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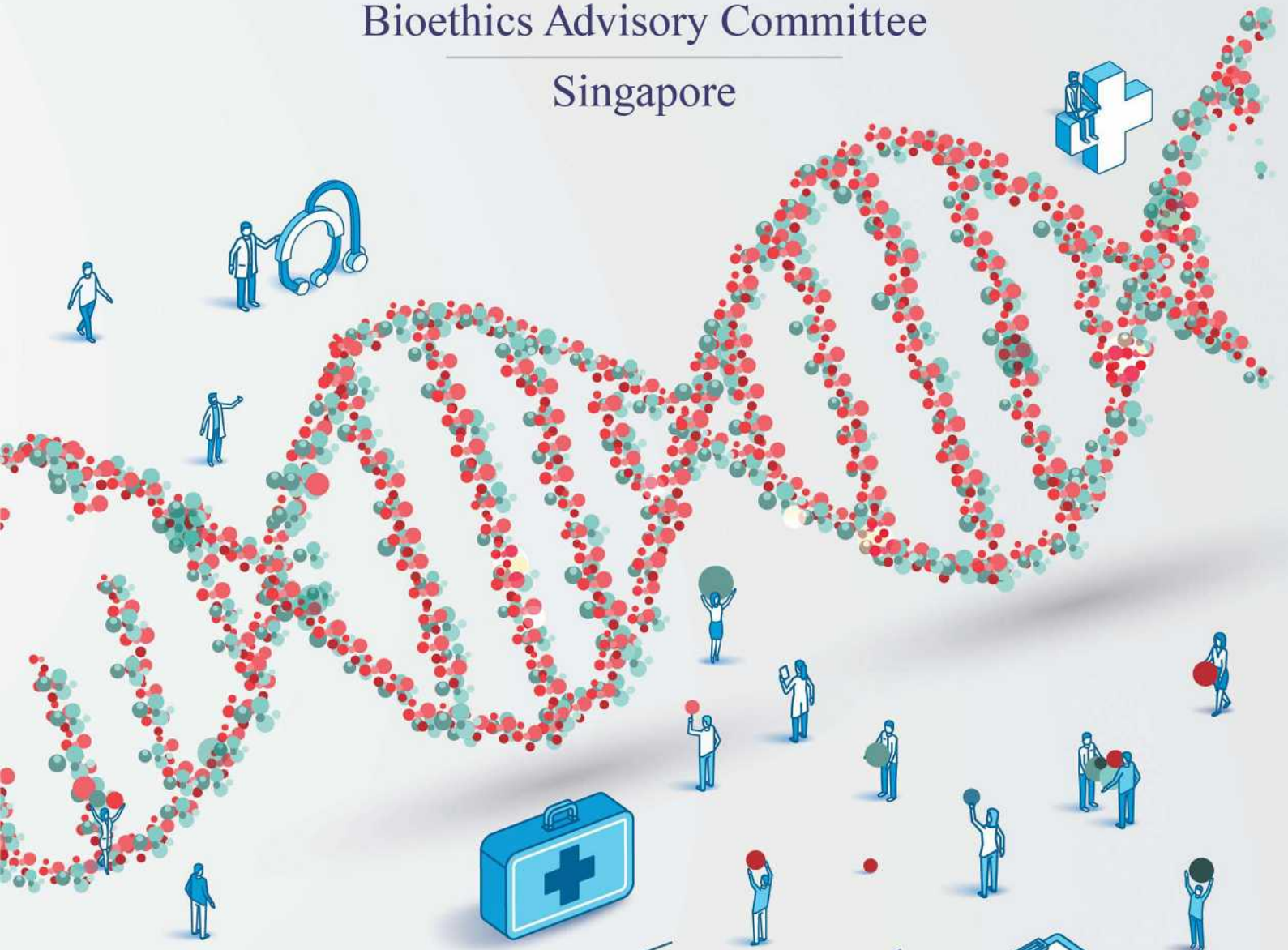

ETHICAL, LEGAL AND SOCIAL ISSUES ARISING FROM HUMAN NUCLEAR GENOME EDITING

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A report by the Bioethics Advisory Committee of Singapore

October 2025

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FOREWORD

Advances in Human Nuclear Genome Editing (HNGE) technology in recent years have resulted in the discovery of more precise tools that hold great promise in advancing both human biomedical research as well as clinical research. These tools allow us to alter genetic material, which can lead to promising breakthroughs in the treatment of genetic disorders, cancers, and infectious diseases. In biomedical research, HNGE technology can facilitate the study of gene function and disease mechanisms, and accelerate drug discovery and personalised medicine. Techniques such as Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) editing allow for precise modifications in the genome, enabling researchers to target specific genes associated with hereditary diseases. This unprecedented manipulation of genetic material offers the potential to eliminate certain health conditions, reduce susceptibility to various illnesses, and the overall improvement of human health. This report examines the far-reaching effects of HNGE technologies (i.e., non-heritable and heritable gene editing) and addresses the ethical, legal and social principles necessary to guide the responsible use of HNGE in biomedical research and clinical applications.

Amid a growing potential to modify the human genome for therapeutic purposes, some key ethical concerns have arisen, such as issues of consent, unintended consequences such as mosaicism and off-target effects, safety, accuracy and the potential for unforeseen health risks. Furthermore, the long-term effects of gene editing, especially across generations, for heritable gene editing, remain uncertain, thus necessitating rigorous research to ensure the safety and wellbeing of individuals in the future. Another important ethical consideration pertains to the potential application of HNGE technology for genetic enhancement, which raises concerns about equitable access, unintended consequences and the shift in attitudes and behaviours towards reproductive choices. Therefore, it is imperative that these ethical issues be addressed, so as to promote safe, responsible and equitable advancements in HNGE.

Responsible and ethical use of HNGE technology is crucial as we explore ways to treat and prevent genetic diseases, improve health outcomes, and enhance human wellbeing. A *'respect for persons'* is a foundational ethical principle in this area, emphasising the inherent dignity, autonomy and rights of individuals participating in biomedical research and clinical applications involving HNGE technology. Researchers and clinicians must demonstrate respect for individuals by ensuring that informed consent is obtained, particularly given the potential long-term and heritable effects of gene editing. Alongside this is the principle of *'proportionality'*, which requires that the potential benefits of gene editing are carefully weighed against the risks, and that risks are minimised as much as possible. By adhering to these ethical principles, and others outlined in this report, researchers, clinicians, research and healthcare institutions can navigate the complex landscape of HNGE, make balanced and fair decisions and promote advancements that align with societal values and ethical standards.

The Bioethics Advisory Committee (BAC) extends its appreciation to all individuals and organisations for their valuable feedback during the public consultation process. In developing our recommendations, we have carefully reviewed all feedback received, and this report includes a thorough overview of the wide range of perspectives expressed.

Finally, I would like to thank the Review Group members, our International Expert and my fellow Committee members for their dedication and commitment to the detailed review of this complex topic. Their insights into the ethical, legal and social issues of HNGE, as well as their openness to diverse viewpoints during the consultation process, have been truly invaluable. I am confident that this report will serve as a useful resource and will provide guidance to academics, researchers, medical practitioners, healthcare professionals and policymakers in addressing ethical considerations around HNGE in their respective fields.

Emeritus Professor Lee Eng Hin

Chair
Bioethics Advisory Committee
2025

EXECUTIVE SUMMARY

1. This report addresses the ethical, legal and social issues arising from Human Nuclear Genome Editing (HNGE). It aims to guide academics, healthcare professionals, researchers, Institutional Review Boards (IRBs) and Clinical Ethics Committees (CECs) on the ethical use of HNGE technologies in biomedical research and clinical applications. A public consultation was conducted by the BAC from 6 June 2024 to 13 August 2024 to collate responses from both stakeholders and members of the public. This feedback has been reviewed and incorporated into the advisory report.

Legislative and Regulatory Frameworks for HNGE

2. Legislation and guidelines play an important role in navigating the ethical, legal and social implications surrounding gene editing. It is important for clinicians, healthcare institutions, researchers and research institutions to adhere to relevant legislation and guidelines to ensure ethical and safe utilisation of gene editing technology. This chapter discusses the legislation and regulatory frameworks for HNGE in Singapore and other countries, as well as international guidelines on HNGE.

General Ethical Principles in HNGE

3. The principle of *respect for persons* refers to the autonomy of individuals making decisions related to biomedical research that involve gene editing or its clinical applications. The autonomy of an individual may be compromised if they are not fully informed of the possible benefits, risks and repercussions of research and clinical applications involving gene editing technologies. It is important to consider not only the autonomy of those put in a position of having to make decisions, but also the best interests of those with a diminished capacity, or even no capacity whatsoever, to give valid informed consent.

4. The principle of *solidarity* reflects the importance of altruism and other pro-social motives as a basis for participation in biomedical research. It also reflects the willingness and moral obligations of individuals to share the costs associated with scientific progress and participation in HNGE research, such as potential risks, in return for the common good.

5. The principle of *justice* requires that gene editing technology and therapy are accessible to the public. However, *justice* involves not only equitable access to HNGE technology but also addressing potential stigmas and promoting inclusive attitudes towards individuals with disabilities.

6. The principle of *proportionality* requires that the potential benefits to individuals and society in general, brought about by the editing of the human genome, should outweigh the anticipated risks of the research and clinical applications outlined above. The stringency of any regulation or governance framework developed for research employing gene editing, including a *de facto* prohibition of specific research activities, must be proportionate to the risks being mitigated.

7. The principle of *sustainability* is broadly understood to support arguments for the conservation of nature and the minimisation of resource depletion for the good of our planet. Therefore, research processes and outcomes involving HNGE technology should not unfairly jeopardise or prejudice the welfare of future generations.

8. The principle of *inclusivity* makes clear that the benefits of research and potential clinical applications of the technology are considered a public good and need to be accessible to everyone. It is important to carefully consider the knowledge and perspectives of HNGE as informed by different social, cultural, and religious beliefs, and to also work closely with the different groups of people to facilitate 'community-engaged research'. Appropriate stakeholders such as patients, prospective parents and the wider public alike should be consulted and engaged to identify, prioritise and reach consensus on the specific areas, topics or questions that the research employing gene editing aims to address.

9. The principle of *transparency* highlights the ethical responsibility and moral and legal liability incumbent upon researchers and their institutions stemming from the decisions and actions that they take as a consequence of their research findings. HNGE research methods, analysis and data must be reported and disseminated openly, clearly, comprehensively and in a timely manner.

10. The principle of *responsible stewardship of science* requires that processes and outcomes of HNGE research be aligned with the values, needs and expectations of society, as identified from stakeholder engagement. This principle extends beyond the dissemination of information and requires taking the views of all stakeholders into consideration.

HNGE Techniques/Technologies and their Relationship with Gene and Cell Therapies

11. This chapter provides an overview of the steps involved in gene editing, and discusses the different types of gene editing technologies used for HNGE research, and the relationship between gene editing, gene therapy and cell therapy.

Potential Research and Clinical Applications of HNGE and Current Established Methods to Treat Diseases

12. This chapter discusses the potential research and clinical applications of HNGE, such as to understand diseases (e.g., the development of cancer), to understand the development of human embryos, diagnostics and drug discovery tools, to improve resistance to diseases, and to reduce predisposition to diseases. The chapter also discusses the current established methods to treat diseases, which include conventional treatments, prenatal testing, adoption, selective termination of pregnancy, embryo selection, the use of donated gametes and intrauterine foetal gene therapy.

Mosaicism, Off-Target Effects, and On-Target Undesirable Modifications

13. Gene editing technology, when used in a controlled manner, can facilitate corrections to the genomic sequence to be achieved with precision, to rectify or remove mutations that might otherwise lead to unfavourable health conditions. However, such technology could also lead to unintended biological outcomes such as chromosomal mosaicism in embryos, and undesirable consequences arising from off-target mutations and deletions.

This chapter discusses the ethical principles of *proportionality, sustainability, solidarity,* and *responsible stewardship of science*, the ethical issues of chromosomal mosaicism, off-target effects and on-target undesirable modifications, along with their impact on both individuals and society as a whole, which would be important considerations for potential applications of HNGE.

Safety and Long-Term Effects of HNGE

14. While gene editing offers new ways of treating diseases and may potentially be used for enhancement of human performance, its widespread use in clinical practice is yet to be readily accepted. This is because the technology is still in the early stages of its development, which raises concerns regarding the safety and long-term side effects of the technology on individuals who receive the treatment. The chapter discusses the ethical principles of *proportionality, sustainability,* and *responsible stewardship of science*, and the ethical issues of long-term side effects and consequences of non-heritable and heritable gene editing. It also discusses the management of these consequences through long-term follow-up and intergenerational monitoring of patients involved in potential interventions of HNGE by researchers and healthcare professionals.

Procurement and Use of Human Embryos and Oocytes in HNGE Research

15. Human embryos have been used by researchers in gene editing as a tool to enhance knowledge about human gene function and early embryonic development, as well as to advance research on infertility, genetic diseases and intractable diseases. While procuring oocytes with the desired genotype from healthy individuals can enable researchers to study gene mutations in oocytes for a given disease-causing gene, or to correct a specific gene mutation, it may lead to health risks for donors. The chapter provides an overview of the 14-day limit for embryo research, the different types of embryos used in HNGE research, and discusses the ethical issues involved in the procurement and use of embryos and oocytes in gene editing research. These include health risks to donors and potential breaches of privacy and of the confidentiality of donors' genomic data. The chapter also discusses the relevant ethical principles of *respect for persons, justice, proportionality,* and *transparency*, which researchers and research institutions should consider to ensure that the autonomy and wellbeing of oocyte donors are respected, and to enhance *transparency* in the research process.

Equitable Access and Allocation of Resources

16. Gene editing technologies extend beyond discovering and developing therapies, particularly for rare genetic disorders, severe diseases such as cancer and treatment of infertility. These technologies can potentially be used for enhancing specific traits. However, as with many new modalities in medicine, gene editing technologies also give rise to concerns such as inequitable access by those who are in need but cannot afford them. The chapter considers the potential issues arising from a lack of access to HNGE technologies for clinical applications due to high costs and under-representation of the Asian population in clinical data involving HNGE research. The chapter also discusses the applicable ethical principles of *justice* and *inclusivity* that researchers and research institutions should consider when seeking to improve gene editing for use in research and clinical applications, and in designing clinical trials for HNGE research.

Genetic Enhancement and the Effects on Society

17. Recent technological advances have given rise to the possibility of gene editing being used in applications that go beyond therapies and medical interventions, including genetic enhancement of physical attributes and cognitive abilities. However, such potential clinical applications of gene editing technologies can raise several ethical issues. The chapter discusses the ethical issues involved in the applications of gene editing technologies for genetic enhancement, including their unintended consequences, social inequity and the shift in attitudes and behaviours towards reproductive choices. The chapter also discusses the relevant ethical principles of *proportionality, sustainability, justice, inclusivity, transparency* and *responsible stewardship of science* that researchers, research institutions and IRBs should consider in the applications of gene editing technologies for enhancement if permitted in the future.

Governance and Framework Tools for HNGE

18. As with other technological advances, gene editing raises ethical and social issues that must be addressed by having proper governance frameworks in place. The chapter discusses the governance and regulatory frameworks for HNGE at various levels: (i) institutional research level; (ii) clinical trial level; and (iii) national level. The chapter also discusses the different tools and approaches to strengthening existing research governance frameworks, which include (i) professional self-regulation; (ii) providing education and training on HNGE for researchers and clinicians; (iii) reinforcement of institutional practices; (iv) setting up of HNGE registries; (v) whistleblowing mechanisms; and (vi) other international mechanisms for reporting unethical HNGE experiments.

Recommendations *(see Chapter 13 for the detailed recommendations)*

General

19. The BAC recommends that researchers and research institutions should put in place an oversight mechanism to ensure HNGE activities are conducted appropriately. The BAC also highlights the need to ensure that there are clear and well-established protocols and processes for oversight and review, so as to ensure that HNGE research is conducted in an ethical manner.

20. Researchers and research institutions should set research priorities based on the needs of society and develop strategies to prevent or reduce the occurrence of errors that are known to arise from HNGE.

21. Clinicians should consider current established intervention methods to treat or prevent diseases among individuals and their offspring until the safety and efficacy of HNGE technologies are clear.

Non-Heritable Gene Editing (for Research and Clinical Applications)

22. Researchers, research institutions and clinicians should achieve a favourable risk-benefit ratio for patients undergoing clinical trials or clinical interventions involving non-heritable gene editing.

23. Governments, regulatory bodies and IRBs should establish an evaluation framework at the institutional level (i.e., guidelines and oversight committees) to assess the benefits of gene editing technologies in relation to its risks, such as off-target effects, the types of tissues affected, unintended genetic changes and the potential for immune responses.

24. Researchers, research institutions and clinicians alike should ensure that patients undergoing gene editing interventions or HNGE clinical trials have a sufficient understanding of the intervention and that they are made fully aware of the potential risks and complications prior to receiving treatment. Patients' informed consent and IRB approval are to be obtained prior to the procedure.

25. Regulatory bodies should establish guidelines on the required information that should be covered in informed consent for researchers and research institutions to refer to. This is to ensure that all relevant information on the gene editing intervention is made known to the patient or participant.

26. Researchers and clinicians who are involved in research and clinical applications involving HNGE technologies should be appropriately trained, so as to be able to accurately assess the potential benefits and risks of gene editing interventions and conduct appropriate counselling for patients, as well as ensuring that those same patients are able to give consent that is entirely informed.

27. Researchers, research institutions and clinicians should ensure that the risks of any unintended consequences from non-heritable gene editing interventions becoming heritable are avoided as far as possible, and that these risks are documented and assessed appropriately.

28. Researchers, research institutions, and clinicians should continuously review whether existing regulations and guidelines are adequate in terms of managing the risks and benefits of HNGE.

29. Researchers and physicians should perform long-term follow-ups on patients and participants in clinical trials evaluating new therapeutic modalities for non-heritable gene editing, to help mitigate the risk of any delayed adverse event due to the treatment.

30. Public agencies, researchers, academics and the government, should consider implementing health-economic analyses and models of funding to ensure that HNGE technology is affordable for all individuals with a corresponding medical need.

Recommendations for Gene Editing on Germline Cells or Embryos for Basic Research

31. The BAC does not recommend culturing human embryos whose genes have been edited beyond 14 days. It has asserted that the creation of human embryos solely for research purposes can only be justified when there is strong scientific merit and potential benefit from such research.

32. Researchers and research institutions should ensure that consent for the donation of surplus oocytes or embryos is kept separate from the consent of treatment for women undergoing fertility treatments.

33. Research institutions should establish an independent panel to interview women who intend to donate eggs specifically for research (i.e., those who are not undergoing fertility treatment).

34. Researchers should ensure that women are fully informed of the risks involved in gene editing and are given sufficient time to give consent prior to undergoing oocyte procurement procedures for gene editing research.

35. Researchers and research institutions should implement safeguards to protect oocyte donors and ensure that there is no coercion or undue influence in their decision to donate.

36. The relevant regulatory authority should consider setting a limit on the amount of compensation under Section 13 of Singapore's Human Cloning and Other Prohibited Practices Act to avoid any inducement.

37. Researchers should only consider using surplus embryos created through assisted reproduction treatment for HNGE research if the risks of procuring oocytes solely for such research outweighs the benefits.

Recommendations for Heritable Gene Editing for Clinical Research and Clinical Applications

38. The BAC does not recommend heritable gene editing for clinical research and applications until the safety and efficacy of such technology can be validated, as its long-term outcomes remain unknown.

39. Researchers and research institutions should conduct more research to develop methods to mitigate off-target effects and other unintended mutations from heritable gene editing on human embryos, so long as the safety of gene-editing established pregnancy is yet to be established.

40. If heritable gene editing for clinical research is deemed safe enough and permitted in the future, researchers and research institutions should conduct intergenerational monitoring which could help researchers determine the long-term side effects of heritable gene editing on an individual that might be passed on to future generations, and assess its safety and efficacy for clinical use.

Recommendations for Non-Heritable and Heritable Gene Editing for Genetic Enhancement

41. Researchers should weigh the benefits against the risks of applications of gene editing for enhancing physical attributes or cognitive abilities if genetic enhancement is permitted in the future.

42. Researchers and clinicians should review the need to limit the applications of gene editing technologies for enhancement to cases where they do not result in unfair advantage or disadvantage to certain individuals.

43. Governments, funding agencies and IRBs should implement oversight measures to ensure that the use of gene editing technologies adheres to the principle of *justice*.

44. Researchers, scientists and the government should engage with the views and shared experiences of people living with the conditions that are targeted for HNGE intervention, and ensure that their viewpoints are considered in shaping policies that reflect the needs and concerns of affected communities.

45. Regulatory authorities and IRBs should conduct more studies to assess the societal impact of permitting genetic enhancement in terms of potential increased vulnerability of particular populations to risks of harm and discrimination, and create frameworks and regulations to prevent discrimination. In addition, they should create policies to ensure equitable access to gene editing technology to reduce potential disparities in access and use.

46. Scientists, research institutions, clinicians, medical institutions and approving authorities must ensure that reporting mechanisms are in place to prevent the misuse or abuse of gene editing technologies for enhancement.

Governance of Research and Clinical Applications Involving HNGE

47. Research institutions should review institutional policies and practices at regular intervals in order to manage the risks and maximise the potential benefits that may arise from HNGE research. They should also consider the views of the public, patients or others with a vested interest in the activities conducted by such institutions.

48. Regulatory bodies, government organisations and funding agencies that are developing internal standard operating procedures (SOPs) for HNGE research or clinical trials should be encouraged to implement guidelines and establish robust systems to understand, monitor and minimise or mitigate the relevant risks and their impact on research subjects and patients undergoing clinical trials.

49. Governments and policy makers should constantly review and update laws and guidelines pertaining to applications and research involving HNGE.

Tools and Approaches to Strengthen Existing Research Governance

50. There should be professional self-regulation within the scientific community so that scientists conducting HNGE research are responsible and accountable to their peers and society as a whole.

51. Academic, research and healthcare institutions should develop educational training or ethics modules specific to HNGE for graduates who are looking to pursue research in gene editing or professions engaged in clinical applications of HNGE.

52. Research and healthcare institutions should continually review existing IRB ethics review processes and develop SOPs for HNGE research, which should be regularly revised and kept up to date with the developments in HNGE research, technologies and legislation.

53. The BAC recommends the setting up of national registries to track and monitor research and clinical trials involving HNGE to allow easy access of HNGE research and clinical trials information to relevant stakeholders.

54. Research institutions or governments should introduce whistleblowing mechanisms at an institutional or national level to establish effective reporting channels and help maintain comprehensive protection and support for those who report illegal, unregistered, unethical or unsafe HNGE research.

Governance Framework for Heritable Gene Editing and Gene Editing in Embryos or Germline Cells for Research Purposes

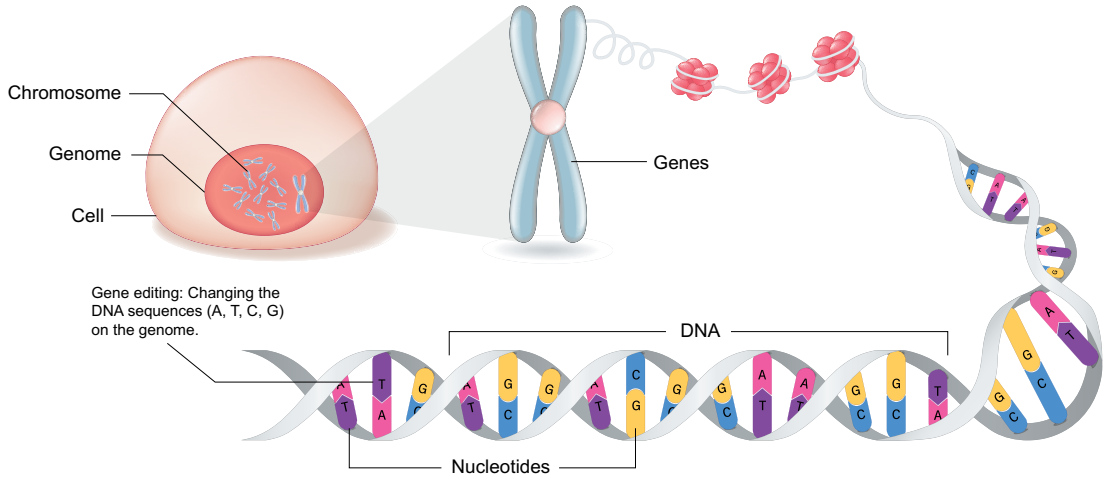
55. Research institutions and relevant regulatory authorities should ensure that the extent of oversight in developing governance and framework tools is commensurate with the extent of ethical, social and health risks involved, whether for clinical research and clinical applications of heritable gene editing, or the basic research activities of gene editing in embryos or germline cells.

CHAPTER 1:
INTRODUCTION

I. Human Nuclear Genome Editing (HNGE)

1.1 The human genome, which is made up of deoxyribonucleic acid (DNA), contains all the information needed for an individual to develop and function (Fig 1.1). As the cells in the body replicate, genetic mutations/changes in the nucleotide sequences of the DNA may take place, which can lead to changes in protein structure and cell function. Genetic mutations such as these could lead either to genetic conditions such as cancer, or they could help humans better adapt to their environment over time. Gene editing offers the potential to treat genetic diseases caused by such genetic mutations. Gene editing is a group of technologies that enable scientists to change an organism's DNA by adding, removing or altering genetic material at particular locations in the genome (Fig 1.1). Gene editing tools allow for a harmful DNA variant to be edited to a healthy variant—one that could potentially prevent or cure a genetic disease, hence representing great potential for breakthroughs in medical treatments.[1] Therefore, researchers have shown great enthusiasm for new technologies in therapeutic gene editing over the years.

Figure 1.1: Diagram portraying the Relationship between Genes, Genomes, DNA, Nucleotides and the Role of Gene Editing



1.2 Scientists use different technologies to edit DNA where these technologies act like scissors, cutting the DNA at a specific spot before removing, adding or replacing the DNA where it was cut. The first attempts at gene editing occurred in the 1980's, since which time many researchers have tried to develop methods to edit a specific gene.[2]

[1] U.S. National Library of Medicine. (n.d.). What are genome editing and CRISPR-Cas9? *MedlinePlus*. https://medlineplus.gov/genetics/understanding/genomicresearch/genomeediting/

[2] Matsumoto, D. & Nomura, W. (2023). The history of genome editing: Advances from the interface of chemistry and biology. *Chemical Communications, 59*, 7676–7684. https://doi.org/10.1039/D3CC00559C

New genomic tools have made it easier than ever to edit DNA, where they have enabled DNA to be edited in a simpler, faster, cheaper, and more accurate manner, such that the desired outcome is achieved with minimal off-target effects. Gene editing tools also have the potential to broaden scientists' knowledge of genetics by generating cellular models, which can mimic various human diseases to help better understand disease consequences and develop new treatments.

1.3 HNGE may be broadly classified into: (a) non-heritable gene editing; (b) heritable gene editing for clinical research and applications; and (c) gene editing in embryos or germline cells for research.

a. Non-heritable (or somatic) gene editing is carried out in cells that cannot, or do not contribute to, gamete formation, which is responsible for the generation of reproductive cells.[3] As such, changes made to these cells cannot be inherited by the offspring of the individual receiving the treatment. Common applications of non-heritable gene editing include clinical treatment of genetic disorders in individuals with cystic fibrosis[4] and severe combined immunodeficiency (SCID) syndrome,[5] or, more broadly, for research purposes.

b. Heritable gene editing refers to genetic modifications made to gametes (eggs or sperms), germline cells or early-stage embryos, which can be applied in both clinical research and clinical applications (if permitted in the future):

   i. Clinical research involving heritable gene editing involves interventions with human subjects to study the safety, efficacy and ethical considerations of editing genes that can be inherited by future generations. For example, editing germline cells or embryos to correct disease-causing mutations that are subsequently transferred into the research subject raises the risk that the patient's future off spring might inherit these modifications. Typically, this includes clinical trials in controlled environments, often with stringent regulations and oversight, to explore potential therapeutic benefits and address possible risks. Clinical research is exploratory and is not intended for routine clinical practice.

   ii. Clinical applications of heritable gene editing refer to the potential use of heritable gene editing techniques in clinical practice, where alterations are made to (i) genomic DNA in gametes; or (ii) any cells that give rise to gametes, including the single cell zygote resulting from fertilisation of an egg by a sperm cell, or cells of an early embryo,[6] leading to the transfer of the resultant embryo to a woman's uterus to initiate a pregnancy that could result in the birth of a child with a modified genome. When the child reaches the age capable of producing gametes, such genetic edits made to these cells will be inherited by the progeny and passed down to future generations. Heritable gene editing can potentially be used in clinical applications for the purposes of treatment of diseases, conferring resistance against diseases, treatment of infertility, and the enhancement of traits (if permitted in the future).

[3] National Academy of Sciences, et al. (2017). *Human genome editing: Science, ethics, and governance*. National Academies. https://www.ncbi.nlm.nih.gov/books/NBK447271/

[4] Hodges, C. A., & Conlon, R. A. (2019). Delivering on the promise of gene editing for cystic fibrosis. *Genes & Diseases, 6*(2), 97–108. https://doi.org/10.1016/j.gendis.2018.11.005

[5] Fischer, A., & Hacein-Bey-Abina, S. (2019). Gene therapy for severe combined immunodeficiencies and beyond. *Journal of Experimental Medicine, 217*(2). https://doi.org/10.1084/jem.20190607

[6] National Academies of Sciences, Engineering, and Medicine. (2020). *Heritable human genome editing*. National Academies. https://www.ncbi.nlm.nih.gov/books/NBK565918/

c. Gene editing may also be applied on germline cells or embryos for basic research, which does not involve interventions with human subjects. It can be used in reproductive medicine to correct mutations in germ cells in testes or ovaries, or in germ cells used to derive gametes *in vitro* for studies involving cellular development or to improve understanding of genetic diseases. Progenitor cells of gametes can also be isolated and genetically modified *in vitro* but are not implanted into a human body to establish pregnancy. For instance, missense mutations in regulator genes in oocytes, which may impede oocyte maturation or early embryonic developmental arrest and lead to failure of fertilisation, may be corrected to recover the oocytes' developmental potential and raise chances of successful pregnancy.[7] In azoospermia patients who suffer from a chromosomal mutation that causes meiotic arrest of sperm cells, spermatogonial stem cells (SSC) may also be genetically corrected in infertile males.[8] However, this investigative therapy is currently in its experimental phase with further studies needed to warrant any translational applications, as changes that are theoretically present in the germ cells can potentially be passed on.

II. Global and Local Trends on the Use of HNGE in Human Biomedical Research and Clinical Applications

1.4 Over the years, gene editing has witnessed a paradigm shift with the advent of techniques in gene editing involving the clustered regularly interspaced short palindromic repeats-CRISPR-associated protein 9 (CRISPR-Cas9), zinc-finger nucleases (ZFNs) and transcription activator-like effector nucleases (TALENs).[9] These enzymatic tools share a common characteristic of changing the DNA sequences within the genome by leveraging a combination of programmable targeting of specific sites, inducing DNA breaks, inserting DNA, deleting DNA, modifying the chemical identity of nucleotides and/or harnessing the endogenous repair mechanism within the cell. Such changes can repair gene mutations associated with disease. Further advancements in gene editing methods have also enhanced our knowledge of human genetics, epigenetics, molecular biology and pathology, enabling disease modelling and allowing drug discovery to be made more viable. As such, gene editing-mediated trials have led to positive treatment outcomes in patients with haematological disorders, such as sickle cell disease[10] and thalassaemia.[11] Nonetheless, as the sample sizes in these trials were small, and follow-up duration could be short, a larger sample size and long-term follow-up would be required to accurately assess the long-term effects and *sustainability* of outcomes.

[7] Fei, C., & Zhou, L. (2022). Gene mutations impede oocyte maturation, fertilization, and early embryonic development. *BioEssays, 44*(10), 2200007. https://doi.org/10.1002/bies.202200007

[8] Tong, M. H., et al. (2021). Rescue of male infertility through correcting a genetic mutation causing meiotic arrest in spermatogonial stem cells. *Asian Journal of Andrology, 23*(6), 590. https://doi.org/10.4103/aja.aja_97_20

[9] Zhou, W., et al. (2022). Current landscape of gene-editing technology in biomedicine: Applications, advantages, challenges, and perspectives. *MedComm, 3*(3). https://doi.org/10.1002/mco2.155

[10] Zarghamian, P., Klermund, J., & Cathomen, T. (2023). Clinical genome editing to treat sickle cell disease—a brief update. *Frontiers in Medicine, 9*. https://doi.org/10.3389/fmed.2022.1065377

[11] Rahimmanesh, I., et al. (2022). Gene editing-based technologies for beta-hemoglobinopathies treatment. *Biology, 11*(6), 862. https://doi.org/10.3390/biology11060862

1.5 Moreover, the increasing prevalence of infectious diseases, cancer and genetic disorders have bolstered the advancement of medical science, which is also being driven by the demand for personalised medicine.[12] However, personalised treatments require a thorough understanding of the factors contributing to the health and disease of that individual. The necessary process includes analysing the molecular dynamics of the cell at the genetic level to diagnose the status of disease, as well as predicting treatment outcomes from biomarkers. For example, CRISPR in particular, but other gene-editing tools too, have demonstrated promise in repairing defective genes found in patients with severe diseases ranging from acquired cancer to inherited genetic diseases. The growth of the gene editing market is also driven by the increase in funding and initiatives by the government to develop complementary markets in vaccines, medical technologies, drugs as well as devices.

1.6 Currently, non-heritable gene editing is being explored via human biomedical research and clinical applications for a wide range of diseases from HIV to muscular dystrophy and even coronavirus disease 2019 (COVID-19).[13] Gene editing in embryos or germline cells is also carried out through properly regulated research. The outcome may hold promise for the treatment and prevention of more complex diseases. Heritable gene editing in clinical research and clinical application, on the other hand, are strictly prohibited in most countries, including Canada, Australia, and across Europe, where any form of research involving germline gene editing is banned.[14]

1.7 The gene editing market is dominated by North America due to the strong growth trend in the continent's pharmaceutical and biotechnology industries, technological innovation in gene editing technology, increasing product approvals, as well as the rising number of clinical trials conducted for gene editing. For example, in March 2021, scientists at the University of California (UC) San Francisco, UC Berkeley, and UC Los Angeles received approval from the United States Food and Drug Administration (FDA) to jointly launch an early phase, first-in-human clinical trial of a gene correction therapy in patients with sickle cell disease using patients' blood-forming stem cells.[15] The trial combined CRISPR technology developed at the Innovative Genomics Institute (IGI), which was founded by Nobel Laureate Jennifer Doudna, and experts at UCSF Benioff Children's Hospital Oakland in cord blood and marrow transplantation, and in gene therapy for sickle cell disease.

1.8 In Europe, the United Kingdom (UK) has been contributing significantly to the growth of the gene editing market due to the nation's growing elderly population and the increasing incidence of chronic diseases. The use of gene editing to treat children with severe diseases such as cystic fibrosis, muscular dystrophy and Tay-Sachs has also received great support based on the results from surveys conducted.[16] While it remains illegal to edit embryonic genomes meant for pregnancies, younger generations are more

[12] Ho, D., et al. (2020). Enabling technologies for personalised and precision medicine. *Trends in Biotechnology, 38*(5), 497–518. https://doi.org/10.1016/j.tibtech.2019.12.021

[13] Collins, F. (n.d.). Non-heritable gene editing. National Institutes of Health. https://directorsblog.nih.gov/tag/non-heritable-gene-editing/ Retrieved on 2 August 2023

[14] Gyngell, C. (2017). Gene editing and the health of future generations. *Journal of the Royal Society of Medicine, 110*(7), 276–279. https://doi.org/10.1177/0141076817705616

[15] Fernandes, L. (2021). UC Consortium launches first clinical trial using CRISPR to correct gene defect that causes sickle cell disease | UC San Francisco. https://www.ucsf.edu/news/2021/03/420137/uc-consortium-launches-first-clinical-trial-using-crispr-correct-gene-defect

[16] Sample, I. (2022). Half in UK back genome editing to prevent severe diseases. *The Guardian.* https://www.theguardian.com/science/2022/jun/22/half-in-uk-back-genome-editing-to-prevent-severe-diseases

open to the idea of designer babies suggesting that the ban could be lifted if it is proved that the procedure can safely prevent severe diseases.

1.9 There has been exponential growth in the gene editing market in the Asia Pacific region due to this vast region's rising elderly population, the modernisation of healthcare practices, technological advancements and government initiatives to control diseases. For instance, in March 2021, scientists from the Genome Institute of Singapore (GIS) developed a novel CRISPR-based gene editor, a C-to-G base editor (CGBE), to correct mutations that lead to genetic disorders.[17] CGBE is a CRISPR-based gene editor which allows substitution of a single base in faulty genomic sequences that are responsible for diseases such as cystic fibrosis, cardiovascular diseases, musculoskeletal diseases and neurological disorders.

III. Advantages and Disadvantages of Non-Heritable Gene Editing, Heritable Gene Editing and Gene Editing in Embryos or Germline Cells for Research Purposes

a. Advantages and Disadvantages of Non-Heritable Gene Editing

1.10 Non-heritable gene editing offers the primary advantage of delivering new treatments or cures for diseases by changing disease-causing genetic mutations solely within somatic cells. This reduces the risk of propagating, particularly potentially detrimental, edit-related changes to future generations. However, the high costs of subscribing to non-heritable gene editing as a therapy may prove unaffordable and inaccessible to many.

1.11 In addition, when gene editing is performed inaccurately, the off-target effects can result in unintended edits, which is an important risk to consider. Unintended edits (mutations) may occur in a subset of cells during gene editing. When these groups of cells include important genes, such mutations could lead to harmful effects such as cancer. However, the probability of off-target effects varies according to the design of the gene editing technology and is often quantified with stringent genomic sequencing. Hence, off-target effects are an important factor to consider when weighing the benefits and risks of each gene editing treatment.

1.12 Non-heritable gene editing may exhibit a lower editing efficiency and less therapeutic outcome when compared to heritable gene editing. This is because while heritable gene editing ensures that all cells of future offspring inherit the edited genomic sequence(s), non-heritable gene editing often results in genetic mosaicism, where only a fraction of the cells is edited with the desired sequences, while the other remaining cells are unedited or unintentionally edited. This could lead to a non-homogeneous population of cells, which may be insufficient in eliciting the desired treatment response. Ongoing advances in more efficient and precise gene editing technology could enhance the efficacy of non-heritable gene editing.

b. Advantages and Disadvantages of Heritable Gene Editing for Clinical Research and Applications

1.13 Heritable gene editing used for clinical research and applications could enable the correction of disease-causing mutations to be passed on from generation to generation

[17] ASTAR. (2021). Singapore scientists develop novel gene editor to correct disease. *ASTAR.* https://www.a-star.edu.sg/News/astarNews/news/press-releases/singapore-scientists-develop-novel-gene-editor-to-correct-disease-causing-mutations-into-healthy-versions

and so prevent the disease from developing in subsequent generations. Such applications could also enable conferring resistance or enhancing traits that are inheritable in future generations. However, unintended edits introduced during genetic modifications may similarly be passed down to future generations, thus introducing potential negative effects to offspring. For instance, off-target effects, due to DNA double strand breaks at the wrong sites because of imprecise edits, have been reported in human zygotes.[18] As with non-heritable gene editing, genetic mosaicism was observed in the same study too. This calls for greater caution and the need for further research aimed at meeting existing risk/benefit standards for the approval of clinical trials and clinical applications of heritable gene editing. Further, approvals are given only for compelling reasons and under strict oversight (discussed in Chapters 6 and 7).[19] The cost of receiving germline gene editing therapy may also be high, given the sophisticated technology involved, and therefore becomes unaffordable and inaccessible for many, potentially aggravating issues arising from societal inequality (discussed in Chapter 10).

1.14 Heritable gene editing for clinical research and applications may also be used to enable pregnancy by correcting mutations in germ cells, such as oocytes and spermatogonial cells, to potentially treat male and female infertility. This would allow parents with inherent fertility challenges to have their own children without receiving gametes from others, which would pose possible legal implications pertaining to the custodial rights of the child born (discussed in Chapter 5).[20] Nonetheless, when mutations are introduced at the wrong site of the DNA in germline cells during the process of germline gene editing, such errors introduced in editing could possibly lead to unknown ramifications with severe consequences, adversely affecting individuals receiving the treatment as well as their future progeny.

c. Advantages and Disadvantages of Gene Editing in Embryos or Germline Cells for Research Purposes

1.15 Gene editing carried out in embryos or germline cells for basic research allows researchers to advance scientific research, including clinical research and clinical applications involving heritable gene editing, and to promote the understanding of human embryonic development. However, the procurement of human embryos for research purposes would be difficult due to risks involved for the donor. Furthermore, human embryos could be destroyed during or after use for research, raising ethical dilemmas, including *non-maleficence* and concerns pertaining to *justice*. To ensure that germline gene editing research is conducted ethically, the BAC adopts the following positions: (i) specific and personal consent from the donors must be obtained before any oocytes or embryos are used for research; (ii) potential donors should be provided with sufficient information and time to make an informed decision; (iii) for women undergoing fertility treatment, consent for donation of surplus oocytes or embryos should be separate from the consent of treatment; (iv) the treating physician should not also be the researcher seeking consent for the donation of eggs and embryos for research; and (v) as the process for donating eggs for research is time-consuming,

[18] Liang, P., et al. (2015). CRISPR/Cas9-mediated gene editing in human tripronuclear zygotes. *Protein & Cell, 6*(5), 363–372. https://doi:10.1007/s13238-015-0153-5

[19] National Academies Press. (2017). Heritable genome editing. In *Human genome editing: Science, ethics, and governance*. https://www.ncbi.nlm.nih.gov/books/NBK447263

[20] Rubeis, G., & Steger, F. (2018). Risks and benefits of human germline genome editing: An ethical analysis. *Asian Bioethics Review,* 10(2), 133–141. https://doi.org/10.1007/s41649-018-0056-x

invasive and associated with a certain degree of discomfort and risk, women who wish to donate eggs specifically for research must be interviewed by an independent panel. The panel must be satisfied that the individual is of sound mind, clearly understands the nature and consequences of the donation, and has freely given their explicit consent, without any inducement, coercion or undue influence.[21]

1.16 Clinical research and clinical applications of both non-heritable and heritable gene editing, and gene editing in embryos or germline cells for research, should be properly and carefully assessed prior to approval, due to the known and unknown risks of gene editing technology. A known risk is off-targeting, where unintended edits can occur in genes. However, as with any new and evolving technology, there may be unforeseen risks that only become apparent over time. It can take many years to fully determine the spectrum of risks associated with gene editing. Clinical studies are one of the key ways intended to uncover these potential long-term and unforeseen effects. Therefore, with technological advancements, continual evaluation is crucial to ensure a well-informed risk-benefit consideration. Such risk-benefit consideration may allow for the research and clinical applications of non-heritable gene editing to be conducted, if the benefits of the therapy outweigh the risks as well as other possible negative consequences that may arise from unintended mutations.

1.17 Nonetheless, heritable gene editing for clinical research and clinical applications for the purposes of treatment of diseases, conferring resistance, or the enhancement of traits, should not be recommended until safety and efficacy are well established and long-term effects are understood. This is because the mutations can be passed down to the future generations, and the unknown negative effects that could arise because of the errors in editing could outweigh the possible benefits of the therapy. This is especially relevant if the technology is used to confer resistance to diseases or enhance certain traits which might expose future generations to harm. Most jurisdictions and international bodies such as the World Health Organization (WHO), and scientific and professional societies such as the International Society for Stem Cell Research (ISSCR), either recommend changes in policy and practice to support the reporting of possible heritable gene editing or do not recommend the use of heritable gene editing.

1.18 Heritable gene editing for clinical research and clinical applications for the purpose of treating infertility should be prohibited until the safety, efficacy and long-term effects are well established. This is because ooplasmic transfer and pronuclear transfer have only been practised for treating intractable infertility in some countries such as the UK, to prevent the inheritance of pathogenic mitochondrial DNA mutations in offspring.[22] Furthermore, off-target effects arising from heritable gene editing can affect future progeny and could also harm the individuals undergoing the treatment when modifications to the genome are made at the wrong site.

1.19 However, gene editing in embryos or germline cells for basic research may be allowed if the research on human embryos is conducted before the 14th day of their creation.

[21] Bioethics Advisory Committee Singapore. (2021). *Ethics guidelines for human biomedical research* (2021, revised). Sections 5.25–5.29. https://www.bioethics-singapore.gov.sg/publications/reports/bac-ethics-guidelines-2021

[22] Ishii, T., & Hibino, Y. (2018). Mitochondrial manipulation in fertility clinics: Regulation and responsibility. *Reproductive Biomedicine & Society Online, 5*, 93–109. https://doi.org/10.1016/j.rbms.2018.01.002

This practice is uniformly regulated across countries given that the embryos were a collection of cells shown to sustain *in vitro* for 12-13 days after fertilisation for research purposes. The Warnock Committee's stand was premised on the view that only after the 14th day would the embryo be considered as an individual and, therefore, a person with rights to life.[23]

IV. Ethical Issues Arising from Heritable Gene Editing and Human Embryo Research

1.20 Heritable gene editing could result in inaccurate editing such as off-target effects and genetic mosaicism, both of which could result in the increased risk of heritable genetic diseases for future progeny. As such, the welfare of future offspring or children may be jeopardised (principle of *sustainability*) and further complications for the mother-to-be, such as psychological distress and infertility (principle of *non-maleficence*) may also arise. There is also a lack of sufficient preclinical studies and clinical trials demonstrating the safety and efficacy of heritable gene editing (principles of *beneficence, non-maleficence*, and *responsible stewardship of science*) given the relative infancy of the technology. The difficulty in predicting potential harmful side-effects that could occur because of heritable gene editing and possible interactions of such resultant genetic changes with other genes or the environment, could render future offspring susceptible to unknown long-term side-effects. These genetic alterations may continue to occur and be introduced to the population, which might then be difficult to ameliorate (principle of *sustainability*).

1.21 Extending the duration in which human embryos whose genes have been edited are cultured (i.e., beyond 14 days) could facilitate further development of heritable gene editing, but potentially risk leading to their misuse (principle of *justice*). Oocyte procurement for gene editing in embryos or germline cells for research is also physically invasive and could, therefore, pose significant risks to the health or life of the donor (principle of *non-maleficence*).

1.22 Furthermore, heritable gene editing for enhancement could exacerbate social inequities, resulting in skewed societal expectations of abilities and traits that are considered ideal, as well as aggravate inequitable access to germline gene therapy. As a result, the technology may be used by consumers in a coercive environment, such as that under societal pressure (principles of *justice* and *sustainability*). The general ethical principles of HNGE will be discussed in Chapter 3.

V. Issues that could Arise when Ethics is not Incorporated into the Conduct of Human Biomedical Research/Clinical Applications Involving HNGE

1.23 The CRISPR babies scandal represents the most high-profile case of heritable gene editing in human embryos, in terms of the strong criticism that it drew from scientific and medical communities.[24] In 2018, Chinese scientist He Jiankui applied germline gene editing to several human embryos resulting in the birth of two genetically modified babies. In doing so, He flouted established norms for safety and human protection.

[23] Bruce, P., & Daniel, R. (2021). Why we should not extend the 14-day rule. *Journal of Medical Ethics, 47*(10), 712–714. https://doi:10.1136/medethics-2021-107317

[24] Guardian News and Media. (2018, November 26). World's first gene-edited babies created in China, claims scientist. *The Guardian*. https://www.theguardian.com/science/2018/nov/26/worlds-first-gene-edited-babies-created-in-china-claims-scientist

Claiming that his aim was to introduce the rare ability to resist infection from HIV, He sought to reproduce the phenotype of a specific mutation in the gene CCR5. However, He generated a frameshift mutation intended to make the CCR5 protein entirely nonfunctional instead of introducing the known mutation.

1.24 He Jiankui's CRISPR experiment has attracted not only widespread attention but also controversy, which could shape research involving gene editing in humans for years to come, such as:

a. Increased interest in research studies on non-heritable gene editing as scientists become cautious about conducting research in gene editing on germline cells;

b. Further tightening of regulations and guidelines[25] on gene editing in germline cells (and incidentally, non-heritable gene editing) due to additional caution practised by the scientific community, which could stifle developments in HNGE; and

c. Adversely impacting the growth of gene editing in germline cells for research[26] such as the number of researchers working in the field, research output and funding, despite the benefits that may be harnessed from such research if conducted ethically.

1.25 Following He Jiankui's CRISPR baby scandal, there were several instances of similar studies involving gene editing carried out on germline cells or human embryos that triggered warnings from bioethicists. For example, several groups in China[27] and the United States of America (US) published results of similar experiments in those ensuing two years, which went from using non-viable embryos to using ones that could conceivably be implanted. Separately, a study conducted in the US in 2017 verified the gene editing ability of CRISPR-Cas9 to correct mutations associated with genetic diseases using human embryos.[28] While research carried out in this area have underlined the need for caution, scientists nevertheless anticipate clinical applications as a feasible outcome arising from these studies.[29] Therefore, it is important to carefully consider the ethical, social and legal implications involved in gene editing, and to put in place regulatory tools and a governance framework to prevent subsequent research from being carried out unethically.

VI. Other Challenges

1.26 Besides ethical issues and considerations, there are other challenges ahead, particularly in the clinical translation of heritable gene editing, where it is often difficult to delineate clinical applications from clinical research. An established clinical translation pathway for new therapies (i.e., a multistage controlled trial system to determine the safety and efficacy of a tested treatment) is not applicable to heritable gene editing, as

[25] Zhang, J. Y., & Lei, R. (2023, March 10). Is Chinese bioethics ready to move forward from the CRISPR baby scandal? *The Hastings Center*. https://www.thehastingscenter.org/is-chinese-bioethics-ready-to-move-forward-from-the-crispr-baby-scandal/

[26] Cyranoski, D. (2020, January 6). What CRISPR-baby prison sentences mean for research. *Scientific American*. https://www.scientificamerican.com/article/what-crispr-baby-prison-sentences-mean-for-research/

[27] Niemiec, E., & Howard, H. C. (2020). Ethical issues related to research on genome editing in human embryos. *Computational and Structural Biotechnology Journal, 18*, 887–896. https://doi.org/10.1016/j.csbj.2020.03.014

[28] Cha, A. E. (2021). First human embryo editing experiment in U.S. "corrects" gene for heart condition. *The Washington Post*. https://www.washingtonpost.com/news/to-your-health/wp/2017/08/02/first-human-embryo-editing-experiment-in-u-s-corrects-gene-for-heart-condition/

[29] Lim, J. & Kim, H. (2022). Basic principles and clinical applications of CRISPR-based genome editing. *Yonsei Medical Journal, 63*(2), 105–113. https://doi.org/10.3349/ymj.2022.63.2.105

clinical trials involving heritable gene editing cannot be considered a controlled study design, given the absence of suitable controls for comparison. Exploratory trials (i.e., phase zero or phase one) that involve microdosing of a new drug in a small number of patients to establish their safety, would be unsuitable for heritable gene editing studies. In standard first-in-human trials, an administered drug can be withdrawn instantaneously upon the discovery of adverse effects, and, if necessary, it might be possible to dispense treatments to counter such adverse effects. However, these are not options for clinical trials involving heritable gene editing, as the intervention cannot be reversed when a genetically modified embryo has been implanted into the uterus.[30] Given that the ethical issues arising from clinical research involving heritable gene editing would be similar to the ethical issues and considerations arising from clinical applications of heritable gene editing, any discussions on the ethical issues arising from heritable gene editing in this report apply to both clinical research and clinical applications, unless otherwise stated.

VII. Overview of Legislations and Regulatory Frameworks Governing HNGE

1.27 Most countries have enacted legislation that prohibits the use of heritable gene editing, such as Australia, Germany, and South Korea, while others such as the UK, the US, Japan and Singapore, have allowed the conditional use of gene editing in embryos or germline cells, namely for research purposes and with strict regulations. For instance, Australia's 'Prohibition of Human Cloning for Reproduction Act (2002, as amended 2017)' prohibits heritable alterations to the genome. Germany's 'Embryo Protection Act (1990, as amended 2011)' has outlawed artificially altering the genetic information of a human germline cell as well as using a human germ cell with artificially modified genetic information for fertilisation. Authorities in Japan have also issued guidelines to restrict the use of human-fertilised embryos for basic research employing gene editing.[31] While Singapore has yet to enact any specific legislation on gene editing, its 'No. S 622 Human Biomedical Research (Restricted Research) Regulations 2017' states that every research institution and researcher conducting restricted research must ensure that such research carried out does not involve a human embryo which is more than 14 days old from the time of its creation (excluding any period when the development of the embryo is suspended). The Regulations also state that the research institution and the researcher must ensure that only surplus embryos created in assisted reproduction treatment may be used for research.

1.28 Most international guidelines recommend against the use of illegal and unsafe heritable gene editing. For instance, the WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing issued new advisory guidelines in 2021 which recommend changes in policy and practice to support the reporting of possible illegal, unregistered, unethical, or unsafe non-heritable gene editing, heritable gene editing and gene editing in embryos or germline cells for research.[32]

[30] Rosemann, A., et al. (2019). Heritable genome editing in a global context: National and international policy challenges. *The Hastings Center Report, 49*(3), 30–42. https://doi.org/10.1002/hast.1006

[31] Ministry of Education, Culture, Sports, Science and Technology (MEXT) & Ministry of Health, Labor and Welfare (MHLW) (Japan). (2019). *Guidelines for research using gene-altering technologies on human fertilized embryos.* https://www.mext.go.jp/lifescience/bioethics/files/pdf/Overview_Human_embryo_geneome-editing_guideline2019JEn.pdf

[32] World Health Organization. (2021). *WHO expert advisory committee on developing global standards for governance and oversight of human genome editing: Report of the sixth meeting*. https://www.who.int/publications/i/item/who-expert-advisory-committee-on-developing-global-standards-for-governance-and-oversight-of-human-genome-editing-report-of-the-sixth-meeting

1.29 Most scientific and professional societies do not recommend the clinical use of heritable gene editing but do allow gene editing in embryos or germline cells for research. The International Society for Stem Cell Research (ISSCR) Guidelines (2021) do not recommend that heritable gene editing should be pursued at this time, as existing approaches are deemed unsafe or raise unresolved ethical issues. Additionally, they recommend that gene editing in embryos or germline cells for research should be allowed only after review and approval through a specialised scientific and ethics review process. International medical bodies such as the World Medical Association (WMA) issued a statement on human gene editing in which it opined that non-heritable gene editing should be implemented according to appropriate evidence that is collected via well-conducted and ethically approved research studies.

VIII. Objective of this Advisory Report

1.30 To address the emerging ethical, legal and social implications of HNGE in biomedical research, the BAC has published an advisory report and recommendations to guide researchers, academics, healthcare professionals, Institutional Review Boards (IRBs) and other ethics committees such as the Clinical Ethics Committees (CECs) on the ethical use of HNGE in biomedical research. While there are other pre-existing reports from the WHO and other global organisations or committees on this topic, the HNGE advisory report serves to guide the national ethical framework for HNGE in Singapore and provide the BAC's recommendations to inform the Singapore government on its policy decisions. The advisory report also serves as a useful reference for local and overseas bioethics counterparts to understand Singapore's position on HNGE.

CHAPTER 2:
LEGISLATIVE AND REGULATORY FRAMEWORKS FOR HNGE

2.1 A complex landscape of legislation and guidelines has emerged in the realm of gene editing, aimed at navigating the ethical, legal, and social implications of its associated technologies. These regulatory measures seek to balance the potential benefits of gene editing with concerns surrounding safety, informed consent and equity. The first part of this chapter provides an overview of the legislation pertaining to HNGE, including those for (i) non-heritable gene editing for research and clinical applications, and (ii) heritable gene editing for both clinical research and clinical applications, as well as gene editing in embryos and germline cells for research. The second part of this chapter provides an overview of the guidelines available to oversee the ethical applications of HNGE and discusses the different guidelines that (i) explicitly recommend against heritable gene editing for clinical applications, and (ii) recommend heritable gene editing for clinical applications based on certain conditions.

I. Local Legislation for HNGE

i. Non-Heritable Gene Editing (for research and clinical applications)

2.2 Non-heritable gene editing is generally allowed for research purposes in Singapore though approval is required from the Institutional Review Boards (IRBs) while detailed and informed consent needs to be obtained from participants. The use of gene editing products for innovative salvage therapy, which is the offering of an untested practice when conventional therapy has proven to be unhelpful in desperate or dire circumstances, is also allowed.[1] However, the prescribed treatment must be first reviewed by the relevant Clinical Ethics Committee (CEC) and found to be ethically appropriate.

a. Human Biomedical Research Act 2015

2.3 The use of non-heritable gene editing for research is currently neither prohibited nor restricted by the Human Biomedical Research Act 2015. As such, non-heritable genome editing for research purposes is permitted in Singapore.

b. Health Products Act 2007

2.4 Therapeutic products and active ingredients used in the manufacture of cell, tissue and gene therapy products (CTGTP) are regulated according to the Health Products Act 2007 and its subsidiary legislation, specifically the Health Products (Cell, Tissue

[1] Ministry of Health. (2020). *Healthcare Services Act 2020*. Licence conditions for all acute hospital service, outpatient dental service and outpatient medical service licensees administering or intending to administer cell, tissue and gene therapy products manufactured in-house by healthcare institutions. https://isomer-user-content.by.gov.sg/7/bc466d1d-44d1-4a5f-bfc5-dcf1da4eca1b/lcs-on-administering-cell-tissue-and-gene-therapy-products_1-0.pdf

and Gene Therapy Products) Regulations 2021.[2] Materials used in gene therapy such as viral or non-viral vectors with genetic material, as well as clinical research materials used in non-heritable gene editing, are classified as Class 2 CTGTP. Class 2 CTGTP comprises gene modified cells, cells grown on scaffold, culture expanded cells, vectors with therapeutic gene and xeno-based products. The conduct of clinical trials and use of clinical research materials classified as Class 2 CTGTP are also regulated by the Health Products (Clinical Trials) Regulations 2016.[3]

c. Healthcare Services Act 2020 (HCSA 2020)

2.5 The Licence Conditions for all Acute Hospital Service, Outpatient Dental Service and Outpatient Medical Service Licensees Administering or Intending to Administer Cell, Tissue and Gene Therapy Products Manufactured In-House by Healthcare Institutions imposed under the Healthcare Services Act 2020 states that the use of in-house manufactured CTGTPs[4] (including human cells or tissues, animal cells or tissues and genetically modified DNA/RNA carrying a therapeutic gene) for innovative salvage therapy must be reviewed by (i) the healthcare institutions' tumour board or specialty board for that particular disease/condition, or at least two medical practitioners qualified to confirm the patient's need for the innovative salvage therapy due to the ineffectiveness or unsuitability of current conventional therapy, and who are independent of the patient's treatment team; and (ii) a CEC.[1] However, mainstream clinical applications of non-heritable gene editing are not approved for use in Singapore, nor are there ongoing clinical trials involving non-heritable gene editing in Singapore either.

ii. Heritable Gene Editing for Clinical Research and Applications, and Gene Editing in Embryos or Germline Cells for Research

2.6 Heritable gene editing for clinical research and applications has not as yet secured the approval of the Ministry of Health (MOH) in Singapore, owing to the fact that there remains insufficient evidence demonstrating the safety of this novel form of technology. Research applications of gene editing in embryos or germline cells are strictly regulated in Singapore under the Human Biomedical Research Act 2015,[5] which falls under the purview of MOH. Specific research projects involving embryonic development, which require the approval of government authorities, must adhere to the requirements set out in the Human Biomedical Research Act 2015. The BAC's 'Ethics Guidelines for Human Biomedical Research (2021 revised edition)' emphasises that written approvals from government authorities such as MOH are required if the research involves human eggs and embryos.[6]

[2] Government of Singapore. (2021). *Health Products Act 2007. Health Products (Cell, Tissue and Gene Therapy Products) Regulations 2021. Singapore Statutes Online*. https://sso.agc.gov.sg/SL/HPA2007-S104-2021

[3] Government of Singapore. (2016). *Health Products Act 2007. Health Products (Clinical Trials) Regulations 2016. Singapore Statutes Online*. https://sso.agc.gov.sg/SL/HPA2007-S331-2016

[4] In-house manufactured CTGTPs refer to the non-commercial production of CTGTPs by a healthcare institution, whether for use by patients of healthcare institutions, or to be distributed for use by patients in another healthcare institution. It also includes the healthcare institution outsourcing this activity to a third-party commercial entity to manufacture and re-supply the CTGTP back to the healthcare institution for use by their own patients only.

[5] Government of Singapore. (2020). *Human Biomedical Research Act 2015*, 2020 Rev. Ed., Part 5: Regulation of Human Biomedical Research. *Singapore Statutes Online*. https://sso.agc.gov.sg/Act/HBRA2015

[6] Bioethics Advisory Committee. (2021). *Ethics guidelines for human biomedical research* (2021 revised edition). https://www.bioethics-singapore.gov.sg/publications/reports/bac-ethics-guidelines-2021

a. Human Cloning and Other Prohibited Practices Act 2004

2.7 In Singapore, the Human Cloning and Other Prohibited Practices Act 2004 stipulates that the placing of a prohibited embryo in the body of a woman is prohibited.[7] A prohibited embryo includes any human embryo that has been developing outside the body of a woman for a period of more than 14 days, excluding any period when the development is suspended, or any embryo that is deliberately removed from the body of a woman with the intention of obtaining a viable human embryo.[7] The Act also strictly regulates the creation and development of human embryos for research purposes in Singapore, stipulating that a person must not develop any human embryo that is created by a process other than the fertilisation of a human egg by human sperm outside the body of a woman for a period of more than 14 days.[8] The duration of embryonic development excludes any period for which the development of the embryo is suspended.[8]

b. Healthcare Services (Assisted Reproduction Service) Regulations 2023

2.8 Separately, the Healthcare Services (Assisted Reproduction Service) Regulations 2023 under the HCSA 2020 sets out that an assisted reproduction procedure involves (i) the collection of oocytes from a woman other than by way of surgical excision of the woman's ovarian tissue; (ii) the fertilisation of an oocyte for the subsequent distribution of the embryo; (iii) the transfer of any oocyte or embryo into the body of a woman; and (iv) any removal of cells from an embryo for the purpose of testing the embryo.[9] The HCSA 2020 defines an embryo as any live embryo that has a human genome or an altered human genome, and that has been developing for less than 14 days since (i) its fertilisation; (ii) the appearance of two pro-nuclei; or (iii) the initiation of its development by other means.[10] When point (iii) of the assisted reproduction procedure mentioned above is read together with the definition of an embryo under HCSA 2020, one can reasonably conclude that the Healthcare Services (Assisted Reproduction Service) Regulations 2023 do not prohibit heritable gene editing for infertility in Singapore.

c. Human Biomedical Research (Restricted Research) Regulations 2017

2.9 The Human Biomedical Research (Restricted Research) Regulations 2017 require that every research institution and researcher in Singapore who is conducting restricted research[11] must ensure that their research does not involve a human embryo that is more than 14 days old from the time of creation, excluding any period when the development of the embryo is suspended.[12] The regulations also require that the

[7] Government of Singapore. (2004). *Human Cloning and Other Prohibited Practices Act 2004*, Part III, Division 2, Section 11. Other prohibited practices. *Singapore Statutes Online*. https://sso.agc.gov.sg/Acts-Supp/35-2004/Published?DocDate=20040927

[8] Government of Singapore. (2004). *Human Cloning and Other Prohibited Practices Act 2004*. Part III, Division 2, Sections 7 and 8. Other prohibited practices. *Singapore Statutes Online*. https://sso.agc.gov.sg/Act-Rev/HCOPPA2004/Published?DocDate=20050731

[9] Ministry of Health. (2023). *Healthcare Services Act 2020*, Part 1: Definitions. Healthcare Services (Assisted Reproduction Service) Regulations 2023. *Singapore Statutes Online*. https://sso.agc.gov.sg/SL/HSA2020-S429-2023?DocDate=20230623

[10] Ministry of Health. (2020). *Healthcare Services Act 2020*, First Schedule: Licensable healthcare Services. *Singapore Statutes Online*. https://sso.agc.gov.sg/Act/HSA2020?=&ProvIds=Sc1-

[11] 'Restricted research' refers to any restricted human biomedical research as set out in the Fourth Schedule of the Human Biomedical Research Act 2015, including human biomedical research involving human eggs or human embryos.

