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WHO Expert Advisory Committee on  
Developing Global Standards for Governance  
and Oversight of Human Genome Editing

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HUMAN GENOME EDITING:  
**A FRAMEWORK FOR  
GOVERNANCE**



World Health  
Organization



**WHO Expert Advisory Committee on Developing  
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# Foreword

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Technological advances hold great opportunities and challenges for global health and society. In order to harness the power of science and innovation, WHO's Science Division was created in 2019 to support Member States in achieving the health-related Sustainable Development Goals (SDGs) and emergency preparedness and response. The Division provides global leadership in translating the latest in science, evidence, innovation, and digital solutions to improve health and health equity for all. This contributes to the WHO's 13th Programme of Work (2019-2023) which stipulates that "...WHO's normative guidance will be informed by developments at the frontier of new scientific disciplines such as genomics, epigenetics, gene editing, artificial intelligence, and big data, all of which pose transformational opportunities but also risks to global health."

Human genome editing has great potential to improve human health and medicine. Human genome editing technologies can be used on somatic cells (non-heritable); germline cells (not for reproduction) and germline cells (for reproduction). Potential benefits of human genome editing include new strategies for diagnosis, treatment and prevention of genetic disorders; new avenues to treat infertility; new ways to promote disease resistance; contribution to vaccine development and enhanced knowledge of human biology. For example, application of somatic human genome editing has already been undertaken, including in vivo editing, to address HIV, sickle-cell disease and transthyretin amyloidosis.<sup>1</sup> Germline human genome editing contributes to deepen our understanding of the role of specific genes and processes in early human development, physiology and diseases. However, there are important areas of ongoing uncertainty as to potential benefits and risks, and gaps in scientific understanding in such key domains as off-target effects and long-term risks.

At the same time, however, somatic, germline and heritable human genome editing raise important and outstanding ethical and social issues. Challenges associated with somatic human genome editing include, for example, rogue clinics, medical travel, as well as the reporting of illegal, unregistered, unethical or unsafe research and other activities including the offer of unproven so-called therapeutic interventions. Heritable human genome editing also gives rise to great concerns as the edit might be passed to subsequent generations. Additional issues include enhancement to improve certain traits, the lack of diversity in collections of human samples and associated data, the need for equity of access to and benefit from human genome editing. There are important differences in the scale of the current challenges posed by somatic, germline and heritable human genome editing.

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1 Gillmore JD et al. CRISPR-Cas9 In Vivo Gene Editing for Transthyretin Amyloidosis. NEJM.org. 26 June 2021. DOI: 10.1056/NEJMoa2107454.

In December 2018, WHO established an Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing. This global multi-disciplinary panel of 18 experts has provided advice and recommendations on appropriate institutional, national, regional and global governance mechanisms for human genome editing, and produced the Governance Framework and Recommendations on Human Genome Editing over a two-year period under the lead of the Health Ethics & Governance Unit in the Science Division.

This work is deliberately future focused. It is situated within wider emerging technologies and makes headway in focusing on addressing systemic issues that will affect the uptake of emerging technologies into public health. The outputs from the Committee are intended to set a footprint for how to harness the power of science and innovation and are already informing the work of WHO in the area of responsible use of the life sciences.

The governance framework intends to provide those responsible for the oversight of genome editing with the tools and guidance they need, putting forward values and principles to inform both how and what decisions are made. The governance framework aims at being scalable, sustainable and appropriate for use at the institutional, national, regional and international levels. Moreover, the Committee produced a series of nine key recommendations on the governance of human genome editing which consider some broader issues associated with the governance of human genome editing. A position paper provides a summary of these two publications.

Finally, I would like to acknowledge and thank all those experts, stakeholders and individuals who have provided inputs throughout the work of the Committee and who contributed to the development of these reports. I hope that these reports will contribute to the safe, effective and ethical uses of human genome editing so all populations can truly benefit from the great potential of these technologies.



Dr Soumya Swaminathan  
Chief Scientist





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All authors and members of the WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing declared their interests according to WHO standard procedures. None of the interests declared were found to be significant.

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# Executive summary

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The recent application of tools, such as CRISPR-Cas9 (clustered regularly interspaced short palindromic repeats; Cas9 nuclease), to edit the human genome with the intention of treating or preventing disease and the gaps in our scientific understanding, in addition to some of the proposed applications of human genome editing, raise ethical issues that have highlighted the need for robust oversight in this area. The COVID-19 pandemic has clearly demonstrated the importance of using new tools and methods to combat serious diseases and highlighted the potential benefits of human genome editing research. It also reminds us of the need to develop technology carefully, with robust testing and quality assurance measures in place to maximize benefit and minimize harm. The balance between benefit and harm, safety and speed, and innovation and access is relevant to all of human genome editing.

In December 2018, the World Health Organization (WHO) established a global, multidisciplinary expert advisory committee (the Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing, hereafter called the Committee) to examine the scientific, ethical, social and legal challenges associated with human genome editing (somatic, germline and heritable). The Committee was tasked to advise and make recommendations on appropriate institutional, national, regional and global governance mechanisms for human genome editing. Its remit did not include a review of matters to do with safety and efficacy. Committee members were drawn from each of the WHO regions – Africa, the Americas, South-East Asia, Europe, Eastern Mediterranean and Western Pacific.

The 18 members of the Committee worked for two years and developed several products and new initiatives. The governance framework on human genome editing, along with the recommendations of the Committee, form a set of two publications that provide advice and recommendations on appropriate institutional, national, regional and global governance mechanisms for human genome editing. A position paper on human genome editing provides a summary of these two publications.

During its work, the Committee reviewed the current literature on human genome editing research and its applications, considered existing proposals for governance and relevant ongoing initiatives, and gathered information on a range of topics relating to the different uses of this technology. The Committee consulted widely with individuals and representatives of organizations including, but not limited to, United Nations (UN) and other international agencies; academies of science and medicine as well as other national or professional bodies; patient groups and civil society organizations. Through dedicated meetings, online sessions and telephone consultations, the Committee actively sought input from institutions, organizations, companies undertaking research on human genome editing, stakeholder communities, individual experts and peoples often under-represented in international science policy processes. These consultations explored how best to promote transparent and trustworthy policies and practices and ensure appropriate assessments of work prior to it being undertaken. To ensure that the governance framework reflected broad input and would be suitably comprehensive, realistic and practical, the Committee shared draft copies of the text during its development.

The Committee held two online consultations on the governance framework. Comments received were used by the Committee to refine and improve the governance framework.

The Committee developed a governance framework that draws from good practices in the governance of emerging technologies and applied them specifically to human genome editing. The governance framework, which can be implemented in different contexts, is intended to help those tasked with strengthening oversight measures, regardless of whether this is at the institutional, national, regional or international level. The Committee recognized that some of the necessary governance structures and processes already exist; these may need to be reinforced or amended. Where such structures and processes are lacking, gaps must be filled.

The governance framework on human genome editing is divided into six parts. Part 1 lays out the rationale and remit of the work of the Committee. It refers to policy reports, including scientific and technical aspects and past bioethical analyses of human genome editing and identifies current, potential and speculative human genome editing research. A 2020 survey of policy documents (legislation, regulations, guidelines, codes and international treaties) for germline human genome editing (not for reproduction) and heritable germline human genome editing (for reproduction)<sup>2</sup> is used to understand what policies governed research and development and clinical use of human genome editing in different countries. The Committee recognizes that current, potential and speculative human genome editing research will go beyond national borders, as will possible societal effects. This applies equally to somatic, germline and heritable human genome editing, although the latter is generally considered to be of greater concern. Therefore, governance for this technology is needed at national levels and transnational levels.

Part 2 defines governance and good governance. Governance is understood as including the norms, values and rules of the processes through which public affairs are managed so as to ensure transparency, participation, inclusivity and responsiveness. Good governance is an iterative, ongoing process that includes mechanisms for regular revision. Ideally, it is proactive, not only reactive. Good governance promotes public confidence; it requires access to adequate resources, capacity and technical knowledge to educate, engage and empower members of the scientific, medical and health care communities as well as the public. Good governance is value-based and principle-driven.

Part 3 identifies the values and principles that help explain why governance measures may be needed and how those charged with reviewing or strengthening governance measures may undertake such a task. The values and principles to inform how decisions are made are (i) openness, transparency, honesty and accountability; (ii) responsible regulatory stewardship; (iii) responsible stewardship of science and (iv) responsible stewardship of research resources. The values and principles to inform what decisions are made are (i) inclusiveness; (ii) caution; (iii) fairness; (iv) social justice; (v) non-discrimination; (vi) equal moral worth; (vii) respect for persons; (viii) solidarity and (ix) global health justice. Careful attention to these values and principles is imperative to create trust in the choice of governance mechanisms and policy options.

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2 Baylis F, Darnovsky M, Hasson K, Krahn T. Human germline and heritable genome editing: the global policy landscape. *CRISPR J.* 2020;3(5):365–77. <https://doi.org/10.1089/crispr.2020.0082>

The questions in Part 3 explore what may need to be considered when revising or strengthening governance measures. To assist in tailoring oversight measures to human genome editing, the governance framework explores five specific challenges in: (i) postnatal somatic human genome editing; (ii) prenatal (in utero) somatic human genome editing; (iii) heritable human genome editing; (iv) human epigenetic editing; and (v) enhancement. For each, the Committee identified a series of questions that should be considered when reviewing or creating oversight measures.

Part 4 reviews 12 sets of tools, institutions and processes and outlines who may need to be involved with the governance of human genome editing. These range from laws and regulations to professional self-regulation and the role of professional bodies, to public advocacy and activism. It is intended as an indicative list of options for those working to strengthen oversight measures and will need to be tailored to the specific circumstances of the user.

Part 5 puts forward seven scenarios to demonstrate how the various components of the governance framework come together in practice. The scenarios bring different elements together to show how they are interrelated in various hypothetical developments, for different purposes, involving different groups and highlighting different challenges: (i) somatic human genome editing clinical trials for sickle-cell disease; (ii) somatic human genome editing clinical trials for Huntington disease; (iii) somatic human genome editing and unscrupulous entrepreneurs and clinics; (iv) somatic human genome editing and epigenetic editing to enhance athletic ability; (v) heritable human genome editing (for reproduction); (vi) heritable human genome editing and unscrupulous entrepreneurs and clinics expanding assisted reproduction; and (vii) in utero human genome editing clinical trials for cystic fibrosis. These scenarios illustrate the practical challenges that might be encountered in the future when implementing good governance for human genome editing research.

Part 6 identifies a number of considerations for the successful implementation of oversight and governance measures for human genome editing. Good governance of human genome editing depends on context and it will vary at institutional, national, regional and global/international levels. It will necessitate addressing differences in national capacity to undertake the oversight and regulation of human genome editing. It includes activities that can be undertaken by WHO and others in relation to reviewing and strengthening governance measures for human genome editing. Good governance of human genome editing promotes public confidence by ensuring that choices are made in a transparent and inclusive way and it includes means to hold policy-makers accountable for those choices.

The Committee considered several approaches for assessing impact as well as processes for reviewing and updating the governance framework. A suitable body should be convened at least every 3 years to review and update this governance framework as necessary.



# Part 1.

## Introduction

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1. The recent application of tools, such as CRISPR-Cas9 (clustered regularly interspaced short palindromic repeats; Cas9 nuclease), to edit the human genome with the intention of treating or preventing disease and the gaps in our scientific understanding, in addition to some of the proposed applications of human genome editing, raise ethical issues that have highlighted the need for robust oversight in this area. The World Health Organization (WHO) established a global, multidisciplinary expert advisory committee (the Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing, hereafter called the Committee) to examine the scientific, ethical, social and legal challenges associated with human genome editing (somatic, that is, non-heritable; germline, involving in vitro studies on early embryos, gametes or their precursors; and heritable, where embryos subject to genome editing are used to establish pregnancies and create individuals who could pass on the edit to their offspring).<sup>3</sup> Committee members were drawn from each of the WHO regions – Africa, the Americas, South-East Asia, Europe, Eastern Mediterranean and Western Pacific.<sup>4</sup>
2. The Committee was tasked to advise and make recommendations on appropriate institutional, national, regional and global governance mechanisms for human genome editing. Its remit did not include a review of matters to do with safety and efficacy. This charge was given to the International Commission on the Clinical Use of Human Germline Genome Editing.<sup>5</sup> During the course of its work, the Committee reviewed the current literature on human genome editing research and its applications, considered existing proposals for governance and relevant ongoing initiatives, and gathered information on a range of topics relating to the different uses of this technology.
3. The Committee consulted widely with individuals and representatives of organizations including, but not limited to, United Nations (UN) and other international agencies, academies of science and medicine as well as other national or professional bodies, patient groups and civil society organizations (Annex). These consultations explored how best to promote transparent and trustworthy policies and practices and ensure appropriate assessments of work prior to it being undertaken.

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<sup>3</sup> <https://www.who.int/ethics/topics/human-genome-editing/en/> (accessed 26 April 2021).

<sup>4</sup> <https://www.who.int/ethics/topics/human-genome-editing/committee-members/en/index1.html> (accessed 26 April 2021).

<sup>5</sup> National Academy of Medicine, National Academy of Sciences, and the Royal Society. Heritable human genome editing. Washington, DC: The National Academies Press; 2020. <https://doi.org/10.17226/25665>

4. During its work, the Committee was regularly questioned about focusing on somatic, germline and heritable human genome editing. Those raising this issue often noted that some countries already have regulatory processes for somatic human genome editing. In response, the Committee noted that its charge from the WHO Director-General explicitly mentioned somatic as well as germline and heritable human genome editing. The Committee also noted that its mandate goes beyond looking at the science of human genome editing and includes its regulation taking into consideration ethical and social issues. The Committee considered important outstanding ethical and social issues existed, including for somatic human genome editing. For example, the Committee saw and heard evidence of challenges associated with rogue clinics, medical travel, as well as the reporting of illegal, unregistered, unethical or unsafe research and other activities including the offer of unproven so-called therapeutic interventions. Furthermore, the Committee noted that there were circumstances where somatic human genome editing could result in heritable changes, including when: (i) after genome editing in somatic cells, these are then reprogrammed into induced pluripotent stem cells (iPSCs) from which gametes are then generated in vitro and used to create zygotes; or (ii) genome editing components are delivered in vivo to somatic cells (including those of the testes or ovaries)<sup>6</sup>, which could be misdirected to the germline. If the genome editing is being carried out to treat infertility of a patient where the target cells are the germ cells in the gonads (most applicable to testes), then, although this is being done to treat individuals, the edit might be heritable. The Committee also noted important differences in the scale of the current challenges posed by somatic, germline and heritable human genome editing in the short to medium term. Application of somatic human genome editing has already been undertaken, including in vivo editing, to address, for example, HIV and sickle-cell disease. Application of heritable human genome editing is likely to be a much more limited activity/endeavour in the coming years.
5. The Committee noted a number of issues connected to, but ultimately outside of, its mandate, including: targeting human disease through genome editing of animals to prevent human diseases, such as gene-drives to eradicate vector-borne diseases; genome editing of animals for human organ transplantation to prevent disease transmission to humans, such as inactivation of porcine retroviruses; agricultural and environmental uses of genome editing; and the collection and use of human biological and genetic materials, and human genetic data.
6. Although somatic human genome editing is well established and acceptable for treatments in some advanced countries with governance mechanisms in place, the Committee noted that there remain challenges when considered globally, especially given the diversity of genomes across populations. Data on human genetic diversity and the role gene variants play in health and disease under different genomic and external environments are foundational to human genome editing. Those data, in turn, depend upon vast collections of human samples and associated data, collected over many years with varying degrees of understanding by and consent from the individuals. Such collections are not currently representative of the global population and genome editing innovations that make use of the available data can target variants that cause disease only in some populations to the exclusion of others (Box 1). In addition, particular distress has been expressed by people who have had little control over the use of biological materials and data drawn from them, especially when involving indigenous or historically exploited communities or among individuals whose perspectives on the human body, privacy or stigmatization and discrimination are much different from the people collecting and using their data. These concerns call for the development of inclusive genome editing innovations that take note of the diversity of the human population and human experience.

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6 For example, to treat types of infertility where Sertoli or granulosa cells are affected or gonadal hormone deficiencies.



**Box 1.**  
**Africa and genome variants<sup>7</sup>**

“Individual studies highlight how much more researchers need to know to understand the intersection of genes and disease. For example, an H3Africa project called the Collaborative African Genomics Network (CAfGEN) aims to come up with a blood test for HIV-positive newborns to show how quickly their infection could progress to AIDS. Researchers scrutinized the genomes of infected children, hoping to find genetic variants associated with slow HIV progression. Children with such variants could postpone treatment and reduce and delay long-term side effects.

But so far, the team has found just one piece of DNA, involved in the immune system, that varies significantly among the children. And candidate variants that popped up in a study of Botswanan children failed to appear in Ugandan children, underscoring the diversity of African genomes. ‘The African genome is much more complex than we anticipated,’ says CAfGEN trainee Lesedi Williams, now a genomicist at the University of Botswana, Gaborone.

‘The sad reality is that genomics data from Africa [are] still too few,’ says geneticist Aimé Lumaka of the University of Liège and the University of Kinshasa. So the medical significance of many variants in people of African descent is unknown.”

7. Through dedicated meetings, online sessions and telephone consultations, the Committee actively sought input from institutions, organizations, companies undertaking research on human genome editing, communities, individual experts and peoples often under-represented in international science policy processes. The Committee also drew on policy reports, including scientific and technical aspects and past bioethical analyses of human genome editing (Box 2).

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<sup>7</sup> Pennisi E. Genomes arising. *Science*. 2021;371(6529):556–9. <https://doi.org/10.1126/science.371.6529.556>

**Box 2.****Selected policy reports and bioethical analysis for human genome editing**

Convention for the protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine (the Oviedo Convention). Council of Europe; 1997 (<https://www.coe.int/en/web/conventions/full-list/-/conventions/treaty/164>, accessed 1 May 2021).

Report of the IBC on updating its reflection on the human genome and human rights. UNESCO International Bioethics Committee; 2015 (<https://unesdoc.unesco.org/ark:/48223/pf0000233258>, accessed 1 May 2021).

Membres Comité d'Éthique de l'Inserm. Saisine concernant les questions liées au développement de la technologie CRISPR (clustered regularly interspaced short palindromic repeat)-Cas9 [Matters concerning issues related to the development of CRISPR technology (clustered regularly interspaced short palindromic repeat) – Case 9]. Institut national de la santé et de la recherche médicale (Inserm); 2016 (<https://www.hal.inserm.fr/inserm-02110670>, accessed 1 May 2021).

Genome editing: an ethical review. Nuffield Council on Bioethics; 2016 (<https://www.nuffieldbioethics.org/publications/genome-editing-an-ethical-review>, accessed 1 May 2021).

Ethical and legal assessment of genome editing in research on human cells. Discussion paper, no.10. German National Academy of Sciences, Leopoldina; 2017 ([https://www.leopoldina.org/fileadmin/redaktion/Publikationen/Diskussionen/2017\\_Diskussionspapier\\_GenomeEditing.pdf](https://www.leopoldina.org/fileadmin/redaktion/Publikationen/Diskussionen/2017_Diskussionspapier_GenomeEditing.pdf), accessed 1 May 2021).

National ethical guidelines for biomedical and health research involving human participants. Indian Council of Medical Research; 2017 ([https://main.icmr.nic.in/sites/default/files/guidelines/ICMR\\_Ethical\\_Guidelines\\_2017.pdf](https://main.icmr.nic.in/sites/default/files/guidelines/ICMR_Ethical_Guidelines_2017.pdf), accessed 1 May 2021).

Editing human DNA. Moral and social implications of germline genetic modification. Netherlands Commission on Genetic Modification; 2017 (<https://cogem.net/en/publication/editing-human-dna-moral-and-social-implications-of-germline-genetic-modification-2/>, accessed 1 May 2021).

Genome editing technology in medical sciences and clinical applications in Japan. Science Council of Japan; 2017 (<http://www.scj.go.jp/ja/info/kohyo/pdf/kohyo-23-t251-1-en.pdf>, accessed 1 May 2021).

Human genome editing. Science, ethics, and governance. United States National Academies of Sciences, Engineering, and Medicine; 2017 (<https://www.nap.edu/catalog/24623/human-genome-editing-science-ethics-and-governance>, accessed 1 May 2021).

