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

A CONSULTATION PAPER

BIOETHICS ADVISORY COMMITTEE

SINGAPORE

JUNE 2024

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FOREWORD

In recent years advances in Human Nuclear Genome Editing (HNGE) technologies have resulted in the discovery of more precise tools that hold great promise in advancing human biomedical research and clinical research, with the potential to improve human health. These technologies can alter genetic material, which can lead to promising breakthroughs in the treatment of genetic disorders, cancers, and infectious diseases. In biomedical research, HNGE technologies can facilitate the study of gene function and disease mechanisms, and accelerate drug discovery and personalised medicine. While the use of HNGE technologies in biomedical research and potential clinical applications (i.e., non-heritable gene editing) can bring along benefits, they also raise ethical concerns including unintended consequences and long-term effects on individuals, social inequalities, and other issues on consent. In addition, potential applications of HNGE technologies for genetic enhancement in areas such as conferring resistance to diseases and enhancement of physical attributes and cognitive abilities (i.e., heritable gene editing) raise considerable ethical issues, such as unintended consequences to future generations, shift in attitudes and behaviours towards reproductive choices, and reduction of genetic diversity in human population. Hence, these issues warrant further review by the Bioethics Advisory Committee (BAC).

2 Recognising the challenges, the BAC has developed this public consultation paper to discuss and obtain feedback on the ethical issues arising from the use of HNGE technologies in biomedical and clinical research and other potential clinical applications. Other concerns such as mosaicism, off-target effects, long-term safety, equitable access, the broad effect of genetic enhancement on society, and how the HNGE governance framework can be implemented in Singapore are also discussed. The paper covers the ethical principles to guide the ethical use of HNGE applications in human biomedical research, clinical research, and clinical translation, such as *respect for persons*, *solidarity*, *justice*, *proportionality*, *sustainability*, and other ethical considerations including *inclusivity*, *transparency*, and *responsible stewardship of science*. The public consultation paper is an adapted version of the final advisory report.

3 The views of the public, stakeholders, research institutions, and interested organisations are important and will assist the BAC in developing recommendations in the final advisory report to guide the academics, researchers, healthcare professionals, Clinical Ethics Committees (CECs) and Institutional Review Boards (IRBs) on the ethical use of HNGE applications in human biomedical research, clinical research, and healthcare.

Emeritus Professor Lee Eng Hin
Chair
Bioethics Advisory Committee
June 2024

EXECUTIVE SUMMARY

The main topics covered in the Public Consultation Paper (adapted from the advisory report) include:

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

2 While gene editing technologies, when used in a controlled manner, can enable corrections to the genomic sequence to be carried out with precision to rectify or remove mutations that could otherwise lead to adverse health conditions, such technologies could also lead to unintended biological outcomes such as chromosomal mosaicism in embryos, and undesirable consequences arising from off-target mutations and deletions. The 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 to individuals and the society, which would be important considerations for potential applications of HNGE.

b. Safety and Long-Term Effects of HNGE

3 While gene editing offers new ways of treating diseases and may potentially be used for enhancement of human performance, it has yet to receive general acceptance for widespread use in clinical practice. This is because the technology is still in its early stage of development, which raises concerns regarding the safety and long-term side effects of the technology on individuals receiving 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.

c. Procurement and Use of Human Embryos and Oocytes in HNGE Research

4 Human embryos have been used by researchers on 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 on 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 breach of privacy and 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 in ensuring the autonomy and well-being of oocyte donors are respected, and enhance transparency in the research process.

d. Equitable Access and Allocation of Resources

5 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 deliberates the potential issues arising from the inaccessibility of 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 improving gene editing for use in research and clinical applications and designing clinical trials for HNGE research.

e. Genetic Enhancement and the Effects on Society

6 Recent advances have increased the possibility that gene editing can 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. The Chapter discusses the ethical issues involved in applications of gene editing technologies for genetic enhancement, including the unintended consequences, social inequity, shift in attitudes and behaviours towards reproductive choices, and reduction of genetic diversity in human population. 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 for applications of gene editing technologies for enhancement if permitted in the future.

f. Governance and Framework Tools for HNGE

7 As with other technological advances, gene editing raises ethical and social issues that must be addressed through having proper governance frameworks in place. The Chapter discusses the governance and regulatory frameworks for HNGE at the following respective levels: (i) institutional research level; (ii) clinical trials level; and (iii) national level. The Chapter also discusses the different tools and approaches to strengthen 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 mechanism(s) for reporting unethical HNGE experiments.