[12] Government of Singapore. (2017). *Human Biomedical Research Act 2015 (Act 29 of 2015)*. S 622, Human Biomedical Research (Restricted Research) Regulations 2017, Part 3, Section 10. Research involving oocytes and embryos. *Singapore Statutes Online*. https://sso.agc.gov.sg/SL/HBRA2015-S622-2017/Historical/20171101

research institution and the researcher ensure that only surplus embryos created in assisted reproduction treatment and embryos that are no longer required for therapeutic purposes may be used for research. While the regulations do not expressly prohibit research on heritable gene editing, specific research projects involving embryonic development would require approval from the relevant government authorities in addition to approval from the relevant IRBs.

II. Overseas Legislation for HNGE

i. Non-Heritable Gene Editing (for research and clinical applications)

2.10 Countries such as Australia, Germany, South Korea, New Zealand, the US, and the UK do not currently regulate non-heritable gene editing for research. As such, non-heritable gene editing for research is allowed in these countries. However, non-heritable gene editing for clinical applications is regulated by the US and Europe.

The US

2.11 In the US, human gene editing falls under the purview of the FDA and the National Institute of Health (NIH).[13] Gene therapy products that seek to modify or manipulate genetic expression to alter biological properties of living cells for treatment purposes are regulated by the Center for Biologics Evaluation and Research (CBER).[14] Most products used in clinical applications of non-heritable gene editing, such as viral or non-viral vectors, are regarded as biologic drugs and are regulated with gene therapy products. While clinical applications of non-heritable gene editing are not prohibited, they must be reviewed by the FDA pursuant to its authority under the Federal Food, Drug, and Cosmetic Act (Public Law 75-717) and the Public Health Service Act (Public Law 78-410).[15] Meanwhile, the US NIH Somatic Cell Genome Editing (SCGE) Consortium was set up with the aim of accelerating the development of safer and more effective methods of non-heritable gene editing in patients.[16] This is because gene editing technologies have been recognised for their potential to develop therapies for common and rare diseases caused by genetic disorders. Therefore, improving the safety and efficacy of techniques employed in non-heritable gene editing would provide greater therapeutic options for patients.

Europe

2.12 In Europe, non-heritable gene editing, along with gene therapy and tissue engineered products, are classified as advanced therapy medicinal products (ATMPs) and are regulated by the European Medicines Agency (EMA).[17] Specifically, the European Union's Regulation (EC) No 1394/2007 provides an overall framework for ATMP

[13] Liu, S. (2020). Legal reflections on the case of genome-edited babies: Global health research and policy. *BioMed Central*. https://ghrp.biomedcentral.com/articles/10.1186/s41256-020-00153-4

[14] Center for Biologics Evaluation and Research. (n.d.). *Cellular & gene therapy products*. U.S. Food and Drug Administration. https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products

[15] National Academies of Sciences, et al. (2017). *Human genome editing: science, ethics and governance*. https://www.ncbi.nlm.nih.gov/books/NBK447266/

[16] National Institutes of Health. (2023). *Somatic cell genome editing*. https://www.commonfund.nih.gov/editing

[17] European Medicines Agency. (2023). *Advanced therapy medicinal products: Overview*. https://www.ema.europa.eu/en/human-regulatory/overview/advanced-therapy-medicinal-products-overview

regulation.[18] This also includes materials used in clinical trials for non-heritable gene editing, which is regulated by the Directive 2001/83/EC.[19] ATMPs require licensing of clinical trials by the Medicines and Healthcare Products Regulatory Agency, and market authorisation from the EMA. The regulatory framework for AMTPs is designed to facilitate distribution of these medicines within the European Union, while also maintaining the highest level of protection for the health and interest of patients.

ii. Heritable Gene Editing for Clinical Research and Applications, and Gene Editing in Embryos or Germline Cells for Research[20]

2.13 Countries such as Australia, Germany, Israel, South Korea, New Zealand and the US prohibit heritable gene editing for clinical research and applications. Gene editing in embryos or germline cells for research is allowed in Australia, South Korea and New Zealand while the US, however, prohibits federal funding for research carried out involving gene editing in germline cells.

Australia

2.14 In Australia, the use of human embryos in research is regulated under the Prohibition of Human Cloning for Reproduction Acts[21], which aims to address ethical concerns about scientific developments pertaining to human reproduction and the utilisation of human embryos by prohibiting certain practices. Practices that are completely prohibited under the Act include heritable alterations to genomes.[22] An individual, therefore, would be committing an offence if they were to alter the gene of a human cell in such a way that the alteration is heritable, or intended to be inherited, by descendants of the human whose cell was altered. The Act also prohibits intentionally developing a human embryo outside the body of a woman for a period of more than 14 days, excluding any period when development is halted.

China

2.15 In China, any individual who is unqualified to practise medicine yet does so in contravention of law, shall be fined, sentenced to a fixed-term imprisonment of up to three years or both, criminal detention or public surveillance, depending on the severity. This is enshrined within Article 336 of the Criminal Law of the People's Republic

[18] European Parliament and Council. (2007). *Regulation (EC) No. 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No. 726/2004*. EUR-Lex. https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=celex%3A32007R1394

[19] European Parliament and Council. (2001). *Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use*. EUR-Lex. https://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1410944582971&uri=CELEX%3A02001L0083-20121116

[20] Most legislation pertaining to heritable genome editing for clinical applications and genome editing in embryos or germline cells for research reference the '14-day rule', which, while an international ethical standard that limits laboratory studies in human embryos and requires scientists and researchers to destroy human embryos grown in lab before they reach 14 days, remains one that some researchers and scientists favour revising in order to further study the embryonic developmental process, which occurs between 14 and 28 days. Extending the '14-day rule' might allow researchers to adopt simple treatment options (i.e., apart from surgical interventions) to reduce the amount of pain that the future child goes through due to congenital abnormalities that develop during this period (quoted by British scientist, Robin Lovell-Badge, a stem cell expert at London's Crick Institute). However, some ethicists argue that extending this period may cross a moral boundary while it is also unclear exactly how such a change would advance research. NBC News. (2021, February 26). *New guidelines suggest lifting '14-day rule' on growing human embryos in the lab* https://www.nbcnews.com/health/health-news/new-guidelines-suggest-lifting-14-day-rule-growing-human-embryos-n1268628

[21] Government of Australia. (2002). *Prohibition of Human Cloning for Reproduction Act 2002*. https://www.legislation.gov.au/Details/C2017C00306

[22] Government of Australia. (2002). *Prohibition of Human Cloning for Reproduction Act 2002.* Section 15. Offence: heritable alterations to genome. *AustLII*. https://www.austlii.edu.au/au//legis/cth/consol_act/pohcfra2002465/s15.html

of China 1979 and also applies to human genome editing for clinical applications or on germline cells.[23] He Jiankui was charged and convicted under this Article for carrying out gene editing on human embryos which were implanted into a woman and later resulted in the birth of twin girls. The Chinese Civil Code, issued in May 2020, states that medical and scientific research activities involving human genes and embryos, among others, shall be performed in accordance with laws, administrative regulations and relevant provisions outlined by the state without endangering human health, violating moral principles or damaging the public interest.[24] According to this framework, anyone who engages in scientific research or medical activities that contravene ethics and morality in China will be considered to have violated personal rights and can be subject to civil liabilities.

Germany

2.16 In Germany, the editing of germline cells is regulated under the Embryo Protection Act.[25] Section 5 of the Act, which pertains to artificial alteration of human germline cells, states that anyone who artificially alters the genetic information of a human germline cell will be punished with imprisonment of up to five years or a fine. However, this does not apply to artificial alteration of the genetic information of a germ cell situated outside the body where that altered germ cell is not used for fertilisation. The Act also states that anyone who uses a human germ cell with artificially modified genetic information for fertilisation will be similarly punished.

Israel

2.17 In Israel, the use of reproductive cells that have undergone permanent intentional genetic modification (germline gene therapy) thus leading to the creation of human life, is prohibited under the Prohibition of Genetic Intervention (Human Cloning and Genetic Manipulation of Reproductive Cells) Law.[26]

South Korea

2.18 In South Korea, the Bioethics and Safety Act permits gene therapy research solely for a hereditary disease, Acquired Immune Deficiency Syndrome (AIDS) or any other disease that threatens lives or causes a severe disability, as well as for situations where there is no applicable therapy at present or where the benefit of gene therapy is expected to be significantly greater than from other therapies.[27] Such research, South Korea's legislation stipulates, should only be conducted before the primitive streak of the embryo appears during embryonic development.[28]

[23] Normille, D. (2023). In wake of gene-edited baby scandal, China sets new ethics rules for human studies. *Science*. https://www.science.org/content/article/wake-gene-edited-baby-scandal-china-sets-new-ethics-rules-human-studies

[24] Yaojin, P., et al. (2022). Responsible governance of human germline genome editing in China. *Biology of Reproduction*, 101(1), 261–268. https://doi.org/10.1093/biolre/ioac114

[25] Federal Law Gazette. (1990). *Act for the protection of embryos (The Embryo Protection Act)*. https://www.bundesgesundheitsministerium.de/fileadmin/Dateien/3_Downloads/Gesetze_und_Verordnungen/GuV/E/ESchG_EN_Fassung_Stand_10Dez2014_01.pdf

[26] Government of Israel. (1999). *Prohibition of genetic intervention (human cloning and genetic manipulation of reproductive cells) Law*, 5759–1999. http://www.hinxtongroup.org/docs/israel.html (English Translation by The Hinxton Group – an international consortium on stem cells, ethics & law)

[27] Bioethics and Safety Act No. 12844. (2014). Article 47: *Gene therapies*. https://elaw.klri.re.kr/eng_mobile/viewer do?hseq=33442&type=part&key=36

[28] Bioethics and Safety Act No. 12844. (2014). Article 29: *Residual embryos research*. https://elaw.klri.re.kr/eng_mobile/viewer.do?hseq=33442&type=part&key=36

New Zealand

2.19 In New Zealand, the Human Assisted Reproductive Technology Act prohibits the implantation of a genetically modified gamete, human embryo or hybrid embryo into a human.[29] The Act also prohibits research on non-viable embryos beyond 14 days.[30]

The US

2.20 The US's National Institutes of Health (NIH) Regulation states that NIH funds may not be used for the creation of a human embryo or embryos for research purposes, or for research in which a human embryo or embryos are destroyed, discarded or knowingly subjected to risk of injury or death greater than that allowed for research on foetuses *in utero* under 45 CFR 46.204(b) and Subsection 498(b) of the Public Health Service (PHS) Act (42 U.S.C. 289g(b)). NIH will not fund any use of gene-editing technology in human embryos for clinical applications.[31]

III. Comparison Between Local and Overseas Legislation for HNGE

a. Non-Heritable Gene Editing (for Research and Clinical Applications)

2.21 As in Singapore, the likes of Australia, Germany, South Korea, New Zealand, the US, and the UK have no legislation currently in place explicitly prohibiting the use of non-heritable gene editing in research.

2.22 The US and Europe generally regulate products of non-heritable gene editing as gene therapies to be conducted under clinical trials, similar to the practice in Singapore. However, in Singapore, in-house CTGTPs may be used for medical treatment if approved by CECs.

b. Clinical research and Applications of Heritable Gene Editing and Gene Editing in Embryos or Germline Cells for Research

2.23 There is legislation in place in Australia, Germany, Israel, South Korea, New Zealand and the US, to prohibit heritable gene editing for clinical research and applications, which are comparable to the Human Cloning and Other Prohibited Practices Act 2004 in Singapore. At the same time, Australia, New Zealand, Germany and South Korea also allow gene editing in embryos or germline cells for research purposes, as does Singapore's Human Biomedical Research Act 2015. Singapore allows research on embryos from inception to 14 days, or up until the appearance of the primitive streak, whichever is earlier. In contrast, legislation in Australia and New Zealand reference only the '14-day rule', whereas South Korean legislation mentions only the appearance of the primitive streak. However, German legislation references neither the '14-day rule' nor the appearance of the primitive streak.

[29] Parliamentary Counsel Office. Human Assisted Reproductive Technology Act 2004. *Schedule 1*: *Prohibited actions*. https://legislation.govt.nz/act/public/2004/0092/latest/whole.html#DLM319832

[30] Parliamentary Counsel Office. Human Assisted Reproductive Technology Act 2004, Part 2. *Prohibited and regulated activities*. https://legislation.govt.nz/act/public/2004/0092/latest/whole.html#DLM319311

[31] Francis, S. (2015). Statement on NIH funding of research using gene-editing technologies in human embryos. National Institutes of Health. https://www.nih.gov/about-nih/who-we-are/nih-director/statements/statement-nih-funding-research-using-gene-editing-technologies-human-embryos

2.24 South Korea's laws specify that gene therapy research should only be conducted for hereditary diseases or diseases that threaten lives or cause a severe disability, and for diseases that have no applicable therapy at present. In contrast, Singapore's Human Biomedical Research (Restricted Research) Regulations 2017 do not specify the scope of gene editing in embryos or germline cells for research purposes, as is the case for the corresponding Australian and New Zealand legislation. Separately, gene editing in embryos or germline cells for research purposes is prohibited with the use of federal funding in the US, but is not otherwise prohibited.[32] However, unlike Singapore, the legislation in the US does not specify the need to conduct such research on embryos before 14 days, or up until the appearance of the primitive streak.

IV. Overview of Guidelines for HNGE

2.25 While there are no specific guidelines on HNGE in Singapore, the BAC had previously recommended in its report on 'Genetic Testing and Genetic Research (2005)' that the clinical practice of germline genetic modification should not be allowed.[33] The BAC has also recommended in its report on 'Ethics Guidelines for Human Biomedical Research (2021 Revised)' that research involving human germline modification for purposes other than the prevention or treatment of serious genetic conditions should not be allowed, reiterating that the clinical practice of germline modification should be prohibited until there is adequate evidence from research that such clinical procedures are safe and effective.[34]

2.26 The World Health Organization (WHO) developed recommendations on the governance and oversight of human gene editing in nine discrete areas, including human genome editing registries and illegal, unregistered, unethical or unsafe research.[35] The International Commission on the Clinical Use of Human Germline Genome Editing recommends that a country should only allow heritable gene editing for clinical applications if it meets the criteria outlined in paragraph 2.32.[36]

2.27 The International Society for Stem Cell Research (ISSCR) recommends against the use of heritable gene editing for therapeutic purposes but supports the use of gene editing in embryos or germline cells for research purposes. Ethics bodies such as the German Ethics Council and the Spanish Bioethics Committee on Genome Editing in Humans have also recommended against the use of heritable gene editing for clinical applications. Japan too, has published guidelines that recommend against the use of heritable gene editing for clinical applications.

[32] Stein, R. (2019). *New U.S. experiments aim to create gene-edited human embryos*. NPR. https://www.npr.org/sections/health-shots/2019/02/01/689623550/new-u-s-experiments-aim-to-create-gene-edited-human-embryos#:~:text=The%20U.S.%20government%20prohibits%20the,embryos%20to%20create%20a%20pregnancy

[33] Bioethics Advisory Committee, Singapore. (2005). *Genetic testing and genetic research report*. https://www.bioethics-singapore.gov.sg/files/publications/reports/genetic-testing-and-genetic-research-full-report.pdf

[34] Bioethics Advisory Committee, Singapore. (2021). *Ethics guidelines for human biomedical research* (2021 rev. ed.). Annexe A, Section 5.33. https://www.bioethics-singapore.gov.sg/publications/reports/bac-ethics-guidelines-2021

[35] World Health Organization. (2021). WHO issues new recommendations on human genome editing for the advancement of public health. https://www.who.int/news/item/12-07-2021-who-issues-new-recommendations-on-human-genome-editing-for-the-advancement-of-public-health

[36] National Academy of Medicine, National Academy of Sciences, & Royal Society. (2020). *Heritable human genome editing*. The National Academies Press. https://doi.org/10.17226/25665

V. HNGE Guidelines Which Explicitly Recommend Against Heritable Gene Editing

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

2.28 In 2021, the WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing developed new recommendations and published two reports, namely a framework for governance and its recommendations, aimed at establishing human (both heritable and non-heritable) gene editing as a means of improving public health across the world.[37] Its framework for governance report serves to provide guidance to different groups of stakeholders to strengthen governance of gene editing technologies at the institutional, national, regional and indeed global levels. The committee's recommendations report pertains to both the clinical and research applications of gene editing and includes advocacy for changes to policy and practice to support the reporting of possible illegal, unregistered, unethical or unsafe non-heritable gene editing, heritable gene editing and gene editing in embryos or germline cells for research purposes. The WHO encourages all its member nations to utilise the tools for governance set out in its report on framework for governance. The WHO also advocates member nations to collaborate with it to ensure that the recommendations of the committee are implemented expeditiously.

b. The International Society for Stem Cell Research (ISSCR)

2.29 The International Society for Stem Cell Research (ISSCR) Guidelines (2021) support the use of gene editing on germline cells for research purposes only after review and approval via a specialised scientific and ethics review process.[38] The ISSCR Guidelines also recommend that a specialised scientific and ethical oversight process may be used to assess whether the scientific objectives require the embryo to be developed in culture for a period greater than 14 days. The guidelines also recommend that research involving human embryos, in which the nuclear genome has undergone modification, are not allowed to be transferred into, or gestated in, a human uterus, as these approaches are currently deemed unsafe and raise unresolved ethical issues.

c. German Ethics Council: Intervening in the Human Germline (Opinion - Executive Summary and Recommendations) (2019)

2.30 The German Ethics Council published a report titled 'Intervening in the Human Germline', which called for an international moratorium on heritable gene editing for medical purposes in humans.[39] The Council's report serves to encourage a discussion and an evaluation of the possible goals of germline interventions in humans; determine the cases and conditions for which germline interventions may be allowable in the future; prevent premature applications of the same; and to allow time for careful basic and preclinical research to determine the safety and efficacy of heritable gene editing for clinical applications.

[37] World Health Organization. (2021). *Human genome editing: Recommendations*. https://www.who.int/publications/i/item/978924003038

[38] International Society for Stem Cell Research. (2021). *ISSCR guidelines for stem cell research and clinical translation*. https://www.isscr.org/docs/default-source/all-isscr-guidelines/2021-guidelines/isscr-guidelines-for-stem-cell-research-and-clinical-translation-2021.pdf?sfvrsn=ced254b1_4

[39] German Ethics Council. (2018). *Germline intervention in the human embryo*. https://www.ethikrat.org/fileadmin/Publikationen/Ad-hoc-Empfehlungen/englisch/recommendation-germline-intervention-in-the-human-embryo.pdf

d. Japan's Guidelines for Research Using Gene-altering Technologies on Human Fertilised Embryos (2019)

2.31 In Japan, the Guidelines for Research Using Gene-altering Technologies on Human Fertilised Embryos support the gene editing of human embryos for research that is aimed at understanding the development of diseases, and to treat genetic diseases. These guidelines, however, recommend against germline gene editing for reproductive purposes and clinical testing.[40]

VI. HNGE Guidelines that Recommend Heritable Gene Editing be Allowed Conditionally

a. The International Commission on the Clinical Use of Human Germline Genome Editing (2020)

2.32 The International Commission on the Clinical Use of Human Germline Genome Editing aims to provide a framework for scientists, clinicians and regulatory authorities to consider when assessing potential clinical applications of heritable gene editing, should heritable gene editing applications become socially acceptable in the future.[37] It recommends that the use of heritable gene editing for treatment of diseases and infertility should be permitted only under the following conditions:

a. Serious monogenic diseases that cause severe morbidity or premature death;
b. Changing a pathogenic genetic variant known to be responsible for the serious monogenic disease to a sequence that is common in the relevant population and that is known not to cause disease;
c. Ensuring that no embryos without the disease-causing genotype will be subjected to the process of genome editing and transfer, and no individuals resulting from edited embryos are exposed to risks of HNGE without any potential benefit; and
d. Situations in which prospective parents have no option for having a genetically related child that does not have the serious monogenic disease because none of their embryos would be genetically unaffected in the absence of genome editing; or have extremely poor options because the expected proportion of unaffected embryos would be unusually low, which the Commission defines as 25 percent or less, and have attempted at least one cycle of preimplantation genetic testing without success.

b. The World Medical Association's Statement on Human Genome Editing

2.33 The World Medical Association issued a statement on human gene editing in 2020, in which it recommended that human gene editing should be implemented according to appropriate evidence that is collated via well-conducted and ethically-approved research studies.[41] The statement added that gene editing on germline cells for research purposes should be allowed only within a separate ethical and legal framework, distinct from any ethical and legal frameworks that apply to non-heritable

[40] Ministry of Education, Culture, Sports, Science and Technology (MEXT), & Ministry of Health, Labor and Welfare (MHLW) (Japan). (2019). *Guidelines for research using gene-altering technologies on human fertilized embryos*. mext.go.jp/lifescience/bioethics/files/pdf/Overview_Human_embryo_geneome-editing_guideline2019JEn.pdf

[41] World Medical Association. (2020). WMA statement on human genome editing. https://www.wma.net/policies-post/wma-statement-on-human-genome-editing/

gene editing. The World Medical Association further recommends that governments should support the continued development of an international consensus, grounded in science and ethics, to determine allowable therapeutic applications of germline gene editing.

2.34 Legislation and guidelines play an important role in navigating the ethical, legal and social implications surrounding gene editing. It is imperative that researchers and research institutions adhere to these acts of legislation and guidelines in order to ensure ethical and safe utilisation of gene editing technology. These frameworks provide the necessary safeguards against potential risks from applications of gene editing technology and protect human health and societal values. This also ensures benefits of gene editing are realised in a manner that respects the autonomy and rights of all individuals and communities.

CHAPTER 3:
GENERAL ETHICAL PRINCIPLES

I. General Ethical Principles

3.1 In its deliberations over the use of HNGE in biomedical research and clinical applications, the BAC remains guided by substantive[1] and governance principles with the former including considerations of *'Respect for persons'*, *'Solidarity'*, '*Justice*', *'Proportionality'* and *'Sustainability'*, all of which are discussed in greater detail below:

a. Respect for persons

3.2 *Respect for persons* behoves us to treat individuals as beings with value in themselves along with autonomy for their own life and, accordingly, to respect their right to make their own decisions without being coerced, misled or kept in ignorance. The welfare and interests of individuals are paramount, especially when their autonomy is impaired or lacking. It is this principle that underlies the importance of obtaining informed consent from potential research participants or those who are making decisions on their behalf. This applies also to entities involved in research, the protection of their privacy alongside information disclosed in confidence, and preventing or minimising harm to them.

3.3 In the context of HNGE, the principle of *respect for persons* denotes the autonomy of individuals making decisions related to biomedical research that involve gene editing or its clinical applications. The autonomy of a person may be compromised if they are not fully informed of the possible benefits, risks and repercussions that follow on from research and clinical applications of gene editing technology. It is important to consider not only the autonomy of those making decisions but also the best interests of people with little or no capacity to give valid informed consent (e.g., children). Individuals have the autonomy and the right to decide whether to undergo non-heritable gene editing, and the autonomous right to engage in germline human gene editing for their offspring. Gene editing in embryos or germline cells for research, heritable gene editing for treatment of diseases, conferring resistance, enhancement of traits, and for infertility if permitted in the future, may indirectly compromise the rights, autonomy and physical integrity of the child born as a consequence of the intervention. While gene editing does not violate the autonomy and rights of modified embryos or germline cells, since they have no autonomy per se that can be violated in the first place, some argue that it infringes the autonomy and rights of the child who is consequently born to an open future,[2] where gene editing limits the range of set life-options,[3] since they are unable to provide consent prior to being genetically modified.

[1] Bioethics Advisory Committee. (2022). Ethical principles. https://www.bioethics-singapore.gov.sg/who-we-are/ethical-principles/

[2] The right to an open future encompasses a set of moral rights children possess that are derived from the autonomy rights of adults, which protects the child against having important life choices determined by others before he or she has the ability to make them for himself or herself.

[3] Mintz, R. L., Loike, J. D., & Fischbach, R. L. (2019). Will CRISPR germline engineering close the door to an open future? *Science and Engineering Ethics, 25(5)*, 1409–1423. https://philpapers.org/rec/MINWCG

b. Solidarity

3.4 The BAC takes the position that some measure of mutual obligation exists between the individual and society such that in certain specific circumstances, individual interests ought to be subordinated to achieve or promote the public good. The principle of *solidarity* reflects the moral obligations of individuals, such as research participants, researchers and research institutions, to share the costs associated with the design and conduct of research, including potential risks, in return for the common good. In the context of biomedical research, acceptance of agreed social benefits is typically considered a public good, thus supporting an in-principle willingness to consider participation in research that yields the accepted benefits. There is also a need to balance the interests of the public or society with the rights and interests of individual participants such that individual interests are not unnecessarily sacrificed but are also advanced for the public good. This would help resolve incompatible and irreconcilable perspectives on the good or right thing to do.

3.5 *Solidarity* reflects the importance of general altruism and other pro-social motives as a basis for participation in biomedical research. For instance, research in human gene editing may reap benefits for society by enabling faster and more accurate diagnosis of diseases or patient conditions, introducing more targeted treatments and enabling early prevention of genetic disorders. While biomedical research is important in realising the long-term benefits from the applications of gene editing, it is also crucial to note that misuse and abuse of such technology for inappropriate purposes, or to effect personal trait preferences, could lead to the neglect or failure to discharge obligations towards certain subgroups, such as those suffering from rare diseases.

c. Justice

3.6 The principle of *justice* encompasses the general principles of fairness and equality for all individuals, which implies that access to the benefits of biomedical research and the burden of supporting it, should be shared across society equitably. This principle also includes rights-based *justice*, which focuses on ensuring that individuals' rights are respected and protected throughout the research process. In the event of research yielding an immediate benefit that could be applied to research participants, the principle of *justice* would dictate that the benefits are shared with them fairly, as a way of reciprocating their contribution to the research. The principle of *justice* also implies that researchers and their institutions shoulder some responsibility for the welfare of participants in the event of adverse outcomes arising directly from their participation in the research.

3.7 In the context of research and clinical applications of HNGE, *justice* requires that gene editing technology and therapy are accessible to the public according to a plausible theory of *justice*. However, the technology involved may raise concerns about ensuring fair access to therapy due to the high cost incurred. As such, treatments involving the use of gene editing technology may not be widely or readily accessible to the entire population, particularly among lower socioeconomic status groups,[4] an inconsistency that may lead to disquiet about societal inequity. Gene editing technology could also

[4] Hildebrandt, C. C., & Marron, J. M. (2018). *Justice* in CRISPR/cas9 research and clinical applications. *AMA Journal of Ethics*, 20(9), E864–E872. https://journalofethics.ama-assn.org/article/justice-crisprcas9-research-and-clinical-applications/2018-09

inadvertently reinforce negative bias or create new forms of discrimination, further prejudicing marginalised groups. Ensuring *justice* in this context involves not only equitable access to HNGE technology, but also addressing potential stigmas and promoting inclusive attitudes towards individuals with disabilities.

d. Proportionality

3.8 The principle of *proportionality* requires that the regulation of research should be proportional to the degree of possible threats to autonomy, individual welfare or the public good. As such, interference with individuals' decisions and/or actions should not exceed what is needed to achieve necessary regulation to promote the public interest. This principle also implies that the risk in any acceptable programme of research, and the stringency of its regulation, should not be disproportionate to any anticipated benefits.

3.9 When assessing the use of gene editing technology in biomedical research or clinical purposes, the potential benefits to individuals and society brought about by the editing of the human genome should outweigh the anticipated risks of such research and clinical applications. The stringency of any regulation or governance framework developed for research employing gene editing, including a *de facto* prohibition of specific research activities, must be proportionate to the risks being mitigated.

3.10 Heritable gene editing interventions may be more acceptable for serious or life-threatening diseases or conditions when no alternative interventions or treatments are available, as the benefits of such applications may outweigh the risks in these circumstances. However, they might be less acceptable when used for conferring resistance against diseases, enhancement of traits or to treat infertility. Hence, researchers and clinicians should determine the aim of the gene editing intervention or research and balance potential benefits against associated risks.

e. Sustainability

3.11 The principle of *sustainability* is understood broadly, to support arguments for the conservation of nature and the minimisation of resource depletion for the good of the planet. Therefore, research processes and outcomes should not unfairly jeopardise or prejudice the welfare of future generations.

3.12 In the context of human gene editing in biomedical research or for clinical purposes, it is recognised that gene editing technology can bring about social benefits. This includes research involving human embryos and heritable gene editing for the treatment of diseases, conferring resistance, enhancement of traits, or treatment for infertility. However, such research might harm the offspring and future generations, directly or indirectly, due to the risks of genetic mutation. Researchers and research institutions are encouraged to allocate and expend research resources to support HNGE research activities, as long as they align with the United Nations (UN) Sustainable Development Goals[5] and are not misused.

[5] United Nations. (2015). *The 17 Sustainable development goals*. https://www.un.org/sustainabledevelopment/sustainable-development-goals/

Other considerations: Beneficence and non-maleficence

While the principles of *beneficence* and *non-maleficence* are not listed explicitly among the BAC's five substantive principles mentioned above, these two principles are instantiated by some of the five principles.

- ***Solidarity and beneficence:*** *Beneficence* preserves individual human welfare, which should be taken into consideration when social benefits are weighed (i.e., principle of *solidarity*).
- ***Proportionality and beneficence:*** The benefits to individuals (i.e., *beneficence*) need to be considered when risks and benefits are weighed (i.e., *proportionality*).
- ***Sustainability and non-maleficence:*** Both principles focus on minimising possible harm, but *sustainability* applies this to the future generations, whereas *non-maleficence* focuses on individual welfare.

II. Governance Principles

3.13 In addition to the five substantive principles discussed above, the BAC has also identified three governance principles as key in the context of HNGE in biomedical research and clinical applications. These three principles aim to guide researchers and institutions in ensuring that an appropriate approach to govern gene editing for research purposes and clinical interventions is adopted.

a. Inclusivity

3.14 Biomedical research and clinical care that is conducted in Singapore should reflect the diversity of the country's population and their benefits should be made accessible worldwide. The advancement of health equity through research is promoted by community engagement and participation. Stakeholders may be engaged by means of dialogue, public consultation and consensus-building within the local community.

3.15 In the context of HNGE, the benefits of research and potential clinical applications of the technology are considered a public good and should be accessible to everyone. However, the ethical implications of HNGE could further widen already divergent views about technology in society, especially among groups aligned by different social, cultural and religious tenets. Hence, there is a need to carefully consider the knowledge and perspectives about HNGE as informed by different social, cultural and religious beliefs. It is important to also work closely with the various groups of people to facilitate 'community-engaged research', where a wide array of opinions and perspectives are considered during the conceptualisation of research plans.

3.16 Decision-makers should consider the views of all stakeholders, taking them into account wherever possible. Appropriate stakeholders such as patients, prospective parents and the wider public as a whole should be consulted and engaged, to identify, prioritise and reach consensus on the specific areas, topics or questions that the research employing gene editing aims to address. This engagement can help researchers understand the needs and concerns of its stakeholders. Meaningful stakeholder engagement occurs when there is an opportunity to influence future

outcomes. In the context of human gene editing in biomedical research, this may include input into research design, ethical oversight or overall governance of the research and its findings.

b. Transparency

3.17 *Transparency* corresponds closely to ethical responsibility and moral and legal liability for the decisions and actions arising directly from research studies that should be attributed to researchers and their institutions. Research methods, analysis and data must be reported and disseminated openly, clearly, comprehensively and in a timely manner. *Transparency* in the reporting of research not only helps ensure that results are reproducible and reliable, but this principle also facilitates proper interpretation and dissemination of findings by other researchers. Transparent reporting mechanisms may also be set up to investigate concerns and possible unlawful actions, as well as to provide support and protection for whistle-blowers. To allow meaningful input from stakeholders such as the public into policy development with regard to the use of HNGE,[6] it is incumbent upon policymakers to institute policies, frameworks and recommendations for research and clinical applications of technologies, including novel and upcoming ones, in a transparent way, so as to promote and uphold public confidence. Meaningful public input with regard to allowing or forbidding HNGE technologies may need to be incorporated into the policy-making process, where government decisions should be subject to transparent social debate.

c. Responsible Stewardship of Science

3.18 The principle of *responsible stewardship of science* refers to the moral requirement to be prudent about resources and to have responsible oversight of all elements, including planning, management and decision-making in research activities in the pursuit of any emerging field in biomedical research.[7] Both evidence-informed basic and applied research need to be pursued with appropriate caution given the uncertainty and risks involved. Established ethical practices, ethical guidelines and legislation should be observed when conducting research on humans, with particular attention given to issues of integrity and conflicts of interest. Research priorities should also be determined by considering the needs of society and how to achieve the maximum social and scientific benefits of research while minimising the potential risks.

3.19 In the context of HNGE in biomedical research, *responsible stewardship of science* requires that the processes and outcomes of HNGE research are aligned with the values, needs and expectations of society, as identified by stakeholder engagement. This extends beyond the dissemination of information and requires taking into consideration the views of all stakeholders, as elaborated earlier under the principle of *inclusivity*.

3.20 In addition, there should be oversight mechanisms in place to ensure research activities are conducted appropriately. For instance, an advisory group could be established within research institutions to oversee the research priority-setting process for gene

[6] National Academies of Sciences, Engineering, and Medicine, National Academy of Medicine, & National Academy of Sciences. (2017). *Human genome editing: Science, ethics, and governance.* National Academies Press. https://www.ncbi.nlm.nih.gov/books/NBK447266/

[7] Sulmasy, D. P. (2017). Ethical principles, process, and the work of bioethics commissions. *Hastings Center Report, 47*(3), S50–S53. https://doi.org/10.1002/hast.722

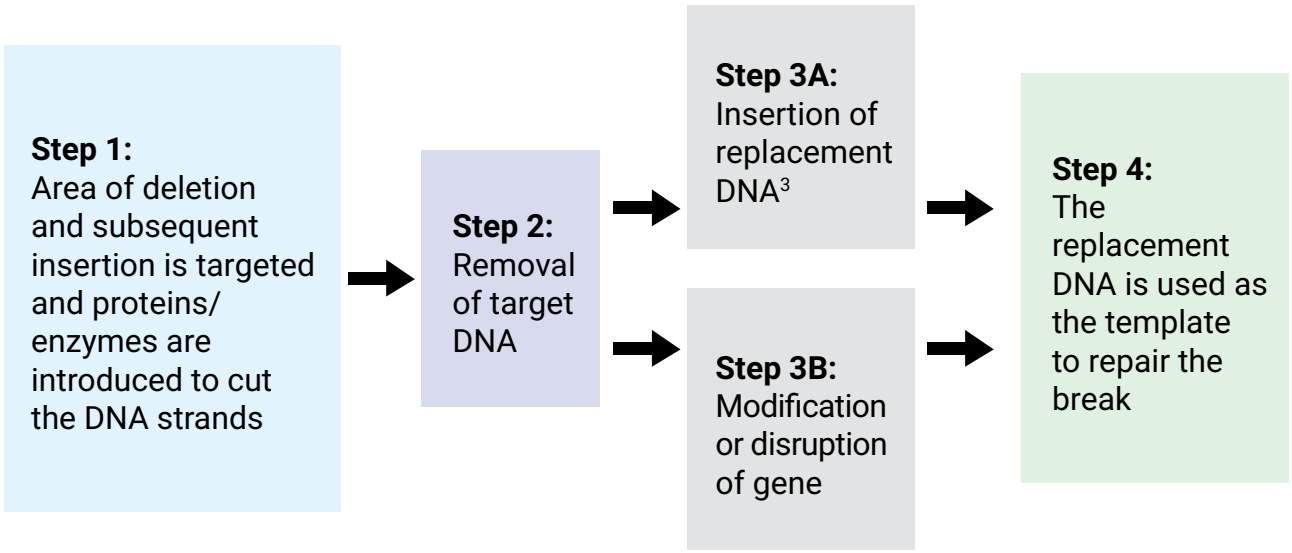
editing research. The group may comprise members from diverse backgrounds (e.g., research, medical, administrative) to advise on the current policy and research considerations, assist with the identification of stakeholders and provide inputs in finalising the research priorities. It is important for researchers and institutions to exercise appropriate caution, given the uncertainty and long-term risks of using gene editing technology in both research and clinical applications. There is also a need to ensure that there are clear and well-established protocols and processes for oversight and review, to ensure that research is conducted in an ethical manner.

CHAPTER 4:
HNGE TECHNIQUES/TECHNOLOGIES AND THEIR RELATIONSHIP WITH GENE AND CELL THERAPIES

I. Gene Editing Technologies Widely Used for Research

4.1 Techniques and tools developed for HNGE have evolved ever since the inception of the technology. Nonetheless, the general steps involved in gene editing for research are similar across these techniques,[1] beginning broadly, with targeting the area of deletion and the subsequent insertion of genes within the genome by introducing proteins or enzymes to cleave the DNA strands. The target DNA is then removed before insertion of replacement DNA or modification/disruption of the gene. The replacement DNA is typically used as a template for repairing the break and generating a healthy form of the gene (see Fig. 4.1).

Figure 4.1: Flowchart Showing the General Steps Involved in Gene Editing[2]



[1] National Human Genome Research Institute. (2017). How does genome editing work? https://www.genome.gov/about-genomics/policy-issues/Genome-Editing/How-genome-editing-works

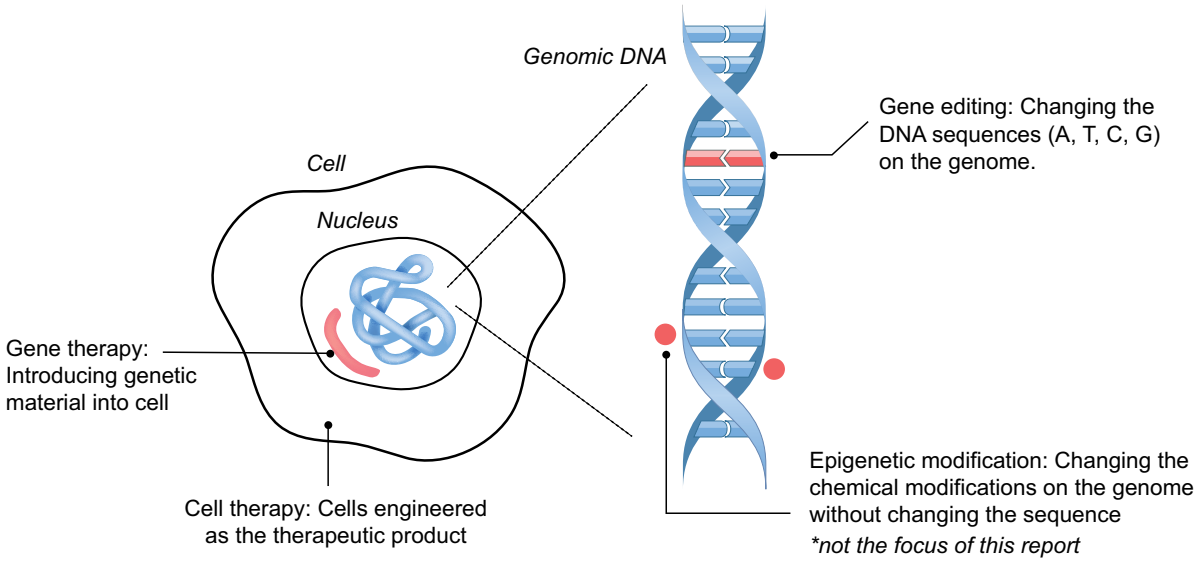
[2] As these are the general steps involved in gene editing, the specific details may vary for different types of gene editing, e.g., base editing does not involve the complete removal of a nucleotide.

[3] Replacement DNA is only required if the break is repaired via a pathway called 'homology-directed repair (HDR)'. Replacement DNA is not necessary if the break is repaired via another pathway, called 'non-homologous end-joining (NHEJ)'. This will be discussed at greater length in later sections.

II. Epigenetic Modifications

4.2 Besides directed genetic alterations, epigenetic modifications can also be made to DNA to regulate its expression by turning the genes on and off and influencing protein production in cells. Unlike gene editing, such processes are reversible, as they do not change the DNA sequences on the genome (Fig. 4.2). As the focus of this report is on heritable genetic changes resulting from human gene editing that causes changes in the DNA sequence, epigenetic modification and its technologies will not be discussed in detail, given that epigenetic modification involves alterations of DNA accessibility and chromatin structure instead of DNA sequence to regulate patterns of gene expression.[4]

Figure 4.2: Cell Diagram Illustrating Gene Editing, Epigenetic Modification, and Cell and Gene Therapy



III. Different Types of Gene Editing Technologies

4.3 While there are many types of gene editing technologies, such as restricted enzymes, Insertion Sequence (IS) elements,[5] retrons,[6] and meganucleases,[7] the core technologies that are now most commonly used by scientists and researchers to facilitate gene editing are ZFNs, CRISPR-Cas9[8] and TALENs (Fig. 4.3 and 4.4).

[4] Diane, E., Rita, C., & Joseph, L. (2011). Epigenetic modifications: Basic mechanisms and role in cardiovascular disease. *Circulation, 110,* 956839. https://doi.org/10.1161/CIRCULATIONAHA.110.956839

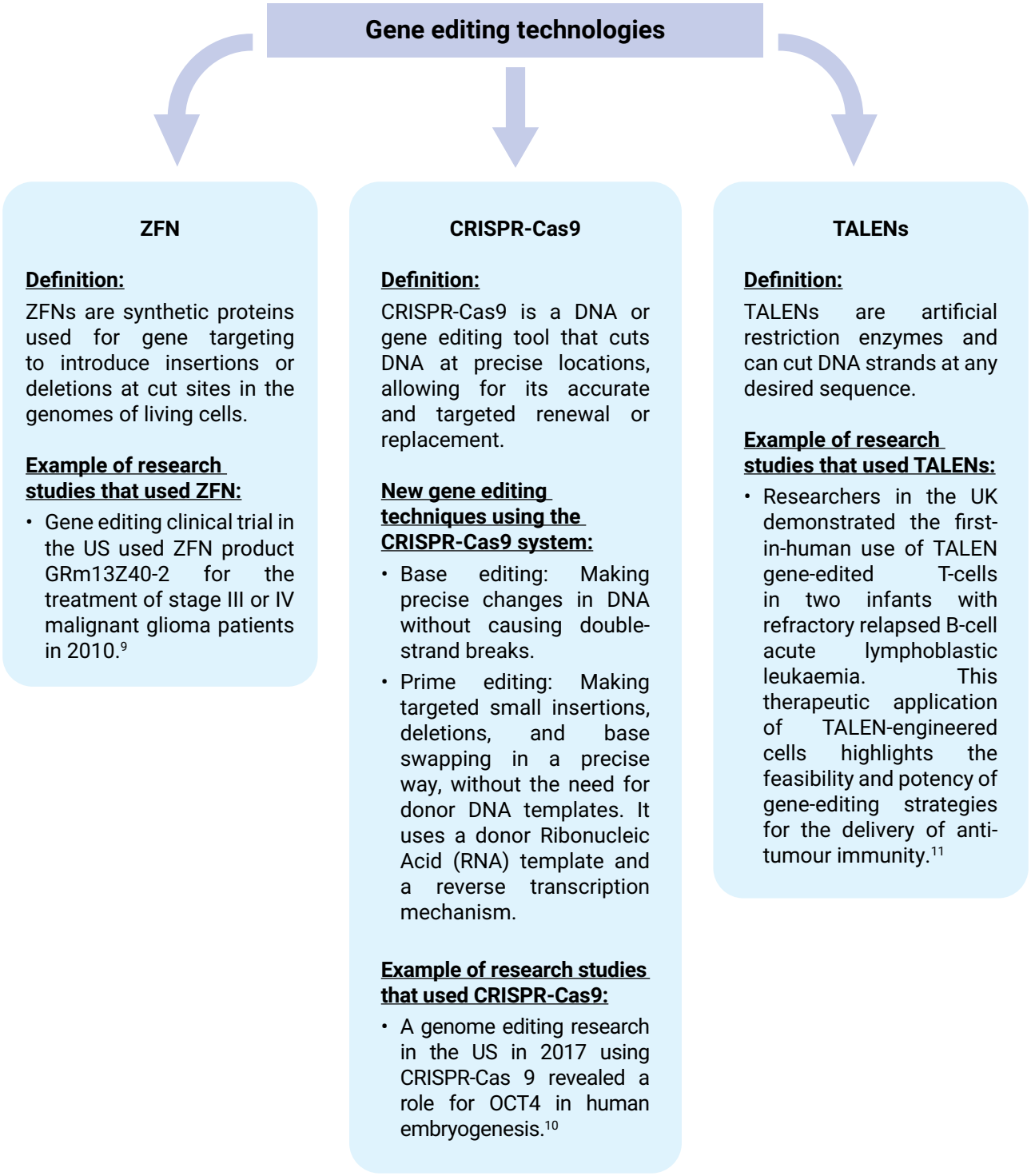
[5] Siddiquee, R., et al. (2024). A programmable seekRNA guides target selection by IS1111 and IS110 type insertion sequences. *Nature Communications, 15*, 5235. https://doi.org/10.1038/s41467-024-49474-9

[6] Zhao, B., et al. (2022). Bacterial retrons enable precise gene editing in human cells. *The CRISPR Journal, 5*(1), pp. 31–39. https://doi.org/10.1089/crispr.2021.0065.

[7] Silva, G., et al. (2011). Meganucleases and other tools for targeted genome engineering: Perspectives and challenges for gene therapy. *Current Gene Therapy, 11*(1), 11–27. https://doi.org/10.2174/156652311794520111

[8] This report focuses on the CRISPR-Cas9 complex as the conventional CRISPR complexes primarily consist of the Cas9 enzyme. Cas3 and Cas12a are other examples of enzymes used in the CRISPR complexes.

Figure 4.3: A Simplified Overview of the Different Types of Gene Editing Technologies

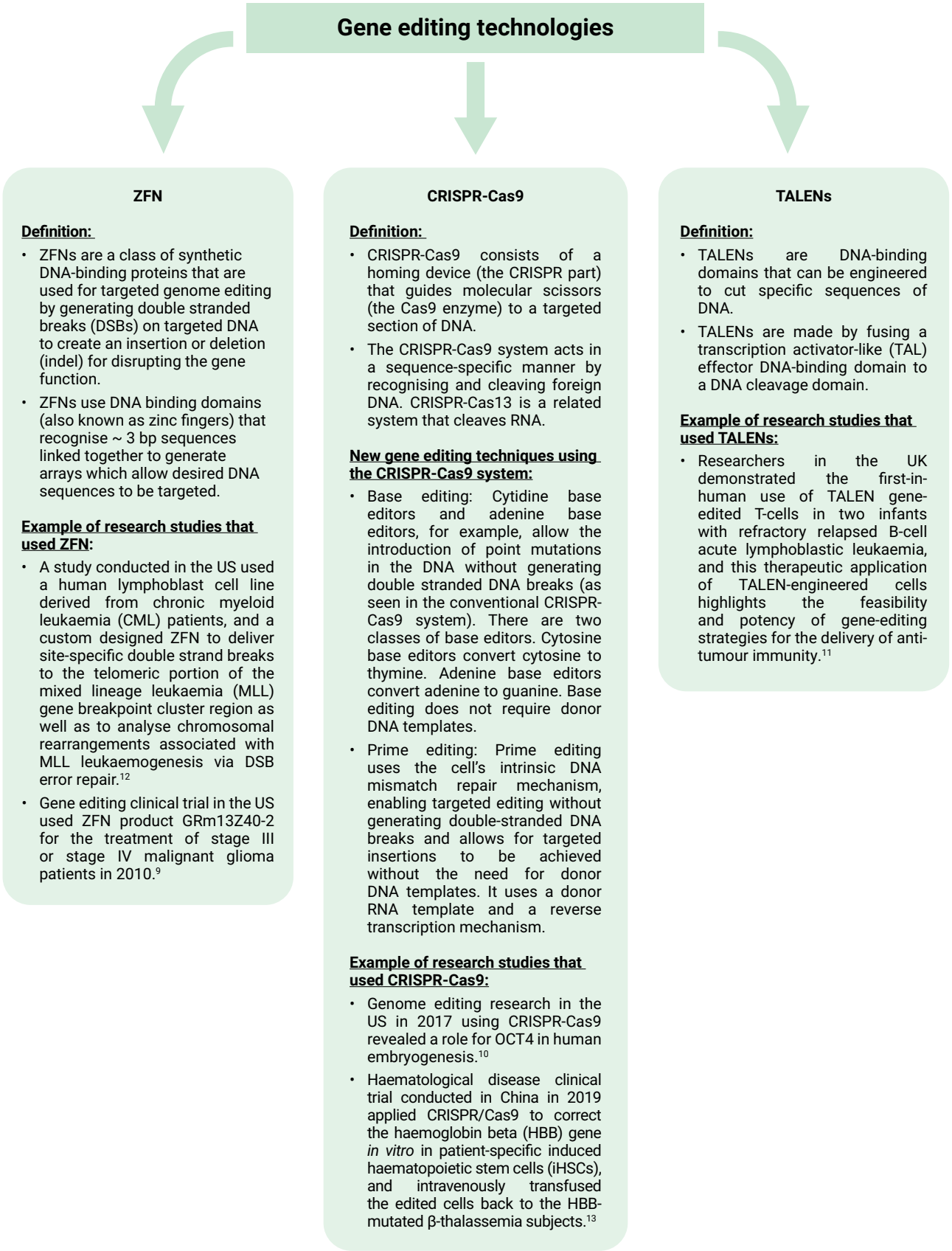


[9] Li, H., et al. (2020). Applications of genome editing technology in the targeted therapy of human diseases: mechanisms, advances and prospects. *Signal Transduction and Targeted Therapy, 5*(1). https://doi.org/10.1038/s41392-019-0089-y

[10] Norah, M., et al. (2017). Genome editing reveals a role for OCT4 in human embryogenesis. *Nature, 550*(7674), 67–73. https://doi.org/10.1038/nature24033

[11] National Health Service, UK. (2015). World first use of gene-edited immune cells to treat 'incurable' leukaemia. Great Ormond Street Hospital. https://www.gosh.nhs.uk/press-releases/world-first-use-gene-edited-immune-cells-treat-incurable-leukaemia/

Figure 4.4: A Detailed Overview of Gene Editing Technologies



[12] Do, T., et al. (2012). A Zinc finger nuclease induced DNA double stranded breaks and rearrangements in MLL. *Mutation Research*, 740, 34–42. https://doi.org/10.1016/j.mrfmmm.2012.12.006

[13] Xie, Y., et al. (2019). CRISPR/Cas9 gene correction of HbH-CS thalassemia-induced pluripotent stem cells. *Annals of Hematology, 98*(1), 85–93. https://doi.org/10.1007/s00277-019-03763-2

IV. The Relationship between Gene Editing, Gene Therapy, and Cell Therapy

4.4 **Gene editing** results in permanent alteration of the genetic material of a living organism by inserting, replacing or deleting a DNA sequence at a particular location in the genome. Gene editing targets the genetic sequence of interest and introduces breaks or chemical modifications to the DNA. In gene editing, breaks among DNA strands are repaired via one of two pathways: homology-directed repair (HDR) or non-homologous end-joining (NHEJ).[9] HDR takes place when a replacement DNA is inserted and used as a template to repair the break, while NHEJ repairs the break without the need for a replacement DNA to act as a template. NHEJ is the less accurate pathway for repairing Cas9-induced DNA double strand breaks and is also the more difficult pathway in terms of controlling outcomes. Gene editing may be carried out using gene editing tools such as ZFNs, CRISPR-Cas9 and TALENs.

4.5 **Gene therapy** refers to the treatment of a patient by altering their genetic composition with exogenous DNA.[14] This may involve using an extra-chromosomal DNA that is not subsequently integrated into the subject's genome, or the modification of the genome via gene editing. Gene therapy is a technique employed to change an individual's genetic makeup with the intent of treating or curing genetic diseases and can work by:

a. Replacing a disease-causing gene with a healthy copy of the gene;
b. Inactivating a disease-causing gene that is dysfunctional;
c. Introducing a new or modified gene into the body to help treat a disease; or
d. Correcting disease-causing mutations.

Gene therapy may be performed either *in vivo*, whereby the therapeutic gene is delivered directly to cells inside the patient's body, or *ex vivo*, where the therapeutic gene is inserted into cells outside the body before being introduced into the body. *Ex vivo* gene therapy is also a form of cell therapy. Gene therapy is generally carried out using genetically modified cell-based immunotherapies, viral vectors, gene editing, and non-viral vectors.

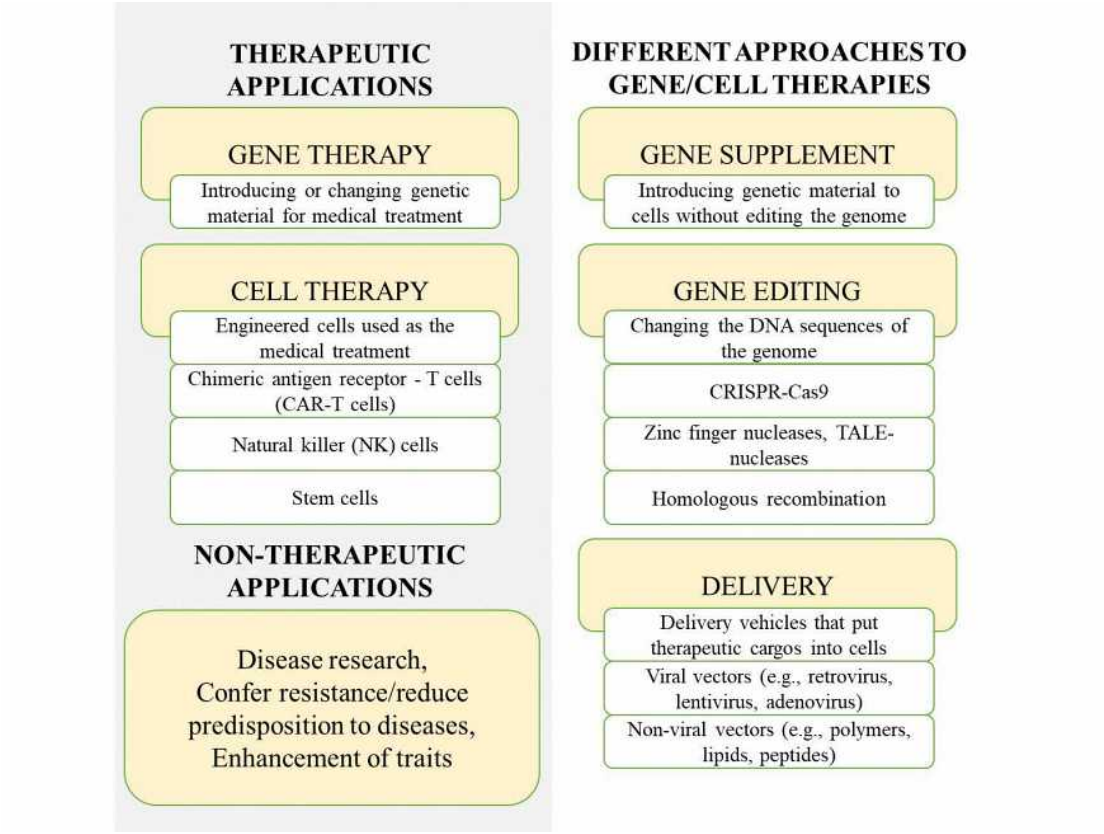
4.6 **Cell therapy** denotes the introduction of new cells into a patient's body to grow, replace or repair damaged tissue in order to treat a disease.[15] The treatment regimen may employ cells from the patient's own body (autologous) or from a donor (allogenic). Cell therapy includes stem cell-based and non-stem cell-based unicellular or multicellular therapies, as well as a variety of different types of cells such as stem cells, lymphocytes, dendritic cells, and pancreatic islet cells. In some cases, such as Chimeric Antigen Receptor – T (CAR-T) and Chimeric Antigen Receptor – Natural Killer Cell (CAR-NK) cell therapies, cells are genetically modified before they are (re)introduced into the patient. This technology interlinks gene therapy and cell therapy. Gene editing techniques such as CRISPR-Cas9, base editing and prime editing may also be applied to correct genetic mutations and/or introduce beneficial edits in targeted stem cells. Gene-edited stem cells are currently, and increasingly, being investigated as a new therapeutic modality.

[14] U.S. Food and Drug Administration. (2018). What is gene therapy? *U.S. Food and Drug Administration*. https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/what-gene-therapy

[15] AstraZeneca. (2023). Harnessing the Power of Cell Therapy. AstraZeneca. https://www.astrazeneca.com/r-d/next-generation-therapeutics/cell-therapies.html

Various studies have shown that genome editing results in priming of stem cells for better therapeutic efficacy, delayed disease progression and protection against genetically driven diseases.[16]

Figure 4.5: Applications of Gene Editing, Gene Therapy, and Cell Therapy[17]



V. Similarities and Differences between Gene Therapy and Gene Editing

4.7 Gene therapy and gene editing, the latter being employed in gene therapy, both target the genetic cause of diseases, such as a variant or mutation in a gene, and treat or halt progression of the disease using genetic material. While gene editing and gene therapy are both used for therapeutic purposes, gene editing does so by delivering genetic material or proteins that can directly edit and change the information that the DNA encodes for in order to correct the protein produced by the DNA and restore proper cellular function.[18] Nonetheless, gene therapy delivers a working gene into a cell using carriers like viral vectors, such as adeno-associated virus (AAVs) and lentivirus vectors, or non-viral vectors such as liposomes to effect the therapy. Gene therapy is used solely for therapeutic purposes while gene editing has applications beyond therapeutics, such as understanding disease development, conferring resistance, reducing predisposition to diseases, enhancement of traits, as well as other non-therapeutic applications of technology underlying human gene editing.

[16] Lee, J., et al. (2020). Recent advances in genome editing of stem cells for drug discovery and therapeutic application. *Pharmacology & Therapeutics, 209*, Article 107501. https://doi.org/10.1016/j.pharmthera.2020.107501

[17] The non-therapeutic applications of gene editing shown in Figure 4.5 are examples and are not exhaustive.

[18] NHS England. (2023). What are genome editing and gene therapy? https://www.genomicseducation.hee.nhs.uk/blog/what-are-genome-editing-and-gene-therapy/

VI. Similarities and Differences between Cell Therapy and Gene Editing

4.8 Cell therapy and gene editing share the objective of modifying the underlying biological mechanism of a disease, by either introducing functional cells (i.e., cell therapy), or altering the genetic material of a living organism (i.e., gene editing). Gene editing technologies, such as CRISPR-Cas9 in particular, are currently being used in cell therapies. While cell therapy provides treatments for inherited or acquired diseases where whole cells are infused or transplanted into a patient, gene editing corrects genetic diseases using enzymes, particularly nucleases that have been engineered to target a specific DNA sequence. Gene editing introduces cuts or chemical modifications into the DNA strands, such that the existing DNA sequence may be changed to another sequence.

CHAPTER 5:
POTENTIAL RESEARCH AND CLINICAL APPLICATIONS OF HNGE AND CURRENT ESTABLISHED METHODS TO TREAT DISEASES

I. Potential Application of HNGE in Research to Understand Diseases or Cancer Development

5.1 Gene editing technology has enabled enzymes such as nucleases to be engineered as biological tools to introduce specific modifications at specific sites within the genomic DNA. Such targeted gene modifications effected by chimeric gene editing tools (e.g., ZFNs, TALENs, and CRISPR-Cas9) are powerful methods of assessing gene function as well as to precisely manipulate cellular behaviour and function. In particular, developments in gene editing technologies have been leveraged by investigators to understand the aetiology behind various diseases and elucidate underlying molecular mechanisms that may be used for better therapeutic strategies.

5.2 Gene editing technology has been applied in research for various purposes and indications. Some examples of research conducted using gene editing technology to understand diseases and cancer development are discussed as follows:

a. Cancer research

5.3 Cancer arises as a result of genomic changes leading to the growth of tumour cells, where undesirable mutations in the gene may lead to the production of proteins harbouring aberrant functions and resulting in uncontrolled cell growth. Gene editing tools such as CRISPR-Cas9 are being used in the field of cancer research to target specific regions of the genome within the cancer cells to understand the causative mechanisms of tumorigenesis and development. For instance, a study conducted in Japan in 2015 modelled colorectal cancer by introducing multiple genetic mutations in human intestinal organoids using CRISPR-Cas9, which allowed researchers to understand the mutation pathway driving cellular growth in the tumour microenvironment.[1] In a similar vein, CAR T-cells[2] and CAR NK-cells[3] have been engineered using CRISPR-Cas9 to specifically target tumour cells. This area of research is also receiving much attention in the pursuit of more effective treatment modalities in cancer.

[1] Matano, M., et al. (2015). Modeling colorectal cancer using CRISPR-Cas9–mediated engineering of human intestinal organoids. *Nature Medicine, 21*(3), 256–262. https://doi.org/10.1038/nm.3802

[2] Dimitri, A., Herbst, F., & Fraietta, J. A. (2022) Engineering the next-generation of CAR T-cells with CRISPR-Cas9 gene editing. *Molecular Cancer, 21*(1), Article 78. https://doi.org/10.1186/s12943-022-01559-z

[3] Pomeroy, E. J., et al. (2020). A genetically engineered primary human natural killer cell platform for cancer immunotherapy. *Molecular Therapy 28*(1), Article 21. https://doi.org/10.1016/j.ymthe.2019.10.009

b. Neurodegenerative Diseases

5.4 Neurodegenerative diseases (NDs), such as Alzheimer's, Huntington's and Parkinson's diseases, are debilitating conditions, each having poor prognosis and clinical outcomes due to the lack of precise diagnostic tools and definite treatments. Studies have found that genetic mutations are one of the causes of neurodegeneration. For example, familial Alzheimer's disease results from mutations in the amyloid precursor protein (APP) and presenilin (PSEN1 and PSEN2) genes, which result in increased production of the amyloid-beta protein responsible for the onset of the neurodegenerative disease.[4] As such, gene editing may offer a novel and promising way of developing ND models for interrogating disease mechanisms as well as to help discover potential drugs for treatment. In 2016, a research group in Rockefeller University (US) generated human-induced pluripotent stem cells (iPSCs) with mutations in the APP and PSEN1 genes using CRISPR-Cas9 to study the early onset of the disease.[5]

c. Hereditary Eye Diseases

5.5 Ocular diseases present with a variety of clinical manifestations, brought about by intrinsic genetic mutations or by external environmental factors. Gene editing technology has been used to probe the mechanisms of hereditary eye diseases too.[6] For example, a research study carried out in China in 2018 employed genetic editing to investigate the molecular mechanism of an inherited retinopathy, retinitis pigmentosa, due to mutation in a GTPase regulator RPGR, which resulted in disorders of the cones and rods in the eye.[7] The study discovered that the correction of the causative mutation in RPGR via CRISPR-Cas9 reverses ciliopathy and rescues photoreceptor loss by restoring gene expression, thus demonstrating the use of CRISPR-Cas9 as a mutation repair strategy.

II. Potential Application of HNGE in Research to Understand the Development of Human Embryos

5.6 The use of human embryos in biomedical research has been heralded as beneficial to the study of human embryo development and understanding of birth defects. In the context of gene editing technology, research involving human embryos may be carried out to potentially discover and develop new treatments for genetic or complex diseases, to enhance the longevity of healthy individuals by delaying ageing and to produce designer babies.[8] In particular, gene editing tools enable the uncovering of the role of specific genes in embryo development in relation to physiology, disease development, pregnancy and miscarriages. In doing so, the underlying genetic causes of these maladies may be established to facilitate the finding of new treatments.