African Statement on Human Germline Genetic Editing. Ethics, Community Engagement, Patient Advocacy and Support working group of the Global Emerging Pathogens Treatment Consortium; 2018 ([https://getafrica.org/wp-content/uploads/2019/09/ECEPAS-Africa-Statement-on-Human-Germline-Genetic-Editing\\_Dec-2-2018\\_Final.pdf](https://getafrica.org/wp-content/uploads/2019/09/ECEPAS-Africa-Statement-on-Human-Germline-Genetic-Editing_Dec-2-2018_Final.pdf), accessed 1 May 2021).

Genome editing and human reproduction: social and ethical issues. Nuffield Council on Bioethics; 2018 (<https://www.nuffieldbioethics.org/publications/genome-editing-and-human-reproduction>, accessed 1 May 2021).

Intervening in the human germline. Opinion, executive summary & recommendations. German Ethics Council; 2019 ([https://www.ethikrat.org/en/publications/publication-details/?tx\\_wwt3shop\\_detail%5Bproduct%5D=119&cHash=bac073cabbb34f6b9179d8ef068a4110](https://www.ethikrat.org/en/publications/publication-details/?tx_wwt3shop_detail%5Bproduct%5D=119&cHash=bac073cabbb34f6b9179d8ef068a4110), accessed 1 May 2021).

Gene editing: legal and regulatory implications. New Zealand Royal Society Te Apārangi; 2019 (<https://www.royalsociety.org.nz/assets/Uploads/Gene-Editing-Legal-and-regulatory-implications-DIGITAL.pdf>, accessed 1 May 2021).

Heritable human genome editing: report of the International Commission. National Academy of Medicine, National Academy of Sciences and the Royal Society; 2020. (<https://www.nap.edu/catalog/25665/heritable-human-genome-editing>, accessed 1 May 2021).

8. While the coronavirus 2019 (COVID-19) pandemic resulted in unavoidable delays to the Committee's work, the pandemic also highlighted the potential benefits of human genome editing research and the importance of tackling public health goals and priorities. For example, as part of the effort to respond to COVID-19, genome editing was used to develop animal models that better reflect the human experience of the disease (that could lead to new diagnostic methods and therapeutic intervention) and to develop vaccines. This pandemic clearly demonstrates the importance of using new tools and methods to combat serious diseases. It also reminds us of the need to develop technology carefully, with robust testing and quality assurance measures in place to maximize benefit and minimize harm. The balance between benefit and harm, safety and speed, and innovation and access is relevant to all of human genome editing. Furthermore, the pandemic has raised awareness of the benefits of collaborative ambition in science, the harms of nationalism and the many ways in which policy choices are constrained by politics. During efforts to develop a vaccine against COVID-19, the Director-General made a clear commitment to public health solidarity and sought to steer the world towards just and equitable access to needed resources. This orientation towards justice and equity underpins much of this governance framework.
9. The Committee recognizes that current, potential and speculative human genome editing research (Box 3) will go beyond national borders, as will possible societal effects. This applies equally to somatic, germline and heritable human genome editing, although the latter is generally considered to be of greater ethical concern. Therefore, governance for this technology is needed at national levels (domestic policy including laws, regulations and guidelines) and transnational levels (including conventions and treaties, as well as coordination of cross-border movement of researchers, clinicians (including clinician or physician scientists) and research participants or patients). Some of the necessary governance structures and processes already exist. These may need to be reinforced or amended; where such structures and processes are lacking, gaps may need to be filled. The Committee encourages but cannot mandate a coordinated global approach. In the absence of a coordinated global approach, the Committee acknowledges that different jurisdictions, with different political regimes and cultural, historical, and religious contexts, will likely have a preference for different regulatory approaches. The Committee has attempted to assist institutional, national and regional efforts through: (i) identification of values and principles to guide policy-making; (ii) attention to the many and complex ways in which various governance mechanisms can be used to provide quality oversight; (iii) sample questions to be considered when strengthening and developing governance measures for human genome editing in general, as well as those specific to a range of special challenges; and (iv) the use of scenarios to explore opportunities and challenges.

### Box 3. Current, potential and speculative human genome editing research

Basic or preclinical research in vitro and in animal models in vivo	Prenatal (in utero) and postnatal somatic genome editing	Heritable genome editing	Somatic or heritable genome editing
<p><b>To alter genes or their activity in:</b> (i) human somatic cells or tissues (including organoids), or germline cells (zygotes, early embryos, pluripotent stem cells, embryo models, germ cells, spermatogonial stem cells, gamete precursor cells or gametes); or (ii) laboratory animals containing human genes, cells or tissues.</p> <ul style="list-style-type: none"> <li>• To study human biology and the role of specific genes and processes in, for example, development, physiology and disease.</li> <li>• To establish a models of human genetic disease.</li> <li>• To screen for human genes that are involved in disease or that respond to substances, including potential therapeutic agents and toxic materials.</li> <li>• To refine techniques of genome editing and test specific reagents for use in somatic and germline human genome editing.</li> </ul>			
<p><b>To treat genetic disorders:</b> to alter genes or their activity ex vivo (e.g. using bone marrow stem cells) or in vivo (e.g. using viral vectors).</p> <ul style="list-style-type: none"> <li>• To treat monogenic disorders by: (i) correcting the mutant allele for autosomal recessive, sex chromosome-linked or dominant mutations in nuclear DNA or by correcting or eliminating mutant mitochondrial DNA; (ii) deleting the disease-causing variant for dominant mutations (e.g. for Huntington disease) or making deletions to promote exon skipping (e.g. for Duchenne muscular dystrophy); (iii) by boosting the expression of a closely related homologue through inactivating genes encoding repressors or by mutating repressor regulatory elements (e.g. to boost gamma globin gene expression for sickle-cell disease or beta-thalassaemia); or (iv) by using so-called safe harbour sites in the genome to integrate a gene whose expression will rescue a loss-of-function mutation (e.g. one leading to an enzyme deficiency).</li> <li>• To boost an immune response against cancer cells (e.g. via chimeric antigen receptor (CAR) Tcells).</li> <li>• To correct somatic mutations in stem cells leading to disease (e.g. acute myeloid leukaemia and chronic lymphocytic leukaemia).</li> <li>• To treat polygenic disorders or disorders influenced by both genes and environment (e.g. coronary heart disease, cancer and autoimmune diseases).</li> </ul>			
<p><b>To avoid inheritance of genetic disorders.</b></p> <ul style="list-style-type: none"> <li>• To correct the mutant allele for monogenic disorders including autosomal recessive, sex chromosome-linked or dominant mutations in nuclear DNA or by correcting or eliminating mutant mitochondrial DNA.</li> <li>• To reduce the likelihood of complex, multifactorial or polygenic disorders (e.g. coronary heart disease, diabetes and autoimmune diseases).</li> </ul>			
<p><b>To treat infertility.</b></p> <ul style="list-style-type: none"> <li>• To alter genes in gonadal supporting cells, such as Sertoli or granulosa cells, so that the germ cells can form functional sperm or oocytes.</li> <li>• To correct mutations in germ cells in the testes or ovaries, or in germ line cells used to derive gametes in vitro.</li> </ul>			
<p><b>To promote disease resistance:</b> to alter an allele associated with increased risk of a disease or disorder to one that is protective.</p> <ul style="list-style-type: none"> <li>• To reduce infectious diseases and parasites, for example, by altering human genes encoding pathogen receptors or that allow pathogen replication (e.g. CC 5 for HIV).</li> <li>• To reduce cancers due to (i) oncogene activation or (ii) tumour suppressor mutations (which can involve loss of heterozygosity, e.g. BRCA1 gene).</li> <li>• To reduce genetic diseases influenced by known genetic risk factors/alleles (e.g. Alzheimer disease and APOE4 versus APOE2 or APOE3).</li> </ul>		<p><b>To improve robustness or quality of life:</b> To alter an allele that may be relatively rare or common to a different common allele.</p> <ul style="list-style-type: none"> <li>• To increase tolerance to, for example, lactose, gluten or alcohol (e.g. improve diet).</li> <li>• To reduce blood cholesterol levels (e.g. improve metabolism).</li> <li>• To avoid adverse drug events or promote better therapy (e.g. so-called reverse pharmacogenomics).</li> </ul>	
<p><b>To enhance human traits:</b> To alter alleles to other variants, which may be common or rare (and give extreme characteristics), that are present within the family or in other human populations.</p> <ul style="list-style-type: none"> <li>• To alter appearance (e.g. eye or hair colour).</li> <li>• To alter abilities (e.g. muscle mass or perfect pitch).</li> <li>• To increase muscle type, height, longevity or intelligence.</li> <li>• To provide resistance to pollutants or other environmental agents such as radiation.</li> </ul>		<p><b>To add non-human traits:</b> To introduce single or multiple genes not present in any human genome (e.g. non-human or synthetic genes).</p> <ul style="list-style-type: none"> <li>• To amuse/entertain (e.g. green fluorescent protein).</li> <li>• To improve sensory systems (e.g. to ultraviolet or infrared light, or electromagnetic fields).</li> <li>• To obtain nutritional benefit from parts of plants plastics and other materials that humans cannot currently digest.</li> <li>• To increase tolerance to drought, heat or cold.</li> <li>• To provide resistance to pollutants or other environmental agents such as radiation.</li> </ul>	

CAR: chimeric antigen receptor; AML: acute myeloid leukaemia; CLL: chronic lymphocytic leukaemia; CCR5: C-C chemokine receptor type 5; APOE: apolipoprotein E.

**Notes:**

- The examples in Box 3 are illustrative not comprehensive and no one-to-one mapping with the content of the governance report or the recommendations has been done as the Committee's focus has been on current and near-term future research involving human genome editing.
- The examples are also descriptive not normative, that is, they are simply meant to provide an overview of what might be possible with the science.
- The examples do not include the methods that might be used, but depending on the specific application, these methods could involve repair of double-stranded DNA breaks (non-homologous end joining and homology-directed repair), nicks or single-strand cuts (base editing and prime editing), and RNA or epigenetic editing, where the last two are unlikely to be heritable.
- Clear differences in the complexity of the science and any ethical considerations will exist depending upon whether the attempt is to modify one or several genes. With current genome editing techniques, altering multiple genes simultaneously would greatly increase the likelihood of, for example, incorrect on-target and off-target events and chromosome rearrangements, such that the risks outweigh any potential benefits.
- In the future, some applications of human genome editing might involve the use of techniques to increase rates of inheritance, for example, using gene-drive technologies to allow humans to cope with extreme climate change.
- There are also potential dual-use applications; for example, human genome editing to give resistance to chemical pollutants or to radiation for space travel could also have military applications with respect to resistance to chemical or nuclear weapons.
- It is important to highlight that the Committee does not endorse or even suggest that any researcher works towards these potential uses. Rather, the Committee advocates the introduction and implementation of national and transnational governance mechanisms that can effectively review and assess not just scientific and clinical evidence, but also relevant ethical and societal views and values.

10. A 2020 survey of documents relevant to policy (legislation, regulations, guidelines, codes and international treaties) for germline human genome editing (not for reproduction) (Table 1) and heritable human genome editing (for reproduction) (Table 2) confirms that governance structures and processes already exist in many jurisdictions.<sup>8</sup>

<sup>8</sup> Baylis F, Darnovsky M, Hasson K, Krahn T. Human germline and heritable genome editing: the global policy landscape. *CRISPR J.* 2020;3(5):365–77. <https://doi.org/10.1089/crispr.2020.0082>. Links to national policy documents are available at <https://bit.ly/3hrjRY6> (accessed 27 May 2021).

**Table 1.** Existence of policies on and permissibility of germline human genome editing (not for reproduction) in selected countries, by World Health Organization region

Region (no. of countries <sup>a</sup> )	Countries that permit, no.	Countries that prohibit, no.	Countries that prohibit with exceptions, no.	Countries that are indeterminate <sup>9</sup> , no.	Countries with no relevant information available, no.
Africa (13)	2	0	0	2	9
Americas (17)	1 <sup>b</sup>	4	2	0	10
Eastern Mediterranean (10)	1	4	0	1	4
Europe (46)	3	10	2	2	29
South-East Asia (2)	2	0	0	0	0
Western Pacific (8)	2	1	0	1	4
Total (96)	11	19	4	6	56

<sup>a</sup>106 countries were included in the survey. Only the 96 countries with relevant policy documents are reported.

<sup>b</sup>With private funding in the United States of America.

Source: Baylis F, Darnovsky M, Hasson K, Krahn T. Human germline and heritable genome editing: the global policy landscape. *CRISPR J.* 2020;3(5):365–77. <https://doi.org/10.1089/crispr.2020.0082>

9 Indeterminate refers to policy documents for which it was not possible to determine with certainty whether the research in question is permitted or prohibited. This includes policy documents that mention human germline or heritable genome editing but are unclear as to their (im)permissibility. In addition, this category was assigned to policy documents that do not mention germline or heritable genome editing, but that might encompass these practices in provisions pertaining to the (im)permissibility of certain aspects of assisted human reproduction; research involving human germ cells, gametes or embryos; or genetic modification.

No relevant information refers to policy documents that do not explicitly reference human germline or heritable genome editing, and where provisions pertaining to assisted human reproduction or related techniques do not obviously bear on their (im)permissibility. This category was included for several reasons: to make explicit the absence of relevant information about the (im)permissibility of human germline or heritable genome editing in existing policy documents where it might reasonably be expected to appear; to flag policy documents that are sometimes referenced in efforts to interpret the current policy situation (for example, legislation on human cloning); or to highlight policy documents that might be updated at some future time to include explicit reference to human germline or heritable genome editing.

**Table 2.** Existence of policies on and permissibility of heritable human genome editing in selected countries (for reproduction), by World Health Organization region

Region (no. of countries <sup>a</sup> )	Countries that permit, no.	Countries that prohibit, no.	Countries that prohibit with exceptions, no.	Countries that are indeterminate <sup>10</sup> , no.	Countries with no relevant information available, no.
Africa (13)	0	5	0	1	7
Americas (17)	0	8	2	0	7
Eastern Mediterranean (10)	0	8	1	0	1
Europe (46)	0	41	2	1	2
South-East Asia (2)	0	2	0	0	0
Western Pacific (8)	0	6	0	1	1
Total (96)	0	70	5	3	18

<sup>a</sup>106 countries were included in the survey. Only the 96 countries with relevant policy documents are reported.

Source: Baylis F, Darnovsky M, Hasson K, Krahn T. Human germline and heritable genome editing: the global policy landscape. *CRISPR J.* 2020;3(5):365–77. <https://doi.org/10.1089/crispr.2020.0082>

11. Some aspects of good governance of human genome editing can be undertaken by WHO. Other aspects should be undertaken by other authorities and entities of influence, with advice and assistance from WHO as appropriate.
12. The Committee concludes that innovation in human genome editing should be driven by anticipated benefit to individuals and society in human health and collective well-being. In turn, good governance of emerging technologies should ensure that adequate protections are in place for people most in need of the potential benefits of human genome editing and people most likely to experience the potential harms, who may or may not be the same people. Equity of access to, and benefit from, human genome editing has been foundational to the Committee's discussions.
13. The Committee considered that for effective dissemination of its guidance and maximum benefit from its work, education, engagement and empowerment related to human genome editing will be vital. This should include activities for the general public but also targeted capacity-building for researchers, clinicians, policy-makers, genetic counsellors and others as needed. Effective dissemination should also include efforts to enhance both science and ethics literacy. The Committee addressed this issue in more depth in its recommendations.

<sup>10</sup> See footnote 9.

# Part 2.

## Good governance of new and emerging technologies

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14. Inspired by the description of governance by the United Nations Educational, Scientific and Cultural Organization (UNESCO),<sup>11</sup> the Committee understands governance to include the norms, values and rules of the processes through which public affairs are managed so as to ensure transparency, participation, inclusivity and responsiveness. Governance also represents the structures and processes that are designed to ensure accountability, transparency, responsiveness, adherence to the rule of law, stability, equity and inclusiveness, empowerment, and broad-based participation.
15. Governance is not limited to formal mechanisms such as legislation, regulations or judicial opinion but includes informal mechanisms such as ethical, social and professional norms or other influences that guide its development. Governance also includes forces to shape the direction and conditions of research and practice, such as well crafted public and private funding priorities and conditions. It also includes professional and industrial best practices, peer review and prepublication verification of ethics approval, and decisions on health care insurance coverage. In addition, possible liability for harmful clinical research or clinical care is an indirect source of governance, mediated by prospects of legal action and liability insurance.
16. Governance structures and processes, approaches and measures depend on context. They will vary at institutional, national, regional and global levels.
17. Good governance is an iterative, ongoing process that includes mechanisms for regular revision in light of technical, practical and ethical developments and changes in societal views and values. Ideally, good governance is proactive, not only reactive.
18. Good governance promotes public confidence by ensuring that choices are made in ways that are transparent and inclusive; and it includes means to hold policy-makers accountable for those choices. As needed, good governance also has mechanisms to handle non-compliance with formal governance mechanisms.

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<sup>11</sup> <http://www.ibe.unesco.org/en/geqaf/technical-notes/concept-governance> (accessed 26 April 2021).



19. Good governance requires access to adequate resources, capacity and technical knowledge to educate, engage and empower members of the scientific, medical and health care communities as well as the public. Of necessity, efforts to educate, engage and empower will include efforts to inform, listen, incorporate a range of perspectives and be transparent about who is responsible for which policy choices, on the basis of which facts, values, principles and goals.
20. Good governance is value-based and principle-driven. It promotes public trust by ensuring public values and viewpoints are carefully considered as part of the policy-making process.

# Part 3.

## Governance of human genome editing

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21. The technology of human genome editing can be used to expand human knowledge, improve human health and contribute to both collective well-being and the common good. To maximize the positive impact and minimize the potential harms of this technology, procedural and substantive values and principles should guide policies and practices (Table 3). Careful attention to these values and principles is imperative to create trust in the choice of governance mechanisms and policy options. While nationally focused, when appropriate, these values and principles should be globally oriented.
22. These values and principles describe *how* governance and oversight measures should be reviewed and strengthened and *what* needs to be considered when they are. The values and principles run through much of the work of the Committee. For example, these values and principles explain the Committee's commitment to consult as widely as possible and engage directly with groups and people traditionally excluded from international science policy-making. Furthermore, they were also central to identifying and addressing the real-world issues explored in the scenarios in Part 5 of this framework.

**Table 3.** Values and principles as applied specifically to human genome editing and the associated commitments

Ethical values and principles	Commitments associated with these ethical values and principles
To inform how decisions are made	
<b>Openness, transparency, honesty and accountability</b>	A commitment to openness that invites collaborative ambition and work, as well as a commitment to use transparent, honest and accountable processes in order to generate and share evidence-informed, accessible and timely information about: (i) best available data (including information about sources of funding, access and outcomes); (ii) guiding ethical values and principles; and (iii) actionable policy options for human genome editing.
<b>Responsible regulatory stewardship</b>	A commitment to support and promote legitimate, evidence-informed: (i) law and regulation; (ii) programme management and measurement; (iii) data collection, storage, processing, distribution and destruction in accordance with established privacy constraints; (iv) research training and capacity-building; and (v) public awareness about the potential benefits, harms and limitations of human genome editing in ways that balance competing influences and demands.
<b>Responsible stewardship of science</b>	A commitment to: (i) pursue rigorous, evidence-informed basic and applied research with appropriate caution for uncertainty and risk; (ii) follow established ethical practices for research involving humans with particular attention to issues of integrity and conflict of interest; (iii) maximize the potential benefits of research while minimizing the potential harms; and (iv) respect research ethics guidelines and applicable legislation. More particularly, a commitment to align the processes and outcomes of human genome editing research with the values, needs and expectations of society, as identified through participatory approaches involving various publics.
<b>Responsible stewardship of research resources</b>	A commitment to use finite research resources responsibly when choosing between research options for human genome editing. This requires careful attention to scientific value and validity, as well as social value and validity. Finite research resources include: (i) biological materials; (ii) research skills; and (iii) research funding.
To inform what decisions are made	
<b>Inclusiveness</b>	A commitment to carefully consider knowledge and perspectives on human genome editing informed by different social, cultural and religious beliefs and moral values, as well as different skill sets. In addition, a commitment to ensure that human genome editing research (basic and applied) and clinical care are representative of global human diversity and are globally accessible.
<b>Caution</b>	A commitment to exercise appropriate caution given existing uncertainty and risk. This uncertainty and the balance of potential harms and benefits will be substantial with first in human or human genome editing trials, and especially so if heritable human genome editing is attempted where potential harms could be imposed on future children and subsequent generations. Heightened attention to the fullest range of risks is therefore needed.