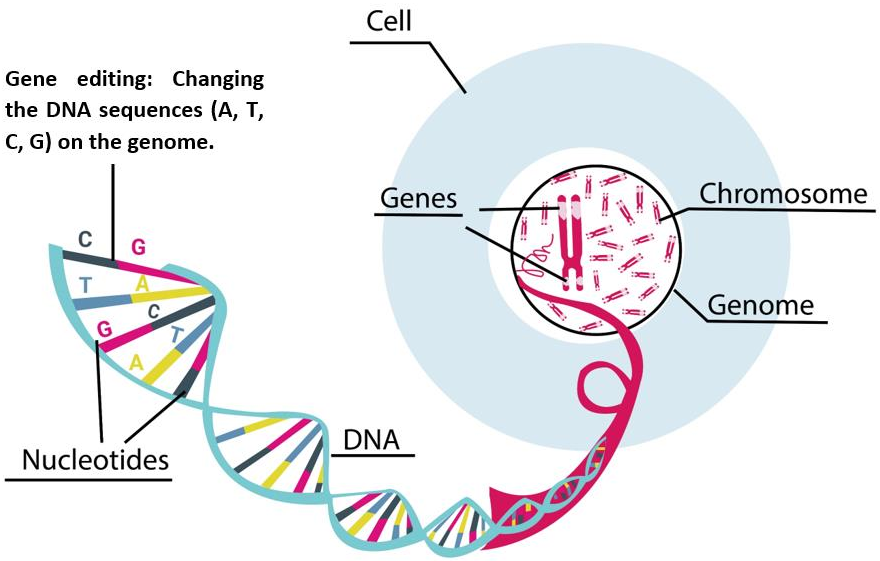
The Executive Summary of recommendations will be included in the final advisory report.

CHAPTER 1: INTRODUCTION

Human Nuclear Genome Editing (HNGE)

1.1 The human genome, made 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 can occur to the nucleotide sequences of the DNA, which can lead to changes in protein structure and cell function. Such genetic mutations could either lead to genetic conditions such as cancer or they could help humans better adapt to their environment over time. In cases where genetic mutations lead to genetic diseases, gene editing has the potential to treat such diseases. 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, which could potentially prevent or cure a genetic disease, hence displaying great potential for breakthroughs in medical treatments.[1] Therefore, researchers have shown great enthusiasm in developing 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 make changes to the DNA. These technologies act like scissors, cutting the DNA at a specific spot before scientists remove, add, or replace the DNA where it was cut. The first attempts at gene editing occurred in the 1980's, and subsequently, many researchers tried to develop methods to edit specific gene.[2] 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

[1] U.S. National Library of Medicine. (n.d.). What are genome editing and CRISPR-Cas9? *MedlinePlus.* https://medlineplus.gov/genetics/understanding/genomicresearch/genomeediting/ Retrieved on 2 August 2023.
[2] Matsumoto, D. & Nomura, W. (2023). The History of Genome Editing: Advances from the Interface of Chemistry & Biology. *Chemical Communications, 59*, 7676 – 7684. https://doi.org/10.1039/D3CC00559C.

outcome is achieved with minimal off-target effects. Gene editing tools also have the potential to diversify scientists' knowledge in genetics by generating cellular models, which can mimic various human diseases to better understand disease consequences and develop new treatments.

