# The ethics of creating genetically modified children using genome editing

*Tetsuya Ishii*

**Purpose of review**
To review the recent ethical, legal, and social issues surrounding human reproduction involving germline genome editing.

**Recent findings**
Genome editing techniques, such as CRISPR/Cas9, have facilitated genetic modification in human embryos. The most likely purpose of germline genome editing is the prevention of serious genetic disease in offspring. However, complex issues still remain, including irremediable risks to fetuses and future generations, the role of women, the availability of alternatives, long-term follow-up, health insurance coverage, misuse for human enhancement, and the potential effects on adoption. Further discussions, a broad consensus, and appropriate regulations are required before human germline genome editing is introduced into the global society.

**Summary**
Before germline genome editing is used for disease prevention, a broad consensus must be formed by carefully discussing its ethical, legal, and social issues.

**Keywords**
CRISPR/Cas9, ethics, genome editing, germline, reproduction

## INTRODUCTION

Human cells harbor their genomes within the nucleus and mitochondria in nuclear DNA (nDNA) and mitochondrial DNA (mtDNA), respectively. Theoretically, the genetic modification of germ cells, including eggs and sperm cells, or zygotes (termed germline) can impact all the cells of the offspring. Genetically modified germ cells can also effect subsequent generations via reproduction. Germline genetic modification has been expected as the ultimate medicine to eradicate genetic disease in families and eventually in society. However, human inheritable genetic modification has been a frequent topic of debate for decades [1]. The reasons for opposition include the serious risk to future generations, the transgression of the natural and divine laws, and misuse for human enhancement for nonmedical (social) purposes [2]. The most compelling reason is, probably, the potential safety issue posed by unprecise genetic modification using older techniques.

Three recent reports have demonstrated that the use of a robust genome editing technique, the clustered regularly interspaced short palindromic repeat (CRISPR)/Cas9, can genetically modify human embryos [3–5]. Although such modified embryos have not been used for human reproduction, advances in human genome editing research raised serious concerns over its rough-and-ready use and misuse, leading to controversies in a number of countries [6–9]. Chief among these was the International Human Gene Editing Summit 2015 at the National Academies of Sciences, Engineering, and Medicine (NASEM). In the concluding remarks, it was noted that 'it would be irresponsible to proceed with any clinical use of germline editing unless and until …' [10]. However, the final NASEM report in 2017 concluded differently, stating that 'clinical trials using heritable germline genome editing should be permitted only within a robust and effective regulatory framework' [11▪]. This raises a central question as to whether a society can agree to the

Office of Health and Safety, Hokkaido University, Sapporo 060-0808, Japan

Correspondence to Tetsuya Ishii, PhD, Office of Health and Safety, Hokkaido University, Sapporo 060-0808, Japan. Tel: +81 11 706 2126; fax: +81 11 706-2295; e-mail: tishii@general.hokudai.ac.jp

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## KEY POINTS

- With the advent of genome editing, human reproduction involving germline genetic modification is becoming feasible.
- Although the most likely purpose is the prevention of serious genetic disease in offspring, there are many ethical, legal, and social issues associated with human germline genome editing.
- Before this unprecedented medicine is introduced into the global society, further discussions, a broad consensus, and appropriate regulations are required.

initiation of human reproduction involving germline genome editing through deliberations on its ethical implications. The present article reviews the complex issues on creating genetically modified children using genome editing. After examining the feasibility and possible purposes, the article scrutinizes the ethical, legal, and social issues associated with human germline genome editing.

## FEASIBILITY AND DOUBLE-EDGED SWORD EFFECTS

Genome editing techniques use an artificial DNA cutting enzyme that is directed by a guiding molecule to a target DNA sequence in the genome. Genome editing has facilitated the repair of gene mutations (or the copying of a variant) and the disruption of endogenous genes, as well as the insertion of exogenous genes in human cells. Moreover, it is possible to simultaneously modify multiple genes in the genome (multiplex genome editing). Indeed, genome editing in the mammalian germline has readily produced animals with several modified genes [9]. However, genome editing can unintentionally cut nontarget DNA sequences (off-target effect) and create small off-target mutations in addition to large-scale genomic alternations.