<b>Fairness</b>	A commitment to fair dealings in the pursuit of human genome editing research and clinical care with individuals, organizations, nations and publics, in support of collective well-being and the common good. A special commitment to benefit sharing that includes giving back to participants and communities whose samples and data are used for research, such as co-research opportunities, sharing of skills and research capacity and priority access to the benefits of research.
<b>Social justice</b>	A commitment to develop human genome editing in ways that: (i) promote human health, collective well-being and the common good; (ii) look after the needs of communities experiencing greater health burdens; (iii) reduce socioeconomic inequality; and (iv) avoid discrimination. In consultation with relevant communities, efforts should be made to ensure access to adequate resources, skills training and capacity-building for researchers, clinicians, policy-makers, genetic counsellors and others as needed.
<b>Non-discrimination</b>	A commitment to celebrate and promote diversity by rejecting concepts of eugenics and patterns of discrimination based on personal or group characteristics including race, ethnicity, colour, religion, sex, gender, sexual orientation, age, and mental or physical ability.
<b>Equal moral worth</b>	A commitment to recognize and treat all people as having equal moral worth and their interests as deserving of equal moral consideration, with a particular need to recognize and protect the interests of persons with disabilities and of future generations.
<b>Respect for persons</b>	A commitment to respect the wishes of competent individuals regarding the most intimate aspects of their lives, including their health and their reproductive options. In addition, a commitment to promote the best interests of individuals who are not competent to make decisions for themselves.
<b>Solidarity</b>	A commitment to live and work in harmony, grounded in the recognition of the interdependence of humans. In addition, a commitment to share the benefits and burdens of research and clinical care among all people, to minimize the risk of exploitation and to promote the common good.
<b>Global health justice</b>	A commitment to equitable access to opportunities and potentially beneficial outcomes from human genome editing for all people, particularly those living in low- and middle-income countries. This includes equitable access to support for health research and for the development of health interventions that are appropriate and affordable for the widest possible range of populations with a view to reducing socioeconomic inequality. It also includes equitable protection from potential coercion, exploitation and other harms.

23. Human genome editing has been the subject of extensive public discussion in many societies, but important differences between human genome editing in somatic cells and germ cells have sometimes been poorly explained or even ignored. Moreover, important differences between genome editing in early embryos and other germline cells for basic research (germline human genome editing) or for reproduction (heritable human genome editing) may have also been overlooked. Good governance must specifically consider the challenges inherent in human genome editing in somatic cells and in germ cells, whether for research or for reproduction.

24. Genome editing can be used on human cells as part of: laboratory-based science research; preclinical and clinical research; clinical care (treatment and prevention); reproduction (both as a means to avoid or help avoid genetic disease and to overcome infertility); and enhancement (to improve certain traits). Good governance should cover all the different uses of human genome editing. While there is considerable overlap between different uses, they pose different challenges and opportunities for governance. In Part 5 of this framework, scenarios 1, 2 and 7 explore practical issues in the governance of clinical trials for somatic human genome editing. Scenarios 3 and 6 discuss unscrupulous uses of human genome editing. Scenarios 5 and 6 explore practical issues in the governance of human genome editing for reproduction. Scenario 4 explores practical issues in the governance of human genome editing for enhancement.
25. To improve decision-making and gain public trust, the people responsible for developing and implementing governance measures must make efforts to educate, engage and empower many publics (Box 4).

**Box 4.****Good practices in public education, engagement and empowerment**

- In public education, information flows in one direction using tools such as public service announcements and advertising campaigns.
- In public engagement (or public dialogue), information flows in two directions using discussion-based tools.
- Public empowerment seeks to promote shared priority-setting by using shared decision-making tools.
- Openness, transparency, honesty and accountability are essential for public education, engagement and empowerment. This means being open with the people who are a part of consultations about the purpose of the consultation and why they are being involved, as well as providing clarity on how deliberations will contribute to the development of governance for human genome editing. In addition to learning from the general public (or at least a representative sample), specific strategies are needed to engage traditionally under-represented groups, such as indigenous peoples, minority ethnic groups or faiths, or specific patient groups.
- Public engagement on human genome editing could be included in public consultations on emerging technologies. Alternatively, there could be new initiatives specific to human genome editing. This could, for instance, involve the creation of an independent body to identify and produce an understanding of public interest(s) through promotion of public debate, engagement with the public and monitoring of technological developments. Efforts at public engagement should consider ethical, social and legal implications as well as technical issues.
- Efforts to engage the public should be inclusive, with active consideration as to how best to include a range of perspectives from those who support and those who oppose the development and use of human genome editing, as well as those who are agnostic. Careful consideration is also needed of how best social media and traditional media can be used to further these aims.

26. Countries will differ in their capacity to comprehensively govern human genome editing research and clinical care. Where personnel, or financial or other resources are insufficient, the focus should be on capacity-building to strengthen governance arrangements more broadly, and not specifically for human genome editing. For immediate needs, provision should be made to draw on regulatory capacity elsewhere, including in other countries or in regional or international organizations.

27. Differences in capacity and interest in governing human genome editing will likely result in its being the subject of comprehensive regulation in some countries and limited or no regulation in others. In this context, the excitement about the technology in some circles introduces three related risks:
- that the technology will be oversold by unscrupulous entrepreneurs and clinics operating in jurisdictions without the capacity to oversee their operation;
  - that people will be enticed to explore unproven and possibly dangerous interventions of no potential benefit; and
  - that potentially harmful research will be deliberately located in countries with little or no oversight.

Good governance of human genome editing must include measures to minimize these risks, with particular attention to the risks associated with travel to a destination country with limited or no regulation.

28. While many countries and organizations with an interest in human genome editing already have governance measures in place (see, for example, Table 1 and Table 2), others do not. The Committee developed a series of questions to assist those responsible for governance arrangements. The questions can readily be adapted for use in different contexts. For example, the question “Will basic science research (or clinical research) on human genome editing be permitted?” can be amended to “Is basic science research (or clinical research) on human genome editing currently permitted or prohibited?”
29. When developing policy on human genome editing, some basic questions should be considered, both by reference to what the policy position will be (for example, where it will fall on a spectrum between prohibitive or permissive approaches) and how and by whom it will be implemented. For a country creating or adapting its own oversight measures to encompass basic research, clinical research, treatment, prophylaxis or enhancement, the following questions should be considered. This list is aimed primarily at policy development (including laws, regulations and guidelines), which may be complemented by the other governance processes identified in this report.
- a. What kind of genome editing is being considered? Research on human cells and tissues in vitro, prenatal somatic, postnatal somatic, germline (not for reproduction), or heritable (for reproduction) human genome editing?
  - b. How should genome editing technologies be used – what are the rationale, objectives and anticipated consequences?
  - c. What are the interests of the public and how will they be served by this new and emerging technology?
  - d. How will the values and principles specific to human genome editing (Table 3) be considered?
  - e. Is there a means to revisit such values and principles over time?
  - f. How would a lack of consensus on such values and principles be managed?
  - g. For each main area of application, should oversight measures lean toward caution (no use of the technology until approved by regulators or other authorities) or promotion (use of the technology permitted unless prohibited or otherwise limited by regulators or other authorities)?
  - h. What are the primary mechanisms to implement oversight measures, for example, legislation or executive decree, government regulation or conditions on government funding?

- i. What are the public health and health cost implications, considering the costs of both action and inaction?
  - j. Will the oversight body have sufficient understanding of human genetics and genetic variation?
  - k. Will genetic counsellors be needed; if so, how will they be recruited and trained?
  - l. If the existing oversight measures are not adequate, are there plans to create new oversight measures or to rely on regulatory review and approvals from an external body? If so, which external body(ies)?
  - m. If developing new oversight measures, how will these measures be coordinated with or embedded in other regulatory bodies in the country?
  - n. Do questions of equitable access to research participation, as well as safe and effective treatment across domestic populations and communities, inform regulatory decisions on public funding?
  - o. How will the cost of clinical trials and therapies be shared among research participants, researchers, funders, clinicians, insurers and third-party (private and public) sources?
  - p. Does the country have the political, technical and economic capacity to fully implement its preferred oversight measures?
  - q. Will transnational collaboration on preclinical and clinical research – for both non-heritable and heritable editing – be permitted when procedural and substantive standards differ in other countries? If so, what limits, if any, will be placed on such collaborations? Will this affect the researchers and clinicians, including their mobility between jurisdictions and prospects for employment or promotion?
30. When developing oversight measures, the following questions on the role of the various publics should be considered.
- a. Is there any formal effort at independent, evidence-informed public opinion polling, and public education, engagement and empowerment?
  - b. Are there opportunities for patient groups, public interest groups, advocacy organizations and civil society to influence the research agenda? If so, in what way?
  - c. Are there opportunities for patient groups, public interest groups, advocacy organizations and civil society to influence domestic or global science policy and science funding? If so, in what way?
  - d. Are there opportunities for patient groups, public interest groups, advocacy organizations and civil society to revisit the domestic policy on the research agenda, science policy and science funding on human genome editing? If so, in what way?
  - e. How will conflicting positions among patient groups, public interest groups, advocacy organizations and civil society be managed in policy-making?
31. When developing oversight measures, the following questions related to international aspects of human genome editing should be considered (other questions may also arise).
- a. Are there declarations, treaties, conventions or other international instruments addressing human genome editing that have been signed or would be signed?
  - b. What is the relevance of professional society guidelines from international bodies or from national societies in other countries? Would violation of such guidelines have an actual effect on domestic decisions on research funding, investigator discipline, physician licensing, clinic licensing or liability for medical malpractice?
  - c. Are there domestic rules in place regarding researchers who go to another country to perform research that would be illegal or unethical in their home country? If so, what are they? If not, are there plans to develop any?

- d. Are there domestic rules in place regarding residents who go to another country to receive human genome editing that would be illegal or unethical in their home country? If so, what are they? If not, are there plans to develop any?
- e. Are there plans to welcome or discourage people from other countries travelling to access human genome editing clinical trials or so-called therapies?
- f. If there are no plans to regulate research on human genome editing, are there plans to regulate foreign researchers travelling from other countries to conduct such research?
- g. If there is limited oversight capacity or no regulation, what means are available to prevent unproven and possibly dangerous interventions from being marketed and provided by clinics?

### 3.1 Special challenges: postnatal somatic human genome editing

- 32. Some countries have domestic policies governing research to develop somatic gene therapy. These policies may need to be reviewed to determine whether they effectively address concerns specific to somatic human genome editing, including unique concerns about patient safety and efficacy. Also important is whether these policies deal with broader issues including fairness, social justice and public engagement.
- 33. So-called traditional somatic gene therapy makes use of viral vectors to introduce additional copies of a gene encoding the missing gene product at random positions in the genome, hoping to provide enough gene product in the right place to give benefit. However, genome editing allows for much more precise targeted gene alterations, with several approaches currently in preclinical or clinical research. While the potential benefits are enormous, they must be weighed against the potential harms. The harms could include incorrect on-target events such as unwanted insertions or deletions, chromosome damage as well as off-target events. When genome editing is carried out on a stem cell line from which single cells are expanded to give a clonally derived stem cell line, it is possible to test for such events. However, if the genome editing is being done on many millions of cells simultaneously, it will be very challenging to show that all are free of such potentially harmful events. In addition, unwanted genetic alterations, such as chromosome rearrangements, which can lead to cell overproliferation can be tolerated by somatic cells and lead to tumours.
- 34. There are two general routes to somatic human genome editing. The first, and most frequently used approach in clinical experiments or trials to date, is ex vivo manipulation of cells, often stem cells such as those of the haematopoietic system (bone marrow), which are reintroduced into research participants, with or without prior interventions to reduce the numbers of endogenous (unedited) stem cells. The second approach is in vivo somatic human genome editing, which takes place without the need to remove cells from the body. Both approaches have specific issues that are relevant to regulation and/or governance.
- 35. The advantage with ex vivo human genome editing in clinical experiments or trials is that it is theoretically possible (although challenging, as mentioned above) to verify that the cells only have the desired on-target alteration before they are put back into research participants. It also avoids issues of an immune response to the components used for genome editing. However, given the need for appropriate facilities and techniques to handle the cells in a clean and safe way while outside the body, ex vivo genome editing is an expensive and labour-intensive approach, which currently can only be performed in a small number of centres, most of which are in high-income countries. Some of the first somatic human genome editing protocols that have been licensed cost more than US\$ 500 000 per patient. Without considerable effort in capacity-building and cost reduction, this approach is therefore difficult to apply at scale in lower-income countries that often have the greatest burden of genetic disease, such as countries with a high incidence of sickle-cell disease and beta-thalassaemia.



36. Apart from a few potential treatments, where the target cells are in relatively accessible sites, such as the retina, skin or mucous membranes and perhaps the liver, in vivo genome editing still has many technical challenges. These challenges include how to introduce enough copies of, for example, the viral vector(s) carrying the genome editing components, in a way that:

- preferably targets only the desired cell type;
- corrects the genetic defect in a sufficient proportion of the cells to give clinical benefit;
- does not lead to excess off-target or inappropriate on-target events; and
- avoids any adverse immune response to the genome editing components, including the viral vector.

While in vivo genome editing offers much promise, it requires new reagents and methods to be developed, including ways to analyse the outcome in tissue taken from research participants. Much preclinical research will be needed for each type of potential treatment. However, once developed and shown to be safe and clinically beneficial, and as long as the methods are not too dependent on an individual person's genotype, the costs of in vivo editing approaches could come down. Good governance will include mechanisms to stay well informed of technical developments and to review safety, clinical benefit and cost.

37. Much publicized advances in somatic genome editing have enabled new, more straightforward and accurate methods for genome editing. One risk is that this will be misunderstood by the public as suggesting that somatic genome editing of humans is simple and safe, which in turn could pave the way to a proliferation of unregulated clinics offering unproven or even unsafe therapies. This happened with stem cell therapies, in which hundreds of such unregulated clinics opened in countries around the world, to the detriment of patients seeking real cures, some of whom were seriously injured by the so-called therapies. In other cases, public enthusiasm for stem cell 'therapies' led national regulators to tolerate clinical practices that would ordinarily be disallowed under their standards for safe and effective care. Another risk is that a public misunderstanding about the ease of genome editing could encourage people to try so-called "do it yourself" somatic editing, something that has been promoted by a handful of individuals. Governance mechanisms for human genome editing will need to discourage opportunistic marketing and premature use of applications. Moreover, these mechanisms need to ensure that authorities do not abandon their usual standards governing research and clinical care.

38. The financial and logistical obstacles for clinical care involving human somatic genome editing in low- and middle-income countries will require considerable attention. Past mistakes, such as exploiting the populations of such countries for data and resources, must be avoided. Instead, researchers and clinicians in high-income countries must partner with their counterparts in low- and middle-income countries to assist with capacity-building for infrastructure and expertise, and to ensure maximum benefit and minimal harm. This will need to be matched by efforts in public education, engagement and empowerment, as well as in ensuring appropriate ethical standards.

### 3.1.1 Strengthening oversight measures for clinical research

39. When strengthening oversight measures for clinical research, the following questions should be considered (other questions may also arise).
- a. What limitations beyond safety and efficacy for research participants (if any) will be placed on somatic human genome editing research?
  - b. Will clinical research on somatic human genome editing fit within existing oversight measures for research involving humans? If using existing oversight measures, do they need specific amendments to cover somatic human genome editing?
  - c. Is there adequate capacity to manage the technical review of proposals for clinical research on somatic human genome editing and to follow up on results?
  - d. What medical, legal and financial assistance (and possibly compensation) will be available to individuals who are harmed as a result of research participation?

### 3.1.2 Strengthening oversight measures for clinical care

40. When strengthening oversight measures for clinical care, the following questions should be considered (other questions may also arise).
- a. How will decisions be made regarding approval and postapproval access to clinical care involving somatic human genome editing?
    - i. What technical standards for safety and efficacy will be adopted?
    - ii. What limits, if any, will be placed on particular uses, patient populations or professional providers?
    - iii. What domestic ethical standards, if any, will apply? How will they be enforced?
  - b. What role could be played by liability insurers, health care coverage rules, research funders, clinics, professional licensing societies, and medical journals?
  - c. Is control exercised at the executive, legislative, judicial or administrative, or medical society level? Is this control central or regional? Or is this control at the discretion of the provider?
  - d. Is control focused on eligibility for funding, permissibility of marketing or permissibility of any use at all? Are there any distinctions about permissibility in private versus public clinics or with use of private versus public funding?
  - e. Will questions of equitable access to safe and effective treatment or prophylaxis across domestic populations and communities affect whether any particular individual will have access to care?

## 3.2 Special challenges: prenatal (in utero) somatic human genome editing

41. Editing the somatic cells at the fetal stage (in utero) may offer benefits for the future child who would otherwise be born with tissue-specific or systemic effects that cannot be corrected using postnatal somatic human genome editing or treated with conventional methods. Research on in utero human somatic genome editing may be a reasonable alternative to heritable human genome editing (for reproduction) when a disease has early onset, irreversible effects and is not easily treated after birth. If in utero somatic human genome editing is done after the development of the gonads, the chance of inadvertent editing of germ cells is minimal, but this must still be monitored to avoid making heritable modifications. While the safety and efficacy of in utero somatic human genome editing is still at the preclinical stage, some early human trials have been proposed. Good governance needs to anticipate advances in in utero somatic human genome editing, develop policies on its permissibility or impermissibility and ensure that any permitted procedures are safe (for all those involved) and effective.

### 3.2.1 Strengthening oversight measures for clinical research

42. When strengthening oversight measures, the following questions should be considered (other questions may also arise).
- a. Are in utero interventions that involve only somatic human genome editing currently permitted? If so, under what oversight measures?
  - b. Will research that involves in utero somatic human genome editing be permitted?
    - i. If not permitted, what are the penalties (civil and criminal) and how will violations be identified; for example, are mechanisms available that allow individuals or institutions to report violations?
    - ii. If not permitted, can the researcher or clinician conduct this research in another jurisdiction where it is explicitly permitted without fear of civil or criminal penalty in the jurisdiction where they typically work? What if there is limited or no oversight in the jurisdiction where the researcher or clinician intends to conduct the research?
    - iii. If permitted, what standards will control the degree of acceptable risk to a fetus and the pregnant women and persons?<sup>12</sup>
    - iv. If permitted, in either a pre or postapproval clinical research context, will pregnant women and persons have the option to terminate the pregnancy, decide on the management of the pregnancy or decide on the management of any neonate born with extreme prematurity or disorders?
    - v. If permitted, are existing oversight mechanisms adequate to manage technical review of risks and possible benefits particular to in utero somatic human genome editing research, including: risk to pregnant women's and persons' health from use of viral vectors; risk of introducing new fetal disease or disability that would be experienced by any live-born child; risk of unintended changes to fetal gametes; and risk that the timing of the genome editing results in loss of opportunity to make decisions on pregnancy termination?
    - vi. If permitted, are the current rules clear about the decision-making roles of: pregnant women and persons (regardless of intent to rear any resulting child); the gamete providers; and the parent(s) intending to rear any resulting child? Are these rules clear about the decision-making role of married and unmarried partners, who may or may not be the same sex as the pregnant woman and person?

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12 Throughout this framework, we will use the term pregnant women and persons to refer to pregnant women and others/gender diverse people who can get pregnant. While a majority of persons who are or can get pregnant are cisgender women, who were born and identify as female, transgender men and other gender diverse people may have the reproductive capacity to get pregnant. Therefore, this framework is inclusive of their experiences.

