



Search for...



ASHG POSITION STATEMENT · Volume 101, Issue 2, P167-176, August 03, 2017

[Open Archive](#)

Download Full Issue

Human Germline Genome Editing

[Kelly E. Ormond](#)^{1,19} · [Douglas P. Mortlock](#)^{2,19} · [Derek T. Scholes](#)^{3,19} · ... · [Daniel Shriner](#)^{15,16} · [Alice Virani](#)^{17,18} · [Caroline E. Young](#)³... [Show more](#)

[Affiliations & Notes](#) [Article Info](#)

Abstract

With CRISPR/Cas9 and other genome-editing technologies, successful somatic and germline genome editing are becoming feasible. To respond, an American Society of Human Genetics (ASHG) workgroup developed this position statement, which was approved by the ASHG Board in March 2017. The workgroup included representatives from the UK Association of Genetic Nurses and Counsellors, Canadian Association of Genetic Counsellors, International Genetic Epidemiology Society, and US National Society of Genetic Counselors. These groups, as well as the American Society for Reproductive Medicine, Asia Pacific Society of Human Genetics, British Society for Genetic Medicine, Human Genetics Society of Australasia, Professional Society of Genetic Counselors in Asia, and Southern African Society for Human Genetics, endorsed the final statement. The statement includes the following positions. (1) At this time, given the nature and number of unanswered scientific, ethical, and policy questions, it is inappropriate to perform germline gene editing that culminates in human pregnancy. (2) Currently, there is no reason to prohibit in vitro germline genome editing on human embryos and gametes, with appropriate oversight and consent from donors, to facilitate research on the possible future clinical applications of gene editing. There

[Download PDF](#)[Outline](#)[Share](#)[More](#)

a compelling medical rationale, (b) an evidence base that supports its clinical use, (c) an ethical justification, and (d) a transparent public process to solicit and incorporate stakeholder input.

Keywords

[gene editing](#) · [genome editing](#) · [germline](#) · [ethics](#) · [society](#) · [gene therapy](#) · [human genome](#)
· [eugenics](#) · [genetics policy](#) · [CRISPR](#)

Main Text

Introduction

The American Society of Human Genetics (ASHG) Workgroup on Human Germline Genome Editing developed the present position statement and explanatory paper between August 2015 and January 2017. This group, composed of a combination of basic and clinical scientists, bioethicists, health services researchers, lawyers, and genetic counselors, worked together to integrate the scientific status of and socio-ethical views toward human germline genome editing (defined as using genome-editing techniques in a human germ cell or embryo) into this statement. The group met regularly through a series of weekly conference calls and email discussions, proposed a draft statement to the ASHG Board of Directors in April 2016, presented the draft policy statement to ASHG and European Society of Human Genetics (ESHG) members at the ASHG-ESHG Building Bridges session in May 2016, and requested comments from ASHG members in June 2016. A total of 27 comments were received, 4 of which were in opposition to the statement. All comments and recommended modifications were reviewed by the committee and discussed as part of the development of this explanatory paper, which was reviewed and approved by the ASHG Board of Directors in March 2017.

The workgroup included representation from the following professional organizations (in alphabetical order), which then also approved the position statement and paper: the Association of Genetic Nurses and Counsellors, Canadian Association of Genetic Counsellors, International Genetic Epidemiology Society, and National Society of Genetic Counselors. This resulting policy statement was then reviewed and endorsed by the following professional organizations (also listed in alphabetical order) before submission for publication: the American Society for Reproductive Medicine, Asia Pacific Society of Human Genetics (APSHG), British Society for Genetic Medicine, Human Genetics Society of Australasia, Professional Society of Genetic Counselors in Asia, and Southern African Society for Human Genetics. (The APSHG would like to add a comment that we also express a concern that in some countries with inadequate ethics committee oversight or strong institutional review boards [IRBs], the potential for abuse exists. Hence, there is a strong need to continue to educate our professionals, researchers, journal reviewers, journals, and IRBs about this



Download PDF

Scientific Background

“Genome editing” collectively refers to a set of technologies, including a new tool based on the CRISPR/Cas9 mechanism discovered in *Streptococcus pyogenes*. This and other organisms use this system to protect themselves from viral infections. The system can be engineered to facilitate the targeted modification of specific DNA sequences in the genomes of living cells. CRISPR/Cas9 and other genome-editing methods have been thoroughly reviewed elsewhere.^{1–3} Like many other robust DNA modification technologies, CRISPR/Cas9 has quickly become a widely used research tool, and its embrace testifies to the ease with which it can be customized and its effectiveness in multiple cell types and species. In many ways, preceding gene-transfer technologies that fell short of “genome editing”—i.e., introduced genes into cells but did not permanently incorporate them into the genome—laid the groundwork for the issues presented in this statement.⁴ Of relevance here are several key issues raised by early somatic gene-therapy trials: (1) a real prospect of treating and even curing previously intractable diseases, especially in cases where the primary cause is a defective gene; (2) the possibility of undesirable side effects, sometimes due to the delivery method or to the random insertion site of the transferred DNA itself; and (3) regulatory oversight.

In the 1980s, true genome-targeting techniques—that is, the targeted modification of a specific sequence at its normal genomic location rather than the insertion of gene copies at other locations—were pioneered for germline engineering in mice. These early studies catalyzed much research and thought into the scientific advantages of gene targeting over traditional gene-transfer methods. By 2010, decades of work had culminated in the development of a variety of engineered nucleases such as zinc-finger nucleases, meganucleases, and transcription activator-like effector nucleases. In early 2013, the introduction of an RNA-guided nuclease—the CRISPR/Cas9 system adapted from the bacterial species *Streptococcus pyogenes*—was shown to specifically cleave target sequences⁵ and enable a new approach to precise genome modification in mammalian cells.^{6–9} Since then, additional RNA-guided nucleases from other bacterial species have been described and are being investigated for their potential as genome-editing tools.

Genome-editing tools all work in a similar fashion. They “target” specific DNA sequences for individual genes or non-coding regions by engineering certain proteins or protein-RNA complexes that can then recognize and bind the sequences and generate single-strand or double-strand DNA breaks. For example, a Cas9 protein along with a CRISPR “guide RNA” can find a target gene among the thousands of genes in a cell’s genome and cleave both DNA strands at the target site. It is this cleavage event that can be exploited to create a mutation in, or “edit,” the target gene.