Reports from China in 2015 and 2016 revealed that the microinjection of CRISPR/Cas9 mRNA into human zygotes can produce genetically modified embryos, but also indicated technical issues, including off-target mutations and mosaic embryos containing both modified and nonmodified cells [3,4]. A similar study in 2017, again from China, showed the production of a genetically repaired embryo with no detectable off-target mutations using RNA-guided Cas9 protein [5]. Such reports suggest that human reproduction involving germline genome editing will soon become feasible. However, an off-target mutation or a large genomic alternation can also systemically affect the resultant fetuses and children. Then, for what purposes should this medicine, which has the potential to be a double-edged sword, be used at fertility clinics?

## POSSIBLE PURPOSES AND INFORMED CONSENT

Nearly two decades ago, two types of germline mtDNA manipulation, oocyte-cytoplasmic transfer and zygote nuclear transfer were carried out in the USA and China, respectively to treat intractable female infertility [9]. Such cases suggest the potential use of germline genome editing for infertility treatment. There would be a huge need for personalized infertility treatment through the repair of causative mutations by genome editing [12,13]. However, at present, such a use is unjustifiable. Common infertility treatment techniques, such as in-vitro fertilization (IVF), are practiced with consent by the beneficiaries: the prospective parent(s). In the USA and China, germline mtDNA manipulation was also carried out after obtaining parental consent; however, it resulted in miscarriage and fetal reduction because of Turner syndrome, fetal deaths, and the onset of a developmental disorder in the offspring. Our expertise in relation to human genetic modification is still insufficient. Even in somatic gene therapy, there are currently fewer than 10 approved products, despite more than 2000 clinical trials having been performed worldwide [12]. Given that such as off-target mutations can potentially affect fetuses and offspring who cannot consent, parental consent to infertility treatment using risky genome editing is not justifiable. From a social standpoint, such genetically invasive infertility treatment is unacceptable because its application in infertility treatment will likely promote its widespread use, potentially leading to huge social harm [12].

Mitochondrial donation is a germline mtDNA manipulation legalized in the United Kingdom [8]. It involves nuclear transfer to an enucleated egg or zygote to reduce pathogenic mtDNA, in order to prevent the onset of life-threatening mitochondrial diseases in the offspring. Although preimplantation genetic diagnosis (PGD) is available for that purpose, its application is sometimes difficult if a woman has a high mtDNA mutation load in her eggs. For a prospective child, the benefit of disease prevention may exceed the risks: the failure of disease prevention and other side effects. Parental consent to mitochondrial donation as a family-building option has been legitimate in the United Kingdom since 2015. Likewise, parental consent to reproduction using germline genome editing seems appropriate in cases involving the definite inheritance of a serious genetic disorder

and in which PGD is not applicable, such as autosomal dominant diseases (e.g. Huntington's disease) in which at least one parent is homozygous, or autosomal recessive diseases (e.g. cystic fibrosis) where both parents are homozygous [9,14]. Indeed, rodent experiments have demonstrated that germline genome editing can achieve genetic repair and the recovery of a phenotype [13]. Thus, its use for disease prevention might be justifiable in rare cases in which the inheritance of serious genetic disease is a certainty, particularly in the case of monogenic diseases [9,13,14]. More optimistically, one may assert that humankind could escape from thousands of genetic diseases with the use of genome editing [8].

Parents frequently have certain desires regarding their prospective child's characteristics. Germline genome editing might allow parents to enhance externally visible traits of their offspring by effectively copying a naturally occurring variant [13]. Its use is intended based on the perceived benefits to or preferences of the parents rather than the benefits to their prospective child. Moreover, genetic enhancement essentially differs from infertility treatment. Parents pursuing genetic enhancement value a social aspect of their child rather than the child itself. For this, various problems, such as family discord and lawsuits between families and physicians can be expected to occur if the child has characteristics that do not meet the parents' expectations. Although the term, 'genetic enhancement' has conceptual problems [14], its use for enhancing the appearance of children would be difficult to justify because of issues such as the commodification of children, as well as the irremediable risks to their health [13,15].