### 3.3 Special challenges: heritable human genome editing

43. Heritable human genome editing commonly refers to editing of nuclear DNA in a way that may be heritable across generations. It includes the prospect of altering individuals by deleting or adding certain traits – this could be preventing the birth of individuals with so-called undesirable traits or facilitating the birth of individuals with so-called desirable traits. Heritable human genome editing also encompasses editing of mitochondrial DNA, which has different technical challenges and harm–benefit profiles. Good governance should have the capacity to evaluate both.
44. Heritable human genome editing is the subject of intense debate over its possible consequences for offspring and for society in general. Because it is associated with human reproduction, it raises spiritual, religious or deeply personal issues for some people. It also raises relevant concerns about fairness, social justice and non-discrimination, as well as potential disregard for the moral respect owed to individuals with disabilities. Good governance will need to be aware of, and sensitive to, these concerns.
45. Heritable modifications resulting from human genome editing may pose greater safety and ethical issues than somatic human genome editing. The potential short- and long-term harm from human embryo genome editing, including the potential consequences of genetic mosaicism, unintended off-target effects and unwanted on-target effects, must be fully understood before options for such medical interventions are considered.<sup>13</sup> The type of genetic alteration to be made also requires careful attention. This alteration should recreate a DNA sequence that is common in the relevant population or family, and is associated with normal function of the gene in question. This may be distinct from somatic human genome editing where it may not matter if DNA sequences are added or deleted at the target site, or even whole genes inserted, for example at so-called safe harbour sites (where disruption of any endogenous sequence is known to have little or no effect on already born individuals). In addition, a range of ethical issues concerning the possible use of heritable human genome editing must be carefully explored. As a part of good governance, regulators must evaluate potential unwanted side-effects of heritable human genome editing, ensure that the most appropriate methods are used to minimize risks, and weigh the potential harms and benefits as well as the individual and social usefulness.
46. Prospective parents who are at risk of having children with a genetic disease, and who want genetically related children unaffected by that disease, may have an interest in participating in heritable human genome editing research. In many cases, however, there may well be safer and cheaper technological and social alternatives (such as preimplantation genetic testing and selection of embryos for implantation, gamete or embryo donation, or adoption), which need to be considered prior to any participation in research on heritable human genome editing. Good governance needs to consider both the desires of prospective parents to have genetically connected offspring and the risks to future offspring, as well as possible effects on society, particularly in light of these alternatives. Good governance should also learn lessons from past experiences in the use of reproductive technologies, including the scale of patient demand, the equity of access, the safety of the procedures, the effectiveness of governance systems and the effects on society generally.

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13 National Academy of Medicine, National Academy of Sciences and the Royal Society. Heritable human genome editing. Washington, DC: The National Academies Press; 2020. <https://doi.org/10.17226/25665>

### 3.3.1 Strengthening oversight measures for research involving germline human genome editing (not for reproduction)

47. When strengthening oversight measures for such research, the following questions should be considered (other questions may also arise).
- a. Will basic science research on germline human genome editing that involves gamete precursor cells, gametes, embryos and embryo models be permitted?
    - i. If not permitted, what are the penalties (civil and criminal) and how will violations be identified; for example, are mechanisms available that allow individuals or institutions to report violations?
    - ii. If not permitted, can the researcher conduct this research in another jurisdiction where it is explicitly permitted without fear of civil or criminal penalty in the jurisdiction where they typically work? What if there is limited or no oversight in the jurisdiction where the researcher intends to conduct the research?
    - iii. If permitted, will this research fit within oversight measures for research involving gamete precursor cells, gametes, embryos and embryo models? Do these oversight measures cover considerations about the individuals (deceased or still alive) from whom the gametes, embryos or other cellular materials were obtained? If using existing oversight measures, do they need specific amendments to cover the use of these materials for germline human genome editing?
    - iv. If permitted, but only for specified purposes such as to develop a better understanding of a serious condition, is there adequate capacity to manage the technical review of proposals for germline human genome editing?
    - v. If permitted, will germline human genome editing research be subject to any special rules on funding or limits on research beyond a particular developmental stage of the human embryo or embryo model?
    - vi. If permitted, will this research be restricted to excess embryos from fertility treatment, or will the creation of human embryos for research purposes also be permitted?
  - b. How will human gamete precursor cells, gametes and embryos be obtained, and with informed consent from whom? Will payment for these materials be permitted or prohibited?

### 3.3.2 Strengthening oversight measures for research involving heritable human genome editing (for reproduction)

48. When strengthening oversight measures for such research, the following questions should be considered (other questions may also arise).
- a. Will clinical research on heritable human genome editing (that is, research that involves the transfer of edited gamete precursor cells, gametes or embryos to a woman or a person's uterus with the aim of establishing a pregnancy) be permitted?
    - i. If not permitted, what are the penalties (civil and criminal) and how will violations be identified; for example, are mechanisms available that allow individuals or institutions to report violations?
    - ii. If not permitted, can the researcher or clinician conduct this research in another jurisdiction where it is explicitly permitted without fear of civil or criminal penalty in the jurisdiction where they typically work? What if there is limited or no oversight in the jurisdiction where the researcher or clinician intends to conduct the research?

- iii. If permitted, will research on heritable human genome editing fit within existing oversight measures for research involving humans and human reproduction? If using existing oversight measures, do they need specific amendments to cover heritable human genome editing?
- iv. If permitted, is there adequate capacity to manage the technical review of proposals for research on heritable human genome editing and to follow up on results?
- v. If permitted, what medical, legal and financial assistance (and possibly compensation) will be available in case of injury to the pregnant women and persons or to any child as a result of research participation?
- vi. If permitted, will heritable human genome editing clinical research be subject to any special rules on funding?
- vii. If permitted, what capacity exists for long-term, possibly multigenerational follow-up on the health and safety of the genetically modified offspring, and for monitoring possible effects on society as a whole?
- b. Are there any domestic policies or ethical rules and standards that govern heritable human genome editing research? If so, how are they enforced?
- c. If the existing oversight measures for research involving human reproduction are not adequate, is there a plan to create new oversight measures or to rely on regulatory review and approvals from an external body? If so, which new measures or which external bodies?
- d. If developing new oversight measures, how will they be coordinated with other regulatory bodies?
- e. Will domestic policy on heritable human genome editing research for enhancement (see section 3.5) be different from domestic policy for somatic human genome editing research for enhancement?
- f. Will questions of equitable access to research participation across domestic populations and communities affect decision-making on a particular research proposal?

### 3.3.3 Strengthening oversight measures for clinical use of heritable human genome editing (for reproduction)

49. When strengthening oversight measures for clinical use, that is, uses outside the context of research, the following questions should be considered (other questions may also arise).
- a. Will clinical use of heritable human genome editing be permitted? How will this decision be made?
    - i. If not permitted, what are the penalties (civil and criminal) and how will violations be identified; for example, are mechanisms available that allow individuals or institutions to report violations?
    - ii. If not permitted in the jurisdiction where a clinician typically works, can the clinician conduct this research in another jurisdiction where it is explicitly permitted without fear of civil or criminal penalty in their jurisdiction? What if there is limited or no oversight in the jurisdiction where the clinician intends to practice?
    - iii. If permitted, will the clinical use of heritable human genome editing be subject to special rules, such as long-term, possibly multigenerational follow-up on the health and safety of genetically modified offspring, and monitoring of possible effects on society in general?
    - iv. If permitted, but only in specific cases, is there adequate capacity for oversight and how will policies on limited uses be enforced?
  - b. What role might there be for liability insurers, private health insurance coverage, clinic accreditation and professional licensing societies?

- c. Will questions of equitable access to safe and effective heritable human genome editing across domestic populations and communities affect an individual's access?

### 3.4 Special challenges: human epigenetic editing

50. Human epigenetic editing offers the possibility of making usually short-term or reversible changes in gene expression, without affecting the sequence of the underlying DNA. It does this through editing the epigenome – proteins and small molecules that latch onto DNA and control when and where genes are switched on or off. For example, expression of genes associated with resistance to chemical, biological or radiation hazards could be temporarily upregulated or downregulated (that is, increased or decreased) without any lasting changes to the genome.<sup>14</sup> Depending on the type of edit and the specific gene involved, epigenetic editing may have long-term effects within an individual. It follows that human epigenetic editing presents a different risk profile to 'conventional' human genome editing for the following reasons.

- a. The DNA sequence is unchanged. This means that there is little chance of damage from DNA repair (such as deletions, insertions, or chromosomal rearrangements).
- b. Very few, if any, epigenetic changes are likely to be heritable. As such, any risks should be limited to the individuals on whom the editing is being done and do not extend to future offspring. This will be the case even if early embryos or other germline cells are being epigenetically edited. Even 'parentally imprinted genes' (ones where either the maternal or paternal allele is normally silenced due to epigenetic mechanisms), will be reset during germ cell development.
- c. Epigenetic changes may be difficult to detect. Though transient, such changes may have long-lasting physiological effects. That is, these changes may be present long after both the tools used to make the edits, and even the edits themselves, have ceased to be present. For example, suppressing the activity of a specific gene that is critical for specifying a particular cell type during embryo or postnatal development, will have long term consequences for the function of the tissue or organ in which that cell type normally resides.
- d. Epigenetic editing research is moving very quickly. A recent important advance could substantially change both the range of uses and the harm–benefit profile of epigenetic editing, through the use of a CRISPRoff tool, which allows scientists to switch off almost any gene in human cells without making a single edit to the genome sequence. The change would persist but could be reversed with the complementary CRISPRon tool.<sup>15</sup>

Efforts have been made to consider good practice in making use of epigenetics for public health.<sup>16,17</sup> Good governance of human genome editing needs to anticipate epigenetic editing and develop policy about the permissibility or impermissibility of potential uses. Epigenetic editing could be carried out on somatic tissues or germline cells (gamete precursor cells, gametes, early embryos and embryo models), even if editing of germline cells does not lead to heritable changes in gene activity. Any permitted procedures need to be safe and effective and conducted with the full knowledge and permission of regulators.

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14 <https://www.darpa.mil/program/preemptive-expression-of-protective-alleles-and-response-elements> (accessed 26 April 2021).

15 Nuñez JK, Chen J, Pommier GC, Hovestadt V, Gilbert LA, Weissman JS, et al. Genome-wide programmable transcriptional memory by CRISPR-based epigenome editing. *Cell*. 2021. <https://doi.org/10.1016/j.cell.2021.03.025>

16 Dyke SOM, Saulnier KM, Dupras C, Webster AP, Maschke K, Rothstein M, et al. Points-to-consider on the return of results in epigenetic research. *Genome Med*. 2019;11(1):31. <https://doi.org/10.1186/s13073-019-0646-6>

17 Points-to-consider on the return of epigenetic research results [online]. International Human Epigenome Consortium; 2019 ([http://ihc-epigenomes.org/fileadmin/user\\_upload/documents/Points-to-Consider\\_on\\_the\\_Return\\_of\\_Epigenetic\\_Research\\_Results.pdf](http://ihc-epigenomes.org/fileadmin/user_upload/documents/Points-to-Consider_on_the_Return_of_Epigenetic_Research_Results.pdf), accessed 19 April 2021).

### 3.4.1 Strengthening oversight measures for human epigenetic editing

51. When strengthening oversight measures for epigenetic editing, the following questions should be considered (other questions may also arise).
- Will epigenetic editing on gametes and embryos be permitted for non-reproductive purposes, for example, to explore gene function? Will any distinction be made between work with public versus private funding?
  - To establish harm–benefit profiles, for how long will the editing changes or their effects persist and what endpoints will be used?
  - For clinical use, will the availability of epigenetic editing approaches have any effect on permissibility or impermissibility of genome editing for more permanent changes?
  - Given the reversibility of epigenetic editing, will considerations on enhancement (see section 3.5) be different when evaluating epigenetic editing applications rather than genome editing for more permanent changes?

## 3.5 Special challenges: enhancement

52. At some time in the future, somatic human genome editing might be able to be used to improve typical and perfectly adequate traits or to add new traits. The potential harms and benefits to individuals seeking enhancement will vary depending on a number of scientific, ethical, personal, societal and legal factors. Furthermore, at some future time, it might be suggested that heritable human genome editing could be used to reduce the number of people born with so-called undesirable traits or increase the number born with improved and possibly new so-called desirable traits. Again, the potential harms and benefits will vary depending on a number of scientific, ethical, personal, societal and legal factors, but in this instance, the potential harms and benefits will need to be assessed from the perspectives of the individuals who may be born of genetically altered embryos, their prospective parents, society and any children in subsequent generations who could inherit the genetic alteration. Good governance needs to explicitly consider whether the use of human genome editing technologies for enhancement purposes should be permitted. At a minimum, this should include an assessment of the potential harms and benefits referred to here, but it need not be limited to these factors.
53. The possibility that human genome editing might be used for the enhancement of human traits is very controversial. One concern is that permitting human enhancement could aggravate existing social or economic inequalities. Governance decisions about the permissibility or impermissibility of using human genome editing for enhancement purposes therefore should be subject to inclusive and transparent societal debate. Such debate might include attention to the full range of temporary and permanent medical and biological enhancements already in use, ranging from nutritional supplements to strength-enhancing steroids to cosmetic surgeries, which often have varying and sometimes inconsistent policies about ethical, societal and legal acceptability.
54. Societal concerns about human enhancement may differ depending on the context. For example, perceptions of potential harms and benefits may be very different if the proposed enhancement aims to improve performance in sport or academic endeavours, as contrasted with efforts to improve military prowess or aptitude for space missions. Good governance should be flexible enough to evaluate proposed enhancements in different contexts taking into account the possibility that enhanced individuals, be they elite athletes or enhanced fighters, could change careers. Governance decisions about the permissibility or impermissibility of using human genome editing for enhancement purposes should therefore take into account dual-use dilemmas.



### 3.5.1 Strengthening oversight measures for human genome editing for enhancement

55. When strengthening oversight measures, the following questions should be considered (other questions may also arise).
- a. Will human genome editing for enhancement purposes be permitted?
    - i. If not permitted, what are the penalties (civil and criminal) and how will violations be identified; for example, are mechanisms available that allow individuals or institutions to report violations?
    - ii. If not permitted, can the researcher or clinician conduct the work in another jurisdiction where it is explicitly permitted without fear of civil or criminal penalty in the jurisdiction where they typically work? What if there is limited or no oversight in the jurisdiction where the researcher or clinician intends to work?
    - iii. If permitted, will human genome editing for enhancement fit within existing oversight measures? If using existing oversight measures, do they need specific amendment to cover the range of research and practice?
  - b. How will distinctions be drawn between disease and disability prevention, and therapy? How will enhancement be defined; for example, will this be the introduction of traits that are beyond ordinary human capacity and health? Or, will this be the introduction of traits beyond those usually present in the human species?
  - c. Will questions of equitable access to research participation, as well as safe and effective treatment across domestic populations and communities, affect whether an individual will be able to use such editing for personal enhancement?

# Part 4.

## Tools, institutions and processes for governance of human genome editing

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56. Governance of human genome editing will best be achieved by taking advantage of the full range of individuals and organizations able to influence or control the direction of research and possible future uses for treatment, prophylaxis and enhancement. Identifying relevant individuals and organizations in each context will depend on the roles played by national and regional governments, civil societies, professional and academic societies, research sponsors and funders, insurers, payors, funders and the general public. The best mix of governance mechanisms will depend on whether they are to be used for national and/or transnational governance. If for transnational governance, the mix will depend on the particular political system within a country. Part 4 describes the many tools, institutions and processes from which choices can be made.

### 4.1 Declarations, treaties, conventions, legislation and regulations

57. Laws governing human genome editing and related technologies can be created by a variety of mechanisms. Some of these laws are broad and human genome editing simply falls within their scope. In other cases, laws are created specifically for this technology. While legal instruments are essential for creating penalties, statute law is harder to change than regulations and guidelines. Given the rapid pace at which human genome editing is evolving and technologies are changing, there are concerns about the benefits and limitations of laws narrowly cast for a specific technology and laws that are broader.
58. For human genome editing, the most likely sources for international law will be declarations, treaties and conventions (often with a requirement for ratification at a national level). In this context, the stakeholders are usually countries that negotiate the terms of the agreements, albeit with each country subject to its own domestic political system. An example of this is the Council of Europe Convention on Human Rights and Biomedicine (Oviedo Convention<sup>18</sup>), ratified by 29 countries, which prohibits any intervention aimed at modifying the genome of any descendent. International organizations are often aided by dedicated ethics and policy committees, such as UNESCO's

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18 <https://www.coe.int/en/web/bioethics/oviedo-convention> (accessed 28 May 2021).

International Bioethics Committee or the Council of Europe's Committee on Bioethics, which help to analyse technological developments and prepare positions for meetings on international agreements and international funding agencies. Their work on human genome editing complements other broad international instruments such as the Declaration of Nuremberg on research ethics and the International Ethical Guidelines for Health-related Research Involving Humans, prepared for the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the WHO.<sup>19</sup> Additional broad treaties and conventions are also relevant where these have similar underlying principles to those the Committee describes as suitable for the governance of human genome editing. Indeed, the Framework proposed here is consistent with human rights law.

59. At the domestic level, legislation is a common tool, often supplemented by enforceable regulations or influential guidance, in order to provide more detail on both substantive rules and procedural mechanisms. Legislation and regulations may be enacted to address a specific aspect of genome editing or, as is more common to date, it may be enacted to address a related field, such as clinical trial regulations or reproductive rights. In this latter case, applicability to genome editing may be unclear or, where applicable, may be unanticipated. Some examples are given below.
- a. In Algeria, access to assisted reproduction is limited to married couples unable to procreate naturally and the donation or sale of gametes, embryos, or sperm, the collection of embryos for research, as well as sex selection or and human cloning are prohibited.<sup>20</sup> These rules would appear to preclude reproductive use of germline editing.
  - b. In Canada, genome editing appears more directly to be addressed, as the Assisted Human Reproduction Act<sup>21</sup> prohibits knowingly altering “the genome of a cell of a human being or in vitro embryos such that the alteration is capable of being transmitted to descendants”.
  - c. In China, the Criminal Law of the People's Republic of China<sup>22</sup> was used to prosecute He Jiankui, who performed the first known human embryo edits resulting in live births, but the prosecution was based on practicing medicine without a license and not specifically based on a provision governing assisted reproduction or genome editing.<sup>23</sup>
  - d. In India, the Assisted Reproductive Technology (Regulation) Bill 2020<sup>24</sup> and the Surrogacy Regulation Bill 2020<sup>25</sup> set standards for clinics and banks offering assisted reproductive technology services, prohibit the practice of sex selection and sale of human embryos or gametes, and protect and safeguard reproductive rights. These are related to but not directly addressed to genome editing, which would require manipulation of gametes or embryos.
  - e. In the United States of America, the current budget authorizations prohibit use of funds by the FDA for the purpose of accepting and reviewing any application to begin a clinical trial for heritable germline editing. As FDA permission is required, this effectively makes such reproductive editing illegal unless and until such a restriction on FDA funds is lifted.

19 International ethical guidelines for health-related research involving humans. Fourth edition. Geneva: Council for International Organizations of Medical Sciences; 2016 (<https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf>, accessed 1 May 2021).

20 Journal officiel de la république algérienne démocratique et populaire. Conventions et accords internationaux – lois et décrets arrêtes, décisions, avis, communications et annonces [Official journal of the Democratic and Popular Republic of Algeria. International conventions and agreements – laws and decrees orders, decisions, opinions, communications and announcements]. Government of Algeria; 2018 (<https://www.joradp.dz/FTP/jo-francais/2018/F2018046.pdf>, accessed 27 May 2021).

21 <https://laws-lois.justice.gc.ca/eng/acts/a-13.4/> (accessed 27 May 2021).

22 <https://www.fmprc.gov.cn/ce/cgvienna/eng/dbtyw/jdwt/crimelaw/t209043.htm> (accessed 27 May 2021).

23 The Committee recalled that He Jiankui was convicted of “illegal medical practices”, rather than a specific offence involving human genome editing. A law making it illegal to carry out heritable human genome editing has now been enacted.

24 The assisted reproductive technology (regulation) bill, 2020. Government of India; 2020 ([https://prsindia.org/files/bills\\_acts/bills\\_parliament/Assisted%20Reproductive%20Technology%20Bill,%202020.pdf](https://prsindia.org/files/bills_acts/bills_parliament/Assisted%20Reproductive%20Technology%20Bill,%202020.pdf), accessed 27 May 2021).

25 <https://prsindia.org/billtrack/the-surrogacy-regulation-bill-2019> (accessed 27 May 2021).