1.3 Human nuclear genome editing (HNGE) may be broadly classified into: (a) non-heritable gene editing; (b) heritable gene editing for clinical 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 are unable to or do not contribute to gamete formation, which are responsible for 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 for research purposes.

b. Heritable gene editing for clinical applications involves gametes (eggs or sperm), germline cells or early-stage embryos with the intent of transferring any resultant embryos to a woman's uterus for gestation.[6] Edits to the genome may be made for purposes of treatment of diseases, conferring resistance against diseases, or enhancement of traits by making changes to the genetic material of gametes, or any precursor cells that lead to their development, which include the cells of early embryos. The genetically modified embryos are then transferred into a uterus to initiate and establish a pregnancy that would result in the birth of a child with 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.

c. Gene editing may also be applied on germline cells or embryos for research. 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. Progenitor cells of gametes can also be isolated and genetically modified *in vitro* but are not implanted into a human body for establishing pregnancy. For instance, missense mutations in regulator genes in oocytes that 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 enable higher chances of successful

[3] National Academy of Sciences, National Academy of Medicine, National Academies of Sciences, Engineering, and Medicine, & Committee on Human Gene Editing: Scientific, Medical, and Ethical Considerations. (2017). Human genome editing: Science, ethics, and governance. *National Academies Press.* https://www.ncbi.nlm.nih.gov/books/NBK447271/ Retrieved on 2 August 2023.

[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] Baylis, F., Darnovsky, M., Hasson, K., & Krahn, T. M. (2020). Human Germline and Heritable Genome Editing: The Global Policy Landscape. https://www.liebertpub.com/doi/10.1089/crispr.2020.0082 Retrieved on 2 August 2023.

pregnancy.[7] In azoospermia patients that 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 and further studies are necessary to warrant any translational applications as changes that are theoretically present in the germ cells can potentially be passed on.

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 through 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 diseases. Further advancements in gene editing methods have also enhanced knowledge in human genetics, epigenetics, molecular biology, and pathology, enabling disease modeling and drug discovery to be made more viable. As such, gene editing-mediated trials have led to positive treatment outcomes in patients with haematological diseases, 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 or sustainability of outcomes.

1.5 Moreover, the increasing prevalence of infectious diseases, cancer and genetic disorders have bolstered advancement of medical science which in turn is driven by the demand for personalised medicine.[12] To personalise treatments for patients, substantial understanding of the factors contributing to the health and disease of the person is necessary. This 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

[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., Li, J.-S., Wang, Y.-H., Yan, M., Zhang, X., Liu, X.-Y., Ding, Y.-F., & Lai, C.-P. (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., Yang, J., Zhang, Y., Hu, X., & Wang, W. (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., Boshtam, M., Kouhpayeh, S., Khanahmad, H., Dabiri, A., Ahangarzadeh, S., Esmaeili, Y., Bidram, E., Vaseghi, G., Haghjooy Javanmard, S., Shariati, L., Zarrabi, A., & Varma, R. S. (2022). Gene editing-based technologies for beta-hemoglobinopathies treatment. *Biology*, *11*(6), 862. https://doi.org/10.3390/biology11060862

[12] Ho, D., Quake, S. R., McCabe, E. R. B., Chng, W. J., Chow, E. K., Ding, X., Gelb, B. D., Ginsburg, G. S., Hassenstab, J., Ho, C.-M., Mobley, W. C., Nolan, G. P., Rosen, S. T., Tan, P., Yen, Y., & Zarrinpar, A. (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

and other gene-editing tools have demonstrated promise of repairing defective genes found in patients with severe diseases ranging from acquired cancer to inherited genetic diseases. The growth of gene editing market is further driven by the increasing need for 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 in human biomedical research and clinical applications for a wide genre 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 purposes. The outcome may hold promise for the treatment and prevention of more complex diseases. Heritable gene editing in clinical application, however, is strictly prohibited in most countries. This includes Canada, Australia, and 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 pharmaceutical and biotechnology industries, technological innovation in gene editing technologies, 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 the patient's blood-forming stem cells.[15] The trial combined CRISPR technology developed at the Innovative Genomics Institute (IGI), founded by Nobel Laureate Jennifer Doudna, and expertise 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 rising geriatric population and 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 is illegal to edit embryonic genomes meant for pregnancies, younger generations have shown greater support for designer babies and that the ban could be lifted if it is demonstrated that the procedure can safely prevent severe diseases.

1.9 The Asia Pacific gene editing market has also been growing exponentially due to the rising geriatric population, modernisation of healthcare practices, technological advancements, and government initiatives for controlling diseases. For instance, in March 2021, scientists

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[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 Retrieved on 2 August 2023.