The cell’s normal DNA repair machinery then attempts to repair the DNA break. The outcome of this process is often the introduction of a mutation, most frequently the deletion of some DNA at the target site. If a separately engineered “donor” DNA fragment is also provided, the repair machinery



Download PDF

replace a pre-existing deleterious mutation or, alternatively, a novel, beneficial variant. In this way, mutations that cause disease could potentially be corrected, or new mutations could be introduced to alter gene function in such a way as to prevent or treat disease.

RNA-guided nucleases such as CRISPR/Cas9 have two clear advantages over previous gene-editing tools. First, they can be easily customized to target specific sequences via alteration of only a small number of nucleotides in the guide RNA (20 nucleotides in the case of *Streptococcus pyogenes* CRISPR/Cas9)—a simple, fast, and inexpensive process that is much simpler than previous gene-editing methods. Second, RNA-guided nucleases are dramatically efficient at cleaving target genomic sequences in some cell types and organs^{10–12}—so much so that for many applications, the delivery of the protein and RNA components into target cells, rather than the targeting itself, is now the main rate-limiting step in genome editing.

Thus, individual genes can be targeted for engineering in cells grown in the laboratory or even within live animal tissues. In fact, engineered nucleases have been shown to be efficient in a wide variety of organisms, including many mammals. Human cells are also readily amenable to genome editing. Accordingly, there is considerable interest in using genome-editing tools to develop cell-based human therapeutics that could potentially deliver lifesaving treatments for diseases such as HIV infection, sickle-cell anemia, and cancers.

Genome editing has been shown to work in embryos from many species. This is already accelerating the pace of many areas of biology as researchers use genome-editing methods to more quickly and cheaply study the function of genes in model organisms and economically important species such as crops, livestock, and energy feedstock. It has been shown that engineered nucleases, especially CRISPR/Cas9, can be easily used to edit genes in mammalian embryos such as mice, rats, and even monkeys.^{11,13,14} These embryos can then be implanted into foster animals and carried to term, generating live-born animals carrying precise changes in their DNA. However, off-target mutagenesis and mosaicism in the resulting animals can be significant drawbacks of the technology.¹⁵

The similarity between human embryos and other animal embryos raises the possibility that genome-editing methods could be incorporated into human-assisted reproduction procedures. Already, CRISPR/Cas9-mediated genome editing of 1-cell-stage mouse zygotes is routine;¹⁶ in this context, reports that human embryos could be similarly edited are not surprising. In early 2015, the first study demonstrating that CRISPR/Cas9 could be used to modify genes in early-stage human embryos was published.¹⁷ Although the embryos employed for those experiments were not capable of developing to term, the work clearly demonstrated that genome editing with CRISPR/Cas9 in human embryos can readily be performed. This report has stimulated many scientists and organizations to clarify their stance on the use of genome-editing methods.



Download PDF

cannot be passed on from the individual to offspring. In contrast, germline genome editing, which is the primary focus of this position statement, refers to genome editing that occurs in a germ cell or embryo and results in changes that are theoretically present in all cells of the embryo and that could also potentially be passed from the modified individual to offspring. In theory, modification of gamete-producing cells at any point in development could permit this. Because human germline genome editing has potential effects on both the treated individual and subsequent generations of persons, it entails ethical considerations beyond those of somatic genome modification.

Regardless of whether it entails somatic or germline genome editing, its efficacy and safety must be established before any consideration is given to a genome-editing method as a potential therapeutic approach. CRISPR/Cas9 is indeed highly efficient in many cell types, but it is seldom 100% effective at introducing alterations at a target site, although double-digit percentages are routine. More concerning is that the desired “editing” event usually competes with the generation of unwanted mutations at the target site. Thus, genome-editing applications usually generate a mixture of genetically heterogeneous cells.

It has also been well documented that DNA cleavage by native CRISPR/Cas9 does not always require perfect pairing between all bases in its guide RNA and the target, sometimes permitting unwanted cleavage at off-target locations.^{18–21} Although these off-target effects are low enough to permit most research applications,^{22,23} the safety requirements for any human clinical genome-editing application are more stringent. New methods and combinations of methods are being used to better estimate the risk that off-target mutations will occur and their potential effects on the patient. We note that rapid strides are being made to reduce the off-target effects of CRISPR/Cas9.^{24,25}

In summary, there remains no agreement as to which specific platforms, methods, and interpretations of benefits and risks will need to be applied in the validation of the safety of genome-editing therapeutic applications. Nevertheless, when considered in the context of somatic therapy, novel methods of genome editing such as CRISPR/Cas9 will probably raise few truly novel ethical issues that have not been addressed in previous contexts, such as with gene-therapy trials. However, CRISPR/Cas9 is so efficacious in human embryos that germline gene editing is also now possible in our species, raising a host of ethical, social, and legal issues that warrant careful consideration and deliberation.

Ethical Issues

The ethical assessment of human germline genome editing falls, broadly, into two categories: (1) those arising from its potential failure and (2) those arising from its success.

Ethical Issues Related to the Potential Failure of Human Germline Genome Editing



Download PDF

editing, the magnitude of the potential risks of off-target or unintended consequences are yet to be determined. For this reason, safeguards against misguided or premature attempts of this intervention should rely, at a minimum, on existing mechanisms governing the clinical introduction of other reproductive therapies.

There are both national and international policies that regulate embryo research and interventions early in human development^{26–28} that apply to research and the potential clinical translation of human germline genome editing. Their underlying normative frameworks typically address the broad ethical context of human-assisted reproduction technologies and human subjects and genomics research and take into consideration core ethical principles of autonomy, beneficence, non-maleficence, and justice. Differences in these policies include the very definition of what constitutes a human embryo or a reproductive cell, the particular policy tool adopted (legislation, regulation, or professional guidance) and the document’s enforcement (legally binding or self-compliance), and oversight mechanisms (e.g., licensing of activities). Overall, the majority of available statements and recommendations (summarized in [Table 1](#)) restrict applications from attempting to initiate a pregnancy with an embryo or reproductive cell whose germline has been altered.

