, Park K H, Zhao L X, et al. CRISPR-mediated genome editing restores dystrophin expression and function in mdx mice. Molecular Therapy, 2016, 24 (3): 564–569.

9 Kang X J, He W Y, Huang Y L, et al. Introducing precise genetic modifications into human 3PN embryos by CRISPR/Cas-mediated genome editing. Journal of Assisted Reproduction and Genetics, 2016, 33 (5): 581–588.

10 Ma H, Marti-Gutierrez N, Park S W, et al. Correction of a pathogenic gene mutation in human embryos. Nature, 2017, 548: 413–419.

11 Lu Y, Xue J X, Deng T, et al. Safety and feasibility of CRISPR-edited T cells in patients with refractory non-small-cell lung cancer. Nature Medicine, 2020, 26 (5): 732–740.

12 Gillmore J D, Gane E, Taubel J, et al. CRISPR-Cas9 *in vivo* gene editing for transthyretin amyloidosis. The New England Journal of Medicine, 2021, 385 (6): 493–502.

13 Frangoul H, Altshuler D, Cappellini M D, et al. CRISPR-Cas9 gene editing for sickle cell disease and β-thalassemia. The New England Journal of Medicine, 2021, 384 (3): 252–260.

14 Fu Y F, Foden J A, Khayter C, et al. High-frequency off-target mutagenesis induced by CRISPR-Cas nucleases in human cells. Nature Biotechnology, 2013, 31 (9): 822–826.

15 Zuo E W, Cai Y J, Li K, et al. One-step generation of complete gene knockout mice and monkeys by CRISPR/Cas9-mediated gene editing with multiple sgRNAs. Cell Research, 2017, 27 (7): 933–945.

16 Crudele J M, Chamberlain J S. Cas9 immunity creates challenges man-embryo-genome-editing.

17 Haapaniemi E, Botla S, Persson J, et al. CRISPR-Cas9 genome editing induces a p53-mediated DNA damage response. Nature Medicine, 2018, 24 (7): 927–930.

18 Ihry R J, Worringer K A, Salick M R, et al. p53 inhibits CRISPR-Cas9 engineering in human pluripotent stem cells. Nature Medicine, 2018, 24 (7): 939–946.

19 Alanis-Lobato G, Zohren J, McCarthy A, et al. Frequent loss of heterozygosity in CRISPR-Cas9-edited early human embryos. PNAS, 2021, 118 (22): e2004832117.

20 Zuccaro M V, Xu J, Mitchell C, et al. Allele-specific chromosome removal after Cas9 cleavage in human embryos. Cell, 2020, 183 (6): 1650–1664.

21 Liang D, Gutierrez N M, Chen T L, et al. Frequent gene conversion in human embryos induced by double strand breaks. bioRxiv, 2020, doi: 10.1101/2020.06.19.162214.

22 Isasi R, Kleiderman E, Knoppers B M. Editing policy to fit the genome?. Science, 2016, 351: 337–339.

23 National Academy of Sciences, National Academy of Medicine. Human Genome Editing: Science, Ethics, and Governance. Washington DC: National Academies Press, 2017.

24 Ormond K E, Mortlock D P, Scholes D T, et al. Human germline genome editing. The American Journal of Human Genetics, 2017, 101 (2): 167–176.

25 Bioethics N C. Genome Editing and Human Reproduction: Social and Ethical Issues. London: Nuffield Council on Bioethics, 2018.

26 World Health Organization. Human genome editing: A framework for governance. (2021–07–12) [2021–10–25]. https://www.who.int/publications/i/item/9789240030060.

27 World Health Organization. Human genome editing: Recommendations. (2021–07–12) [2021–10–25]. https://www.who.int/publications/i/item/9789240030381.

28 Galvin M. Statement from the Organizing Committee on Reported Human Embryo Genome Editing. (2018–12–26) [2021–03–03]. https://www.nationalacademies.org/news/2018/11/statement-from-the-organizing-committee-onreported-hu man-embryo-genome-editing.

29 Dzau V J, McNutt M, Bai C L. Wake-up call from Hong Kong. Science, 2018, 362: 1215.

30 Lander E S, Baylis F, Zhang F, et al. Adopt a moratorium on heritable genome editing. Nature, 2019, 567: 165–168.

31 Doudna J. CRISPR's unwanted anniversary. Science, 2019, 366: 777.

32 Dryzek J S, Nicol D, Niemeyer S, et al. Global citizen deliberation on genome editing. Science, 2020, 369: 1435–1437.

33 Vassena R, Heindryckx B, Peco R, et al. Genome engineering through CRISPR/Cas9 technology in the human germline and pluripotent stem cells. Human Reproduction Update, 2016, 22 (4): 411–419.

34 Doudna J A. The promise and challenge of therapeutic genome editing. Nature, 2020, 578: 229–236.

35 Quétier F. The CRISPR-Cas9 technology: Closer to the ultimate toolkit for targeted genome editing. Plant Science, 2016, 242: 65–76.
36 James S, Collins F H, Welkhoff P A, et al. Pathway to deployment of gene drive mosquitoes as a potential biocontrol tool for elimination of malaria in sub-Saharan Africa: Recommendations of a scientific working group. The American Journal of Tropical Medicine and Hygiene, 2018, 98 (6_Suppl): 1–49.
37 Breed M F, Harrison P A, Blyth C, et al. The potential of genomics for restoring ecosystems and biodiversity. Nature Reviews Genetics, 2019, 20 (10): 615–628.
38 Lei R P, Zhai X M, Zhu W, et al. Reboot ethics governance in China. Nature, 2019, 569: 184–186.
39 Lei R P, Zhai X M, Zhu W, et al. Human Genome Editing: Science, Ethics, and Governance. Beijing: Peking Union Medical College Press, 2019. (in Chinese)
40 Collins F S, Gottlieb S. The next phase of human gene-therapy oversight. The New England Journal of Medicine, 2018, 379 (15): 1393–1395.

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