[4] Lanoiselée, H. M., et al. (2017). APP, PSEN1, and PSEN2 mutations in early-onset Alzheimer disease: A genetic screening study of familial and sporadic cases. *PLOS Medicine, 14*(3), Article 1002270. https://doi.org/10.1371/journal.pmed.1002270

[5] Kwart, D., et al. (2019). A large panel of isogenic APP and PSEN1 mutant human iPSC neurons reveals shared endosomal abnormalities mediated by APP β-CTFs, not Aβ. *Neuron*, 104(2), 256–270. https://doi.org/10.1016/j.neuron.2019.07.010

[6] Sundaresan, Y., et al. (2023). Therapeutic applications of CRISPR/Cas9 gene editing technology for the treatment of ocular diseases. *The FEBS Journal, 290*(2), 305–321. https://doi.org/10.1111/febs.16771

[7] Deng, W. L., et al. (2018). Gene correction reverses ciliopathy and photoreceptor loss in iPSC-derived retinal organoids from retinitis pigmentosa patients. *Stem Cell Reports*, 10(4), 1267–1281. https://doi.org/10.1016/j.stemcr.2018.02.003

[8] Savulescu, J. (2015). Five reasons we should embrace gene-editing research on human embryos. *Phys.org*. https://phys.org/news/2015-12-embrace-gene-editing-human-embryos.html

[9] Addie, S., et al. (2020). Stem cell-based models of human embryos. In *Examining the state of the science of mammalian embryo model systems: Proceedings of a workshop.* The National Academies Press. https://www.ncbi.nlm.nih.gov/books/NBK560186

5.7 Human embryos may also be used to construct new disease models for unravelling pathologies of genetic diseases.[9] Screening methods for drug discovery and development in human embryos may be developed for genetic diseases arising from exposure to toxic substances and evaluate potential therapeutic agents for cure. However, it is imperative that the use of gene editing technology for such purposes be further refined and validated before being considered as a therapeutic option.

5.8 Consistent with the use of human embryos for other research purposes, the 14-day rule should be applied for any nuclear gene editing research carried out in human embryos.[10] This rule stipulates that biomedical research is allowed only in early human embryo development.[11] It is prescribed in science policy and regulation to limit all research work carried out on human embryos up to a maximum of 14 days after their creation, or to the equivalent stage of development that is normally attributed to a 14-day-old embryo. Considering that there could be scope for further research developments in the gene editing of human embryos, there might well be a need to revisit and revise the scope and duration (i.e., beyond 14 days) of allowable research in early embryo development. Naturally, substantial efforts would be required to engage large stakeholders (e.g., legislators, medical practitioners and scientists) and indeed the wider public, to ensure that the views of scientists and laymen alike are considered before any changes to the 14-day rule are made.

5.9 In 2017, researchers from The Francis Crick Institute (UK) employed CRISPR-Cas9-mediated gene editing to investigate the function of the pluripotency transcription factor Octamer-binding transcription factor 4 (OCT4) during human embryogenesis.[12] OCT4 was specifically targeted in human zygotes (fertilised human eggs) and found to disrupt blastocyst development. Such studies exemplify the potential of gene editing as a powerful tool for studying early human development.

III. Potential Application of Technology Underlying HNGE as Diagnostics and Drug Discovery Tools

5.10 Rapid and accurate methods of diagnosing diseases are equally and increasingly important in detecting the onset of symptoms and allowing for early interventions. While nucleic-acid-based sensors are the most specific and sensitive, given that trace amounts of DNA and ribonucleic acid (RNA) can be readily amplified and recognised via complementary base-pairing, such technologies require costly equipment and skilled personnel.[13] CRISPR-based diagnostics, such as the CRISPR-Cas9 system, circumvent these issues through a target-specific binding mechanism that is based on nucleotide sequence, and enable the technology to advance diagnostic methods in detecting the disease-related gene, microRNAs, and genetic variations such as single nucleotide polymorphism (SNP) and DNA methylation.

[10] Government of Singapore. (2017). *No. S 622 Human Biomedical Research (Restricted Research) Regulations. Singapore Statutes Online*. https://sso.agc.gov.sg/SL/HBRA2015-S622-2017

[11] Blackshaw, B. P., & Rodger, D. (2021). Why we should not extend the 14-Day rule. *Journal of Medical Ethics, 47*(10), 712–714. https://doi.org/10.1136/medethics-2021-107317

[12] Fogarty, N. M., et al. (2017). Genome editing reveals a role for OCT4 in human embryogenesis. *Nature, 550*(7674), 67–73. https://doi.org/10.1038/nature24033

[13] Zhang, Z., et al. (2023). Functional nucleic acid-based biosensors for virus detection. *Advanced Agrochem, 2*(3), 246–257. https://doi.org/10.1016/j.aac.2023.07.006

5.11 CRISPR-based diagnostics not only allow for a faster and more accurate diagnosis of diseases in the clinic, but also bolster progress in the field of personalised medicine, such as by enabling point-of-care testing (i.e., testing is conducted near a patient/person outside a clinical laboratory setting) by untrained personnel at the individual's home. CRISPR-Cas9 diagnostics may be categorised into two broad classes, six types and several subtypes based on evolutionary relationships. While applications of CRISPR as diagnostics are mostly still in development, three of note are discussed here:

a. Diagnostic Tool: Specific high sensitivity enzymatic reporter UnLOCKing (SHERLOCK)

5.12 SHERLOCK is a CRISPR-based diagnostic system that is guided by RNA, and which was developed in 2017 by the Broad Institute.[14] This technology is able to identify low-frequency mutations in cancer cells that are not easily identifiable by other sequencing methods and may be used to detect specific viral strains as well as differentiate between bacterial strains. Similarly, in Nigeria where a Lassa fever epidemic claimed the lives of approximately 69 people in 2019, a new CRISPR-based diagnostic test has been developed to detect the viral infection.[15] The test relies on CRISPR's ability to detect RNA from the Lassa virus. If the approach is successful, the test could be further programmed to detect a wide range of viral infections including dengue, Zika and strains of the human papillomavirus (HPV), allowing treatments to be administered early. Consequently, healthcare workers would be able to curb the spread of infections such as these.

b. Diagnostic Tool: DNA endonuclease targeted CRISPR trans reporter (DETECTR)

5.13 In 2018, a CRISPR-based diagnostic method, DETECTR, which harnesses the ability of the Cas12a single-stranded DNase (ssDNase) to generate single-stranded DNA breaks, was developed in combination with isothermal amplification.[16] The diagnostic tool is highly sensitive and has provided a simple platform for rapid and specific detection of human papilloma virus (HPV) in patient samples, displaying promise in molecular diagnostics.

c. Personalised Treatment

5.14 CRISPR-Cas9-based screening for identifying new drug targets and biomarkers represents another avenue in precision medicine.[17] This is particularly relevant in cancer studies due to the heterogeneity in tumour cells and the underlying genetic causes responsible for their resistance to drug treatment. Targeted gene editing approaches employing CRISPR can be used not only in high-throughput screening to discover novel therapeutics but also in elucidating pathways driving drug resistance in cancer cells, and ultimately, leading to the development of personalised treatments for patients.

[14] Gootenberg, J. S., et al. (2017). Nucleic acid detection with CRISPR-CAS13A/C2C2. *Science, 356*(6336), 438–442. https://doi.org/10.1126/science.aam9321

[15] Nesathurai, A. (2019). Lassa epidemic: Nigeria uses CRISPR to get early jump on viral outbreaks, *Genetic Literacy Project*. https://geneticliteracyproject.org/2019/03/04/lassa-epidemic-nigeria-uses-crispr-to-get-early-jump-on-viral-outbreaks/

[16] Chen, J. S., et al. (2018). CRISPR-CAS12A target binding unleashes indiscriminate single-stranded DNase activity. *Science, 360*(6387), 436–439. https://doi.org/10.1126/science.aar6245

[17] Xing, H., & Meng, L. (2019). CRISPR-Cas9: A powerful tool towards precision medicine in cancer treatment. *Acta Pharmacologica Sinica, 41*(5), 583–587. https://doi.org/10.1038/s41401-019-0322-9

IV. Potential Application of HNGE to Confer Resistance to Certain Diseases and for Genetic Enhancement

5.15 Gene editing has been explored for its potential application to enhance or confer disease resistance in individuals. This could be achieved by altering genes commonly found among the general population to variants that are known or expected to be beneficial, thereby enhancing certain traits of the individual. For instance, the β-globin (HBB) gene in the genetic blood disorder beta-thalassaemia was first modified in zygotes in 2015.[18] However, findings from this study showed low efficiency in genetic recombination, as well as genetic mosaicism and off-target cleavages. It is also worth noting that while gene editing has been widely used for research in the field of disease treatment, there is scope for gene editing tools to be misused to prevent certain diseases or enhance certain features.

5.16 The controversy over the use of gene editing to confer resistance against disease can be illustrated by the experiment conducted by He Jiankui in China. The experiment was conducted on seven serodiscordant couples (i.e., one partner is HIV-positive and the other is HIV-negative) to prevent their offspring from being infected and led to the birth of genetically enhanced babies.[19] He had used CRISPR-Cas9 to modify the CCR5 gene in human embryos with the intention of producing babies with an increased resistance to HIV infections. CCR5 is a co-receptor expressed on the surface of immune cells involved in the signalling and coordination of immune responses, acting like a 'door' that allows the HIV entrance into the cell and thereby playing an essential role in HIV pathogenesis. The mutation in the CCR5 gene locks "the door", which prevents HIV from entering the cell.[20] However, He failed to consider the possible off-target effects of the technique used, the downstream effects associated with heritable gene editing[21] and possible health risks to the offspring. This led to criticisms of his procedure, which was labelled as risky, ethically contentious and medically unjustified[22] (see Chapter 7 for a detailed discussion on the ethical issues). While the same approach to introduce the mutation to the same gene in zygotes has been reported previously, mosaicism and low efficiency of the gene editing were observed in the zygotes.[23] Hence, the fidelity and maturity of gene editing technology for the purpose of enhancing specific traits have to be clearly evaluated before the technology can be approved for widespread use.

V. Potential Application of HNGE for Polygenic Editing to Reduce Predisposition to Diseases

5.17 Gene editing strategies that are being developed or studied in clinical trials largely target lethal diseases that are typically associated with single nucleotide variants (SNVs) and are relatively less prevalent among the general population. Polygenic

[18] Liang P., et al. (2015). CRISPR/Cas9-mediated gene editing in human tripronuclear zygotes. *Protein & Cell, 6*(5), 363–372. https://doi.org/10.1007/s13238-015-0153-5

[19] Normile, D. (2018). CRISPR bombshell: Chinese researcher claims to have created gene-edited twins. *Science*. https://www.science.org/content/article/crispr-bombshell-chinese-researcher-claims-have-created-gene-edited-twins

[20] Julia, P. (2013). HIV resistant mutation. *Nature*. https://www.nature.com/scitable/blog/viruses101/hiv_resistant_mutation/#:~:text=The%20mutation%20causes%20the%20CCR5,from%20entering%20into%20the%20cell

[21] Tim, M. (2022). Are designer babies ethical? CRISPR and how to avoid the slippery slopes of heritable genetic editing. *The Lovepost*. https://www.thelovepost.global/biotech-change/articles/are-designer-babies-ethical-crispr-and-how-avoid-slippery-slopes-heritable

[22] Hannah, D. (2023). Scientist who edited babies' genes says he acted 'too quickly'. *The Guardian*. https://www.theguardian.com/science/2023/feb/04/scientist-edited-babies-genes-acted-too-quickly-he-jiankui

[23] Kang, X., et al. (2016). Introducing precise genetic modifications into human 3PN embryos by CRISPR/Cas-mediated genome editing. *Journal of Assisted Reproduction and Genetics, 33*(5), 581–588. https://doi.org/10.1007/s10815-016-0710-8

or complex diseases, on the other hand, are attributed to multiple genetic variants. CRISPR may be used to perform multiple edits to the gene simultaneously to address polygenic diseases caused by the combined action of more than one genetic variant or mutation.[24]

5.18 Multi-gene editing has been reported in several instances. In 2022, engineers at Rice University developed the "drive and process" (DAP) array, a streamlined CRISPR-based technology that is able to correct dozens of errors simultaneously with high precision and efficiency.[25] The approach is time-efficient and has been shown to work in human cell models for heart disease, Type 2 diabetes, muscular dystrophy, sickle cell disease and beta thalassaemia caused by a combination of mutations. Separately, Verve Therapeutics announced in July 2022 that a clinical trial would be conducted for their gene therapy, named VERVE-101.[26] This first-in-class gene editor converts an adenine base to a guanine base within the gene, encoding a protein called PCSK9, which is a key regulator of blood cholesterol levels. Disabling PCSK9 has been shown to be able to reduce cholesterol levels and, by extension, the risk of heart diseases. Therefore, the trial aims to study the efficacy of lowering levels of functional PCSK9 in individuals with heterozygous hypercholesterolaemia, a condition that causes high cholesterol, which may lead to cardiac complications.

VI. Potential Application of HNGE to Correct Disease-causing Mutations as a Therapeutic Strategy

5.19 Gene editing for the treatment of diseases is widely studied due to its potential to correct aberrant genetic mutations with a high degree of precision and accuracy. Gene editing tools such as CRISPR are not only employed to study mutations in disease-causing genes, but more importantly, they can be used to correct mutations for the treatment of diseases, which are discussed as follows:

a. Human Immunodeficiency Virus (HIV)

5.20 HIV is a major public health concern, infecting millions around the world and causing widespread deaths as many succumb to its complications every year.[27] However, there is as yet no effective vaccine or cure for HIV infections. The current prescribed treatment for HIV infections involves combination antiretroviral therapy (cART), which targets the replication cycle of the HIV virus, and is a life-long treatment.[28] The development of anti-HIV therapy is particularly challenging, due in large part to a poor understanding of HIV reservoirs, from which the virus may persist and regenerate upon integration into the cellular genome. Gene therapy, which is used to target and inactivate integrated viral genomes, provides an alternative pathway to achieving a functional HIV cure. For example, research conducted in the US in 2014 focused on the NHEJ-mediated

[24] Guo, N., et al. (2022). The power and the promise of CRISPR/Cas9 genome editing for clinical application with gene therapy. *Journal of Advanced Research, 40*, 135–152. https://doi.org/10.1016/j.jare.2021.11.018

[25] Rice University. (2022). CRISPR-based strategy edits multiple genes and could treat polygenic diseases. *ScienceDaily*. www.sciencedaily.com/releases/2022/05/220519115354.htm

[26] Verve Therapeutics. (2022). Verve Therapeutics doses first human with an investigational in vivo base editing medicine, VERVE-101, as a potential treatment for heterozygous familial hypercholesterolemia. *Verve Therapeutics*. https://ir.vervetx.com/news-releases/news-release-details/verve-therapeutics-doses-first-human-investigational-vivo-base

[27] Joint United Nations Programme on HIV/AIDS. (n.d.). Global HIV & AIDS statistics - Fact sheet. *UNAIDS*. https://www.unaids.org/en/resources/fact-sheet#:~:text=Since%202010%2C%20new%20HIV%20infections,–210%20000%5D%20in%202022

[28] Hussein, M., et al. (2023). A CRISPR-Cas cure for HIV/AIDS. *International Journal of Molecular Sciences, 24*(2), 1563. https://doi.org/10.3390/ijms24021563

inactivation of the CCR5 gene in autologous CD4 T-cells of persons infected with HIV using ZFNs.[29] The study found that infusion of the CCR5-modified CD4 T-cells was feasible and generally safe, although limited by the small sample size.

b. Spinocerebellar Ataxia

5.21 Spinocerebellar ataxia refers to a class of rare neurodegenerative diseases that is autosomal, dominantly inherited and manifests in the loss of various cognitive and motor functions.[30] Potential treatment options for the disease typically include pharmacological interventions as well as speech and physiotherapy. Most conditions associated with spinocerebellar ataxia are caused by higher than normal levels of genetic sequence coding for glutamine, due to polyglutamine-encoding repeat expansions within the gene, which results in protein aggregation and cell death.[31] This may be corrected by gene editing. A study conducted in China in 2021 demonstrated the feasibility of CRISPR-Cas9-mediated homologous recombination strategy to precisely repair spinocerebellar ataxia Type 3 in iPSCs and reverse the corresponding abnormal disease phenotypes such as mitochondrial dysfunction and oxidative stress disorders.[32]

c. Spinal Muscular Atrophy (SMA)

5.22 Spinal Muscular Atrophy (SMA) is a neuromuscular disease caused by mutations in the Survival Motor Neuron 1 (SMN1) gene where outcomes of existing therapies have been suboptimal.[33] Gene editing may be employed to restore the levels of SMN protein expression by precisely editing Survival Motor Neuron 2 (SMN2), promising a new treatment option for SMA. For instance, the US Food and Drug Administration (FDA) approved the first gene therapy, onasemnogene abeparvovec (or Zolgensma™), for the treatment of SMA for children under 2 years of age.[34] Zolgensma™ is a biologic administered intravenously to deliver the SMN1 transgene as well as synthetic promoters, using viral capsids as delivery vectors, that could promote the expression of functional SMN and improve muscle activity in a child with SMA.

d. Beta-Thalassaemia

5.23 Beta-thalassaemia is a genetic blood disorder caused by beta-chain deficiency in haemoglobin production. The standard treatment for beta-thalassaemia is allogeneic bone marrow transplantation (BMT) from a completely matched donor, which requires long-term use of immunosuppressants and may invoke other immunological complications such as higher susceptibility to infections as well as graft-versus-host

[29] Tebas, P., et al. (2014). Gene editing of CCR5 in autologous CD4 T cells of persons infected with HIV. *New England Journal of Medicine, 370*(10), 901–910. https://doi.org/10.1056/nejmoa1300662

[30] Ghanekar, S. D., et al. (2022). Current and emerging treatment modalities for spinocerebellar ataxias. *Expert Review of Neurotherapeutics, 22*(2), 101–114. https://doi.org/10.1080/14737175.2022.2029703

[31] Sagar, D., et al. (2005). Molecular origin of polyglutamine aggregation in neurodegenerative diseases. *PLoS Computational Biology, 1*(3), 30. https://doi.org/10.1371/journal.pcbi.0010030

[32] He, L., et al. (2021). CRISPR/Cas9 mediated gene correction ameliorates abnormal phenotypes in spinocerebellar ataxia type 3 patient-derived induced pluripotent stem cells. *Translational Psychiatry, 11*(1), Article 43. https://doi.org/10.1038/s41398-021-01605-2

[33] Alves, C. R., et al. (2023). Base editing as a genetic treatment for spinal muscular atrophy. *BioRxiv Preprint*. https://doi.org/10.1101/2023.01.20.524978

[34] Mahajan, R. (2019). Onasemnogene Abeparvovec for spinal muscular atrophy: The costliest drug ever. *International Journal of Applied and Basic Medical Research, 9*(3), 127. https://doi.org/10.4103/ijabmr.ijabmr_190_19

diseases.[35] Gene editing applied to beta-thalassaemia can treat the disorder without involving the use of immunosuppressants and graft-versus-host disease prophylaxis, garnering attention to the modality for treatment of this disease.[36] For example, the first attempt to correct mutation in the HBB gene responsible for beta-thalassaemia in human embryos was reported in a study conducted in China in 2017.[36] The CRISPR-adapted base editing tool was shown to precisely modify the HBB gene with efficiency of over 23% and repaired more than 20% of the blastomeres, although this study observed mosaicism in the edited embryos. In 2019, Allife Medical Science and Technology Co. Ltd. conducted a clinical trial for the application of CRISPR-Cas9 in the treatment of beta-thalassaemia. In the study, the HBB gene was corrected in induced haematopoietic stem cells (iHSCs) derived from patients and transfused intravenously back to the subjects, demonstrating the potential of gene therapy to treat beta-thalassaemia.

VII. Current Established Methods of Treatment/Prevention of Diseases in Individuals or Offspring

5.24 This section will discuss only the scientific and medical advantages and disadvantages of the current established methods of treating or preventing diseases in individuals or future offsprings. The ethical issues involved in the applications of HNGE are discussed in depth in the subsequent chapters (i.e., from Chapters 6 to 10).

a. Conventional treatments

5.25 While gene editing offers new and promising strategies in the treatment of severe diseases that currently lack effective cures, the technology is still in development and requires considerable scrutiny prior to approval for widespread clinical application. Hence, conventional treatments (e.g., chemotherapy, radiation or surgery for cancer) remain the primary choice of therapy or clinical management, even though the safety and efficacy of non-heritable gene editing is more well-established than that of heritable gene editing.

5.26 Conventional treatments are generally regarded to be safe for clinical use and have demonstrated good clinical efficacy, as they have been put through rigorous scientific testing and clinical trials. Therefore, prescribing treatment regimens with conventional therapies and established management or procedures would be desirable for patients. However, conventional treatments may not be effective for patients who have developed resistance to treatments (e.g., chemotherapy resistance in cancer), suggesting that other forms of therapeutics such as gene editing may be required.

b. Prenatal testing or No testing

5.27 Prenatal testing refers to tests carried out during pregnancy to assess a pregnant woman and the health of her foetus, consisting primarily of prenatal screening and prenatal diagnosis.[37] Screening tests are used to identify the likelihood of abnormalities

[35] Rahimmanesh, I., et al. (2022). Gene editing-based technologies for beta-hemoglobinopathies treatment. *Biology, 11*(6), 862. https://doi.org/10.3390/biology11060862

[36] Liang, P., et al. (2017). Correction of β-thalassemia mutant by base editor in human embryos. *Protein & Cell, 8*(11), 811–822. https://doi.org/10.1007/s13238-017-0475-6

of the foetus (e.g., birth defects and genetic disorders) while diagnostic tests are invasive tests that confirm the preliminary outcomes obtained from the screening test. Prenatal tests comprise maternal blood or saliva tests, urine tests, ultrasound (including nuchal translucency), amniocentesis, Chorionic Villus Sampling (CVS), and Percutaneous Umbilical Blood Sampling (PUBS) (also known as Foetal Blood Sampling (FBS)). Alternatively, parents also have the option of choosing not to undergo any prenatal testing for such abnormalities.

5.28 Prenatal testing assures parents of the foetus's condition, thus giving them information about the possibility of predispositions to certain genetic conditions that might develop in the foetus prior to birth.[38] This allows the parents to decide on the follow-up actions required, such as consulting a specialist doctor for medical advice, consideration for foetal therapy if applicable[39], and appropriate preparation for the birth of an affected baby. Parents may also choose not to take any further actions and continue pregnancy as usual. Prenatal testing also informs and provides parents with the option for termination of a pregnancy with an affected foetus (i.e., interruption of pregnancy), if necessary.

5.29 However, specific types of prenatal diagnostic testing (e.g., amniocentesis, CVS, PUBS) are invasive and involve inserting a thin catheter or needle either through the abdomen or the cervix to collect samples of amniotic fluid or placental tissue.[40] While dependent on the specific type of test employed, such procedures are generally accompanied by an increased risk of miscarriage and other complications of pregnancy. For instance, the rate of miscarriage with amniocentesis is about 1 in 200, carrying with it a low risk of uterine infection, which could also lead to miscarriage, leakage of amniotic fluid and injury to the foetus.[41] The rate of miscarriage with CVS is approximately less than 1 in every 200, or slightly higher than that of amniocentesis.[42] In PUBS (i.e., FBS), the rate of miscarriage is about 1 to 2 in every 100 procedures, where the test could result in bleeding from the foetal blood sampling site, leaking of amniotic fluid and infection.[43] While there are tests available such as non-invasive prenatal testing (NIPT) which are non-invasive, these are used primarily for screening purposes and would require confirmatory diagnostic tests.[44] For example, NIPT primarily screens for common chromosomal conditions but is unable to detect genetic or structural abnormalities, or other birth defects. A certain amount of cell-free foetal DNA (cffDNA) is also required in the maternal blood for a test result to be generated.

[37] Mayo Clinic. (2022). Prenatal testing: Is it right for you? *Mayo Clinic*. https://www.mayoclinic.org/healthy-lifestyle/pregnancy-week-by-week/in-depth/prenatal-testing/art-20045177

[38] Women's Health Institute. (2023). The benefits of prenatal testing. *Women's Health Institute*. https://www.whisanantonio.com/the-benefits-of-prenatal-testing/

[39] Sparks, T. N. (2021). The current state and future of fetal therapies. *Clinical Obstetrics and Gynecology, 64*(4), 926-932. https://doi.org/10.1097/GRF.0000000000000651

[40] Bringman, J. J. (2014). Invasive prenatal genetic testing: A Catholic healthcare provider's perspective. *The Linacre Quarterly, 8*1(4), 302–313. https://doi.org/10.1179/2050854914y.0000000022

[41] March of Dimes. (2017). Amniocentesis. *March of Dimes*. https://www.marchofdimes.org/find-support/topics/planning-baby/amniocentesis

[42] National Health Service. (2023). Chorionic villus sampling: Complications. *NHS*. https://www.nhs.uk/conditions/chorionic-villus-sampling-cvs/risks/

[43] Ghidini, A., et al. (1993). Complications of fetal blood sampling. *American Journal of Obstetrics and Gynecology, 168*(5), 1339–1344. https://doi.org/10.1016/s0002-9378(11)90761-3

[44] Jayashankar, S. S., et al. (2023). Non-invasive prenatal testing (NIPT): Reliability, challenges, and future directions. *Diagnostics (Basel), 13*(15), 2570. https://doi.org/10.3390/diagnostics13152570

5.30 Despite the benefits of prenatal screening testing for parents, results obtained from the tests may not always be reliable. Erroneous results of such tests may lead to the failure to identify birth defects accurately. Prenatal testing can also be expensive, costing anywhere from a few hundred to several thousand dollars, depending on the type of screening or diagnostic test used. In general, non-invasive tests such as maternal blood testing and ultrasound (e.g., combined first trimester screening) are more affordable[45] than invasive tests such as amniocentesis, CVS and PUBS. It should be noted too that termination of pregnancy is prohibited after 24 weeks of gestation in Singapore, except in the circumstances of a mother's life being in danger.[46] Therefore, the prenatal diagnosis test must be completed within this window if the parents are considering the option of terminating a pregnancy with an affected foetus.

c. Adoption

5.31 Adoption is a legal process in which an individual takes over the parenting of a child from the child's biological or legal parents. It is a long-term commitment and responsibility for the upbringing of a child, which is distinct from other types of relationships, such as fostering, which is a temporary care arrangement where the foster children remain the legal children of their natural parents.

5.32 Adoption provides couples, who are unable to produce children of their own that are genetically healthy, an opportunity to complete their family. However, the fact remains that these couples do not share a biological link with the adopted child.[47]

d. Selective termination of pregnancy

5.33 Selective termination is used primarily to prevent or reduce complications caused by the birth of an affected foetus(es), particularly in higher-order multiple pregnancies, and increases the survival odds of the remaining foetus(es). Multifoetal gestations (e.g., twins, triplets, and higher-order multiples) are often at a higher risk of various maternal, foetal, and neonatal complications, as compared to singleton pregnancies, which attribute to a higher proportion of preterm births.[48] For instance, neurodevelopmental morbidity such as cerebral palsy in twin births or higher-order pregnancies are markedly higher than in singleton births. Besides multifoetal pregnancy reduction (MPR), which is used to reduce the number of foetuses in the gestation and improve maternal and survival outcomes of the foetus(es), selective termination involves reducing the foetal number by removing the foetus(es) with a known genetic, structural or other abnormality identified during prenatal testing.[49]

[45] Tan, T. (2015). Combined first trimester screen or noninvasive prenatal testing or both. *Singapore Medical Journal, 56*(1), 1–3. https://doi.org/10.11622/smedj.2015001

[46] Ministry of Health Singapore. (2004). Guidelines on termination of pregnancy. *Ministry of Health Singapore*. https://www.moh.gov.sg/docs/librariesprovider4/default-document-library/(2)_guidelines-on-termination-of-pregnancy.pdf

[47] Brodzinsky, D. M. (2011). Children's understanding of adoption: Developmental and clinical implications. *Professional Psychology: Research and Practice, 42*(2), 200–207. https://doi.org/10.1037/a0022415

[48] Beriwal, S., Impey, L., & Ioannou, C. (2020). Multifetal pregnancy reduction and selective termination. *The Obstetrician & Gynaecologist, 22*(4), 284–292. https://doi.org/10.1111/tog.12690

[49] Rochon, M., & Stone, J. (2022). Multifetal pregnancy reduction and selective termination. *UpToDate*. Retrieved from https://www.uptodate.com/contents/multifetal-pregnancy-reduction-and-selective-termination

5.34 However, the procedure is not without risks, such as retained placenta,[50] infection, miscarriage, and pre-labour rupture of membranes.[51]

e. Embryo selection

5.35 During *in vitro* fertilisation (IVF), multiple embryos are created to increase the likelihood of obtaining a viable embryo. However, the chances of a viable embryo being successfully implanted are subject to various factors including biological variation.[52] Pre-implantation genetic testing for monogenic/single gene defects (PGT-M), pre-implantation genetic testing for chromosomal structural rearrangements (PGT-SR) or pre-implantation genetic testing for aneuploidies (PGT-A) are used to test and diagnose embryos for specific genetic or chromosomal abnormalities.[53] The embryo that is not affected with the genetic dysfunctionality tested for will be selected and implanted into the woman's uterus to maximise the chance of successful and normal pregnancy. Hence, PGT-M/SR/A reduces the risk of passing on inherited conditions or genetic disorders and allows couples to avoid an abnormal pregnancy.

5.36 Unlike gene editing, which may cause unintentional mutation(s) to be passed down to future offspring, embryo selection is deemed to be safer as PGT-M/SR/A does not cause genetic aberrations in the embryo, while enabling couples to have a genetically identical child but without the inherited genetic disorder. However, embryo selection is limited and may not be a feasible option in situations where all or a majority of embryos are affected by genetic dysfunctionality. This is relevant in the case of Huntington's disease, where all embryos would carry the dominant disease-causing allele. In polygenic conditions, caused by the combination of two different mutations in a gene, and combinations of specific alleles of two or more genes, it may be challenging to select embryos by PGT-M/SR/A and thus render limited use.

f. Donated gametes

5.37 Use of donated gametes may be helpful particularly in cases where the couple's sperms and/or eggs are not healthy enough to produce a successful pregnancy, or when one or both parents are affected by genetic condition(s), which may prevent or impair the birth of the child.

5.38 Using donated eggs or sperms allows one of the intended parents to maintain the genetic relationship with the child, while avoiding the propagation of any inherited condition that may be passed down to the child. Furthermore, the procedures involved (i.e., intrauterine insemination and IVF) are simple, safe, and carry a low risk of serious complications. However, unlike donated eggs or sperms, using donated embryos from others does not allow either of the intended parents to have children that are genetically associated with them.

[50] Weiran, Z., et al. (2021). Retained placenta creta after selective fetal reduction in twin pregnancy: A case report. *Medicine*. https://mednexus.org/doi/full/10.1097/FM9.0000000000000117

[51] Miremberg, H., et al. (2023). Adverse outcome following selective termination of presenting twin vs non-presenting twin. *Ultrasound in Obstetrics & Gynecology, 61*(6), 705–709. https://doi.org/10.1002/uog.26170s

[52] Mastenbroek, S., et al. (2011). Embryo selection in IVF, *Human Reproduction, 26*(5), 964–966. https://doi.org/10.1093/humrep/der050

[53] Elpida, F. (2007). Preimplantation genetic diagnosis: Present and future. *Journal of Assisted Reproduction and Genetics, 24*(6), 201–207. https://doi.org/10.1007/s10815-007-9112-2

g. Intrauterine foetal gene therapy

5.39 Gene editing technology may be used to treat monogenic disorders in foetus(es) via intrauterine foetal gene therapy.[54] The procedure involves injecting the therapeutic agent (e.g., vectors encoding therapeutic genes) into an umbilical blood vessel, the amniotic fluid, or occasionally directly into foetal tissue, with the guidance of an ultrasound probe. While intrauterine foetal gene therapy is not currently available for clinical use, it might yet become an alternative to heritable gene editing for fertility issues in the future.

5.40 Foetal gene therapy can be employed to treat monogenic disorders prior to the pathological development of the disease, thus significantly decreasing morbidity and mortality. Unlike heritable gene editing, foetal gene therapy has the advantage of robust preclinical data. Several clinical trials in animal models have shown that viral vectors are efficient vehicles in foetal gene therapy, thus making foetal gene therapy a promising alternative to heritable gene editing. However, as with other genetic modifying technologies, foetal gene therapy may cause insertional mutagenesis, oncogenesis, genetic mutation transfer from mother to child and foetal disruption.

5.41 The applications of HNGE stretch across various indications and may be used in investigative studies of diseases, enhancement of specific traits, therapeutic intervention, diagnosis of diseases as well as treatment of fertility. However, many findings reported by the many aforementioned research groups are largely preliminary and warrant further studies to determine the long-term safety and efficacy of gene editing technologies. Studies of the differences in idiosyncratic effects due to individual genetic variations should also be taken into consideration. Therefore, until the safety and efficacy of HNGE technology are demonstrated in pre-clinical studies and in clinical trials approved under regulated clinical trial frameworks, the current established methods would be preferable for treating or preventing diseases in individuals and their offsprings.

[54] Mattar, C. N., et al. (2021). Ethical considerations of preconception and prenatal gene modification in the embryo and fetus, *Human Reproduction, 36*(12), 3018–3027. https://doi.org/10.1093/humrep/deab222

CHAPTER 6:
MOSAICISM, OFF-TARGET EFFECTS, AND ON-TARGET UNDESIRABLE MODIFICATIONS

6.1 Targeted modifications to nuclear DNA and gene editing technology offer the potential to prevent, treat or even cure certain inherited genetic disorders,[1] and might even be used to enhance traits and confer resistance to diseases. When used in a controlled manner, corrections to the genomic sequence could be carried out with precision using molecular scissors, which are mostly enzyme-based, to rectify or remove mutations that could otherwise lead to deleterious health conditions.[2] Yet these technologies could also lead to unintended biological outcomes such as chromosomal mosaicism in embryos and undesirable consequences arising from off-target mutations and deletions.[1] This chapter discusses the ethical principles of *proportionality, sustainability, solidarity* and *responsible stewardship of science*, the ethical issues of chromosomal mosaicism, off-target effects and on-target undesirable modifications, and their impact on individuals and society as a whole, which would be important considerations for potential applications of HNGE.

Issue 1: Chromosomal mosaicism in embryos and miscarriage

6.2 Chromosomal mosaicism is a condition that occurs when a person has two or more sets of cells that are genetically different from one another. For example, a person with this condition might possess some cells that have 46 chromosomes and others that have 47 chromosomes. This phenomenon may arise when gene editing is conducted on embryos beyond the single-cell stage (i.e., after significant DNA replication and cell division take place)[3] and can lead to genetic disease if the abnormal cells begin to outnumber the normal cells, thereby undermining disease prevention. With technological improvements and better understanding of gene editing mechanisms, chromosomal mosaicism in embryos could be reduced with more precise modifications or adjustments in dosage regimens.[4] However, with current technology, it remains highly possible that chromosomal mosaicism in embryos could lead to preimplantation embryo wastage, miscarriages and an increased risk of birth disorders and genetic diseases as there is currently no non-destructive way of determining whether all the cells in the embryo carry exactly the same edits.[3] Physiological defects arising from the genetic aberrations could potentially be passed on to future generations, who may then be afflicted by severe genetic diseases that could prove more fatal than

[1] Li, H., et al. (2020). Applications of genome editing technology in the targeted therapy of human diseases: Mechanisms, advances and prospects. *Signal Transduction and Targeted Therapy, 5*(1), Article 89. https://doi.org/10.1038/s41392-019-0089-y

[2] Broeders, M., et al. (2020). Sharpening the molecular scissors: Advances in gene-editing technology. *iScience, 23*(1), Article 100789. https://doi.org/10.1016/j.isci.2019.100789

[3] National Academies Press (US). (2020). *Heritable human genome editing.* (Chapter 2: The state of science). National Academies of Sciences, Engineering, and Medicine. https://www.ncbi.nlm.nih.gov/books/NBK565923.

[4] Lamas-Toranzo, I., et al. (2019). Strategies to reduce genetic mosaicism following CRISPR-mediated genome edition in bovine embryos. *Scientific Reports, 9*, Article 51366. https://doi.org/10.1038/s41598-019-51366-8

the initial benign condition that was meant to be treated by the genetic modification. Therefore, researchers are advised to consider the following ethical principles when conducting heritable genome editing for the treatment of diseases, conferring resistance, enhancement of traits or for infertility (for both clinical research and clinical applications, if permitted in the future):

a. Proportionality

6.3 The principle of *proportionality* requires that researchers ensure the risks of HNGE biomedical research and clinical applications are not disproportionate to their benefits by minimising the harm to individuals and future offspring while maximising benefits using heritable gene editing technology for treatment of diseases, conferring resistance, enhancement of traits or for the treatment of infertility. Given a dearth of sufficient safety and efficacy data for interventions employing heritable gene editing, the occurrence of chromosomal mosaicism as a result of inaccuracy or imprecision in such techniques could pose harm to the individual receiving the treatment. This could outweigh the benefits of the therapy.[5] Medical interventions for infertility employing heritable gene editing could also have ramifications for the prospective mother, as the risk of miscarriage due to chromosomal mosaicism in embryos could outweigh the perceived benefits (i.e., correction of mutations in germ cells that could possibly treat infertility to enable pregnancy). The risk of miscarriage could be attributed to abnormalities in the chromosomes which occur because of aberrant cell division and growth.[6] Miscarriages might also lead to further complications such as psychological distress and future risk of infertility for the expectant mother. Therefore, heritable gene editing for treatment of diseases, conferring resistance, enhancement of traits or for infertility (in both clinical research and clinical applications) should be considered only if scientific and technological advancements are able to reduce mosaicism or mitigate its effects.

b. Sustainability

6.4 The principle of *sustainability* provides that the use of HNGE in biomedical research and clinical applications should not harm the offspring and their future generations. Given that the use of gene editing technology may result in chromosomal mosaicism, implanting or transferring mosaic embryos could lead to an increased risk for a child to be born with a chromosome disorder, thus potentially compromising the welfare of the offspring. While more than 100 live births have been documented with reassuring outcomes and no abnormal phenotype after mosaic embryo transfer, there are questions that remain unanswered, such as the long-term outcomes of infants born via mosaic embryo transfer.[7] Therefore, it is important to validate the long-term safety and efficacy of gene editing technology before it is used for clinical research and applications involving heritable gene editing. Further *in vitro* research on embryos or gamete precursors is also required to fully understand the implications of heritable gene editing technology.

[5] Mehravar, M., et al. (2019). Mosaicism in CRISPR/cas9-mediated genome editing. *Developmental Biology. 445*(2), 156–162. https://doi.org/10.1016/j.ydbio.2018.10.008

[6] Yang, G., et al. (2022) Comparison of chromosomal status in reserved multiple displacement amplification products of embryos that resulted in miscarriages or live births: A blinded, nonselection case–control study. *BMC Medical Genomics, 15*(1). https://doi.org/10.1186/s12920-022-01187-y

[7] Sina, A., & Jennifer, F. K. (2021). Pregnancy and neonatal outcomes after transfer of mosaic embryos: A Review. *Journal of Clinical Medicine, 10*(7). https://doi.org/10.3390/jcm10071369

c. Solidarity

6.5 The principle of *solidarity* asserts that benefits harnessed through research and from applications of HNGE, supported by individuals' altruistic participation, should extend to wider society and that risks should be minimised. Given that heritable gene editing for the treatment of diseases, conferring resistance, enhancement of traits or for infertility, carry the risks of chromosomal mosaicism and miscarriages, research participants and individuals undergoing such procedures may be exposed to harm that could also affect future generations. The principle of *solidarity* and mindfulness of the public good deserve greater consideration in ensuring that advances in HNGE become shared benefits.[8] Hence, heritable gene editing should not be conducted for clinical research and clinical applications until they are proven safe and beneficial to the research participants and wider society. Until then, current established methods of treatment or prevention of diseases described in Chapter 5 would be recommended and clinicians should ensure that patients' expectations are realistic.

Consideration: *The above issue may not be applicable to embryos that would not have existed if gene editing was not performed, or to embryos that were affected by genetic mutations leading to catastrophic conditions. The risk of mosaicism may not outweigh the risks involved if the embryos do not undergo gene editing, and therefore heritable gene editing may be attempted for such cases.*

Issue 2: Off-target mutations, deletions, and rearrangements in DNA

6.6 While HNGE introduces desired changes at the intended target sequence, unintended modifications could be introduced elsewhere in the genome and are known as off-target effects. Off-target changes arising from gene editing can include unintended mutations, insertions or deletions in the genome, which may result in varying consequences depending on the location and nature of the change. These can range from benign effects to harmful disruptions of critical genes or regulatory regions of the genes, and which may result in unintended consequences for the health of individuals. Advancements in recent years have improved our ability to reduce the frequency of unwanted changes as well as to detect off-target mutations when they occur. Frequencies of off-target mutagenesis below 0.01 percent at individual at-risk sites have been achieved in some cases.[3] However, current tools in gene editing (both heritable and non-heritable) still harbour the risk of causing DNA deletions and rearrangements that might eventually lead to genome instability and disruption of the functional genes.[9] As such, this may result in aberrant cell cycles and unprecedented changes in gene expression and regulation.[10] The risk of further complications, such as the development of cancer and allergic reactions, would be dependent on the type

[8] John, J. M., et al. (2017). Ethical issues of CRISPR technology and gene editing through the lens of *solidarity*. *British Medical Bulletin, 122*(1), 17–29. https://doi.org/10.1093/bmb/ldx002

[9] Rayner, E., et al. (2019). CRISPR-Cas9 causes chromosomal instability and rearrangements in cancer cell lines, detectable by cytogenetic methods. *The CRISPR Journal, 2*(6), 406–416. https://doi.org/10.1089/crispr.2019.0006

[10] Begley, S. (2018). CRISPR-edited cells linked to cancer risk in 2 studies. *Scientific American*. https://www.scientificamerican.com/article/crispr-edited-cells-linked-to-cancer-risk-in-2-studies

of gene editing approach employed, as well as the adverse reactions associated with the modality.[11] Therefore, researchers are advised to consider the following ethical principles when conducting non-heritable and heritable gene editing (if permitted in the future) for clinical research and clinical applications:

a. Proportionality

6.7 The principle of *proportionality* provides that the risks of biomedical research and clinical applications involving HNGE are not disproportionate to their benefits by minimising the harm to individuals and their future offspring while maximising the benefits. While modern gene editing tools may alleviate some safety concerns due to the targeted nature of the technology, other concerns persist, such as the potential for off-target effects that could impair a healthy gene function[12] and thus compromise the health and wellbeing of patients undergoing clinical trials of non-heritable gene editing.[13] Undesirable consequences such as these could outweigh the benefits of non-heritable gene editing, for instance, in the correction of disease-causing mutations. Researchers and clinicians are thus obligated to ensure a favourable risk-benefit ratio for patients undergoing HNGE clinical trials and should ensure that clinical trials of non-heritable gene editing are designed to minimise any unprecedented harmful effects to patients. However, this would be challenging to achieve in the short-term, given the lack of understanding of the extent to which non-heritable gene editing can cause unintended secondary edits in the target genome.[14] Therefore, it is essential to conduct further studies of non-heritable gene editing to fully understand the unintended consequences of HNGE. Governments, regulatory bodies and IRBs should establish an evaluation framework at the institutional level (i.e., guidelines and oversight committees) to assess the benefits of gene editing technology vis-à-vis the risks associated with mosaicism and off-target effects.

b. Sustainability

6.8 The principle of *sustainability* holds that biomedical research and clinical applications involving HNGE must ensure that adverse effects or harm rendered by the use of the technology are not perpetuated to future generations. Although heritable gene editing offers promise in preventing and treating debilitating inherited diseases, and enabling infertile couples to conceive children, a study at Oregon Health and Science University has revealed that gene editing to correct disease-causing mutations in early human embryos could lead to unintended and potentially harmful changes in the genome.[15] This unintended effect could be passed on to future offspring and jeopardise their wellbeing. In another research study, scientists at Columbia University, seeking to fix defective DNA in human embryos using CRISPR-Cas9, discovered that the editing caused unintended changes, such as loss of an entire chromosome in more than

[11] National Heart, Lung, and Blood Institute. (2022). Genetic therapies. Benefits and risks. https://www.nhlbi.nih.gov/health/genetic-therapies/benefits-risks#:~:text=Potential%20risks%20could%20include%20certain,use%20in%20the%20United%20States.

[12] PHG Foundation. (2023). Somatic genome editing: Ethics and regulation. https://www.phgfoundation.org/briefing/somatic-genome-editing-ethics-regulation.

[13] Li, H., et al. (2020). Applications of genome editing technology in the targeted therapy of human diseases: Mechanisms, advances and prospects. *Signal Transduction and Targeted Therapy, 5*(1). https://doi.org/10.1038/s41392-019-0089-y

[14] Khoshandam, M., et al. (2024). Clinical applications of the CRISPR/Cas9 genome-editing system: Delivery options and challenges in precision medicine. *Genes & Diseases, 11*(1), 268–282. https://doi.org/10.1016/j.gendis.2023.02.027

[15] Erik, R. (2023). Study reveals limitations in evaluating gene editing technology in human embryos. *OHSU News*. https://news.ohsu.edu/2023/03/07/study-reveals-limitations-in-evaluating-gene-editing-technology-in-human-embryos

half of the embryos experimented on.[16] These changes could be passed on to future generations if the embryos are used to establish pregnancy, indicating that it is too early to know whether heritable gene editing can be conducted safely. Therefore, more research would need to be conducted to develop ways of mitigating off-target effects and other unintended mutations as a result of heritable gene editing on human embryos before gene-editing established pregnancy can be considered safe. For example, researchers can aim to enhance the precision of gene editing technology with high fidelity variants[17] or platforms to minimise any off-target effects.

c. Responsible stewardship of science

6.9 The principle of *responsible stewardship of science* refers to the moral requirement incumbent upon researchers to be prudent about resources utilised in the pursuit of HNGE research and to observe ethical guidelines governing its application. This includes setting research priorities while considering the needs of society so that social and scientific benefits are maximised and potential risks are minimised. Researchers have been developing strategies to prevent or reduce the occurrence of known errors arising from HNGE. For instance, gene editing tools that have greater precision, such as base editors, have been investigated in preclinical disease models to determine their editing efficiencies and accuracy.[18] Patients undergoing gene editing interventions should understand the intervention and be made fully aware of the potential risks prior to receiving the treatment, while their informed consent should be obtained prior to the procedure.

6.10 Regulatory bodies should establish guidelines for the information that must be included in informed consent for researchers and research institutions to refer to, to ensure that all required information on the gene editing intervention is made known to the patient or participant. Due to the complexity of gene editing technology, patients may not fully understand all its aspects. Therefore, researchers and clinicians should ensure that patients are sufficiently informed and understand the potential benefits and risks involved. Researchers and clinicians should also obtain the patient's consent and ensure their safety by continually engaging the patient for follow-up and having further discussion should new information relating to the intervention arise. As off-target effects can now be sensitively and comprehensively quantified,[19] patients should be informed of these risks, including their likelihood and severity (from low to extremely high severity) during genetic consultation. For clinical applications of non-heritable gene editing involving patients with diminished or no capacity (e.g., minors), clinicians should obtain valid informed consent from legally authorised persons (e.g., parents or next of kin) in accordance with the Singapore Medical Council (SMC) Ethical Code and Ethical Guidelines[20] and the Mental Capacity Act 2008.[21] For non-heritable gene

[16] Associated Press. (2020). Lab tests show risks of using CRISPR gene editing on embryos. *STAT News*. https://www.statnews.com/2020/10/29/lab-tests-show-risks-of-using-crispr-gene-editing-on-embryos/.

[17] A high-fidelity variant refers to a genetic sequence that is highly accurate and closely resembles the original or reference DNA sequence without introducing errors or alterations. High-fidelity gene editing tools, such as CRISPR-Cas systems, must ensure that changes are made only to the specific target sequence, without affecting other areas of the genome, which could potentially lead to harmful outcomes.

[18] Katti, A., et al. (2023). Generation of precision preclinical cancer models using regulated in vivo base editing. *Nature Biotechnology*. https://doi.org/10.1038/s41587-023-01900-x

[19] Park, S. H., et al. (2022). Comprehensive analysis and accurate quantification of unintended large gene modifications induced by CRISPR-Cas9 gene editing. *Science Advances, 8*(42). https://doi.org/10.1126/sciadv.abo7676

[20] Singapore Medical Council. (2016). *Ethical Code and Ethical Guidelines.* https://www.healthprofessionals.gov.sg/docs/librariesprovider2/guidelines/2016-smc-ethical-code-and-ethical-guidelines---(13sep16).pdf?sfvrsn=80e05587_4

[21] Attorney-General's Chambers Singapore. (2008). *Mental Capacity Act 2008. Singapore Statutes Online*. https://sso.agc.gov.sg/Act/MCA2008

editing research involving patients with diminished or no capacity, researchers should obtain valid informed consent from legally authorised persons in compliance with the Human Biomedical Research Act 2015.[22]

6.11 Additionally, researchers and clinicians conducting research and clinical applications involving HNGE technology should be appropriately trained to accurately assess the potential benefits and risks of gene editing interventions. This may include training in genetics, the field of genomics and gene editing technology. Researchers and clinicians should also be appropriately trained in relevant topics in ethics, law and sociology so as to be fully equipped with skills and knowledge to consider the potential risks and implications for patients and future generations, and conduct appropriate counselling for patients and obtain their informed consent. There should also be institutional oversight to ensure continuous training of researchers and clinicians involved in HNGE technology.

6.12 It has been widely expected that HNGE will help to significantly advance medicine, given its potential to offer novel methods of curing diseases, enhancing traits, conferring resistance and treating infertility. However, the technology is currently at a nascent stage, lacking sufficient safety and efficacy data. Therefore, the potential risks associated with gene editing technology largely outweigh the perceived benefits—an imbalance that essentially compromises the principle of *proportionality*. Given the current understanding of gene editing tools, it would be difficult to be confident that future generations of individuals receiving the treatment would be free of harm, which then also clouds the principles of *sustainability* and *solidarity*. Nevertheless, research in HNGE has continued to improve the precision of gene editing technology, thus ensuring *responsible stewardship of science*.

[22] Attorney-General's Chambers Singapore. (2015). *Human Biomedical Research Act 2015. Singapore Statutes Online*. https://sso.agc.gov.sg/Act/HBRA2015?ProvIds=P13-#pr8-

CHAPTER 7:
SAFETY AND LONG-TERM EFFECTS OF HNGE

7.1 Gene editing offers new ways of treating diseases and may potentially be used for enhancement of human performance. However, gene editing has yet to receive unequivocal acceptance for widespread use in the clinic. This is because the technology is still in early development, which raises concerns about its safety and unknown long-term side effects of the technology on individuals receiving the treatment. This chapter discusses the ethical principles of *proportionality, sustainability*, and *responsible stewardship of science*, the ethical issues of long-term side effects and consequences of non-heritable and heritable gene editing, and recommendations for managing these consequences.

Issue 1: Possibility of long-term repercussions following non-heritable gene editing

7.2 Since the development of CRISPR as a tool for gene editing, several therapeutics involving this technology are currently being evaluated in non-heritable gene editing clinical trials and have been approved for use.[1,2] Among those that have been conferred with the Regenerative Medicine Advanced Therapy (RMAT) designation by the FDA for accelerated approval are exagamglogene autotemcel (exa-cel) for sickle cell disease (SCD) and transfusion-dependent beta thalassaemia (TDT).[3] This same treatment was approved in the UK, where it is sold under the brand name *'Casgevy'*, and is meant to prevent episodes of excruciating pain that are associated with sickle cell disease, thus freeing those suffering with beta thalassaemia from regular blood transfusions.[2] Another treatment that has received accelerated approval by the FDA is CRISPR-modified chimeric antigen receptor T (CAR-T) cells, which target cancer cells for leukaemia and lymphoma, bringing hope to afflicted patients who would otherwise lack effective treatment options.

7.3 While clinical trials for non-heritable gene editing may lead to the development of new solutions to treat complex genetic diseases in the future, the long-term safety and stability of non-heritable gene editing have not as yet been adequately addressed, even in preclinical studies.[4] As such, unforeseeable repercussions could surface years after patients received treatment from non-heritable gene editing clinical trials and may result in undesirable biological consequences or side effects. For instance,

[1] Henderson, H. (2023). CRISPR clinical trials: A 2023 update. *Innovative Genomics Institute*. https://innovativegenomics.org/news/crispr-clinical-trials-2023/

[2] Mullin, E. (2023). First CRISPR drug: UK approves Casgevy to prevent pain from sickle cell disease and beta thalassaemia. https://geneticliteracyproject.org/2023/11/20/first-crispr-drug-uk-approves-casgevy-to-prevent-pain-from-sickle-cell-disease-and-beta-thalassaemia

[3] Vertex Pharmaceuticals. (2023). Vertex and CRISPR therapeutics complete submission of rolling biologics license applications (Blas) to the US FDA for exa-Cel for the treatment of sickle cell disease and transfusion-dependent beta thalassaemia. https://investors.vrtx.com/news-releases/news-release-details/vertex-and-crispr-therapeutics-complete-submission-rolling

[4] Doudna, J. A. (2020). The promise and challenge of therapeutic genome editing. *Nature, 578*(7794), 229–236. https://doi.org/10.1038/s41586-020-1978-5

off-target modifications resulting from the treatment of gene editing could trigger activation of cancer-causing genes and thus compromise the health of patients in the long term.[5] Therefore, researchers are advised to consider the following ethical principles when conducting non-heritable gene editing for biomedical research and clinical applications:

a. Proportionality

7.4 The principle of *proportionality* requires researchers to ensure that the risks of HNGE technology are not disproportionate to its benefits, by minimising the harm to individuals and their future offspring while maximising benefits using non-heritable gene editing (i.e., a favourable risk-benefit ratio). While clinical trials and clinical applications involving non-heritable gene editing can benefit research participants and patients by allowing them to correct mutations that cause underlying diseases, the potential harmful side effects and long-term consequences might outweigh the benefits. Hence, principal investigators of HNGE clinical trials, as well as clinicians providing treatment involving non-heritable gene editing, need to ensure that the risks are not disproportionate to the anticipated benefits by maximising the potential benefits while maintaining a favourable risk-benefit ratio for clinical trial participants and patients. Researchers, research institutions and clinicians should ensure that the risks of any unintended consequences from non-heritable gene editing interventions becoming heritable are reduced, and that these risks be documented and assessed appropriately.

b. Responsible stewardship of science

7.5 The principle of *responsible stewardship of science* refers to the moral requirement of researchers to be prudent about the resources utilised in the pursuit of HNGE research and to consider the ethical guidelines governing applications of non-heritable gene editing. Given the as yet largely unknown long-term effects of gene editing technology, it would be difficult to predict and avoid consequences that clinical trial patients may face in the future.[6] Hence, conducting such clinical trials may expose patients to possible long-term ramifications in the future despite achieving short term benefits. Appropriate measures, such as establishing guidelines for evaluating off-target effects[7] and risk-benefit assessments,[8] should be taken by researchers to anticipate and/or manage uncertainties and long-term consequences associated with non-heritable gene editing in order to ensure *responsible stewardship of science*. The risk-benefit assessments should be presented clearly to patients and participants to ensure that they understand and are fully informed of the potential benefits and risks. Furthermore, researchers, research institutions and clinicians should continuously review whether existing regulations and guidelines are capable of managing the risks and benefits of HNGE.

[5] Teboul, L., et al. (2020) Variability in genome editing outcomes: Challenges for research reproducibility and clinical safety. *Molecular Therapy, 28*(6), 1422–1431. https://doi.org/10.1016/j.ymthe.2020.03.015

[6] The Swedish National Council on Medical Ethics. (2022). Editing of the human genome: Summary of a report from the Swedish National Council on Medical Ethics. https://smer.se/wp-content/uploads/2022/04/smer-2022_1_english_summary_webb.pdf

[7] Ishii, T. (2016). Somatic genome editing for health: Disease treatments and beyond. *Current Stem Cell Reports, 2*(4), 313–320. https://doi.org/10.1007/s40778-016-0061-5d

[8] Bittlinger, M., et al. (2022). Risk assessment in gene therapy and somatic genome editing: An expert interview study. G*ene and Genome Editing, 3*(4), 100011. https://doi.org/10.1016/j.ggedit.2022.100011

7.6 Given that the long-term safety of non-heritable gene editing has not been fully established, it is essential that researchers and physicians conduct long-term follow-up on all patients and participants in clinical trials evaluating new therapeutic modalities for non-heritable gene editing. This will allow them to monitor adverse developments and evaluate the risks and benefits, which would aid in mitigating the risk of any delayed adverse development occurring due to the treatment.[9] For instance, four out of nine patients successfully treated in a clinical study investigating the use of gene therapy for severe combined immunodeficiency (SCID) were found to develop leukaemia even as long as 68 months after gene therapy.[10] In addition, the FDA updated the guidelines in 2020 on the design of long-term follow-up studies for the collection of data on delayed adverse events following the administration of a gene therapy product. This suggests that studies using gene editing products should follow up with patients for at least 15 years, and highlights the importance of long-term follow-up.[11] Nonetheless, it should be noted that such long-term monitoring of patients after the trial faces some technical and ethical challenges:

a. Experimental approaches commonly employed in clinical trials such as randomised controlled trials are seldom suitable for long-term monitoring.[12] This is because subjects randomly assigned to a particular treatment regimen for prolonged periods (e.g., five years or longer) or into a placebo group, may choose to opt out of the study in the event that a better treatment becomes available, or may decide to switch therapy for other reasons, such as poor prognosis or treatment-related side effects.[13]

b. The use of a placebo may become less ethical and relevant for trials of a lengthy duration, especially in situations where patients with dilapidating conditions, such as cardiovascular diseases or cancer, are placed in the placebo control group.[14] Clinical trials performed over a longer duration also necessitate an open label study design where both researchers and participants are aware of the treatment being administered. Otherwise, researchers may conduct an uncontrolled trial (i.e., without a placebo group), with all participants receiving the same treatment if there is no standard of care, which might then reap results that are insufficient in terms of establishing the efficacy of the intervention.[12] Notwithstanding these challenges, an open label study or an uncontrolled trial may be considered more ethical compared to the use of placebo, as patients are not denied any treatment, which may prevent or delay death or other major consequences from the disease.

c. As the duration of a study increases, the number of research participants may decline. It was reported that one in four participants drop out on average, citing reasons such as fear of side effects, study procedures, inconvenient location and lack of support

[9] Meredith, L. (2022). Long-term follow-up studies: Gene therapy products, protocols and potential issues. *Precision for Medicin*e. https://www.Precisionformedicine.com/blogs/long-term-follow-up-studies-gene-therapy-products-protocols-potential-issues/

[10] Hacein-Bey-Abina, S., et al. (2008). Insertional oncogenesis in four patients after retrovirus-mediated gene therapy of SCID-X1. *Journal of Clinical Investigation, 118*(9), 3132–3142. https://doi.org/10.1172/jci35700

[11] Nature Medicine. (2021). Gene therapy needs a long-term approach. *Nature Medicine, 27*, 563. https://doi.org/10.1038/s41591-021-01333-6

[12] Herbert, R. D., Kasza, J., & Bø, K. (2018). Analysis of randomised trials with long-term follow-up. *BMC Medical Research Methodology, 18*(1), 49. https://doi.org/10.1186/s12874-018-0499-5

[13] Morden, J. P., et al. (2011). Assessing methods for dealing with treatment switching in randomised controlled trials: A simulation study. *BMC Medical Research Methodology, 11*, 4. https://doi.org/10.1186/1471-2288-11-4

[14] Ellenberg, S. S. (2003). Scientific and ethical issues in the use of placebo and active controls in clinical trials. *Journal of Bone and Mineral Research, 18*(6), 1121–1124. https://doi.org/10.1359/jbmr.2003.18.6.1121

from family.[15] This may result in missing or incomplete data due to participants not completing the study (i.e., loss of follow-up), thus undermining the reliability and validity of efficacy studies for the non-heritable gene editing treatment.

d. It is important to ensure that study protocols for long-term monitoring of HNGE are comprehensive and address the potential ethical challenges posed by invasive procedures for obtaining samples for such long-term studies. For example, bone marrow biopsies, direct sequence testing[16] or other invasive methods meant to assess the long-term effects of gene editing, could result in undue physical and psychological burdens on patients. Therefore, researchers need to carefully weigh the invasiveness of procedures against the importance of the data being gathered. Devising non-invasive alternatives or minimising the frequency of invasive sampling could be necessary to protect patient wellbeing, while also ensuring robust data collection.

Issue 2: Difficulty in predicting how the gene alterations as a result of heritable gene editing interact with genetic variants and the environment, and the subsequent side effects

7.7 Compared to non-heritable gene editing, the clinical research and clinical applications of heritable gene editing raise significantly more concerns about the safety and long-term consequences of its use.[17] While heritable gene editing may prove to be useful in eradicating genetic diseases, especially in children at birth by precisely correcting the genetic sequence, there is a likelihood of creating permanent unintended changes that could be passed down to future generations. Such modifications made to the genome may invoke unprecedented biological consequences, including disrupting inherent protection from infection as well as activation of genes with harmful effects.[18]

7.8 Mutations introduced to genes may interact with inherent gene variants present within an individual and render unprecedented biological outcomes.[19] Inherent gene variants are changes in a person's DNA sequence which exist prior to gene editing and can be inherited or non-inherited. Inherited variants, also known as germline variants, are passed down from parent to child and are present throughout a person's life. Non-inherited variants occur at some point during a person's life and may manifest themselves during natural cellular processes such as cell division, or due to environmental factors such as exposure to ultraviolet radiation from the sun or smoking.[20] While heritable gene editing can present prospective parents with the opportunity to have a biological child without passing on a genetically-heritable disease, the current technology is still unable to predict how these exogenous genetic alterations might interact with existing gene variants within the child. The difficulty in anticipating, and in turn, mitigating possible side effects arising from the intrinsic

[15] Poongothai, S., et al. (2023). Strategies for participant retention in long-term clinical trials: A participant-centric approach. *Perspectives in Clinical Research, 14*(1), 3. https://doi.org/10.4103/picr.picr_161_21

[16] Food and Drug Administration. (2020). *Long-term follow-up after administration of human gene therapy products. Guidance for industry*. https://www.fda.gov/media/113768/download

[17] Almeida, M., & Ranisch, R. (2022). Beyond safety: Mapping the ethical debate on Heritable genome editing interventions. *Humanities and Social Sciences Communications, 9*(1). https://doi.org/10.1057/s41599-022-01147-y

[18] Rubeis, G., & Steger, F. (2018). Risks and benefits of human germline genome editing: An ethical analysis. *Asian Bioethics Review, 10*(2), 133–141. https://doi.org/10.1007/s41649-018-0056-x

[19] Mani, R., et al. (2008). Defining genetic interaction. *Proceedings of the National Academy of Sciences, 105*(9), 3461–3466. https://doi.org/10.1073/pnas.0712255105

[20] NHS England Genomics Education Programme. (2022). Constitutional (germline) vs somatic (tumour) variants. https://www.genomicseducation.hee.nhs.uk/genotes/knowledge-hub/constitutional-germline-vs-somatic-tumour-variants/

genetic interaction as well as that with the environment, could expose future offspring to lethal long-term ramifications. Furthermore, the lack of studies on the side effects of gene editing on intrinsic gene-gene interaction and the environment underlines the unpredictability of the long-term consequences of the technology.

7.9 The inability to predict the undesirable outcomes and consequences of heritable gene editing could be attributed to the fact that control experiments are performed only on small groups of cells.[21] The current ability to perform quality control experiments only on a subset of cells means that the precise effects of genetic modification on an embryo may be impossible to predict until after the child is born.[6] In some cases, potential problems and side effects may not surface until years after the child is born, making it difficult to predict the side effects of heritable gene editing. Wei and Nielsen reported in their study in 2019 that CCR5Δ32 homozygote carriers in the UK Biobank were shown to suffer from a 21% increase in their mortality rate. The CCR5 gene has been widely shown to play a part in the human immune system. While the loss of its function may be protective against diseases such as multiple sclerosis, spontaneous hepatitis C viral clearance, chronic and aggressive periodontitis as well as confer resistance against HIV-1 infection,[22] the authors of this study postulated that the Δ32 mutation could be highly pleiotropic and likely increase susceptibility of an individual with the mutation to develop other common diseases.