[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 Retrieved on 2 August 2023.

from the Genome Institute of Singapore (GIS) developed a novel CRISPR-based gene editor, 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 responsible for diseases such as cystic fibrosis, cardiovascular diseases, musculoskeletal diseases and neurological disorders.

Advantages and Disadvantages of Non-Heritable Gene Editing, Heritable Gene Editing for Clinical Applications 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 potential high costs of subscribing to non-heritable gene editing as a therapy may prove to be unaffordable and inaccessible for many people.

1.11 In addition, when gene editing does not occur accurately, 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 group 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 technologies and is often quantified with stringent genomic sequencing. Hence, the off-target effect is an important factor to consider when weighing the benefits and risks of each gene editing treatment.

1.12 Compared to heritable gene editing, non-heritable gene editing may exhibit lower editing efficiency and therapeutic outcome. 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 other cells comprise of unedited or unintendedly edited genomes. This could lead to a non-homogeneous population of cells which may be insufficient to elicit 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 Applications

1.13 Heritable gene editing used for clinical applications could enable correction of disease-causing mutations to be passed on from generation to generation and prevent the disease from developing in subsequent generations. Such applications could also enable conferring of resistance or enhancement of traits that is inheritable in future generations. However, unintended edits introduced during genetic modifications may similarly be passed down to future generations and bear potential negative effects on offspring. For instance, off-target effects due to DNA double strand breaks at the wrong sites because of imprecision in edits

[17] ASTAR. (n.d.). Singapore scientists develop novel gene editor to correct disease. 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 Retrieved on 2 August 2023.

made have been reported in human zygotes.[18] Similar to that of non-heritable gene editing, genetic mosaicism was observed in the same study as well, urging caution and the need for further studies of heritable gene editing for clinical applications (discussed in Chapter 6). The cost of receiving germline gene editing therapies may also be high given the sophisticated technology involved and therefore become unaffordable and inaccessible for many, potentially aggravating issues arising from societal inequality (discussed in Chapter 10).

1.14 Heritable gene editing 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 difficulties in fertility to bear and 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).[19] 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 research allows researchers to advance scientific research including those on clinical applications involving heritable gene editing and promote 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, 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 they are of sound mind, clearly understand the nature and consequences of the donation, and have freely given explicit consent, without any inducement, coercion, or undue influence.[20]

1.16 Research and clinical applications of non-heritable and heritable gene editing, and gene editing in embryos or germline cells for research, should be properly and carefully assessed

[18] Liang, P. *et al.* (2015) 'CRISPR/Cas9-mediated gene editing in human tripronuclear zygotes', *Protein & Cell*, 6(5), pp. 363–372. doi:10.1007/s13238-015-0153-5.
[19] 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.
[20] 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 Retrieved on 2 August 2023.

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 instruments 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 as a result of unintended mutations.

1.17 Nonetheless, heritable gene editing for treatment of diseases, conferring resistance, or enhancement of traits, should not be recommended until safety, efficacy and long-term effects are well established. 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 technologies are used to confer resistance to diseases or enhance certain traits which can cause potential harm to the future generations. Most jurisdictions and international bodies such as the World Health Organization (WHO), scientific and professional societies such as the International Society for Stem Cell Research (ISSCR), either recommends changes in policy and practice to support the reporting of possible heritable gene editing or does not recommend the use of heritable gene editing.

1.18 Heritable gene editing for 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.[21] 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 is made at the wrong site.

1.19 However, gene editing in embryos or germline cells for research may be allowed if the research on human embryos is conducted before the 14th day of their creation. 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.[22] The Warnock Committee's stand was premised on the view that only after the 14th day, the embryo would be considered as an individual and potential person with rights to life.[23]

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 increased risk of heritable genetic diseases for future progeny. As such the welfare of future offspring or children may be jeopardised

[21] 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

[22] 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

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

(principle of *sustainability*) and further complications for the prospective mother 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 or children susceptible to unknown long-term side effects. These genetic alterations may continue to occur and be introduced to the population which can be difficult to ameliorate (principle of *sustainability*).