- f. South Africa's Choice on Termination of Pregnancy Act<sup>26</sup> preserves the right to obtain an abortion, but has implications for the debate about heritable human genome editing, which may in practice rely on the availability of abortion as a safeguard in the event of adverse effects on the developing embryo and fetus.
60. Regulations can add detail to both substantive rules and procedural mechanisms of their authorizing legislation. The following are examples of such regulatory frameworks in some countries.
- a. In Egypt, the Professional Ethics Regulations of the Egyptian Medical Syndicate cover assisted reproduction<sup>27</sup>. The regulations prohibit sperm, egg and embryo donations, gestational surrogacy, the creation of egg, sperm or embryo banks, and trade in human embryos.
  - b. In India, in 2019, the government disseminated its National Guidelines for Gene Therapy Product Development and Clinical Trials<sup>28</sup>, which prohibit germline or in-utero human genome editing.
  - c. In Japan, the Guideline for Gene Therapy Clinical Research (Ministry of Health and Welfare Note No. 23) prohibits genetic modification of germ cells or embryos. A 2019 revision explicitly includes genome editing as a part of gene therapy; in addition, the government in 2019 disseminated ethical guidance (Ethical Guideline on Research to use Genetic Modification Technologies in Human Embryo).
  - d. In Turkey, updated regulations on applications of assisted reproduction therapy and assisted reproduction therapy centres were adopted in March 2010<sup>29</sup>. These regulations clarify the rules of access and use of infertility treatments for married couples who cannot have children. Storage of reproductive cells is prohibited except in certain cases where there is a medical necessity.
  - e. In the United Kingdom of Great Britain and Northern Ireland, the Human Fertilisation and Embryology Authority was created under parliamentary legislation. The authority details permissible and impermissible forms of embryo research and assisted reproduction, and approves personnel and facilities for this work. The authority is a government regulator that has a reasonable amount of independence to make its own decisions as long as these fall within the bounds of the Human Fertilisation and Embryology Act 2008<sup>30</sup>. The authority also conducts robust oversight and maintains records of all procedures that are authorized for research or treatment. There are penalties for contravening the Act, which include fines and/or imprisonment.
61. Legislation and regulations are subject to public control through mechanisms such as testifying at legislative and regulatory rulemaking hearings, lobbying by interest groups, commenting on proposed rules, bringing judicial challenges to unwanted policies, and elections. The strength of public control varies according to the specifics of the political system and the power of its various interest groups as well as the voting public. Many civil society organizations have articulated stands on human genome editing by: organizing briefings, webinars and other public events; writing or signing open letters; and testifying or commenting at meetings of regulatory bodies. Many (although not all) advocates of reproductive, disability and racial justice, human rights, and environmental protections have expressed support for somatic human genome editing (conditional on its safety, efficacy and equitable accessibility), but remain troubled about heritable human genome editing. It is important that best practice with regard to public engagement is followed by all countries intending to regulate human genome editing research and possible future uses for treatment, prophylaxis and enhancement.

26 Choice on termination of pregnancy act [updated to 18 February 2008]. Government of South Africa; 2008 [http://www.saflii.org/za/legis/consol\\_act/cotopa1996325.pdf](http://www.saflii.org/za/legis/consol_act/cotopa1996325.pdf) (accessed 27 May 2021).

27 <http://new-v.ems.org.eg/ar/page/rules/9> (accessed 27 May 2021).

28 National guidelines for gene therapy product development and clinical trials. Government of India; 2019 ([https://www.nhp.gov.in/NHPfiles/guidelines\\_GTP.pdf](https://www.nhp.gov.in/NHPfiles/guidelines_GTP.pdf), accessed 27 May 2021).

29 <https://www.mevzuat.gov.tr/mevzuat?MevzuatNo=20085&MevzuatTur=7&MevzuatTertip=5> (accessed 27 May 2021).

30 <https://www.legislation.gov.uk/ukpga/2008/22/contents> (accessed 27 May 2021).

62. In many countries, advisory committees play an important role in formulating law and regulating life sciences technologies. For example, Argentina has the National Committee of Ethics in Science and Technology, France has the Consultative Committee on the Ethics of Health and Life Sciences, Germany has the Ethics Council, Saudi Arabia has the Standing Committee for Research Ethics on Living Creatures, and the United Kingdom has the Nuffield Council on Bioethics. The functions of such committees vary depending on the branch of government they are tasked with advising, the degree of public participation in their deliberations, the methods by which members are selected and the scope of life sciences research and clinical care within their remit. Their influence also varies: provided their methods are sound, such committees may provide an important source of extended deliberation, often accompanied by publications laying out evidence-based analyses of a technology and its current and expected future capabilities and probable effect on individuals and society in general. In some cases, these committees make recommendations for laws, regulations and guidelines, which have varying degrees of influence on governmental bodies. It is important that best practice with regard to advisory committees is followed by all countries intending to regulate human genome editing research and possible future uses for treatment, prophylaxis and enhancement.

## 4.2 Judicial rulings

63. At times, law can be developed by courts, in their role as interpreters of constitutional guarantees or legislative language, or more indirectly by virtue of setting precedents in their decisions on individual criminal and civil cases. For example, in the immediate aftermath of He Jiankui's announcement of gene-edited babies, some observers attributed the reckless experiment to a regulatory vacuum in China. Others pointed to administrative regulations and ethical norms that, in their view, clearly prohibited this kind of experimentation. The Ethical Principles for Human Assisted Reproductive Technology and Human Sperm Bank (Order of the Ministry of Public Health of the People's Republic of China, No. 176 of 2003), for example, makes explicit reference to protecting future generations and stipulates that medical professionals should not implement human assisted reproductive technology if its implementation will cause serious physical, psychological, and social harms to future generations. In December 2019, the Nanshan District People's Court in Shenzhen found He and two others guilty of "deliberate violation of China's relevant regulations and medical ethics"<sup>31</sup> and of violating Article 336 of the Criminal Law of the People's Republic of China<sup>32</sup>, which prohibits engaging in medical activities without a licence.
64. Civil cases concerning authority on disposal of gametes and embryos have been brought in many countries, often between former spouses or by survivors where the deceased has left unused reproductive materials. Genome editing of human gametes or human embryos would, with current technology, probably take place outside the body and be affected by these rulings.
65. Civil cases can also be brought to assert malpractice, as when negligent genetic screening or counselling has occurred. Malpractice is understood as falling below the generally accepted level of care, which is measured by reasonable standards of practice among similarly situated providers, compliance with legislative and regulatory standards, and conformity with guidelines offered by professional societies.
66. While only those who are party to the litigation are immediately affected by judicial rulings, the precedents set by the decisions can solidify a consensus on a standard of practice, which in turn may affect the availability and affordability of liability insurance. Because insurers engage in risk assessment to determine coverage, they not only reflect the standard of care (and help to enforce it) but at times may help to set the standard of care, by the choices they make regarding various interventions and coverage in their policies.

31 <https://www.thehastingscenter.org/chinese-bioethicists-he-jiankuis-crime-is-more-than-illegal-medical-practice/> (accessed 27 May 2021).

32 <https://www.fmprc.gov.cn/ce/cgvienna/eng/dbtyw/jdwt/crimelaw/t209043.htm> (accessed 27 May 2021).

### 4.3 Ministerial decrees

67. In 2019, Russian geneticist Denis Rebrikov made a series of public statements suggesting he planned to follow He Jiankui and use heritable human genome editing to provide resistance to HIV infection in resulting children. Specifically, Rebrikov announced that he planned to enrol couples where the female partner was living with HIV and the offspring were at risk of parental transmission of HIV. (He Jiankui's experiment involved couples where the male partner had HIV, where sperm washing would have been a reasonable alternative to human genome editing.) When Rebrikov was unable to find willing research participants, he said he would look at other targets: he named "dwarfism, deafness, or blindness" as possible alternatives. In October 2019, the Ministry of Health of the Russian Federation noted that the use of germ cells and embryos was regulated by a 2012 ministerial decree that lists contraindications and restrictions on the use of assisted reproductive technologies. The ministry also announced that heritable genome editing research was premature and that it would not approve Rebrikov's plans.<sup>33,34</sup>
68. Ministerial or government decrees may also have the opposite aim, that is, they can be used to promote activities. However, if such decrees are not expressed with care, or include exclusions, they could have unwanted consequences. For example, enthusiastic statements from local and central government about the importance of doing innovative science for the national benefit can encourage innovators to take steps beyond those intended, or wanted, by those making the statements, such as the premature use of heritable human genome editing.

### 4.4 Conditions on research funding

69. Human genome editing is funded from both private and public sources, and one powerful source of governance arises from decisions determining priorities and setting funding rules. Particularly in the public sphere, decisions about funding priorities can speed or slow the development of whole areas of basic science or preclinical and clinical research. Priorities may be set to reflect: unmet needs in the population; areas of anticipated progress in tackling difficult problems; or simply the interests of individual members of the government or lobbyists. Funding may be denied, reflecting a dominant or particularly powerful viewpoint. In a number of countries, public funding of research using human embryos is prohibited. For example, in the United States, there is no law prohibiting heritable human genome editing. However, there is a clause (which needs renewing each year) to a broad spending bill that prevents the United States Food and Drug Administration from reviewing applications for clinical trials involving heritable human genome editing. This effectively makes it impossible to do heritable human genome editing research wholly within the United States.
70. Rules governing the funding of private and public research may impose a range of conditions that may function as a governance tool. For example, there may be: conditions on the source of the gametes or embryos (especially on payment to and consent from the providers); limits on the degree of development of an embryo or embryo model or the length of time they<sup>35</sup> may be maintained in vitro; rules on creation of chimeric or hybrid embryos; rules on ownership of, and authority for disposal of, the gametes and embryos; and rules about intellectual property ownership, and sharing of data and materials. Depending on available sources of funding, a single large-scale national funder may effectively govern almost the entire field of human genome editing research within a country. Not providing public funding for an area of research can discourage other private and philanthropic funders from becoming involved. Alternatively, absence of public funding can drive the research into the private and business sector, thus reducing government oversight.

33 Grebenshchikova EG. Russia's stance on human genome editing. *Nature*. 2019;575(7784):596. <https://doi.org/10.1038/d41586-019-03617-x>

34 <https://tass.ru/obschestvo/6968512> (accessed 1 May 2021).

35 Embryo model refers to what some call synthetic embryos.

71. Funding for clinical research in human genome editing will be subject to general research rules where these exist. These rules tend to focus on: (i) independent review of risks and possible benefits to society and to individuals enrolled in the clinical trials; (ii) informed consent (on the part of the people with decision-making capacity); and (iii) monitoring for adverse events. Clinical trials of somatic human genome editing are still very new, and assessment of risks – necessary both for informing potential research participants and for drafting inclusion or exclusion criteria – may be difficult in the immediate future.

## 4.5 Moratoria

72. Moratoria on one or more aspects of human genome editing have been the subject of considerable discussion, most especially with respect to heritable human genome editing for those countries that do not already have some kind of prohibition (Table 2). By definition, a moratorium is a temporary prohibition of an activity. To be effective, it requires either voluntary compliance on the part of researchers or some form of external control, such as government regulation with enforcement powers. The usefulness of a moratorium is improved by clear articulation of the reasons for the temporary prohibition and specific milestones that must be reached for the moratorium to be partially or fully lifted. Alternatively, instead of stipulating conditions for lifting a moratorium, an explicit expiry date may be stipulated at the outset. A stipulated expiry date avoids a situation where a moratorium intended to be temporary and provisional, proves difficult to terminate because of lack of clarity as to who has authority to decide whether, when and why the moratorium can be lifted.
73. Currently, the Oviedo Convention limits the purposes of any intervention on the human genome (including in research) to prevention, diagnosis or therapy, and prohibits any intervention that aims to introduce a modification in the genome of any descendants (article 13). Major concerns detailed by the drafters of the Oviedo Convention were the possible health hazards to future generations that could result from an intentional modification of human genetic inheritance, without having adequate knowledge of the human genome and without using sufficiently precise techniques so as not to cause damage.
74. For countries not party to the Oviedo Convention, the possibility of some form of moratorium on heritable human genome editing has been discussed largely as a voluntary time-limited mechanism to provide opportunity for informed public discussion and decision-making about a range of individual and societal issues. While some commentators appear to support a moratorium that could be lifted if technical benchmarks were met, others advocate more broadly that preconditions must include satisfaction of societal and regulatory concerns and/or public engagement and empowerment criteria. The measure of how such concerns would be met is not always identified.

## 4.6 Accreditation, registration or licensing

75. In addition to regulating what can be done with human genome editing, governance can focus on who may do such editing, where it may be undertaken and how it will be monitored. An example of this in general medicine is the common approach to licensing medical practitioners, who are required to undergo training and demonstrate competence before being allowed to treat patients. Similarly, facilities may be required to meet conditions for staffing, hygiene and manufacturing practices. In the field of assisted reproduction, the United Kingdom's Human Fertilisation and Embryology Authority imposes conditions in this way, allowing it very close control over who may perform procedures and where. Monitoring is facilitated by requiring registration of people and facilities providing a service so that inspections can be done.

76. Registries of relevant activities can also be created. Such an effort already exists for clinical trials, where national and regional registries are indexed by WHO's International Clinical Trials Registry Platform. In the context of human genome editing, the WHO Registry, discussed in more detail in the Committee's recommendations, will make it possible to track and examine research entered in the Registry that involves human genome editing.

#### 4.7 National science and medicine societies and institutions

77. National science and medicine societies and institutions serve both as honour societies and as centres for evidence-based analysis of technologies and the development of recommendations for funding and regulation. They can also serve as organizers of public events aimed at bringing greater attention to a technology with a view to helping the field maintain a good network of professional connections and develop ethical norms, the violation of which may result in justified condemnation. Recent examples of professional norm-setting in the field of human genome editing include the following actions.

- a. The 2015 international summit hosted by the Chinese Academy of Sciences, the United Kingdom Royal Society and the United States National Academies of Medicine and of Science, and the 2018 international summit hosted by the Academy of Science of Hong Kong, the United Kingdom Royal Society and the United States National Academies of Medicine and of Science, which explored both scientific developments as well as the ethical and societal impact of human genome editing;
- b. The founding in 2018 of the Association for Responsible Research and Innovation in Genome Editing (ARRIGE), which is open to a broad membership beyond scientists and health professionals, and which hosts active online information exchange and face-to-face meetings;
- c. The 2018 Statement on Germline Gene Editing Practices by the American Society of Gene and Cell Therapy, which advocates for responsible use of gene and cell-based technology and organizes events that address heritable human genome editing and other issues related to its responsible and ethical use; and
- d. The Genome Editing Technology in Medical Sciences and Clinical Applications in Japan recommendation, issued in 2017 by the Science Council of Japan, which is the representative organization of all fields of the scientific community in Japan.

#### 4.8 Patents and licences

78. Patents and licences may be an avenue for a form of governance, by directing research investment towards certain areas, as well as by allowing patent holders to limit or even prohibit a particular use of a process or product.

79. A patent is a property right granted by a sovereign authority to an inventor for a new product or process. In exchange for publicly sharing details of the design, so that others may build on the knowledge underlying the invention, the inventor is granted a period of exclusive rights to the patented invention. The inventor may make use of the invention or may grant a licence to others, usually for a fee, to let them make use of it. Licences can be exclusive, that is, only one party is granted a licence, or can be non-exclusive, allowing a wider range of actors to access the invention.



80. The system has multiple effects.<sup>36</sup> The prospect of a period of time in which an inventor can maximize returns on investment is an incentive for research and development, and has been shown to promote innovation. At the same time, however, patents can stifle innovation by denying others access to a crucial tool or element. Conflicts over competing claims for similar inventions or the need for an innovator to obtain licences for multiple underlying patented processes and products can also become an obstacle. Furthermore, overall, the patent system directs effort towards those activities that may develop into opportunities for profit. As such, patents, at times, govern by deferring to and deepening the influence of the market in determining which scientific questions get asked and investigated, and what knowledge gets shared or hidden. This can suppress or prevent equitable use of new technology as when innovations of primary benefit to communities that cannot afford to pay high prices go underexplored by inventors, or may not attract potential licencees. On occasion, governmental action is required to correct patent inequity and injustice.
81. During the period of exclusive rights, the inventor may grant others a licence to use the invention. Such a licence can contain conditions on how a licensee may use the invention. It is in these conditions that a patent holder may impose restrictions on use that amount to a form of governance. For example, in the 1990s, an individual tried to patent a so-called humanzee (a chimeric animal made from human and chimpanzee embryos) solely for the purpose of having the power to refuse all licensing, thus preventing anyone from making one. Having an exclusive right to the invention and then refusing to license it to anyone, would have made it illegal – in any country that recognized and enforced this patent – for anyone to make the patented product or use the patented process. In practice, if the patent is globally recognized, this becomes a form of global prohibition, solely at the discretion of one person.<sup>37</sup>
82. Another example from the 1990s can be found in the use of embryonic stem cell lines. A patent owner, the Wisconsin Alumni Research Foundation, held consultations about whether to write restrictions into its licensing agreements that would forbid the use of the patented stem cell lines for research involving reproductive cloning or the development of human–nonhuman chimeras. As above, such a condition written into licence agreements could become in reality a ban on such efforts, if enforced globally. However, such conditions can also be used to ensure that research uses conform to the limits specified in the consent documents used when first obtaining the biological materials needed to make the stem cell lines.<sup>38</sup>
83. These considerations are relevant to genome editing, which is the subject of numerous patents. Two examples of interest are the 2018 filing on human gene correction (methods “for correcting a mutant allele of a gene of interest” including in human embryos)<sup>39</sup> and the 2020 filing for gene editing to correct aneuploidies and frame shift mutations (editing embryos to remove the extra chromosome associated with Down syndrome).<sup>40</sup> Whether any or all of these uses would be sufficiently safe and effective to be permitted for clinical use, or acceptable according to the mores and policies of a particular country, remains in the realm of national law. But such patents, if granted, can place the patent holders in a position of considerable influence with respect to whether particular uses would be legally permissible, even if meeting relevant regulatory standards, at least in those countries recognizing the underlying patent.

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36 National Research Council of the National Academies. *Patents in the knowledge-based economy*. Washington, DC: National Academies Press; 2003.

37 <https://www.sciencemag.org/news/1999/06/legal-fight-over-patents-life> (accessed 27 May 2021).

38 Streiffer R. Informed consent and federal funding for stem cell research. *Hastings Cent Rep*. 2008;38(3):40–7. <https://doi.org/10.1353/hcr.0.0013>

39 <https://patentscope.wipo.int/search/en/detail.jsf?docId=US323259958&tab=NATIONALBIBLIO> (accessed 27 May 2021).

40 <https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2021072361> (accessed 27 May 2021).

84. Countries are, of course, free to construct their own patent rules and, in some countries, patents will not be granted for developments such as embryonic stem cell lines or genetically manipulated embryos, for a variety of reasons related to local understandings of morality and the public good.<sup>41</sup> But where an invention is patentable, the invention is fundamental to the field, and the patent is defended against encroachment, patent holders may find themselves with a reasonable amount of influence over how a technology develops, by choosing whether to write in restrictions on particular uses when negotiating a licence. This is an efficient method compared with legislative efforts to outline restrictions, which are often slow and usually need to proceed separately in every country. On the other hand, it is certainly not democratic, as the choice of whether to include restrictions is not made by the body politic.

## 4.9 Professional self-regulation

85. Professional self-regulation can be an effective way to hold scientists accountable to their peers when formal policy found in legislation, regulation or judicial decisions does not address potential uses of a technology. The prospect of becoming an outcast among one's peers – if one transgresses generally accepted scientific or medical boundaries, or established ethical norms, in an intolerable way – may thus function as an important deterrent to improper, hasty conduct. Professional self-regulation may be undertaken by specific committees made up entirely of those actively pursuing research and patient care and fail to include values and views of the larger society, or it can include social scientists, ethicists, lawyers and clergy. Self-regulation processes may also include representatives of patient groups, public interest groups, self-styled advocacy organizations and civil society. The quality of professional self-regulation and the degree of public confidence in its contribution to good governance is enhanced by broader consultations.

86. Professional guidelines, rules and regulations, as well as certification and best practices for facilities management, recruitment of research participants and treatment of patients (Box 5) can be useful resources or reference points if lawmakers draft legislation and regulations. This has been the case in the field of stem cell research, in which guidelines produced by a committee of the United States National Academies of Sciences, Engineering and Medicine were a powerful influence on the legal conditions later developed for federal funding of this research in the United States. In addition, guidelines prepared by the International Society for Stem Cell Research have strongly influenced national and international policies and regulations.

### Box 5.

#### Examples of professional societies and organizations with guidelines on human genome editing

American Society of Human Genetics  
American Society for Reproductive Medicine  
European Society of Human Genetics  
European Society of Human Reproduction and Embryology  
International Society for Stem Cell Research  
Japan Society of Human Genetics

41 <https://www.californialawreview.org/print/morality-consideration-at-patent-office/> (accessed 30 May 2021).

87. The processes for amending professional guidelines can be less difficult than those for amending legislation and regulations. Professional guidelines, rules and regulations, as with other forms of so-called soft law (meaning authoritative norms with the effect but not the status of law), can more easily be revised in response to a rapidly evolving area of science. The ease with which guidelines can be changed is seen as a benefit by some and is a matter of concern for others, especially those who worry that professional self-regulation is a means to avoid legislative initiatives that might be overly restrictive.
88. With professional self-regulation, potential conflicts of interest exist: those setting best practices may have a self-interest in pursuing the research or treatment; those responsible for the regulation of best practices may not take sufficiently rigorous action against those who violate established standards because of professional solidarity or corresponding interests.