7.10 Given the aforementioned considerations, researchers are advised to consider the following ethical principles when conducting heritable gene editing for clinical research and clinical applications (if permitted):

a. Responsible stewardship of science

7.11 The principle of *responsible stewardship of science* requires researchers to be committed to ensuring that scientific knowledge, data, processes, and know-how around gene editing technology are put to good use not only to improve health outcomes, but also to acknowledge the difficulties and uncertainties alongside the benefits of heritable gene editing for clinical applications (if permitted in the future). Researchers also have an obligation to minimise potential risks to individuals and their future offspring associated with gene editing intervention. With the current lack of long-term safety and efficacy data on gene editing technology, the use of heritable gene editing is currently deemed unsafe for future offspring with long-term implications, where possible exposure to serious side effects may be fatal for future offspring. The use of heritable gene editing can only be considered safe for clinical research and clinical applications following further research studies that prove the safety and efficacy of gene editing technology.

b. Sustainability

7.12 The principle of *sustainability* provides that research and applications of HNGE should ensure that the adverse effects or harm rendered by gene editing technology are not passed down to future generations. Given that the long-term consequences of the

[21] Lanphier, E., et al. (2015). Don't edit the human germ line. *Nature, 519*(7544), 410–411. https://doi.org/10.1038/519410a

[22] Li, T., & Shen, X. (2019). Pleiotropy complicates human gene editing: CCR5Δ32 and beyond. *Frontiers in Genetics, 10,* Article 669. https://doi.org/10.3389/fgene.2019.00669

heritable gene editing cannot be predicted or mitigated until the birth of the genetically modified child, clinical research and clinical applications involving heritable gene editing would infringe the principle of *sustainability*, as the welfare of the offspring and future generations would likely become compromised when exposed to serious side effects.

7.13 Intergenerational monitoring, which refers to long-term follow-up studies of research participants and their descendants, could help researchers determine the long-term side effects of heritable gene editing on the individual that may be subsequently passed on to future generations and also help assess its safety and efficacy for clinical use.[23] One example of intergenerational monitoring in biomedical research is the Framingham Heart Study of the natural history, risk factors and prognosis of cardiovascular, lung and other diseases. This study began recruitment of research subjects in 1948, before enrolling the second and third generations of the original subjects in 1971 and 2002, respectively. The follow-up studies included clinical and laboratory assessments of cardiac structure and function.[24] However, intergenerational monitoring in clinical trials, much like other procedures in biomedical research, poses the primary ethical challenge with respect to a person's right to autonomy and privacy:

a. Personal and medical information of subjects involved in intergenerational monitoring have to be collected with the appropriate consent of the participants.[25] However, the descendants of a child conceived from an edited embryo in a clinical trial may invoke a limited waiver of privacy during occasions requiring the management of risks associated with heritable gene editing and communication of any adverse findings with recipients of intergenerational monitoring.[23] The waiver could apply to certain key aspects of the child's life as well as their descendants, which could raise difficult issues involving informed consent: the reason being that parents are unable to provide consent that binds their children past the legal age when the children can exercise their own judgement and decide whether to continue as participants of the study, as this would violate their autonomy.[23]

7.14 In view of the ethical consideration outlined above, patients could opt for PGT as an alternative procedure to heritable gene editing for clinical applications (if permitted) to ensure their children do not inherit their own genetic conditions. While not a curative therapy, PGT could ensure that future offspring are not affected by this genetic condition by evaluating embryos for specific genetic conditions (see Chapter 5 for alternatives to HNGE).

Consideration: *Issue 2 may not be applicable to embryos that would not have existed if gene editing was not performed/embryos that were affected by genetic mutations that lead to catastrophic conditions. The risk of possible side effects may not outweigh the risks involved when the embryos do not undergo gene editing, and therefore heritable gene editing may be attempted for such cases, if permitted.*

[23] Cwik, B. (2019). Intergenerational monitoring in clinical trials of germline gene editing. *Journal of Medical Ethics, 46*(3), 183–187. https://doi.org/10.1136/medethics-2019-105620

[24] Splansky, G. L., et al. (2007). The third generation cohort of the National Heart, Lung, and Blood Institute's Framingham heart study: Design, recruitment, and initial examination. *American Journal of Epidemiology, 165*(11), 1328–1335. https://doi.org/10.1093/aje/kwm021.

[25] Ranisch, R., Trettenbach, K., & Arnason, G. (2022). Initial heritable genome editing: Mapping a responsible pathway from basic research to the clinic. *Medicine, Health Care and Philosophy, 26*(1), 21–35. https://doi.org/10.1007/s11019-022-10115-x

Issue 3: Lack of sufficient safety and efficacy data for the use of heritable gene editing for infertility

7.15 Heritable gene editing presents as a possible infertility treatment for individuals with fertility issues, through unravelling of underlying genetic causes[26] as well as modifying the genes associated with infertility in germ cells.[27] For example, CRISPR-Cas9 technology is used to identify and study potential infertility mutations, by modelling infertility-causing mutations in mice and evaluating whether the human mutation renders the mice infertile. For example, researchers have been using the CRISPR-Cas9 system to produce mice that lack testis-specific genes, with studies revealing that several genes are indispensable for male fecundity.[28] However, preclinical studies have yet to establish the safety of such gene editing technology for humans, or even in human and mammalian models other than mice.[29] Hence, heritable gene editing is still considered to be unsafe for clinical research and clinical applications to treat male or female infertility, as they can be exposed to unwanted side effects such as mutagenesis.[30] For example, while studies have shown that gene therapy involving viral vectors could correct spermatogenesis in infertile mice, there are major concerns pertaining to translating these studies to clinical applications, such as insertional mutagenesis, cell-specific targeting and pronounced inflammation.[29]

a. Proportionality

7.16 The principle of *proportionality* requires that researchers ensure risks of heritable gene editing for infertility are not disproportionate to the benefits by minimising the harm to individuals and future offspring. Given the lack of safety data on current gene editing technology for the treatment of human infertility, clinical research and applications could harm the individuals undergoing the treatment and might outweigh the benefits of helping prospective parents conceive. Infertile couples are recommended to address their fertility problems through safer alternatives, such as medicines, surgical procedures and assisted reproduction technology such as IVF procedures, until the efficacy of gene editing for infertility is well established (see Chapter 5 for alternatives to HNGE).

Issue 4: Reduction of genetic diversity in human population

7.17 Heritable gene editing could contribute to the reduction or even elimination of some serious inherited diseases within a population. However, variants associated with disease might also be associated with other beneficial characteristics, which would then also be lost[31] and might be important for survival.[32] For example, the Chinese

[26] Singh, P., & Schimenti, J. C. (2015). The genetics of human infertility by functional interrogation of SNPs in mice. *Proceedings of the National Academy of Sciences*, 112(33), 10431–10436. https://doi.org/10.1073/pnas.1506974112

[27] Hall, S. S. (2016). The first tinkering with human heredity may happen in the infertility clinic. *Scientific American*. https://www.scientificamerican.com/article/the-first-tinkering-with-human-heredity-may-happen-in-the-infertility-clinic1/

[28] Park, S., et. al. (2020). CRISPR/Cas9-mediated genome-edited mice reveal 10 testis-enriched genes are dispensable for male fecundity. *Biology of Reproduction*, 103(2), 195–204. https://doi.org/10.1093/biolre/ioaa084

[29] Chapman, K. M., et al. (2015). Targeted germline modifications in rats using CRISPR/Cas9 and spermatogonial stem cells. *Cell Reports*, *10*(11), 1828–1835. https://doi.org/10.1016/j.celrep.2015.02.040

[30] Pathak, S., Sarangi, P., & Jayandharan, G. R. (2022). Gene therapy for female infertility: A farfetched dream or reality? *Cell Reports Medicine, 3*(5), 100641. https://doi.org/10.1016/j.xcrm.2022.100641

[31] Nuffield Council on Bioethics (2018). Genome editing and human reproduction: social and ethical issues short guide. https://www.nuffieldbioethics.org/assets/pdfs/Genome-editing-and-human-reproduction-short-guide.pdf

[32] Sufian, S., & Garland-Thomson, R. (2021). The dark side of CRISPR. *Scientific American*. https://www.scientificamerican.com/article/the-dark-side-of-crispr/.

scientist, He Jiankui, disabled the C-C chemokine receptor 5 (CCR5) gene to confer resistance to HIV in human embryos, resulting in the birth of twin girls. However, a mouse experiment published in 2005 showed that CCR5 promotes trafficking of important immune cells to the brain during the infection with West Nile Virus. It was also found that humans who lack this protein are more susceptible to severe encephalitis and even death compared to others when infected with West Nile Virus.[33] Therefore, the gene-edited babies created as a result of He's experiment may be resistant to HIV but may be more susceptible to certain viral infections in the future. Hence, researchers and research institutions are advised to consider the following ethical principles when considering applications of heritable gene editing if permitted in the future:

a. Proportionality

7.18 The principle of *proportionality* requires that risks of research and clinical applications involving gene editing technology are not disproportionate to their benefits by minimising harm while maximising benefits to individuals and future offspring. It is incumbent upon researchers to reduce potential harm, or limit to reasonable risks, to individuals and their future offspring, while also maximising benefits as a result of gene editing intervention. Applications of heritable gene editing to confer resistance to a particular disease could, unknowingly, harm future offsprings by removing beneficial characteristics associated with that disease that may be vital for survival or integral to good health. This means the potential risks emanating from such applications of gene editing (e.g., more susceptible to viral infections that may be fatal) could be disproportionate to the potential benefits (e.g., to be resistant to a particular disease).

7.19 Hence, while non-heritable and heritable gene editing hold tremendous promise in addressing genetic disorders and advancing medical science, their long-term safety and efficacy remain a paramount concern. These safety and ethical issues demand a cautious and well-regulated approach to ensure responsible application of gene editing technology until these concerns are addressed in the future. Rigorous research, ongoing monitoring and clear ethical guidelines are essential to mitigate risks and uphold the wellbeing of individuals. It would be important too, to weigh the potential benefits from the advancements in HNGE against the risks as well as ethical considerations to ensure the long-term safety and efficacy of the technology.

[33] Jon, C. (2019). Did CRISPR help – or harm – the first-ever gene-edited babies? *Science*. https://www.science.org/content/article/did-crispr-help-or-harm-first-ever-gene-edited-babies.

CHAPTER 8:
PROCUREMENT AND USE OF HUMAN EMBRYOS AND OOCYTES IN HNGE RESEARCH

8.1 Human embryos have been used by researchers in gene editing as a means of expanding our knowledge base of the human gene function and early embryonic development, as well as to advance research on infertility, genetic diseases and intractable diseases. In 2015, the first case of gene editing in early-stage human embryos was reported in China, where CRISPR was employed to edit the human beta-globin gene associated with beta-thalassaemia.[1] The use of embryos in gene editing research, however, raises several ethical issues. This chapter provides an overview of the 14-day limit for embryo research and the different types of embryos used in HNGE research. Furthermore, the chapter also discusses the panoply of ethical issues involved in the procurement and use of embryos and oocytes in gene editing research, the application of relevant ethical principles of *respect for persons, justice, proportionality*, and *transparency*, and recommendations for managing each of these ethical issues.

The 14-day rule

8.2 The BAC, in its 'Ethics Guidelines for Human Biomedical Research (2021 revised edition)', recommends against developing human embryos for research after the 14th day.[2]

8.3 The 14-day rule was first proposed by the Ethics Advisory Board of the US Department of Health, Education, and Welfare and later endorsed by the Warnock Committee in the UK.[3] It is used in science policy and regulation to limit research, including gene editing research, on human embryos to a maximum period of 14 days after their creation or to the equivalent stage of development that is normally attributed to a 14-day-old embryo.[4] The placing of the boundary at 14 days can be attributed to the primitive streak that appears after the 14th day of human embryo development, signalling the onset of cell differentiation and growth of organs including the nervous system. This rule has been highly influential and is one that has been adopted by many countries to facilitate ethical research on embryos.

8.4 While it was not possible to culture human embryos *in vitro* for 14 days when the rule was first implemented, scientific advancements are increasingly making maintaining physiologically normal embryos in culture beyond 14 days a foreseeable reality.[5]

[1] Liang, P., et al. (2015). CRISPR/Cas9-mediated gene editing in human tripronuclear zygotes. *Protein & Cell, 6*(5), 363–372. https://doi.org/10.1007/s13238-015-0153-5

[2] Bioethics Advisory Committee Singapore. (2021). *Ethics guidelines for human biomedical research* (2021, revised). https://www.bioethics-singapore.gov.sg/publications/reports/bac-ethics-guidelines-2021/

[3] Hyun, I., Wilkerson, A., & Johnston, J. (2016). Embryology policy: Revisit the 14-day rule. *Nature, 533,* 169–171. https://doi.org/10.1038/533169a

[4] Bryant, J., & Elmoine, A. (2018). Should the 14-day rule for embryo research become the 28-day rule? *EMBO Molecular Medicine, 10*, e9437. https://doi.org/10.15252/emmm.201809437

[5] Embryo Research. (2021). Culturing human embryos beyond 14 days: A call for public debate. https://www.focusonreproduction.eu/article/News-in-Reproduction-Embryo-research

Hence, there has been continuing pressure to modify the rule. For example, many UK scientists are now calling for the current 14-day limit on embryo research to be doubled to 28 days, so that they can study the unexplored areas of early human development. Such a change could yield major scientific breakthroughs for infertility, miscarriage and birth defects.[6]

8.5 However, given that culturing embryos for up to 14 days only became possible in 2016, research into embryos between 7 and 14 days is still in its early stages.[7] In addition, most discoveries to date have been within the first seven days, where researchers have been using gene editing technology to reveal the role of key genes in human embryos in the first few days of development.[8] Hence, it might be premature to consider an extension of the 14-day limit. Accordingly, the BAC's position on this issue remains unchanged, even for gene editing research.

Different types of embryos used in research

8.6 The different types of embryos used in gene editing research can be distinguished based on their source:

a. Surplus embryos left over from clinical IVF procedures where couples could choose to save the embryos for subsequent cycles in the treatment or donate them to research or to other couples with fertility difficulties[9];

b. Embryos created specifically for the purpose of research using gametes procured specifically for research on specific gene mutations or profiles.

8.7 The BAC, in its 'Ethics Guidelines for Human Biomedical Research 2021', recommended that the creation of human embryos solely for research purposes in Singapore can be justified only when there is strong scientific merit and potential benefits to be had from such research.[2] However, the Human Biomedical Research (Restricted Research) Regulations 2017 allow only surplus embryos created in assisted reproduction treatment to be used for biomedical research, pursuant to IRB approval.[10] This effectively prohibits the creation of embryos for research purposes, even when there is strong scientific merit and potential benefit. Hence, there may be a need for the regulatory authority to review current regulations for restricted research to enable further advancements in biomedical research, including gene editing research.

8.8 The BAC's position on the use of oocytes or embryos in biomedical research is that specific and personal consent from the donors must be obtained before any oocyte or embryo can be used for this research. The potential donors should be afforded sufficient information and time to make an informed decision.[2] In particular, consent

[6] Michelle Roberts. (2023). Scientists: Allow forbidden 28-day embryo experiments. *BBC News*. https://www.bbc.co.uk/news/health-67204553.

[7] Bruce, P., & Daniel, R. (2021). Why we should not extend the 14-day rule. *Archives of Disease in Childhood - Fetal and Neonatal Edition, 107*(1):20-25. https://pubmed.ncbi.nlm.nih.gov/34112721/

[8] The Francis Crick Institute. (2017). *Genome editing reveals role of gene important for human embryo development*. https://www.crick.ac.uk/news/2017-09-20-genome-editing-reveals-role-of-gene-important-for-human-embryo-development

[9] Machado, C. S. (2020). The fate of surplus embryos: Ethical and emotional impacts on assisted reproduction. *JBRA Assisted Reproduction, 24*(3), 310–315. https://doi.org/10.5935/1518-0557.20200015

[10] Government of Singapore. (2017). *Human Biomedical Research (Restricted Research) Regulations 2017*. https://sso.agc.gov.sg/SL/HBRA2015-S622-2017.

for donation of surplus oocytes or embryos should be kept separate from the consent for treatment of women undergoing fertility treatments. Further, the researcher seeking consent for the donation of eggs and embryos for research should not be the physician administering the fertility treatment.[2] The BAC also asserts that women who intend to donate eggs specifically for research (i.e., those who are not undergoing fertility treatment) must be interviewed by an independent panel, given that the process of donating eggs for research is time-consuming, invasive and associated with a certain degree of discomfort and risk. The panel must be satisfied that the women are of sound mind, understand the nature and consequences of their donation and have freely given explicit consent, without any inducement, coercion or undue influence.[2]

8.9 While surplus embryos from IVF are commonly used by researchers in various countries for gene editing research, the availability of gametes with desired genotypes or genetic profiles may be limited.[11] If a scientist becomes interested in studying gene mutations in oocytes for a given disease-causing gene, or to correct a specific gene mutation, it is essential that oocytes obtained possess the desired genotype.[12] Researchers may have to procure oocytes from women for such oocyte gene editing research, which raises ethical issues as described below.

Issue 1: Risks involved in the procurement of human oocytes for HNGE research

8.10 The invasiveness of the medical procedures involved in procuring oocytes entails some risk to donors. A woman would have to undergo stimulation of her ovaries through multiple hormone injections. Thereafter, the oocytes are collected under mild anaesthesia via a special needle that is attached to an ultrasound vaginal probe. Such ovarian stimulation carries some health risks as the process can lead to ovarian hyperstimulation, a condition in which the ovaries become swollen and painful because of receiving shots of fertility medicines to trigger ovulation.[13] The condition may even be life-threatening if severe, although such cases are rare.[14] This very risk to donors was observed in a study to correct a heterozygous MYBPC3 mutation, which causes hypertrophic cardiomyopathy, in human preimplantation embryos using CRISPR-Cas9 editing. In this study, oocytes had to be procured from healthy donors, which were subsequently fertilised by sperm carrying the mutation. The consent forms provided to these healthy donors mentioned the risk of 'death' three times in the context of different procedures, highlighting the significant risks inherent in oocyte procurement from healthy donors.[15] Other potential risks could also be psychological in nature, including anxiety, mood swings and post-donation adjustment.[16]

[11] Niemiec, E., & Chadwick, H. (2020). Ethical issues related to research on genome editing in humans. *Computational and Structural Biotechnology Journal, 18,* 887–896. https://doi.org/10.1016/j.csbj.2020.03.014

[12] Zhang, Y., Yin, T., & Zhou, L. (2023). CRISPR/Cas9 technology: Applications in oocytes and early embryos. *Journal of Translational Medicine, 21*, 746. https://doi.org/10.1186/s12967-023-04610-9

[13] Mayo Clinic. (2024). *In vitro fertilisation (IVF).* https://www.mayoclinic.org/tests-procedires/in-vitro-fertilization/about/pac-20384716

[14] Bioethics Advisory Committee Singapore. (2008). *Donation of Human Eggs for Research.* https://www.bioethics-singapore.gov.sg/files/publications/reports/donation-of-human-eggs-for-research-full-report

[15] Ma, H., et al. (2017). Correction of a pathogenic gene mutation in human embryos. *Nature, 548*(7668), 413–419. https://doi.org/10.1038/nature23305

[16] National Academies of Sciences, Engineering, and Medicine. (2007). A*ssessing the medical risks of human oocyte donation for stem cell research: Workshop report.* National Academies Press. https://nap.nationalacademies.org/read/11832/chapter/3

8.11 The scarcity of human embryos and gametes, particularly oocytes that are available for biomedical research, gives rise to various concerns, including the risk of exploitation through commercialisation of eggs as an unintended consequence of substantial compensation amounting to an inducement.[14] This situation could risk undermining the autonomy of the donors (e.g. such as to take undue risks against their better judgment).[17] Healthy women who volunteer to donate oocytes specifically for research incur a loss of their time and earnings.[14] However, in such cases, it would be difficult to determine a level of compensation that would not amount to undue influence or inducement, as this would depend on various factors, such as the financial status of the women concerned.[14] Therefore, caution must be taken to ensure that no one is exploited.

8.12 Given these considerations, researchers are advised to consider the following ethical principles when procuring oocytes for the purpose of HNGE research on specific gene mutations:

a. Respect for persons

8.13 The principle of *respect for persons* maintains that individuals participating in HNGE research are respected as human beings and treated accordingly, including respect for their rights to make their own decisions and ensuring that their welfare and interests are protected. It is important for women to be fully informed of the risks involved and given sufficient time to express consent prior to undergoing oocyte procurement procedures for gene editing research, so that their autonomy is not compromised. It is also important that there are safeguards to protect oocyte donors and to ensure that there is no coercion or undue influence on their decision. For example, Singapore's Human Cloning and Other Prohibited Practices Act 2004 prohibits the offering of valuable consideration for the supply of any human egg, human sperm or human embryo,[18] to avoid commodification of oocytes or embryos, and to ensure that donation remains an act of altruism, made without inducement. The Act does, however, allow for the reimbursement of any reasonable expenses incurred by a donor in relation to the supply of human egg, human sperm or human embryo.

b. Justice

8.14 The principle of *justice* implies the need to equitably reciprocate individuals' contributions to HNGE research, and that researchers and their institutions shoulder some degree of responsibility for the welfare of participants in the event of adverse outcomes arising directly from their participation in HNGE research. Based on this principle, the BAC, in its 'Donation of Human Eggs for Research' advisory report, recommends that women should be compensated for loss of time and earnings as a result of the procedures required to obtain the eggs, albeit only if the eggs were procured specifically for research purposes and not as a result of clinical treatment.[14] Such compensation should be in addition to any reimbursement of expenses incurred and should not be dependent on the quantity nor the quality of the eggs obtained, as that does not represent payment for the eggs.[14] This is also applicable for gene editing research in embryos or germline cells. Nonetheless, given that Singapore's Human Cloning and Other Prohibited Practices Act allows only for reimbursement of

[17] Rosario, M., & Bartha, M. (2007). Monetary payments for the procurement of oocytes for stem cell research: In search of ethical and political consistency. *Stem Cell Research*, 1(1), 37–44. https://doi.org/10.1016/j.scr.2007.09.003

[18] Government of Singapore. (2004). *Singapore Human Cloning and Other Prohibited Practices Act*. https://sso.agc.gov.sg/Act/HCOPPA2004

reasonable expenses incurred by a person in relation to the supply of human gamete, and not compensation for loss of time and earnings in particular, what is less clear is whether compensation for the loss of a donor's time and earnings is permitted. The relevant regulatory authority should provide greater clarity on this grey area and may also wish to consider setting a limit on the amount of compensation to avoid any inducement. In the case of donors who are not employed, authorities should determine an appropriate compensatory amount, based on the time spent as a result of the procedures required to obtain the eggs for research. Authorities may need to review current legislation to determine whether legislative changes need to be enacted to implement such compensatory schemes.[14]

8.15 In addition, the BAC, in its 'Donation of Human Eggs for Research' advisory report, also recommends that egg donors should be provided with prompt and full medical care when complications occur as a direct and proximate result of donating eggs specifically for research.[14] Given that the donation of eggs for research purposes is not a commercial proposition, it is the responsibility of researchers and research institutions to provide medical care when needed.[14] This also applies to gene editing research in embryos or germline cells.

c. Proportionality

8.16 The principle of *proportionality* requires researchers to ensure that the risks of HNGE research are not disproportionate to the benefits, by minimising the harm to individuals and future offspring while maximising benefits gained from using gene editing. As oocyte procurement could result in potential harm to the donor (and even the risk of death), it would be important for researchers to weigh the benefits of procuring oocytes solely for gene editing research against the risks that such procurement could pose. Researchers should consider using surplus embryos created through assisted reproduction treatment for HNGE research if the risks of procuring oocytes solely for such research outweighs the benefits. Researchers may also consider alternative sources for oocytes.

Issue 2: Risks involved in the use of human embryos for HNGE research

A. Risk of invalid consent and privacy breach as a result of genome sequencing

8.17 Genome sequencing of embryonic cells is conducted to verify whether an embryo has been edited in the desired way and to assess for off-target effects.[11] The entire genome of gamete donors is also sequenced (i.e., from blood) to act as a reference sequence. During this process, researchers may obtain genomic sequencing information from gamete donors, though it could be that not all gamete donors are adequately informed of this aspect of the research and its implications.[11] For example, the informed consent forms used in the study on heterozygous MYBPC3 outlined above did not explicitly mention the genome sequencing aspect of the research. Inadequate information and a poor understanding of what research participation entails, serves to undermine consent for research. This may also lead to subsequent withdrawal of consent and loss of trust if donors find out that they have not been told about genomic sequencing. Indeed, genomic sequencing could also lead to a breach of privacy and confidentiality of donors' genomic data. For example, genomic sequencing can query nearly all the protein-coding regions of the human genome at once, including most genes believed to have roles in disease. For researchers to find meaning in this data requires accompanying phenotypic and demographic information. This increases

the likelihood that data may be linked back to the individuals from whom the data was sourced, even when de-identified, thus breaching the confidentiality of donors' genomic data. In addition, researchers may share this data in biorepositories and databases, which may lead to misuses of genetic information that relate to risks of discrimination and social stigma.[19] Therefore, researchers are advised to consider the following ethical principles when using surplus embryos or oocytes procured from healthy individuals for gene editing research:

a. Transparency

8.18 The principle of *transparency* in HNGE research emphasises openness and clarity about the research process, methods and findings, which help ensure the credibility and reproducibility of the study. It is important for researchers to ensure that donors of surplus embryos or oocytes for gene editing research are fully informed of all aspects of the research study, including any potential data that may be collected and their implications. Researchers should ensure that the information provided during the consent process is translated to the appropriate language, if needed. This *transparency* ensures valid consent and fosters trust and respect for donors' autonomy in HNGE research.

b. Respect for persons

8.19 The principle of *respect for persons* underlies the importance of protecting research participants' privacy and the confidentiality of information that they disclose, in order to minimise harm that they may be exposed to. Researchers and research institutions should adhere to existing guidelines and regulations, such as the Human Biomedical Research Act 2015[20] and the Personal Data Protection Act 2012.[21] Researchers should conduct genome sequencing only for legitimate scientific and medical purposes, and have a duty to ensure that only information necessary for the research is collected, avoiding unnecessary intrusion into the genetic makeup of embryo or oocyte donors. In addition, researchers should adopt ethical data retention practices, ensuring that data is stored securely (e.g., through de-identification of research data where appropriate) and retained only for the necessary duration. They should ensure that data obtained from genome sequencing during gene editing research on human embryos is not misused, and that the privacy and confidentiality of embryo or gamete donors are not breached.

8.20 The ethical considerations surrounding oocyte procurement and the use of surplus embryos or oocytes procured for biomedical research, including HNGE research, are intricate, raising concerns related to potential harm to the donor and infringement of informed consent as well as possible breach of privacy and confidentiality of donors' genomic data. Balancing potential scientific advancements offered by gene editing research with the ethical imperatives of informed consent and potential consequences is paramount. This can be achieved when researchers and research institutions prioritise respect for the autonomy and wellbeing of oocyte donors, as well as when they strive to ensure *transparency* in the research process.

[19] Jamal, L., et al. (2014). Research participants' attitudes towards the confidentiality of genomic sequence information. *European Journal of Human Genetics, 22*, 964–968. https://doi.org/10.1038/ejhg.2013.276

[20] Government of Singapore. (2020). *Human Biomedical Research Act 2015* (2020 Rev. Ed.). https://sso.agc.gov.sg/Act/HBRA2015

[21] Government of Singapore. (2020). *Personal Data Protection Act 2012* (2020 Rev. Ed.). https://sso.agc.gov.sg/Act/PDPA2012

CHAPTER 9:
EQUITABLE ACCESS AND ALLOCATION OF RESOURCES

9.1 Technologies involving HNGE extend beyond discovering and developing therapies, particularly for rare genetic disorders, severe diseases such as cancer and treatment of infertility. This technology can also be potentially used to enhance specific traits. However, as with many new modalities in medicine, gene editing technology gives rise to concerns of inequitable access for those who are in need but cannot afford them. This affects low- and middle-income countries in particular, where there is inadequate funding and support for healthcare, and where high patient caseloads often hamper the timely delivery of treatment options to patients.[1] At the same time, allocation of resources to further the research and development of gene editing for clinical applications must be carefully considered, given that the technology continues to be intensely debated, particularly in regard to its ethical, legal and social implications.[2] This chapter deliberates the potential issues arising from inequitable access and allocation of resources in the use of HNGE in research and clinical applications, as well as the ethical principles associated with the issues.

Issue 1: Inaccessibility of HNGE technologies due to high costs

9.2 Therapies involving gene editing tools are costly due to the heavy investments by pharmaceutical companies in research and development and the market exclusivity granted by patents.[3] It is estimated that in 2016, gene therapies had an average cost of around USD $1 to $2 million (approximately SGD $1.3 to $2.6 million) per dose.[4] In 2022, the US Food and Drug Administration (FDA) approved Hemgenix, the first gene therapy to treat haemophilia B, a genetic disease that impairs blood clotting. However, the therapy costs USD $3.5 million (approximately SGD $4.6 million) per treatment, making it the most expensive drug in the world.[5] The high costs of cell and gene therapies can be attributed to the complexity of producing, handling and controlling the cells or viral vectors required to make them, and is far more complicated than working with the chemicals used to develop and produce traditional pharmaceutical therapies.[6] As monogenic diseases are rare, the treatments developed are often targeted at a small pool of patients with such rare diseases, along with costs that are

[1] Mohiuddin, A. K. (2019). Affordability issues of biotech drugs in low- and middle-income countries. *Juniper Online Journal of Public Health, 5*(1). https://doi.org/10.19080/jojph.2019.05.555654

[2] Howard, H. C., et al. (2017). One small edit for humans, one giant edit for humankind? Points and questions to consider for a responsible way forward for gene editing in humans. *European Journal of Human Genetics, 26*(1), 1–11. https://doi.org/10.1038/s41431-017-0024-z

[3] Muigai, A. W. (2022). Expanding global access to genetic therapies. *Nature Biotechnology, 40*(1), 20–21. https://doi.org/10.1038/s41587-021-01191-0

[4] Marsden, G., et al. (2017). *Gene Therapy: Understanding the science, assessing the evidence, and paying for value* (Report from the 2016 ICER Membership Policy Summit). Institute for Clinical and Economic Review. https://icer.org/assessment/gene-therapy-2016/

[5] Naddaf, M. (2022). Researchers welcome $3.5-million haemophilia gene therapy - but questions remain. *Nature*. https://www.nature.com/articles/d41586-022-04327-7

[6] Genetic Engineering & Biotechnology News. (2023). Cell and gene therapy manufacturing costs limiting access. https://www.genengnews.com/insights/cell-and-gene-therapy-manufacturing-costs-limiting-access/

set higher to maximise the return on investments for these companies. Nevertheless, it is possible that gene editing interventions may be scaled up and made accessible to more people at affordable prices in the longer term as the technology advances and becomes increasingly prevalent following the availability of generics after the expiry of patents.[3] In addition, the Rare Disease Fund in Singapore was expanded at the end of 2023 to cover CTGTPs, which would help to mitigate the high costs faced by patients.[7] However, gaining equal access to HNGE technology-based gene therapy may still be a challenge for the economically disadvantaged part of the population. This, inevitably, results in health disparities due to inequalities in socioeconomic status. Therefore, researchers and research institutions should consider the following ethical principles when working on improving gene editing for use in research and clinical applications:

a. Justice

9.3 The principle of *justice* encompasses the general principles of fairness and equality for all individuals, which implies that access to the benefits of biomedical research involving HNGE should be shared equitably in society. While therapeutic interventions employing gene editing may subsequently become more affordable abetted by the economies of scale of greater production, the current high cost of the technology may deny the less advantaged in society access to such medical treatments.[8] This would exacerbate inequity in healthcare since the benefits of gene editing technology would not be equally accessible to everyone, thereby compromising the principle of *justice*. To address this, public agencies (e.g., the Agency for Care Effectiveness (ACE) in Singapore), researchers, academics and the government, should consider implementing health-economic analyses and devise models of funding to ensure that HNGE technology is affordable to all individuals with a medical need. For example, the Innovative Genomics Institute (IGI) created an expert Affordability Task Force in January 2022 to investigate the underlying drivers of high prices of CRISPR genomic therapies and to explore development of alternative pathways to manage high prices of therapies.[9] Reforming patent protection is also important in order to balance incentivising research through robust patent protection with keeping the costs of gene editing interventions manageable. Patent offices should also be equipped with the necessary resources and information to effectively assess the validity and effectiveness of innovations in gene editing technology proposed by manufacturers. These would help to further mitigate inequitable access and ensure that innovative gene editing treatments are truly accessible and affordable to all.

b. Inclusivity

9.4 The principle of *inclusivity* maintains that benefits of research and clinical applications involving HNGE are considered a public good and should be accessible to society as a whole. If medical treatments employing gene editing are costly, individuals

[7] Ministry of Health. (2023). Rare Disease Fund. https://www.moh.gov.sg/news-highlights/details/rare-disease-fund

[8] Subica, A. M. (2023). CRISPR in public health: The health equity implications and role of community in gene-editing research and applications. *American Journal of Public Health, 113*(8), 874–882. https://doi.org/10.2105/AJPH.2023.307315

[9] Witkowsky, L., et al. (2023). Towards affordable CRISPR genomic therapies: A task force convened by the Innovative Genomics Institute. *Gene Therapy, 30*(10–11), 747–752. https://doi.org/10.1038/s41434-023-00392-3

with a lower socioeconomic status would not be able to access them even if they really needed them.[10] As such, this inequity in access to medicine may be seen as differential treatment, especially if those denied access belong to minorities, which would undermine *inclusivity*. In March 2023, the organising committee for the Third International Summit on Human Genome Editing argued that as interventions based on non-heritable gene editing become more widespread, a global commitment to equitable, financially sustainable and accessible treatments becomes ever more urgent and will require appropriate planning for costs and infrastructural needs for gene therapy treatments.[11] The European Union (EU) is currently discussing updates to its pharmaceuticals legislation, with one of its goals to create a balanced system for pharmaceuticals in the region that promotes affordability for health systems, including advanced therapy medicinal products (ATMPs), while also rewarding innovation.[12]

Issue 2: Under-representation of Asian population in clinical data involving HNGE research

9.5 As with most novel therapeutics, any research activity or clinical application involving HNGE would require clinical trial data for validation purposes. Participation in ongoing research or clinical trials for gene editing could allow patients to receive experimental interventions for a disease before it receives approval for human use.[13] However, it was perceived that more clinical trials were funded and conducted in the US, Europe and the UK than in Asia.[14] This was evident in the low participation of Asians in clinical trials according to a 2020 analysis of global participation in clinical trials conducted by the FDA.[15] It was reported that of 292,537 clinical trial participants globally, 76% were white, 11% were Asian, and 7% were black. As such, this may lead to insufficient representation or under-representation of Asian genomes and phenotypes where population- or ethnicity- specific insights or trends relevant to the comprehensive understanding of the gene editing intervention outcomes cannot be obtained. For example, ethnicity and pharmacogenomics are inextricably linked, and drug responses can vary based on the allele frequencies present in different ethnic populations.[16] Some populations may respond better to specific drugs that result in better clinical outcomes. Therefore, the design of clinical trials for HNGE research should consider the following principles:

[10] Hildebrandt, C., & Marron, J. (2018). *Justice* in CRISPR/Cas9 research and clinical applications. *AMA Journal of Ethics, 20*(9), 826–833. https://doi.org/10.1001/amajethics.2018.826

[11] Byrne, J. (2023). Urgent action needed to reduce high costs of gene therapies. *BioPharma Reporter.* https://www.biopharma-reporter.com/Article/2023/03/13/urgent-action-needed-to-reduce-high-costs-of-gene-therapies

[12] European Parliamentary Research Service (EPRS). (2023). *Revision of the EU pharmaceutical legislation. Initial Appraisal of a European Commission Impact Assessment.* European Parliament. https://www.europarl.europa.eu/RegData/etudes/BRIE/2023/747464/EPRS_BRI(2023)747464_EN.pdf

[13] Hamzelou, J. (2023). More than 200 people have been treated with experimental CRISPR therapies. *MIT Technology Review.* https://www.technologyreview.com/2023/03/10/1069619/more-than-200-people-treated-with-experimental-crispr-therapies/

[14] World Health Organization. (2020). Number of clinical trials by year, country, WHO region and Income Group (1999-2019). https://www.who.int/observatories/global-observatory-on-health-research-and-development/monitoring/number-of-clinical-trials-by-year-country-who-region-and-income-group-mar-2020

[15] Sharma, A., & Palaniappan, L. (2021). Improving diversity in medical research. *Nature Reviews Disease Primers,* 7(1). https://doi.org/10.1038/s41572-021-00316-8

[16] Patrinos, G. P., Quinones, L. A., & Sukasem, C. (2023). Pharmacogenomics and ethnicity: Prevalence and clinical significance of pharmacogenomic biomarkers in indigenous and other populations. *Frontiers in Pharmacology, 14,* Article 1180487. https://doi.org/10.3389/fphar.2023.1180487

a. Justice

9.6 The principle of *justice* ensures fairness and equality for all individuals, whereby the benefits derived from research and clinical applications of HNGE should be equitably shared in society. Greater Asian representation in gene editing research or clinical trials will provide deeper insights and reveal trends which are specific to the Asian population that are currently lacking. If there is insufficient representation of Asians, it may not be possible to garner insights relevant to the Asian demographic needed to tailor customised healthcare for the Asia-Pacific region.[17] This would also mean that this population may not have equal access to, or reap all the benefits from, technology or research thus undermining the principle of *justice*.

b. Inclusivity

9.7 The principle of *inclusivity* maintains that research and applications involving HNGE should be representative of a diverse population and that the benefits of research should be shared worldwide. In order to increase the number and diversity of participants in clinical research and trials for gene editing technology, researchers, healthcare institutions and the government can strengthen recruitment and community engagement strategies to communicate the benefits of participating in biomedical research to the individual and to society. The purpose of this would be to ensure that the demographics of trial participants reflect the principle of *inclusivity* as well as the various genomic profiles of a multi-ethnic society like Singapore. Researchers should also improve access to information on clinical trials involving gene editing to promote the potential benefits of research. For example, in 2019, the World Health Organization (WHO) Expert Advisory Committee on developing Global Standards for Governance and Oversight of Human Genome Editing launched the Human Genome Editing (HGE) Registry, which is a central database that collates information of clinical trials using human gene editing technology. In accordance with the principles of *transparency* and *inclusivity*, the HGE registry aims to make information on clinical trials using gene editing technology easily available to all interested stakeholders, including the public.[18]

9.8 Developing new biotechnology in unchartered areas requires channelling of substantial funds and resources into the domain. Given that HNGE technology remains early stage, careful consideration should be given to the eventual delivery of resultant therapies and prudent allocation of resources, so as to ensure equitable access to healthcare, following the principles of *justice* and *inclusivity*, such that the benefits of HNGE are available to all individuals regardless of socioeconomic status. At the same time, clinical studies of experimental treatments employing HNGE should be representative of Singapore's diverse population, as this would enable insights into clinical outcomes relevant to the local demographic, which could be harnessed in order to uphold the principles of *justice* and *inclusivity*. Nevertheless, as clinical trials are context-specific to the type and severity of the disease, small numbers of participants may be appropriate for such clinical trials.

[17] Nguyen, H. A. T., et al. (2021). Asians and Asian subgroups are underrepresented in medical research studies published in high-impact generalist journals. *Journal of Immigrant and Minority Health, 23*(3), 646–649. https://doi.org/10.1007/s10903-021-01142-6

[18] World Health Organisation (WHO). (n.d.). Human genome editing (HGE) registry. https://www.who.int/groups/expert-advisory-committee-on-developing-global-standards-for-governance-and-oversight-of-human-genome-editing/registry

CHAPTER 10:
GENETIC ENHANCEMENT AND EFFECTS ON SOCIETY

10.1 Gene editing is playing an increasing role in a variety of therapeutic applications aimed at the treatment and prevention of diseases. Advances in recent years have increased the possibilities of using gene editing for purposes that go beyond therapies and medical interventions discussed in previous chapters. We can now envisage applications of gene editing technology that include, for example, the genetic enhancement of physical attributes and cognitive abilities. This chapter discusses the ethical issues involved in applications of gene editing technology for genetic enhancement alongside the application of relevant ethical principles, namely *proportionality, sustainability, respect for persons, justice, inclusivity, transparency* and *responsible stewardship of science*.

10.2 Enhancing the features of the human body is by no means an unfamiliar concept.[1] Biomedical technologies such as drugs and surgical techniques are being increasingly used to combat disease and augment the capacities of normal and healthy individuals. The best-established examples of enhancement are cosmetic surgery and doping in sports. In addition, some drugs that are used to treat narcolepsy and attention deficit hyperactivity disorder have also been shown to have small enhancing effects on attention and memory in normal individuals.[2] There are various drugs and biomedical techniques that promise dramatic effects. One such technique is brain-machine interfacing, which some predict may allow human brains to be connected directly to computers to improve our information processing abilities.[2] Given their incremental use and progress in scientific technology, many forms of enhancements have found broad acceptance in society today and are recognised as improving the lives of people with disabilities.[1] While many of the methods that are currently used for physical, functional or mental enhancements only affect the individuals and not future generations, this may not be the case if gene editing technology is used for genetic enhancements.

10.3 Genetic enhancement is the alteration of genes to improve human traits or characteristics beyond what is considered "normal" for humans.[3] Unlike traditional medical interventions that are aimed at treating or preventing diseases, genetic enhancement focuses on enhancing abilities, characteristics or features that provide an advantage or improve quality of life. Genetic enhancement comprises both non-heritable as well as heritable genetic intervention, and can be performed for both medical or non-medical purposes. For example, non-heritable gene editing to lower the cholesterol of a healthy child of a patient with severe coronary artery disease to reduce their risk of disease to a level that is below what is average or considered

[1] Masci, D. (2016). *Human enhancement*. Pew Research Center. https://www.pewresearch.org/science/2016/07/26/human-enhancement-the-scientific-and-ethical-dimensions-of-striving-for-perfection/

[2] University of Oxford. (n.d.). Enhancement. https://www.practicalethics.ox.ac.uk/enhancement/

[3] National Academies of Sciences, Engineering, and Medicine. (2017). *Human genome editing: Science, ethics, and governance*. National Academies Press. https://www.ncbi.nlm.nih.gov/books/NBK447264/

"normal" in the general population may be deemed enhancement for medical purposes,[3] while non-heritable gene editing aimed at improving muscle strength in a normal individual may be considered enhancement for non-medical purposes. Likewise, for heritable gene editing, interventions that enable conferring of resistance to diseases (e.g., genetically altering a human embryo or parental gametes so that the resulting child's immune system can resist the common cold and flu viruses), or for remediation purposes (e.g., bringing an intellectually disabled child's cognitive ability to within normal limits)[4] may fit best into the category of prevention and medical intervention, as they help achieve the medical goals of maintaining health and obviating a later need for treatment. However, heritable gene editing intervention such as genetically altering an individual's gametes to imbue their offspring with greater than average memory, intelligence and even musical talent, for example, may be considered enhancement for non-medical purposes. This chapter will only include discussions on the ethical issues arising from genetic enhancement for non-medical purposes, as it is this aspect of the technology that raises more profound ethical implications.

10.4 Pew Center conducted a survey between October 2019 and March 2020 in 20 countries across Europe, Russia, the Americas and the Asia-Pacific region, polling views on specific circumstances where gene editing may be used.[5] The survey was conducted with representative samples of adults aged 18 years and older. In general, most of the countries surveyed drew distinctions when it came to specific applications of human gene editing, including showing wide support for therapeutic uses.[5] A demographically representative sample of 1,501 people in Singapore, which included participants of different genders, ages, education backgrounds, and regions, found that although 29% of respondents agreed that gene editing to change a baby's genetic characteristics and boost its intelligence would be appropriate, 62% felt that such application would be a misuse of technology. While support for the notion was conceivably low, it was still substantially greater than the 14% median found in other surveyed countries.[5] In the same survey, 68% of respondents felt that it would be appropriate to use gene editing to change a baby's genetic characteristics in order to treat a serious disease or conditions that the baby would have at birth, while just 22% thought such application would be considered a misuse of technology.[5] As such, the local perspectives towards the applications of gene editing technology are largely supportive if it is used for therapeutic purposes, but not for genetic enhancement.

10.5 The primary ethical concern about permitting gene editing for the purpose of enhancement is that changes made to the genes may affect the individual as well as future generations in the case of heritable gene editing. Heritable gene editing modifies germline cells or embryos, making these changes permanent and so potentially passing them down to future generations. This raises the concern that future offsprings may be at risk from the unintended or negative consequences that might arise from genetic enhancement, potentially compromising their wellbeing, whereas the impact of non-heritable gene editing is limited to the individual undergoing the enhancement.

[4] Lagay, F. (2001). Gene therapy or genetic enhancement: Does it make a difference? *AMA Journal of Ethics*. https://pubmed.ncbi.nlm.nih.gov/23272813/

[5] Funk, C., et al. (2020). *Biotechnology research viewed with caution globally, but most support gene editing for babies to treat disease. Pew Research Center.* https://www.pewresearch.org/science/2020/12/10/biotechnology-research-viewed-with-caution-globally-but-most-support-gene-editing-for-babies-to-treat-disease/

While the long-term effects of non-heritable gene editing on the individual must still be considered, the risk of affecting future generations is far lower. However, concerns about the social and psychological impacts of such enhancements remain significant for both non-heritable and heritable gene editing.

Issue 1: Risks of gene editing for enhancement are disproportionate to its benefits

10.6 Heritable gene editing, if permitted in the future, will be employed in genetic enhancement where germline cells or human embryos are genetically modified to acquire advantageous features.[6] Non-heritable gene editing may also be used for enhancement, namely by modifying somatic cells, where the changes would not be passed down to offspring, thus affecting only the individual undergoing the intervention. Although the perceived risks associated with gene editing technology (e.g., unintended consequences) used for treatment of disease and enhancement of traits are similar, these risks may be disproportionate to the benefits offered by gene editing for enhancement purposes. For example, despite the risks involved, applications of gene editing to treat or prevent serious genetic disorders and diseases may nevertheless be justifiable, as there is a clear medical need for this technology. However, risks involved in the applications of gene editing that go beyond addressing medical conditions per se may be less justifiable, when the goals are not directly related to improving health. Therefore, researchers, research institutions and IRBs are advised to consider one particular ethical principle in relation to applications of gene editing for enhancement if indeed they are permitted in the future:

a. Proportionality

10.7 The principle of *proportionality* requires that risks of research and applications of gene editing technology are not disproportionate to its benefits by minimising the harm to individuals and future offspring while maximising its benefits. Gene editing for therapeutic purposes often targets well-understood genetic mutations, reducing the likelihood of their unintended consequences. In addition, severe illnesses caused by genetic disorders such as blood cancers and lymphomas often lack effective treatment options, yet there is gene editing that can provide a form of life-saving therapy, albeit an alternative one. For such applications of gene editing, the risks involved may actually be proportionate to their benefits. On the other hand, non-heritable and heritable gene editing for genetic enhancement may involve manipulating multiple genes to achieve desired traits, but the intricate interplay of genes in complex traits make it inherently challenging to accurately predict and control the outcomes.[5] Genetic enhancement of physical or cognitive abilities, for example, are often subjective, and may be risky, especially if enhancement is not intended for medical purposes—and may be passed down to future generations in the case of heritable gene editing. Therefore, researchers are advised to carefully weigh the benefits against the risks of applications of gene editing for enhancement should they be permitted in the future.

[6] Cwik, B. (2019). Moving beyond "therapy" and "enhancement" in the ethics of gene editing. *Cambridge Quarterly of Healthcare Ethics, 28*(4), 695–707. https://doi.org/10.1017/S0963180119000641

Issue 2: Exacerbation of social inequity due to misuse of gene editing technologies for enhancement

10.8 Given that gene editing technologies for prevention and treatment of serious or rare diseases *are* currently available, it may not require significant innovation to performing intentional alterations on the human genome for enhancement of physical or intellectual traits.[7] Heritable gene editing for the purpose of enhancement could help to select for desirable traits by correcting natural biological variants. However, it may also be misused and abused for the purpose of creating "designer babies" by removing unwanted genes.[8] To illustrate this, gene editing technologies such as CRISPR may be used for cognitive enhancement (e.g., increased memory), physical enhancement (e.g., change of eye colour) and athletic enhancement (e.g., gene doping for greater performance). This could reinforce discrimination between genetically modified and unmodified individuals and thereby exacerbate social inequities.[9] Non-heritable gene editing may also be employed for non-medical purposes, such as to boost memory or athletic performance, without altering the germline. However, non-heritable gene editing enhancements, despite not being passed down to future generations, could still exacerbate social inequalities by creating divisions based on access to such technology. Additionally, the use of gene editing technology for enhancement purposes may reinforce stereotypes, prejudices and harmful practices related to persons with disabilities,[10] thereby exacerbating discrimination against certain marginalised groups, such as persons with disabilities. This may create demand for programs designed to produce "more desirable" and "better" kinds of human beings—an approach that borders on eugenics.[6] Therefore, researchers and research institutions are advised to consider several ethical principles, outlined below, when considering applications of gene editing for enhancement if these are permitted in the future:

a. Justice

10.9 The principle of *justice* encompasses the general principles of fairness and equality for all individuals. It implies that access to the benefits of research and clinical applications involving gene editing technology should be equitably shared in society. In reality, however, the high costs of gene editing would mean that only a small group of wealthy individuals may gain access to the technology for the purpose of enhancement,[11] which could then skew the distribution of perceived advantages and disadvantages of genetic enhancement among people. As a result, the selected or desirable traits would become the exclusive domain of a privileged, wealthy group, and could subject future generations to discrimination[8] thus exacerbating and reinforcing existing social division and inequality. Protecting the interests of future generations is important, particularly those who are vulnerable to discrimination or social inequities,

[7] Friedmann, T. (2019). Genetic therapies, human genetic enhancement, and … eugenics? *Gene Therapy, 26*(9), 351–353. https://doi.org/10.1038/s41434-019-0088-1

[8] Sufian, S., & Garland-Thomson, R. (2021). The dark side of CRISPR. *Scientific American.* https://www.scientificamerican.com/article/the-dark-side-of-crispr/

[9] Lau, P. L. (2023). Evolved eugenics and reinforcement of "othering": Renewed ethico-legal perspectives of genome editing in reproduction. *BioTech, 12*(3), 51. https://doi.org/10.3390/biotech12030051

[10] United Nations. (2006). Convention on the rights of persons with disabilities. *Office of the High Commissioner for Human Rights.* https://www.ohchr.org/en/instruments-mechanisms/instruments/convention-rights-persons-disabilities

[11] Muigai, A. W. (2022). Expanding global access to genetic therapies. *Nature Biotechnology, 40*(1), 20–21. https://doi.org/10.1038/s41587-021-01191-0

such as individuals with disabilities or those from lower-income backgrounds. This must be considered as the collective and shared responsibility of both the research community and the wider public. If permitted, the current generation's decisions to use gene editing technologies to enhance the traits of their children-to-be could affect subsequent offspring. Given that applications of gene editing technology for enhancement could exacerbate social inequity, it may be necessary to limit their uses to cases where they do not result in unfair advantage or disadvantage for certain individuals. Other uses of gene editing technology, such as editing genes to enhance physical traits or cognitive abilities that could create unequal opportunities in sports, education, or employment, may need to be limited, as they could worsen existing social inequalities. Researchers, scientists and society as a whole should also develop a strong sense of stewardship of environmental, biological and social factors to ensure the wellbeing and interests of future generations are not compromised if such applications of gene editing technology are permitted in the future.

b. Inclusivity

10.10 The principle of *inclusivity* maintains that benefits of research and clinical applications involving gene editing technology are considered a public good and should be accessible to everyone within society. Gene editing technology for genetic enhancement, if permitted in the future, can promote *inclusivity* by providing individuals with the opportunity to enhance traits such as intelligence or physical strength, thereby narrowing disparities that arise from natural genetic variations. This could lead to a more inclusive society where everyone has access to the means to improve themselves, regardless of their initial genetic makeup. However, potential applications of gene editing technology for genetic enhancement could also create disparities among those who cannot afford or are unable to access such enhancements. Therefore, it would be prudent to ensure equitable access to this technology for genetic enhancement, to prevent widening existing inequalities. Gene editing for enhancement may reduce the number of disabled individuals and, consequently, able-bodied individuals may develop less empathy and sensitivity towards persons with disabilities. Hence, inclusive policymaking is important and requires researchers, scientists and the government to engage with the views and shared experiences of people living with the conditions that are targeted for intervention. Their perspectives are essential in shaping policies that reflect the needs and concerns of affected communities. If the use of gene editing technology for genetic enhancement is permitted in the future, research and governance frameworks should be established by research institutions and relevant regulatory authorities to ensure that such technology is accessible to the public. Researchers and scientists should ensure that the benefits of applications of gene editing technology for genetic enhancement are made available to everyone, to prevent any further widening of social disparities.

10.11 In view of the potential discrimination that may arise from the use of gene editing technology for enhancement, regulatory authorities and IRBs should conduct more studies to assess the societal impact of permitting genetic enhancement, in terms of whether it will increase the vulnerability of particular populations to risks of harm and discrimination, and create frameworks and regulations to prevent discrimination. In addition, they should also create policies to ensure equitable access to gene editing technology, which reduce potential disparities in the access and use. Initiatives

or programmes to foster inclusion and support for those who are vulnerable to discrimination should be developed and implemented. Social inclusion can also be promoted by eliminating discriminatory practices, educating the public and implementing inclusive workplace policies that provide equal opportunities. These policies may include guidelines for improving communication with people with disabilities by taking into consideration their disabilities, providing assistive devices and allowing them to feel a sense of belonging at the workplace. Social inclusion objectives such as improving the ability, opportunity and dignity of the disadvantaged on the basis of their identity should also be put in place, so as to foster an inclusive environment.

c. Transparency

10.12 The principle of *transparency* requires researchers and their institutions to report and disseminate research methods, analysis and data openly, clearly, comprehensively and in a timely manner to ensure that results are reproducible and reliable, and to facilitate proper interpretation and dissemination of findings by other researchers. Given that researchers in studies that misuse gene editing technology for enhancement may not disclose their methods, analysis and data as accurately and openly as the researchers in permitted research would, it is important for researchers, research institutions and approving authorities to ensure that reporting mechanisms are in place to prevent misuse or abuse of the technology.

Issue 3: Shift in attitudes and behaviours towards reproductive choices

10.13 Heritable gene editing for enhancement purposes could lead to undesirable societal expectations and alter the perception of conventional reproductive choices among future generations. This is because reproductive technology offers a more certain way to select the characteristics of the next generation than does choice of reproductive partners. For example, one study on Down's syndrome screening in England and Wales concluded that although the frequency of births of people with Down's syndrome had not changed much over the study period, the availability of prenatal screening and termination has had a significant impact on the number of children who would have otherwise been born with the conditions for which screening is available.[12] With the advent of prenatal screening technology, parents now have the choice of selectively reproducing only healthy children (i.e., children with no genetic diseases or conditions), and terminating pregnancies that are diagnosed as having severe genetic conditions. Heritable gene editing could represent a prospective reproductive technology that would further increase the power and range of reproductive choice by enabling prospective parents to have genetically-related children while excluding or including certain heritable characteristics (e.g., predisposition to certain diseases, enhancement of physical or cognitive abilities, etc.).[12] If gene editing technology was to become more common and widely utilised, this could bring into question the choices of people who refuse to use such technology. A shift in behaviours and expectations may affect the evaluation of the responsibilities of prospective parents towards their future children. This could, in turn, place pressure on prospective parents to have children using gene editing technology to secure commonly accepted

[12] Nuffield Council on Bioethics. (2018). *Genome editing and human reproduction: Social and ethical issues*. https://www.nuffieldbioethics.org/publications/genome-editing-and-human-reproduction

conventional outcomes,[13] resulting in less tolerance for natural human flaws and weaknesses. Furthermore, some are concerned that parents who genetically enhance their children could burden them with unrealistic expectations. The choice of "desirable traits" that do not have a medical basis could be quite subjective. Therefore, researchers and research institutions are advised to consider the following ethical principles when considering applications of gene editing for enhancement if permitted in the future:

a. Sustainability

10.14 The principle of *sustainability* provides that research and clinical applications involving gene editing technology should ensure that adverse effects or harm rendered by the use of such technology are not perpetuated to future generations. The use of gene editing technology for enhancement could lead to the future generation facing psychological distress to conform to society's perception of 'normal' reproductive choices, and could compromise the welfare of future offspring. Hence, such applications of gene editing technology may not be sustainable.

b. Responsible stewardship of science

10.15 The principle of *responsible stewardship of science* emphasises the moral requirement of researchers to consider the ethical guidelines governing applications of heritable gene editing in the pursuit of biomedical research. Outcomes of biomedical research involving gene editing technology should always be aligned with society's values and perceptions in order to ensure r*esponsible stewardship of science*. However, since heritable gene editing for the purpose of enhancement may result in a shift in social norms and behaviours towards reproductive choices, any research or clinical trials involving the use of gene editing technology for enhancement may not be in alignment with society's values and perceptions, as they may lead to undesirable expectations that could harm society.

c. Respect for persons

10.16 The principle of *respect for persons* refers to the autonomy of individuals making decisions related to biomedical research involving gene editing or its clinical applications. The autonomy of a person may be compromised if they are not fully informed of the possible benefits, risks and repercussions arising from research and clinical applications of gene editing technology. In the context of heritable genetic enhancement (if permitted in the future), parents make decisions on behalf of their unborn children. While this may be consistent with the responsibility of parents to act in the best interests of their offspring, some may consider it important to ensure that such decisions respect the autonomy of the child-to-be. Hence, researchers and research institutions should be mindful of the ethical considerations to ensure that parents responsibly safeguard the best interests of their children and respect their autonomy when they are mature and intelligent enough to make their own decisions, and ensure that the life opportunities of the enhanced children are not constrained.

[13] Nuffield Council on Bioethics. (2018). *Genome editing and human reproduction: Social and ethical issues* [Short guide]. https://www.nuffieldbioethics.org/assets/pdfs/Genome-editing-and-human-reproduction-short-guide.pdf

10.17 Applications of gene editing technology for both non-heritable and heritable genetic enhancement have potential benefits in terms of enhancing cognitive, physical and functional abilities. However, such applications of gene editing technology raise many ethical implications and profound questions of fairness, societal norms and unintended consequences, which will require careful consideration. Therefore, applications of gene editing technology for genetic enhancement should only be considered after thorough public consultation and social debate, as well as once the safety and efficacy of such applications become well-established.

CHAPTER 11:
GOVERNANCE AND FRAMEWORK TOOLS FOR HNGE

11.1 New and emerging technologies in biomedicine, such as HNGE, hold great potential in improving human health.[1] Gene editing tools such as CRISPR-Cas9 may be used to correct aberrant genes and modify sequences within the human genome to treat genetic diseases, improve fertility and enhance desirable traits.[2] However, HNGE technology is currently still in its infancy, with many efficacy and safety concerns yet to be addressed. Teething issues with the technology include off-target effects, unintended genetic changes and genetic mosaicism, that could be passed down to future generations in cases such as heritable gene editing for treatment of diseases or infertility.[3] High costs of existing therapy regimens involving HNGE may also limit the technology to just an elite group of privileged people, and in doing so, exacerbate social inequality.[4] In the event that gene editing for enhancing specific traits is allowed, the move would also be detrimental to human population diversity, if genes for the same desirable traits are selectively altered.[5]

I. Governance Framework for HNGE Research

11.2 As with other technological advances, gene editing raises ethical and social issues that must be addressed by having proper governance frameworks put in place. In 2021, the WHO published a governance framework for HNGE derived from good practices on the governance of emerging technologies.[1] The recommended framework identifies values and principles that justify the need for governance measures, and how the review or strengthening of such measures may be carried out. It also sets out an assessment of the tools, institutions, processes and considerations necessary for the successful implementation of oversight and governance measures for HNGE. Proper governance is not limited to legislative frameworks and regulations, but also includes other norms that may influence the development of the technology at various levels.[1] We elaborate here on the governance and framework tools for HNGE that should be put in place at the following respective levels:

[1] World Health Organization. (2021). *Human genome editing: A framework for governance.* World Health Organization. https://www.who.int/publications/i/item/9789240030060

[2] Furtado, R. N. (2019). Gene editing: The risks and benefits of modifying human DNA. *Revista Bioética, 27*(2), 223–233. https://doi.org/10.1590/1983-80422019272304

[3] Davies, B. (2019). The technical risks of human gene editing. *Human Reproduction, 34*(11), 2104–2111. https://doi.org/10.1093/humrep/dez162s

[4] Subica, A. M. (2023). CRISPR in public health: The health equity implications and role of community in gene-editing research and applications. *American Journal of Public Health, 113*(8), 874–882. https://doi.org/10.2105/AJPH.2023.307315

[5] Sufian, S., & Garland-Thomson, R. (2021). The dark side of CRISPR. *Scientific American*. https://www.scientificamerican.com/article/the-dark-side-of-crispr/

a. Institutional research level: Institutional policies and Institutional Review Boards (IRBs)

11.3 Policies and practices put in place for HNGE research warrant regular reviews by institutions to manage the risks and maximise the potential benefits emanating from such research. Notably, the review should take into consideration the views of the public, patients, or others with a vested interest in the activities conducted by such institutions. For instance, a study carried out in Japan found that stakeholder involvement in the governance of emerging medical technologies—for example, through collaboration between the scientific research community and other parties (e.g., government bodies, experts and the general public) within society—was critical to establishing an effective regulatory system.[6] This is because perceptions about the use of HNGE may vary from one individual to another and the interests of a representative public should be examined in policy-making.

11.4 Institutions should ensure that all staff involved in HNGE research share responsibility and accountability for the institution's research being conducted according to appropriate regulatory, ethical and scientific standards within the levels of acceptable institutional risk. For example, institutions in Singapore conducting any gene editing research on germline cells or oocytes that falls within the scope of 'restricted research' under the Human Biomedical Research (Restricted Research) Regulations 2017, should adhere to the requirements of the Human Biomedical Research Act 2015, and seek the necessary approval from the Ministry of Health prior to conducting the research.[7]

11.5 In Singapore, IRB review is required when a research study is conducted at institutions or partner institutions under the IRB's purview (e.g., hospitals and polyclinics). IRB review is also required if the research involves human subjects and/or patients from that IRB or healthcare cluster[8], or is conducted by, or under the direction of, an employee under the purview of the IRB or healthcare cluster. IRBs should ensure that the research is conducted in accordance with high ethical standards, adheres to regulatory frameworks, and that appropriate measures are taken to protect the rights and welfare of human participants in HNGE research.[9]

b. Clinical level: Regulatory bodies, government and funding agencies, and standard operating procedures (SOPs)

11.6 Regulatory bodies, government organisations and funding agencies[10] that are developing internal standard operating procedures (SOPs) for research and/or clinical trials of HNGE, should implement guidelines and put in place robust systems, to understand, monitor and minimise or mitigate the relevant risks and their impact

[6] Aikyo, T., Kogetsu, A., & Kato, K. (2023). Stakeholder involvement in the governance of human genome editing in Japan. *Asian Bioethics Review, 15*(4), 431–455. https://doi.org/10.1007/s41649-023-00251-8

[7] Restricted research refers to any restricted human biomedical research as set out in Fourth Schedule of the Human Biomedical Research Act 2015, including that involving human eggs and embryos. https://sso.agc.gov.sg/Act/HBRA2015?ProvIds=Sc4-#Sc4-

[8] A healthcare cluster is an integrated system consisting of a range of healthcare institutions including acute and community hospitals, primary care providers, nursing homes and other long term care providers, and medical schools.

[9] Bioethics Advisory Committee Singapore. (2004). *Research involving human subjects: guidelines for IRBs*. https://www.bioethics-singapore.gov.sg/files/publications/reports/research-involving-human-subjects-guideline-for-irbs-full-report.pdf

[10] Regulatory bodies, government organisations and funding agencies include the Health Sciences Authority of Singapore (HSA), Agency for Science, Technology and Research (A*STAR), and the National Medical Research Council (NMRC).

on research subjects and patients undergoing clinical trials. This may be achieved by considering the anticipated limitations of the proposed technology and via a comparison with available standards for safety and efficacy studies.[1] One example would be the "Cellular & Gene Therapy Guidances" published by US FDA for industry, FDA reviewers and FDA staff.[11]

c. National level: Legislation and regulatory guidance

11.7 Governments and policy makers should ensure that laws and guidelines pertaining to the application and research involving HNGE are reviewed and revised regularly. National policies should be developed after careful analysis of the latest scientific evidence, and be in alignment with prevailing societal values. Such reviews may be conducted by advisory committees convened to examine safety concerns, sound practices and the scope of allowable activities, in order to make informed recommendations for decision making.[1] Stakeholder consultations with the scientific community, patient advocates, and the general public should be carried out with feedback sought, to ensure that policies properly take into consideration the varied interests of all stakeholders in society.