1.21 Extending the duration in which gene editing on germ line cells and human embryos could be conducted (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 which could 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 aggravating 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*). Heritable gene editing for enhancement could also result in the permanent removal of beneficial characteristics important for survival, hence posing harm to the offspring (principles of *justice* and *sustainability*). The general ethical principles of HNGE will be discussed in Chapter 3.

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

1.23 The CRISPR babies scandal constitutes the most notable instance in which heritable gene editing in human embryos has drawn strong criticism from the scientific and medical communities.[24] In 2018, Chinese scientist He Jiankui applied germline gene editing to several human embryos which resulted in the birth of two genetically modified babies. By doing so, he flouted established norms for safety and human protection. With the claimed purpose of introducing the uncommon ability to resist infection from HIV, he tried 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 garnered widespread attention and 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 researchers become cautious of conducting research in gene editing on germline cells;

[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 Retrieved on 2 August 2023.

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 from China,[27] and the United States of America (US) have published results of similar experiments in the next two years following the scandal, and the studies 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 disease using human embryos.[28] While research works carried out in this area have prompted the need for caution, scientists anticipate clinical applications as a possible outcome arising from these studies.[29] Therefore, it is important to carefully consider the ethical, social, and legal implications involved in gene editing and put in place relevant regulatory tools and governance framework to prevent subsequent research from being carried out unethically.

Other Challenges

1.26 Besides ethical issues and considerations, there are other challenges faced, particularly in the clinical translation of heritable gene editing where it is often difficult to delineate clinical applications from clinical research. Established clinical translation pathway for new therapies (i.e., multistage controlled trial system to determine safety and efficacy of a tested treatment) is not applicable for heritable gene editing, as clinical trials involving heritable gene editing cannot be considered a controlled study design since there are no suitable controls for comparison. Exploratory trials (i.e., phase zero or phase one) that carries out microdosing of a new drug in a small number of patients to establish its safety would not be suitable for heritable gene editing studies. In standard first-in-human trials, an administered drug can be withdrawn instantaneously after the emergence of adverse effects, and if necessary, treatments can possibly be provided to counter adverse effects. However, these options do not exist for clinical trials involving heritable gene editing, as the intervention cannot be reversed when a genetically modified embryo has been implanted into the uterus. Therefore, this report will not discuss the ethical issues arising from clinical trials involving

[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/ Retrieved on 2 August 2023.
[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/ Retrieved on 2 August 2023.
[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/ Retrieved on 2 August 2023.
[29] Lim, J. and Kim, H. (2022) 'Basic principles and clinical applications of CRISPR-based genome editing', *Yonsei Medical Journal*, 63(2), pp. 105–113. doi:10.3349/ymj.2022.63.2.105.

heritable gene editing, as they would be similar to the ethical issues and considerations arising from clinical applications of heritable gene editing.[30]

Overview of Legislations and Regulatory Frameworks Governing HNGE

1.27 Most countries have put in place legislations that prohibit the use of heritable gene editing, such as Australia, Germany, and Korea, while others such as the UK, the US, Japan and Singapore, have conditionally allowed the use of gene editing in embryos or germline cells for research purposes under 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)' punishes anyone who artificially alters the genetic information of a human germline cell, or anyone who uses 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 does not have any specific legislation on gene editing, Singapore's 'No. S 622 Human Biomedical Research (Restricted Research) Regulations 2017' states that every research institution and researcher conducting restricted research must ensure that restricted research carried out does not involve a human embryo which is more than 14 days old from the time of creation of the embryo (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 developed new advisory guidelines in 2021 which recommend the 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]

1.29 Most scientific and professional societies do not recommend the clinical use of heritable gene editing but allow gene editing in embryos or germline cells for research. The International Society for Stem Cell Research (ISSCR) Guidelines (2021) does not recommend that heritable gene editing should be pursued at this time as approaches are currently unsafe or raise unresolved ethical issues. Additionally, it recommends 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 associations such as the World Medical Association issued a statement on human gene