#### **4.10 Public advocacy and activism**

89. Patient groups (organized on the basis of common experience with a particular disease that might be amenable to treatment or prevention with human genome editing), public interest groups (organized around religious, spiritual or historical identities associated with particular value systems that support or resist some applications of human genome editing), self-styled advocacy organizations and civil society (organized around common concerns about the direction of science and its impact on society) are voices that should be part of the debate and the process of policy formation, whether through participation in regulatory rulemaking or voting in elections for legislative and executive branch representatives. Through their advocacy and activism, these groups have influenced the research agenda and shaped science policy and science funding. It is important that these influences also be part of the policy-making that governs human genome editing research. Beyond formal opportunities available in democracies, the activities commonly undertaken by these groups include expression of viewpoints through lobbying, distribution of educational materials, participation in conferences and publication in news media, social media and other available forums. Funding for these groups varies considerably. In some cases, funding is provided by those pursuing human genome editing research. In other cases, funding is provided by philanthropic sources or popular campaigns. Transparency of funding is an important element of good governance.
90. In addition, some interest groups are made up of citizen scientists, do-it-yourself biologists, futurists, transhumanists, biohackers, artists or philanthropists, each with some interest and capacity for entering the general public debate and the government policy-making arena in order to express views on whether, and if so how, human genome editing technology should be developed. Also influencing public attitudes, although often without the intent to explicitly engage in policy debate, are the creative artists such as science fiction writers, who find in the possible applications of genetic technologies a rich setting for developing stories about the transformations these technologies may cause in the fabric of social life. Films such as *Gattaca* and *Jurassic Park*, television series such as *Star Trek*, or novels such as *Frankenstein* and *Brave New World* can have a profound influence on the wider public's instinctive reaction to news of new technological developments and possible applications of human genome editing.

#### **4.11 Research ethics guidelines and research ethics review**

91. In addition to government regulation and professional self-regulation, existing ethics systems can play an important complementary role in good governance of human genome editing. This can involve both operational guidelines to help shape good practice and associated review bodies to ensure that good practices are implemented in research design and execution.

92. Research ethics guidelines may be more readily amended than government legislation and regulation, thus helping to keep pace with technical, cultural and societal developments. Research ethics guidelines are particularly capable of benefitting from community investment and ownership through community engagement (specifically noted in Guideline 7 of the International Ethical Guidelines for Health-related Research Involving Humans<sup>42</sup>). Community engagement can meaningfully enhance understanding of the potential harms and benefits of human genome editing as different communities may be affected differently.
93. Research ethics efforts may be institutional or national, but they may also be international. They can address a broad range of issues or focus in on a specific topic. For example: acting as a clearing house for ethical and policy responses; tracking and analysing important conceptual developments, tensions and emerging areas of consensus; serving as a vehicle for convening periodic meetings; and instigating international discussion informed by insights drawn from data collection and analysis. The Committee identified the Global Observatory for Genome Editing as one such effort.<sup>43</sup>
94. Many countries ensure independent research ethics review of protocols by creating local, regional or national research ethics oversight boards. With human genome editing, however, which is both relatively new and rapidly evolving, some discussion has arisen about the need to create centralized research ethics review bodies with deeper expertise in the science or centralized forums for exchange of information and debate about possible uses of human genome editing. In the past, the United States National Institutes of Health Recombinant DNA Advisory Committee performed both of these functions in the United States for federally funded work and, when asked, also for other recombinant DNA clinical trials. The United Kingdom has both regional ethics committees and centralized specialized research ethics review bodies, such as the Medicines and Healthcare Products Regulatory Agency and the Human Fertilisation and Embryology Authority. These bodies have, or may co-opt, the necessary expertise. Approval is generally required from both the ethics committee and the regulator.

#### 4.12 Collaboration with publishers and conference organizers

95. Journal editors can influence ethical norms by insisting on compliance with applicable law and professional standards as a precondition for publication. This practice has already been adopted by leading journals for clinical trial registration, standards for research on animals (the ARRIVE guidelines),<sup>44</sup> and stem cell-based research and applications disseminated by the International Society for Stem Cell Research (ISSCR)<sup>45</sup>. Authors typically must provide documentation of compliance, in line with recommendations of the International Committee of Medical Journal Editors<sup>46</sup>. Adherence to these recommendations is also one of the means used to address concerns about publications that present dual-use dilemmas, that is, where applications of the science of human genome editing may raise concerns about biosafety and biosecurity.
96. Results and conclusions from human genome editing can also be disseminated in other ways, for example, preprint platforms such as bioRxiv, and publication by press release or conference presentation. It has become increasingly common for preprint servers to use automated screening to identify ethics issues that might require expert review. There are also external efforts to address ethics issues, such as PubPeer<sup>47</sup> and Retraction Watch.<sup>48</sup>

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42 International ethical guidelines for health-related research involving humans. Fourth edition. Geneva: Council for International Organizations of Medical Sciences (CIOMS); 2016 (<https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf>, accessed 27 May 2021).

43 <https://global-observatory.org/> (accessed 1 May 2021).

44 <https://arriveguidelines.org/> (accessed 1 May 2021).

45 <https://www.isscr.org/> (accessed 27 May 2021).

46 <http://www.icmje.org/recommendations/> (accessed 27 May 2021).

47 <https://pubpeer.com/> (accessed 1 May 2021).

48 <https://retractionwatch.com/> (accessed 1 May 2021).

97. It is difficult and even undesirable to control what is said during conference presentations, as long as it is clear that such presentations have not been subject to any form of verification.
98. For human genome editing, requiring documentation of compliance with applicable laws, regulations, ethics guidelines and accepted professional standards would help deter non-compliant research by researchers interested in recognition from peers.

#### **4.13 Education and training of researchers and clinicians**

99. Ethics education and training is already part of the medical school curriculum in many countries, but its content and depth vary widely. For graduate training in fields for which human genome editing will become a commonly used tool and for medical specialties that may eventually use human genome editing, adding modules on research integrity and ethics relevant to human genome editing is a means to encourage a culture of responsibility and create shared norms concerning contested uses, such as heritable modifications, aesthetic enhancement or use in competitive sports. Modules might include information on different national policies, history of genetics research and engineering, updates on gene transfer research and gene therapy, and a survey of appropriate areas of bioethics, philosophy, law, sociology and science and technology studies. Such modules would supplement, not replace, basic training in the ethics of clinical trials and clinical care, and the safe conduct of basic research.
100. Training in best practices of public education, engagement and empowerment, and how to interact with the media would also be of benefit. This knowledge can help facilitate understanding between scientists and the public, particularly to understand the needs of the public. It can also help to lessen concerns over new technology and reduce exaggerated promotional assertions, which can greatly distort public perceptions and expectations about human genome editing.

# Part 5.

## Scenarios

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101. These scenarios are intended to show how the various elements discussed in this governance framework come together in practice. They illustrate the types of practical challenges that might be encountered in the future when implementing good governance for human genome editing research. Many of the issues raised in the scenarios are cross-cutting; that is they could also apply to other scenarios.
102. Each scenario explores a different aspect of good governance. It begins with a short description of a possible future event. Components from the governance framework are then identified, including the values, principles and questions to be considered when developing oversight measures (discussed in Part 3) and potentially useful tools, institutions and processes (discussed in Part 4).
103. The Committee explored the following range of scenarios.
- Different time horizons. Some of the events described have already occurred since the Committee began to work on these scenarios. Others are not expected to be realized in the near term.
  - Different levels of likelihood. Some of the events described are already the subject of research. Others are much more speculative.
  - Different degrees of support from within the Committee. Some of the scenarios represent a shared view of possible future events. Other scenarios do not.

The Committee wishes to stress that it does not necessarily endorse any of the uses of human genome editing explored in the scenarios.

## 5.1 Scenario 1. Somatic human genome editing: clinical trials for sickle-cell disease<sup>49</sup>

*An international research team wants to begin a clinical trial of somatic human genome editing for sickle-cell disease. Such a trial could be very important, given its potential to cure the condition. Proponents of the trial argue that, if successful, it would totally change the future of sickle-cell disease. The research team is located in a high-income country with citizens originally from sub-Saharan Africa, India and the Middle East. Because the condition is most prevalent in West Africa, the team proposes to do the research there. Due to resource limitations, patients in West Africa generally only receive the standard hydroxyurea therapy when available, and often are not supported and managed through specialist clinics as would be the case in other parts of the world. If the somatic human genome editing trial for sickle-cell disease is successful, and safe and effective therapies become available, it is expected that these will be affordable primarily in high-income countries and will be too expensive for all but the wealthiest individuals in the country where the research will be conducted. Proponents of the proposed research argue that this will change over time and somatic human gene editing treatments may become more widely available in the future.*

104. This scenario highlights the following issues.

- a. **Good practices in international research collaborations and clinical trials** (*ethical values and principles: openness, transparency, honesty and accountability; responsible stewardship of science; inclusiveness*). Reasonable efforts should be made to ensure collaborative codevelopment of solutions. For example, it may be desirable to recruit local clinicians as coinvestigators in these trials, in which case local capacity to undertake such research would be part of the trial design. A successful clinical trial for West Africans, by West Africans, and for a disease that disproportionately affects them might be a notable source of pride.
- b. **Regulatory capacity** (*ethical values and principles: responsible regulatory stewardship*). If clinical trials for somatic human genome editing are conducted in resource-constrained settings, it will be important to ensure that appropriate regulatory frameworks are in place to oversee the research. An important question to resolve is how best to address current gaps in regulatory capacity so that these do not become barriers to the adoption of new technologies.
- c. **Competing approaches to providing a public health response** (*ethical values and principles: responsible stewardship of research resources*). Should health systems in resource-poor countries concentrate on improving the standard of care for sickle-cell disease instead of investing in technology that ultimately may not be available locally? For example, are resources better spent on newer drugs, blood exchange and apheresis equipment, access to bone marrow or stem cell transplantation and improving blood supply safety?
- d. **Patient access** (*ethical values and principles: fairness; social justice; global health justice*). The potential benefits and risks for resource-poor countries in participating in such trials must be clearly explained. For example, one potential benefit could be that research participants receive privileged access to a successful genome editing therapy once it has been approved. Alternatively, the clinical trials could take place in a high-income country which has citizens with sickle-cell disease. The therapy could be made available to the resource-poor country after it has been tried, tested and made affordable in the high-income country.
- e. **Standard of care** (*ethical values and principles: solidarity*). Research participants who are randomized to the control arm should be provided with global standard of care. The emerging consensus is that local resource limitations are no excuse for using a local standard of care if the clinical trial funder comes from a high-income country.

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<sup>49</sup> Since the Committee developed this scenario, the Food and Drug Administration in the United States has approved a clinical trial on somatic human genome editing for sickle-cell disease, see, for example: <https://news.berkeley.edu/2021/03/30/fda-approves-first-test-of-crispr-to-correct-genetic-defect-causing-sickle-cell-disease/> (accessed 1 May 2021).

105. The following questions should be considered when developing oversight measures (other questions may also arise).
- a. If the existing oversight measures are not adequate, are there plans to create new oversight measures or to rely on regulatory review and approvals from an external body? If so, which external body(ies)? (Part 3: paragraph 29(l)).
  - b. Do questions of equitable access to research participation, as well as safe and effective treatment across domestic populations and communities, inform individual decisions on a particular proposal? (Part 3: paragraph 29(n)).
  - c. How will the cost of clinical trials and therapies be shared among research participants, researchers, funders, clinicians, insurers and third-party (private and public) sources? (Part 3: paragraph 29(o)).
  - d. Does the country have the political, technical and economic capacity to fully implement its preferred governance measures? (Part 3: paragraph 29(p)).
  - e. Will transnational collaboration on preclinical and clinical research be permitted when procedural and substantive standards differ in other countries? If so, what limits, if any, will be placed on such collaborations? Will this affect the researchers and clinicians, including their mobility between jurisdictions and prospects for employment or promotion? (Part 3: paragraph 29(q)).
  - f. Will clinical research on somatic human genome editing fit within existing oversight measures for research involving humans? If using existing oversight measures, do they need specific amendments to cover somatic human genome editing? (Part 3.1.1: paragraph 39(b)).
  - g. Is there adequate capacity to manage the technical review of proposals for clinical research on somatic human genome editing and to follow up on results? (Part 3.1.1: paragraph 39(c)).
  - h. What medical, legal and financial assistance (and possibly compensation) will be available to individuals who are harmed as a result of research participation? (Part 3.1.1: paragraph 39(d)).
  - i. Are there domestic rules in place regarding researchers who go to another country to perform research that would be illegal or unethical in their home country? If so, what are they? If not, are there plans to develop any? (Part 3: paragraph 31(c)).
  - j. If there are no plans to regulate research on human genome editing, are there plans to regulate foreign researchers travelling from other countries to conduct such research? (Part 3: paragraph 31(f)).
106. Governance tools, institutions and processes.
- a. **Declarations, treaties, conventions, legislation and regulations** (Part 4.1). Countries approached to host the clinical trials should have policies (legislation, regulations and guidelines) in place before allowing the trials to take place. Countries with advanced research and development pipelines likely to be involved in international clinical trials should ensure that researchers and clinicians working in their jurisdictions meet the same standards when working abroad as they would domestically. Countries that do not have policies governing human genome editing research and who wish to participate in such research should develop relevant legislation, regulations and guidelines.
  - b. **Conditions on research funding** (Part 4.4). The funder of the clinical trials should require oversight measures, such as compliance with a specific code of conduct or reviews by appropriate ethics committees.
  - c. **Professional self-regulation** (Part 4.9). The professional bodies of researchers and clinicians conducting the clinical trials might review their codes of conduct to ensure that their members are following best practices and acting ethically regardless of where they work.



- d. **Public advocacy and activism** (Part 4.10). The patient groups representing those likely to be taking part in the trials should be actively engaged and involved in designing and implementing the clinical trials. Furthermore, public debate in West Africa as to the desirability, implications and accessibility of resulting treatments would be important.
- e. **Research ethics guidelines and research ethics review** (Part 4.11). Existing ethical guidelines could be important for overseeing the clinical trials and ensuring good practice is being followed. This might include following international guidance and professional standards. Existing networks of bioethics committees in West Africa, and Africa more broadly could also be used.
- f. **Education and training of researchers and clinicians** (Part 4.13). The training courses used to prepare researchers and clinicians to conduct such trials might also be reviewed. This review would help to ensure they were aware of existing good practices, sources of support and further information, as well as the professional and personal potential benefits and risks of being involved in such work.

## 5.2 Scenario 2. Somatic human genome editing: clinical trials for Huntington disease

*Researchers are interested in somatic human genome editing as a possible future treatment for Huntington disease, a late-onset condition. This will involve in vivo gene editing of a difficult to access organ: the brain. Because it would take years to determine if an edit was successful in slowing or preventing onset, the researchers propose using surrogate markers as endpoints. A clinical trial's endpoints measure the outcomes in the trial. Clinical outcomes directly measure whether people in a trial feel or function better, or live longer. The benefit or likely benefit of a therapy, as measured by clinical outcomes (for example, improvement in symptoms), is assessed to determine whether it outweighs any adverse effects. Surrogate endpoints may be used instead of clinical outcomes in some clinical trials. For example, surrogate endpoints are used when the clinical outcomes, such as determining whether a disease that affects people late in life has been prevented or delayed, might take a very long time to study. Surrogate endpoints, which may have come from preclinical research on animal models or correlation studies in patients, may be molecular, histological, radiographic or physiological biomarkers that are expected to correlate with longer-term clinical outcomes.*

107. This scenario highlights the following issues.

- a. **Use of surrogate endpoints in somatic human genome editing trials** (*ethical values and principles: openness, transparency, honesty and accountability; responsible regulatory stewardship*). Many of the potential benefits of somatic cell gene therapies can and should be measured over the patient's entire lifetime because a defining advantage of such therapies is that they are potentially curative, or at least durable with few doses. However, in the interest of providing timely access to patients with few treatment options, regulatory bodies should consider appropriate surrogate endpoints when evaluating the durability and performance of a potential genome editing therapy in the necessarily compressed time frame of clinical trials. It will be important to consider how well surrogate endpoints correlate with and are validated against longer-term clinical outcomes.
- b. **Balancing potential harms and potential benefits** (*ethical values and principles: responsible stewardship of science*). The trial design including the number of research participants will have to be meticulously thought out to answer the question of efficacy while addressing the potential harms, which may not manifest until much later. It will also be important to address the likely psychological effects of long-term uncertainty in terms of potential harms and potential benefits.

- c. **Importance of long-term follow-up** (*ethical values and principles*: responsible stewardship of science). Especially when surrogate endpoint measurements indicate a case for approval, it is important that measures are put in place to facilitate long-term follow-up and confirmation of durability. Surrogate endpoints for adverse events may also be difficult to detect, thereby strengthening the need for long-term follow-up of trial participants.
- d. **Existence of conditions for which somatic human genome editing may be the only option** (*ethical values and principles*: responsible stewardship of research resources; equal moral worth). When there are no effective treatments, somatic human genome editing may be desirable, even if resource intensive.
- e. **Need to consider longer-term implications** (*ethical values and principles*: caution). If adverse events occur, especially if they occur much later, this may affect the harm–benefit analysis of the trial. It may be impossible to reverse the trial or to stop it in a timely manner.

108. The following questions should be considered when developing oversight measures (other questions may also arise).

- a. What are the public health and health economic implications, considering the costs of both action and inaction? (Part 3: paragraph 29(i)).
- b. How will the cost of clinical trials and therapies be shared as among research participants, researchers, funders, clinicians, insurers, and third-party (private and public) sources? (Part 3: paragraph 29(o)).
- c. What limitations beyond safety and efficacy for research participants (if any) will be placed on postnatal somatic human genome editing research? (Part 3.1.1: paragraph 39(a)).
- d. Will clinical research on somatic human genome editing fit within existing oversight measures for research involving humans? If using existing oversight measures, do they need specific amendments to cover somatic human genome editing? (Part 3.1.1: paragraph 39(b)).
- e. How will decisions be made regarding approval and postapproval access to clinical care involving somatic human genome editing? What technical standards for safety and efficacy will be adopted? (Part 3.1.2: paragraph 40(a)(i)).
- f. Are there opportunities for patient groups, public interest groups, advocacy organizations and civil society to influence the research agenda? If so, in what way? (Part 3: paragraph 30(b)).

109. Governance tools, institutions and processes.

- a. **Declarations, treaties, conventions, legislation and regulations** (Part 4.1). Regulations should require a plan for long-term follow-up as a condition of research ethics approval and provide a mechanism for withdrawing approval if the plan is not followed.
- b. **Professional self-regulation** (Part 4.9). Professional codes and standards of practice already stress a need for a solid evidence base. Professional bodies can also play an important role in ensuring a meticulous assessment of the burden and impact of disease and the potential for benefit from somatic human genome editing. This assessment will in turn inform decisions on whether such trials should go ahead. There needs to be in-depth analysis of the therapeutic options for Huntington disease.

- c. **Public advocacy and activism** (Part 4.10). Close interaction and liaison with patient associations and advocacy groups is extremely important in such rare but life-threatening diseases. Governance will need to be aware that individuals may request access to treatment, especially if there are no viable therapeutic alternatives. Working closely with patients and advocacy groups will enable health systems to better understand the disease burden and disease impact on these individuals.