11.8 In this regard, a study assessing the national governance capacity of the development of non-heritable gene editing technology in eight geographically, socially, economically and culturally diverse countries, broadly found that at the national level, the ministries of health, science and technology play the lead role in deciding how governance mechanisms (e.g., laws and regulations, codes of ethics or research review processes) are framed and in terms of allocating responsibilities for biosafety and research ethics.[12] The study also found that there was a lack of clarity on the scope of the governance measures, such as the differentiation between non-heritable gene editing and heritable gene editing, as well as between research and treatment. Public consultations would be desirable in order to address the inadequacy of available information, short timelines for responses and the lack of public awareness about the consultation processes. The study also discovered a lack of information about enforcement or organisations that actively monitor for non-compliance, which may suggest that while governance measures do in theory exist, the reality may be entirely different.

II. Tools and Approaches to Strengthen Existing Research Governance

11.9 There is a wide variety of strategies that could be introduced to fortify existing research governance frameworks, such as self-regulation by professional bodies, development of guidelines, ethics and training courses, strengthened institutional practices, the introduction of HNGE registries and implementation of whistle-blowing mechanisms. Each of these strategies is explored in detail below.

[11] U.S. Food & Drug Administration. (n.d.). *Cellular & gene therapy guidances.* https://www.fda.gov/vaccines-blood-biologics/biologics-guidances/cellular-gene-therapy-guidances

[12] Millett, P., et al. (2023). Somatic genome editing governance approaches and regulatory capacity in different countries. *Social Science Research Network*. http://dx.doi.org/10.2139/ssrn.4375726

a. Professional self-regulation

11.10 Professional self-regulation within the scientific community can be an effective way to hold scientists conducting HNGE research accountable to their peers and society, thereby serving as an important deterrent to misconduct in this arena. Professional self-regulation may rely on ethical codes developed by advisory committees[13] and could include representatives from patient groups, public interest groups, advocacy organisations and other parts of society. Professional societies can also help develop guidelines for the sector, setting out best practices, standards and ethical considerations in HNGE research. Well-crafted guidelines would have the flexibility to be reviewed regularly in response to the rapidly evolving field of gene editing technology, in contrast to legislative reform.

11.11 However, professional self-regulation may give rise to potential conflicts of interest[14] as the party laying out guidelines or best practices may have certain self-interests in pursuing the research or treatment. In addition, there might not be sufficiently rigorous action taken against those who violate established standards because of professional *solidarity* or other secondary interests, such as financial gain. For instance, conflicts of interests in research or clinical practice may arise due to financial relationships between researchers or medical professionals and entities such as biopharmaceutical or biotechnology companies.

b. Providing education and training specific to HNGE for researchers and clinicians

11.12 Additional educational training or ethics modules specific to HNGE may be developed for graduates who are looking to pursue research in gene editing or professions that may involve clinical applications of gene editing.[1] These modules could cover topics on research integrity, ethics and the latest scientific developments in HNGE, as well as various national policies and guidelines relevant to the field. Providing training through public education, engagement, empowerment of individual rights and media communication will facilitate better understanding and communication between researchers and the public.[15] This would, in turn, enable the scientific community to better understand public concerns and needs, thereby ensuring that information is conveyed accurately and thus preventing any distortion of public perceptions and expectations relating to HNGE.

11.13 Institutions can fund or support educational or training programmes for their staff and IRB members, so as to equip them with knowledge of gene editing technology, developments in HNGE research, appropriate ethical standards, national guidance documents and advisories, as well as legislative updates.

c. Reinforcement of institutional practices

11.14 Institutions may review existing IRB ethics review processes and develop SOPs for HNGE research. Institutions should also ensure that these SOPs are revised regularly

[13] Conley, J. M., et al. (2020). A new governance approach to regulating human genome editing. *North Carolina Journal of Law & Technology, 22*(2), 107–141.

[14] Christian, A. (2022). Addressing conflicts of interest and conflicts of commitment in public advocacy and policy making on CRISPR/Cas-based human genome editing. *Frontiers in Research Metrics and Analytics, 7*, Article 775336.

[15] World Health Organisation. (2021). *Human genome editing: Recommendations*. https://apps.who.int/iris/bitstream/handle/10665/342486/9789240030381-eng.pdf?sequence=1

and updated to keep pace with the changes and developments in HNGE research, technologies and legislation.

11.15 In addition, institutions may put in place annual reporting requirements, declaration mechanisms and processes for self-monitoring of HNGE research. These mechanisms may also be used to monitor achievements and other outcomes achieved in ongoing gene editing research, including any advances in knowledge, as well as to report on any adverse events arising from clinical trials.

11.16 Institutions may also review existing training programmes for IRBs to ensure members are kept abreast of the latest trends and developments in HNGE, and remain informed and competent in order to be able to review HNGE research applications. Institutions can also encourage greater discussion amongst staff and researchers about ongoing HNGE research protocols and their safeguards, in order to enhance understanding of how HNGE research should be conducted to appropriate ethical standards.

d. Setting up HNGE registries

11.17 National registries tracking germline gene editing research on embryos and non-heritable gene editing clinical trials can be set up to monitor all research and clinical trials involving human gene editing. Such registries help enable information about HNGE research and clinical trials to be made easily accessible to relevant stakeholders. For instance, the WHO has set up a Human Genome Editing (HGE) Registry, which is a global centralised database that collates information pertaining to clinical trials for human gene editing technology.[16] In accordance with the principles of *transparency* and *inclusivity* (refer to Chapter 3 on the definitions of ethical principles), the HGE Registry aims to allow information regarding clinical trials of HNGE technologies to be made easily accessible to all interested stakeholders such as researchers, medical professionals and potential clinical trial participants (i.e., patients). Failure to register any research that falls within the scope of the HGE Registry may prevent appropriate oversight and valuable feedback from stakeholders, which may amount to a violation of the principle of *responsible stewardship of science, transparency, and inclusivity*.

(i) Germline gene editing research

11.18 In the wake of the CRISPR baby scandal, there is an urgent need to better regulate HNGE research, and to ensure that any ongoing and subsequent germline gene editing research activities are on a safe and sensible path.[17] Proposals for all ethically-approved basic research[18] studies that employ gene editing tools in human embryos and gametes, including those for evaluating treatment efficacy and safety, could be placed in an open registry. Setting up a registry for germline gene editing research could encourage legitimate submissions for fundamental and pre-clinical research and avert abuse by businesses seeking to commercialise gene editing technologies

[16] World Health Organisation. (n.d.). Human genome editing registry. https://www.who.int/groups/expert-advisory-committee-on-developing-global-standards-for-governance-and-oversight-of-human-genome-editing/registry#:~:text=The%20Human%20Genome%20Editing%20(HGE,Trials%20Registry%20Platform%20(ICTRP)

[17] Xue, Y., & Shang, L. (2022). Governance of heritable human gene editing world-wide and beyond. *International Journal of Environmental Research and Public Health, 19*(11), Article 6739. https://doi.org/10.3390/ijerph19116739

[18] Basic research is a form of scientific research aimed at improving scientific theories for the better understanding and prediction of natural or other phenomena.

prematurely. Such registries could also enable early recognition of any research that risks overstepping pre-defined boundaries, by allowing researchers or interested stakeholders to flag up potentially dangerous germline gene editing research. The set up of such registries for germline gene editing research should involve a collaborative effort among scientific institutions, governmental bodies, regulatory agencies and ethicists.

(ii) Non-heritable gene editing clinical trials

11.19 For clinical trials involving non-heritable gene editing, well-established registries can provide valuable information on the safety of treatments and the therapeutic efficacy of non-heritable gene editing. This is applicable to HNGE where long-term monitoring may be necessary to assess the safety and efficacy of the technology.[19] Non-heritable gene editing clinical trial registries could help prevent selective publication and reporting of research outcomes, reduce unnecessary duplication of research effort and allow patients and the wider public access to the available clinical trials that are planned or ongoing, to facilitate decisions on participation.[16] These registries could also provide an overview of the landscape and data of existing research to ethics review boards that might be considering approval of new research studies of similar work or scope.

(iii) Non-heritable gene editing clinical applications

11.20 Data may not always be made publicly available for treatments employing non-heritable gene editing technology carried out under the hospital exemption rule (i.e., innovation salvage therapy cases) but which fall outside the scope of clinical trials. Setting up open-access registries of such treatments could help widen access to treatment strategies and data, provide evidence of the efficacy of treatments and also help identify treatment-related costs that may be considered for reimbursement.

e. Whistleblowing mechanisms

11.21 In addition to a registry to collect clinical trial data involving gene editing applications, the WHO has also recommended the introduction of whistleblowing mechanisms[20] at an institutional or national level. This is to establish effective reporting channels and to help maintain comprehensive protection and support for those who report illegal, unregistered, unethical or unsafe HNGE research.[21]

11.22 Research institutions can provide a well-advertised, safe, and confidential internal mechanism for reporting allegations. To enable and encourage researchers or the public to report concerns about unethical HNGE research from outside an institution, a new reporting mechanism can be set up in the form of a confidential portal, website or hotline, which would allow individuals to file a report at any time and from any location. Follow-up procedures should be put in place to review any reports filed

[19] U.S. Food and Drug Administration. (2020). *Long term follow-up after administration of human gene therapy products*. https://www.fda.gov/media/113768/download

[20] Delaye, F. (2021). Genome editing: WHO banks on whistleblowers. *Geneva Solutions*. https://genevasolutions.news/global-health/genome-editing-who-banks-on-whistleblowers

[21] Perrin, N. (2021). *Enabling researchers to report concerns about human genome editing research: report for the WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing. World Health Organization*. https://apps.who.int/iris/bitstream/handle/10665/345331/WHO-SCI-RFH-2021.05-eng.pdf

and to demonstrate that action has been taken where appropriate.[1] A two-stage investigative process can be implemented, beginning with a preliminary enquiry to verify that the reported concern is valid and not frivolous, followed by a more detailed, rigorous investigation if warranted. It would be important to establish the foregoing investigative and sanctioning functions via government legislation, in consultation with the relevant research institutions or funding agencies, and with clear levers to address misconduct.

11.23 Protective mechanisms should be set up to mitigate potential harm that may result to individuals (e.g., researchers or members of the public) for reporting on unethical HNGE research. Individuals who do bring such incidents to light should have their identities kept confidential and be provided with appropriate guidance and professional advice throughout the reporting process.

f. International mechanism for reporting unethical germline gene editing experiments

11.24 In 2006, the WHO's Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing established an International Clinical Trials Registry Platform (ICTRP) for clinical trials involving gene editing, through a World Health Assembly resolution.[16] While the ICTRP system can be leveraged to report unethical experiments, establishing a system supported by WHO sends a signal to the world that reporting of unethical experiments is the responsibility of researchers globally.

III. Governance Framework for Heritable Gene Editing and Gene Editing in Embryos or Germline Cells for Research Purposes

11.25 Heritable gene editing requires proper governance frameworks, since any genetic modifications made may be passed down to successive generations. In particular, heritable gene editing for clinical research and clinical applications are deemed to pose greater risks to future progeny, due to the deleterious long-term health effects stemming from the manipulation of germline cells or embryos.[22] Furthermore, the clinical use of heritable gene editing may heighten social tensions such as inequity and undesirable social expectations. In comparison, the risks associated with gene editing in embryos or germline cells for basic research purposes are lower, as research conducted on germ line cells *in vitro* do not affect future generations. Therefore, the extent of oversight in developing governance and framework tools should be commensurate with the extent of corresponding risk and sensitivity, whether for clinical research and clinical applications of heritable gene editing, or for the basic research activities of gene editing in embryos or germline cells.

11.26 Due to the ethical issues involved in HNGE, as well as the potential for misuse and downstream implications for patients, and potentially, their progeny, robust and comprehensive governance frameworks will be critical in ensuring the safety and welfare of patients undergoing such treatments or clinical trials. Institutions, professional bodies and governments should collaborate to develop policies, guidelines and regulatory frameworks that accord with prevailing societal values, minimising risks and maximising potential healthcare benefits to the public.

[22] Baylis, F., et al. (2020). Human germline and heritable genome editing: The global policy landscape. *The CRISPR Journal, 3*(5), 365–377. https://doi.org/10.1089/crispr.2020.0082

CHAPTER 12:
CONCLUSION

12.1 Applications of gene editing in human biomedical research have helped to advance developments in genetics, disease modelling and therapeutics. The increasing use of gene editing in clinical applications offers promise for treating genetic disorders, infertility, enhancing personalised medicine and improving health outcomes. While the technology has the potential to confer resistance to diseases and enhancement of traits in the future, they may also bring about unintended consequences and expose individuals and future generations to unknown long-term effects. Hence, it would be imperative that these issues be reviewed holistically and to develop appropriate recommendations to guide researchers, healthcare professionals and IRBs on the ethical use of gene editing to ensure patient safety and welfare.

12.2 The BAC has conducted a comprehensive review of the ethical, legal and social issues arising from gene editing in human biomedical research and clinical applications. From its review, it has issued recommendations to guide the responsible use of such technology. These recommendations consider the ethical implications that may arise from such use, and the potential benefits and risks to individuals and future generations. The objectives of the BAC's recommendations include not only encouraging greater ethical debates around genetic enhancements and discourse to address emerging ethical concerns involved in HNGE, but to also encourage and enable researchers to conduct HNGE research in an ethical manner. This could also potentially lead to safer and more effective medical treatments for various genetic disorders. The BAC's recommendations on HNGE will help shape policies that balance scientific progress with ethical considerations and thereby facilitate decision making.

12.3 In its advisory report, the BAC recommends that researchers, research institutions, IRBs, and healthcare professionals consider the five substantive principles, namely (i) *respect for persons*; (ii) *solidarity*; (iii) *justice*; (iv) *proportionality*; and (v) *sustainability*, as well as the three governance principles of (i) *inclusivity*; (ii) *transparency*; and (iii) *responsible stewardship of science* for HNGE research and clinical applications. The BAC's recommendations for the safe and ethical use of gene editing technology are summarised as follows (refer to Chapters 6, 7, 8, 9 and 10 for a detailed discussion of these recommendations):

a. Non-heritable gene editing (for research and clinical applications)

12.4 For any research on, and clinical application of, non-heritable gene editing, the BAC recommends that researchers, research institutions and clinicians should ensure a favourable risk-benefit ratio for patients undergoing clinical trials or clinical interventions involving non-heritable gene editing. Patients must be informed of the potential risks and possible complications, and informed consent and IRB approval should be obtained from patients prior to their procedure.

12.5 Given that the long-term safety and efficacy of non-heritable gene editing are not fully established, the BAC recommends that researchers, research institutions and clinicians should conduct long-term follow-up on patients in clinical trials involving non-heritable gene editing in order to mitigate the risk of any adverse development arising from the treatment manifesting itself only later. It would also be important for researchers and research institutions to take appropriate measures, such as establishing guidelines on the duration of follow-ups and monitoring the frequency of follow-ups when developing guidelines for evaluating and managing off-target effects. The guidelines should also include other aspects and risks of the treatment, such as the specificity of the gene editing tool, the types of tissues affected, unintended genetic changes and the potential for immune responses. Researchers and research institutions should also develop comprehensive frameworks for risk assessments, which involve creating standardised protocols for identifying, evaluating and managing risks, in order to ensure consistent implementation across different studies. These would help to anticipate and manage uncertainties and long-term consequences associated with non-heritable gene editing.

12.6 Furthermore, the BAC recommends communication strategies for reporting outcomes and educating patients about the potential risks and benefits of non-heritable gene editing. Clear and consistent communication can help patients make informed decisions and remain vigilant for any potential delayed effects. Additionally, researchers should refer to the BAC's advisory report on the 'Ethical Use of Big Data and Artificial Intelligence (AI) in Biomedical Research', which provides guidance to decision-makers who work with big data and AI in health and research, and recommends good practices for the safeguarding of data and collaborative data sharing practices.

b. Gene editing on germline cells or embryos for research

12.7 The BAC does not recommend culturing human embryos whose genes have been edited beyond 14 days, maintaining that the creation of human embryos solely for research purposes can only be justified when there is strong scientific merit in, and potential benefit from, such research. It is conceivable that the BAC may reconsider its position at some point in the future should stronger evidence come to light of scientific merit in culturing human embryos whose genes have been edited after 14 days, subject to public consultations and engaging with stakeholders. Furthermore, the BAC currently recommends that women donating surplus embryos or undergoing oocyte procurement for any approved gene editing research should be fully informed of all aspects of the research study by researchers and research institutions. This includes the risks involved, any potential data that may be collected, and the implications thereof. Donors should also be afforded sufficient time to give their consent prior to undergoing the procedures. The BAC also recommends that researchers and research institutions take responsibility to ensure that data obtained from genome sequencing during gene editing research on human embryos are not misused and to safeguard the security of data storage.

12.8 With regard to compensation of women undergoing oocyte procurement for gene editing research, the BAC recommends that the relevant regulatory authority clarify its stance on whether compensation for loss of time and earnings should be allowed, given that Singapore's Human Cloning and Other Prohibited Services Act

2004 allows only for reimbursement of reasonable expenses incurred by a person in relation to the supply of human gamete. The BAC also recommends that the relevant regulatory authority consider capping compensation to avoid inducements.

c. Heritable gene editing for clinical research and clinical applications

12.9 Clinical research and clinical applications of heritable gene editing for (i) treatment of diseases; (ii) infertility; (iii) conferring resistance to diseases; and (iv) enhancement of traits, have raised ethical and safety concerns including unintended consequences, long-term effects and other issues around consent, autonomy and inequality. The BAC does not recommend clinical research and clinical applications of heritable gene editing for any purpose in the near future, as there is insufficient evidence from current research to give confidence that such applications of HNGE technology are irrefutably safe and ethical. Hence, more research would need to be conducted to determine whether clinical research and clinical applications of heritable gene editing are genuinely safe and ethical before they can be recommended in the future.

12.10 Nonetheless, if and when the risks involved (including those of exacerbating genetic discrimination and social inequalities) in the applications of gene editing technology are sufficiently mitigated in the future, the BAC may then reconsider whether heritable gene editing may be recommended for use as experimental intervention in certain situations to prevent catastrophic conditions, or to combat diseases for which there are no other treatment options available. Such situations may potentially benefit the future child where the benefits involved may outweigh the risks. The experimental intervention involving heritable gene editing must be conducted as a clinical trial with the appropriate approvals from ethics and regulatory bodies. Given that the oversight of heritable gene editing is complex involving ethical, scientific, and regulatory considerations, having a national review (i.e., input from experts in genetics, bioethics, law, and various stakeholders such as policymakers, and the public) for such experimental intervention would be important, to provide an additional layer of oversight. This would enable a comprehensive evaluation from a broader perspective, embracing potential societal impacts and international implications.

12.11 The governance of research and clinical applications of gene editing technology is important and serves to uphold ethical principles, foster responsible innovation and promote ethical advancement of such technology. The BAC's recommendations, which are aimed at governing the ethical and responsible use of gene editing technology are summarised as follows (refer to Chapter 11 on 'Governance and Framework Tools for HNGE' for a detailed discussion):

a. The BAC recommends that research institutions regularly review policies and practices in place to manage risks and maximise potential benefits that may arise from HNGE research. The BAC also recommends that IRBs should ensure that HNGE research is conducted in accordance with high ethical standards, adheres to regulatory frameworks and that appropriate measures are taken to protect the rights and welfare of human participants in HNGE research.

b. The BAC recommends that regulatory bodies, government and funding agencies encourage the implementation of guidelines and put in place robust systems to understand, monitor, and minimise or mitigate the risks and their impact on research subjects and patients undergoing HNGE clinical trials. This is carried

out by also giving due consideration to the anticipated limitations of gene editing technology and comparison with available standards for safety and efficacy studies.

c. The BAC recommends that governments and policy makers should regularly review and revise legislation and guidelines pertaining to applications and research involving HNGE. National policies should be developed after careful review of scientific evidence and in alignment with societal values. The BAC also recommends stakeholder consultations to be conducted with the scientific community and patient advocates, to obtain feedback from the general public, so as to ensure that policies pertaining to HNGE are well aligned with societal values.

d. The BAC recommends various approaches and tools be introduced to enhance existing research governance frameworks for HNGE, such as self-regulation by professional bodies, development of guidelines, ethics and training courses, reinforcement of institutional practices, establishment of HNGE registries and implementation of a whistle-blowing mechanism.

e. With regard to heritable gene editing for clinical applications, the BAC recommends that the extent of oversight in developing governance and framework tools should be commensurate with the extent of risks and sensitivity involved in clinical applications of heritable gene editing. Given that clinical applications of heritable gene editing for (i) conferring resistance to diseases and (ii) enhancement of traits pose more significant ethical concerns, as compared to clinical applications of heritable gene editing for treatment of diseases or infertility, the BAC recommends that clinical applications of heritable gene editing to confer resistance to diseases and to enhance traits be subject to more stringent governance.

12.12 In addition to the BAC's recommendations on the governance of research and clinical applications of HNGE as summarised above, it would also be important to maintain flexibility in the governance of HNGE, given that gene editing technology is a rapidly evolving field. This flexibility would allow scientific advancements to be adapted to reflect ethical considerations and thereby help foster a responsiveness to emerging ethical challenges, while also ensuring responsible and ethical use of constantly evolving gene editing technology. Achieving a balance between flexibility and ethical oversight is crucial for navigating the complex landscape of research and clinical applications of gene editing technology. In short, the governance of research and clinical applications of gene editing technology should be guided by the following considerations:

a. Guidance from international organisations

12.13 International organisations such as WHO develop guidelines and recommendations on a regular basis (e.g., WHO's framework for governance of human genome editing[1]). It would be important to consider international organisations' guidance on gene editing, and ensure a consistent ethical framework and standards are adopted across borders, which would help promote global collaboration. This would also avert disparities in regulatory approaches, fostering a unified stance on responsible gene editing. As the field of gene editing is continuously evolving, the BAC's

[1] World Health Organization. (2021). *Human genome editing: A framework for governance*. https://www.who.int/publications/i/item/9789240030060

recommendations should remain aligned with the latest international guidelines and recommendations, and fine-tuned to fit the local context.

b. International governance and collaborations

12.14 International governance and collaborations on HNGE are important, as they encourage research and clinical applications of gene editing to adhere to universally accepted principles. Such collaborations can also promote responsible development through joint research and sharing of best practices, while also promoting international ethical standards in gene editing.[2] It would also be important for policymakers and organisations developing recommendations and guidelines pertaining to gene editing technology, to collaborate with international institutions and bodies that have an interest in the field of gene editing, such as WHO, International Bioethics Committee (IBC) of the United Nations Educational, Scientific and Cultural Organization (UNESCO), and American Society of Human Genetics, to discuss and share ethical issues arising from such technology. Sharing of information on laws and legislations relevant to gene editing, as well as engaging in collaborative international governance and oversight of gene editing, will enable better alignment of ethical standards.

c. Continuous stakeholders and public engagement

12.15 Stakeholders and public engagement are, and should continue to play, an important part in research and clinical applications of gene editing technology and its advancement. Such engagement is crucial for ethical and transparent decision-making, helping ensure diverse perspectives are considered and that policies are shaped to align with broader societal values. Through continuous engagement of the relevant stakeholders and the public, the feedback obtained will allow policy makers, researchers and healthcare professionals to understand the public's concerns and ensure that HNGE progresses in a way that best serves the public's interests.

d. Public education to raise awareness of the benefits and risks of HNGE applications

12.16 Public education plays a vital role in raising the public's awareness of the benefits, risks and ethical issues involved in research and clinical applications of gene editing technology while also enhancing the public's knowledge of the latest developments in gene editing. Public education also provides opportunities for the public to reflect and have discussions on developments pertaining to gene editing technology. Education also enables the public to make informed decisions about supporting or participating in gene editing research or clinical trials that involve gene editing technology. In addition, public education clarifies any misperceptions regarding gene editing and equips individuals to whom this knowledge has been imparted, to differentiate between legitimate scientific advancements and potential misconceptions or fraudulent activities. This, in turn, reduces the risk that individuals unwittingly participate in unethical or questionable gene editing technology clinical trials.

[2] Shampa, G., et. al. (2023). Balancing potential benefits and ethical considerations of gene editing. *The Lancet, 401*(10392), 1850–1860. https://doi.org/10.1016/S0140-6736(23)01084-X

12.17 In conclusion, the ethical landscape surrounding gene editing requires that academics, researchers, healthcare professionals, IRBs and research and healthcare institutions consider the ethical principles highlighted in this report when using gene editing technology for research or clinical applications. With further advancements in this field, it would be imperative that the potential benefits of technology are balanced against their associated risks, as well as their ethical and societal implications. Public education and continuous stakeholder engagement are pivotal in fostering a responsible and ethical approach to gene editing. Striking this balance will not only guide the scientific community, but will also encourage the broader public to remain informed and be actively involved in shaping the ethical framework that governs the responsible use of gene editing technology.

CHAPTER 13:
RECOMMENDATIONS FOR CLINICIANS, RESEARCHERS, RESEARCH INSTITUTIONS, REGULATORY AUTHORITIES, AND INSTITUTIONAL REVIEW BOARDS (IRBS)

This chapter summarises the key ethical principles that are applicable to HNGE in biomedical research and clinical applications. It also sets out recommendations for clinicians, researchers, research institutions, regulatory authorities and IRBs in the process and evaluation of HNGE applications. As the HNGE technology is constantly evolving, this report will be reviewed periodically to ensure that the BAC recommendations are kept up to date.

I. Ethical Principles Applicable to the Use of HNGE in Biomedical Research and Clinical Applications

13.1 The principle of *respect for persons* underlies the need for informed consent of individuals participating in biomedical research involving gene editing or its clinical applications, to protect their autonomy and rights. This would enable individuals to decide whether to undergo non-heritable gene editing and engage in germline human gene editing for their offspring, if and when the safety, efficacy and long-term effects are well-established and if and when gene editing is approved for use.

13.2 The principle of *solidarity* reflects the importance of general altruism and other pro-social motives as a basis for participation in biomedical research. For instance, research in human gene editing may reap benefits for society by enabling faster and more accurate diagnosis of diseases or conditions in patients, introducing more targeted treatments, and allowing early prevention of the occurrence of genetic disorders. Yet at the same time, the misuse and abuse of the technology for inappropriate purposes or the enhancement of personal trait preferences could lead to the neglect or failure to discharge obligations towards certain subgroups, such as those afflicted by a rare disease.

13.3 The principle of *justice* holds that gene editing technology and therapy be accessible to the public according to a plausible theory of *justice*. However, the technology involved may raise concerns about ensuring fair access to therapy due to the high cost. As such, treatments involving the use of gene editing technology may not be widely and readily accessible to the entire population, particularly the lower socioeconomic strata, which may lead to societal inequity issues.

13.4 The principle of *proportionality* requires that the regulation of research should be proportional to the degree of possible threats to autonomy, individual welfare or the public good. As such, any interference with individuals' decisions and/or actions,

should not exceed what is sufficient to achieve necessary regulation to promote public interest. The principle also implies that the risk in any acceptable programme of research, and the stringency of its regulation, should not be disproportionate to any anticipated benefits. When assessing the use of gene editing technology in biomedical research or clinical purposes, the potential benefits to individuals and society brought about by the editing of the human genome should outweigh the anticipated risks emanating from such research and clinical applications. The stringency of any regulation or governance framework developed for research employing gene editing, including a *de facto* prohibition of specific research activities, must be proportionate to the risks being mitigated.

13.5 The principle of *sustainability* maintains that research processes and outcomes should not unfairly jeopardise or prejudice the welfare of future generations. In the context of human gene editing in biomedical research or clinical purposes, while gene editing technology can bring about social benefits, research involving human embryos and heritable gene editing for treatment of diseases, conferring resistance, enhancement of traits, or treatment for infertility, might harm the offspring and their future generations directly or indirectly due to the risks of genetic mutation. Researchers and research institutions are encouraged to allocate and expend research resources appropriately to support HNGE research activities, as long as the resources are not misused and their research is aligned with the United Nations (UN) Sustainable Development Goals.

II. Governance Principles Applicable to the Use of HNGE in Biomedical Research and Clinical Applications

13.6 The principle of *inclusivity* stipulates that the benefits of HNGE research and potential clinical applications are considered a public good, and as such, should be accessible to everyone. However, the ethical implications of HNGE could exacerbate already divergent views of technology in society. Hence, there is a need to carefully consider the knowledge and perspectives of HNGE that are informed by different social, cultural and religious beliefs, and to work closely with different groups of people to facilitate 'community-engaged research', where a wide range of opinions and perspectives are considered in the conceptualisation of research plans.

13.7 The principle of *transparency* relates closely to ethical responsibility and moral and legal liability for the decisions and actions arising directly from research studies which should be attributed to researchers and their institutions. Research methods, analysis and sampled data must be reported and disseminated openly, clearly, comprehensively and in a timely manner to ensure that results are reproducible and reliable, and to facilitate proper interpretation and dissemination of findings by other researchers. Transparent reporting mechanisms may also be devised to investigate concerns about possible unlawful doings, as well as to provide support and protection for whistle-blowers.

13.8 According to the principle of *responsible stewardship of science*, the processes and outcomes of HNGE research should be aligned with the values, needs, and expectations of society, which can be identified through stakeholder engagement. This principle extends beyond the dissemination of information and demands that the views of all stakeholders be considered, as elaborated in the principle of *inclusivity*.

III. General Guidelines and Recommendations

13.9 The BAC recommends that research and research institutions should put in place an oversight mechanism for any research involving HNGE, to ensure that research activities are conducted appropriately. For instance, an oversight committee could be established within research institutions to oversee the research priority setting process for gene editing research. An oversight committee may comprise members from diverse backgrounds (e.g., research, medical, administrative) to advise on current policy and research considerations, assist with the identification of stakeholders and provide inputs into finalising the research priorities. It is important for researchers and institutions to exercise caution in view of the uncertainty and long-term risks associated with gene editing technology in both research and clinical applications. It is also important to put in place clear and well-established protocols and processes for oversight and review, to ensure that research is conducted in an ethical manner.

13.10 Researchers and research institutions should set research priorities based on societal needs while formulating strategies to prevent or mitigate the occurrence of existing errors arising from HNGE. This would ensure that social and scientific benefits are maximised, and that potential risks are minimised. In addition, established ethical practices, ethical guidelines and legislation should be adhered to by researchers when conducting research on humans, with particular attention given to issues of integrity and conflicts of interest.

13.11 Clinicians should consider current established methods of intervention to treat or prevent diseases in individuals and future offspring until the safety and efficacy of HNGE technology are demonstrated. For while HNGE may be used for a variety of indications and in investigative studies of diseases (e.g., enhancement of specific traits, therapeutic interventions, determining genetic targets for diagnostic purposes as well as in the treatment of fertility), many research groups' findings are largely preliminary and require further studies to determine the long-term safety and efficacy of gene editing technology.

IV. Recommendations for Non-Heritable Gene Editing (for Research and Clinical Applications)

13.12 For any research and clinical applications involving non-heritable gene editing, researchers, research institutions and clinicians should ensure a favourable risk-benefit ratio for patients undergoing such clinical trials or clinical interventions.

13.13 Governments, regulatory bodies and IRBs should establish an evaluation framework at the institutional level, comprising guidelines and oversight committees, to assess the benefits of gene editing technology vis-à-vis the risks such as off-target effects, the types of tissues affected, unintended genetic changes and the potential for immune responses.

13.14 Researchers, research institutions and clinicians should ensure that patients undergoing gene editing interventions or HNGE clinical trials have an appropriate understanding of the intervention and are made fully aware of the potential risks and complications prior to receiving the treatment. They should also ensure that patients' informed consent and IRB approval are obtained prior to the procedure.

13.15 Regulatory bodies should establish guidelines on the required information that should be covered in informed consent for researchers and research institutions to refer to, in order to ensure that all relevant information on the gene editing intervention is made known to the patient or participant. Due to the complexity of gene editing technology, researchers and clinicians should ensure that patients are sufficiently informed and understand the potential benefits and risks involved. Researchers and clinicians should also obtain patient consent and ensure their safety by continually engaging patients with follow-ups and further discussions, should new information relating to the intervention arise. Given that the off-target effects could be sensitively and comprehensively quantified, researchers, research institutions and clinicians should inform patients of the potential off-target risks, including their likelihood and severity during genetic consultations, in accordance with the principle of *respect for persons*.

13.16 For clinical applications of non-heritable gene editing involving patients with diminished or no capacity (e.g., minors), clinicians must obtain valid informed consent from their persons (e.g., parents or next of kin), in accordance with the SMC Ethical Code and Ethical Guidelines and the Mental Capacity Act 2008. For non-heritable gene editing research, again involving patients with diminished or no capacity, researchers are required to obtain valid informed consent from their legally authorised persons in accordance with the Human Biomedical Research Act 2015.

13.17 Researchers and clinicians who are involved in research and clinical applications involving HNGE technology should be properly trained to assess the potential benefits and risks of gene editing interventions accurately, and to be able to conduct the necessary counselling and informed consent for patients. This may include training in the fields of genetics, genomics and gene editing technology along with ethics, law and sociology. Institutional oversight should also be established for continuous training of researchers and clinicians involved in HNGE technology.

13.18 Researchers, principal investigators of HNGE clinical trials, as well as clinicians providing treatment involving non-heritable gene editing should take responsibility to ensure that clinical trials of non-heritable gene editing or therapies are designed to minimise any unprecedented harmful effects to patients in accordance with the principle of *proportionality*. Appropriate measures, such as establishing guidelines for evaluating off-target effects and risk-benefit assessments, should be adopted by researchers to anticipate and/or manage uncertainties and long-term consequences associated with non-heritable gene editing to uphold *responsible stewardship of science*.

13.19 Researchers, research institutions and clinicians should ensure that the risks of any unintended consequences arising from non-heritable gene editing interventions becoming heritable are avoided as much as possible, and that these risks are documented and assessed appropriately.

13.20 Research institutions should implement robust quality management systems and standard operating procedures, while also ensuring that good manufacturing practices are adhered to, in order to achieve consistency, safety and ethical compliance in the HNGE research conducted.

13.21 Researchers, research institutions, and clinicians should continuously review whether existing regulations and guidelines are adequate for managing the risks and benefits of HNGE.

13.22 Researchers and physicians should conduct long-term follow-ups on patients and participants in clinical trials, evaluating new therapeutic modalities for non-heritable gene editing, to help mitigate the risk of any delayed adverse event arising from the treatment. This is particularly important, as the long-term safety of non-heritable gene editing has not been fully established.

13.23 Public agencies (e.g., the Agency for Care Effectiveness (ACE) in Singapore), researchers, academics, and the government, should consider implementing health-economic analyses and models of funding, to ensure that HNGE technology is affordable to all individuals with a medical need.

13.24 Researchers, healthcare institutions and the government should strengthen recruitment and community engagement strategies to communicate the individual and societal benefits of participating in biomedical research. These initiatives would help increase the number, and widen the spectrum, of participants in clinical research and trials involving gene editing technology, thereby allowing the diverse genomic profiles of a multi-ethnic society in Singapore to be appropriately represented.

13.25 Given that the clinical development of non-heritable gene editing remains at an early stage, researchers and research institutions should accord careful consideration to the eventual delivery of resultant therapies and prudent allocation of resources, taking into account the principles of *justice* and *inclusivity*. This is to ensure equitable access to healthcare across the population and also help ensure that benefits reaped from HNGE could be made available to all individuals regardless of socioeconomic status.

13.26 Researchers and research institutions should ensure that clinical studies of experimental treatments employing HNGE technology for non-heritable gene editing are representative of Singapore's diverse population. This would yield valuable insights into clinical outcomes relevant to the local demographic to be harnessed for use, while also upholding the principles of *justice* and *inclusivity*.

V. Recommendations for Gene Editing on Germline Cells or Embryos for Basic Research

13.27 The BAC does not recommend culturing human embryos whose genes have been edited beyond 14 days, and that the creation of human embryos solely for research purposes can only be justified when there is strong scientific merit and potential benefit from such research. Singapore's Human Biomedical Research (Restricted Research) Regulations 2017 prohibits research involving human embryos that are more than 14 days old from the time of creation, excluding any period when the development of the embryos was suspended. The regulations also only allow surplus embryos created in assisted reproduction treatment to be used for biomedical research following IRB approval. This effectively prohibits the creation of embryos for research purposes, even when there is strong scientific merit and potential benefit to be had. In light of this, regulatory authorities should review current regulations pertaining to restricted research in order to enable further advancements in biomedical research, including gene editing research.

13.28 Researchers and research institutions should ensure that consent for donation of surplus oocytes or embryos is kept separate from the consent for treatment of women undergoing fertility treatment. Researchers and institutions should ensure that the researcher seeking consent for the donation of eggs and embryos for research is not the physician administering the fertility treatment.

13.29 Research institutions should establish an independent panel to interview women who intend to donate eggs specifically for research (i.e., those who are not undergoing fertility treatment), given that the process of donating eggs for research is time-consuming, invasive and associated with a certain degree of discomfort and risk. The panel must be satisfied that the women are of sound mind, understand the nature and consequences of their donation and have given explicit consent of their own free will, without any inducement, coercion or undue influence.

13.30 Researchers should ensure that women are fully informed of the risks involved and given sufficient time to express consent prior to undergoing oocyte procurement procedures for gene editing research, thus safeguarding their autonomy. Researchers and research institutions should also implement safeguards to protect oocyte donors and ensure that there is no coercion or undue influence on their decision to donate.

13.31 The relevant regulatory authority should consider setting a limit on the amount of compensation under Section 13 of Singapore's Human Cloning and Other Prohibited Practices Act, to avoid any inducement. In the case of donors who are not employed, the regulatory authority should determine an appropriate compensatory amount for these donors based on their time spent undergoing the procedures required to obtain the eggs for research. The regulatory authority should also review current legislation to determine whether legislative amendments are required to implement proposed compensation.

13.32 Researchers should weigh the benefits of procuring oocytes solely for gene editing research against the risks that such procurement could pose, as oocyte procurement could result in potential harm to the donor including the risk of death. Researchers should only consider using surplus embryos created through assisted reproduction treatment for HNGE research if the risks of procuring oocytes solely for such research outweighs the benefits, so as to ensure *proportionality*. Researchers may also consider alternative sources for oocytes.

13.33 In upholding *respect for persons*, researchers and research institutions should take responsibility to ensure that data obtained from genome sequencing during gene editing research on human embryos are not misused and safeguard the security of data storage, so that the privacy and confidentiality of embryo or gamete donors are not breached. Researchers and research institutions should adhere to existing guidelines and regulations, such as the Human Biomedical Research Act 2015 and the Personal Data Protection Act 2012.

VI. Recommendations for Heritable Gene Editing for Clinical Research and Clinical Applications

13.34 The BAC, presently, does not recommend heritable gene editing for clinical research and applications until such time that the safety and efficacy of such technology can be

validated and as the long-term outcomes are as yet unknown. Therefore, researchers and clinicians must validate the safety, including the long-term safety, and efficacy of gene editing technology before it can be used for clinical research and applications involving heritable gene editing.

13.35 Heritable gene editing for clinical research and clinical applications should not be conducted until they are proven to be safe and beneficial to the research participants and society as a whole, since heritable gene editing could result in unintended off-target mutations, chromosomal mosaicism and other unforeseen adverse consequences, which could expose research participants and people undergoing such procedures to potential harm, affecting future generations.

13.36 Researchers and research institutions should conduct more research to develop ways of mitigating off-target effects and other unintended mutations from heritable gene editing on human embryos, so long as the safety of gene editing-established pregnancy is yet to be established. Further *in vitro* research on embryos or gamete precursors is also required to fully understand the implications of heritable gene editing technology.

13.37 If heritable gene editing for clinical research is deemed safe enough and permitted in the future, researchers and research institutions should conduct intergenerational monitoring which could help determine the long-term side effects of heritable gene editing on the individual that may be passed on to future generations and assess its safety and efficacy for clinical use.

VII. Recommendations for Non-Heritable and Heritable Gene Editing for Genetic Enhancement (if and when permitted)

13.38 If genetic enhancement is permitted in the future, researchers should weigh the benefits of applications of gene editing for the enhancement of physical attributes or cognitive abilities against their risks. This is because such applications are often subjective and may be risky, especially if the enhancement is for non-medical reasons and may be passed down to future generations, in the case of heritable gene editing.

13.39 Researchers and clinicians should review the need to limit the applications of gene editing technology for enhancement to cases where it does not lead to either an unfair advantage or disadvantage for certain individuals, as genetic enhancement for other uses could exacerbate social inequity. The BAC does not recommend other uses of gene editing technology, such as editing genes to enhance physical traits or cognitive abilities with the sole intention to create unequal opportunities in sports, education or employment, as this could perpetuate existing social inequalities. Governments, funding agencies and IRBs should consider implementing oversight measures to ensure that the use of gene editing technology adheres to the principle of *justice*. These could include developing regulatory frameworks to control the application of gene editing to prevent misuse for non-therapeutic enhancements that favour certain groups.

13.40 Researchers, scientists, and society as a whole should foster a strong sense of stewardship of environmental, biological and social factors to protect the wellbeing and interests of future generations if such applications of gene editing technology are permitted in the future.

13.41 If the use of gene editing technology for genetic enhancement is indeed permitted in the future, research institutions and relevant regulatory authorities should establish research and governance frameworks to ensure such technology is accessible to the public. Scientists, clinicians, institutions and regulatory authorities should also ensure that the benefits of applications of gene editing technology for genetic enhancement are made available to everyone, thereby averting any further widening of social disparity. Researchers, scientists and the government should engage with the views and shared experiences of people living with conditions that are targeted for HNGE intervention, and ensure that their perspectives are considered in shaping policies that reflect the needs and concerns of affected communities.

13.42 Given that individuals who are not genetically enhanced (if permitted in the future) or have disabilities may face exclusion or bias in education or employment settings, regulatory authorities and IRBs should conduct further studies to assess the societal impact of permitting genetic enhancement in terms of increasing the vulnerability of particular populations to risks of harm and discrimination, and create frameworks and regulations to prevent discrimination. In addition, they should create policies to ensure equitable access to gene editing technology in order to reduce potential disparities in access and use.

13.43 Scientists, research institutions, clinicians, medical institutions and approving authorities must ensure that reporting mechanisms are in place to prevent misuse or abuse of gene editing technology for enhancement. This is in consideration that researchers may not disclose their research methods, analyses, and data for research studies that misuse gene editing technologies for enhancement as accurately and openly as compared to when researchers conduct gene editing research that is permitted.

13.44 The BAC does not recommend applications of gene editing technology for enhancement that could lead to future generations facing psychological distress to conform to society's perception of 'normal' reproductive choices, which could compromise the future offspring's welfare.

13.45 Researchers and research institutions should ensure that the outcomes of biomedical research involving gene editing technology are always aligned with society's values and perceptions to ensure *responsible stewardship of science*.

13.46 Researchers and research institutions should take ethical considerations into account to ensure that parents responsibly safeguard the best interests of their children and respect their autonomy when they have sufficient maturity and intelligence to make their own decisions, and ensure that the life opportunities of genetically enhanced children are not constrained in the context of heritable genetic enhancement (if permitted in the future).

VIII. Recommendations for the Governance of Research and Clinical Applications Involving HNGE

a. Institutional research level: Institutional policies and Institutional Review Boards (IRBs)

13.47 Research institutions should regularly review institutional policies and practices to manage risks and maximise potential benefits that may arise from HNGE research

and consider the views of the public, patients or others with a vested interest in the activities conducted by such institutions. Institutions should also ensure that all staff involved in HNGE research share responsibility and accountability for the institution's research being conducted according to appropriate regulatory, ethical and scientific standards within the levels of acceptable institutional risk. IRBs should also ensure that the research is conducted in observance of high ethical standards, adheres to regulatory frameworks and that appropriate measures are taken to protect the rights and welfare of human participants in HNGE research.

b. Clinical level: Regulatory bodies, government and funding agencies, and standard operating procedures (SOPs)

13.48 Regulatory bodies, government organisations and funding agencies that are developing internal standard operating procedures (SOPs) for HNGE research or clinical trials should be encouraged to implement guidelines and establish robust systems to help understand, monitor, and minimise or mitigate the relevant risks and their impact on research subjects and patients undergoing clinical trials. This should allow for the anticipated limitations of the proposed technology in comparison to available standards for safety and efficacy studies.

c. National level: Legislation and regulatory guidance

13.49 Governments and policy makers should constantly review and update legislation and guidelines pertaining to the application and research involving HNGE. National policies should be built upon careful review of the latest scientific evidence and be in alignment with prevailing societal values. Such reviews may be conducted by advisory committees convened to examine safety concerns, sound practices and the scope of allowable activities, in order to issue policy recommendations.

13.50 Stakeholder consultations with the scientific community, patient advocates and indeed the wider public should be conducted to solicit opinion that would help ensure that policy decisions reflect the varied interests of differing stakeholders in society.

IX. Tools and Approaches to Strengthen Existing Research Governance

a. Professional self-regulation

13.51 There should be professional self-regulation within the scientific community so that scientists conducting HNGE research are responsible and accountable to their peers as well as to society as a whole. They should adhere to ethical codes developed by advisory committees or guidelines developed by professional societies, and set out best practices, standards, and ethical considerations in HNGE research.

b. Providing education and training specific to HNGE for researchers and clinicians

13.52 Academic, research and healthcare institutions should develop educational training or ethics modules specific to HNGE for graduates who are looking to pursue research in gene editing or professions engaged in clinical applications of HNGE. These would cover topics such as research integrity, ethics, the latest scientific developments in HNGE as well as the relevant national policies and guidelines. Institutions are

also recommended to fund or support educational or training programmes for their staff and IRB members, to equip them with knowledge of gene editing technology, developments in HNGE research, appropriate ethical standards, national guidance documents and advisories, as well as legislative reform in this area.

c. Reinforcement of institutional practices

13.53 Research and healthcare institutions should continually assess existing IRB ethics review processes and develop SOPs for HNGE research. These should be revised regularly and incorporate the latest developments in HNGE research, technology and legislation. Research and healthcare institutions may also implement annual reporting requirements, declaration mechanisms and processes for self-monitoring of HNGE to track achievements and outcomes, as well as to report any adverse events arising from clinical trials. The BAC also recommends that institutions review existing training for IRBs to ensure members are kept abreast of the latest trends and developments in HNGE, and so remain informed and competent in terms of their ability to review HNGE research applications.

d. Setting up HNGE registries

13.54 The BAC recommends for establishing national registries to track and monitor research and clinical trials involving HNGE, such as germline gene editing research on embryos and non-heritable gene editing clinical trials, to allow easy access of HNGE research and clinical trials information to relevant stakeholders.

e. Whistleblowing mechanisms

13.55 Research institutions or governments could introduce whistleblowing mechanisms at institutional or national levels, respectively, in order to establish effective reporting channels and provide comprehensive protection and support to those who report illegal, unregistered, unethical or unsafe HNGE research. Research institutions are recommended to set up a reporting mechanism via a confidential portal, website or hotline, that would allow individuals to report at any time and from anywhere. Governments and regulatory bodies should also put in place follow-up procedures to investigate any information disclosed and demonstrate that action has been taken where appropriate. It would also be important for governments and regulatory bodies to establish the foregoing investigative and sanctioning functions through national legislation, in consultation with the relevant research institutions or funding agencies, with clear levers to address misconduct.

13.56 Research institutions should set up protective mechanisms to mitigate potential harm to the individuals who report unethical HNGE research. Their identities should be protected and they should be provided appropriate guidance and professional advice throughout the reporting process.

X. Governance Framework for Heritable Gene Editing and Gene Editing in Embryos or Germline Cells for Research Purposes

13.57 Research institutions and regulatory authorities should ensure that the extent of oversight in developing governance and framework tools is commensurate with the

extent of ethical, social and health risks involved, whether for clinical research and clinical applications of heritable gene editing, or basic research activities of gene editing in embryos or germline cells. This is in consideration of the greater risks that heritable gene editing poses to future progeny, such as potential deleterious long-term health effects which may exacerbate social inequity.

GLOSSARY

Alzheimer's disease – A degenerative brain disorder that is common in the elderly, characterised by progressive deterioration of mental functions, leading to impaired cognition and increased reliance on others for daily activities.

Amniocentesis – A procedure in which a small amount of the amniotic fluid surrounding the foetus is withdrawn for testing for chromosomes and genetic disease.

Autologous (of cells or tissues) – Obtained from an individual's own tissues, cells or DNA.

Azoospermia – A medical condition where there is no measurable sperm in a man's ejaculate (semen). Common causes include blockage or decreased sperm production by the testis.

Carrier – Someone who carries only one copy of a **mutant gene** in question. A carrier usually shows no symptoms or very mild symptoms for the disease gene that he or she carries, as two copies of the disease gene are required for a full-blown manifestation of the disease. A carrier has the risk of transmitting the mutant gene to the next generation.

Chromosome – A threadlike structure of nucleic acids and proteins found in the nucleus of most living cells, carrying genetic information in the form of genes.

Clinical Ethics Committees (CECs) – Hospitals are required under Singapore's Healthcare Services Act (HCSA) to set up CECs to advise clinicians on clinical ethical issues and also review other specific ethical issues relating to care and management of patients in the healthcare institutions. While CECs primarily play an advisory role, they also assume an adjudicatory role in specific instances where the prescribed medical treatment involves complex ethical dilemmas.

Chorionic Villus Sampling (CVS) – A prenatal test that involves taking a sample of tissue from the placenta to test for chromosomal abnormalities and other genetic problems.

Cystic fibrosis – Cystic fibrosis (CF) is an inherited disorder that causes severe damage to the lungs, digestive system and other organs in the body. It affects the cells that produce mucus, sweat and digestive juices. These secreted fluids are normally thin and slippery. But in people with CF, a defective gene causes the secretions to become sticky and thick. Instead of acting as lubricants, the secretions plug up tubes, ducts and passageways, especially in the lungs and pancreas.

DNA – Deoxyribonucleic acid (DNA) is the molecule that carries genetic information for the development and functioning of an organism. Each DNA is a linear molecule made up of nucleotides or bases. There are four different types of bases in DNA and the order in which these bases are arranged determines the protein to be formed. Each individual's body contains an identical set of DNA in nearly all of its cells. A great fraction of cellular DNA is located in the cell nucleus (where it is called nuclear DNA), while the remaining can be found in the mitochondria (where it is called mitochondrial DNA).

DNA methylation – An epigenetic mechanism that occurs by the addition of a methyl group to DNA; this regulates gene expression by changing the activity of a DNA segment.

Epigenetics – The study of heritable changes in gene expression that are caused by factors such as DNA methylation without a change in the DNA sequence itself.

Embryo – The initial stage of development of a multicellular organism. At eight weeks of gestation, the embryo becomes known as a foetus.

Extra-chromosomal DNA (ecDNA) – Refers to any DNA that is found off chromosomes, either inside or outside of the nucleus of a cell.

Foetal blood sampling (FBS) – A procedure to draw foetal blood from the umbilical cord of the foetus during pregnancy.

Frameshift mutation – An insertion or deletion involving a number of base pairs that is not a multiple of three. As the formation of proteins involves reading the RNA sequence in multiples of three, this disrupts the reading frame and causes premature termination of translation.

Gamete – Sperm or egg cell.

Gene – A gene is the basic physical and functional unit of heredity. It is made up of DNA which carries instructions to make molecules of **RNA** and proteins.

Gene therapy – Treatment of a genetic disorder by inserting functional genes to replace, supplement or manipulate the expression of nonfunctional or abnormal genes.

Genetic variant – An alteration in the most common DNA nucleotide sequence.

Genome – The complete set of DNA (genetic material) in an organism. The genome contains the master blueprint for all cellular structures and activities for the lifetime of the cell or organism. Found in every nucleus of a person's many trillions of cells, the human genome consists of tightly coiled threads of DNA and associated protein molecules, organised into structures called chromosomes.

Genotype – A specific set of alleles (variant forms of a gene) at particular position on the chromosome.

Germ cell (Germline) – The cell (or cell line) from which sperm and egg (gametes) are derived.

Human immunodeficiency virus (HIV) – A virus that attacks the body's immune system. If HIV is not treated, it can lead to AIDS (acquired immunodeficiency syndrome), a condition in which there is progressive failure of the immune system.

Induced haematopoietic stem cells (iHSCs) – An adult somatic cell, such as a human skin cell, that has been reprogrammed (or induced) into self-renewing stem cells capable of replenishing all blood lineages.

Induced pluripotent stem cells (iPSCs) – An adult somatic cell, such as a human skin cell, that has been reprogrammed (or induced) into an embryonic pluripotent state.

Institutional Review Board (IRB) – A committee that reviews for a proposed research study to ensure adherence to relevant ethical, legal and institutional standards. Such boards are designated to approve (or reject), monitor and review biomedical and behavioural research involving humans. For biomedical research, IRB approval is required by law before any subjects can be recruited.

Intrauterine insemination – A procedure for treating infertility where sperm is placed directly into the uterus using a small catheter.

***In vitro* fertilisation (IVF)** – A clinical and laboratory procedure whereby the eggs and sperm from a couple are extracted and fertilised outside their bodies. Such a procedure is a type of assisted reproduction aimed at increasing the chances of a couple conceiving a baby.

Low-frequency mutation – Somatic mutation with allele frequency lower than 1% in an individual's DNA.

Meiotic arrest – During the formation of oocytes in females, meiosis (cell division of germ cells that produces the gametes) arrests twice. The first arrest occurs during prophase 1 in embryogenesis and lasts until puberty. The second meiotic arrest occurs after ovulation during metaphase 2.

microRNA (miRNAs) – A class of non-coding RNAs that play important roles in regulating gene expression.

Monogenic diseases – Diseases caused by variation in a single gene and are typically recognised by their striking familial inheritance patterns. Examples include sickle cell anaemia, cystic fibrosis, Huntington disease and Duchenne muscular dystrophy.

Muscular dystrophy – Caused by changes (mutations) in the genes responsible for the structure and functioning of a person's muscles. These mutations cause changes in the muscle fibers that interfere with the muscles' ability to function. Overtime, this causes increasing disability.

Mutation – A gene mutation is a permanent change in the DNA sequence that makes up a gene. It ranges in size from one DNA base to a large segment of a chromosome. Gene mutations can be inherited from a parent or acquired during a person's lifetime. If a mutation occurs in an egg or sperm cell during a person's life, there is a chance that the person's children will inherit the mutation. Most mutations do not cause genetic disorders. For example, some mutations alter a gene's DNA base sequence but do not change the function of the protein made by the gene.

Missense mutations – Missense mutations occur when a single nucleotide base in a DNA sequence is swapped for another one, resulting in a different amino acid being encoded at a particular position in the resulting protein.

Mosaicism – A condition in which cells within the same person have a different genetic makeup.

Off-target edits – Non-specific and unintended genetic modifications that occur at untargeted sites in the genome that are genetically similar to the target site.

Oncogenesis – The process through which healthy cells become transformed into cancer cells.

Oocyte – An egg cell.

Percutaneous umbilical blood sampling (PUBS) – A test that takes foetal blood directly from the umbilical cord.

Phenotype – The observable characteristics of the expression of a gene.

Pleiotropic – The phenomenon in which a single gene affects two or more apparently unrelated phenotypic traits, resulting in multiple phenotypic expressions.

Polygenic disease – Disease caused by the joint contribution of a number of independently acting or interacting genes. Examples include hypertension, coronary heart disease and diabetes.

Preimplantation genetic testing for aneuploidies (PGT-A) – A technique used to analyse the number of chromosomes present in IVF embryos.

Preimplantation genetic testing for chromosomal structural rearrangements (PGT-SR) – A test performed on embryo biopsies to screen embryos for chromosomal imbalances (extra or missing chromosome material) resulting from a parental structural rearrangement.

Preimplantation genetic testing for monogenic gene defects (PGT-M) – A treatment which involves checking the genes or chromosomes of embryos for a specific genetic condition.

Prenatal – During pregnancy and before birth.

Primitive streak – A transient structure whose formation, on day 15 of human development, marks the start of gastrulation which is the early developmental process in which an embryo transforms from a one-dimensional layer of epithelial cells (blastula) and reorganises into a multi-layered and multi-dimensional structure called the gastrula.

Protein – Large and complex molecules of amino acid residues that play many critical roles in the body. They do most of the work in cells and are required for the structure, function and regulation of the body's tissues and organs.

Retinitis pigmentosa (RP) – A group of rare eye diseases that affect the retina (the light-sensitive layer of tissue in the back of the eye). RP makes cells in the retina break down slowly over time, causing vision loss.

RNA – RNA, or ribonucleic acid, is a nucleic acid present in all living cells. Its principal role is to act as a messenger carrying instructions from DNA for controlling the synthesis of proteins.

Severe Combined Immunodeficiency (SCID) syndrome – A group of rare disorders caused by mutations in different genes involved in the development and function of infection-fighting immune cells.

Sickle-cell anaemia – One of a group of inherited disorders known as sickle cell disease. It affects the shape of red blood cells, which carry oxygen to all parts of the body.

Single nucleotide polymorphism (SNP) – A genomic variant at a single base position in the DNA.

Somatic cell – All the body cells except the reproductive (germ) cells.

Somatic or adult stem cells – An unspecialised cell, present in a tissue or organ, that is able to replicate itself and develop into specialised cell types of that tissue or organ, or into some other cell types.

Spinal muscular atrophy (SMA) – A genetic disorder where cells of the spinal cord die, resulting in progressively weaker muscles.

Spinocerebellar ataxia – A group of inherited brain disorders. It affects the cerebellum, a part of the brain vital to coordination of physical movement, and sometimes the spinal cord. This inherited condition worsens over time and causes specific problems with coordination with, usually affecting eyes, hands, legs and mobility, and speech.

Stem cell – An unspecialised cell that is able to replicate itself and develop into specialised cell types (such as a red blood cell, nerve, or heart cell). Stem cells divide to form daughter cells, in which some daughter cells differentiate into specialised cell types, and some daughter cells retain the stem cell property to divide and make more new stem cells.

Spermatogonial stem cells (SSC) – Adult stem cells in the testis which continuously generate daughter cells that differentiate into sperm cells. They keep their cellular pool constant through self-renewal.

Thalassaemia – An inherited blood disorder caused when the body does not make enough of a protein called haemoglobin, an important part of red blood cells.

ANNEXE A – DISTRIBUTION LIST FOR CONSULTATION PAPER ON ETHICAL, LEGAL AND SOCIAL ISSUES ARISING FROM 'HUMAN NUCLEAR GENOME EDITING'

(PUBLIC CONSULTATION PERIOD: JUN TO AUG 2024)

The public consultation paper can be accessed from https://www.bioethics-singapore.gov.sg/bioethics-resource/publications

Healthcare Organisations/Departments

Alexandra Hospital
Centre for Personalised and Precision Health
Changi General Hospital
Farrer Park Hospital
Gleneagles Hospital
Khoo Teck Puat Hospital
Mount Elizabeth Hospital
National Cancer Centre Singapore
National Healthcare Group
National University Health Systems
National University Hospital
Parkway East Hospital
Parkway Shenton
Raffles Medical Group
Sengkang General Hospital
Singapore General Hospital
Tan Tock Seng Hospital

Research Institutes and Academics

Agency for Science, Technology and Research
A*STAR Centre for Genome Diagnostics
A*STAR Research Entities
A. Menarini Singapore Pte Ltd
Academic Medicine Research Institute
Advanced Cell Therapy and Research Institute, Singapore
Advanced Medicine Imaging Private Limited
Aesculape CRO Pte Ltd

Agency for Integrated Care Pte Ltd
Amili Pte ltd
Ang Mo Kio Thye Hua Kwan Hospital
Chugai Pharmabody Research Pte Ltd
Cutis
DotBio
Dover Park Hospice
DSO National Laboratories
Duke-NUS Medical School
Duke-NUS Stem Cell and Gene Editing Core Facility
Eagle Eye Centre Pte Ltd
Essilor R&D Centre Singapore
Eye & Retina Surgeons
Gene Solutions Genomics Pte Ltd
Genome Institute of Singapore
HCA Hospice Limited
Health Promotion Board
Health Sciences Authority
Hummingbird Bioscience
I & Vision Research Centre Pte Ltd
Icon Cancer Centre
KYAN Therapeutics
Lilly Centre for Clinical Pharmacology Pte Ltd
Lions Befrienders Service Association (Singapore)
Lucence
Lundbeck Singapore Pte Ltd
M Diagnostics
MiRXES Lab Pte Ltd
Myopia Specialist Centre
Nanyang Polytechnic
Nanyang Technological University
National Healthcare Group Pte Ltd
National Heart Research Institute Singapore
National Kidney Foundation
National University Health System
National University of Singapore
National Youth Sports Institute
Ngee Ann Polytechnic
NTU College of Sciences
NTU College of Science, School of Biological Sciences
NTU Institute of Science and Technology for Humanity
NTU Lee Kong Chian School of Medicine

NUHS Cardiovascular Research Institute
NUS Centre for Biomedical Ethics
NUS Faculty of Law
NUS Law
NUS LKY School of Public Policy
NUS Saw Swee Hock School of Public Health
NUS School of Biological Sciences
NUS School of Medicine
NUS Science
Radlink Diagnostic Imaging(S) Pte Ltd
Raffles Hospital
Raffles Medical Group Clinical Trials Unit
Renci Hospital
Republic Polytechnic
Research by Curie Oncology Ltd
SGH Clinical Trials and Research Centre
SGH Department of Clinical Translational Research
Singapore Armed Forces Medical Corps
Singapore Chung Hwa Medical Institution
Singapore Eye Research Institute
Singapore Health Services Pte Ltd
Singapore Institute of Technology
Singapore Polytechnic
Singapore University of Social Sciences
Singapore University of Technology & Design
SingHealth Duke-NUS Cell Therapy Centre
SingHealth Duke-NUS Genomic Medicine Centre
Sivantos Pte Ltd
SMU Yong Pung How School of Law
Sport Singapore
St Andrew's Mission Hospital
ST Engineering Innosparks Pte Ltd
St Luke's Hospital
Stroke Support Station
Temasek Polytechnic

Boards & Society

Academy of Medicine, Singapore
Allied Health Professions Council
Biomedical Engineering Society
Chapter of Genomic Medicine, Academy of Medicine, Singapore
College of Clinician Scientists, Academy of Medicine, Singapore

College of Family Physicians Singapore
Law Society of Singapore
NUS Law Club
NUS Medical Society
Pharmaceutical Society of Singapore
Singapore Academy of Law
Singapore Association of Social Workers
Singapore Dental Association
Singapore Dental Council
Singapore Medical Association
Singapore Medical Council
Singapore National Academy of Science
Singapore Nurses Association
Singapore Nursing Board
Singapore Pharmacy Council

Clinical Ethics Committees (CEC)
Changi General Hospital (CGH) CEC
Concord International Hospital (CIH) CEC
Farrer Park Hospital (FPH) CEC
Gleneagles Hospital (GH) CEC
Institute of Mental Health (IMH) CEC
Jurong Health Campus (JHC) CEC
Khoo Teck Puat Hospital (KTPH) CEC
KK Women's and Children's Hospital (KKH) CEC
Mount Alvernia Hospital (MAH) CEC
Mount Elizabeth and Mount Elizabeth Novena Hospital CEC
National University Hospital (NUH) CEC
Parkway East Hospital (PEH) CEC
Parkway Independent Ethics Committee (PIEC)
Raffles Hospital (RH) CEC
Sengkang General Hospital (SKH) CEC
Tan Tock Seng Hospital (TTSH) CEC
Temasek Poly Humanity & Social Sciences (HSS) Ethics Committee
Thomson Medical Centre (TMC) CEC
Woodlands Health Campus (WHC) CEC

Institutional Review Boards (IRB)
Defence Science Organisation (DSO) IRB
James Cook University (JCU) IRB
Nanyang Technological University (NTU) IRB (RIEO)
National Healthcare Group (NHG) Domain Specific Review Board (DSRB)
National University of Singapore (NUS) IRB

Ngee Ann Polytechnic (NP) IRB
Singapore Institute of Technology (SIT) IRB
Singapore Management University (SMU) IRB
Singapore University of Technology and Design (SUTD) IRB
SingHealth (SH) Centralised Institutional Review Board (CIRB)
Social Service institute (SSI) IRB

Industry Stakeholders

Advanced Cell Therapy and Research Institute, Singapore
Amgen Singapore
Avecris
Biomedical Sciences Industry Partnership Office
Biosyngen Pte Ltd
CellVec
CytoMed Therapeutics
Enterprise SG
Esco Aster
GDMC
Genetech Biotechnology Pte Ltd
GenScript Biotech Corporation
GSK
Lerna
Macrogen Asia Pacific Pte Ltd
Novartis Singapore
Nuevocor
SCG Cell Therapy Pte Ltd
SG Vector
Tikva

Asian Bioethics Network - Countries

Australia
Bhutan
Brunei
China
India
Japan
Myanmar
Nepal
New Zealand
South Korea
Sri Lanka
Thailand

The Philippines
Vietnam

Government Agencies
Chief Health Scientist Office
Health Sciences Authority
National Research Foundation, Human Health and Potential

Religious Groups
Buddhist Fellowship
Catholic Archdiocese of Singapore
Hindu Advisory Board
Jewish Welfare Board
Majlis Ugama Islam Singapura Council
National Council of Churches Singapore
Sikh Advisory Board
Singapore Buddhist Federation
Singapore Humanist Society
Singapore Jain Religious Society
Singapore Taoist Federation
Taoist Mission (Singapore)
The Parsi Zoroastrian Association of Singapore
The Spiritual Assembly of the Bahá'is of Singapore

Patient Advocacy Groups
Breast Cancer Foundation
Muscular Dystrophy Association
Rare Disorders Society
Singapore Cancer Society
SingHealth Patient Advocacy Network

Local Ethics Committee
National Medical Ethics Committee
Healthcare Ethics Capability Committee

International Organisations / Departments
Chief Medical Officer, England
Deputy Chief Medical Officer, England
Health and Human Services, United States
National Academy of Sciences
Nuffield Council on Bioethics
The Hastings Center

U.S. HHS Secretary's Advisory Committee on Human Subject Protections
United Nations Educational, Scientific and Cultural Organization (UNESCO)
UNESCO World Commission on the Ethics of Scientific Knowledge and Technology (COMEST)
UNESCO International Bioethics Committee (IBC)
World Health Organisation
Mayo Clinic, United States
Department of Health and Social Care, United Kingdom
Comité Consultatif National d'Ethique, France

ANNEXE B – WRITTEN RESPONSES TO CONSULTATION PAPER ON 'ETHICAL, LEGAL AND SOCIAL ISSUES ARISING FROM HUMAN NUCLEAR GENOME EDITING'

A comprehensive range of responses from various organisations and institutions and including those from individual respondents were received. While most of the responses were included in the review, there remains a small number of feedback that were less relevant to the scope/contents of the consultation report. As such, these responses have not been included to maintain the objectivity of the report.