[30] Rosemann, A, Balen, A, *et. al.* (2019). Heritable Genome Editing in a Global Context: National and International Policy Challenges. *The Hastings Center Report. 49(3)*, pp 30 – 42. https://doi.org/10.1002/hast.1006.
[31] Public Notice of the Ministry of Education, Culture, Sports, Science and Technology (MEXT) and Ministry of Health, Labor and Welfare (MHLW) (2019). Guidelines for research using gene-altering technologies on human fertilized embryos are established as follows, and shall come into force as from the date of promulgation. https://www.lifescience.mext.go.jp/files/pdf/Overview_Human_embryo_geneome-editing_guideline2019En.pdf Retrieved on 17 January 2024.
[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 Retrieved on 2 August 2023.

editing that non-heritable gene editing should be implemented according to appropriate evidence that is collected via well-conducted and ethically approved research studies.

Objective of this Advisory Report

1.30 To address the emerging ethical, legal, and social implications of HNGE in biomedical research, the BAC has developed 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 BAC's recommendations to inform the Singapore government on policy decisions. The advisory report will also serve 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 In the realm of gene editing, a complex landscape of legislation and guidelines has emerged to navigate the ethical, legal, and social implications of gene editing technologies. These legislation and guidelines 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 for HNGE, including those for (i) non-heritable gene editing for research and clinical applications, and for (ii) heritable gene editing for clinical applications and gene editing in embryos and germline cells for research. The second part of this chapter provides an overview of the guidelines available to guide 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 on 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, but approval is required from the Institutional Review Boards (IRBs) and 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 under desperate or dire circumstances, is also allowed.[1] However, the prescribed treatment must first be reviewed by the relevant Clinical Ethics Committee (CEC) as ethically appropriate.

a. Human Biomedical Research Act 2015

2.3 Currently, the use of non-heritable gene editing for research is not prohibited or restricted under 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 under the Health Products Act 2007 and its subsidiary legislation, specifically under the Health Products (Cell, Tissue 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

[1] Ministry of Health. 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. Healthcare Services Act 2020. www.moh.gov.sg/docs/librariesprovider5/licensing-terms-and-conditions/lc-for-ctgtp_260623.pdf?sfvrsn=e87f03b0_0. Retrieved on 8 February 2024.

[2] Health Products Act 2007, Health Products (Cell, Tissue and Gene Therapy Products) Regulations 2021. https://sso.agc.gov.sg/SL/HPA2007-S104-2021. Retrieved on 25 August 2023.

materials classified as Class 2 CTGTP are also regulated under 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 and there are no ongoing clinical trials on non-heritable gene editing in Singapore.

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

2.6 Heritable gene editing for clinical applications is not approved by the Ministry of Health (MOH) in Singapore. This is because currently there is insufficient evidence to demonstrate the safety of this novel 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 purview of the MOH in Singapore. Specific research projects involving embryonic development, which require approval from government authorities, are required to adhere to the requirements set out under 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]

a. Human Cloning and Other Prohibited Practices Act 2004

2.7 In Singapore, the Human Cloning and Other Prohibited Practices Act 2004 stipulates that placing of prohibited embryo in the body of a woman is prohibited.[7] Prohibited embryo

[3] Health Products Act 2007, Health Products (Clinical Trials) Regulations 2016. https://sso.agc.gov.sg/SL/HPA2007-S331-2016. Retrieved on 28 August 2023.

[4] In-House Manufactured CTGTPs refers to the non-commercial production of CTGTPs by a healthcare institution, whether for use by patients of the 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] Human Biomedical Research Act 2015, 2020 Rev Ed. *Part 5: Regulation of Human Biomedical Research*. https://sso.agc.gov.sg/Act/HBRA2015. Retrieved on 28 August 2023.

[6] Ethics guidelines for human biomedical research (2021 revised edition) (2021). *Bioethics Advisory Committee*. https://www.bioethics-singapore.gov.sg/publications/reports/bac-ethics-guidelines-2021. Retrieved on 25 August 2023.

[7] Human Cloning and Other Prohibited Practices Act 2004. *Part III, Division 2, Section 11*: Other prohibited practices. https://sso.agc.gov.sg/Acts-Supp/35-2004/Published?DocDate=20040927&Provlds=pr13-sso.agc.gov.sg/Act/HCOPPA2004?ViewType=Within&Phrase=14%20days. Retrieved on 28 August 2023.