## COMPLEX ISSUES

It is worth further considering disease prevention using germline genome editing. However, there are many, complex issues surrounding this unprecedented medicine [Fig. 1]. Prospective parents who consider germline genome editing should receive

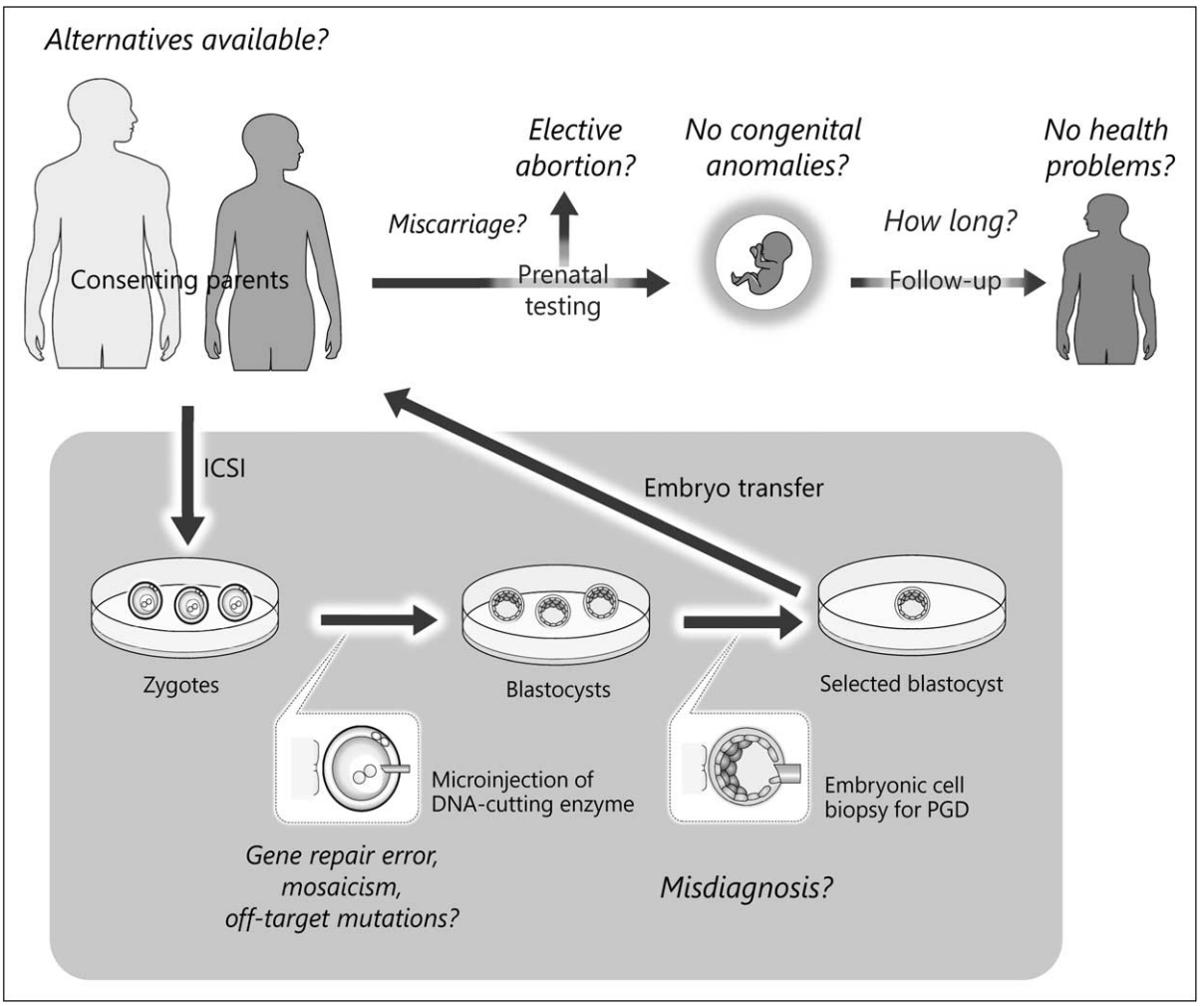


**FIGURE 1.** Complex issues associated with human reproduction involving germline genome editing. Some key issues are shown in italics. ICSI, intracytoplasmic sperm injection; PGD, preimplantation genetic diagnosis.

sufficient information on alternative family-building options because it is inappropriate to offer only germline genome editing, which is associated with substantial risks to the prospective child. Although one parent has no genetic link to the offspring, gamete donation is a simpler and probably less expensive option that is available in many countries [13]. However, in some countries, gamete donation is prohibited (e.g. Bangladesh, Jordan, the Philippines, Saudi Arabia, and Turkey.) or mostly unavailable (e.g. China, France, Iran, Italy, and Japan) [16]. Disease prevention by germline genome editing is difficult to justify in such countries. Adoption can also be an alternative. However, this alternative is difficult to consider in countries, wherever genetic relatedness is considered to be very important [13].

Establishing a follow-up scheme to monitor the children who are born via risky germline genome editing is crucial; however, the proponents of germline genome editing do not address this issue [8,14]. Considering that somatic gene therapy requires several years of follow-up, how long should the children born via germline genome editing be followed? Although germline genome editing can potentially impact future generations, the feasibility of transgenerational follow-up is uncertain. In the United Kingdom, planning of follow-up is mandatory whenever a clinic applies a license to perform mitochondrial donation; however, patients have no obligation to participate in the follow-up program [17]. Even if parents agree to participate in the follow-up, parents may withdraw their consent at a later stage. Evitt *et al.* [18] proposed 15-year Phase I–III clinical trials to monitor children who underwent germline genome editing. However, the time frame is insufficient in the case of late-onset diseases. For example, the age of onset in patients with Huntington's disease is frequently in the thirties or later. A likely scenario is that children born via germline genome editing will initially undergo periodic examinations, and will be left later. As stated in the concluding remarks of the Summit [10], 'It would be irresponsible to proceed with any clinical use of germline editing unless and until' a reasonable and ethical follow-up protocol is established.