Arguments	Organizations					
	The Hinxton Group ⁵¹	NAS, NAM, CAS, and UK Royal Society International Summit ⁵²	NAS and NAM Committee on Human Gene Editing ⁵³	ASGCT and JSGT ⁵⁴	ISSCR ⁵⁵	Baltimore et al. ⁵⁶
Basic research should be conducted	x	x	x	x	x	x
Preclinical research should be conducted		x	x			

Table 1
Summary of Recommendations in Major Group, Organizational, and Government Statements



Download PDF

Only main, overt arguments made in each statement are marked by an “x.” Thus, the lack of an “x” does not necessarily indicate disagreement. The table includes only major recommendations from each statement rather than background and is not exhaustive. Also, because this table cannot capture every nuance of each statement, whether a statement addresses a particular point is in some cases subjective. Many groups speaking independently have made statements about human germline gene editing and related research. These organizations vary in composition from coalitions of experts to professional societies to government entities or representatives, but the content of many of the reports and recommendations is fairly similar. Most statements agree that basic research should be conducted but that clinical applications should be avoided at least in the short term. Many of the statements outline criteria that must be met before clinical use of human germline gene modification should be considered, including overcoming safety and technological barriers, achieving societal consensus on bounds, putting appropriate and transparent oversight mechanisms in place, and addressing equity concerns. The most significant area of disagreement is with regard to the types of research that should be allowed currently, including whether there should be a partial or full moratorium. Abbreviations are as follows: NAS, US National Academy of Sciences; NAM, US National Academy of Medicine; CAS, Chinese Academy of Sciences; ASGCT, American Society for Gene and Cell Therapy; JSGT, Japan Society of Gene Therapy; ISSCR, International Society for Stem Cell Research; EGE, European Group on Ethics in Science and New Technologies; ACMG, American College of Medical Genetics; NIH, National Institutes of Health; HFEA, UK Human Fertilization and Embryology Authority.

a “NIH will not fund any use of gene-editing technologies in human embryos.”

[Open table in a new tab](#)

Across jurisdictions, the regulation of human embryo and/or germline manipulation could be categorized as restrictive, intermediate, and permissive. Under the restrictive approach, wide-ranging prohibitions (or moratoria) to activities carried out in a human embryo or germ cell are adopted. In contrast, the intermediate and permissive approaches allow some degree of research and clinical activities to be carried out, although with limitations and oversight in place for research activities linked to reproductive purposes. It is important to note that restrictive policies and limited availability or use of basic research funding do not necessarily prevent certain research or the development of new technologies from taking place.²⁹ For example, in 2001, President George W. Bush restricted federally funded embryonic stem cell research in the US to the use of a small number of cell lines available at the time.³⁰ This, however, did not prevent individual states (e.g., California funded the California Institute for Regenerative Medicine through proposition 71), private funders, and other countries from providing research dollars for embryonic stem cell research, sometimes in settings with limited transparency and oversight. From a broader perspective, the



Download PDF

public domain. The latter enables oversight and transparency through data sharing, peer-reviewed publication, and dissemination of research resources.³¹ It ultimately ensures that the research is in the public interest.

Ethical Issues Related to the Success of Human Germline Genome Editing

Beyond the potential and yet unknown risks of human germline genome editing, there are a number of ways in which the impact of these novel technologies could be ethically problematic if and when they function as intended. Concerns regarding the impact of these technologies on an individual, a family, and society more broadly are similar to those raised by gene therapy in general, as well as embryo research and reproductive technologies (e.g., in vitro fertilization, pre-implantation genetic diagnosis, and prenatal testing).

Impact on the Individual and Family: One of the most significant issues related to human genome editing relates to the impact of the technology on future individuals whose genes are modified de facto without their consent. Clinical ethics accepts the idea that parents are, almost always, the most appropriate surrogate medical decision makers for their children until the children develop their own autonomy and decision-making capacity. This is based on the assumption that, except under rare circumstances, parents have the most to lose or gain from a decision and will ultimately make decisions that reflects the future values and beliefs of their children.^{32,33} By extension, we might assume that parents are the most appropriate decision makers for their future children as well. Although there are anecdotal reports of children and adults who disagree with the medical decisions made by a parent during pregnancy or early childhood, particularly when death was a possible outcome, the idea that a person would have been better off if they had not existed has not gained much traction with the public or in the judicial system, which have usually rejected so-called “wrongful life” suits on the basis of the same principle.³⁴ Of note, there are also published patient stories by individuals who feel strongly that they would not wish to change or remove their own medical condition if given the choice³⁵ and individuals who disagree with medical decisions made by their parents during childhood (e.g., surgical decisions around sex assignment for disorders of sexual differentiation and surgical decisions for craniofacial disorders).

Although these examples provide important considerations regarding the lack of consent for individuals most directly affected by genome editing, they compare non-existence and existence with a disability, which is not an exact parallel to comparing existence with and without genetic alterations. It is worth considering, however, whether germline genome editing involves something fundamentally different or new that would change the alignment between the interests of parents and those of their children, as well as where the range of opinions regarding the value of treatment is diverse enough to warrant preserving autonomous choice at the point of decision-making capacity. This recalibrates the argument against genetic testing in childhood for adult-onset



Download PDF

Ethical concerns about non-maleficence also surface in contemplating the potential for creating unsanctioned pressure on the resulting child and imbalance within the family. Arguably, the ability to “easily” request interventions intended to reduce medical risks and costs could make parents less tolerant of perceived imperfections or differences within their families. Clinical use of germline genome editing might not be in the best interest of the affected individual if it erodes parental instincts for unconditional acceptance. At a minimum, the potential for harm to individuals and families, ramifications on which we can only speculate, provide a strong argument for prudence and further research. By proceeding with caution, we can ensure better understanding of the potential risks and benefits of gene editing from a scientific perspective and, as such, provide families with a more fulsome exercise of their autonomous decision making through the consent process. Moving with less haste also limits reliance on early and often inadequate models of cause and effect in our understanding of genetic inheritance and could mitigate the impact of decisions based on unsubstantiated notions of genetic determinism.

Impact on Society: Two major ethical questions related to germline editing occur at a societal level: (1) concerns related to eugenics and (2) concerns related to social justice and equal access to technologies.

Eugenics refers to both the selection of positive traits (positive eugenics) and the removal of diseases or traits viewed negatively (negative eugenics). Eugenics in either form is concerning because it could be used to reinforce prejudice and narrow definitions of normalcy in our societies. This is particularly true when there is the potential for “enhancement” that goes beyond the treatment of medical disorders. Historically, eugenics has also been associated with exaggerated notions of genetic determination and pseudoscience, and its use through force or tacit support by the state has resulted in devastating consequence.