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, and stipulates 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 assisted reproduction procedure involves (a) the collection of oocytes from a woman, other than by way of surgical excision of the woman's ovarian tissue; (b) the fertilisation of an oocyte for the subsequent distribution of the embryo; (c) the transfer of any oocyte or embryo into the body of a woman; and (d) any removal of cells from an embryo for the purpose of testing the embryo.[9] Under the HCSA 2020, an embryo is defined 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 (a) its fertilisation; (b) the appearance of two pro-nuclei; or (c) the initiation of its development by other means.[10] When point (c) of the assisted reproduction procedure mentioned above is read together with the definition of an embryo under HCSA 2020, it can be interpreted 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 requires that every research institution and researcher in Singapore conducting restricted research[11] must ensure that the research carried out 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 research institution and the researcher ensure that only surplus embryos created in assisted reproduction treatment and

[8] Human Cloning and Other Prohibited Practices Act 2004. *Part III, Division 2, Sections 7 and 8*: Other prohibited practices. https://sso.agc.gov.sg/Act-Rev/HCOPPA2004/Published?DocDate=20050731&Provlds=pr7-,pr8-https://sso.agc.gov.sg/Act/HCOPPA2004?ViewType=Within&Phrase=14%20days. Retrieved on 28 August 2023.

[9] Ministry of Health. Healthcare Services (Assisted Reproduction Service) Regulations 2023. *Healthcare Services Act 2020. Part 1: Definitions.* https://sso.agc.gov.sg/SL/HSA2020-S429-2023?DocDate=20230623. Retrieved on 8 February 2024.

[10] Ministry of Health. Healthcare Services Act 2020. First Schedule: Licensable Healthcare Services. https://sso.agc.gov.sg/Act/HSA2020?=&Provlds=Sc1-. Retrieved on 15 February 2024.

[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 egg or human embryos.

[12] 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. https://sso.agc.gov.sg/SL/HBRA2015-S622-2017/Historical/20171101?DocDate=20230621&ValidDate=20230501&Provlds=pr10-#pr10-. Retrieved on 28 August 2023.

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 United States of America (US), and the United Kingdom (UK) currently do not 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 are regulated by the US and Europe.

The US

2.11 In the US, human gene editing falls under the purview of the Food and Drug Administration (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 are required to 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] The US NIH Somatic Cell Genome Editing (SCGE) Consortium was set up with the aim to accelerate the development of safer and more effective methods for 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

[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. Retrieved on 25 August 2023.
[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. Retrieved on 25 August 2023.
[15] National Academies of Sciences, Engineering, and Medicine; National Academy of Medicine; National Academy of Sciences; Committee on Human Gene Editing: Scientific, Medical, and Ethical Considerations. (2017). Human Genome Editing: Science, Ethics, and Governance. https://www.ncbi.nlm.nih.gov/books/NBK447266/. Retrieved on 25 August 2023.
[16] National Institutes of Health (2023). Somatic cell genome editing https://www.commonfund.nih.gov/editing. Retrieved on 25 August 2023.

by the European Medicines Agency (EMA).[17] Specifically, the European Union's Regulation (EC) No 1394/2007 provides the overall framework for ATMP 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 maintaining the highest level of protection for the health and interest of patients.

ii. Heritable Gene Editing for Clinical 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 applications. Gene editing in embryos or germline cells for research is allowed in Australia, South Korea, and New Zealand. 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 Act.[21] The Act aims to address ethical concerns on the scientific developments in relation to human reproduction and utilisation of human embryos by prohibiting certain practices. Practices that are completely prohibited under the Act include heritable alterations to genome.[22] A person therefore commits an offence if the person alters 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

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[17] European Medicines Agency (2023). Advanced therapy medicinal products: Overview, European Medicines Agency. https://www.ema.europa.eu/en/human-regulatory/overview/advanced-therapy-medicinal-products-overview. Retrieved on 28 August 2023.

[18] 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 (no date) EUR. https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=celex%3A32007R1394. Retrieved on 28 August 2023.

[19] 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 (no date) EUR. https://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1410944582971&uri=CELEX%3A02001L0083-20121116. Retrieved on 28 August 2023.