### 5.3 Scenario 3. Somatic human genome editing: unscrupulous entrepreneurs and clinics

*Somatic human genome editing has entered clinical trials for a limited number of diseases. Advertisements have appeared on the internet for clinics offering what are claimed to be somatic genome editing therapies for a number of conditions. The clinics offering these services are not connected to the clinical trials. They can, however, offer their services globally. They provide little or no evidence to support the safety or efficacy of the services they are offering. They are offering hope to those without alternative interventions. There may also be unintended health consequences from the so-called therapies being marketed, for example, increased risk of tumour formation or other unwanted side-effects.*

110. This scenario highlights the following issues.

- a. **Clinics promoting unproven cellular therapies may add somatic human genome editing to their list of services** (*ethical values and principles*: openness, transparency, honesty and accountability). Unscrupulous clinics offering unproven somatic human genome editing are a threat to vulnerable patients. They also jeopardize legitimate efforts by researchers and clinicians to pursue ground-breaking treatments. These clinics have the potential to undermine the ethical, safe and responsible use of somatic human genome editing.
- b. **Fake news is not restricted to the world of politics** (*ethical values and principles*: openness, transparency, honesty and accountability). False, unsubstantiated claims about the safety and efficacy of unproven somatic human genome editing will be increasingly hard to control. Strong legislation and regulation can help, as can working with professional bodies and patient associations to ensure reputable information sources are available. Equally, technology platforms and social media companies are increasingly active in identifying and acting on inaccurate information, especially where it could lead to harm.
- c. **Gaps in regulatory oversight are likely to be exploited by unscrupulous entrepreneurs and clinics** (*ethical values and principles*: responsible regulatory stewardship). Some countries may lack the necessary laws, regulations or guidelines, capacity for oversight, or means to enforce rules to prevent unproven therapies being offered to the public. Difficulties may include, for example, lack of personnel, lack of awareness or training, understaffed or under-equipped forensic laboratories and budgetary restrictions. The costs to government to investigate malfeasance may be disproportionately high when compared to the penalties imposed on clinics or people guilty of bad practices and the perceived danger to society. As a result, preventing unscrupulous clinics offering unproven therapies might not be prioritized, especially in countries where there are other pressing resource needs. Ideally, a harmonized global regulatory system would prevent gaps in rules and enforcement capabilities from existing or being exploited, however this may be impractical.
- d. **Value of differentiating between proven and unproven therapies** (*ethical values and principles*: responsible stewardship of science). Therapies that have undergone robust clinical trials and regulatory review will have a strong evidence base to demonstrate their safety and efficacy. Unproven therapies may show promise but have yet to be substantiated or validated. In the absence of a strong national regulator to differentiate between the two, other trusted sources of advice (for example, relevant professional societies or respected organizations such as Genetic Alliance) on which therapies have been proven, and which have not, may be useful.

- e. **Ability to advertise and deliver products and services directly to consumers** (*ethical values and principles*: caution; respect for persons). While governments have traditionally been able to regulate access to treatments, the internet allows potential customers to be directly targeted with placebos, defective or low-quality devices and the unsupervised and/or illegal sale of prescription-only medicines, dangerous chemicals or prohibited or highly regulated substances. It is likely that genome editing will also be affected by this phenomenon, for example, by the online promotion of counterfeited or falsified genome editing kits as a cure for a number of ailments, as well as for cosmetic use or enhanced performance.
111. The following questions should be considered when developing oversight measures (other questions may also arise).
- a. Should oversight measures lean toward caution (no use of the technology until approved by regulators or other authorities) or promotion (use of the technology permitted unless prohibited or otherwise limited by regulators or other authorities)? (Part 3: paragraph 29(g)).
  - b. What are the primary mechanisms to implement oversight measures, for example, legislation or executive decree, government regulation or conditions on government funding? (Part 3: paragraph 29(h)).
  - c. If the existing oversight measures are not adequate, are there plans to create new oversight measures or to rely on regulatory review and approvals from an external body? If so, which external body(ies)? (Part 3: paragraph 29(l)).
  - d. If developing new oversight measures, how will these measures be coordinated with or embedded in other regulatory bodies in the country? (Part 3: 29(m)).
  - e. Does the country have the political, technical and financial capacity to fully implement its preferred oversight measures? (Part 3: paragraph 29(p)).
  - f. How will decisions be made regarding approval and postapproval access to clinical care involving somatic human genome editing? What technical standards for safety and efficacy will be adopted? What limits, if any, will be placed on particular uses, patient populations or professional providers? (Part 3.1.2: paragraph 40(a) (i) and (ii)).
  - g. What role could be played by liability insurers, health care coverage rules, research funders, clinics, professional licensing societies and medical journals? (Part 3.1.2: paragraph 40(b)).
  - h. Are there domestic rules in place regarding researchers who go to another country to pursue human genome editing research that would be illegal or unethical in their home country? If so, what are they? If not, are there plans to develop any? (Part 3: paragraph 31(c)).
  - i. Are there plans to welcome or discourage people from other countries travelling to access human genome editing clinical trials or so-called therapies? (Part 3: paragraph 31(e)).
112. Governance tools, institutions and processes.
- a. **Declarations, treaties, conventions, legislation and regulations** (Part 4.1). In many cases, local and regional enforcement mechanisms are already in place, but sufficient resources must be provided to facilitate enforcement. A whistleblowing mechanism may be appropriate, but should be set up with great care, allowing for an appropriate appeal process to prevent misuse. In other cases, capacity-building may be needed. In some countries, dealing with unscrupulous entrepreneurs and clinics may not be seen as a priority, especially given competing demands on resources. Some degree of international harmonization of regulations may be required to support the development of evidence-based therapies and prevent clinics

selling unproven genome editing or cell-based treatments from moving among jurisdictions. Regulators could also strengthen scientific understanding of the potential benefits and risks of genome editing or cell-based interventions. This could help clarify the path researchers must follow in moving from unproven to proven therapies for interventions that show promise. This might also help reduce incentives for the premature introduction of new therapeutic interventions.

- b. **Judicial rulings** (Part 4.2). Successful prosecution of unscrupulous behaviour of entrepreneurs and clinics providing unproven unauthorized genome editing services can be an effective deterrent for clinics considering offering similar services. It might also strengthen professional norms against such behaviour. Judicial rulings could also encourage responsible reporting and discourage entrepreneurs and clinics from making deceptive advertising claims.
- c. **Accreditation, registration or licensing** (Part 4.6). Formal accreditation and certification schemes could be important for distinguishing legitimate health care providers from clinics with unscrupulous practices. Standards for accreditation or registration might also help provide accurate information to patients and help to promote and publicize good practices. Accredited clinics could also be actively involved in identifying and exposing unscrupulous entrepreneurs and clinics. They might also support and assist regulatory bodies, where they exist, in similar efforts. In practice it is important that different governance actions do not conflict with each other. This is particularly relevant to potential unintended consequences of private and corporate governance tools; for example, licensing tools with special conditions may result in conduct that is discriminatory, contrary to competition and antitrust rules or unnecessarily hinders valid and ethically approved research.
- d. **Public advocacy and activism** (Part 4.10). Collaboration and communication among all those with an interest in the safe and responsible use of somatic human genome editing is crucial to ensuring that the public is well informed about these practices. It is important to empower patients, families and caregivers by providing accurate and helpful information. Informed choice depends on access to accurate information and proper guidance from the scientific and medical community. Professional engagement of societies and charitable organizations supporting patients with specific diseases can be helpful as they are often central to patient advocacy and providing information and advice to patient communities across countries and languages.

## 5.4 Scenario 4. Somatic human genome editing and epigenetic editing to enhance athletic ability

*Athletes have been showing interest in the use of somatic human genome editing to increase muscle strength. Epigenetic editing may also offer the potential to increase an individual's performance within the bounds of natural variation. In both cases, this application of somatic human genome editing or epigenetic editing is not intended for health or quality of life but rather to enhance athletic ability.*

113. This scenario highlights the following issues.

- a. **Motivations other than health may drive somatic human genome editing or epigenetic editing** (*ethical values and principles*: openness, transparency, honesty and accountability; caution; respect for persons). The top tiers of many sports offer personal and financial rewards. Indeed, excellence in sport has provided some individuals with a clear path to success. Personal, professional, societal and financial incentives may encourage individuals to make use of any competitive advantage, including through the use of somatic human genome editing or epigenetic editing. In addition, sport is often closely connected to national pride and prestige. This may provide additional incentives for governments and national sports organizations to

pursue somatic human genome editing or epigenetic editing. In many countries, competitive sport is well financed; it has the potential to fund its own research and development initiatives. In this way, it may be possible to sidestep oversight systems that only govern public research funds.

- b. **Tolerance of adverse events** (*ethical values and principles*: responsible stewardship of science; caution). When using somatic human genome editing or epigenetic editing to address disease, there may be a greater tolerance of possible adverse events than when such editing is used for the purpose of enhancement. It will be important to consider the overall, or net, potential benefit and risk profile when determining how and why human genome editing might be used. In the case of enhancing athletic ability, the human system is so finely tuned that it is likely that the ability to run faster or be stronger or more agile would also have its disadvantages – for example, does this enhanced muscle have the same life span; if one enhances power, does that lead to a reduction in fine balance and precision movements?
- c. **Natural variation** (*ethical values and principles*: inclusiveness; non-discrimination). Humans are inherently different. Some people are stronger or have a greater innate athletic ability than others. Would the use of somatic human genome editing or epigenetic editing, if limited to within natural human variation, pose the same ethical challenges as efforts to go beyond natural variation? Would we be able to detect efforts to increase athletic ability if they remained within the limits of natural variation? What would that mean for competitive sport? Do religious, cultural and societal values and beliefs come into play?

114. The following questions should be considered when developing oversight measures (other questions may also arise).

- a. How should somatic human genome editing technologies and epigenetic editing be used – what are the rationale, objectives and anticipated consequences? (Part 3: paragraph 29(b)).
- b. How will the values and principles specific to somatic human genome editing and epigenetic editing be considered? (Part 3: paragraph 29(d)).
- c. What are the primary mechanisms to implement oversight measures, for example, legislation or executive decree, government regulation or conditions on government funding? (Part 3: 29(h)).
- d. How will distinctions be drawn between disease and disability prevention, and therapy? How will enhancement be defined; for example, will this be the introduction of traits that are beyond ordinary human capacity and health? Or, will this be the introduction of traits beyond those usually present in the human species? (Part 3.5.1: paragraph 55(b)).
- e. Will the rules differentiate between prophylactic, therapeutic and enhancement uses, or is each proposal reviewed solely on its individual risks and possible benefits?
- f. If such distinctions will be made, are there existing rules about how to evaluate technologies used to enhance rather than to prevent or treat disease and disability?
- g. Will questions of equitable access to research participation, as well as safe and effective treatment across domestic populations and communities, affect whether an individual will be able to use such editing for personal enhancement? (Part 3.5.1: paragraph 55(c)).

115. Governance tools, institutions and processes.

- a. **Declarations, treaties, conventions, legislation and regulations** (Part 4.1). Legislation, regulation and associated guidance could be updated to distinguish between treating a disease or preventing disease progression versus enhancement of what is considered normal. It may be necessary to explore how best to regulate human genome editing involving efforts to improve athletic ability. As noted earlier, international harmonization of legislative and regulatory frameworks may be desirable.
- b. **Ministerial decrees** (Part 4.2). Individual ministries may opt to make policies governing this use of human genome editing. For example, the sports ministry may choose to make a policy statement about the use of somatic human genome editing or epigenetic editing.
- c. **Conditions on research funding** (Part 4.4). Government may prohibit the use of research funds for enhancing athletic ability. Current health funding, for example, may be reviewed to ensure that it is used for health purposes, rather than for other purposes, such as improving athletic ability. It is possible that corporate or private funds may be used instead. This may require government to engage with non-traditional funders to explore possible benefits and risks, explain the principles behind the rules for health funding, and establish new norms and good practices in a wider range of fields.
- d. **Moratoria** (Part 4.5). There are global governing bodies for professional and elite sport. These bodies set standards of practice that incentivize or punish certain behaviours. They directly influence the potential desirability of the use of somatic human genome editing or epigenetic editing to improve athletic performance. These bodies may have already banned, or could opt to ban, their use in competitive sport.
- e. **Professional self-regulation** (Part 4.9). Professional bodies can help produce ethical guidelines. These guidelines can be reviewed by governments and regulatory bodies who can use them to develop legal frameworks and legislation, including punitive measures for those who break the rules. Such legal measures may, for example, effectively prohibit some researchers or clinicians from providing non-health applications of somatic human genome editing or epigenetic editing to improve athletic performance.
- f. **Public advocacy and activism** (Part 4.10). Wide-ranging public debate is needed on whether, how and why human genome editing is used. Fostering such a debate will need to involve many different interest groups and public influencers. Careful consideration may be necessary should the views held by those involved with setting and implementing policy differ from those of the general public.
- g. **Research ethics guidelines and research ethics review** (Part 4.11). It may be desirable to ensure that all somatic human genome editing or epigenetic editing falls under the jurisdiction of research ethics review committees.

## 5.5 Scenario 5. Heritable human genome editing (for reproduction)

*At an international meeting, a maverick researcher announces plans to use heritable human genome editing to alter the physical appearances of offspring, such as ensuring the absence of an epicanthic fold. The research is expected to progress through preclinical research phases before any attempt to transfer an edited embryo. The researcher has secured funding for some initial exploratory work from a private donor. They are actively seeking partners to provide more funding (hence the announcement). They have a very broad approval from their host institution and its ethics committee to work on reproductive technologies. Their plans are subsequently published in the popular scientific press and picked up more broadly in other forms of media. The researcher has stated that they are in compliance with national rules, will continue to work with national authorities and have altruistic motives.*

116. This scenario highlights the following issues.
- a. **Potential for unethical use** (*ethical values and principles*: openness, transparency, honesty and accountability; responsible stewardship of science; non-discrimination; equal moral worth). This scenario intentionally envisages highly ethically contentious uses of heritable human genome editing. Some such uses would increase inequality and discrimination as well as conflict with human rights.
  - b. **Potential to open the door to other types of research** (*ethical values and principles*: responsible regulatory stewardship; social justice; global health justice). This scenario raises questions on how best to control specific uses of heritable human genome editing. In many jurisdictions, approval of one form of clinical research allows other types of clinical research and additional uses to be introduced, sometimes at the discretion of individual researchers and clinicians. Careful consideration is needed in determining whether this is a door that should be opened.
  - c. **Differences in societal and cultural norms around the world** (*ethical values and principles*: respect for persons; solidarity). What is considered beneficial or altruistic in one community may be contrary to social norms in another depending on whether the focus is on collective benefits or individual rights. The development and potential use of heritable genome editing occur in a social context characterized by deep-rooted patterns of discrimination and injustice. As a result, societal pressures in some communities, for example, over the desirability of physical features common in other parts of the world, might motivate individuals to seek to make heritable changes in the physical appearance of their offspring.
117. The following questions should be considered when developing oversight measures (other questions may also arise).
- a. How should heritable human genome editing technologies be used – what are the rationale, objectives and anticipated consequences? (Part 3: paragraph 29(b)).
  - b. What are the interests of the public and how will they be served by this new and emerging technology? (Part 3: paragraph 29(c)).
  - c. How will the values and principles specific to heritable human genome editing be considered? Is there a means to revisit such values and principles over time? (Part 3: paragraph 29(d)(e)).
  - d. How would a lack of consensus on such values and principles be managed? (Part 3: paragraph 29(f)).
  - e. Will transnational collaboration on preclinical and clinical research on heritable human genome editing be permitted when procedural and substantive standards differ in other countries? If so, what limits, if any, will be placed on such collaborations? Will this affect the researchers, including their mobility between jurisdictions and prospects for employment or promotion? (Part 3: paragraph 29(q)).
  - f. Will clinical research on heritable human genome editing (that is, research that involves the transfer of edited gamete precursor cells, gametes, or embryos to a uterus with the aim of establishing a pregnancy) be permitted? (Part 3.3.2: paragraph 48(a)).
  - g. Are there any domestic policies or ethical rules and standards that govern heritable human genome editing research? If so, how are they enforced? (Part 3.3.2: paragraph 48(b)).
  - h. If the existing oversight measures for research involving human reproduction are not adequate, is there a plan to create new oversight measures or to rely on regulatory review and approvals from an external body? If so, which new measures or which external bodies? If developing new oversight measures, how will they be coordinated with other regulatory bodies? (Part 3.3.2: paragraph 48(c)(d)).



- i. Will domestic policy on heritable human genome editing for enhancement be different from domestic policy for somatic human genome editing for enhancement? (Part 3.3.2 paragraph 48(e)).
  - j. What capacity exists for long-term, possibly multigenerational follow-up on the health and safety of genetically modified offspring, and for monitoring possible effects on society as a whole? (Part 3.3.2: paragraph 48(a)(vii)).
  - k. Are there any domestic policies or ethical rules and standards that govern heritable human genome editing research? If so, how are they enforced? (Part 3.3.2: paragraph 48(b)).
  - l. How will distinctions be drawn between disease and disability prevention, and therapy? How will enhancement be defined; for example, will this be the introduction of traits that are beyond ordinary human capacity and health? Or, will this be the introduction of traits beyond those usually present in the human species? (Part 3.5.1: paragraph 55(b)).
  - m. If such distinctions will be made, are there existing rules about how to evaluate technologies used to enhance rather than to prevent or treat disease and disability?
118. Governance tools, institutions and processes.
- a. **Declarations, treaties, conventions, legislation and regulations** (Part 4.1). Research deemed highly ethically contentious such as the research proposed in this scenario could be prohibited by law. This could happen at the international level through a treaty or convention, or at the national level through laws and regulations. It may be possible to use existing laws and regulations in innovative ways.
  - b. **Judicial rulings** (Part 4.2). If the country in which the controversial research occurred considered it illegal, the researchers or clinicians could be prosecuted through the legal system. A conviction would send a clear message to the research community that this kind of research is not permitted in this country.
  - c. **Ministerial decrees** (Part 4.3). A surprise announcement such as that described in this scenario might warrant a ministry making a policy statement or decree to clarify that specific activities are prohibited, or that rules already exist which the ministry interprets as prohibiting the planned research.
  - d. **Moratoria** (Part 4.5). A country may elect to introduce a legal prohibition or a moratorium.
  - e. **Professional self-regulation** (Part 4.9). The researchers or clinicians could be censured by their peers and professional bodies.
  - f. **Public advocacy and activism** (Part 4.10). There could be a public debate around the use of these technologies for these purposes, and how, when and why such plans might be announced, reviewed and governed.
  - g. **Research ethics guidelines and research ethics review** (Part 4.11). In this scenario, the ethics committee had provided a very broad approval for embryo research that may have unintentionally enabled research that would not have been approved had the research constraints been more specific. Ethics guidelines might need to be revised to prevent broad open-ended approval of all human embryo research.
  - h. **Collaboration with publishers and conference organizers** (Part 4.12). Academic conferences and publications can play an important role in bringing unethical research to the attention of those who need to know about it. They also play an important role in not furthering unethical research through conference presentations and publications.
  - i. **Education and training of researchers and clinicians** (Part 4.13). There continues to be room to improve the education and training of all those involved in carrying out and commissioning research in order to reduce the likelihood that they conduct unethical research.

## 5.6 Scenario 6. Heritable human genome editing: unscrupulous entrepreneurs and clinics expanding assisted reproduction

*A clinic that provides heritable human genome editing following in vitro fertilization and preimplantation genetic diagnosis has deliberately located itself in a country with minimal rules and oversight mechanisms governing heritable human genome editing. The clinic advertises its services internationally.*

119. This scenario highlights the following issues.

- a. **Difficulty in differentiating between different uses of a technology** (*ethical values and principles: responsible regulatory stewardship; global health justice*). Unscrupulous entrepreneurs and clinics exist within the international fertility industry that have already shown themselves prepared to use controversial and risky interventions. Unscrupulous entrepreneurs and clinics have, in some cases, actively evaded domestic laws. This scenario highlights potential commercial interests in packaging heritable human genome editing techniques as advanced assisted reproduction services, thereby attempting to evade regulatory and ethical oversight.
- b. **Potential for financial interests to drive policy** (*ethical values and principles: responsible stewardship of science; social justice; global health justice*). Given the potential financial returns from leading the field in advanced assisted reproduction services, commercial interests may override health and ethical interests in pursuit of heritable human genome editing. Questions of collective well-being, socioeconomic inequality and avoidance of discrimination are important here. How might these practices affect discrimination and inequality in both the country where the clinic is located and the country where a potential user is located? Are health resources in the country where the clinic is located being diverted to fertility services intended to benefit mainly wealthy foreign individuals? What elements of exploitation should be considered in the country where the clinic is located, for example with respect to women recruited to serve as egg providers or gestational surrogates?
- c. **Differences in national policy on human genome editing** (*ethical values and principles: caution; equal moral worth; respect for persons; solidarity*). Regulations on human genome editing are not harmonized internationally, which allows individuals to seek or offer services in some locations that are prohibited in others. This means that even if local legislation, regulations and guidelines restrict, prohibit or impose safety conditions on heritable human genome editing, individuals may access them in jurisdictions where the regulatory framework is different or non-existent. This could result in a negative effect to a pregnant woman and person with genome-edited embryos, any children born and subsequent generations.

120. The following questions should be considered when developing oversight measures (other questions may also arise).

- a. What are the interests of the public and how will they be served by this new and emerging technology? (Part 3: paragraph 29(c)).
- b. What are the public health and health economic implications, considering the costs of both action and inaction? (Part 3: paragraph 29(i)).
- c. Will genetic counsellors be needed; if so, how will they be recruited and trained? (Part 3: paragraph 29(k)).
- d. Do questions of equitable access to research participation, as well as safe and effective treatment across domestic populations and communities, inform regulatory decisions on public funding? (Part 3: paragraph 29(n)).