Further, questions abound in relation to the social introduction of germline genome editing for disease prevention. Some are addressed in the following. Proponents assert that public funding should support basic research on human germline genome editing [14]. In contrast, Israel and European countries cover the cost of disease prevention using PGD by health insurance [16]. Then, should health insurance cover the costs of the clinical use of germline genome editing for disease prevention? The WHO estimates that there are currently approximately 10 000 known monogenic diseases. Is it truly possible to cover the cost of preventing so many disorders using genome editing? If countries do not cover the cost, the benefit of disease prevention by germline genome editing will be confined to the wealthier segment of society, potentially widening social disparities [15].

Consider the role of women [19▪]. The introduction of germline genome editing may lead to unanticipated fetal anomalies that present the woman with the dilemma of whether to electively terminate her pregnancy. Although PGD would be indispensable prior to embryo transfer, it will likely fail to screen out embryos that are unsuited for embryo transfer because of the limitations in the ability to completely detect small off-target mutations using very small DNA samples, in addition to the naturally underlying mosaicism in human embryos [12]. Some resultant fetuses will be prenatally diagnosed as having an off-target mutation causative of another disease. In doing so, a woman may regret her consent, or feel distressed by the prospect of undergoing elective abortion. Previous germline mtDNA manipulations in the USA and China have illustrated such possibilities [9].

As no prenatal tests are perfectly accurate, off-target mutations or large genomic alternations in germline genome editing may lead to the birth of children with congenital anomalies. Again, this possibility is suggested by the case of germline mtDNA manipulations in the USA [9]. Can such suffering and loss be adequately compensated?