Although the use of human germline genome editing seems unlikely to result in the loss of genetic diversity in future generations in the population as a whole, it could have a greater effect within select subgroups with both the desire and the means to implement specific changes as has already been seen in the case of Down syndrome.³⁸ One concern that arises in discussions of trait selection, prenatal testing, and the potential for gene therapy or gene editing is the possibility that allowing parents the choice to control aspects of their child’s genetic inheritance (procreative autonomy) could create expectations of this sort of control or even obligations to “create the best children” in what has been called procreative beneficence.^{39,40}

These are among the specific concerns about eugenics expressed by the bioethics community and the public, but perhaps the most deeply felt uneasiness is conceptual: the sense that in identifying some individuals and their traits as “unfit,” we experience a collective loss of our humanity. Often articulated as a concern is that we might be “overstepping” and “playing God” by making such



Download PDF

against individuals.⁴² However, others point out that any form of selection of individuals (including through already existing prenatal diagnosis and testing) sends a message about the “fitness” of such traits or conditions, thereby reflecting on the worth and value of people who have that trait in our society.

Finally, one of the most important and far-reaching effects of human germline genome editing, if it is successful and implemented clinically, might be increasing the already troubling inequities within and between societies. The clinical use of human germline genome editing is hypothetical at this point, and any discussion of access or price is speculative. That said, human germline genome editing is likely to be expensive, and access, should it ever become a reality, is likely to be limited geographically and might not be covered by all payors and health systems. Unequal access and cultural differences affecting uptake could create large differences in the relative incidence of a given condition by region, ethnic group, or socioeconomic status. Genetic disease, once a universal common denominator, could instead become an artifact of class, geographic location, and culture. In turn, reduced incidence and reduced sense of shared risk could affect the resources available to individuals and families dealing with genetic conditions.^{38,43,44}

Accordingly, we have come to an agreement on the positions below and include clarifications and elaborations:

1. *At this time, given the nature and number of unanswered scientific, ethical, and policy questions, it is inappropriate to perform germline gene editing that culminates in human pregnancy.*

As summarized above, there is not yet a high quality evidence base to support the use of germline genome editing, there remains an unknown risk of health consequences, and the ethical issues have not been fully explored and resolved by society.

Scientifically, preclinical studies should establish reliability, validity, safety, and efficacy before attempting any germline genome editing that leads to the potential for implantation or human pregnancy at any post-implantation stage. Here, we define some issues that pertain to establishing acceptable thresholds for safety in the context of human gene editing. Two major categories of safety concerns are the effect of unwanted or off-target mutations and the potential unintended effects of the desired on-target base changes (edits) being made. Various methods are being explored for the monitoring of off-target mutations in genome-editing experiments. It is reasonable to presume that any human genome-editing therapeutic application will require stringent monitoring of off-target mutation rates, but there remains no consensus on which methods would be optimal for this or what a desirable maximum off-target mutation rate would be when these techniques are translated clinically.

Deep next-generation DNA sequencing at specific sites in the genome is feasible, allowing for the interrogation of selected sites in thousands or even millions of cells. However, it is not yet practical to identify rare off-target mutations comprehensively by deep whole-genome sequencing; this is even more challenging when biased material is limited. Recently reported unbiased techniques



Download PDF

measurements in vitro could be considered sufficient to pre-validate in vivo editing approaches. Therefore, new methods will need to be developed for identifying and monitoring off-target mutation sites in vivo after somatic genome editing (whether in preclinical animal models or, eventually, in humans) and—if human germline genome editing is to be at all considered—within human germ cells and embryos.

Identification and monitoring of potential off-target mutation sites are further complicated by the existence of naturally occurring polymorphisms, meaning that off-target predictions should not be based solely on the analysis of a single person's genome but rather on a collection of genomes that represent a genotypically diverse group of individuals. On the other hand, the relative health risk of off-target mutations is not clear; clearly, the genome can tolerate a burden of new mutations that might already exceed the risk posed by current gene-editing methods (given that we are each born with 50–100 new genetic variants), but it is not clear how this burden translates into disease risk. At the same time, it seems that these risks might be modest in relation to the health consequences of the serious diseases that genome editing could be used to treat.

With regard to potential unintended effects of the desired on-target mutations, this could be uncontroversial for many genome-editing applications, particularly those for which a clearly deleterious variant is replaced by a common variant that restores normal gene function. Less clear are editing approaches that introduce novel variants that are known to either augment or disrupt gene function and/or variants that are rare or not known to exist in human populations. Ethical issues regarding novel gene modifications are not new with regard to somatic applications, given that they pertain to other types of somatic gene therapy. But one of the major differences between germline gene editing and somatic gene editing is that the former introduces edits to all cells in the body—and potentially to future generations—thus warranting deeper consideration.

Given these considerations, minimum necessary developments should include the following:

- Definitions of broadly acceptable methodologies and minimum standards for measuring off-target mutagenesis.
 - Consensus regarding the likely impact of, and maximum acceptable thresholds for, off-target mutations.
 - Consensus regarding the types of acceptable genome edits with regard to their potential for unintended consequences.
2. *Currently, there is no reason to prohibit in vitro germline genome editing on human embryos and gametes, with appropriate oversight and consent from donors, to facilitate research on the possible future clinical applications of gene editing. There should be no prohibition on making public funds available to support this research.*

Consistent with the sentiment of the 2001 ASHG Statement on Stem Cell Research, animal studies should occur to provide the foundation for human investigation. Human germline gene-editing research is acceptable when performed on already existing embryos that are donated for research with appropriate written donor consent. Rigorous basic scientific research covering multiple



Download PDF

can be performed ethically via compliance with all applicable laws and policies and can be beneficial through potential discoveries that might occur around the biological processes of pregnancy and infertility and underlying related diseases and their potential treatments. Any study involving in vitro genome editing on human embryos and gametes should be conducted under rigorous and independent governance mechanisms, including approval by ethics review boards and meeting any other policy or regulatory requirements. Second, although we acknowledge that different countries will have different prohibitions on federal funding of embryo research, we feel strongly that without public funding to support germline-editing research, there is a risk that research will move offshore and/or to areas where it is subject to fewer regulations and less oversight and where work is done without transparency.

3. *Future clinical application of human germline genome editing should not proceed unless, at a minimum, there is (a) a compelling medical rationale, (b) an evidence base that supports its clinical use, (c) an ethical justification, and (d) a transparent public process to solicit and incorporate stakeholder input.*

If the preclinical research, as described above, supports the potential clinical translation of human germline genome editing, many more things need to happen before translational research in human germline genome editing is considered. We encourage the global community to begin to address the following medical, ethical, and societal questions in a deliberative and inclusionary way while answering the relevant scientific questions that have been discussed above.