The BAC appreciates the feedback from the various organisations and institutions and respondents involved in the public consultation process and have carefully considered the responses in the review and finalisation of the human nuclear genome editing advisory report.

Responses from Organisations and Institutions

1. French National Advisory Ethics Council for Health and Life Sciences
2. Taoist Mission (Singapore)
3. Cultivate SG
4. Human Fertilisation and Embryology Authority (UK)
5. Agency for Science, Technology, and Research (A*STAR)
6. National Council of Churches of Singapore

Individual Responders (Email Responses and FormSG Responses)

The responses are compiled in no particular order of merit.

Summary of key discussion points from HNGE Focus Group Discussion Sessions

1. First Focus Group Discussion Session on 26 Jul 2024
2. Second Focus Group Discussion Session on 13 Aug 2024

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Responses from Organisations and Institutions

1. French National Advisory Ethics Council for Health and Life Sciences

Commented by the French National Advisory Ethics Council for Health and Life Sciences (Comité Consultatif National d'Ethique, CCNE)

ANNEX A

[Invitation to Comment] Public Consultation Paper: Ethical, Legal, and Social Issues Arising from Human Nuclear Genome Editing

Reminder:
The mission of the French National Advisory Ethics Council for Health and Life Sciences (hereinafter referred to as "CCNE" or "Committee") is to give opinions on ethical problems and social issues raised by advances in knowledge in the fields of biology, medicine and health, or by the health consequences of advances in knowledge in any other field.
The Committee carries out its mission in complete independence. (Article L.1412-1 of the French Public Health Code[1])

a. Mosaicism[2], Off-Target Effects, and On-Target Undesirable Modifications

1 Gene editing technologies could enable corrections to the genomic sequence to rectify or remove mutations that lead to adverse health conditions. Such technologies could also lead to unintended biological outcomes such as chromosomal mosaicism in embryos, and undesirable consequences (e.g., development of cancer and allergic reactions) arising from off-target mutations and deletions.

Ethical Considerations:

i. How should researchers and clinicians balance the potential benefits of gene editing technologies against the risks associated with mosaicism and off-target effects?

As the CCNE pointed out in its Opinion No. 133 of 2019[3], "the possibility of unwanted targets, "mosaic" embryos and other complications with unpredictable consequences cannot be excluded in the case of an effect on the epigenome or an unwanted modification during DNA repair" (at p. 26). In fact, the repair of the cut resulting from the new "genome surgery" technique, CRISPR-Cas9, is only partially understood and cannot exclude the appearance of unwanted DNA sequences (at p.11).

Therefore, according to the CCNE, it is necessary to:

(1) Encourage basic research laboratories using the new targeted genome modification techniques to develop "experimental approaches to make them safer or even reversible, and to monitor their application to the living world (at p. 6);

[1] Article L.1412-1 of the French Public Health Code:
https://www.legifrance.gouv.fr/codes/id/LEGISCTA000006171074
[2] Mosaicism is a condition that occurs when a person has two or more sets of cells that differ genetically from one another. For example, a person with this condition might possess some cells that have 46 chromosomes while other cells have 47 chromosomes.
[3] Opinion No. 133, Ethical challenges of gene editing: between hope and caution, 2019. URL:
https://www.ccne-ethique.fr/sites/default/files/2024-03/Avis%20133%20-%20%20def%201702.pdf

Commented by the French National Advisory Ethics Council for Health and Life Sciences (Comité Consultatif National d'Ethique, CCNE)

(2) Given that "the applications of targeted genome modification, when they concern the genome of somatic cells, open up the prospect of progress in human therapeutics (treatment of cancers, certain viral infections, etc.) (at p. 23)", they therefore constitute, according to the CCNE, a medical advance that should be supported;

(3) In the case of targeted genome modifications that can be transmitted to human offspring, the CCNE considers that the level of technical and scientific uncertainty regarding the short- and long-term consequences "requires an international moratorium, over and above French legislation, before any implementation" (at p.7). In addition, further experimental work is needed to study the safety and reproducibility of this approach before it can be considered for use in human therapeutics (at p. 26). If these technical and scientific uncertainties were to diminish, the major ethical issue would still be the care of the individual as opposed to the eugenic approach to the transformation of the human race (at p. 7);

(4) With regard to genome modification, whether somatic or not, the CCNE has maintained the same ethical recommendations since 1990 (Opinion No. 22[4]). In fact, the Council is opposed to "any modification of general genetic characteristics, whether physical (e.g. height) or psychological (e.g. behavior), in the field of hereditary diseases" and considers that "gene therapy research should only be envisaged for diseases resulting from an anomaly concerning a single gene (monogenic diseases) and leading to a particularly serious pathology" (at p. 24);

(5) Finally, the CCNE insists on considering that "the human genome is not the property of any culture, nation or region of the world; it is even less the property of science alone. It belongs equally to all members of our species, and the decisions we have to make about how far to go in tinkering with this genome must be accountable to humanity as a whole". (Opinion No. 133, p. 12)

ii. How can researchers, clinicians, and regulatory bodies ensure that patients or participants undergoing non-heritable gene editing interventions are fully informed of the risks associated with such applications?

[4] Opinion No. 22, Opinion on gene therapy, 1990. URL: https://www.ccne-ethique.fr/sites/default/files/2024-07/avis036.pdf

Commented by the French National Advisory Ethics Council for Health and Life Sciences (Comité Consultatif National d'Ethique, CCNE)

As early as 1993 (Opinion No. 36[5]), the CCNE pointed out that patients or participants in clinical trials or clinical interventions involving the editing of non-heritable genes benefit from the general rules governing therapeutic trials. (p. 4)

In France, therapeutic trials are regulated by law.

Regarding the information of patients or participants undergoing non-heritable gene editing interventions, the article L.1122-1 of the French Public Health Code states that:

> "Prior to the performance of research involving the human person, information is provided to the person participating in the research by the investigator or by a physician representing the investigator. When the investigator is a qualified person, this information is provided by that person or by another qualified person representing him or her. In particular, the information covers:
>
> 1° The objective, methodology and duration of the research;
>
> 2° The expected benefits and, in the case of research mentioned in 1° or 2° of article L. 1121-1[6], the foreseeable risks and constraints, including in the event of early termination of the research;
>
> 3° In the case of research mentioned in 1° or 2° of article L. 1121-1, any medical alternatives;
>
> 4° In the case of research mentioned in 1° or 2° of Article L. 1121-1, the medical treatment planned at the end of the research, if such treatment is necessary, in the event of premature termination of the research, and in the event of exclusion from the research;
>
> 5° The opinion of the committee referred to in article L. 1123-1 and the authorization of the competent authority referred to in article L. 1123-12;
>
> 6° Where applicable, the prohibition on simultaneous participation in other research or the period of exclusion stipulated in the protocol, and registration in the national database provided for in article L. 1121-16;
>
> 6° bis In the case of research for commercial purposes, the terms and conditions for the payment of compensation in addition to the payment of additional costs related to the research, where applicable, under the conditions set out in article L. 1121-16-1;

[5]Opinion No. 36, Opinion on the use of somatic gene therapy-procedures. Report. 1993. URL: https://www.ccne-ethique.fr/sites/default/files/2024-07/avis036.pdf

[6] Article L. 1121-1 :

- 1° Interventional research involving an intervention on a person not justified by their usual care;
- 2° Interventional research involving minimal risks and constraints, the list of which is established by decree of the Minister of Health, after consultation with the Director General of the National Agency for the Safety of Medicines and Health Products;

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> 7° Where applicable, the need to process personal data in accordance with the provisions of Article 69 of Law No. 78-17 of January 6, 1978, on data processing, data files and individual liberties.
>
> The person whose participation is requested is informed of his or her right to have access, during or at the end of the research, to information concerning his or her health held by the investigator or, where applicable, the doctor or qualified person representing him or her.
>
> The person whose participation is sought or, where applicable, the persons, bodies or authorities responsible for assisting, representing or authorizing the research are informed of his or her right to refuse to participate in the research or to withdraw consent or, where applicable, authorization at any time, without incurring any liability or prejudice as a result.
>
> [...]
>
> The information provided is summarized in a written document given to the person whose consent is being sought. At the end of the research, the person who has consented has the right to be informed of the overall results of the research, in accordance with the procedures specified in the information document".

Thus, researchers and clinicians carrying out such research need to apply the law. In doing so, they can ensure that participants are informed of the risks they face from such interventions.

iii. Should clinical applications of heritable gene editing be allowed, such as for the treatment of diseases or infertility, given the possibility that future generations may potentially suffer from unintended consequences associated with such applications?

At present, any therapeutic intervention on the human genome is prohibited in France, both by:

- Article 13 of the Oviedo Convention: "Interventions whose purpose is to modify the human genome may be carried out only for preventive, diagnostic or therapeutic reasons and only if their purpose is not to introduce a modification in the genome of the descendants"

And,

- Article 16-4 of the French Civil Code: "Without prejudice to research aimed at the prevention and treatment of genetic diseases, no alteration of genetic characteristics may be carried out with the aim of modifying the person's descendants". (Opinion No. 133, p. 26)

As noted above, the CCNE believes that the level of technical and scientific uncertainty regarding the short and long-term consequences of heritable gene editing "requires an international moratorium" (at p. 7) and that further experimental work is needed to

Commented by the French National Advisory Ethics Council for Health and Life Sciences (Comité Consultatif National d'Ethique, CCNE)

study the safety and reproducibility of this approach before it can be considered for use in human therapeutics (Opinion 133 at p.26).

b. Safety and Long-Term Effects of HNGE

2 Gene editing may potentially offer new ways of treating genetic disorders, infertility, enhancing personalized medicine and improving health outcomes. However, it has not yet seen widespread use in clinical practice nor evaluated over long periods of time in humans as the technology is still in its early phase of development and there are concerns regarding the safety and long-term side effects of the technology on individuals receiving the treatment.

Ethical Considerations:

i. How should researchers, research institutions, and clinicians ensure a favorable risk-benefit ratio is achieved for patients or participants undergoing clinical trials or clinical interventions involving non-heritable gene editing?

As previously stated, patients or participants in clinical trials or clinical interventions involving the editing of non-heritable genes are regulated by the therapeutic trials rules (Opinion No. 36, at p. 4), consequently by articles L.1121-1 to L.1128-12 of the French Public Health Code.

With regard to research, Article L.1121-2 of the French Public Health Code sets out the conditions that must be met to ensure a favorable risk-benefit ratio in clinical trials or interventions:

> "No research involving human subjects shall be performed:
>
> - If it is not based on the latest scientific knowledge and sufficient preclinical experimentation;
>
> - If the foreseeable risk to the persons participating in the research is out of proportion to the anticipated benefit to those persons or to the interest of the research;
>
> - If it is not aimed at advancing scientific knowledge concerning human beings and the means likely to improve their condition;
>
> - if the research involving human subjects has not been designed in such a way as to minimize pain, discomfort, fear and any other foreseeable inconvenience associated with the disease or the research, taking particular account of the degree of maturity of minors and the capacity for understanding of adults unable to express their consent.

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> The interests of persons participating in research involving human subjects shall always take precedence over the sole interests of science and society.
>
> Research involving human subjects can only begin when all these conditions are met. Respect for these conditions must be maintained at all times."

Thus, Article L.1121-2 of the French Public Health Code is the means used by French researchers, research institutions and clinicians to ensure that a favorable risk-benefit ratio is achieved for patients or participants undergoing clinical trials or clinical interventions involving non-heritable gene editing.

ii. What can researchers do to mitigate challenges and alleviate long-term consequences associated with non-heritable gene editing to ensure responsible stewardship of science?

As mentioned above, in its Opinion No. 36[7],

Thus, the CCNE stated that:

(1) "These trials must comply with the general rules governing therapeutic trials;

(2) The protocols for these trials must be submitted to an [ethics research committee];

(3) Somatic gene therapy trials must be preceded by sufficient prior animal experiments to clarify the possible efficacy and probable safety of the techniques used;

(4) They should only be considered for patients suffering from a disease for which there is no effective treatment and whose prognosis is sufficiently serious to justify the potential risks of using a largely experimental treatment;

(5) Careful monitoring of the results of these trials is essential;

(6) Protocols for these trials must comply with European directives and the French law on the use of genetically modified organisms." (at p. 4)

Finally, as mentioned above, the Council is opposed to any modification of general genetic, physical or psychological characteristics in the field of hereditary diseases and will only consider gene therapy research for diseases resulting from an anomaly affecting a single gene and leading to a particularly serious pathology. (Opinion No. 133, at p. 24)

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iii. Should clinical applications of heritable gene editing be allowed, given the difficulty in predicting the long-term consequences of such applications on future generations?

As already said, the CCNE considers that without an international moratorium on heritable gene editing and further experimental work to study the safety and reproducibility of this approach, it should continue to be prohibited. (Opinion No. 133, at p. 7 and 26)

iv. What are the ethical challenges involved in conducting follow-up studies to determine the long-term side effects of gene editing interventions in research participants?

As the CCNE points out in its Opinion No. 145[8], clinical research in France benefits from a legal framework based on ethical principles and institutions responsible for their implementation.

These principles include:

- The free and informed consent of the subject to the proposed trials. This consent implies clear and complete information on the risks involved and on the altruistic dimension of participation. Altruism in clinical research derives from its very purpose: with few exceptions, its primary aim is not to benefit the patient personally (which distinguishes it from medical care), but to advance scientific knowledge about the disease or remedy in question, for the subsequent benefit of the population as a whole";
- Respect for an ethic of beneficence that seeks to maximize good and minimize harm;
- The seriousness of the scientific objective pursued and the method used to achieve progress in knowledge;
- The publication of research results, even if they are negative".

In addition, French law and European regulations state that clinical research must undergo a double review before it is authorized:

- The first concerns the scientific quality of the project: the administrative authorities (the Agence nationale de sécurité du médicament et des produits de santé, ANSM, in France) assess the scientific relevance of the project;

[8] Opinion No. 145, The ethical evaluation of clinical research. Encouraging clinical research without weakening the protection of individuals? 2024. URL, in French: https://www.ccne-ethique.fr/sites/default/files/2024-05/Avis%20145_02052024.pdf

Commented by the French National Advisory Ethics Council for Health and Life Sciences (Comité Consultatif National d'Ethique, CCNE)

- The other is ethical: an independent, multidisciplinary ethics committee (known in France as the "Comité de Protection des Personnes", CPP) assesses whether the proposed project complies with the main ethical principles of medical research. (at p.7)

c. Procurement and Use of Human Embryos and Oocytes in HNGE Research

3 Regulated research with human embryos have greatly enhanced knowledge about human gene function and early embryonic development, as well as advanced research on infertility, genetic diseases, and intractable diseases. While procuring oocytes with the desired genotype from individuals can enable researchers to study gene mutations in embryos for a given disease-causing gene, or to evaluate the treatment for a specific gene mutation, it may lead to health risks for donors during the oocyte extraction procedure. Another ethical issue involved in the use of embryos for gene editing research is potential privacy breach.

Ethical Considerations:

i. How do researchers and research institutions weigh the potential benefits of gene editing research on human embryos and oocytes against the ethical and safety concerns?

Please note that there are the opinions described below are not very recent. As there are no recent opinions of the CCNE on the subject, we cannot say if the Council would carry a different or a similar opinion should it publish one today.

First, as stated in its Opinion No. 112[9], the CCNE's various opinions on the question of genetic modification of human embryos and oocytes are in line with the main points of its Opinion No. 1[10], proposing:

- "A refusal to objectify the human embryo and the recognition of the respect due to it as a "potential human person";
- A refusal to give a "normative definition" of the human embryo;
- A respect manifested in the type of conduct prescribed for the human embryo;
- A distinction between ethical problems and permissible conduct depending on whether the embryo is pre-implantation, in vitro, or developing in the mother's body;"

[9] Opinion No. 112, Ethical considerations on research on cells of human embryonic origin and research on the human embryo in vitro, 2010. URL: https://www.ccne-ethique.fr/sites/default/files/2024-05/AVIS_112Eng.pdf

[10] Opinion No. 1, Opinion on sampling of dead human embryonic and foetal tissue for therapeutic, diagnostic, and scientific purposes. Report, 1984. URL: https://www.ccne-ethique.fr/sites/default/files/2024-07/avis001.pdf

Commented by the French National Advisory Ethics Council for Health and Life Sciences (Comité Consultatif National d'Ethique, CCNE)

In addition, by making a number of specific recommendations of a legal nature, including:

- "Authorizing the destruction of supernumerary human embryos when the parental project is abandoned and other couples do not accept the embryos;
- Conditional authorization of research on cells derived from human embryos destroyed in vitro under the above conditions;
- Conditional authorization of certain research on human embryos conceived in vitro before their authorized destruction under the above conditions;
- A ban on the creation of human embryos for research purposes, with "the introduction of an exception to this principle in the context of the evaluation of new MPA (Medical assistance for procreation) techniques" (at p. 13).

Then, in its Opinion No. 133, the CCNE recognizes that, "with the advent of targeted genome modification techniques, a major ethical issue for human beings is linked to the potential ease of germ line modification, whether this involves the modification of gametes (reproductive cells) or the pre-implantation embryo" (at p.24).

Thus, for the CCNE, "great caution is still required regarding the therapeutic use of human embryos, because, in addition to the technical uncertainties, the ethical question of modifying the genome of an individual and of the human population is a major issue". Consequently, "further experimental work is required to study the safety and reproducibility of this approach before it can be considered for human therapeutics, bearing in mind that the quality of the manipulation could only be partially verified in the embryo (correction of the gene to be modified, genome sequencing) during preimplantation diagnosis or after implantation, during prenatal diagnosis" (at p.26).

Moreover, even in the case of conception projects in families with a proven risk of transmission of a serious genetic disease, the Council considers that "the prospect of correcting the genetic heritage of embryos or gametes cannot hide the risks of eugenics through transmissible modification of the genome and requires, beyond this opinion, a specific ethical reflection on the limits between care and eugenics" (at p.27).

Finally, the CCNE considers that targeted genomic modifications "cannot replace the development of prenatal, preimplantation and preconception diagnostics (cf. the CCNE's reflections on this subject in its Opinions No. 124 and 129), especially as, given the current state of technology, it is impossible to combine preimplantation diagnostics (performed on d3) and targeted genome modification (performed on d0)" (at p.27).

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ii. What can regulatory authorities do to ensure that embryo or oocyte donors are not receiving any inducement but fairly reciprocated for their contributions to gene editing research?

In its Opinion No. 18[11] of 1989, the CCNE already considered that "embryo donation, if desired by the parents-authors, can only be envisaged if it is subject to very strict rules which will have to be established by law":

- "All steps involved in the embryo donation process must not be subject to any form of remuneration or profit. The non-commercialization of embryo donation is an inviolable principle".

Today, the French Public Health Code requires that:

- Article L. 1244-2: "Prior to the donation, the donor is duly informed of the legislative and regulatory provisions relating to gamete donation, in particular the provisions of Article L. 2143-2[12] relating to access by persons conceived by medically assisted procreation with a third-party donor to non-identifying data and to the identity of the third-party donor.
  The donor's consent is obtained in writing and may be revoked at any time up until the gametes are used.
  A follow-up study is offered to the donor, who consents in writing."

- Article L.1241-1: "The procurement of tissues or cells or the collection of products of the human body from a living person for the purpose of donation may only be carried out for therapeutic or scientific purposes"

- Article L. 1244-7: "The oocyte donor must be particularly informed of the conditions of ovarian stimulation and oocyte retrieval, and of the risks and constraints associated with this technique, during interviews with the multidisciplinary medical team. She is informed of the legal conditions of donation, in particular the principle of anonymity and the principle of free donation. She is reimbursed for expenses incurred in connection with the donation."

[11] Opinion No. 18, Update on studies undertaken by the committee regarding gamete and embryo donation, 1989. URL: https://www.ccne-ethique.fr/sites/default/files/2021-02/avis018.pdf

[12] Article L. 2143-2 French Public Health Code: "Any person conceived by medically assisted procreation with a third-party donor may, if he or she so wishes, have access at the age of majority to the identity and non-identifying data of the third-party donor as defined in article L. 2143-3.
Persons wishing to donate gametes or offer their embryo for reception expressly consent in advance to the communication of such data and their identity, under the conditions set out in the first paragraph of this article. In the event of refusal, these persons may not proceed with the donation or offer the embryo for reception.
The death of the third-party donor has no effect on the communication of such data and identity.
This information may be updated by the donor."

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iii. What can researchers and research institutions do to ensure that the dignity and rights and privacy and confidentiality of individuals who donate embryos or oocytes are protected?

Concerning privacy:

In its Opinion No. 124[13], the CCNE addresses the issue of the management of genetic data (DNA sequence), which is part of a more general framework, that of personal data, and in particular health data.

With regard to the protection of personal data in the medical field, the CCNE considers that "there is no compelling reason to exempt the sequencing of the human genome from the general principles applicable to the processing of personal data, as defined in articles 6 and 7 of law no. 78-17 of January 6, 1978" (at p. 54).

Thus, in principle, the processing of genetic data is prohibited, but exceptions are provided for in the conditions set out in the 1978 Law and in Article 9 of Regulation (EU) 2016/679 of 27 April 2016.

Consequently, the processing of genetic data is permitted if the following conditions are met, as recalled by the CCNE:

- "Purpose (a specific and legitimate use);
- Proportionality (collection of only relevant and necessary information);
- Relevance of the data (data that is adequate, relevant and not excessive in relation to the objectives pursued);
- Limited duration (data retention in accordance with the purposes assigned to the processing);
- Security and confidentiality (authorized personnel, data security measures, prevention of unauthorized access);
- Transparency (information to be provided to data subjects);" (at p.54).

Concerning anonymity:

In its Opinion No. 18, the CCNE was unanimous in insisting on the following point: "all donations must respect the anonymity of donors, which does not necessarily exclude the communication of certain non-identifying data" (at p. 4).

Today, the French Public Health Code defines the conditions of this anonymity:

[13] Opinion No. 124, Ethical Reflection on Developments in Genetic Testing in Connection with Very High Throughput Human DNA Sequencing, 2016. URL: https://www.ccne-ethique.fr/sites/default/files/2024-02/CCNE%20Avis%20124%20EngFinal.pdf

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- Article L. 2143-2 :

  "Any person conceived by medically assisted procreation with a third-party donor may, if he or she so wishes, have access at the age of majority to the identity and non-identifying data of the third-party donor as defined in article L. 2143-3.
  Persons wishing to donate gametes or offer their embryo for reception expressly consent in advance to the communication of such data and their identity, under the conditions set out in the first paragraph of this article. In the event of refusal, these persons may not proceed with the donation or offer the embryo for reception.
  The death of the third-party donor has no effect on the communication of such data and identity.
  This information may be updated by the donor."

- Art. L. 2143-3 :

  "When collecting the consent provided for in articles L. 1244-2 and L. 2141-5, the physician collects the identity of persons wishing to donate gametes or offer their embryo for reception, as well as the following non-identifying data:
  "1° Their age;
  "2° Their general condition as described at the time of donation;
  "3° Their physical characteristics;
  "4° Their family and professional situation;
  "5° Their country of birth;
  "6° The reasons for their donation, in their own words;
  "The doctor referred is the recipient of information relating to the progress of the pregnancy resulting from medically assisted procreation with a third-party donor and its outcome. He/she will collect the identity of each child born as a result of third-party donation, as well as the identity of the recipient person or couple."

d. Equitable Access and Allocation of Resources

4 Gene editing technologies extend beyond discovering and developing therapies, particularly for rare genetic disorders, severe diseases such as cancer, and treatment of infertility. These technologies can also be used for enhancing specific traits. However, as with many new modalities in medicine, gene editing technologies could be prohibitively expensive and would give rise to concerns of inequitable access by those who are in need but cannot afford them.

Ethical Considerations:

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i. What are the ethical considerations in ensuring equitable access to gene editing technologies?

In its Opinion No. 78[14], the CCNE has already touched on a number of key points to overcome inequalities in access to health care:

- "All access to care and all research must be long-term;
- Research must aim at universal standards;
- [...] Access to treatment should be self-evident once individuals or groups of individuals have participated in research in a therapeutic area" (at p 24).

In its Opinion No. 135, the CCNE again addresses the issue of access to therapeutic innovations, which are often very costly.

It tries to answer the following question: "How can we reconcile access to these very expensive treatments for all those who need them and the sustainability of the French health insurance system with the interests of the pharmaceutical companies? How can such prices be justified and how can fair prices be defined?"

The CCNE's recommendations "aimed at reconciling two objectives: optimizing access to the best care for everyone and optimizing the search for the lowest price in negotiations", are as follows (note: they are adapted to the French and European health systems and to "therapeutic innovations" in general, including "medicines" in particular):

(1) Demand transparency:

- "By creating a "Ségur[15] of the medication" that brings together all stakeholders in the sector, including representatives of society, to discuss ways to develop a policy of transparency based on the definition of explicit cost rules;
- Introduce measures to limit the impact of influence on marketing authorizations on the European territory, by limiting the authorized lobbying expenses of pharmaceutical companies and by monitoring the practices of medical sales representatives, as well as the practices of prescribers, who should be encouraged to develop the ethical and multidisciplinary dimension in the decision-making processes for the allocation of innovative medicines".

(2) Strengthen and/or broaden the skills of public authorities preparing for negotiations:

- "By calling on public researchers and academics to carry out medico-economic analyses, and by developing real-life assessments of the effectiveness of innovative and costly medicines;

[14] Opinion No. 78, Disparity in access to health care and participation in research on a global level – ethical issues, 2003. URL: https://www.ccne-ethique.fr/sites/default/files/2024-06/avis078.pdf
[15] A consultation of key figures in the French healthcare system

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- By strengthening patent offices so that they have the resources and information they need (legal and regulatory provisions) to assess the effectiveness of innovations proposed by manufacturers;

(3) Develop a policy of cooperation at the European and even international level:

- "Reflect on the issues related to the legal qualification of certain innovative medicines as "global public goods";
- To consider the possibility of creating a European agency specializing in the economic analysis of health products or extending the remit of the EMA;
- More generally, to strengthen health sovereignty at national and European level" (at p. 5).

ii. How do we ensure equitable access to gene editing technologies across different socio-economic groups and regions?

In Opinion No. 78, the CCNE quoted Jonathan Mann, founding director of the AIDS Program at WHO: "A careful analysis of the major causes of preventable morbidity and mortality worldwide, including cancer, cardiovascular disease, injuries, infectious diseases, and violence, shows that these problems are inextricably linked to social discrimination and lack of respect for basic human rights".

Thus, to overcome inequalities in access to health care, the CCNE recommended the following actions:

- "By making an inventory of the needs [by region], first ensuring the competence and independence of the bodies responsible for defining and implementing this assessment method; "by recognizing the distinction between the population's needs (real or expressed) and its expectations" (at p. 8).
- Accompany this assessment of needs with an assessment of resources: "every health policy has a cost that cannot be ignored by the ethical bodies called upon to guide political decisions" (at p. 9).

Finally, in its Opinion No. 140[16], the CCNE states that "combating social inequalities means paying particular attention in health policies to the most vulnerable social groups, while guaranteeing good health for all": this means improving the situation of the most vulnerable, but even more so "reducing the social gradient in health" by also improving the health of people from modest or middle-class backgrounds, who "have a better state of health and access to resources than the most vulnerable, but well below that of the most privileged" (at p. 38).

[16] Opinion No. 140, Rethinking the Care System on an Ethical Basis. Lessons from the Health and Hospital Crisis, Diagnosis and Perspectives, 2022. URL, in French: https://www.ccne-ethique.fr/sites/default/files/2022-11/Avis140_Final_0.pdf

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iii. How can researchers and research institutions encourage more Asian participation in clinical trials for gene editing technologies to ensure inclusivity?

We don't have an answer to this query.

e. Genetic Enhancement and the Effects on Society

5 Recent advances have increased the possibility that gene editing can also be used for purposes that go beyond therapies and medical interventions, and the possible applications of gene editing technologies include genetic enhancement in areas such as conferring resistance to diseases and enhancement of physical attributes and cognitive abilities. Such potential clinical applications of gene editing technologies raise several ethical issues.

Ethical Considerations:

i. What are the ethical considerations involved in using gene editing technologies for genetic enhancement?

In its Opinion No. 133, the CCNE stated: "Eugenics can be defined as all the methods and practices aimed at improving the genetic heritage of the human species. It can be the result of a policy deliberately pursued by a state and contrary to human dignity. It can also be the collective result of the sum of convergent individual decisions taken by future parents in a society where the search for the "perfect child", or at least a child free of numerous serious afflictions, takes precedence".

The CCNE went on to acknowledge "the application to humans of techniques enabling targeted genome modification is certainly a source of hope for alleviating human suffering. However, it would appear that such techniques can only be applied to health care with very strict control and supervision, especially when they are likely to modify the germ line. Mechanisms involving not only patients and their associations, and doctors, but also other personalities (jurists, ethnologists) are essential" (at p.30).

In its Opinion No. 138,[17] the CCNE reiterates that "genome-editing techniques, if used on the germ cell genome transmissible to offspring, hold out the prospect of updating the goal of improving the species". Faced with these possibilities, the CCNE calls not only for "caution, but even more fundamentally for sincere humility in the face of a very long and powerful evolutionary process of selection, which does not put the best forward, as has been thought for too long, but places itself at the service of living beings and their diversity" (at p.33).

[17] Opinion No. 138, Eugenics: what exactly are we talking about? 2021. URL: https://www.ccne-ethique.fr/sites/default/files/2024-03/CCNE-%20Avis%20138%20-%20L%27eugenisme%20de%20quoi%20parle-t-on_en.pdf

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ii. How might potential clinical applications of gene editing for genetic enhancement impact future generations?

According to the CCNE in its Opinion No. 133, the application to human beings of techniques enabling the targeted modification of the genome for therapeutic purposes requires a choice to be made "between individual benefit (elimination of disease/disability) and collective risk (risk of transgression against society, rejection of 'difference')."

The Council asks the following question:

"On what ethical basis, for example, could a choice be made between the practice of selecting embryos that do not carry the causal mutation of a disease during pre-implantation diagnosis and the possibility of correcting this mutation by targeted genome modification in affected embryos in order to prevent the occurrence of the disease in the unborn child after reimplantation of the treated embryo? In the same spirit, would it be acceptable to modify the human genome, including germ cells, in order to prevent the occurrence of a serious hereditary pathology for which preimplantation diagnosis is ineffective, if all the embryos are affected (parents both affected by a common autosomal* recessive disease such as cystic fibrosis)"? Although the CCNE acknowledges that this is an exceptional case, it admits that its frequency is likely to increase in the future due to medical progress (at p. 30).

The question of conceiving a "healthy child" also raises many questions, according to the CCNE:

"To what extent does this request, in the case of families with hereditary diseases, resemble a request for medically assisted procreation, which can put the specific wishes of the child in tension with global health policies?"

Furthermore, "the lack of consent of the unborn child raises questions: how will the child experience this change, and what responsibility will the parents bear? Would not there be a risk of "claims" on the part of the "modified" child?

Finally, according to the CCNE, an analysis of the risks of a certain genetic standardization is necessary:

"What would be the meaning of a world in which difference, disability, for example, or even a particular trait, would be "unwelcome"? What would be the disadvantages of creating irreversible distortions in human evolution, whose standards would be set by certain people in the name of their own principles? "

The Committee emphasizes: "In the present context, we must not minimize the development of eugenics, which is based not only on the rejection of disability and

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difference, but also on the individual or social prospect of enhanced capacities that are attractive to the proponents of transhumanism and constitute a kind of emancipation of human nature (Opinion No. 133, at p. 30).

iii. Should we allow clinical applications of gene editing for genetic enhancement?

As mentioned above, genome editing techniques, especially when applied to germ cell genomes that can be transmitted to offspring, offer the possibility of updating the goal of improving the species.

Faced with these possibilities, the CCNE calls not only for caution but, more fundamentally, "for sincere humility in the face of a very long and powerful evolutionary process of selection, which does not put the best first, as has been thought for too long, but which puts itself at the service of living beings and their diversity" (Opinion No. 138, at p.33).

Finally, the CCNE recalls what French law states in article 16-4 of the Civil Code:

> "No one may undermine the integrity of the human species (1). Any eugenic practice aimed at organizing the selection of individuals is prohibited (2). Any intervention intended to produce a child genetically identical to another person, living or dead, is prohibited. (3). Without prejudice to research aimed at the prevention, diagnosis, and treatment of genetic diseases, no alteration of genetic characteristics may be carried out with the aim of modifying the person's descendants (4)". (p. 13)

In parallel with this necessary vigilance and humility, the CCNE "welcomes and encourages all progress in these techniques for their potential therapeutic use on the genome of somatic cells, which may offer prospects for the cure or attenuation of serious diseases, especially those for which medical abortion is currently being discussed (Opinion No. 138, at p. 27).

iv. What can be done to ensure that gene-editing technologies are used responsibly and ethically?

The CCNE, in its Opinion No. 133, underlines the following points:

> - "There is a need to inform society at large about the state of our knowledge of the genome and to engage in an ethical debate, both on the health risks of genome interventions and on the possible tensions - between individual desires

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and the loss of global solidarity - that could arise if these technologies become commonplace. What is done with scientific discoveries is a matter of collective responsibility, and in this respect scientists are citizens among others, even if their scientific and technical knowledge gives them a special responsibility to inform society about their advances and their doubts" (at p.32).

- "From a deontological point of view, the scientific and medical communities must also fight against conflicts of interest that are likely to alter their credibility in society, at the risk of hindering the development of research. All too often, such conflicts of interest arise between researchers and commercial companies, or even within scientific institutions, including in the field of techniques for targeted modification of the human genome, because of the financial rewards to be expected";

- "The development of rules for responsibility, governance, risk management and public decision-making in situations of scientific uncertainty is essential for the necessary understanding and appropriation of increasingly complex knowledge. The scientific community has a particular responsibility in helping society embrace the process of innovation, and it would be good if it followed closely the discussions led by the WHO (World Health Organization) and contributed to the creation and reflection of international scientific advisory bodies, such as the Genome Editing Summits and ARRIGE, (Association for Responsible Research and Innovation in Genome Editing), French Inserm's Committee on Ethics (CEI) etc.";

- "In addition to the responsibility of the scientific community, it should also be emphasized that society should participate in the debate and define the world we want to leave to future generations";

- Finally, "the scientific community, its staff, and its institutions, must show humility by acknowledging their ignorance of the sometimes unforeseeable consequences engendered by new techniques. At a time when international competition is fierce and certain funding sources favor applied research, researchers must know and be able to expose the doubts and questions raised by the applications of their research work. Scientific evaluation must consider ethical issues, through careful and continuous monitoring of research projects, which can only be effective if it is not limited to the national level, but takes place on a global scale. It is essential to raise awareness of ethical issues among young researchers and students, by providing them with appropriate training".

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PUBLIC CONSULTATION ON ETHICAL, LEGAL, AND SOCIAL ISSUES ARISING FROM HUMAN NUCLEAR AND GENOME EDITING

Human nuclear genome editing (HNGE) involves the modification of DNA within the nucleus in human cells tagerting to rectify the genetic diseases cause by gene defects. It has significant potential in biomedical research as well as in the clinical applications. Technology like CRISPR-Cas9 has been one of the advanced genome editing technologies to edit and correct the mutations leading to potential treatments for genetic disorders such as sickle cell anemia and Huntington's disease. The advancement in research aspects has help researchers to understand the functions and the roles of specific genes in certain diseases, providing more accurate and precise treatments. Despite the vital potential for both research and clinical applications, it also raises questions about the ethical and safety concerns of HNGE including the off-target effects, mosaicism, long-term effects, procurement and use of human embryos, equitable access and allocation of resources, as well as the genetic enhancement and its effects on society.

Researchers and clinicians should achieve the balance between the advantages and the risks of gene editing by adopting certain approaches, for instance:

i. Enhancing the precision of gene editing technologies with high fidelity variants to reduce and minimize the off-target effects
ii. Conduct extensive studies and protocol modification to assess the efficacy and safety of the gene editing technologies before and after the treatment along with the observation of long-term effects
iii. Establish guidelines and oversight committees to provide evaluation of the benefits against the risk of gene editing
iv. Engagement with the patients and their family members for follow-up and further discussion priotizing on patients' consent and safety.

Furthermore, clinical applications of heritable gene editing is a highly complex issue as it encounters risks and ethical issue although it could potentially eliminate severe genetic disorders in future generations, resolve the infertility problem and elevating the chances of

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勿以善小無益而不爲 勿以惡小無損而爲之

having genetically related children. However, these could lead to a new health problems or diseases that might be passed on to the future generations due to unintended consequences and carry out some unpredictable outcomes. Nevertheless, the ethical questions still remain whether altering the human genes are natural and ethical?

In Taoism perspective, genome editing could be a potential violation to the natural order. We believe the concept of "道法自然" Tao follows nature. Taoism emphasizes the harmony with nature and that everything in the universe should obey the law of nature. Interfering and changes in human genome could potentially disturb and disrupt the natural process and the Yin and Yang balance and further lead to unforeseen consequences of an individual.

Quoting a line from 《道德经》 Tao Te Ching by Laozi

"人法地 地法天 天法道 道法自然"

This highlights the Taoism belief in natural orders.

If the alteration of human genome technology is to advance the treatment and research of severe diseases like genetic disorders, it is the integration and the advancement of the era and the biotechnology providing the opportunities to extend one's lifespan and less suffering from certain illnesses or even to increase the possibility for disease prevention. However, if this technology is to be used for other purposes, it will become a challenge to the natural harmony and the balance of life and disobey the natural law in Taoism.

Heavenly Blessings

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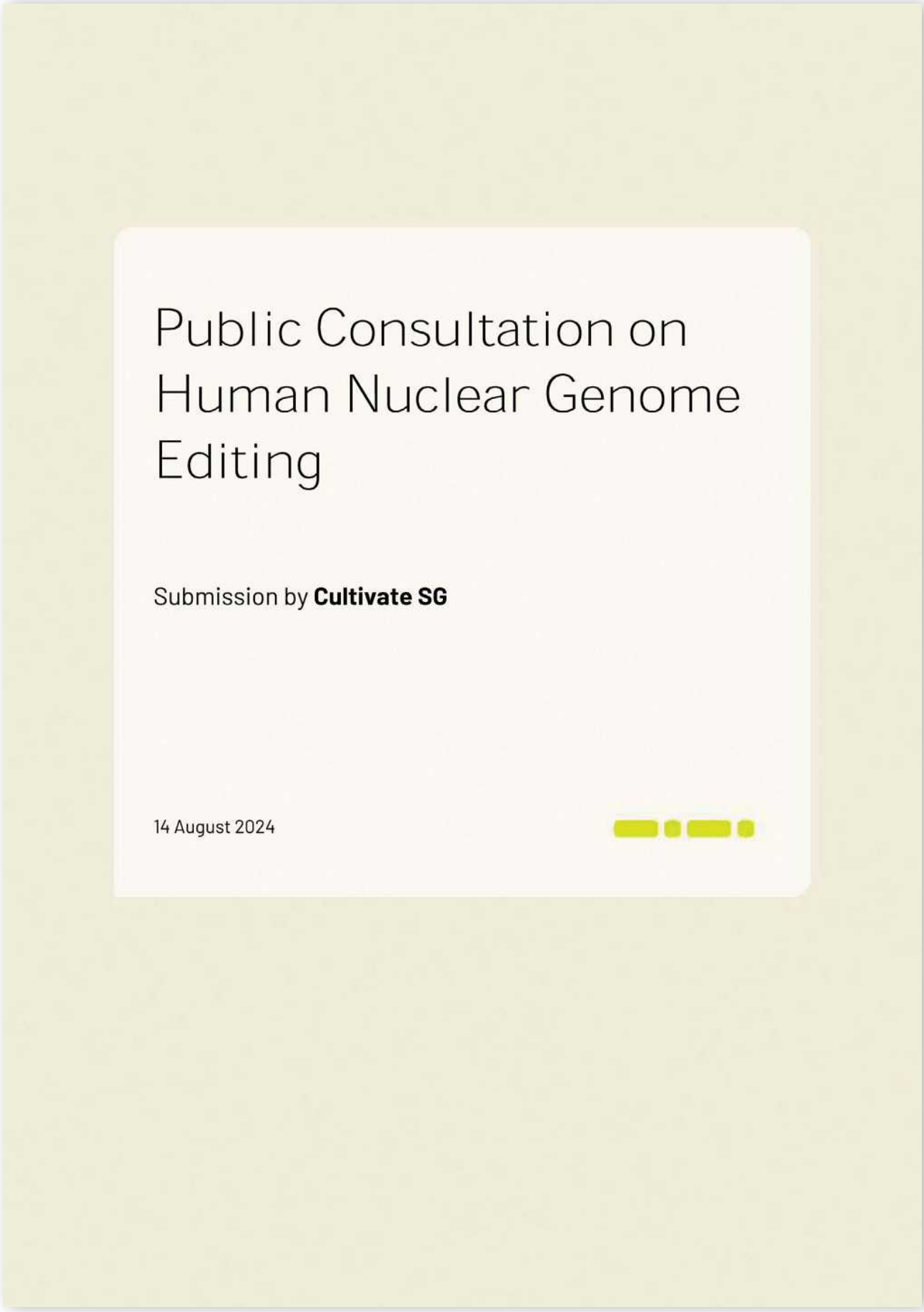
tm/mlzw:pa/cqy

3. Cultivate SG



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Executive Summary

1. Many of the ethical debates and controversies of today turn on this one question: *If we cannot agree on what it means to be "human", how can we agree on what human rights are?* At the core of the issue lies a philosophical debate over human nature:

   (1) Dynamic Unity view, which sees humans as a dynamic unity of mind (or soul) and body. This view emphasises the integral roles of biology and the human body in relation to human nature and relationships. The human person comes into existence at the same time the human organism does (i.e. at conception).

   (2) Dualist view, which tends to place less significance on the physical human body. Essential criteria for "personhood" – and thus rights – include self-awareness, sentience and the capacity to feel pain. This view does not accept that an embryo has a moral status as a human "person" with rights, even though it is recognised that embryos are "human entities".

2. The BAC too narrowly restricted the approach to "respect for persons" in a manner which focuses primarily on autonomy, and omitting the notion of bodily integrity. It does not adequately take into account the rights of people who have no or diminished capacity to give valid informed consent.

3. We would urge the BAC to emphasise that all human beings have inherent worth and dignity. This includes the right to bodily integrity (or personal security), among other rights. The BAC should also be mindful of the stereotypes, prejudices and harmful practices relating to persons with disabilities that may be directly or indirectly associated with gene editing technology.

4. Without a shared humanity, there can be no coherent system of ethics, rights and responsibilities among human beings. Gene editing potentially undermines our shared humanity in two significant and related ways:

   (1) Genetic discrimination.

   In this pursuit for "better" and healthier outcomes, there is a real risk that the pursuit of genetic "normalisation" may instead usher in an age of genetic discrimination, including concerns about eugenics. We caution about the risk that gene editing is likely to increase rather than decrease discrimination against persons with disabilities, as the inequalities between the genetic 'haves' and 'have-nots' are greater exacerbated (all in the aim of normalising the possible genetic contributions to disabilities).

   (2) Accentuating the income divide.

   Due to the high cost of gene editing, gene editing may be a luxury only the wealthy will be able to afford, giving them an added social advantage. In the long run, this may create an "endowment effect" where wealth and other privileges – in both monetary and genetic terms – are passed on through generations may cement into divisions and fissures in society that cannot be easily unravelled.

5. We express doubt that the traditional ethical **distinction between "therapy"** (restoring **to a "typical" state) and "enhancement"** (alteration to improve upon what is **"normal")** can be implemented in practice, in the context of gene editing. This is because what **is "typical" and "normal" are difficult to define, can be complicated by normative** debates about human nature, and may shift if more individuals benefit from gene therapies.

6. One key difficulty – as noted by the BAC – with any risk-benefit analysis lies in the problem with unknowns (both short- and long-term) and unknowability of certain risks; in an area like gene editing, this means that there may be numerous unanticipated risks that have not been or cannot be accounted for. There is an additional problem of irremediable consequences, since there is virtually no adequate remedy (legal or otherwise) that can restore the person to his or her original state of being if a person suffers complications from gene editing. The problem is aggravated if the complications are heritable, as this affects future generations.

7. **Our specific responses to the BAC's recommendations** are as follows:

(1) Non-heritable gene editing (for research and clinical applications).

We do not oppose, in principle, non-heritable gene editing, provided that all of the following conditions are fulfilled: free and full prior informed consent, use only for treatment of serious or life-threatening conditions (that can be predicted reliably within a reasonable time frame) rather than enhancement, equitable access in clinical applications (based on medical need), ensuring these are strictly non-heritable (including any secondary effects), long-term follow-up, adequate legal recourse and no gene editing of human embryos.

At the moment, it is not assured that gene editing (including secondary effects) will be strictly non-heritable. Therefore, we are of the view that non-heritable gene editing for research purposes should not be allowed. For this and the additional reason that it is not assured that clinical applications of non-heritable gene editing can be made available in an equitable manner, we do not support such clinical applications at the moment.

(2) Gene editing on germline cells or embryos for research.

We are of the view that gene editing on germline cells or embryos for research should not be permitted, due to the actual or potential impact on future generations. We urge against gene editing on human embryos (whether before or after the 14th day), as this undermines their human dignity and bodily integrity.

(3) Heritable gene editing for clinical applications.

We are of the view that heritable gene editing for clinical applications should not be permitted. This is because of the implications of heritable gene editing on society and on future generations (including genetic discrimination, eugenics and accentuating income inequalities) as well as other long-term consequences. It undermines our shared humanity.

I. Introduction

8. Cultivate SG is a non-profit organisation which wants to see families and our society thrive for generations. We call this 'social sustainability'. This involves individual rights and responsibilities, stable marriages, strong families, a cultural climate that supports personal and family growth, and social harmony. We believe that culture – as the sum total of values, beliefs and practices of people in society – is not a battle to be fought, but a garden to be cultivated.

9. These are the submissions of Cultivate in response to the Consultation Paper published by the Bioethics Advisory Committee ("BAC") on the "Ethical, Legal, and Social Issues Arising from Human Nuclear Genome Editing" (hereinafter, "Human Nuclear Genome Editing" shall be referred to as "HNGE" or "gene editing") dated June 2024 (the "Consultation Paper").[1]

II. Human Nature, Rights and Ethical Implications

10. Many of the ethical debates and controversies of today turn on this one question: *If we cannot agree on what it means to be "human", how can we agree on what human rights are?*

11. As poet and environmental activist Wendell Berry wrote, the question of human limits "finally rests upon our attitude toward our biological existence, the life of the body in this world". "What value and respect do we give to our bodies? What uses do we have for them? What relation do we see, if any, between body and mind (or body and soul)?"[2]

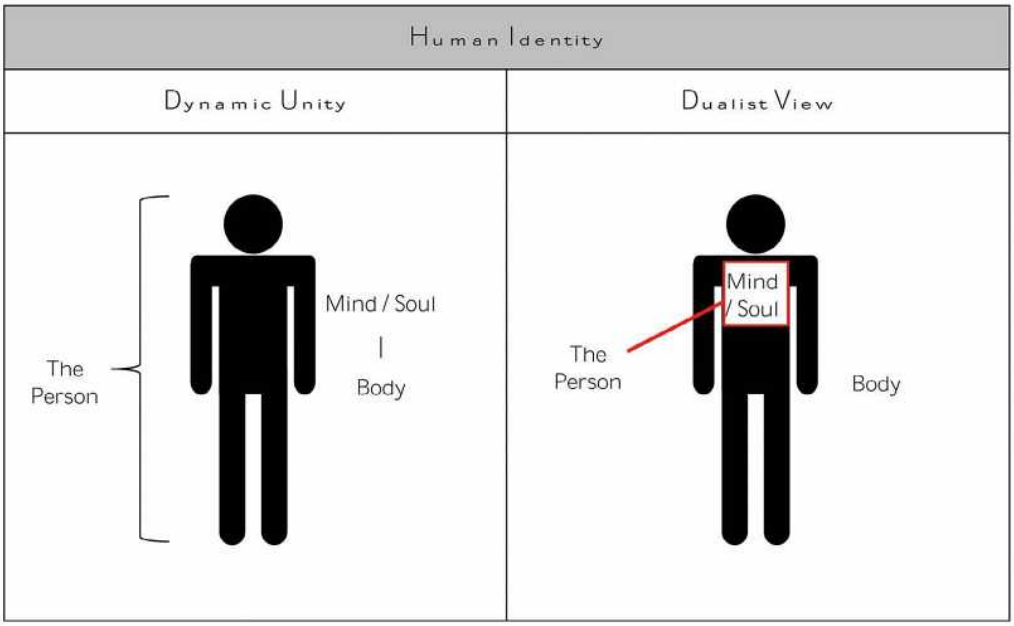
12. At the core of the issue lies a philosophical debate over human nature, particularly a debate over the relationship between the mind (or, in religious terms, the soul) and the body. The answers to these questions have profound consequences, including direct implications on our understanding of human identity, family, and thus the ordering of society and the State as a whole.

[1] Bioethics Advisory Committee, "Ethical, Legal, and Social Issues Arising from Human Nuclear Genome Editing: A Consultation Paper" (June 2024): https://www.bioethics-singapore.gov.sg/files/publications/consultation-papers/hnge_public_consultation_paper.pdf (the "**Consultation Paper**").
[2] Wendell Berry, "The Body and the Earth" (1994) 81(1) *Psychoanalytic Review* 125.

A. Different Views of Human Nature, and Ethical Implications

13. Most contemporary debates on bioethics implicate two broadly different views of human nature. These have implications on a wide range of ethical issues as a result:

Two Opposing Views of Human Nature



14. According to the first view **(the "Dynamic Unity" view), human beings are "rational animals", a dynamic unity of mind (or soul) and body. The body is no mere extrinsic** instrument of the human person (or **"self"), but is an integral part of the personal reality of the human being. My body is an essential part of who "I" am and is part of** my personal identity across time. The body is not property, but *personal* in nature.[3] This view emphasises the integral roles of biology and the human body in relation to human nature and relationships.

15. **In normal sexual reproduction, the father's sperm unites with the ovum (or "egg") of** the mother to form the zygote. Within the chromosomes of these gametes are the **deoxyribonucleic acid ("DNA") molecules which constitute the information that** guides the development of the new human organism.[4] Accordingly, the human person comes into existence at the same time the human organism does (i.e. at conception), and survives – as a person – at least until the organism ceases to be.[5]

[3] Patrick Lee and Robert P. George, "Body–Self Dualism in Contemporary Ethics and Politics" (New York: Cambridge University Press, 2008) at 4 to 49.
[4] Patrick Lee and Robert P. George, "Body–Self Dualism in Contemporary Ethics and Politics" (New York: Cambridge University Press, 2008) at 42.
[5] Patrick Lee and Robert P. George, "Body–Self Dualism in Contemporary Ethics and Politics" (New York: Cambridge University Press, 2008) at 50 to 94.

16. The second view **(the "Dualist" view)** tends to place less significance on the physical human body and the biological reality of **one's** mere belonging to the species *homo sapiens*.[6] Instead, essential criteria for "personhood" – and thus rights – include self-awareness, sentience and the capacity to feel pain.[7] In order to have rights, one must **have** "the immediately exercisable capacity to reason and make free choices".[8] Thus, the **"self" or "person" is viewed as being constituted in an inviolable spirit, mind or** psyche, whereas the body is merely a material vehicle.[9]

17. Accordingly, the Dualist view does not accept that an embryo has a moral status as a human "person" with rights, even though it is recognised that embryos **are "human entities".**[10] This is because, on this view, an embryo merely has **"potential to become a mature human being"** or **"the genetic coding" which "may, under favorable circumstances, lead it to develop into a being rational nature".**[11]

18. Based on the discussion above, two things are evident:

    (1) Firstly, contemporary debates on bioethics implicate different, even diametrically opposite views on human nature. It is not possible to adopt a **"neutral"** position on the matter which is devoid of any moral stance.

    (2) Secondly, **one's perspective on human nature** has profound implications on bioethics, laws and policies.

B. Critique of the BAC's Assumptions About Human Nature

19. **The BAC has aligned itself with the Warnock Committee's view**, namely – as phrased in the Consultation Paper – that "*only after the 14th day*, the embryo would be considered as an individual and *potential person* with rights to life" (emphasis added).[12] It bears emphasising that such a view of human nature is not universally shared, and is at odds with the **"Dynamic Unity" view**.

20. The ethical implications of such an understanding of human nature can be further seen in the way that **the BAC has formulated the ethical principle of "respect for persons",** which is **"to treat individuals as beings with value in themselves** *or* autonomy over their own life and, accordingly, to respect their right to make their

[6] Peter Singer, "Speciesism and Moral Status" (2009) 40(3/4) *Metaphilosophy* 567.
[7] Agata Sagan and Peter Singer, "The Moral Status of Stem Cells" (2007) 38(2/3) *Metaphilosophy* 264 at 280.
[8] Agata Sagan and Peter Singer, "The Moral Status of Stem Cells" (2007) 38(2/3) *Metaphilosophy* 264 at 277.
[9] Robert P. George, "Gnostic Liberalism" *First Things* (December 2016): https://www.firstthings.com/article/2016/12/gnostic-liberalism.
[10] See, for example, Agata Sagan and Peter Singer, "The Moral Status of Stem Cells" (2007) 38(2/3) *Metaphilosophy* 264 at 265.
[11] Agata Sagan and Peter Singer, "The Moral Status of Stem Cells" (2007) 38(2/3) *Metaphilosophy* 264 at 271 and 276.
[12] Consultation Paper, at para. 1.19. It is worth pointing out that the Warnock Committee had acknowledged that "[the] beginning of a person is not a question of fact but of decision made in the light of moral principles". It further opined that "Scientific observation and philosophical and theological reflection can illuminate the question but they cannot answer it." (Department of Health and Social Security, *Report of the Committee of Inquiry into Human Fertilisation and Embryology*, July 1984 (London: Her Majesty's Stationery Office) at para. 2)

own decisions without being coerced, misled, or kept in ignorance" **(emphasis added).**[13]

21. A comparison **of the two paragraphs discussing the concept of "respect for persons"** reveals an obvious omission of the ethical imperative **"to treat individuals as beings with value in themselves"** (including and especially *the right to bodily integrity*):

Comparison

BAC's Formulation of "Respect for Persons	
Paragraph 3.2	Paragraph 3.3
Respect for persons directs us to treat individuals as beings with value in themselves *or* autonomy over their own life and, accordingly, to respect their right to make their own decisions without being coerced, misled, or kept **in ignorance...** (emphasis added)	In the context of HNGE, the principle of *respect for persons* refers to the autonomy of individuals making decisions related to biomedical research involving gene editing or its clinical applications... (emphasis added)

22. This omission is likewise evident in the manner that the BAC analyses gene editing **purely from the angle of "autonomy"** (omitting bodily integrity), reasoning as such in **both the way it presents the arguments 'for' and 'against'** gene editing of embryos or children:

> "While gene editing does not violate autonomy and rights of modified embryos or germline cells since they have *no autonomy per se that can be violated*, some argue that it infringes the autonomy and rights of the child who is consequently born to an open future, where gene editing limits the range of set life-options, since he is *unable to provide consent* prior to being genetically modified."[14] (emphasis added)

23. This analysis – both in the argument and counter-argument – omit the importance of bodily integrity. It does not adequately take into account the rights of people who have no or diminished capacity to give valid informed consent.[15]

[13] Consultation Paper, at para. 3.2.
[14] Consultation Paper, at para. 3.3.
[15] This is telling because it is only by framing the principle as a choice between treating people with (either) inherent value "or" (instead of "and") autonomy over their own life, that the BAC can plausibly hold the principle of "respect for persons" consistent while arguing for the permissibility of gene editing, at least in certain circumstances for the time being. (Consultation Paper, at paras. 12.4 to 12.9)

24. Similarly, the concept of "fairness and equality for all individuals" (as a facet under the principle of *justice*) as framed by the BAC has been defined as "[implying] that access to the benefits of biomedical research, and the burden of supporting it, should be equitably shared in society" (emphasis added).[16] There is scant discussion of the concept of equality of human beings (or persons) as individuals with inherent value, and their right not to be discriminated against on grounds such as disability.

C. Key Ethical Considerations on Personhood and Rights

25. All human beings have inherent worth and dignity. This is a cardinal principle of ethics and human rights, and is embodied in various human rights treaties that Singapore has signed and ratified.[17]

26. In light of these principles, we would like to offer a few key ethical (including legal and human rights) considerations on personhood and rights, which we would urge the BAC to emphasise:

(1) Right to bodily integrity (or personal security). Inherent in the concepts of personhood and "respect for persons" is the right to bodily integrity or personal security. This is embodied in the right to "life" – which has been interpreted to encompass personal security – under Article 9(1) of the Singapore Constitution.[18] The right to personal security is protected under various human rights treaties.[19]

(2) Medical or scientific experimentation without consent. The absolute prohibition against "torture" or "cruel, inhuman or degrading treatment or punishment" is part of customary international law, and is a peremptory norm (or *jus cogens*) having a higher status in international law than ordinary rules.[20] One important facet of this rule is that: "In particular, no one shall be subjected without his or her free consent to medical or scientific experimentation".[21] The Human Rights Committee has opined that "special protection" is necessary for persons who are unable to give valid consent, and such persons "should not be

[16] Consultation Paper, at para. 3.6.
[17] *Convention on the Rights of the Child*, United Nations, *Treaty Series*, vol. 1577, p. 3 ("***CRC***"); *Convention on the Elimination of All Forms of Discrimination against Women*, United Nations, *Treaty Series*, vol. 1249, p. 13 ("***CEDAW***"); *International Convention on the Elimination of All Forms of Racial Discrimination*, United Nations, *Treaty Series*, vol. 660, p. 195 ("***ICERD***"); *Convention on the Rights of Persons with Disabilities*, United Nations, *Treaty Series*, vol. 2515, p. 3 ("***CRPD***").
[18] *Yong Vui Kong v Public Prosecutor* [2015] 2 SLR 1129 at para. 22. In the case, the Singapore Court of Appeal considered that the right to life encompassed the concept of "personal security", which refers to "a person's legal and uninterrupted enjoyment of his life, his limbs, his body, his health, and his reputation" (at para. 18).
[19] See, for example, Article 14, CRPD; Article 5, ICERD.
[20] *Prosecutor v Anto Furundzija (Trial Judgement)*, IT-95-17/1-T, International Criminal Tribunal for the former Yugoslavia (ICTY), 10 December 1998; see also *Yong Vui Kong v Public Prosecutor* [2015] 2 SLR 1129 at para. 27.
[21] Article 15 of the CRPD – to which Singapore is a party – provides that: "No one shall be subjected to torture or to cruel, inhuman or degrading treatment or punishment. In particular, no one shall be subjected without his or her free consent to medical or scientific experimentation." In *Yong Vui Kong v Public Prosecutor* [2015] 2 SLR 1129, the Singapore Court of Appeal confirmed that the scope of this provision is not limited to persons with disabilities, but applies to "all persons" (at para. 44).

subjected to any medical or scientific experimentation that *may be* detrimental to their health" (emphasis added).[22]

(3) Non-discrimination on the grounds of disability.[23] The Convention on the Rights of Persons with Disabilities ("CRPD") – to which Singapore is a party – protects "persons with disabilities", a term defined to include "those who have long-term physical, mental, intellectual or sensory impairments which in interaction with various barriers may hinder their full and effective participation in society on an equal basis with others".[24] The CRPD prohibits discrimination on the basis of disability, and requires States Parties to take measures to "combat stereotypes, prejudices and harmful practices relating to persons with disabilities... in all areas of life".[25]

(4) Definition of a "child". Under the Convention on the Rights of the Child ("*CRC*") – to which Singapore is a party – a "child" is defined as "every human being below the age of eighteen years unless under the law applicable to the child, majority is attained earlier".[26] Notably, the CRC does not specify a minimum age for a child. On the other hand, preamble of the CRC recites that "the child, by reason of his physical and mental immaturity, needs special safeguards and care, including appropriate legal protection, before as well as after birth".[27] Thus, the CRC does not rule out the possibility of legal protections for unborn children.

(5) Best interests of children. The "best interests" of children is a key principle in the protection of children's rights. This is embodied in the *CRC*, which states that: "In all actions concerning children, whether undertaken by public or private social welfare institutions, courts of law, administrative authorities or legislative bodies, the best interests of the child shall be a primary consideration."[28] This is likewise embodied in Singapore law, where the paramountcy of the child's welfare has been described as the "golden thread" that runs through all proceedings directly affecting the interests of children.[29]

[22] UN Human Rights Committee, "CCPR General Comment No. 20: Article 7 (Prohibition of Torture, or Other Cruel, Inhuman or Degrading Treatment or Punishment)", 10 March 1992, UN Doc. HRI/GEN/1/Rev.1 at 30 (1994).
[23] In an earlier paper, the BAC accepted "without qualification" that "people with disabilities are of no less value than able-bodied people, and are similarly entitled to be treated with respect and dignity". (Bioethics Advisory Committee, "Mitochondrial Genome Replacement Technology: An Interim Report by the Bioethics Advisory Committee, Singapore" (2021): https://file.go.gov.sg/bacmgrt2021.pdf)
[24] Article 1, CRPD.
[25] Articles 5 and 8(1)(b), CRPD.
[26] Article 1, CRC.
[27] Preamble, CRC.
[28] Article 3(1), CRC.
[29] *UKM v Attorney-General* [2019] 3 SLR 874 at para. 50.