- e. Are there domestic rules in place regarding researchers and clinicians who go to another country to perform heritable human genome editing that would be illegal or unethical in their home country? If so, what are they? If not, are there plans to develop any? (Part 3: paragraph 31(c)).
- f. Are there plans to welcome or discourage people from other countries travelling to access heritable human genome editing clinical trials or so-called therapies? (Part 3: paragraph 31(e)).

121. Governance tools, institutions and processes.

- a. **Declarations, treaties, conventions, legislation and regulations** (Part 4.1). This scenario reinforces the importance of international cooperation on governance of human genome editing. The societal consequences of human genome editing would be global, as is the fertility industry through which this practice would likely be introduced. Taking governance action should not assume that the action will be solely domestic, nor that it will necessarily move towards greater permissibility.
- b. **Accreditation, registration or licensing** (Part 4.6). Formal accreditation and certification of health care facilities and providers could be important in limiting the credibility and reputation of providers and clinics engaged in unscrupulous practices. Standards for accreditation or registration might also help provide accurate information to potential customers, and promote and disseminate good practices, such as through codes of conduct. Accredited or registered clinics could also be actively involved in identifying and exposing unscrupulous entrepreneurs and clinics. They might also support and assist regulatory bodies, where they exist, in similar efforts.
- c. **Public advocacy and activism** (Part 4.10). Wide-ranging public debate is needed on whether, how and why heritable human genome editing is used. Such debate will need to include many different interest groups and public influencers. Careful consideration may be necessary should the views held by those setting the research agenda and implementing policy differ from members of the wider general public.
- d. **Education and training of researchers and clinicians** (Part 4.13). Training courses for researchers and clinicians might be reviewed in countries in which heritable human genome editing would be prohibited. Such courses would help to reduce the number of trained individuals willing to work in clinics offering controversial services.

## 5.7 Scenario 7. Prenatal (in utero) somatic human genome editing: clinical trials for cystic fibrosis

*In light of those who object to discarding affected embryos or terminating pregnancies with affected fetuses, an international research team wants to begin a clinical trial of prenatal (in utero) somatic human genome editing for cystic fibrosis. Such a trial could be very important given its potential to improve the prospects for restoring typical function in the systems most affected by the disease, including lung function, nutrition absorption and fertility. Proponents of the trial argue that in utero approaches allow for more effective editing in tissues difficult to access after birth, such as some areas of the lungs. But cystic fibrosis treatments have been improving in recent years, with mean life span increasing in northern European and North American countries where the disease is most prevalent, so critics of the proposal argue the risks are unwarranted.*

*In utero administration of a somatic genome editing intervention may: allow early intervention before tissue damage is established; permit more effective biodistribution of the intervention within the intended tissue while interstitial diffusion is facilitated and tissue barriers are still immature; and have a low risk of eliciting an immune response to the stem cell-based or gene product and vehicle because of the incomplete development of the adaptive immune system.*

*On the other hand, early exposure to gene editing may increase the risk of genotoxicity, because of the high rate of cell proliferation. In addition, broad biodistribution of the therapeutic product may also reach unintended tissues or cell populations that are otherwise shielded at older ages, such as germline cells. Furthermore, toxicity triggered by the editing at the target and off-target tissues may have damaging consequences at later stages of life, including teratogenicity. Comprehensive studies should thus be designed in small and large animal models to assess these risks and investigate any long-term consequences of the intervention.*

122. This scenario highlights the following issues.

- a. **Regulatory capacity** (*ethical values and principles: responsible regulatory stewardship*). Is there experience with in utero interventions and is there clarity on the roles of the pregnant women and persons with regard to the genetic father and/or the intended coparent rearing the child? What rules and resources will govern long-term monitoring of children born following the intervention?
- b. **Competing approaches to providing a public health response** (*ethical values and principles: responsible stewardship of research resources*). Should health systems concentrate on improving the standard of care in postnatal cystic fibrosis disease rather than focusing on research to develop a new therapeutic approach which ultimately may only be available to a very few?
- c. **Informed choice** (*ethical values and principles: equal moral worth; respect for persons*). This research involves both pregnant women and persons, and their fetuses. Competent pregnant women and persons can choose to consent or refuse research participation. Disclosure prior to decision making should include a full discussion of alternative postnatal therapeutic interventions, as well as the possibility that even if this prenatal research is successful, there might nonetheless be a miscarriage, a stillbirth or a child born with serious health problems. In some countries, the consent of the genetic father or the intended coparent rearing the child (who may not be the genetic father) may be required. Clarity on the legal rights and responsibilities of all these adults with regard to their consent to the research is essential.
- d. **Research trial design and standard of care** (*ethical values and principles: responsible stewardship of science, solidarity*). Will there be a control arm; if so, how will it be constructed given the likely significant variations between those for whom in utero interventions are an available option (economically, legally and morally) and those for whom they are not?

123. The following questions should be considered when developing oversight measures (other questions may also arise).

- a. What are the legal restrictions on genetic screening, in vitro fertilization, preimplantation genetic diagnosis, heritable human genome editing and/or abortion, and do they affect the choice of whether to consider in utero human genome editing? For example, do the restrictions make it difficult or impossible for prospective parents to learn about the chance of a child being born with cystic fibrosis and to act on that information by using assisted reproduction techniques (including, possibly in the future, heritable human genome editing) or by terminating a pregnancy? What resources (financial or medical) exist to assist parents whose children have cystic fibrosis, and how will that affect the likely interest in exploring in utero editing options?
- b. If the existing research oversight measures are not adequate, are there plans to create new oversight measures or to rely on regulatory review and approvals from an external body? If so, which external body(ies)? (Part 3: paragraph 29(l)).
- c. How will the cost of clinical trials and therapies be shared as among research participants, researchers, funders, clinicians, insurers and third-party (private and public) sources? (Part 3: paragraph 29(o)).

- d. Does the country have the political, technical and financial capacity to fully implement its preferred oversight measures? (Part 3: paragraph 29(p)).
- e. Will research that involves in utero somatic human genome editing be permitted? If permitted, what standards will control the degree of risk to a fetus and pregnant women and persons? If permitted, in either a pre or postapproval clinical research context, will pregnant women and persons have the option to terminate the pregnancy, decide on the management of their pregnancy, or decide on the management of any neonates born with extreme prematurity or disorders? Are existing oversight mechanisms adequate to manage technical review of risks and possible benefits particular to in utero somatic human genome editing research, including: risk to a pregnant women's and persons' health from use of viral vectors; risk of introducing new fetal disease or disability that would be experienced by any live-born child; risk of unintended changes to fetal gametes; and risk that the timing of the genome editing results in loss of opportunity to make decisions on pregnancy termination? Are the current rules clear about the decision-making roles of: pregnant women and persons (regardless of intent to rear any resulting child); the gamete providers; and the parent(s) intending to rear any resulting child? Are these rules clear about the decision-making role of married and unmarried partners, who may or may not be the same sex as the pregnant woman and person? (Part 3.2.1: paragraph 42(b)(iii–vi)).
- f. Are there domestic rules in place regarding researchers who go to another country to perform research that would be illegal or unethical in their home country? If so, what are they? If not, are there plans to develop any? (Part 3: paragraph 31(c)).
- g. If there are no plans to regulate research in in utero somatic human genome editing, are there plans to regulate foreign researchers travelling from other countries to conduct such research? (Part 3: paragraph 31(f)).

124. Governance tools, institutions and processes.

- a. **Conditions on research funding** (Part 4.4). In addition to any decisions taken by governments, the funders of the clinical trial should require specific oversight measures, such as compliance with a specific code of conduct or reviews by appropriate ethics committees.
- b. **Professional self-regulation** (Part 4.9). The professional bodies of those conducting the trials might review their codes of conduct to ensure that their members are following best practices and acting ethically regardless of where they practice. These codes of conduct should also speak to conscience-based objections and duty of care to patients, given that interventions during pregnancy may raise religious objections among some practitioners if they are seen as increasing the risk of miscarriage or intentional abortion following an adverse event.
- c. **Public advocacy and activism** (Part 4.10). There could be a public debate on the use of these technologies for these purposes and the comparative risks and potential benefits compared with alternative approaches.
- d. **Research ethics guidelines and research ethics review** (Part 4.11). Existing ethical guidelines could be important in overseeing the clinical trials and ensuring good practice is being followed.

# Part 6.

## Implementation, metrics and review

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125. The Committee identified a number of considerations for the successful implementation of oversight and governance measures for human genome editing. These included metrics for assessing impact as well as processes for reviewing and updating the governance framework.

### 6.1 Implementation of the governance framework and associated measures

126. As noted earlier in this document, the Committee considers good governance of human genome editing has the following features.

- a. **It depends on context.** The Committee has produced a governance framework which can be implemented in different contexts. The values and principles in Part 3 help explain *why* governance measures may be needed and *how* those charged with reviewing or strengthening governance measures may undertake such a task. The questions in Part 3 explore *what* may need to be considered when revising or strengthening governance measures. The tools, institutions and processes discussed in Part 4 outline *who* may need to be involved with governance of human genome editing. The scenarios in Part 5 bring these different elements together to show how they are interrelated in practice in various hypothetical developments, for different purposes, involving different groups and highlighting different challenges.
- b. **It will vary at institutional, national, regional and global levels.**
  - i. The individual elements in the governance framework should allow an institution to review the policies and practices they have in place to manage risks and take advantage of potential benefits. Such a review should include senior management, compliance officers and ethics bodies, and be integrated into institutional management arrangements. The review may also need to take into account the views of customers, patients or others with a vested interest in the institutional activities. The individual elements in the framework can also be readily adapted. For example, while an institution cannot pass laws, it can put in place rules that carry sanctions for non-compliance, which can be used to promote values and principles; these rules, values and principles will need to be disseminated and integrated into institutional culture. Although this is implementation of good governance on a small scale, it should be taken seriously.

- ii. National and regional efforts to implement the governance framework, and review and strengthen governance measures for human genome editing will differ from one country to another. The procedures and practices will need to be integrated into existing arrangements. The governance framework is intended to provide a toolkit for a national process – indicating: the values and principles to guide the work; the different groups that may need to be involved; the tools that could be used; as well as specific questions that may need to be answered during such a process. While each tool, institution, process and questions may not be appropriate in a specific national context, the Committee concludes it is important they are considered. If they are to be set aside, this should be the result of an active decision supported by a strong rationale as to why they are not relevant.
  - iii. Global efforts are needed to: identify and develop good practice; map institutional, national, regional and international governance measures; build capacity; and help harmonize a global response. The elements in the governance framework are also intended to support global initiatives. Efforts to review and strengthen the governance of human genome editing are connected to broader efforts, including other applications of genome editing and other emerging technologies. Possible international arrangements to support governance and oversight of human genome editing are explored in more detail in the Committee’s recommendations.
- c. **It will necessitate addressing differences in national capacity to undertake the oversight and regulation of human genome editing.** Countries will differ in their capacity to comprehensively govern human genome editing research and clinical care. Where there are insufficient personnel, financial or other resources, capacity-building to ensure effective development and implementation should be emphasized in efforts to strengthen governance arrangements more broadly – rather than specifically addressing human genome editing. For immediate needs, provision should be made to draw on regulatory capacity elsewhere, including in other countries or in regional or international organizations.
- d. **It includes activities that can be undertaken by WHO and others in relation to reviewing and strengthening governance measures for human genome editing.**
- i. WHO can strengthen its capacity to work on governance. The Committee notes that the governance of human genome editing is relevant to many different aspects of the Organization’s work. WHO will need to build capacity to support the implementation of this framework, keep informed of developments, gather impact metrics and support the review and revision of the framework. In part, capacity-building may make use of existing capabilities, for example the WHO Office of the Chief Scientist and its foresight work, efforts on public health bioethics, initiatives on harmonization of regulations and strengthening of regulatory systems, and the International Clinical Trials Registry Platform. The Committee notes that placing additional burdens on existing efforts requires additional resources, and stresses that the activities listed above should not be unfunded mandates. Additional staff and associated resources will likely be needed to support these efforts.
  - ii. WHO should make use of its existing communications resources to promote the need for good governance of human genome editing, including highlighting the existence of this governance framework and associated institutional, national, regional and international follow-up activities. Promotion of good governance may also include issuing policy statements and requires senior leaders within the Organization to continue to focus on human genome editing.
  - iii. More broadly, WHO should initiate a programme of activities distributed around the Organization and beyond to support efforts to review and strengthen governance of human genome editing. These activities might include organizing events through its regional offices to introduce the governance framework, making the case for reviewing and strengthening oversight measures, exploring the scenarios and how the framework can be used to address current and future challenges in different contexts, as well as equipping staff at offices in individual countries, territories, and areas to support institutional,

national, regional and international efforts to review and strengthen governance arrangements. These activities and events should not be restricted to WHO and might usefully involve other organizations, groups and bodies with an interest in, or who might be affected by, human genome editing. Other activities that might be usefully undertaken by WHO and others (beyond those directly connected to reviewing and strengthening governance measures) are discussed in more detail in the Committee's recommendations.

- e. **It promotes public confidence by ensuring that choices are made in a transparent and inclusive way, and it includes means to hold policy-makers accountable for those choices.** WHO should be open, transparent, accountable and inclusive about its governance efforts on human genome editing. The Committee has tried to work in this way and all follow-up activities or subsequent committee initiatives should be conducted similarly. The Committee further recommends that the Director-General regularly brief the World Health Assembly on human genome editing and its governance, perhaps as part of a broader process focusing on emerging technologies.

## 6.2 Metrics

127. It is important to look for indicators of change as a result of the implementation of the governance framework and associated efforts to review and strengthen the governance of human genome editing. This will help ensure that the time and effort invested are having the desired impact. The Committee carefully considered the following approaches (both quantitative and qualitative) to assessing impact.

- a. **Changes in the availability of information on laws, regulations and guidelines.** In Part 1 of this document, the Committee outlined currently available information on laws, regulations and guidelines. For many countries, available information is indeterminate and for many countries no information is available. Regardless of the nature of the national policies developed (whether they permit or prohibit certain applications of human genome editing), greater clarity on national rules may be an indicator of increased interest in effectively governing this emerging technology. Furthermore, the willingness of countries to commit resources to review and revise their laws, regulations and guidelines may be an indicator of how seriously this issue is being taken.
- b. **Number, frequency and location of meetings, workshops and events.** Many events on human genome editing and associated governance arrangements have already taken place. The number and frequency of these events over time may provide insight into policy interest and commitment to this topic. As many of the initiatives to date have been driven by and taken place in a relatively small number of technologically advanced countries, tracking where there is interest in human genome editing (using events as a proxy) might provide important indicators on whether global interest in taking action on this topic is increasing. Given the global nature of the uptake of associated genome editing technologies, the emergence of unscrupulous entrepreneurs and clinics offering unproven therapies and the potential for researchers or companies to locate activities in countries with limited or no regulatory infrastructure solely to avoid laws, regulations and ethics guidelines, a global effort at governance is crucial.



- c. **Changing views of participants in institutional, national, regional and international implementation activities organized by WHO.** Surveys can be used to assess how the views of members of the public do or do not change as a result of implementation activities. Polling tools and interactive sessions and activities can also provide valuable insights into how actively participants in institutional, national, regional and international implementation activities are engaging in debate and discussion on human genome editing, what issues seem most relevant in different contexts and how different approaches might better meet local needs. It is important to note, however, that some of the tools routinely used to gauge changing views have major limitations, including recruitment bias, bias in translation, missing information, inability to confirm understanding of the science or the survey questions and ambiguity in the questions.
- d. **Entries in the Registry of basic and preclinical research or the clinical trials Registry.** Such information may provide important insight into the scale and distribution of relevant activities. This information may help assess whether sufficient effort and resources are being invested in addressing governance concerns for a range of genome editing activities. In addition, identifying and quantifying research not captured in the Registry would also provide useful information.
- e. **Monitoring of social and traditional media.** This can allow both quantitative and qualitative analysis of levels of concern, risk acceptance, and prevailing views on and levels of satisfaction with current governance measures associated with human genome editing. Tracking these factors over time may allow insight into the impact of the governance framework and associated implementation activities.
- f. **High profile events and announcements.** Tracking, for example, the illegal, unregistered, unethical and unsafe use of human genome editing research and other activities, or the emergence of clinics offering associated services, or plans to develop applications for these technologies (for elite sport, academic endeavours, military exercises or space missions) could provide insight into whether efforts to review and strengthen governance are commensurate with the risk that these technologies are used inappropriately. Assessing messaging around such events might be used as an indicator of how prevalent concepts and approaches for good governance have become. For example, does such an announcement specifically address elements of this governance framework?

### 6.3 Reviewing and updating the governance framework

128. The Committee asserted early in this document that good governance is an iterative, ongoing process that includes mechanisms for regular revision in light of technical, practical and ethical developments, and changes in societal views. Ideally, the process will be proactive, not solely reactive. As a result, the Committee stressed the importance of WHO building its internal capacity to support the implementation of this governance framework, keep informed of developments, gather impact metrics, and support review and revision. Furthermore, the Committee, as part of its recommendations, explored international arrangements to support governance and oversight of human genome editing. A suitable body should be convened at least every 3 years to review and update this governance framework as necessary.

# Annex.

## Meetings, consultations and webinars: participants

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The following lists give the participants in the meetings, consultations and webinars held by the Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing (the Committee).

### Committee meetings

*First committee meeting, 18–19 March 2019, Geneva, Switzerland*

#### Experts

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**Topic-specific meetings**

*Sickle Cell Disease-Genome Editing Consultation Meeting, 24 February 2020, Cape Town, South Africa*

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*Human Genome Editing satellite meeting – Engagement and Ethics Dumping, Global Forum on Bioethics in Research (GFBIR), 14 November 2019, Singapore*

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*Virtual consultations on the human genome editing registry, July 2019–January 2020*

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*Virtual meeting between the European Group on Ethics in Science and New Technologies and the WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing on the ethics and governance of human genome editing, 2 December 2020<sup>50</sup>*

## **Online consultations**

*First online consultation, 15 January–7 February 2020*

The Committee received 325 unique responses from individuals and organizations in 32 countries; 45 responses came from organizations, mostly in the United States (15), United Kingdom (5) and Mexico (3). Organizations providing responses included biotechnology associations, professional scientific bodies, patient groups and bioethics committees

*Second online consultation, 14 July 2020–19 August 2020*

The Committee received 69 unique responses from individuals and organizations in 23 countries. Countries with the highest response rates included Burkina Faso, United States, United Kingdom and Japan. Respondents were mostly affiliated with universities and medical schools, associations, foundations and councils, research centres and institutes, as well as professional organizations and societies.

## **Webinars**

*Public engagement on human genome editing, 9 April 2020*

- Council of Europe's Guide to Public Debate on Human Rights and Biomedicine

### **Ms Tesi Aschan**

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<sup>50</sup> [https://ec.europa.eu/info/news/governing-genome-editing-humans-ec-and-who-committee-probe-ethical-questions-together-2020-dec-03\\_en](https://ec.europa.eu/info/news/governing-genome-editing-humans-ec-and-who-committee-probe-ethical-questions-together-2020-dec-03_en) (accessed 7 May 2021).

- Global Observatory for Genome Editing

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*Indigenous perspectives on human genome editing, 30 April 2020*

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*Faith perspectives on human genome editing, 28 May 2020*

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*Biohackers, DIY community labs and transhumanist perspectives on human genome editing, 11 June 2020*

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*Groups and organizations that made statements on human genome editing, 9 July 2020*

- European Group on Ethics in Science and New Technologies (2016). Statement on Gene Editing

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- The Hinxton Group. An international consortium on stem cells, ethics & law (2015). Statement on Genome Editing Technologies and Human Germline Genetic Modification

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*Engagement with human genome editing, 30 July 2020*

- World wide views

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*Whistleblowing and human genome editing, 1 October 2020*

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*Epigenetics and human genome editing, 8 October 2020*

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*Stem cells and human genome editing, 13 October 2020*

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*Ethics dumping and human genome editing, 22 October 2020*

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*Patents and human genome editing, 3 November 2020*

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*Scientific updates on human genome editing, 3 December 2020*

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*Perspectives of patient groups and genetics professionals on human genome editing, 21 January 2021*

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*Launch of the final outputs of the Committee, 28 January 2021*

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*Perspectives of regulators on human genome editing, 18 February 2021*

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