First, ASHG feels strongly that there should be a compelling medical rationale for any conditions for which germline genome editing might occur. Using a conceptual model that addresses various aspects of disabling conditions and quality of life,⁴⁵ this might include consideration of the following: the medical severity of the condition, treatability, risk of occurrence, and potential availability of other options for treatment, including somatic gene editing and prenatal or preimplantation diagnosis.

Second, the clinical translation of technologies to health care is typically preceded by health technology assessment (HTA), which provides a rigorous means of informing clinical and policy decision making through systematic assessment of the supporting evidentiary base. This includes consideration of clinical effectiveness (e.g., validity, utility, and safety), cost effectiveness (e.g., economic evaluation), and risks and benefits for health-care delivery and society (e.g., impact on health services and consistency with societal and ethical values).⁴⁶ As an example, in the US, the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) was established as an advisory body to the Office of Public Health Genomics at the Centers for Disease Control and Prevention to provide evidence reviews for genomic technologies. This independent group adopted review methods similar to HTA frameworks,⁴⁷ although HTA frameworks typically include broader considerations of health service delivery, economic analysis, and ethical or social issues. Although evaluation of the evidentiary base of a technology is a fundamental step in the translation of any new therapeutic, procedure, or diagnostic test into clinical care, emerging developments could



Download PDF

sidestepping its formal review and approval before large-scale use. Nonetheless, once evidence begins to build on the validity, utility, safety, and health-care impacts, independent advisory bodies, taking an approach similar to that of EGAPP, ought to be funded and tasked to review and make recommendations about the clinical use and reimbursement of germline genome editing in clinical practice.

Third, ethical and social values regarding germline genome editing need to be solicited and considered. There are three general approaches to addressing the ethical justification and stakeholder assessment of germline genome editing: conducting primary research; conducting secondary analyses of published literature on the perceptions, acceptability, quality of life, attitudes, or values of stakeholders; and commissioning an expert review.^{48,49} Surveys of the general public⁴¹ and various scientific and health professional groups on their views toward genome editing have already begun (Alyssa Armsby et al., unpublished data; A.V. et al., unpublished data), but it is difficult to assess the impact of these attitudes in a population that has limited understanding of the technologies they are evaluating, as well as their generalizability to other populations and societies. New approaches to public engagement for addressing ethical and social issues in such complex topics include deliberative democracy, citizen juries, and community-based participatory research. Such public-engagement techniques are increasingly being used—and even mandated by some jurisdictions (e.g., the UK National Institute for Health Care and Excellence)⁵⁰—in an effort to incorporate citizen values or patient perspectives into technology assessment and ensuing guidance.⁴⁸ Engaging broader stakeholder groups, including the medical and scientific communities, persons and families dealing with genetically based disabilities, and the general public, would be warranted given the potential uses and impacts of germline genome-editing technology. These debates and engagements should weigh the risks, benefits, alternatives, unknown consequences, and access, as well as distributive and procedural justice, both on a societal level (across and within societies) and on an individual or community basis. Given the global diversity in culture and social norms around health, illness, and disability, it will be challenging to develop representative stakeholder groups and to know when enough data on public views have been collected. Ultimately, these debates and engagements will inform the frameworks to enable ethical uses of the technology while prohibiting unethical ones.

Summary and Conclusion

Many scientific, medical, and ethical questions remain around the potential for human germline genome editing. ASHG supports somatic genome editing and preclinical (in vitro human and animal) germline genome research but feels strongly that it is premature to consider human germline genome editing in any translational manner at this time. We encourage ethical and social consideration in tandem with basic science research in the upcoming years.





Download PDF

We thank T.J. Cradick and Beverly Davidson for helpful input and comments in various stages of developing this policy paper, as well as members of the American Society of Human Genetics and other organizations (including those that endorsed the statement, the International Genetic Epidemiology Society's Committee on Ethical, Legal, and Social Issues, and the European Society of Human Genetics when it was presented at the 2016 Building Bridges session) who provided comments at various points. We also thank Mary Rose Stoltz and Nalini Padmanabhan for editing and formatting the statement. D.S. was supported by the Intramural Research Program of the Center for Research on Genomics and Global Health (CRGGH). The CRGGH is supported by the National Human Genome Research Institute, National Institute of Diabetes and Digestive and Kidney Diseases, Center for Information Technology, and Office of the Director at the NIH (1ZIAHG200362). L.C.B. and D.S. report that the opinions expressed in this article are their own and do not reflect the view of the NIH, the Department of Health and Human Services, or the US Government.

Web Resources

DNA Learning Center Cold Spring Harbor Laboratory,
<http://www.eugenicsarchive.org/eugenics/list3.pl>

References

1. Hsu, P.D. · Lander, E.S. · Zhang, F.
Development and applications of CRISPR-Cas9 for genome engineering
Cell. 2014; **157**:1262-1278
[Full Text](#)  [Full Text \(PDF\)](#) [Scopus \(4221\)](#) [PubMed](#) [Google Scholar](#)
2. Gupta, R.M. · Musunuru, K.
Expanding the genetic editing tool kit: ZFNs, TALENs, and CRISPR-Cas9
J. Clin. Invest. 2014; **124**:4154-4161
[Crossref](#) [Scopus \(362\)](#) [PubMed](#) [Google Scholar](#)
3. Komor, A.C. · Badran, A.H. · Liu, D.R.
CRISPR-based technologies for the manipulation of eukaryotic genomes
Cell. 2017; **168**:20-36
[Full Text](#)  [Full Text \(PDF\)](#) [Scopus \(681\)](#) [PubMed](#) [Google Scholar](#)



Download PDF

Gene. 2013; **525**:162-169

[Crossref](#)

[Scopus \(434\)](#)

[PubMed](#)

[Google Scholar](#)

-
5. Jinek, M. · Chylinski, K. · Fonfara, I. ...

A programmable dual-RNA-guided DNA endonuclease in adaptive bacterial immunity

Science. 2012; **337**:816-821

[Crossref](#)

[Scopus \(11706\)](#)

[PubMed](#)

[Google Scholar](#)

-
6. Mali, P. · Yang, L. · Esvelt, K.M. ...