27. Similarly, both **the Singapore Medical Council ("SMC") Ethical Code and Ethical** Guidelines and Handbook on Medical Ethics frame the principles of respect for bodily integrity (in the context of beneficence and non-maleficence) and autonomy as separate and distinct principles, both of which should be upheld:

Extracts from Singapore Medical Council**'s Documents on Ethics**

Singapore Medical Council	
Ethical Code and Ethical Guidelines (2016 Ed.), pages 12 – 13	Handbook on Medical Ethics (2016 Ed.), pages 9 – 10
(a) Ensure beneficence and non-maleficence: (i) Maintain due respect for human life. (ii) Uphold **patients' welfare and best** interests as your highest consideration. ... (b) Respect autonomy: ... (ii) Treat patients with honesty, dignity, respect and consideration, upholding their desire to be adequately informed and (where relevant) their desire for self-determination.	(a) Beneficence You are committed to helping your patients by providing medical benefit **through your activities...** (b) Non-maleficence You are required to do no harm to patients, or in your treatment of patients, to minimise harm whilst **maximising possible medical benefit...** (c) Respect for autonomy Patients have a right to decide for **themselves what treatment to accept...**

28. Thus, BAC **too narrowly restricted the approach to "respect to persons" in the** following ways:

(1) By *omitting the notion of bodily integrity* and focusing solely on autonomy in the context of its discussion on gene editing. The rights to bodily integrity and autonomy in medical decisions are not mutually exclusive, and should not be framed as an "either-or" choice between one or the other. Instead, both ought to be respected and upheld. The consideration of the right to bodily integrity is particularly relevant in the context of those who have no capacity to give valid informed consent (e.g. children).

(2) By focusing primarily on unequal or inequitable *access to (or burden of supporting)* gene editing technologies in its analysis of the right to equality. According to the SMC, the principle of justice encompasses not only distributive justice, but also **respect for people's rights** ("rights-based justice") and the laws of **the country** ("legal justice").[30] Thus, among other things, the BAC should be **mindful of the "stereotypes, prejudices and harmful practices relating to persons with disabilities"** that may be directly or indirectly associated with gene editing technology.

III. Concerns About Gene Editing

29. In this section, we express the following concerns about gene editing:

A. Firstly, we are concerned about the impact of gene editing on our shared humanity, due to the risk of genetic discrimination and accentuating of income inequalities;

B. Secondly, we express doubt about the traditional distinction in medical ethics **between "therapy" and "enhancement"**, in the context of gene editing;

C. Thirdly, attention is drawn to the limits of human knowledge, and the problem of unknowns, unknowability and irremediable consequences in risk-benefit analysis;

D. **Finally, we give our specific responses to the BAC's** recommendations on gene editing.

A. Creating Genetic Discrimination, Accentuating Inequalities

30. **"Without shared ideas on politics, morals and ethics no society can exist," wrote Sir** Patrick Devlin.[31] This principle can be taken a step further: Without a shared humanity, there can be no coherent system of ethics, rights and responsibilities among human beings.[32] This is because, *if we cannot agree on what it means to be "human", how can we agree on what human rights are?*

[30] Singapore Medical Council, *Handbook on Medical Ethics* (2016 Ed.) at page 10.
[31] Sir Patrick Devlin, "The Enforcement of Morals" in *Proceedings of the British Academy*, vol. 45 (1959), 129 at 137 to 138.
[32] "Common humanity" identity politics is essential towards building a cohesive society, transcending fractious and narrow group identities to enable people to share in a common destiny and morality. (See, in this regard, Greg Lukianoff and Jonathan Haidt, *The Coddling of the American Mind: How Good Intentions and Bad Ideas are Setting Up a Generation for Failure* (United States of America: Penguin Books, 2019) at 59 to 67; see also, Cultivate SG, "Is Identity Politics Always Bad?" (24 May 2024): https://cultivate.sg/is-identity-politics-always-bad/)

31. Gene editing potentially undermines our shared humanity in two significant and related ways:

(i) Genetic Discrimination

32. The advent of the life sciences has opened the door to and accelerated the human quest for genetic "normalisation". Yet, in this pursuit for "better" and healthier outcomes, there is a real risk of undermining the commitment to the intrinsic worth and equality of all human beings – a commitment which underpins all human rights – where the pursuit of genetic "normalisation" may instead usher in an age of genetic discrimination.[33] The risk of discrimination and inequality between genetic 'haves' and 'have-nots' is serious and real.

33. We thus agree with the BAC's concern that gene editing "could reinforce discrimination between the genetically modified and unmodified individuals and exacerbate social inequities", and share its concern about the risk of discrimination against vulnerable people (e.g. individuals with disabilities or developmental needs).[34] We further agree with the BAC's concern about the risk that gene editing may lead to design and preferential reproduction of "more desirable" and "better" kinds of human beings which "borders on eugenics".[35]

34. However, we would urge the BAC to go further by recognising that gene editing would risk entrenching "stereotypes, prejudices and harmful practices relating to persons with disabilities... in all areas of life",[36] in contravention of the CRPD. In a world where gene editing is permitted, discrimination against persons with disabilities is likely to increase rather than decrease, as the inequalities between the genetic 'haves' and 'have-nots' are greater exacerbated (all in the aim of normalising the possible genetic contributions to disabilities). This would be contrary to the goals of promoting greater access, opportunities and inclusion of persons with disabilities in various areas of life.

[33] Eric Cohen and Robert P. George, "The Problems and Possibilities of Modern Genetics: A Paradigm for Social, Ethical, and Political Analysis" *Governance Studies at Brookings* (5 July 2011): https://www.brookings.edu/wp-content/uploads/2016/06/0705_genetics_cohen_george.pdf.
[34] Consultation Paper, at paras. 10.7 and 10.10.
[35] Consultation Paper, at para. 10.7.
[36] Articles 5 and 8(1)(b), CRPD.

(ii) Accentuating the Income Divide

35. Singapore is a highly developed country, and the Government has identified the **"twin challenges"** of income inequality and social mobility as issues to be addressed.[37] In 2023, our Gini coefficient was 0.371 (after Government transfers and taxes); before such transfer and taxes, the figure was 0.433.[38]

36. We note that the BAC has estimated the current cost of gene therapies to be in the millions of dollars, and share the concerns that such gene editing technologies (if permitted) would be inaccessible to individuals with lower socioeconomic status despite their needs.[39] Given these factors, we are concerned that gene editing may become a luxury only the wealthy will be able to afford.

37. Hence, in light of our concerns about genetic discrimination, gene editing would give the wealthy an added social advantage of genetic improvement. It will likely add a further dimension to the income and social divide between the higher and lower income groups, as well as social mobility.

38. Thus, we share **the BAC's concern that** "selected or desirable traits would be concentrated within a privileged wealthy group and could subject future generations to discrimination".[40] We are concerned that, **in the long run, the "endowment effect"** where wealth and other privileges – in both monetary and genetic terms – are passed on through generations may cement into divisions and fissures in society that cannot be easily unravelled.[41]

B. Therapy, or Enhancement? Can a Line Be Drawn?

39. Traditionally, the distinction in **medical ethics is between "therapy" and "enhancement". "Therapy" is defined as** "an intervention designed to maintain or **restore bodily organization and functioning to states that are typical for one's species,** age, and sex". **"Enhancement" is** "alteration to improve upon normal organization, appearance, health, and functioning".[42] **This "bright line" determines whether a** medical professional is **acting in the patient's best interest**.

[37] Prime Minister's Office, "DPM Lawrence Wong at the Economic Society of Singapore Annual Dinner 2023" (26 September 2023): https://www.pmo.gov.sg/Newsroom/DPM-Lawrence-Wong-at-the-Economic-Society-of-Singapore-Annual-Dinner-2023.
[38] Department of Statistics, "Median Household Income from Work Grew in Both Nominal and Real Terms" (7 February 2024): https://www.singstat.gov.sg/-/media/files/news/press07022024.ashx.
[39] Consultation Paper, at paras. 9.2 to 9.4.
[40] Consultation Paper, at paras. 10.8.
[41] See, in this regard, "Speech by Minister Chan Chun Sing at the IPS 35th Anniversary Conference: Revisit" (12 June 2023): https://www.moe.gov.sg/news/speeches/20230612-speech-by-minister-chan-chun-sing-at-the-ips-35th-anniversary-conference-revisit.
[42] Faith Lagay, "Gene Therapy or Genetic Enhancement: Does It Make a Difference?" (Feb 2001) 3(2) *AMA Journal of Ethics* 37.

40. While correct in principle, terms like **"typical" and "normal"** are difficult to define, and inadequate for ethical analysis in a broader picture.[43] They can be complicated by normative debates over fundamental questions involving human nature (see above). In a world where gene editing is permitted, **even what is considered "typical" or "normal"** may shift as more individuals benefit from gene therapies; indeed, the BAC has noted the potential of gene editing to reduce genetic diversity in the human population.[44]

41. We note that the BAC has taken the position that:

> "Given that applications of gene editing technologies for enhancement could exacerbate social inequity, it may be necessary to limit their uses to cases where they do not result in unfair advantage or disadvantage for certain individuals, such as disease prevention, or improving quality of life by restoring physical or cognitive abilities and functions. Other uses of gene editing technologies, such as editing genes to enhance physical traits or cognitive abilities that could create unequal opportunities in sports, education, or employment, and may need to be limited as they could perpetuate existing social inequalities."[45]

42. While this may be attractive at first blush, these principles would be very difficult to implement in the practice of gene editing. This is because a medical professional administering gene editing therapies would have no reasonable way of assessing whether it "could create unequal opportunities" for any given patient. Furthermore, when "restoring physical or cognitive abilities and functions", how is a medical professional supposed to ensure that **these are restored to a "normal" or "typical"** level and no more than that?[46]

43. As such, we would recommend that *gene editing (if permitted) should only be used for strictly therapeutic purposes and limited to treatment of serious or life-threatening conditions (that can be predicted reliably within a reasonable time frame)*, so that a clear line is drawn against the use of gene editing for genetic enhancement.

[43] Leon R. Kass, "Ageless Bodies, Happy Souls: Biotechnology and the Pursuit of Perfection" (Spring 2003) *The New Atlantis* 9.
[44] Consultation Paper, at paras. 10.15 to 10.17.
[45] Consultation Paper, at paras. 10.8.
[46] Leon R. Kass writes: "Furthermore, in the many human qualities (like height or IQ) that distribute themselves 'normally,' does the average also function as a norm, or is the norm itself appropriately subject to alteration? Is it therapy to give growth hormone to a genetic dwarf but not to a very short fellow who is just unhappy to be short? And if the short are brought up to the average, the average, now having become short, will have precedent for a claim to growth hormone injections." (Leon R. Kass, "Ageless Bodies, Happy Souls: Biotechnology and the Pursuit of Perfection" (Spring 2003) *The New Atlantis* 9 at 13)

C. Unknowns, Unknowability and Irremediable Consequences

44. **Friedrich Hayek once cautioned against the "fatal conceit"** in the notion that "man is able to shape the world around him according to his wishes". He cautioned against the reliance on moral guidance through factual knowledge alone, given that benefits (and risks) cannot be fully known or foreseen.[47]

45. The ethical principle of *proportionality* – "the potential benefits to individuals and the society brought about by the editing of the human genome should outweigh the *anticipated* risks of such research and clinical applications" (emphasis added), as per the BAC[48] – is not wrong in and of itself. However, one key difficulty with any such risk-benefit analysis lies in the problem with *unknowns* (both short- and long-term) and *unknowability* of various risks; in an area like gene editing, this means that there may be numerous "unanticipated risks" that have not been or cannot be accounted for. Such uncertainties have an impact on the question of autonomy and informed consent.[49]

46. We appreciate the BAC in its efforts to **document various** "unintended biological outcomes" (such as chromosomal mosaicism in embryos, and undesirable consequences arising from off-target mutations and deletions), **as well as "concerns** regarding the safety and unknown long-term side effects" of HNGE.[50] However, given the sheer novelty of HNGE and the ethical concerns surrounding it, there remains – and will likely remain – numerous unknowns and unknowable risks.

47. There is an additional problem of *irremediable consequences* in relation to all risks, anticipated and unanticipated. Take the example of off-target mutations cited by the BAC. It has been noted that gene editing (heritable or non-heritable) may cause causing DNA deletions and rearrangements which can eventually lead to genome instability and disruption of the functional genes. Further complications include development of cancer and allergic reactions.[51]

48. In such a situation where a person suffers complications, there is virtually no adequate remedy (legal or otherwise) that can restore the person to his or her original state of being. In cases where such genetic changes are heritable, the negative impact is even greater, as it would extend to future generations, who would have even fewer avenues to seek remedy for their suffering.

[47] Friedrich A. Hayek, *The Fatal Conceit: The Errors of Socialism*, Vol. I, W. W. Bartley, III (ed.) (London: Routledge, 1992) at 27, 71 to 75.
[48] Consultation Paper, at para. 3.9.
[49] See, for example, the discussion in Victoria Chico, "Known Unknowns and Unknown Unknowns: The Potential and the Limits of Autonomy in Disclosure of Genetic Risk" (2012) 28(3) *Journal of Professional Negligence* 162. Although the discussion was in the context of genetic testing and unwanted disclosure of genetic information to the patient, the principles apply with equal (if not greater) force in the context of gene editing.
[50] See Chapters 6 and 7 of the Consultation Paper (pages 58 to 70).
[51] Consultation Paper, at para. 6.6.

D. Specific Responses to the BAC's Recommendations

49. In light of the above, we give our specific responses to **three of the BAC's** recommendations, regarding (i) non-heritable gene editing (for research and clinical applications), (ii) gene editing on germline cells or embryos for research, and (iii) heritable gene editing for clinical applications.

(i) Non-heritable gene editing (for research and clinical applications)

50. We note that the BAC is favourable to non-heritable gene editing for research and clinical applications. This is provided that there is a favourable risk-benefit ratio, informed consent, Institutional Review Board approval and long-term follow-up (for patients of clinical trials).[52]

51. We do not oppose, in principle, non-heritable gene editing, provided that all of the following conditions are fulfilled:

(1) Free and full prior informed consent should be obtained at all times. Individuals should be made aware of all potential risks and benefits. In cases of medical or scientific experimentation, patients or participants should be fully informed of the nature of the experiment, including all known risks and the possibility of unknown risks.

(2) In situations involving persons with no or diminished capacity to give valid informed consent (e.g. children), valid prior informed consent should be obtained from persons duly authorised to give such consent (e.g. parents of children), strictly in accordance with their best interests.

(3) Non-heritable gene editing should only be used for therapeutic purposes (as opposed to enhancement), with clear evidence that the benefits significantly outweigh the risks. As such, the use of non-heritable gene editing should be restricted to treatment of serious or life-threatening conditions (that can be predicted reliably within a reasonable time frame).

(4) In clinical applications, access to non-heritable gene editing should be provided equitably according to medical need (as opposed to financial ability to afford the intervention).

(5) All efforts should be made to ensure that the gene editing is strictly non-heritable (including any secondary effects).[53]

[52] Consultation Paper, at para. 12.4 to 12.5.
[53] In this regard, we express doubts as to whether a clear and bright line can be drawn between non-heritable and heritable gene editing, including questions as to whether apparently "non-heritable" gene editing may result in heritable off-target mutations and a host of other erstwhile-unknown consequences which are heritable.

(6) As a safeguard, all patients should be subject to long-term follow-up, in order to monitor for adverse events, evaluate risks and benefits, and manage any issues that may arise.

(7) Adequate legal frameworks for compensation should be established in order to provide legal recourse for persons harmed by malpractice or negligence arising out of gene editing interventions.

(8) No gene editing on human embryos should be permitted.

52. At the moment, it is not assured that gene editing (including secondary effects) will be strictly *non-heritable*. Therefore, we are of the view that non-heritable gene editing for research purposes should not be allowed.

53. For this same reason and, additionally, it is not assured that clinical applications of non-heritable gene editing can be made available in an equitable manner. Thus, we do not support such clinical applications at the moment.

(ii) Gene editing on germline cells or embryos for research

54. We note that the BAC "does not recommend any gene editing research on human embryos after the 14th day", though it may reconsider this position if there is "stronger evidence of scientific merit" for such research.[54] It has also made recommendations in relation to informed consent regarding women donating surplus embryos or undergoing oocyte procurement, and compensation.[55]

55. For reasons stated above, particularly in relation to our perspectives on human nature, we do not share the BAC's position on this matter. We are of the view that gene editing on germline cells or embryos for research should not be permitted, due to the actual or potential impact on future generations. We urge against any gene editing on human embryos (whether before or after the 14th day), as this undermines their human dignity and bodily integrity.

(iii) Heritable gene editing for clinical applications

56. We note that the BAC "does not recommend clinical applications of heritable gene editing for any purpose in the near future, as there is insufficient evidence from current research to ascertain that such applications of HNGE technologies are safe and ethical."[56] Included among the "ethical and safety concerns" are "unintended consequences, long-term effects, and other consent, autonomy and inequality issues".[57] However, the BAC may reconsider this "if and when" the risks involved are "sufficiently mitigated in the future", and may recommend heritable gene editing "in

[54] Consultation Paper, at para. 12.6.
[55] Consultation Paper, at para. 12.6 to 12.7.
[56] Consultation Paper, at para. 12.8.
[57] Consultation Paper, at para. 12.8.

certain situations to prevent catastrophic conditions or for diseases where there are no other treatment options available".[58]

57. We are of the view that heritable gene editing for clinical applications should not be permitted. This is because of the implications of heritable gene editing on society and on future generations (including genetic discrimination, eugenics and accentuating income inequalities) as well as other long-term consequences. It undermines our shared humanity.

IV. Conclusion

58. The promise of gene editing is vast, even utopian. Things that were only dreamed about in science fiction are fast becoming reality today. However, with every leap forward in technological development, we risk a greater **"cultural lag" where** technological advancements risk outpacing our legal and ethical norms.

59. We thus appreciate the BAC for taking the opportunity to examine the topic of gene editing, and for giving us the opportunity to submit our feedback on the matter.

60. Just as it is important to develop in a sustainable manner in the economic and environmental spheres, it is likewise important to develop in a socially sustainable manner in the context of bioethics. In the same way we should respect the natural world, we should likewise respect human nature.

[58] Consultation Paper, at para. 12.9.

4. Human Fertilisation and Embryology Authority (UK)

The UK's Human Fertilisation and Embryology (HFE) Act 1990 (as amended) does not permit interventions in the nuclear DNA of gametes or zygotes for the purpose of germline genome editing in reproduction. Genetically modified embryos are currently only permitted in research and cannot be grown in culture for more than 14 days. This technique might be useful for some patients to avoid passing on a serious heritable condition in the future. Embryo testing for such a purpose has long been allowed in the UK by means of PGT-M (preimplantation genetic testing for monogenic disorders), but this can only be used in certain circumstances. It is possible that genome germline editing technology combined with PGT-M may eventually be more efficient than use of PGT-M alone.

It is widely accepted that genome editing is not sufficiently precise and controllable to permit its safe and effective use in an IVF clinic, even if such a thing were lawful in the UK. Concerns are raised about the possibility of genome editing techniques to modify the epigenome or mitochondrial DNA of early embryos.

The HFEA last reviewed studies using genome editing techniques on human and animal embryos in February 2024. Significant further scientific research into improving the accuracy of genome editing technologies is required before human germline applications can be considered. It is unlikely that CRISPR-Cas9 systems will be used for early genome editing due to their potential to induce catastrophic off-target effects. At present there is no research into the application of other techniques - such as prime editing. Experience from somatic gene editing trials will go some way to inform understanding, however further research on embryos or gamete precursors (in vitro derived) is required to fully understand the application of genome editing techniques on the germline.

At present there are significant safety and efficacy issues raised by the application of nuclear germline genome editing in treatment and there are of course serious ethical considerations given the long-term impact of altering the germline. Since the First International Summit on Human Genome Editing of 2015, there has been significant legal and ethical debate, resulting in many reports and papers from international bodies and national ethics committees. Most reports consider that heritable applications of human genome editing may be acceptable in the future in certain circumstances, while noting that there remains significant concern about the safety and efficacy of the technique.

However, scientific work in the field of genome editing continues to advance, as do novel techniques of genome editing. Should these issues be resolved, the technique could be a safe and effective treatment option for the avoidance of passing on heritable conditions in certain defined circumstances. Nevertheless, given the important issues involved at this point, the HFEA think that it is currently unsafe to proceed with heritable genome editing for clinical practice, as prohibited by the HFE Act.

See recent UK work into heritable nuclear germline genome modifications including: Genome editing and human reproduction: social and ethical issues - Nuffield Council on Bioethics, UK Citizens' Jury on Genome Editing – Wellcome Connecting Science (https://societyandethicsresearch.wellcomeconnectingscience.org/project/uk-citizens-jury-on-genome-editing/)

5. Agency for Science, Technology, and Research (A*STAR)

Dear Biomedical Ethics Coordinating Office

A*STAR has reviewed the BAC Consultation Paper on the Ethical, Legal, and Social Issues Arising from Human Nuclear Genome Editing. We are generally supportive of BAC's recommendations.

A suggestion is that given that BAC's recommendations are pitched at a fairly high level, we think researchers, healthcare professionals and IRBs could benefit from guidelines leveraging examples to contextualize and help with on the ground implementation.

1. As BAC has rightly pointed out, *"…with technological advancements, continual evaluation is crucial to ensure a well-informed risk-benefit consideration…" (Section 1.16, pg 17) and "… hence, principal investigators of HNGE clinical trials, as well as clinicians providing treatment involving non-heritable gene editing, have to ensure that the risks are not disproportionate to anticipated benefits, by maximising potential benefits while maintaining a favourable risk-benefit ratio for clinical trial participants and patients…"* (Section 7.4, pg 64). Although the importance of a favourable risk-benefit ratio is clear, guidance on relevant considerations when determining the risk-benefit ratio (e.g. via a non-exhaustive checklist) and on what is considered a "favourable risk-benefit ratio" would provide a backbone to align relevant considerations across the ecosystem.

2. BAC recommended that long-term follow-up on patients of clinical trials involving non-heritable gene editing should be conducted, and that appropriate measures are taken to anticipate and manage uncertainties and long-term consequence associated with non-heritable gene editing (Section 12.5, pg 97-98). As to how such follow-up studies and measures may be implemented is open to interpretation. Guidelines on follow-up durations and monitoring frequencies, potential considerations when establishing guidelines for evaluating and managing off-target effects, and frameworks for risk assessment for consistent implementation would be helpful.

3. BAC may also wish to consider recommending baseline communication strategies for reporting outcomes and educating patients, as well as collaborative data-sharing practices and training for researchers to help ensure consistent and effective monitoring and management of long-term safety and efficacy of non-heritable gene editing.

4. Finally, A*STAR supports BAC's recommendation to continually monitor and review advancements in gene editing technologies, and agrees that consultations with other stakeholders such as the local scientific community as well as patient advocates should be carried out before the relevant regulatory agencies or ministries revise any legislation and guidelines pertaining to the application and research involving HNGE to ensure that policies pertaining to HNGE are aligned with societal values.

For your consideration, please.

Thanks!

Best regards
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6. National Council of Churches of Singapore

Executive Summary

The following contains an executive summary of our response from The National Council of Churches in Singapore (NCCS) to the Bioethics Advisory Committee (BAC) consultation paper "Ethical, Legal and Social Issues Arising from Human Nuclear Genome Editing".[1]

1. We first set out our understanding of Christian bioethics as part of our deliberation of Christian ethics, which in turn aims to paint a picture of the Christian moral vision. The Christian moral vision is concerned with human identity and the protection and flourishing of that identity in response to the Gospel of Jesus Christ.
2. We highlight, from a Christian standpoint, the danger of the philosophy driving much of our general bioethics and biotechnology toward a vision of human flourishing that consists solely in the elimination of suffering and the expansion of the boundaries of human choice.
3. We resonate with the BAC paper on its reasonable optimism regarding the promise of HNGE, and throw caution by drawing attention to the dangers of hype surrounding HNGE. In addition, we question what are the safeguards and limits that will enable us (as humanity) to say 'enough' in our pursuit of the further developments in HNGE.
4. We reflect on the kind of collective moral vision that will likely happen in a genetically-focused or a genetically-obsessed society, and question aspects of that society where genetic solutions are sought after at the expense of other more morally appropriate or proportionate techniques, or that pre-disease risk states are treated as if they were a disease in themselves.
5. While agreeing with the BAC paper's recommendation that the '14-day rule' remains (and not be extended to 28 days), we lay out our Christian position that the nascent human being in the form of an embryo is a human person even at the earliest stage. And since human persons are made in the image of God, they possess inviolable dignity and value from conception. As such, we are unable to support any means that involves the creation, destruction, and/or the eugenic selection of human embryos. With specific reference to heritable germline editing, we hold that the inevitable alteration of our human nature will have an inimical effect on our capacity to pursue the human good in terms of our flourishing.
6. We consider the impact on society, and state our concern that the advent of widespread genetic screening and therapies will lead to a society that sees genetic diseases as a condition to be avoided at all costs, even life itself. To that concern, the church declares unambiguously that the presence of genetically compromised persons in society is good, simply because they are there and they are the gift of a loving God who welcomes us all. If this last statement is affirmed, steps must be taken to ensure that the development of HNGE in medical care and research does not come with an increase in discrimination or stigmatisation (e.g., only a certain

[1] Bioethics Advisory Committee, *Ethical, Legal and Social Issues Arising from Human Nuclear Genome Editing* (Singapore: 2024), https://www.bioethics-singapore.gov.sg/

affluent segment of society can afford it) that results in an economic distributive injustice.

7. We recommend that yardsticks be clearly stated in order that we can draw the line and distinguish between therapy and enhancement.

In conclusion, we affirm our response that the Church is neither a pure advocate nor opponent of technology or advancement. Instead, it is in being captured by our moral vision that grants us the dignity, freedom, and responsibility to choose what is right and sound, and not only what is expedient or popular. We find our bearings within that moral vision in the givens of human life, the dignity of the human person, and our care for the common good, not just the individual. The key question that is addressed in the public bioethics of gene editing is the question about what it means to be human: what vision of humanity lives at the heart of our public reasoning? To that question we are appreciative of BAC's stance that a human project as large and momentous as HNGE must continue to consider the vast wealth of human wisdom: social, political, scientific, philosophical, and, critically, moral and religious capital. In the process, we must hope and pray that we do not end up trading in wisdom for knowledge.

Introduction

In June 2023, the Bioethics Advisory Committee (BAC) published their consultation paper "Ethical, Legal and Social Issues Arising from Human Nuclear Genome Editing".[2] The National Council of Churches in Singapore (NCCS) has gratefully accepted an invitation from the BAC to respond to the paper.

The NCCS commends the BAC for a wide-ranging and cogitative discussion surrounding the vast hinterland of issues associated with human nuclear genome editing (HNGE). Given the gravity of the subject, the considerable expertise of the review group, comprehensive coverage of the issues, and careful examination are all praiseworthy features of the consultation paper.

The BAC paper covers ethical, legal and social issues. We thank the BAC for the invitation to comment on the consultation paper. As Albert Jonsen recognises, the discipline of bioethics has been enhanced by the salutary contributions of moral theology.[3] Certainly, the same is true for the NCCS and the BAC. We are grateful for the invitation to offer this paper, and what follows is not an expository critique of the BAC's valuable consultation paper but part of extending the excellent partnership that Christian moral reflection offers to the BAC and society as we reason together on the vision of human identity and the laws and public policies that exist for the protection and flourishing of humanity.

Moral Vision and Christian Bioethics

Christian bioethics is part of Christian ethics and, as such, springs forth from the response of the Church to the Gospel of Jesus Christ, a response which takes the form of loving worship and faithful witness. Christian ethics provides not one abstract rule after another but an education in a "large-scale interpretive framework with which to discern the meaning of things in relation to God."[4] Christian bioethics aims to situate developments in life in their proper relation and, therefore, to their right status.

The temptation to reduce bioethical discussions to specific technologies or concrete case studies arises from a view of ethics as a tool to resolve or illuminate dilemmas, cases of conscience or moral quandaries. Yet, as has been cogently argued by theologians such as Stanley Hauerwas, focus on moral quandaries neglects how quandaries are construed. What appears to one as a moral quandary may, in fact, be the result of one's moral vision. As Hauerwas rightly observes, "'Situations' are not 'out there' waiting to be seen but are created by the kind of people we are."[5]

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[2] Bioethics Advisory Committee, *Ethical, Legal and Social Issues Arising from Human Nuclear Genome Editing* (Singapore: 2024), https://www.bioethics-singapore.gov.sg/

[3] Albert R. Jonsen, *The Birth of Bioethics* (Oxford: Oxford University Press, 1998)

[4] John F. Kilner, ed., *Why the Church Needs Bioethics* (Grand Rapids, MI: Zondervan, 2011), 175.

[5] Stanley Hauerwas, *The Peaceable Kingdom: A Primer in Christian Ethics* (London: SCM, 1984), 116.

For this reason, one of the priorities of Christian ethics, bioethics included, is to distance itself from purely issue-centred bioethics. Christian bioethics has a goal of communal shaping and discernment of the Church. This ethical discernment is a corporate activity, not just the sole preserve of theologians or ethicists. It cannot evade broader questions of justice, such as costs, data privacy, proper governance, or resource allocation.

Most of all, Christian bioethics cannot narrow its focus simply to biomedical research, practice, and regulation. It extends its gaze wider to the social and ecological dimensions of biomedical research and practice and to the cultural commitments which they embody. This is even more acute than in questions raised by the spectre of HNGE in conjunction with other developments such as Big Data and Artificial Intelligence.[6] The rapid advances and technological developments in these areas make this a frontier science. This underlies the unsuitability of an issue-by-issue response, not least because there is no conceivable situation where our capacity for moral reflection can keep pace with new technologies as they appear on the horizon.

Reflection is needed on the underlying frameworks of thought and practice that have helped create these technologies and will continue to shape their future development—a failure to consider these limits bioethics to attend only to presenting issues of each new technology. But to do so is to admit of a failure to understand any such technology meaningfully. Without an appreciation of these developments' underlying cultural and ideological currents, bioethics is doomed to be endlessly reactive, only capable of responding if and when the next moral crisis over a technology erupts. In recent memory, one landmark case in genetic technologies is that He Jiankui, a genome-editing researcher who claimed to have impregnated a woman with embryos edited to turn off the genetic pathway HIV uses to infect cells. Reporting on the international outrage, David Cryanoski and Heidi Ledford nonetheless note that "many in the field thought it was inevitable that someone would use genome-editing tools to make changes to human embryos for implantation".[7] In the face of the seemingly unstoppable juggernaut of technology, and perhaps the immovable temptation to deploy these technologies, we need sustained reflection which attends to the broader historical and cultural movements that animate our moral sense of these technologies.

Christian bioethics is committed to just such reflection, not least because it is interested in going beyond solving dilemmas to perhaps more fundamentally articulating the moral vision that illuminates and reveals whether these dilemmas genuinely exist or are conditioned by the way we have come to see things.

The Baconian Project

An example of this is Gerald McKenny's *To Relieve the Human Condition.* McKenny traces the modern bioethics project to what he calls "the Baconian project", named after

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[6] See "NCCS Response to Big Data and Artificial Intelligence in Human Biomedical Research", 2023.
[7] David Cyranoski and Heidi Ledford, "International outcry over genome-edited baby claim," *Nature* 563 (November 2018), 608.

the British philosopher Francis Bacon.[8] The project centres on two imperatives: eliminating suffering and expanding the boundaries of human choice. This had its roots in the convergence of practical compassion to secure the well-being of one's neighbour with a new natural science that disposed of a classical teleological account of nature in favour of a mechanistic philosophy of efficient causes. This rendered nature suitable for technological and instrumental control, which could be manipulated at will to benefit human beings. This, together with subsequent developments in utilitarianism, reduced the determination of human good to a calculus of pleasure and pain. With this grew an increasing doubt about finding any meaning in suffering. Suffering, therefore, became something to be avoided or eliminated wherever possible. Contemporary ideals of individual autonomy allied with developments in technology that dramatically increased the scope of our medical interventions have only fuelled the emphasis on self-determination in relation to one's body. As McKenny puts it, "the commitment to realise one's uniqueness leads to cultural expectations that medicine should eliminate whatever anyone might consider to be a burden of finitude or to provide whatever anyone might require for one's natural fulfilment."[9] The body, in other words, is subordinated to the autonomous will with the expectation of its indefinite plasticity. The human good has been reduced in the modern moral imagination to something essentially biological.

McKenny's erudite account of the Baconian Project and others like it help us see through the fog of technological quandaries in the present.[10] The upshot is that we can more clearly see the existential dimension of modern biotechnology. By showing how existence is conceived as a matter of escaping the clutches of blind fate by means of technology, McKenny helps us to see how modern bioethics might be complicit with absolutist commitments to personal liberty, technological control, and relief from actual and potential suffering. Any alternative view which asks not how biotechnology can be subordinated to the desire to transcend the fragility of human existence but instead how sickness and health might be integrated into a morally valuable life that has come to terms with finitude and mortality is, as a matter of course, dismissed. Insofar as mainstream bioethics is unavoidably and unwittingly complicit in this project of personal autonomy, technological mastery, and relief from suffering, it is unlikely to be able to sustain any substantial critique of it. This reductive vision of the body is what Pope Francis calls the technocratic paradigm: an endless search for control over nature.[11]

In such a mode, bioethics might even arise from a similar desire to master contingency and relieve the human condition. In the face of chance and fate, ethics becomes a form of justification, a way of elevating ourselves above the auspices of pure chance and assuaging our conscience of having done our very best to do what is right in our own eyes. Karl Barth's observation that "what the serpent has in mind is the establishment of

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[8] Gerald McKenny, *To Relieve the Human Condition: Bioethics, Technology and the Body* (Albany, NY: State University of New York Press, 1997). What follows is a *precis* of his argument in 17-24.
[9] Ibid, 20.
[10] Another salient example of this kind of broader analysis is Charles Taylor's *Sources of the Self. The Making of Modern Identity* (Cambridge: Cambridge University Press, 1989).
[11] Pope Francis, *Laudato Si,* especially §106-114.

ethics" is a salubrious reminder that a bioethics unaware of its complicity in such projects stands in danger of the idolatry of self-justification.[12]

It goes without saying that Christians do not uncritically reject all individual technologies that attempt to relieve suffering or elevate the human condition above the level of fatalism. Relieving suffering and exercising choice are not bad goals. On the contrary, Christians accept that it is precisely because they are good that it is difficult to recognise when they might be distorted or alloyed with ideals which are morally problematic.[13] The aim of restoring health is proper to the right exercise of biotechnology, but it is another thing altogether to reform it.

The fact is that Christian bioethics can offer to the world much more than our caution. We can and do confidently speak of the distinctive witness of the Church that unmasks idols, deflates unreasonable expectations, liberates us to ask how much medical and technological progress is suited to the flourishing of humanity, fears no irrelevance more than irrelevance to God, and also confidently asserts God's desire for the healing of the nations.[14]

Human Nuclear Genome Editing

The BAC consultation paper is laudable for its clear-eyed articulation of issues related to HGNE. The paper does not gloss over the severity of concerns raised by the development and deployment of HNGE, such as mosaicism, off-target effects and other undesirable consequences. It rightly raises questions over safety and long-term effects, particularly because the technology is still considered in its nascent phase. Other issues addressed include the procurement and use of human embryos and oocytes for research, the allocation of resources and access to these new technologies, and questions of governance and framework.

The paper does not only cover bioethical points of concern. Fittingly, the paper highlights many promising ways that HNGE might be applied in research and clinical applications to treat diseases. Promising applications of HNGE discussed in the paper include cancer research to understand tumorigenesis, developing effective treatment modalities for targeting tumour cells, growth in understanding genetic mutations that lead to neurodegenerative diseases, and genetic enhancement for conferring resistance to diseases.[15]

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[12] Karl Barth, *Church Dogmatics*, IV/1 (Edinburgh: T&T Clark, 1956), 448. An observation that augments our application of Barth's axiom is that secular bioethics around the world has integrated much of what was once morally and scientifically controversial into medical practice: abortion, surrogacy, organ transplantation, gender reassignment surgery, plastic surgery and so on.

[13] Robert Song, *Human Genetics: Fabricating the Future* (Cleveland, OH: Pilgim Press, 2002), 118.

[14] Robert Song, "Christian Bioethics and the Church's Political Worship", *Christian Bioethics* 11:3 (2006), 347.

[15] For this and other benefits addressed, see Bioethics Advisory Committee, *Human Nuclear Genome Editing*, 45-57.

However, as mentioned earlier, if Christian bioethics is to meaningfully contribute to the discussion of HNGE, it must raise questions about the broader currents situating the development of genetic biotechnologies.

HNGE: Hope or Hype?

In 1997, Craig Venter and Daniel Cohen, two of the world's leading genetic scientists at the time, published an article declaring the 21st century "the century of biology". According to Venter and Cohen's exuberant description,

> for the first time, we will have a complete description of life at the most fundamental level of the genetic code. This map will describe for us the exact content and structure, not only of each and every gene associated with a species but also the precoded information… that controls when a particular gene is turned 'on' or 'off', leading to a biological effect. In humans… this means we will know exactly what genetic predisposition makes a person susceptible, say to prostate cancer or Alzheimer's disease. We will also know how to manipulate a gene to produce blue eyes or dark skin.[16]

Yet, the same year this article was republished, Elizabeth Pennisi also cooled Venter and Cohen's seemingly untrammelled optimism by explaining that "molecular biologists may have sequenced the human genome, but it's going to take molecular cryptographers to crack its complex code." As she goes on to explain, genes cannot by themselves provide full explanation for what makes cows cows and corn corn, as "the same genes have turned up in organisms as different as, say, mice and jellyfish." In fact, Pennisi suggests that it is not the genes *per se* but the genome's control of each gene's activity that matters the most.[17] To say that humans share 98% of our genes with chimpanzees, most of our genes with mice, or even 50% of our genes with flowers might imply that we are genetically related to plants, close to mice, and practically siblings with primates. Yet the truth is, as Celia Deane-Drummond states, the same gene can code very different physical characteristics or phenotypes.[18]

It must be said that the BAC paper does not hit the same optimistic heights as Venter and Cohen. The paper relies on established principles of bioethics, such as solidarity, sustainability, proportionality, and justice, to anchor and temper the expectations of HNGE in research and clinical applications. The paper repeatedly asserts the need for further studies on HNGE in different contexts to be conducted to understand its consequences fully.

The truth is that, as Joshua Hordern has perceptively pointed out, HNGE emerges amidst an ethos of promise, and there is a real cost to lives because human finitude

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[16] The 1997 article was republished later in Craig Venter and Daniel Cohen, "The Century of Biology", *New Perspectives Quarterly* 21 (2004): 73.
[17] Elizabeth Pennisi, "Searching for the Genome's Second Code", *Science* 306: 5696 (2004): 632.
[18] Celia Deane-Drummond, *Genetics and Christian Ethics* (Cambridge: Cambridge University Press, 2006), 125.

means that promises always involve uncertainty.[19] There is always the danger that the scientific community and society might lose themselves in the idea and promise of precision medicine and for that promise to become distorted into hype. Lurking nearby is the related danger of immodest promises.

Hordern draws our attention to how hyped-up promises shape people's lives and the procedures they might consent to in response to the hope or fear engendered by the promise of HGNE. For example, he cites how patients being excluded from certain trials led to immense disappointment or pressure to participate in future trials. In his reading, there is a need for more qualitative research on the perception of risk and the future. Furthermore, he explains that the patient's journey can be disrupted as compassionate companionship suffers in the face of rising complexity. As research or clinical pathways cease or fragment, the patient nonetheless journeys through life towards suffering, disability, and even death.[20]

For researchers, Hordern asks if the promise of precision in fields like HNGE might so captivate researchers so as to unduly pressure them to ensure that trials don't fail. In other words, there is a felt requirement to make history right. For policymakers and governments, Hordern posits that the promise of precision medicine is that it seems to bypass intractable problems in societal health and that it seems to be at the cost of further attention to other important aspects of treatment, such as patient behaviour and environmental outcomes. Hordern's description of the costs of the hype and promise of HGNE matches Theresa Feiler's description of genomic medicine and the way the scientific community thinks of it. In Feiler's view, the promise of genomic medicine can result in an environment where "critique is seen as suspicious: anti-progressive and Luddite" because the inward discovery of humanity was said to culminate in the genome.[21] In such an environment, diverting resources from genomic research can be controversial.

Our responsibility is to complement the BAC consultation paper by drawing attention to the dangers of hype surrounding HNGE. The question of overhyping or fantastic promises about HNGE raises a cluster of related issues. One such issue, already hinted at earlier, is our gap in knowledge of both intended and unintended consequences. Somatic gene therapy, for example, raises the possibility of mosaicism or insertional mutagenesis, which can result in cancer. We simply have no way of knowing the long-term outcomes of gene therapy. A study published in 2010 showed that four out of nine patients who received gene therapy for SCID-X1, a congenital immunodeficiency, developed acute leukaemia. Although the therapy successfully corrected the immune dysfunction, the

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[19] Swiss Academy of Medical Sciences, *Summary Report of the FEAM Conference 2018 on Precision Medicine and Personalized Health* (Geneva: 2018), 23.
[20] Joshua Hordern, "Ethical Imperatives for Personalised Medicine: A Costly Promise?" (Presentation, FEAM Conference 2018 on Precision Medicine and Personalized Health, Geneva, September 28 2018).
[21] Theresa Feiler, "The Ontology of Personhood: Distinguishing Sober from Enthusiastic Personalised Medicine", *Studies in Christian Ethics* 32 No. 2 (2019): 257.

treatment is associated with a significant risk of acute leukaemia. The follow-up period was a median of nine years.[22]

The most famous example of somatic gene therapy producing lethal side effects was the case of Jesse Gelsinger, who died in 1999 after a somatic gene therapy trial for ornithine transcarbamylase deficiency. A healthy volunteer who had suffered only relatively mild effects of the disease, Jesse died in phase I of the trials, four days after receiving his first injection of the trial.[23] Other examples include two boys in another SCID trial who developed leukaemia and a haemophilia trial that was halted because seven patients developed signs of mild toxicity.[24]

Our mention of these examples is not to cast aspersions on the genuine promise of HNGE. Gene therapy is complex, and reductionist conclusions fail to consider poorly understood or unexpected factors such as immune response, environmental effects, pleiotropy or variable expressivity, and reduced or incomplete penetrance. Researchers must be prepared to admit that a veil of ignorance still hangs over our genetic knowledge. Gene-editing targeting specific somatic diseases is, in some ways, a frontier medicine, and building on prior research is only sometimes possible. Even with research, as is the case for the SCID-X1 study, it could take up to nine years to confidently conclude both gene therapy's success and dangers. When a deleterious mutation is edited out, the consequences of the edit may not be fully known, especially in cases where mutations have multiple implications for an organism.

The incompleteness and opacity of our knowledge challenge the principle of informed consent. It would be difficult to explain or get a firmer grasp on the perception of risk and reward. Regarding the hype, there might be a tendency to over-promise or overly optimistic in benefit projections, especially when researchers seek consent. We would be cautious of the potential of HNGE generating a mystique of unrealisable promises and undeliverable expectations about precise genetic treatments. Tim Maughan explains that biomedical research is "suffused with optimism" regarding the ability to "deliver massive improvements in clinical outcomes, built on the remarkable benefits of novel therapeutics in disorders driven by a single genetic alteration."[25] This can lead to destructive risks in research funding where grants are allocated to areas of apparent (but overhyped) success to the detriment of other important areas. It also risks exaggerated expectations distorting clinical commissioning. Perhaps most concerning is the risk Maughan outlines of abandonment of proven ways of treatment for a highly risky, unrestricted use of novel therapies in the hope of a breakthrough.[26] The risk of hype affecting clinical consultations, resource allocation, and funding prioritisation is real. We will need sober-minded researchers and policymakers who can communicate when one

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[22] Salima Hacein *et al*, "Efficacy of gene therapy for X-linked severe combined immunodeficiency," *The New England Journal of Medicine,* 363 No. 4 (2010): 355-64.

[23] Adam Bostanci, "Blood Test Flags Agent in Death of Penn Subject," *Science* 295 No. 5555 (2002): 604.
[24] As mentioned in Celia Deane-Drummond, *Genetics*, 129.
[25] Tim Maughan, "The Promise and the Hype of 'Personalised Medicine'," *The New Bioethics* 23 No. 1 (2017): 16.
[26] Ibid., 17-19.

might reasonably expect wide-scale genetic therapies. Indeed, ensuring that HNGE and technologies like CRISPR "do not become touted as a panacea for all genetic illness is crucial for proper application and dissemination of the technology."[27]

We would raise one final caution on the promise of HNGE. As the BAC paper rightly emphasises, any proposed applications or research must first have evidence of its safety and efficacy. This is right; if any treatments were unsafe or ineffective, they would be morally impermissible on even the most permissive analysis. Given the examples above, this raises the issue how researchers, doctors, and scientists might consider forms of gene editing, the long-term effects of which are not, in principle, determinable or reasonably predictable. We would counsel policymakers to reserve the freedom to say perhaps that some forms of editing – such as heritable germ-line editing – are off-limits. In any case, Bill McKibben's *Enough* helps us to ask ourselves a question: can humanity learn to exercise our ability to say *enough* when it comes to new technologies, or are we destined to lust for more and higher capacities that cloud our human capacity to say no?[28]

A sober approach to HNGE will, without doubt, prize the role that genomics can play in the medical care and cure of disease, but in a way that situates it properly as one of a suite of treatment options. Christians take seriously the reality of suffering and certainly treat death as the last enemy. But we do not see suffering and death as something to be denied, in the final place, at all costs; neither do we view death as a traumatic failure of technology. Against the backdrop of choice, consent and control as noble but ultimately futile means of eradicating death, Christianity offers us the theological virtue of hope, which allows us to trust in God's providence, knowing that his plan is far superior to our fears and efforts to overcome them.[29] A sobered optimism – hope, not hype – in HNGE faces up to rather than postpones engagement with human limits and frailty.

The Danger of Overmedicalisation in An Overtly Genetically Focused Society

Christian bioethics is concerned with moral vision, character, and agency. That is to say, it is not simply issue-based dilemmas we are concerned about, but the kind of moral vision that society seeks to instantiate and by which it views reality. This, as has been mentioned, is important because our moral vision frames whether something occurs to us as a problem or not. One example of this is seen in genetic screening. The BAC paper refers to HNGE in research in terms of helping us to understand the pathology and aetiology of diseases. One such example is in the area of prenatal screening. Celia Deane-Drummond thinks that once a pregnant woman has accepted the invitation to be screened, she has ventured on a path that almost inexorably leads to medical intervention. Since the most likely form of treatment following the discovery of a genetic

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[27] Arther Caplan *et al*, "No Time to Waste – The Ethical Challenges Created by CRISPR," *EMBO Rerports* Vol. 16 No. 11 (2015): 1426.
[28] Bill McKibben, *Enough: Staying Human in an Engineered Age* (New York: Henry Holt Co., 2003)
[29] Joseph Tham, "Resisting the Temptation of Perfection", *The National Catholic Bioethics Quarterly* 17.1 (2017): 61.

disease is likely termination, the number of live births judges the effectiveness of genetic screening. "That is to say, the number of terminations is considered to be the measure of the effectiveness of genetic services."[30] Here, the dark shadow of negative eugenics casts a pall on genetic screening.

One could argue that the dark shadow of negative eugenics would be dispelled if genetic screening led to therapeutic uses of HNGE. However, it is worth pausing to ask what would happen if mass screening and treatment were *di rigeur.* In effect, we would all be patients, all with a genetic profile that lists our propensity for disease. What kind of life would we lead if we discovered all the diseases that could or are likely to affect us in the future? Genetic prediction leads to the expectation that we would manage the present by adjusting our lives according to these genetic parameters. Christiane Woopen predicts that the future will be where "more and more tests are done, more and more diseases feared, the worries about health take on a growing space in people's consciousness, in their responsibility and lifestyle."[31] Likewise, Giovanni Maio thinks that

> the more we know about predispositions through genetic testing, the more our health and our diseases will seem to be results, products of our own actions, indeed products of our own will… In return, the person who is ill will be confronted with the underlying question of why they became ill and, if not genetically advised, whether they could not have prevented the outbreak of the disease by taking a predictive genetic test.[32]

This should prompt reflection on the kind of collective moral vision happening in a genetically focused society. Would a genetically focused society be in danger of tending towards dehumanisation? Would a genetically focused society overlook other ways of addressing issues? One possible answer to this could be to refer back to He Jiankui's attempt at clinical gene editing for the sake of genetic enhancement. His stated goal was to make babies more resistant to HIV infection because so many children in China are affected by the virus and face discrimination.[33] However, HIV infection can be avoided altogether by non-genetic means. Discrimination is also a social problem rather than a medical one. His stated motivations for his maverick experiment seem particularly ill-fitting and serve as a reminder that a genetically focused society may reach for genetic solutions at the expense of other more morally appropriate or proportionate techniques.

What we mean by proportionality and HNGE can be illustrated with reference to the Christian just war tradition. Oliver O'Donovan reminds us that proportion has to do with the "rational form which such an act assumes", that is to say, with the shape of a successful act of judgment. On the one hand, an act of judgment is reflexive. It looks

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[30] Celia Deane-Drummond, *Genetics*, 90.
[31] Christiane Woopen, "Individualisierte Medizin als zukunftsweisendes Leitbild", as quoted by Feiler in "The Ontology of Personhood," 259.
[32] Giovanni Maio, "Chancen und Grenzen der personalisietern Medizin – eine ethische Betrachtung, as quoted by Sebastian Wäscher, "'Personalised Medicine' in Oncology: Physicians' Perspectives on Contributions to and Challenges for Clinical Practice", in Jochen Vollmann, et al, eds., *The Ethics of Personalised Medicine: Critical Perspectives* (Abingdon: Routledge, 2015).
[33] Suzanne Sataline and Ian Sample, "Scientist in China defends human embryo gene editing", *Guardian* Nov 28 2018.

backwards, pronouncing a judgment on a current state of affairs brought about by previous acts or failures to act. This requires a "truthful description of what the wrong that is done." On the other hand, since an act of judgment also looks forward, it must be proportionate to the state of affairs which it attempts to bring about. What is undertaken must correspond to what is purposed, and what is purposed must correspond to a reasonable complaint. [34] As Hugo Grotius says: "The danger must be immediate… those who accept fear of any sort as a justification for preemptive slaughter are themselves greatly deceived and deceive others."[35]

The Christian just war teaching on proportionality might be meaningfully applied to preventative measures and the treatment of risk. Paul Scherz's caution against the increasing encroachment of healthcare in terms of mitigating and reducing risk comes to mind. For Scherz, seeing health in terms of reducing the risk of disease quickly slides into defining the risk itself as a disease. Interventions to reduce risk lead to increased risks, uncertainty, excessive medical expense, and iatrogenic effects.[36] This also endangers our moral vision by reinforcing an unhealthy focus on efficiency and autonomy. Moreover, because there is an unlimited scope for risk reduction, the focus tends overtly to individual changes rather than social changes, undermining care for the common good and solidarity. Endless individual medications or interventions replace social changes in light of risk calculations based on individual genetic sequences.[37]

Furthermore, in *Risk Society*, Ulrich Beck argues that

> gene technology puts humankind in an almost godlike position, in which it is able to create new materials and living creatures and revolutionise the biological and cultural foundations of the family. This generalisation of the principle of design and constructability… exponentiates the risks and politicises the places, conditions and means of their origin and interpretation.[38]

In other words, the possibility of genetic intervention heightens rather than reduces anxiety about the future. A risk-averse society attempts to tame chance by making interventions based on probabilistic guesses derived from genetic services – screening, counselling, prenatal diagnosis, etc.

In our view, one of the dangers of the promises of HNGE is the slide towards treatment of pre-disease risk states as if it were a disease, thus uncritically sanctioning the genetic equivalent of a pre-emptive strike. Biotechnological triumph, in this construal, can

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[34] Oliver O'Donovan, *The Just War Revisited* (Cambridge: Cambridge University Press, 2003), 48; 52.
[35] Grotius, *De iure*, 2.1.5.
[36] Paul Scherz, "Risk, Health, and Physical Enhancement: The Dangers of Health Care as Risk Reduction for Christian Bioethics,", *Christian Bioethics: Non-Ecumenical Studies in Medical Morality* Vol 26. No. 2 (2020), 146.
[37] Consider, for example, Nicanor Austriaco's argument to make people "healthier than healthy", as he argues in favour of a genetic therapy to eliminate the function of the *PCSK9* gene, resulting in greatly reduced blood LDL levels. Austriaco seems to suggest that there is no straightforward response to how low LDL levels should be, opening up the endless pursuit of lower numbers beyond even traditional LDL thresholds indicative of health. Nicanor Austriaco, "Healthier than Healthy: The Moral Case for Therapeutic Enhancement", *The National Catholic Bioethics Quarterly* 17 No. 1 (2017): 43-9.
[38] Ulrich Beck, *Risk Society: Towards a New Modernity* (London: Sage, 1992), 51-2.

become an end in itself, rather than traditional forms of healthcare that see medical interventions for the reasonable and feasible goal of restoring a patient's health. A forward-looking proportion must proportion an action in relation to its end. Our concern is that a failure to discuss these ends will lead to a failure in proportionate discriminatory acts of judgment. This is a kind of deficiency of moral vision and judgment that the Church should be on guard against.

HNGE and the Human Future

The question of moral vision leads us to reflect deeply on the bioethics of future possible applications of HNGE to gene editing in embryos, germline editing, and even heritable gene editing for clinical applications. As the BAC paper observes, heritable gene editing is currently under a worldwide moratorium. Yet human ingenuity and technological progress are not to be dismissed. The discovery of CRISPR made targeted gene editing possible in ways researchers and scientists could not imagine before. Even if the technology or the will to heritable gene editing is further afield, it behoves us to consider what bioethics limits, if any, exist to aid our reflection. There is a feedback loop between our ideals of autonomy and the technologies we craft to pursue those ideals. If we are beholden to something like the Baconian Project, then not only will our norms guide our innovations – but our subsequent innovations will also shape or focus our norms. We must not easily dismiss the culture-shaping form of technology. Those who choose the beginnings of a road also choose its destination. The issue of embryonic and germline genetic interventions concretises what we are getting at, regarding notions of unqualified autonomy, mastery over nature, and the flight from suffering and contingency.

We note at the outset that it would be near-impossible to discover the myriad undoubted benefits of heritable or germline gene editing without multi-generational tests, including the developing human in embryonic form. If there were fewer limits on the creation of embryos, e.g., allowing embryos to be genetically modified to study the relationship between genetic deficits, mutations and disease pathology, we would probably learn much more than we already know. The BAC consultation paper refers to a '14-day rule', a limit against developing human embryos for research after the 14th day of development. Raising the example of researchers in other countries calling for the 14-day rule to be doubled to 28 days, the BAC rightly deems this to be premature, and the BAC's position is that the 14-day limit should remain unchanged for now.[39]

But should the 14-day rule stand? The question of the moral status of the early embryo is most clearly seen in pre-implantation genetic diagnosis and embryo creation for research. It is also relevant to germline gene therapy and editing because this would most certainly require the destruction of at least some embryos or the discarding of embryos in the case of unsuccessful procedures. The 14-day rule is sometimes built on arguments that before 14 days and the appearance of the primitive streak, the embryo is more akin to a mass of undifferentiated cells, each containing the potency to specialise into any cell in the body. Only after the appearance of the primitive streak does it become an organised whole with

[39] Bioethics Advisory Committee, *Human Nuclear Genome Editing*, 72.

the capacity to develop into a unique human individual. Because twinning also happens in the first 14 days, some argue that genuine personhood, and therefore the moral rights that accrue to the embryo, only starts after 14 days.[40] Another popular argument about personhood appeals to developmental notions of personhood, where an embryo grows into a person.[41]

As Roland Chia has explained, according to the Christian faith, human beings made in the image of God possess inviolable dignity and value from conception.[42] The Church's stance is that the nascent human being in the form of an embryo is a human person even at the earliest stage. Any means that involves the creation, destruction, and/or the eugenic selection of human embryos is something we simply cannot support. All approvable therapy means should respect the inviolable life and bodily integrity of all individuals involved. Embryonic human beings, as living members of the species, must be included in the mutual networks of giving and receiving the likes of which every human being depends for existence and flourishing. Their good is as integral to the human good as is the good of others. Furthermore, we should not simply regard the embryo as just any person but recognise the embryo as someone's *child*.[43] The question of the status of the embryo, in Christianity, turns not only on the embryo's moral status but also on the networks of relations the embryo will be a part of throughout his or her life. Christianity, in the main, does not rely on prevarications of personhood because "to be willing to kill what for all one knows is a person is to be willing to kill a person."[44] For this reason, we disagree strongly with any destructive interference with the embryo, even surplus embryos created by IVF.[45] The status of the embryo demands our respect.

Some examples of what this might mean in practice would be that we treat embryos as patients and not mere experimental subjects. If interventions, especially genetic ones, are to be made at the level of embryonic life, they should, as a matter of course, be directly related to the safety and health of the embryo. In our view, this rules out the creation of embryos for the express purpose of genetic research. But even allowing for gene therapy at the level of embryonic life, our knowledge of what gene editing does to the embryo is still far too primitive and uncertain at this juncture for it to be commended. For example, Nada Kubikova reports that the cells of early human embryos often cannot repair damage to their DNA, which has implications for CRISPR gene editing. Kubikova's

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[40] So, for example, Norman Ford, *When Did I Begin? Conception of the Human Individual in History, Philosophy and Science* (Cambridge: Cambridge University Press, 1988), 136.
[41] This is the argument in Michael Tooley, *Abortion and Infanticide* (Oxford: Oxford University Pres, 1984).
[42] Roland Chia, "Embryo Editing", *ETHOS* (Feb 4, 2019), https://ethosinstitute.sg/embryo-editing/ (accessed 20 Aug, 2024)
[43] O. Carter Snead, *What It Means To Be Human: The Case for the Body in Public Bioethics* (Cambridge, MA: Harvard University Press, 2020), 134.
[44] Germain Grisez, *The Way of the Lord Jesus: Living a Christian Life* (Quincy, IL: Franciscan Press, 1993), 497.
[45] As, for example, recommended in the Bioethics Advisory Committee, *Human Nuclear Genome Editing*, 75: "Researchers should consider using surplus embryos created through assisted reproduction treatment for HNGE research if the risks of procuring oocytes solely for such research outweighs the benefits." We note also that the later discussion (pp. 75ff) in the BAC paper of respect for persons and risks involved in embryonic research appear to operate on the premise that the embryo is not a person, since questions of risks to the embryo or respect for the embryo are not discussed.

report showed that in their study, 40% of double-stranded breaks caused by gene editing remained unresolved, eventually causing segmental abnormalities known to be detrimental to viability and higher risks of congenital abnormalities. In their view, "the results provide a warning against the therapeutic use of CRISPR-Cas9 in human embryos.[46]

One possible consequence of this discovery would be increasing attempts to correct genetic mutations upstream of fertilisation. But editing at this level casts into relief a whole host of other concerns. The shadow of eugenics writ large in the 20th century is certainly one concern. However, other concerns might be raised regarding cultural preferences, what constitutes genetic therapy or genetic enhancement, equitable access and resource allocation, and increased discrimination or stigmatisation for adopters or rejectors of such techniques. Is science and biotechnology simply the craft of manipulating, substituting, and deflecting the forces of nature? Surely not.

Returning, however, to the question of heritable germline editing, the NCCS simply notes that there is a profound Christian tradition of moral and theological reflection on human nature and human limits. This line of thinking is what we might broadly term the natural law tradition. This tradition teaches that we can discover, within our nature, obligations and laws that dictate our behaviour.[47] These truths of human nature are perennial because they are a metaphysically grounded basis for human nature and are thus integral to our understanding of what constitutes human flourishing and the design willed by God.[48] That is to say, humanity's flourishing consists of the fulfilment of our shared human nature. The natural law is that which, if followed, will satisfy our inclinations in accord with reason and help actualise our definitive capacities.[49] Gene editing that alters our human nature has an inimical effect on our capacity to pursue the human good in terms of our flourishing. This is not to say that there is no horror in nature. Good medicine understands, respects, and treats that. But there is also plenty of order and significance in nature that is worthy of respect – including a healthy respect for limits. Would, for example, human eyesight be *truly* human if we could enhance our eyesight to the levels of animal eyesight?

Ronald Cole-Turner aptly states that "genetic engineering will change nature by altering the genetic arrangement inside living things" since it would alter the "inward principles that guide" human development, inward principles that once "set limits both physical and moral on our technological alterations."[50] To place nature beyond human responsibility is simply to acknowledge the limits of our knowledge and powers. To

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[46] Nada Kubikova *et al*, "Deficiency of DNA double-strand break repair in human preimplantation embryos revealed by CRISPR-Cas9", *Human Reproduction* Vol. 38 No. 1 (2023).
[47] Joseph, "The Decline of Natural Law Reasoning: The Influence of Recent Cultural and Intellectual Currents on the Tradition," *The National Catholic Bioethics Quarterly* 14.2 (2014): 245-255.
[48] Tham, "Resisting the Temptation", 55.
[49] For a helpful treatment of this, see Richard Berquist, *From Human Dignity to Natural Law: An Introduction* (Washington, DC: Catholic University of America Press, 2019). The definitive natural law thinker in the Christian tradition is Thomas Aquinas, who discusses this at length in *Summa Theologiæ*, in the so-called Treatise on law, IaIIæ, Q.90-108.
[50] Ronald Cole-Turner, *The New Genesis: Theology and the Genetic Revolution* (Lousiville, KY: Westminster John Knox Press, 1993).

suppose that nature has a moral order and teleological purpose that we should respect is to impose limits on those powers. The Genesis account of humanity's fall tells us that nature became hostile and lost its moral order as a result of human acts; the temptation we have before us now is to use that knowledge and ponder the possibilities that await us as we attempt to reconstruct a second nature. Perhaps some boundaries, such as those that limit attempts to reform human nature in our image, constitute such a considerable hedge that, for all intents and purposes, research into changes to our human nature should be considered morally impossible.

Engineering the human genome, especially in relation to future generations, makes us increasingly responsible for human nature. The issue of the human future looms large in these questions. Christianity compels us to consider the moral severity of consequences to later generations. Should we genetically modify our children or modify in ourselves heritable genes that can be passed down to subsequent generations of progeny? C.S. Lewis warns us that what we call man's power over nature can often turn out in reality to be some men's power over other men, with Nature simply as the locus of the exercise of that power. "All long-term exercises of power… must mean the power of earlier generations over later ones."[51] One way in which C.S. Lewis's warning might be helpful is in considering the mythology of parental rights over our children, especially in relation to heritable gene editing. Karl Barth, however, is surely right to remind Christians that

> it is one of the consolations of the coming kingdom and expiring time that this anxiety about posterity… that we should and must bear children, heirs of our blood and name and honour and wealth… is removed from us by the fact that the Son on whose birth alone everything seriously and ultimately depended has now become our Brother. No one now has to be conceived and born. We need not expect any other than the One of whose coming we are certain because He is already come. Parenthood is now only to be understood as a free and in some sense optional gift of the goodness of God.[52]

Thus, children are never really ours in an absolute sense. We do not own them, and we do not have sole preserve over the moral order of the future. Since children are gifts, genetic editing for restoring health or treatment should be seen as part of our moral responsibility to care for and nurture God's gift of children. Issues arise where children are regarded as the objects of production, which opens the door to genetic editing for enhancement, such as genetic engineering to enhance features of future children, to engineer novel features, and to revise behavioural tendencies, for example.[53] One might object that many of these technologies are a matter of science fiction, not science fact. But once more, we would reiterate an earlier point: moral vision and unmasking hidden idols are as crucial in Christian bioethics as are issues or cases. Ethical and policy discussion concerning the use or potential use of genetic technologies for these ends is already underway, and discussion on this also shapes the kinds of technology we aspire

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[51] C.S. Lewis, *The Abolition of Man* (New York: Macmillan, 1947), 69.
[52] Karl Barth, *Church Dogmatics* III/4 (Edinburgh: T&T Clark, 1961), 266.
[53] A good discussion of this can be found in Roberta Berry, "The Posthumanist Challenge to a Partly Naturalized Virtue Ethics", in Mark Cherry, ed., *The Normativity of the Natural: Human Goods, Human Virtues, and Human Flourishing* (New York: Springer, 2009).

to create. The quest to develop better gene editing tools to precisely engineer children to engineer them in the ways mentioned above or to design new capacities is not conceptually unimaginable.