PGD was initially developed to select embryos with no genetic disease-causing mutations, and was then repurposed for aneuploidy screening to enhance the live birth rate after infertility treatment, despite the potential risk of embryonic cell biopsy in the resultant children. In some countries, PGD has lapsed into social sex selection and disability selection [13]. Because multiplex genome editing can 'molecularize' the human identity [20], the use of germline genome editing for disease prevention will likely slide down a slope toward enhancement via infertility treatment in some countries with lax regulations [2,21]. The introduction of germline genome editing implies an increase in family-building options [15]. Its widespread use to enable couples to have healthy, genetically related children may jeopardize or lead to the breakdown of adoption systems. Children in orphanages may completely lose the opportunity to be placed with foster parents.

## TO GO OR NOT TO GO?

As a result of the potential misuse of genome editing, it is necessary to establish regulations on

germline genome editing even for disease prevention. A recent survey suggests that 74% of 39 countries prohibit human germline genetic modification by laws or guidelines [13]. As a result of the complex ethical issues, some countries will establish or maintain the legal prohibition on human germline genetic modification. Recently, some countries have established such prohibitive policies. In 2016, Israel approved Amendment Law No. 3 Prohibition on Genetic Intervention (Human Cloning and Genetic Change in Reproductive Cells), 5776/2016 (valid till May 23, 2020). Immediately after the Summit, the USA established Consolidated Appropriations Act 2016 Sec. 749 that prohibits the Food and Drug Administration from spending federal budget on reviewing or approving applications for exemption on the investigational use of biologics in which a human embryo is intentionally created or modified to include a heritable genetic modification. However, it is inappropriate to take such legal action without social discussions [22]. People in such countries might participate in reproductive tourism to seek human germline genome editing, because they do not sufficiently understand the ethical implications.

Meanwhile, some countries may go forward with initiating germline genome editing at fertility clinics. Where is this likely to happen? The United Kingdom will likely discuss the use of mitochondria-targeted DNA-cutting enzymes to eliminate pathogenic mtDNA remaining in oocytes or zygotes following mitochondrial donation. However, there are many legal questions. For instance, should modifying nDNA as well as mtDNA in the germline be permitted? Some nDNA mutation also cause mitochondrial disease. Genetic modification by older techniques implies only gene insertion, whereas genome editing can perform various genetic modifications. Although gene repair by genome editing will likely be considered positively, should the regulation prohibit gene insertion, gene disruption, and variant copying? Should multiplex genome editing be permitted in the regulations? [13]. Prior to this, discussions must again be held at the domestic and international levels [15,23▪▪]. The initiation of human germline genome editing in one country could also influence people in other countries, as illustrated by a recent case of egg nuclear transfer in Mexico [24]. Although the Summit 2015 successfully reached a minimal consensus among scientists and other experts, the NASEM final report was not a true international consensus. Each country should begin public participatory consensus processes aimed at establishing a national political regulation process, while interacting with international consensus processes [23▪▪].

## CONCLUSION

Germline genome editing has the potential to bring transformative changes to human reproduction throughout the world. In countries with no clear norms with regard to reproductive medicine, the widespread use of germline genome editing for disease prevention will likely bring social harm, in addition to benefits for some couples who seek a healthy, genetically related child. Before human germline genome editing is introduced into the global society, it is necessary to conduct further discussions on the ethical, legal, and social implications and to reach a broad consensus.

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*There are no conflicts of interest.*

## REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
- ▪▪ of outstanding interest

1. US President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. Splicing life: a report on the social and ethical issues of genetic engineering with human beings. Washington, DC; 1982. Available online at: https://bioethics.georgetown.edu/documents/pcemr/splicinglife.pdf
2. Baylis F, Robert JS. The inevitability of genetic enhancement technologies. Bioethics 2004; 18:1–26.
3. Liang P, Xu Y, Zhang X, *et al.* Crispr/cas9-mediated gene editing in human tripronuclear zygotes. Protein Cell 2015; 6:363–372.
4. Kang X, He W, Huang Y, *et al.* Introducing precise genetic modifications into human 3pn embryos by CRISPR/Cas-mediated genome editing. J Assist Reprod Genet 2016; 33:581–588.
5. Tang L, Zeng Y, Du H, *et al.* Crispr/cas9-mediated gene editing in human zygotes using cas9 protein. Mol Genet Genomics 2017; 292: 525–533.
6. Lanphier E, Urnov F, Haecker SE, *et al.* Don't edit the human germ line. Nature 2015; 519:410–411.
7. Church G. Perspective: encourage the innovators. Nature 2015; 528:S7.
8. Harris J. Germline manipulation and our future worlds. Am J Bioeth 2015; 15:30–34.
9. Ishii T. Germline genome-editing research and its socioethical implications. Trends Mol Med 2015; 21:473–481.
10. Committee on Science, Technology and Law; Policy and Global Affairs. National Academies of Sciences, Engineering, and Medicine International Summit on human gene editing: a global discussion. Available online at: https://www.ncbi.nlm.nih.gov/books/NBK343652/ (2015).
11. ▪ National Academies of Science, Engineering, and Medicine (NASEM). Human genome editing: science, ethics, and governance (the National Academies Press) https://www.Nap.Edu/catalog/24623/human-genome-editing-science-ethics-and-governance (press release 2017).

A comprehensive investigation regarding the ethics of genome editing in humans and human germline. It should be noted that the viewpoints may not be applicable to countries other than the USA, the United Kingdom, and China.

12. Ishii T. Reproductive medicine involving genome editing: clinical uncertainties and embryological needs. Reprod Biomed Online 2017; 34:27–31.
13. Ishii T. Germ line genome editing in clinics: the approaches, objectives and global society. Brief Funct Genomics 2017; 16:46–56.

14. Gyngell C, Douglas T, Savulescu J. The ethics of germline gene editing. J Appl Philos 2017; 34:498–513.
15. Baylis F. Human germline genome editing and broad societal consensus. Nat Hum Behav 2017; 1:0103.
16. International Federation for Fertility Societies. IFFS Surveillance 2016. Glob Reprod Health 2016; 1:1–143.
17. Human Fertilisation & Embryology Authority: Code of practice 33. Mitochondrial donation. Available online at: Http://www.Hfea.Gov.Uk/9931.Html#guidancesection10063.
18. Evitt NH, Mascharak S, Altman RB. Human germline CRISPR-Cas modification: toward a regulatory framework. Am J Bioeth 2015; 15:25–29.
19. Simonstein F. Gene editing, enhancing and women's role. Sci Eng Ethics ■ 2017; doi: 10.1007/s11948-017-9875-5. [Epub ahead of print]
Whenever discussing the ethics of human germline genetic modification, experts tend to focus on the future generations. Simonstein sharply indicates the role of women in human germline genome editing, which proponents have insufficiently addressed.
20. McGonigle IV, Benjamin R. The molecularization of identity: science and subjectivity in the 21st century. Genet Res 2016; 98:e12.
21. Walton D. The slippery slope argument in the ethical debate on genetic engineering of humans. Science and engineering ethics 2016; doi: 10.1007/s11948-016-9861-3. [Epub ahead of print]
22. Cohen IG, Adashi EY. The FDA is prohibited from going germline. Science (New York) 2016; 353:545–546.
23. Gregorowius D, Biller-Andorno N, Deplazes-Zemp A. The role of scientific ■■ self-regulation for the control of genome editing in the human germline: the lessons from the asilomar and the napa meetings show how self-regulation and public deliberation can lead to regulation of new biotechnologies. EMBO Rep 2017; 18:355–358.
The authors propose an insightful model that combines self-regulation with national and international governance in the context of human germline genome editing.
24. Palacios-González C, Medina-Arellano MdJ. Mitochondrial replacement techniques and Mexico's rule of law: on the legality of the first maternal spindle transfer case. J Law Biosci 2017; 4:50–69.