RNA-guided human genome engineering via Cas9

Science. 2013; **339**:823-826

[Crossref](#)

[Scopus \(7286\)](#)

[PubMed](#)

[Google Scholar](#)

-
7. Cong, L. · Ran, F.A. · Cox, D. ...

Multiplex genome engineering using CRISPR/Cas systems

Science. 2013; **339**:819-823

[Crossref](#)

[Scopus \(11673\)](#)

[PubMed](#)

[Google Scholar](#)

-
8. Jinek, M. · East, A. · Cheng, A. ...

RNA-programmed genome editing in human cells

eLife. 2013; **2**:e00471

[Crossref](#)

[Scopus \(1706\)](#)

[PubMed](#)

[Google Scholar](#)

-
9. Cho, S.W. · Kim, S. · Kim, J.M. ...

Targeted genome engineering in human cells with the Cas9 RNA-guided endonuclease

Nat. Biotechnol. 2013; **31**:230-232

[Crossref](#)

[Scopus \(1534\)](#)

[PubMed](#)

[Google Scholar](#)

-
10. Ding, Q. · Regan, S.N. · Xia, Y. ...

Enhanced efficiency of human pluripotent stem cell genome editing through replacing TALENs with CRISPRs

Cell Stem Cell. 2013; **12**:393-394

[Full Text](#)



[Full Text \(PDF\)](#)

[Scopus \(428\)](#)

[PubMed](#)

[Google Scholar](#)

-
11. Wang, H. · Yang, H. · Shivalila, C.S. ...

One-step generation of mice carrying mutations in multiple genes by CRISPR/Cas-



[Download PDF](#)

[Full Text](#)[Full Text \(PDF\)](#)[Scopus \(2864\)](#)[PubMed](#)[Google Scholar](#)

-
12. Ding, Q. · Strong, A. · Patel, K.M. ...

Permanent alteration of PCSK9 with in vivo CRISPR-Cas9 genome editing

Circ. Res. 2014; **115**:488-492

[Crossref](#)[Scopus \(418\)](#)[PubMed](#)[Google Scholar](#)

-
13. Li, D. · Qiu, Z. · Shao, Y. ...

Heritable gene targeting in the mouse and rat using a CRISPR-Cas system

Nat. Biotechnol. 2013; **31**:681-683

[Crossref](#)[Scopus \(571\)](#)[PubMed](#)[Google Scholar](#)

-
14. Niu, Y. · Shen, B. · Cui, Y. ...

Generation of gene-modified cynomolgus monkey via Cas9/RNA-mediated gene targeting in one-cell embryos

Cell. 2014; **156**:836-843

[Full Text](#)[Full Text \(PDF\)](#)[Scopus \(864\)](#)[PubMed](#)[Google Scholar](#)

-
15. Yen, S.T. · Zhang, M. · Deng, J.M. ...

Somatic mosaicism and allele complexity induced by CRISPR/Cas9 RNA injections in mouse zygotes

Dev. Biol. 2014; **393**:3-9

[Crossref](#)[Scopus \(239\)](#)[PubMed](#)[Google Scholar](#)

-
16. Singh, P. · Schimenti, J.C. · Bolcun-Filas, E.

A mouse geneticist's practical guide to CRISPR applications

Genetics. 2015; **199**:1-15

[Crossref](#)[Scopus \(260\)](#)[PubMed](#)[Google Scholar](#)

-
17. Liang, P. · Xu, Y. · Zhang, X. ...

CRISPR/Cas9-mediated gene editing in human tripronuclear zygotes

Protein Cell. 2015; **6**:363-372

[Crossref](#)[Scopus \(864\)](#)[PubMed](#)[Google Scholar](#)

-
18. Fu, Y. · Foden, J.A. · Khayter, C. ...

High-frequency off-target mutagenesis induced by CRISPR-Cas nucleases in human



Download PDF

[Crossref](#)[Scopus \(2533\)](#)[PubMed](#)[Google Scholar](#)

-
19. Hsu, P.D. · Scott, D.A. · Weinstein, J.A. ...

DNA targeting specificity of RNA-guided Cas9 nucleases

Nat. Biotechnol. 2013; **31**:827-832

[Crossref](#)[Scopus \(3460\)](#)[PubMed](#)[Google Scholar](#)

-
20. Mali, P. · Aach, J. · Stranges, P.B. ...

CAS9 transcriptional activators for target specificity screening and paired nickases for cooperative genome engineering

Nat. Biotechnol. 2013; **31**:833-838

[Crossref](#)[Scopus \(1450\)](#)[PubMed](#)[Google Scholar](#)

-
21. Pattanayak, V. · Lin, S. · Guilinger, J.P. ...

High-throughput profiling of off-target DNA cleavage reveals RNA-programmed Cas9 nuclease specificity

Nat. Biotechnol. 2013; **31**:839-843

[Crossref](#)[Scopus \(1212\)](#)[PubMed](#)[Google Scholar](#)

-
22. Veres, A. · Gosis, B.S. · Ding, Q. ...

Low incidence of off-target mutations in individual CRISPR-Cas9 and TALEN targeted human stem cell clones detected by whole-genome sequencing

Cell Stem Cell. 2014; **15**:27-30

[Full Text](#)[Full Text \(PDF\)](#)[Scopus \(408\)](#)[PubMed](#)[Google Scholar](#)

-
23. Smith, C. · Gore, A. · Yan, W. ...

Whole-genome sequencing analysis reveals high specificity of CRISPR/Cas9 and TALEN-based genome editing in human iPSCs

Cell Stem Cell. 2014; **15**:12-13

[Full Text](#)[Full Text \(PDF\)](#)[Scopus \(293\)](#)[PubMed](#)[Google Scholar](#)

-
24. Slaymaker, I.M. · Gao, L. · Zetsche, B. ...