A final concern must be raised on this. Will the desire to grant advantages to our offspring through genetic enhancement potentially alter genetic inheritance in unpredictable ways? When we take up the project of shaping future generations in such a fundamental way, we cannot state with any degree of certainty what good or ill we may accomplish. Our understanding of the interactions among and between genes, gene expressivity, epigenetics and environmental factors is underdeveloped. There is a veil of ignorance about many of these. To be precise, we do not know what project we are undertaking.

Even if an enhancement – longer life expectancy, for example – is regarded as an intrinsic good, the question remains if the risks and uncertainties of off-target effects or long-term devastating genetic diseases released into the public have been considered. Virtues of solidarity and care for the common good are not always the priorities of a project aimed at freeing the individual from the vicissitudes of life. The NCCS expresses our firm conviction that policies and research in this area prioritise moral commitments to the present and future generations. There can be no societal obligation to provide non-natural endowments that may create new capabilities foreign to human nature.

The Impact on Justice and Society

Talk of future generations can sometimes disguise the painful reality of eugenics. It bears mentioning that the actual victims of eugenics are those silenced lives who will never be given the chance to exist. After all, "the investment of a genetic disease with the spectre of an inevitably terrible life and early death fuels the sense that genetic screening is not only necessary but the only possible response."[54]

Understandably, the mention of eugenics in genomic medicine and research seems unfairly offensive. After all, it must be made clear that there is nothing in the BAC consultation paper to suggest any move towards the kind of cruel eugenic atrocities perpetuated in human history. However, the BAC rightly picks up on how gene editing for screening and prevention of disease might require little innovation to be applied for genetic enhancement. This, they warn, might lead to the development of programs of preferential reproduction of more desirable humans, a development the BAC claims "borders on eugenics".[55]

But, perhaps even that is not far enough. Robert Song warns us that "eugenics may not so much have died as adopted a new mask" in "the pre-natal screening suite, the genetic counsellor's office, the general practitioner's surgery, the abortion clinic."[56] Elof Carlson

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[54] Rebecca Steinberg, *Bodies in Glass: Genetics, Eugenics, Embryo Ethics* (Manchester: Manchester University Press, 1997), 118.
[55] Bioethics Advisory Committee, *Nuclear Genome*, 84.
[56] Song, *Human Genetics*, 49-50.

disagrees that for contemporary genetic screening to be truly eugenic, carriers would have to be eliminated from a population, not just embryos. In his estimation, "the use of prenatal diagnosis with elective abortion does not constitute a eugenic procedure because it does not change gene frequency."[57] But perhaps the impact on society is eugenic not only in the sense of terminating genetically compromised embryos or removing genes from a population but also in the sense that it assumes that genetically compromised lives are socially undesirable.

One related fear is that the advent of widespread genetic screening and therapies will lead to a society that sees genetic diseases as a condition to be avoided at all costs, even life itself. Broad acceptance of testing appears to be triggered by society and policymakers who generally support ending lives considered undesirable by genetic deficiencies. As we have sounded elsewhere, here is the phantasm of the Baconian Project once again. Here, we might discern a certain ableism from policymakers and researchers who have failed to recognise that the lives and abilities they enjoy are a matter of grace, not merit. Will there come a time when prenatal testing proves to be an ever-present reminder that those born with genetic pathologies for diseases take their place in society not by right but by having the luck to have parents who resisted the implied degeneracy of keeping them? Into such a culture, let the Church boldly declare to all persons – genetically compromised or not – that it is good that they exist. The existence of those diagnosed with genetic issues is good in itself, not because their presence exists for our sake, to work out our anxieties. Neither are they good because they deserve love or care, for they may be unreceptive to our attention. Instead, let the Church boldly declare that their presence in society is good, simply because they are there, the gift of a loving God who welcomes us all.

If their presence is good, then we will take steps to ensure that the development of HNGE in medical care and research does not come with an increase in discrimination or stigmatisation, for example. As discussed earlier, it is not inconceivable that people who do not subscribe to genetic screening or therapy, where they are readily available or accessible, may be accused of negligence. But what if the costs are prohibitively expensive, accessible only to the most well-off in society? Should the surging inequality evident elsewhere in society be introduced into the heritable human genome? Other forms of discrimination are possible. For example, sharing DNA genetic variance data impacts the costs of insurance premiums. Companies or governments could also use such data to make discriminatory decisions based on genetic codes – such as hiring employees genetically predisposed to be healthier, give more work hours, or have generally lesser health risks.

From here, the discussion naturally turns to questions of justice. How will the prohibitively expensive genetic research projects be funded - through public coffers or private funding? Subsidies, grants, and funding from public monies occasion concerns over opportunity costs over funding other projects. Overseers must be on guard not to privilege funding the most profitable forms of therapy over the most beneficial ones. We

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[57] Elof Axel Carlson, *The Unfit: A History of a Bad Idea* (Cold Spring Harbor, NY: Cold Spring Harbor Laboratory Press, 2001), 370.

would also ask policymakers to pay far more attention to contributive justice by companies or researchers that gain disproportionate benefits from biotechnology. For example, advanced genetic technologies for enhancement would likely be developed in the private sector. This would result in them being measured more expensively than genetic therapeutics. François Baylis reminds us of Luxturna, the first gene therapy for an inherited eye disease approved in the United States. Luxturna was made available to the public in 2018, with an entry cost of USD 850,000. Baylis's "modest" speculation is that a somatic gene editing therapy could cost $1,000,000 USD to cure a single-gene disorder.[58] This would virtually guarantee that genetic enhancements are only available to a narrow segment of society.

Related questions of justice and access follow. Would the purported economic benefits of patenting lead to hermetically sealed silos of resources that should be made available to a broader number of people? Access is not always fairly distributed throughout society. How would therapies be paid for, through health insurance or private wealth? Insurance providers are generally reluctant to cover high-technology services, as seen in the high cost and sometimes prohibitively long waiting periods for maternity coverage to take effect. New technologies are higher in risk, but also likely to be more lucrative. This could result in situations where genetic therapies are limited to narrow segments of society with the means to pay for the latest and most expensive treatments.

Therapy and Enhancement

The advent of wider applications and innovations in HNGE alerts us to the distinction between therapy and enhancement. Slowly but steadily the role of medicine has been extended, driven by our appetites and ambitions, to encompass dimensions of life not previously considered matters of health, altering and revising the very frame of nature. Increasingly, we expect from medicine not just freedom from disease but from all that is unattractive, imperfect, or inconvenient.

Although it may seem easy to draw the line between therapy and enhancement, this is not always the case. According to Nick Bostrum and Rebecca Roache, it is difficult to map therapies and enhancement to standard contemporary medicine and the type of medicine that will be practiced. They name, for example, palliative care, cosmetic procedures, and fertility treatments as examples where therapy and enhancement overlap. This is particularly true of interventions that reduce the probability of disease, such as vaccination. They opine that vaccination can be seen as the enhancement of the immune system, or the preventative therapeutic intervention against specific diseases.[59] Bostrum and Roache also list other issues with this distinction, such as the problem of defining what is normal due to the variance in presentation of capacities such as

[58] François Baylis, *Altered Inheritance: CRISPR and the Ethics of Human Genome Editing* (Cambridge, MA: Harvard University Press, 2019), 23.
[59] Nick Bostrum and Rebecca Roache, "Ethical Issues in Human Enhancement", in Jesper Ryberg, Thomas Petersen, and Clark Wolf, eds., *New Waves in Applied Ethics* (New York: Palgrave Macmillan, 2008): 120.

intelligence, even within a single person and that person's lifespan. They also discuss how internal an intervention must be before it is considered enhancement.[60]

Distinguishing therapy from enhancement might be no easy task, but that does not mean that distinctions do not exist or are trivial. Gilbert Meilaender encourages Christians to be wary of expansive definitions of health, such as the 1946 World Health Organizations definition of health as "the state of complete mental and social well-being, and not merely the absence of disease or infirmity." The drawing of distinctions between therapy and enhancement are needed to prevent capitulating to a bioethics without limits other than the limits of technology.[61] Pauline Taboada agrees, providing a helpful distinction between gene enhancement for the sake of significant therapeutic goal and gene enhancement *per se*, which requires consideration of the object of the act (enhancement of primary vs. secondary traits), the intention (enhancement *per se* vs. related to clear therapeutic goals) and the circumstances (associated risks, etc.).[62] The benefit of this is to foreground, at the heart of HNGE, the dignity of the human person.

There may well be a case for enhancement, as in Bostrum and Roache's argument on the necessity of slowing ageing by investigating and altering senescence processes.[63] However, we strongly disagree that the ends justify the means. Neither are the means equivocally the same from the perspective of ethics. Biological manipulation is substantively different from environmental improvement in kind, not just degree, and genetic manipulation is so different as to appear to operate on another plane altogether. For this reason, the NCCS disagree with arguments for enhancement on purely hedonistic grounds or for the mere exercise of autonomy narrowly and individually construed. There cannot be a moral obligation to choose enhancement without due regard for classical moral considerations of purpose, consequences, virtues, and the common good, to name a few.

An example of this might be discerned from *Enhancing Human Capacities,* which rejects as "ideological" any understanding of enhancement that rests upon metaphysical concepts, and adopts a "welfarist" definition, in which an enhancement is "any change in the biology or psychology of a person which increases the chances of leading a good life in the relevant set of circumstances."[64] What the authors seem to completely miss is that the welfarist definition of leading a good life is also overtly ideological, and insofar as it is a definition of the kind of human good to be pursued, is equally susceptible to the accusation of being a metaphysical conception. There also appears to be in this definition a brusque reticence to consider theological and philosophical accounts for the human

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[60] Ibid., 121-3.
[61] Gilbert Meilaender, *Bioethics: A Primer for Christians* (Grand Rapids, MI: William B. Eerdmans, 2020), 39.
[62] Pauline Tabaoda, "Human Genetic Enhancement: Is it Really a Matter of Perfection? A Dialog with Hanson, Keenan and Shuman", *Christian Bioethics* Vol. 5. No. 2 (1999): 195.
[63] Bostrum and Roache, "Human Enhancement", 123-4.
[64] Julian Savulescu, Anders Sandberg, and Guy Kahane, "Well-Being and Enhancement", in Julian Savulescu, Ruud ter Meulen and Guy Kahane, eds., *Enhancing Human Capacities* (Oxford: Wiley-Blackwell, 2011), 34.

good. One is reminded of the Baconian Project's stubborn rejection of grappling with how, if at all possible, suffering might be drawn into the ambit of the good life before the face of God.

Besides, if, as the authors suggest, the improvement sought is some good change, whether biological or psychological, then why is it not possible that the human good consists of a peaceful acceptance of bodily vulnerability, content with the practice and lifelong acquisition of the virtues (such as gratitude and humility)? And what about that definition results in turning to genetic enhancement as a matter of first resort?

Could it be that what is truly at work here is one of the consequences of the Baconian Project, as it has travelled through the centuries and embedded itself more firmly in the ethos and cultural consciousness of biotechnological research and ethics? Consider the language of gene "editing". As Paul Scherz shrewdly notes, "the metaphor of editing is much more consistent with the vision of the body that now drives molecular biology."[65] The body is seen to be a machine, a piece of software or textual information encoded in our genes that can simply be edited or reprogrammed as we see fit. Seen in this way, enhancements are simply software upgrades.

Yet a major obstacle stands in the way. The genome is not easily enhanced by editing. The ongoing discussion in this paper has cited strong evidence proving this. The idea that diseases could be traced to one or a few mutations faded when it was discovered that humans have fewer genes (about 20,000) than previously thought (about 100,000).[66] This means that they have to interact with each other to cause certain traits. To genetically enhance hearing, one would need to edit not just one gene, but hundreds. Complicating this further is that most genes have multiple functions, most of which are not yet known or understood by researchers.

The language of gene "editing" is only one manifestation of our desire to gain control over our bodies and offspring. It tends towards overly simplistic or reductive explanations of the body. But we should take to heart Scherz's witty suggestion that the body is "a living thing rather than a machine, flesh rather than text." If we think of the body as a text, let it not be a software programme but a work containing wisdom that must be engaged hermeneutically.[67] As a classic work requiring interpretation, so too is the body. Learning to interpret such an intricate text will require commentaries, corrections, or translations. Recovering older, wiser understandings of the body may help us garner the humble perspective needed to deal with HNGE in the face of the complexity of living things.

Conclusion

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[65] Paul Scherz, "Editing the Body", *Humanum Review: Issues in Family, Culture and Science* 1 (2022)
[66] Iakes Ezkurdia and Michael Tress, *et al*, "The Shrinking Human Protein Coding Complement: Are There Now Fewer Than 20,000 Genes?"
[67] Scherz, "Editing".

We once again thank the BAC for their thought-provoking consultation paper and for inviting the NCCS to respond to it. The BAC recognizes that an irrevocably large and momentous human project such as HGNE must consider the vast wealth of human wisdom: social, political, scientific, philosophical, and, critically, moral and religious capital.

We acknowledge HNGE's incredible potential for human good and the breathtaking pace at which it continues to advance. The Church, too, is grateful for human ingenuity and innovation in genetic science. These advances "increasingly reveal the Creator's greatness, because they allow man to discover the intrinsic order of creation and to appreciate the wonders of his body, in addition to his intellect, which to a certain extent reflects the light of the Word through whom 'all things were made' (*Jn* 1:3)."[68] It is easy for us to thank God for the many invaluable gifts He has bestowed on humanity, not least in the lives and creativity of the modern scientific community and enterprise. The work done by genetic science is a gift to mankind and can serve the common good.

Yet, as we have attempted to show, bioethics in the modern era can also be tempted by more dangerous aspirations, such as those in the Baconian project. The drive to relieve the human condition of all suffering, to master nature, and to increase the scope of the individual to choose whatever seems right to him, has led to a strong inclination to seek knowledge not so much for admiration or contemplation or pursuing the good, as for increasing power and control. Concerning the editing of the human genome, Pope John Paul II warned that such a mentality could lead to "interference with the internal structure of human life itself with a view to subduing, selecting and manipulating the body and, ultimately, the person and future generations."[69]

This danger is particularly acute in genetics since trust in technological and scientific progress in genetic science has taken on salvific proportions. But finitude and our propensity for wickedness cannot be eliminated by technology, and thus, salvation from suffering cannot finally be solved through science. The evil and sin that is part of human history shall endure until Jesus, the one in whom all things hold together, comes again in glory. For this reason, our gratitude for the remarkable progress that HNGE is accompanied by cautious advocacy.

In *Orthodoxy*, G.K. Chesterton shares an analogy of children playing football on a field atop a tall island in the sea. With walls built around the cliff's edge, the game is boisterous and their enjoyment is unhindered. When the walls are taken down, leaving "the naked peril of the precipice", the children do not fall over but are huddled in terror in the island's centre. Chesterton's point was that the walls constructed by Christianity are the "walls of a playground". [70] They were there precisely to give the freedom of play,

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[68] Pope John Paul II, *Address to the Pontifical Academy for Life* (Feb 1998), §3.
[69] Ibid.
[70] G.K. Chesterton, *Orthodoxy* (London: John Lane, 1909), 267.

safe in the knowledge that the ability to plunge into the threatening waters below was kept at bay.

If our response to HNGE has seemed cautious so far, it is because restraint and reflection are precisely what we counsel. Though it may seem counterintuitive, at this juncture of human progress and extraordinary potential, we agree with the proposals for "slow science", which challenges the dominant culture of speed in science. It requires acknowledging our shared interest in the common good, viewing science as a public resource and thus a shared responsibility. Slow science requires a reflective, moral science that seeks to improve the human condition but also accepts the need for consensus-building from every sector of society – not just the scientific and medical community, pharmaceutical companies, and policymakers, but also patients, people with disabilities, members of the general public, and, importantly, religious communities.[71]

Now that the wondrous prospects of HNGE have appeared on the horizon, we must take the time to define the boundaries we are trying to defend with clarity and precision; we can open a wider arena of legitimate study without excessive fear of the dangers posed by a breach of the fundamental moral assumptions that sustain our civilisation. Our support for a slow science approach is especially suited for genomic research. The plurality of creative technologies needed to move forward on gene editing suggests that regulatory frameworks and legal guidelines will quickly become outdated in a failure to keep up-to-date with frontier science. It is well-recognized that research in emerging biotechnologies is characterised by uncertainty, ambiguity, and transformative potential—these present unique ethical and societal challenges with critical implications for policy and governance.

The Church is not against technology or advancement. To describe our stance in these categories is neither helpful nor particularly Christian. We are neither pure advocates nor opponents. We refuse to reduce our response to these categories because the moral vision we hold grants us the dignity, freedom, and responsibility to choose what is right and sound, and not only what is expedient or popular. We find our bearings in the givens of human life, the dignity of the human person, and our care for the common good, not just the individual. To repeat what we have said at the outset of this paper, the only irrelevance we fear is irrelevance to God.

In general, we find that interventions of a therapeutic nature can be morally acceptable if the process does not destroy or impede essential components and processes of human nature, such as the nature capacities outlined to us by the natural law tradition, and if other issues such as safety, efficacy, and the free, informed consent of future generations could be meaningfully addressed. This might include safeguards, speed bumps, more regulatory oversight, or stricter laws. In addition, we ask if society is truly free to refuse some forms or avenues of research in the name of human flourishing, or is becoming a genetically focused society inevitable?

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[71] Baylis, *Altered Inheritance*, 123-146.

In other words, the question of public bioethics of gene editing raises important and substantive questions about what it means to be human. What vision of humanity lives at the heart of our public reasoning? Is it a world where the person is atomised, solitary, and defined only by the capacity to pursue autonomous plans of his or her invention? Is it a world where nature and the human body are understood as merely inchoate matter to be harnessed and remade to relieve the human condition? Is technological transformation permissible, nay, required in the quest for happiness and human perfection? These are not questions one group in a plural society may impose on another. Still, they are questions worthy of our shared reflection and commitment to listen to one another.

As we offer our response, the NCCS is reminded of what Venter and Cohen, who coined the 21st century as the century of biology, had to say at the end of their agenda-setting article:

> As it is, the scientist is focused on the task in front of him. He or she does not appreciate the bigger picture. The philosophers, on the other hand, rarely understand the science. Decision-makers are driven by political or stockholder expediency. Given the advancing state of science, this is a recipe for a catastrophe of the human essence. By the end of this century, the human genome project could be judged as the Manhattan Project of our time and us scientists as tinkering Frankensteins who couldn't leave well enough alone. Or, mapping the human genome could be judged as the greatest advance in the history of our species since we stood up on two legs.
>
> Everything depends on the prudent application of the accumulated wisdom of human experience to the stunning new scientific discoveries of our age. Cognizant of both the great possibilities and risks knowledge of the human genetic code brings, our hope is that future generations will never have to ask, with T. S. Eliot, "Where is the wisdom we have lost in knowledge?"[72]

Thomas Aquinas spoke of science as a gift, but also a gift that is chiefly concerned with *knowledge*, which is concerned with human or created things. For him, true wisdom comes from judging created things in the light of divine things.[73] Real happiness can come only from contemplating God, rather than from creaturely things, so creaturely goods cannot arouse spiritual joy except insofar as they are recognised as being charged with divine good. In this way spiritual peace and the resulting joy correspond directly to the gift of wisdom.[74] The bioethical challenges of the century of biology are manifold, but with humility for our frailty but confidence in the Lord, we offer these reflections as part of our God-given responsibility to give voice to and be a public witness of the Triune God, for in the knowledge of the true God comes the wisdom to know and rightly discern created things.

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[72] Venter and Cohen, "Century of Biology", 77.
[73] Aquinas, *Summa Theologiæ* IIaIIæ, q.9.2.
[74] Ibid., q.9.4.

Individual Responders (Email Responses)

1. Respondent 1

https://www.technologyreview.com/2024/07/31/1095509/he-jiankui-hopeful-gene-editing/

His idea for Alzheimer's treatment is to modify one letter in the human DNA sequence to simulate a natural mutation found in some Icelandic and Scandinavian people, which previous research found could be related to a lower chance of getting Alzheimer's disease. JK said it would take only about two years to finish the basic research for this treatment, but he won't go into human trials with the current regulations.

He compares these gene-editing treatments to vaccines that everyone will be able to get easily in the future. "I would say in 50 years, like in 2074, embryo gene editing will be as common as IVF babies to prevent all the genetic diseases we know today. So the babies born at that time will be free of genetic disease," he said.

For all that he's been through, JK seems pretty optimistic about the future of embryo gene editing. "I believe society will eventually accept that embryo gene editing is a good thing because it improves human health. So I'm waiting for society to accept that," he said.

2. Respondent 2

Thank you for giving me this opportunity to respond to the Bioethics Advisory Committee BAC) public consultation on human nuclear genome editing. In this response, I highlight three points about human germline editing that were not directly addressed in the Consultation Paper, for your consideration. I also raise a concern about the Paper's terminology on abortion under heading four, below.

1. Eradicating Disability Through Germline Gene-Editing

I note that the BAC has no immediate plans to permit any clinical applications of heritable gene editing:[1] a stance which I agree with. However, if germline gene editing were to be recommended in the future for therapeutic purposes, then it is important to consult people with the conditions that are being targeted for treatment, to understand their perspectives and lived experiences. The input of disabled people is crucial for making an informed decision about which diseases and disabilities to include on the list of qualifying conditions for 'therapeutic germline gene editing', for the following reasons.

First, fatal conditions which are life-limiting and produce extreme suffering, such as Tay-Sachs disease, are likely to be appropriate candidates for 'therapeutic germline gene editing'. However, it may be harder to justify applying this technology to genetically caused disabilities which are not fatal and are not directly associated with extreme suffering, such as sensory disabilities (blindness, deafness) and achondroplasia. On 3 June 2024, I attended a panel discussion on gene editing and pre-implantation genetic diagnosis (PGD) in Oxford, which had a blind woman as a panellist. When a representative from the UK's Human Fertilisation and

[1] Bioethics Advisory Committee, 'Ethical, Legal, and Social Issues Arising from Human Nuclear Genome Editing: A Consultation Paper' (2024) 98 at [12.8].

Embryology Authority (HFEA) mentioned that genetically caused blindness can be screened out through PGD and this is legal, the blind woman had a strong emotional reaction. She said she was genuinely shocked that PGD would be used to screen out the potential lives of people like her – and the same argument applies to gene editing technology. She urged the other panellists to please consult disabled people before deciding whether to use gene-editing to edit away the conditions of people like her. I also have blind and deaf friends. When I asked them how they would feel if gene editing were to be used to edit away blindness or deafness, they had the same reaction as the blind panellist. They saw their conditions as 'difference' rather than 'deficit'. They explained that being disabled opened them up to perceiving the world differently and that since they lived fulfilling lives, future children like them could do so too. For example, the bioethical literature describes how Deaf people flourish in unique ways, through the richness of sign language and visual communication in Deaf culture,[2] which is a point that my deaf friend also emphasised.

Second, germline gene editing can significantly reduce the number of people with a particular condition in society. This appears to be a good thing from a disease-prevention standpoint. Able-bodied parents may think that 'a special needs child will have a pitiful life, he/she will find it difficult to integrate into society, and there are additional costs of special needs schooling and care that he/she will require' so it is better for the child not to be born. It is fair to acknowledge these concerns. However, if we consider that perspective, then we should also consider the alternative view from disabled people themselves. The bioethics literature describes a phenomenon called the 'disability paradox', where scientific studies have found that able-bodied people consistently rate the quality of life of disabled people lower than how people with those conditions rate their own quality of life.[3] Disabled scholars like Tom Shakespeare (who has achondroplasia) have argued that editing away or selecting against disability could devalue the lives of existing people with those traits.[4] Therefore, inclusive policymaking requires us to engage with the views of people living with the conditions that are targeted for intervention, who can speak to their lived experiences and challenge unconscious biases.

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[2] Sara Goering, 'Gene Therapies and the Pursuit of a Better Human' (2000) 9 Cambridge Quarterly of Healthcare Ethics 330, 333.

[3] Gary L Albrecht and Patrick J Devlieger, 'The Disability Paradox: High Quality of Life Against All Odds' (1999) 48 Social Science & Medicine 977; Jamie O'Hara and others, 'Evidence of a Disability Paradox in Patient-Reported Outcomes in Haemophilia' (2021) 27 Haemophilia 245; D Lulé and others, 'Life Can Be Worth Living in Locked-in Syndrome' (2009) 177 Progress in Brain Research 339.

[4] Tom Shakespeare, 'Choices and Rights: Eugenics, Genetics and Disability Equality' (1998) 13 Disability & Society 665, 669; Susan Wendell, *The Rejected Body Feminist Philosophical Reflections on Disability* (Routledge 1996) 153.

Third, we should consider the value that disabled people bring to society. Disabled scholars like Sandy Sufian and Rosemarie Garland-Thomson describe the human diversity that disabled people bring to society, their capacity to engage with the world uniquely, and their resilience to live flourishing lives, which we sometimes underestimate.[5] Sara Goering and Erik Parens have argued that such human diversity is important, because encountering disabled people encourages abled-bodied people to become more compassionate and have empathy towards those who are different.[6] Conversely, people's capacity for empathy and willingness to accommodate disability through social interventions or inclusive attitudes, would be reduced if disabled people were consistently edited away through germline gene editing. If parents consistently choose to edit away disability without considering (or having access to) alternative viewpoints, this would have the cumulative, eugenic consequence of significantly reducing the total number of disabled people in society,[7] which would limit opportunities for able-bodied people to encounter and develop sensitivity towards persons with disabilities.[8] Moreover, the BAC Consultation Paper explains in paragraph [10.15] that 'variants associated with disease might also be associated with other beneficial characteristics, which would also be lost'. This is another reason to hesitate before using gene editing to diminish genetic diversity.

In summary, if the BAC eventually decides to recommend clinical applications of 'therapeutic germline gene editing', then it is important to exercise caution in deciding which genetically caused 'diseases' or 'disabilities' qualify for this intervention. Consulting directly affected groups in decisions about applications of human genome editing – including disabled people who live with the genetically-caused conditions under consideration – is an important part of inclusive policymaking. This is in line with the World Health Organisation (WHO) recommendations on 'Education, engagement, and empowerment' for human germline editing, which Dr Kazuto Kato mentioned during the BAC consultation session on 26 July 2024: 'Meaningful public engagement that increases the voices of those outside traditional science and policy circles and encourages the circulation of information, views and values is imperative to establish trust and legitimacy in any governance process.'[9] Importantly, these

[5] Sandy Sufian and Rosemarie Garland-Thomson, 'The Dark Side of CRISPR' (*Scientific American*, 16 February 2021) <https://www.scientificamerican.com/article/the-dark-side-of-crispr/> accessed 7 August 2024.
[6] Goering (n 2) 332; Erik Parens, 'The Goodness of Fragility: On the Prospect of Genetic Technologies Aimed at the Enhancement of Human Capacities' [1995] 5(2) Kennedy Institute of Ethics Journal 141.
[7] This has been the consequence of extensive pre-natal screening for Down Syndrome in Denmark: Sarah Zhang, 'The Last Children of Down Syndrome' [2020] *The Atlantic* <https://www.theatlantic.com/magazine/archive/2020/12/the-last-children-of-down-syndrome/616928/> accessed 7 August 2024.
[8] Sonia M Suter, 'A Brave New World of Designer Babies?' (2007) 22 Berkeley Technology Law Journal 897, 955-956.
[9] WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing, 'Human Genome Editing: Recommendations' (2021) 16.

concerns similarly apply to PGD and non-invasive prenatal testing, and it would be good if these recommendations could be applied to those interventions as well.

2. Concerns about Genetic Enhancement

We should be wary of the potential social consequences of allowing parents to genetically enhance their children to make them stronger, fitter, smarter, and so on. While this aligns with a 'survival of the fittest' paradigm, it has the potential to reduce people's capacity for compassion towards 'weaker' members of society. Every child/individual is endowed with his/her own unique traits, capacities, strengths, and weaknesses. In a society without germline gene editing for enhancement, people are encouraged to relate to one another (and parents learn to relate to their children) by accepting and accommodating each other's strengths and weaknesses. People are also encouraged to overcome their shortcomings through nurture, perseverance and self-growth. However, in a society where parents are given the option to genetically enhance their children's physical and intellectual traits, parents may feel social pressure to use this technology,[10] and people may become less tolerant of natural human flaws and weaknesses as a result. Parents who use germline gene editing to enhance their children may also impose unrealistic expectations upon them and project unnecessary disappointment onto children who fail to live up to their genetically engineered potential.[11]

Additionally, it is important to reject the fallacy of 'genetic determinism' which implies that humans are merely a product of our genes. If parents were to be offered germline gene editing for enhancement, some parents may gain the wrong impression that they can control their child's personality and outcomes in life through this technology. Yet this is not necessarily the case. A person's genes may not be solely or even primarily responsible for determining his/her traits, as social, cultural, educational and familial factors also play a part.[12] It is important to remember the contributions of nurture, a supportive environment, and access to educational resources towards people's development of talents and traits. This is an important point to discuss with potential users of this technology when counselling them for informed consent.

3. The Non-Identity Problem

Changing the heritable genes of a human embryo, for the purpose of eliminating genetic diseases or enhancing certain traits, is often described as 'treatment' or 'enhancement'. Yet

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[10] Suter (n 8) 935.
[11] ibid, 963.
[12] ibid, 962.

changing the fundamental genetic composition of an embryo, may alter it to become a different individual from the one which was originally there. Likewise, changing the genes in gametes before conception, may produce a different individual from the child which would otherwise have been conceived. This is sometimes referred to as the 'non-identity problem'.[13] If germline gene editing changes the identity of an embryo, then it may be inaccurate to describe 'therapeutic germline gene editing' in terms of 'curing', 'treating' or 'benefiting' an embryo or future child. If clinical applications of heritable gene editing were to be permitted in the future, it may be important to draw the following distinction when counselling parents for informed consent, i.e. heritable gene editing might not 'benefit the future child',[14] but is a process which fundamentally changes the embryo to become a different individual.

4. Terminology Regarding Abortion

The BAC Consultation Paper at page 54, paragraph [5.30], states that:

> *'Despite the benefits of prenatal screening testing for parents, results obtained from the tests may not always be reliable, and such errors in results may lead to failure in identifying birth defects accurately. Prenatal testing can also be expensive, costing anywhere from a few hundred dollars to several thousand dollars, depending on the type of screening or diagnostic test used. Generally, non-invasive tests such as maternal blood testing and ultrasound (e.g., combined first trimester screening) are more affordable than invasive tests such as amniocentesis, CVS, and PUBS. It should also be noted that termination of pregnancy is prohibited after 24 weeks of gestation in Singapore, except under the circumstances for which the mother's life is in danger. Therefore, the prenatal diagnosis test must be done within this window period if the parents are considering the option of* ***therapeutic termination*** *of an affected foetus.'*
>
> [Emphasis added]

The term 'therapeutic termination' is misleading, because 'therapeutic' implies curing a disease through medical intervention or restoring a person back to a state of good health. Yet abortion eliminates the life of an embryo or a foetus; it does not restore health for the embryo/foetus or provide a cure for a disease of the pregnant woman. Therefore, it cannot be

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[13] MA Roberts, 'The Nonidentity Problem' in Edward N Zalta and Uri Nodelman (eds), *The Stanford Encyclopedia of Philosophy* (Fall 2024, Metaphysics Research Lab, Stanford University 2024) <https://plato.stanford.edu/archives/fall2024/entries/nonidentity-problem/> accessed 7 August 2024.
[14] Bioethics Advisory Committee (n 1) [12.9]

described as ‘therapeutic’. It is more accurate to describe abortion simply as ‘termination’ or ‘termination of pregnancy’, and it would be good to amend this language in the final report.

Thank you for taking time to read my inputs. I would be grateful if these inputs could be incorporated into the BAC’s final report on human nuclear genome editing.

3. Respondent 3

Dear Bioethics_singapore Team,

A quick response to this initiative: Singapore should NEVER manipulate the natural genetic configuration of any individual with nuclear means.

Untold and irreversible drastic abysmal destruction and harm awaiting to rear its most horrible ugly head in the future.

Nor we should depend on Nuclear Plants and Solar Panels for energy.

Similar most destructive and harmful adverse consequences are lurking and will pounce on the tiny Red Dot in the future.

Please read the scientific literature, learn from the experience of Western countries.

Most importantly, it is crucial to investigate, examine and evaluate alternative safer options.

Risk Management is wanting. Especially, all these are affecting the Sustainability and it is Life-&-Death issues that can bring about the demise of a nation.

Please raise the 2nd part on Energy and Nuclear Plants and Solar Panels to the relevant Authority.

Thank you soooo much!

4. Respondent 4

ANNEX A
[Invitation To Comment] Public Consultation Paper: Ethical, Legal, and Social Issues Arising from Human Nuclear Genome Editing
a. Mosaicism1, Off-Target Effects, and On-Target Undesirable Modifications
1 Gene editing technologies could enable corrections to the genomic sequence to rectify or remove mutations that lead to adverse health conditions. Such technologies could also lead to unintended biological outcomes such as chromosomal mosaicism in embryos, and undesirable consequences (e.g., development of cancer and allergic reactions) arising from off-target mutations and deletions.

Much research has already been done on the safety, efficacy and applicability of HNGE. These have been reviewed in the HNGE Consultation paper and Annex.

HNGE does appear to hold considerable promise, although such promise must not be mistaken for it being a 'magic bullet'.

It is my view that one's personal human genome is exactly that – personal. It represents one of the last 'frontiers' in the modern world, and altering it raising serious questions relating to privacy and heritability.

Nevertheless, it is important to consider balancing the risks versus potential benefits.

It will be of paramount importance to consider:
a. why such technology is needed in Singapore, which is a small country with good social cohesion and identity, which have been achieved through painstaking work over decades?
b. how will the use of such technology be regulated, and not subject to medico-commercial exploitation?
c. both of the above will feed into answering, how will this actually improve the lives of regular Singaporeans?

Ethical Considerations:
i. How should researchers and clinicians balance the potential benefits of gene editing technologies against the risks associated with mosaicism and off-target effects?

Clinicians will need to be properly trained to make such clinical opinions.
Their training will be central in evaluating if there is a genuine clinical need for such treatments.

Training will need to include:
i. attaining high-level knowledge of genome regulation, genetics and heritability in mammals and in particular human biology.
ii. understanding the complex technology involved in genome editing.
iii. high-level training in ethics, philosophy, and sociology as the impact of treatment has the potential for transgenerational inheritance, and most of all
iv. **merits of such treatment should not be considered in commercial / cash terms.**

Clinicians will need the full involvement of scientists to gauge and evaluate potential treatments and hazards. The involvement of other specialist academics, legal experts and ethicists is also required.

All of these requirements, which aren't themselves exhaustive, cannot rest in the hands of individual clinicians or even at the level of hospital department committees, but will need to

be discussed and managed at the level of the Ministry of Health, perhaps under the oversight of the Health minister.

Each potential treatment should be further discussed at the level of a parliamentary select committee, which will report to prime-minister and parliament as a whole. The requirement is onerous but very necessary, as the impacts from genetic inheritance post treatment will have significant societal consequences. This way, public opinion of acceptability of the treatment can be gauged in an open and fair manner.

It is important to note that clinical training is lacking in this area.

ii. How can researchers, clinicians, and regulatory bodies ensure that patients or participants undergoing non-heritable gene editing interventions are fully informed of the risks associated with such applications?
iii. Should clinical applications of heritable gene editing be allowed, such as for the treatment of diseases or infertility, given the possibility that future generations may potentially suffer from unintended consequences associated with such applications?
b. Safety and Long-Term Effects of HNGE

ii. This will be a challenge. I have already highlighted the importance of appropriate training and exposure for researchers / clinicians. Regulatory bodies will require the help and support of knowledgeable experts. And every "treatment" will need to be appraised and scrutinised. Potential patients will need to be properly counselled by a treatment team.

Such requirements may be reminiscent of counselling for patients undergoing IVF / pre-implantation genetic testing, although I will highlight that genome editing goes steps further and I envisage this to be even more complex.

How the genome is regulated is in itself a fascinating field still being actively researched, and not fully understood by several experts in the fields of genome research and human genetics. Critically the patient will need to achieve some degree of understanding of this area in order to make an informed judgement, e.g. particularly regarding heritability, mutation, unintended genomic changes.

iii. It is my belief that heritable gene editing should not yet be allowed.

However patients with debilitating disorders (e.g. severe thalassaemia, others) may disagree, as anything that offers hope of a so-called "normal" or improved life will be appealing.

Ultimately, are regulatory bodies willing to have to monitor such patients transgenerationally? And even if so, is this ethical? How will such a body do this?
It is fraught with ethical conundrums, as intrusion into privacy / confidentiality is likely, and basic freedoms could be impacted.

Perhaps focussing on empathic approaches in managing expectations of patients with debilitating disorders, supporting them and informing them about the natural history / limitations of such illnesses could be prioritized instead.

b. Safety and long-term effects of HNGE are really not known in humans, but can have lasting impacts. It is possible that heritable changes to an individual's genome can have (intended and unintended) worldwide impacts, over a long time.

2 Gene editing may potentially offer new ways of treating genetic disorders, infertility, enhancing personalised medicine and improving health outcomes. However, it has not yet seen widespread use in clinical practice nor evaluated over long periods of time in humans as the technology is still in its early phase of development and there are concerns regarding the safety and long-term side effects of the technology on individuals receiving the treatment.

Ethical Considerations:

i. How should researchers, research institutions, and clinicians ensure favourable risk-benefit ratio is achieved for patients or participants undergoing clinical trials or clinical interventions involving non-heritable gene editing?

Gene editing should not be used to treat infertility, and should be classified as misuse.
Personalized medicine and improving health outcomes is a possibility that holds promise. Such promises can be evaluated over time.

ii. What can researchers do to mitigate challenges and alleviate long-term consequences associated with non-heritable gene editing to ensure responsible stewardship of science?

1 Mosaicism is a condition that occurs when a person has two or more sets of cells that differ genetically from one another. For example, a person with this condition might possess some cells that have 46 chromosomes while other cells have 47 chromosomes.

iii. Should clinical applications of heritable gene editing be allowed, given the difficulty in predicting the long-term consequences of such applications on future generations?

iv. What are the ethical challenges involved in conducting follow-up studies to determine the long-term side effects of gene editing interventions in research participants?

c. Procurement and Use of Human Embryos and Oocytes in HNGE Research

iii. This should be prohibited, precisely for the reason highlighted – "the difficulty in predicting the long-term consequences of such applications on future generations".

One may argue that heritable changes to the genome are occurring all the time, naturally.
And so questions are: is genome editing more accurate than changes occurring naturally to the genome, and how can this be measured in individuals?
These are difficult questions, and is an area that my research group are aimed at understanding.

I have discussed some aspects to this in my answers in Q1.

c. Use of surplus (i.e. otherwise will be discarded) human embryos and oocytes in HNGE research is acceptable, and should be regulated as such under existing frameworks (e.g. research regulation in the UK and elsewhere). The use of these have so far been to understand early developmental processes and oocyte development. Uses for these should not be conflated with therapeutic HNGE.
Such material is precious and can be useful in understanding human disease / disorders, and hence patient involvement and consent will no doubt be key.

Material from this should never be replaced into humans.

3 Regulated research with human embryos have greatly enhanced knowledge about human gene function and early embryonic development, as well as advanced research on infertility, genetic diseases, and intractable diseases. While procuring oocytes with the desired genotype from individuals can enable researchers to study gene mutations in embryos for a given disease-causing gene, or to evaluate the treatment for a specific gene mutation, it may lead to health risks for donors during the oocyte extraction procedure. Another ethical issue involved in the use of embryos for gene editing research is potential privacy breach.
Ethical Considerations:
i. How do researchers and research institutions weigh the potential benefits of gene editing research on human embryos and oocytes against the ethical and safety concerns?
ii. What can regulatory authorities do to ensure that embryo or oocyte donors are not receiving any inducement but fairly reciprocated for their contributions to gene editing research?
iii. What can researchers and research institutions do to ensure that the dignity and rights and privacy and confidentiality of individuals who donate embryos or oocytes are protected?
d. Equitable Access and Allocation of Resources

A important concern is medico-commercialization of supposed benefits to patients. Ethical review will need input from scientists and should not only be driven by clinicians. The latter group may only be focussed on 'delivery'.

4 Gene editing technologies extend beyond discovering and developing therapies, particularly for rare genetic disorders, severe diseases such as cancer, and treatment of infertility. These technologies can also be used for enhancing specific traits. However, as with many new modalities in medicine, gene editing technologies could be prohibitively expensive and would give rise to concerns of inequitable access by those who are in need but cannot afford them.
Ethical Considerations:
i. What are the ethical considerations in ensuring equitable access to gene editing technologies?
ii. How do we ensure equitable access to gene editing technologies across different socio-economic groups and regions?
iii. How can researchers and research institutions encourage more Asian participation in clinical trials for gene editing technologies to ensure inclusivity?
e. Genetic Enhancement and the Effects on Society

I believe that we are not yet at a point to be discussing issues regarding equitable access, while very substantial issues regarding safety, acceptability, applicability, consent and regulation remain.

Research aimed at understanding and informing the wider community about HGNE should be prioritized, as it can improve wider knowledge, participation and overall governance.

Merits / risks of individual clinical trials advancing non-heritable genome editing technology need to be evaluated and regulated. It is context-specific (e.g. those ameliorating disease severity or the need for repetitive invasive treatments), and depending on circumstances and individual cases, small numbers may be suitable for participation in these.

Genetic enhancement must remain in the realms of science fiction – and science fiction is a genre that generally holds a mirror at humanity to be able to reflect on itself.

5 Recent advances have increased the possibility that gene editing can also be used for purposes that go beyond therapies and medical interventions, and the possible applications of gene editing technologies include genetic enhancement in areas such as conferring resistance to diseases and enhancement of physical attributes and cognitive abilities. Such potential clinical applications of gene editing technologies raise several ethical issues.
Ethical Considerations:
i. What are the ethical considerations involved in using gene editing technologies for genetic enhancement?
ii. How might potential clinical applications of gene editing for genetic enhancement impact future generations?
iii. Should we allow clinical applications of gene editing for genetic enhancement?
iv. What can be done to ensure that gene editing technologies are used responsibly and ethically?

i. answered in earlier section.

ii. It could have a massive impact. I have discussed some of the issues in earlier sections which are related. Key question re: HNGE is how will regulatory bodies be able to draw a line to be able to discriminate between genuine treatments and opening the “back-door” to let in science fiction genetic enhancements? This is a grey area and can be subject to misuse.

iii. As mentioned Genetic enhancement must remain in the realms of science fiction.

iv. It should only be led by and performed by reputable researchers (e.g. clinicians / scientists) who know and understand the technology and biology, and can remain accountable over a long-term. Such individuals should also be supported, as there remain risks from unknowns.

There should be individual and organizational accountability.

And it should not be performed for personal / organizational profit, which can distort actual clinical need.

Individual Responders (FormSG Responses)

Chapter 7: Safety and Long-Term Effects of HNGE

How should researchers, research institutions, and clinicians ensure favourable risk-benefit ratio is achieved for patients or participants undergoing clinical trials or clinical interventions involving non-heritable gene editing?

Name of Respondent	Response
Respondent 9	In this consultation paper regarding ethical use of HNGE, the following critical issues are lacking or are not mentioned in whole or in part: 1. Lack of Quality Management Systems like ISO9000 in all aspect of HNGE research and healthcare deployment, in particular but not limiting, to its intents, plans, goals, objectives, key performance indicators targets and corresponding initiatives, design, concept, detail, build, changes, modify, review, report, monitoring, resources of whatever kind, responsibilities, warranties, guarantees, obligations, liabilities, finance, initiation, delay, abort, success criteria and factors, risk analysis and assessment, risk benefits justifications formulation and justification disclosures, policing, enforcement like regulatory, court or justice judgement actions against violations and or deviation for whatever reasons, whistleblowing measures of protection, *sustainability*, sources, improvement, power, authority, rights and their limitations, trigger, cost expenses, interest and conflict of interest and conflict, resolutions, mediation, arbitration, settlements, losses, gains, traceability, accountability, contingency, prevention and or punishment measures and watchdogs to adequate enforcement and re-enforcements. 2. Lack of Good Manufacturing Practices as according to PIC/S including but not limited to regulation in production premises, qualification, documentation, training, technology transfer, consultants, compliants and product recall, batch processing records and procedure, processing, packaging, practices, production, quality testing, quality design, control and assurance, starting materials, validation, investigation (defects), statistics, specifications, return and rejects etc. 3. Lack of Prevention and or deviation of cross contamination and compromise of product amount, label, intent safety, integrity, efficiency and effectiveness. Minimise short and long term known and unknown side effects

	4. Lack of Product, therapy, healthcare and or Service Failure analysis and prevention 5. Lack of Timely, comprehensive and Just Dispute Resolution and compensation 6. Lack of mention of good intent, faith and good wills and address whatever failures or inadequacy, audits, self and external inspection quality management systems I hope all these issues mentioned above should be agreed with the public with drafted standardise operating procedures with their quality management system in place and enforce These are the minimum requirements.

Chapter 8: Procurement and Use of Human Embryos and Oocytes in HNGE Research

What can regulatory authorities do to ensure that embryo or oocyte donors are not receiving any inducement but fairly reciprocated for their contributions to gene editing research?

Name of Respondent	Response
Respondent 18	Singapore needs to learn from the mistakes of Hwang Woo-suk. This incident has also shown how vulnerable people are exploited for gene editing research (e.g., women who worked in the labs were encouraged to donate eggs as research material). This incident has also shown that gene editing is an emerging technology which will likely play a significant role in the future of healthcare. That said, there is no clear ethical resolution to these answers. As a philosophy undergraduate, the public consultation's questions are not new. These are the subject of debate when it comes to bioethics. Perhaps the advisory committee would stand to benefit from consulting with bioethicists in NTU, NUS and across the country. Singapore should consider putting limits on monetary incentives for medical or research recruitment when it comes to gene editing. If participants are compensated as per industry standard, i.e., in comparison with studies of the same nature, then it would minimise risk of exploitation.

	A robust, independent ethics committee for gene editing should be set up, so that there is oversight in the industry. This agency can then work with the government, with medical institutions, hospitals, universities, and other stakeholders to ensure progress is made ethically, and to ensure safety measures are in place. That said, who should be in such a committee is another ethical question to consider. How such a committee would regulate the landscape is another question. For starters, all usage of gene editing technologies should be reported to a committee for oversight and regulatory purposes. This ensures that no major procedures are done without oversight. Clinical applications of heritable gene editing should be allowed if it has clear potential to saves lives. It would be best if we fully understood the mechanisms and consequences of editing specific genes. For example, we know certain genes are responsible for cancer or allergies. However, we can't say for certain that editing these genes will lead to positive outcomes. Thus, there is an inherent risk in gene editing. As such, this risk should only be undertaken by patients with fully informed consent, and for life saving scenarios only. Singapore should also highly discourage procedures which are aesthetic in nature, i.e., gene editing done to tailor one's eye or hair colour. Such procedures should be legal, but 100% non-subsidised, or taxed.

Other general comments regarding the HNGE paper

Name of Respondent	Response
Respondent 1	Currently, there are many aspects on the ethical use of Human Nuclear Genome Editing in human biomedical research, clinical research, and healthcare in which Singaporeans as a whole are ill-prepared to deal. It is a multi-faceted issue which requires careful and deliberate considerations.
Respondent 2	I am supportive of HGE provided that the reason behind HGE is valid, the sole purpose should be to prevent passing on of genetic issues to the future generation if parents have existing conditions. This should be supported, and potential parents should be able to use MediSave to do so.

Respondent 3	I think it's a good step in the right direction to allow gene editing in Singapore. Especially in the aspects of removing illness and genetic disorders. In terms of enhancing intelligence and physical attributes, probably best to not allow at this moment.
Respondent 4	No to gene editing. More research needs to be done. The results so far suggest failure more than success. The mRNA vaccines should be stopped as it can alter the human genome.
Respondent 5	It is definitely unethical and Singaporeans should not be subjected to ANY form of human testing for any reason and especially in the name of crazy science. It is noted that there could be deleterious long serve adverse consequences to anyone subjected to testing. This is highly objectionable and oppressive to Singapore Citizens. No form of consent could alleviate such objectionable use of another human being.
Respondent 6	Disagree and it's unethical. Stop experimenting on human lives.
Respondent 7	Editing the human genome (except to heal congenital diseases) is effectively playing God. Nobody knows the consequences of activating certain genes or deactivating certain ones. I would therefore humbly submit strong dissent and request not to proceed on this direction.
Respondent 8	I do not think the human DNA should be played around. I'm not even religious and yet I know it is completely unethical to try to play God. What good outcome can this even have?
Respondent 10	Don't agree on ethical use of HNGE
Respondent 11	The created human genome is sovereign and should not be edited in any form. Human life is sacred, and it should be respected / honoured as such. No part of it should be tampered with. It is as good as it is.
Respondent 12	I think it is totally not ethical to force this on anyone who is not comfortable with editing of their genome.
Respondent 13	I agree with the responses. It's well thought through and debated

Respondent 14	My personal feedback on the ethical use of HNGE application: (1) Utilising modern technology of genetic engineering to "create" made-to-order products that are consumer driven and market based, e.g. "Genetically Modified" food. (2) Exploring human genetic engineering (Human Nuclear Genome Editing or maybe "Eugenics") to "create" children is considered as made-to-order consumer products? (3) The film "Gattaca" presents a future society driven by "Eugenics" where children are conceived through genetic selection to ensure they possess the best hereditary traits of their parents.
Respondent 15	The source tissues should be taken with consent, and used, with consent on the human patients without profiteering off patients and their families. Set legal provisions to ensure the clinical/lab procedures, the results and medical solutions are well regulated.
Respondent 16	In human history, it has been a natural human trait to want to change the probabilistic natural environment into a deterministic one to improve survivability. This has extended into the modern medical intervention techniques that we are familiar with that helps us overcome survive many odds. Although discussions into what is natural or ethical have always been ongoing, we have nevertheless accepted these interventions in order to survive. Pursuits into HNGE have not been stopped and medical professions have been known to bring their practices to less regulated jurisdictions to benefit those who could pay, or they carry it out in the dark. Ref: Scientist claims he helped create world's first genetically-modifiedbabieshttps://youtu.be/b0HvLaXOhEY?si=7_E9JiYebwYvAAyD Ref: https://geneticliteracyproject.org/2021/01/15/100-countries-have-outlined-legal-restrictions-on-editing-human-embryos-heres-a-guide Many countries put in regulations to restrict or stop research or activities involving editing human embryos largely out of their fear of the unknown and their lack of ability to manage public communication on the human rights and other ethical issues including if the technology would result in only the rich could benefit.

	The same distrust of scientific research and advances can be said for many other scientific pursuits including nuclear medicine. Isn't advanced medical therapy or other modern technology also out of the financial reach of the general mass public, and similarly contributing to social inequity now? The matter relating to accessibility, affordability, social equity should and must remain an economical problem and how resources can and should be equitably distributed be discussed as an economical, resource distribution topic and leave out the discussions pertaining to medical or scientific research. To me, the ultimate question is if we should have the knowledge and the means to remove diseases, increase human lifespans, or be able to modify human beings such that we can create some human castes such as labourers, soldiers, politicians, and scientists to enable the survivability of the human species, should we? I do not have an answer to this question and would leave this question to be answered in the future. But considering that even without supporting such researches, it is very likely scientists will still continue to pursue such research in the dark or in less regulated jurisdiction or in less actively enforced but regulated jurisdiction. There is a risk the human population could be genetically polluted if genetically modified babies were released into the human population in the dark. It would become an even more difficult situation to control then. Thus there must be a platform developed to enable or support such research so that there can be governance and oversight into the development and use. As an international city, Singapore has the means to attract the right talent and we have a multi-racial, multi-religion society to support discussions on ethics, legal and social issue in a balance way to promote the right development.
Respondent 17	The effects of this scientific possibility are far beyond our capacity on our children and future. In creating a more perfect world, we omit the human-ness of naturally conceiving.
Respondent 19	Genome editing should only be used under strict regulation by an independent committee comprising members from various inter- disciplines; when lives are at stake and with informed consent of all stake holders.

Respondent 20	As per discussed during the breakout sessions, vast substantive research may be needed to evaluate the responses of the patients who may require genetic tests given the pertinent clinical necessity. A whole suite of factors may affect on the receptiveness of this therapy but there needs to be more cogent and compelling evidence presented on its effectiveness and an exhaustive list of usage which insurance companies could assist to offset in a plausibly relevant fraction. Patients are eventually at the core.
Respondent 21	As a person with inborn hyperplasia, on behalf of others with similar afflictions, I request collaboration to consider to Repeal Section 18A of the Human Cloning and Other Prohibited Practices Act 2004. We respectfully petition the Government to consider repealing Section 18A of the Human Cloning and Other Prohibited Practices Act 2004. This repeal would enable access to user-end applications, services, and products related to Human Nuclear Genome Editing (HNGE), cloning and modern eugenics for certain concerned individuals. The current legislation restricts access to these technologies, hindering the potential benefits for individuals seeking to utilise them for legitimate purposes. By repealing Section 18A, the Government can facilitate responsible innovation and provide opportunities for those who may benefit from these advancements.

Summary of key discussion points from Human Nuclear Genome Editing (HNGE) Focus Group Discussions (26 Jul and 13 Aug 2024)

This segment summarises the key points of discussion from the two Focus Group Discussions (FGDs) of the Human Nuclear Genome Editing (HNGE) Public Consultation held via Zoom on 26 July and 13 August 2024. There was a total of 54 participants, of which 28 attended the first FGD and 26 attended the second FGD. The participants comprised researchers, academics, healthcare and legal professionals, representatives from healthcare institutions, religious organisations, and industries to discuss about the ethical issues arising from the use of HNGE technologies in biomedical research, clinical research, and healthcare. Among the attendees, many were also leading experts or senior executive members in their respective fields. The two FGD sessions were chaired by Emeritus Prof Lee Eng Hin, BAC Chair and HNGE Review Group Chair, Mr Gregory Vijayendran, BAC Deputy Chair, and Dr Chew Wei Leong, HNGE Review Group Co-Chair. Prof Kazuto Kato, International Panel of Expert (IPE) member was also invited to do a presentation on 'International/Global Perspective of HNGE'. The FGD sessions were moderated by 10 members (Dr Chew Wei Leong, Emeritus Prof Roy Joseph, Prof Kazuto Kato, A/Prof Lai Poh San, Prof Julian Savulescu, Dr Owen Schaefer, Adj A/Prof Tan Ee Shien, A/Prof Tan Meng How, Mr Gregory Vijayendran, and Dr Voo Teck Chuan) of the BAC and HNGE Review Group, and supported by Biomedical Ethics Coordinating Office (BECO), MOH staff.

S/N	Ethical Question	Summary of Key Discussion Points
Chapter 6: Mosaicism, Off-Target Effects, and On-Target Undesirable Modifications		
1	How should researchers and clinicians balance the potential benefits of gene editing technologies against the risks associated with mosaicism and off-target effects?	i) There is a need to define what is considered as off-target effects as the impact of these effects varies. ii) There is also a need to define the aim/intent of gene editing interventions or research (type and severity of disease being targeted). As there are unknown risks, gene editing interventions are more acceptable when they are used for serious or life-threatening diseases/conditions, or diseases where there are no other alternative treatments/ interventions available. iii) Clinicians face challenges in understanding and balancing the benefits and risks and may be unable to counsel patients properly which leads to concerns on the validity of patient informed consent.

2	How can researchers, clinicians, and regulatory bodies ensure that patients or participants undergoing non-heritable gene editing interventions are fully informed of the risks associated with such applications?	i) Establish a nationally standardised template for consent e.g., use of mobile applications can allow patients/participants to interact and learn the benefits and risks associated with the non-heritable gene editing intervention. ii) Regulatory bodies should provide clear guidelines on the requirements that should be covered in informed consent for non-heritable gene editing interventions. iii) There is a need to consider whether the main goal of informed consent is to be "fully informed" vs "sufficiently informed" as information is complex and specialised. For non-heritable gene editing, patients/ participants should minimally understand what disease is being targeted for treatment/ mitigation (i.e., potential benefits) and what will happen to the patient/participant and the potential risks involved.
3	Should clinical applications of heritable gene editing be allowed, such as for the treatment of diseases or infertility, given the possibility that future generations may potentially suffer from unintended consequences associated with such applications? Why or why not?	i) There is a need to distinguish between the use of heritable gene editing technologies for enhancement versus treatment, however this is challenging as there is a spectrum in the severity of diseases. Most supported its use for treatment of diseases where there are no alternative interventions but were against its use for conferring resistance or enhancements. ii) Some argued that unless the benefits of heritable gene editing can be well defined and understood, a conservative approach with existing therapeutics/interventions should be used instead. iii) A higher bar should be set for heritable gene editing interventions as the treatment will affect future generations. More research and clinical trials with strict ethical guidelines are also necessary before heritable gene editing can be permitted. iv) Heritable gene editing for enhancement will cause inequity and worsening social norms as there would be certain groups that have more access to such gene editing. v) Sentiments will differ between different cultures and populations, and there is a need to assess whether the gene editing intervention will provide a common good and benefit to the population as a whole.

Chapter 7: Safety and Long-Term Effects of HNGE		
4	What are the ethical challenges involved in conducting follow-up studies to determine the long-term side effects of gene editing interventions in research participants? What can researchers do to mitigate the challenges and alleviate long-term consequences associated with non-heritable gene editing to ensure *responsible stewardship of science*?	i) There is a need to identify long-term effects and consequences, although it is challenging to assess these effects as they are not well-known due to the lack of sufficient data and unknown frequencies and scale. ii) Funding for long-term follow-up studies is a challenge as they require extensive resources and long-term commitment, which may not always be available. iii) Study protocols must be comprehensive and address potential challenges such as invasive procedures for obtaining samples and the ethics of testing on future offspring.
5	How should researchers, research institutions, and clinicians ensure favourable risk-benefit ratio is achieved for patients or participants undergoing clinical trials or clinical interventions involving non-heritable gene editing?	i) It is important to assess whether existing systems (i.e., rules, regulations, and guidelines) are adequate for managing the risks and benefits of HNGE. ii) There is a need for proper regulations to mitigate the risk of HNGE technology falling into "rogue hands", which may lead to unintended consequences. iii) Risk-benefit assessments must be presented clearly to trial participants and patients, and clinicians must ensure that the potential risks are not exaggerated or underestimated, which could discourage participation or bias the assessment.

Chapter 8: Procurement and Use of Human Embryos and Oocytes in HNGE Research		
6	What can regulatory authorities do to ensure that embryo or oocyte donors are not receiving any inducement but fairly reciprocated for their contributions to gene editing research?	i) Researchers should ensure a comprehensive consent process where detailed and specific information is included, i.e., research procedures, gene editing involved, procedures that will not be conducted (e.g., cloning). The consent should be appropriate to the patients' educational level and should be translated if necessary. ii) Consent for research/donation should be separated from consent for clinically indicated procedures. Researchers may also consider separating the donation procedure from the research staff such as establishing a national repository or independent tissue bank for the collection of oocytes. iii) Regulatory bodies should review current regulations where only allow surplus embryos to be used for research and does not allow the creation of embryos specifically for research and consider whether this should be allowed in future. iv) Due to the risks involved in oocyte donation, there is a need to consider alternative sources for oocytes for research purposes.
7	What can researchers and research institutions do to ensure that the dignity and rights and privacy and confidentiality of individuals who donate embryos or oocytes are protected?	i) While de-identification of donors ensures the protection of privacy and confidentiality, it may be less appropriate when there is a possibility of returning secondary or incidental findings. ii) It may be beneficial to establish confidentiality agreements between researchers as well as a disciplinary framework. Researchers can also be blinded to patient information and the dignity of donors can be protected by using a separate agency to manage donors (separate from researchers). iii) With research being highly competitive and lucrative, there may be risk of researchers resorting to cloning oocytes for gene editing purposes (misuse of oocytes). Hence, it is important for research oversight at the institutional and national level to be established.

Chapter 9: Equitable Access and Allocation of Resources		
8	What are the ethical considerations in ensuring equitable access to gene editing technologies? How do we ensure this across different socio-economic groups and regions?	i) Regulations are essential to prevent HNGE technologies from being misused and disproportionately benefiting affluent groups. ii) It is important to avoid assuming that disabilities are conditions that need to be "fixed" through HNGE, and ethical decision-making should involve input from people with disabilities. iii) Gene editing is expensive and often not covered by insurance or government subsidies, raising concerns about accessibility and financial equity. Expanding government support for therapies involving HNGE is necessary to ensure equitable access. iv) There is a need to reform patent protection, given the trade-off between encouraging research and development through robust patent protection and potentially exacerbating the high costs of HNGE interventions.
Chapter 10: Genetic Enhancement and the Effects on Society		
9	Should we allow clinical applications of gene editing for genetic enhancement? Why or why not? What are the ethical considerations involved?	i) Gene editing for enhancement could exacerbate inequality, as affluent individuals may have better access. There is a need to evaluate whether such enhancements should be allowed or banned. ii) There is a need for national oversight and standards to ensure enhancements do not undermine the principle of *justice*. iii) There is a need for oversight mechanisms to monitor the societal and psychological impacts of genetic enhancement on those who are vulnerable to discrimination. iv) There is a need to define who can exercise autonomy in making decisions with regard to gene editing for enhancement. v) There is a need to differentiate between gene editing for genetic enhancement and foĺr conferring of resistance to diseases.

10	How might potential clinical applications of gene editing for genetic enhancement impact future generations? What can be done to ensure that gene editing technologies are used responsibly and ethically?	i) There is a need to clearly define what constitutes “enhancement” and its purpose (i.e., for non-heritable or heritable). ii) Ethical concerns arise regarding societal pressures on parents to enhance their children’s traits through gene editing. This could lead to societal issues, including discrimination, if parents are expected to enhance their offspring. iii) There is a need for a robust regulatory framework to oversee the responsible use of gene editing technologies, such as establishing reporting systems for misuse. It is also important to balance the feasibility of the reporting system versus overly litigious regulations which may inhibit the growth of HNGE technologies.

Representatives from the following organisations/institutions participated in the focus group discussions:

- Agency for Science, Technology and Research
- Catholic Medical Guild
- Changi General Hospital
- Chapter of Genomic Medicine, Academy of Medicine, Singapore
- Health Sciences Authority
- Hindu Advisory Board
- Humanist Society (Singapore)
- Icon Cancer Centre
- KK Women's and Children's Hospital
- Lee Kong Chian School of Medicine, Nanyang Technological University
- Medical Imaging Pte Ltd
- Nanyang Polytechnic
- National Cancer Centre Singapore
- National Council of Churches of Singapore, and Trinity Theological College
- National Healthcare Group
- National Kidney Foundation
- National University Hospital
- National University of Singapore
- National University of Singapore, Faculty of Law
- National University of Singapore, NUS College
- National University of Singapore, Yong Loo Lin School of Medicine
- NUS Centre for Biomedical Ethics
- Orange Valley Nursing Home
- Preventive Medicine Department (Ministry of Defence)
- Sensemake
- Singapore General Hospital
- Singapore Health Services Pte Ltd
- Singapore United Party
- SingHealth
- SingHealth Duke-NUS Blood Cancer Centre
- SingHealth Duke-NUS Centre of Memory and Cognitive Disorders
- SingHealth Duke-NUS Institute of Precision Medicine
- SingHealth Duke-NUS Supportive & Palliative Care Centre
- SingHealth Duke-NUS Vascular Centre
- Tan Tock Seng Hospital

Bioethics Advisory Committee

Singapore