Rationally engineered Cas9 nucleases with improved specificity

Science. 2016; **351**:84-88

[Crossref](#)[Scopus \(1774\)](#)[PubMed](#)[Google Scholar](#)

Download PDF

[Crossref](#)[Scopus \(1947\)](#)[PubMed](#)[Google Scholar](#)

26. Araki, M. · Ishii, T.

International regulatory landscape and integration of corrective genome editing into in vitro fertilization*Reprod. Biol. Endocrinol.* 2014; **12**:108[Crossref](#)[Scopus \(112\)](#)[PubMed](#)[Google Scholar](#)

27. Ledford, H.

Where in the world could the first CRISPR baby be born?*Nature.* 2015; **526**:310-311[Crossref](#)[Scopus \(22\)](#)[PubMed](#)[Google Scholar](#)

28. Isasi, R. · Kleiderman, E. · Knoppers, B.M.

GENETIC TECHNOLOGY REGULATION. Editing policy to fit the genome?*Science.* 2016; **351**:337-339[Crossref](#)[Scopus \(87\)](#)[PubMed](#)[Google Scholar](#)

29. Drazen, J.M.

Embryonic stem-cell research--the case for federal funding*N. Engl. J. Med.* 2004; **351**:1789-1790[Crossref](#)[Scopus \(11\)](#)[PubMed](#)[Google Scholar](#)30. Office of the Press Secretary (2001). President Discusses Stem Cell Research. The White House, <https://georgewbush-whitehouse.archives.gov/news/releases/2001/08/20010809-2.html>[Google Scholar](#)31. National Institutes of Health, Office of Extramural Research (2016). 4 Public Policy Requirements, Objectives, and Other Appropriation Mandates. NIH, https://grants.nih.gov/grants/policy/nihgps/HTML5/section_4/4_public_policy_requirements__objectives_and_other_appropriation_mandates.htm[Google Scholar](#)

32. Canadian Pediatric Society

Treatment decisions regarding infants, children and adolescents*Paediatr. Child Health* 2004; **9**:99-114

Download PDF

-
33. Diekema, D. · Mercurio, M. · Adam, B.

Clinical Ethics in Pediatrics: A case based textbook

Cambridge University Press, 2011

[Crossref](#) [Scopus \(19\)](#) [Google Scholar](#)

34. Botkin, J.R.

The legal concept of wrongful life

JAMA. 1988; **259**:1541-1545

[Crossref](#) [Scopus \(14\)](#) [PubMed](#) [Google Scholar](#)

35. Check Hayden, E.

Should you edit your children's genes?

Nature. 2016; **530**:402-405

[Crossref](#) [Scopus \(20\)](#) [PubMed](#) [Google Scholar](#)

36. Botkin, J.R. · Belmont, J.W. · Berg, J.S. ...

Points to consider: ethical, legal, and psychosocial implications of genetic testing in children and adolescents

Am. J. Hum. Genet. 2015; **97**:6-21

[Full Text](#)  [Full Text \(PDF\)](#) [Scopus \(351\)](#) [PubMed](#) [Google Scholar](#)

37. Committee on Bioethics, Committee on Genetics, American College of Medical Genetics and Genomics Social, Ethical, and Legal Issues Committee

Ethical and policy issues in genetic testing and screening of children

Pediatrics. 2013; **131**:620-622

[Crossref](#) [Scopus \(293\)](#) [PubMed](#) [Google Scholar](#)

38. Egan, J.F. · Smith, K. · Timms, D. ...

Demographic differences in Down syndrome livebirths in the US from 1989 to 2006

Prenat. Diagn. 2011; **31**:389-394

[Crossref](#) [Scopus \(24\)](#) [PubMed](#) [Google Scholar](#)

39. Savulescu, J.

Procreative beneficence: why we should select the best children

Bioethics. 2001; **15**:413-426

[Crossref](#) [Scopus \(565\)](#) [PubMed](#) [Google Scholar](#)



Download PDF

J. Med. Ethics. 2015; **41**:696-700

[Crossref](#)

[Scopus \(5\)](#)

[PubMed](#)

[Google Scholar](#)

41. Funk, C., Kennedy, B., and Sciupac, E.P. (2016). U.S. public opinion on the future use of gene editing. Pew Research Center, <http://www.pewinternet.org/2016/07/26/u-s-public-opinion-on-the-future-use-of-gene-editing/#> .

[Google Scholar](#)

42. Cho, M.K. · Magnus, D. · Caplan, A.L. ...

Policy forum: genetics. Ethical considerations in synthesizing a minimal genome

Science. 1999; **286**:2087-2090

[Crossref](#)

[Scopus \(106\)](#)

[PubMed](#)

[Google Scholar](#)

43. Hawkins, A.K. · Hayden, M.R.

A grand challenge: providing benefits of clinical genetics to those in need

Genet. Med. 2011; **13**:197-200

[Full Text](#)



[Full Text \(PDF\)](#)

[Scopus \(46\)](#)

[PubMed](#)

[Google Scholar](#)

44. Smith, C.E. · Fullerton, S.M. · Dookeran, K.A. ...

Using Genetic Technologies To Reduce, Rather Than Widen, Health Disparities

Health Aff. (Millwood). 2016; **35**:1367-1373

[Crossref](#)

[Scopus \(65\)](#)

[PubMed](#)

[Google Scholar](#)

45. Rolland, J.S. · Walsh, F.

Facilitating family resilience with childhood illness and disability

Curr. Opin. Pediatr. 2006; **18**:527-538

[Crossref](#)

[Scopus \(132\)](#)

[PubMed](#)

[Google Scholar](#)

46. Bombard, Y. · Bach, P.B. · Offit, K.

Translating genomics in cancer care

J. Natl. Compr. Canc. Netw. 2013; **11**:1343-1353

[Crossref](#)

[Scopus \(61\)](#)

[PubMed](#)

[Google Scholar](#)

47. Teutsch, S.M. · Bradley, L.A. · Palomaki, G.E. ..., EGAPP Working Group

The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Initiative: methods of the EGAPP Working Group



[Download PDF](#)

-
48. Bombard, Y. · Abelson, J. · Simeonov, D. ...

Eliciting ethical and social values in health technology assessment: A participatory approach

Soc. Sci. Med. 2011; **73**:135-144

[Crossref](#) [Scopus \(65\)](#) [PubMed](#) [Google Scholar](#)

49. Lehoux, P. · Williams-Jones, B.

Mapping the integration of social and ethical issues in health technology assessment

Int. J. Technol. Assess. Health Care. 2007; **23**:9-16

[Crossref](#) [Scopus \(84\)](#) [PubMed](#) [Google Scholar](#)

50. Davies, C. · Wetherell, M. · Barnett, E. ...

Opening the box

Evaluating the Citizens Council of NICE, 2005

[Google Scholar](#)

51. The Hinxton Group (2015). Statement on Genome Editing Technologies and Human Germline Genetic Modification. The Hinxton Group, http://www.hinxtongroup.org/Hinxton2015_Statement.pdf .

[Google Scholar](#)

52. National Academies of Sciences, Engineering, and Medicine. (2015). On human gene editing: International summit statement. Eureka Alert, https://www.eurekalert.org/pub_releases/2015-12/naos-ohg120315.php .

[Google Scholar](#)

53. National Academy of Sciences, National Academy of Medicine

Human Genome Editing: Science, Ethics, and Governance

National Academies Press, 2017

[Google Scholar](#)

54. Friedmann, T. · Jonlin, E.C. · King, N.M.P. ...

ASGCT and JSCT Joint Position Statement on Human Genomic Editing

Mol. Ther. 2015; **23**:1282

[Full Text](#)  [Full Text \(PDF\)](#) [Scopus \(44\)](#) [PubMed](#) [Google Scholar](#)

55. International Society for Stem Cell Research (2015). The ISSCR Statement on Human
-



Download PDF

[Google Scholar](#)

56. Baltimore, D. · Berg, P. · Botchan, M. ...

Biotechnology. A prudent path forward for genomic engineering and germline gene modification

Science. 2015; **348**:36-38

[Crossref](#)[Scopus \(474\)](#)[PubMed](#)[Google Scholar](#)

57. European Group on Ethics in Science and New Technologies (2016). Statement on Gene Editing. EGE, https://ec.europa.eu/research/ege/pdf/gene_editing_ege_statement.pdf#view=fit&pagemode=none .

[Google Scholar](#)

58. Lanphier, E. · Urnov, F. · Haecker, S.E. ...

Don't edit the human germ line

Nature. 2015; **519**:410-411

[Crossref](#)[Scopus \(367\)](#)[PubMed](#)[Google Scholar](#)

59. ACMG Board of Directors

Genome editing in clinical genetics: points to consider—a statement of the American College of Medical Genetics and Genomics

Genet. Med. 2017; Published online January 26, 2017

[Google Scholar](#)

60. Collins, F.S. (2015). Statement on NIH funding of research using gene-editing technologies in human embryos. NIH, <https://www.nih.gov/about-nih/who-we-are/nih-director/statements/statement-nih-funding-research-using-gene-editing-technologies-human-embryos> .

[Google Scholar](#)

61. Human Fertilisation and Embryology Authority (2016). HFEA approval for new “gene editing” techniques. The Francis Crick Institute, <https://www.crick.ac.uk/news/science-news/2016/02/01/hfea-decision/> .

[Google Scholar](#)

Article metrics



Download PDF

163

Citations

798

Captures

43

Mentions

19

Social Media



[View details](#)

Related articles (40)

Germline genome-editing research and its socioethical implications

Tetsuya Ishii

Trends in Molecular Medicine, June 12, 2015

Evaluation of guide-free Cas9-induced genomic damage and transcriptome changes in pig embryos

Ge et al.

Molecular Therapy - Nucleic Acids, September 19, 2023

Retained chromosomal integrity following CRISPR-Cas9-based mutational correction in human embryos

Bekaert et al.

Molecular Therapy, June 26, 2023

[Show more](#)



LIFE & MEDICAL SCIENCES JOURNALS

Cell

Cancer Cell



Download PDF

Cell Genomics

Cell Host & Microbe

Cell Metabolism

Cell Reports

Cell Reports Medicine

Cell Stem Cell

Cell Systems

Current Biology

Developmental Cell

Immunity

Med

Molecular Cell

Neuron

Structure

American Journal of Human Genetics (*partner*)

Biophysical Journal (*partner*)

Biophysical Reports (*partner*)

Human Genetics and Genomics Advances (*partner*)

Molecular Plant (*partner*)

Molecular Therapy (*partner*)

Molecular Therapy Methods & Clinical Development (*partner*)

Molecular Therapy Nucleic Acids (*partner*)

Molecular Therapy Oncology (*partner*)



Download PDF

Stem Cell Reports (*partner*)

Trends in Biochemical Sciences

Trends in Cancer

Trends in Cell Biology

Trends in Ecology & Evolution

Trends in Endocrinology & Metabolism

Trends in Genetics

Trends in Immunology

Trends in Microbiology

Trends in Molecular Medicine

Trends in Neurosciences

Trends in Parasitology

Trends in Pharmacological Sciences

Trends in Plant Science

PHYSICAL SCIENCES & ENGINEERING JOURNALS

Cell Biomaterials

Cell Reports Physical Science

Chem

Chem Catalysis

Device

Joule

Matter

Newton



Download PDF

MULTIDISCIPLINARY JOURNALS

Cell Reports Methods

Cell Reports Sustainability

Heliyon

iScience

One Earth

Patterns

STAR Protocols

Nexus (*partner*)

The Innovation (*partner*)

Trends in Biotechnology

Trends in Cognitive Sciences

AUTHORS

Submit article

Multi-Journal Submission

STAR Methods

Sneak Peek – Preprints

REVIEWERS

Information for reviewers

NEWS & EVENTS

Newsroom

Cell Symposia

Consortia Hub



Download PDF

MULTIMEDIA

[Cell Press Podcast](#)

[Cell Press Videos](#)

[Coloring and Comics](#)

[Figure360](#)

[Cell Picture Show](#)

[Research Arc](#)

ABOUT

[About Cell Press](#)

[Open access](#)

[COVID Hub](#)

[Sustainability hub](#)

[Inclusion and diversity](#)

CONTACT

[Contact us](#)

[Help & Support](#)

CAREERS

[Cell Press Careers](#)

[Scientific job board](#)

ACCESS

[Subscribe](#)

[Claim](#)



[Download PDF](#)

[Recommend to Librarian](#)[Publication Alerts](#)

COLLECTIONS

[Best of Cell Press](#)[Cell Press Reviews](#)[Cell Press Selections](#)[Nucleus Collections](#)[SnapShot Archive](#)

INFORMATION

[For Advertisers](#)[For Recruiters](#)[For Librarians](#)[Privacy Policy](#)[Terms and Conditions](#)[Accessibility](#)

The content on this site is intended for healthcare professionals and researchers across all fields of science.

We use cookies to help provide and enhance our service and tailor content. To update your cookie settings, please visit the [Cookie settings | Your Privacy Choices](#) for this site.

All content on this site: Copyright © 2025 Elsevier Inc., its licensors, and contributors.

All rights are reserved, including those for text and data mining, AI training, and similar technologies.

For all open access content, the relevant licensing terms apply.

[Privacy Policy](#) [Terms & Conditions](#) [Accessibility](#) [Help & Support](#) [Contact](#)



Download PDF