[20] Most of the legislation on heritable genome editing for clinical applications and genome editing in embryos or germline cells for research include the mention of '14-day rule'. While the '14-day rule' is 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, some researchers and scientists favour revising the rule to further study the embryonic developmental process, which happens 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 the future child goes through due to congenital abnormalities that develop during this period (quoted by British scientist, Robin Lovell-Badge, who is a stem cell expert at London's Crick Institute). However, some ethicists argue that such extension may cross a moral boundary and it is also unclear how such a change would advance research. [Reference: See New guidelines suggest lifting '14-day rule' on growing human embryos in the lab (2021) NBCNews.com. https://www.nbcnews.com/health/health-news/new-guidelines-suggest-lifting-14-day-rule-growing-human-embryos-n1268628]

[21] Prohibition of Human Cloning for Reproduction Act 2002. https://www.legislation.gov.au/Details/C2017C00306. Retrieved on 28 August 2023.

[22] Prohibition of Human Cloning for Reproduction Act 2002. *Section 15: Offence: heritable alterations to genome.* https://www.austlii.edu.au/au//legis/cth/consol_act/pohcfra2002465/s15.html. Retrieved on 28 August 2023.

prohibits developing a human embryo intentionally 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, without obtaining the qualification for practising medicine, unlawfully practises medicine shall be sentenced to a fixed-term imprisonment of not more than three years, criminal detention, or public surveillance, and with or only fine if the circumstances are serious. This is enshrined within Article 336 of the Criminal Law of the People's Republic of China and 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 born as twin girls. The Chinese Civil Code, issued in May 2020, states that medical and scientific research activities concerning human genes and embryos, among others, shall be performed according to laws and administrative regulations and relevant provisions outlined by the state without endangering human health, violating moral principles, or damaging public interest. According to this, anyone who engage in relevant scientific research and medical activities that contravene ethics and morality in China will be considered to have violated personal rights and can be subject to civil liabilities.[24]

Germany

2.16 In Germany, the editing of germline cells is regulated under the Embryo Protection Act.[25] Section 5 on artificial alteration of human germline cells under the Act 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. This does not apply to the artificial alteration of the genetic information of a germ cell situated outside the body where the 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 a permanent intentional genetic modification (germline gene therapy) to cause the creation of a person is prohibited under the Prohibition of Genetic Intervention (Human Cloning and Genetic Manipulation of Reproductive Cells) Law.[26]

South Korea

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[23] Normille, D. (2023). In wake of gene-edited baby scandal, China sets new ethics rules for human studies. https://www.science.org/content/article/wake-gene-edited-baby-scandal-china-sets-new-ethics-rules-human-studies. Retrieved on 28 August 2023.

[24] Yaojin, P.; Jianwei, Lv.; et. al. (2022). Responsible governance of human germline genome editing in China. Biology of Reproduction; 101(1); pp 261-268. doi: 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. Retrieved on 28 August 2023.

[26] Ornit (2004). Prohibition of Genetic Intervention (Human Cloning and Genetic Manipulation of Reproductive Cells) *Law*, 5759-1999, The Hinxton Group: An International Consortium on Stem Cells, Ethics & Law. http://www.hinxtongroup.org/docs/israel.html. Retrieved on 28 August 2023.

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

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, and 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 technologies in human embryos for clinical application.[31]

III. Comparison Between Local and Overseas Legislation for HNGE

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

2.21 Similar to Singapore, the countries of Australia, Germany, South Korea, New Zealand, the US, and the UK do not have legislation 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, which is similar to the practice in Singapore. However, in Singapore, in-house CTGTPs may be used for medical treatment if approved by CECs.

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

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[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. Retrieved on 28 August 2023.

[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. Retrieved on 29 January 2024.

[29] Parliamentary Counsel Office. Human Assisted Reproductive Technology Act 2004 - New Zealand legislation. *Schedule 1: Prohibited actions.* https://legislation.govt.nz/act/public/2004/0092/latest/whole.html#DLM319832. Retrieved on 28 August 2023.

[30] Parliamentary Counsel Office. Human Assisted Reproductive Technology Act 2004 - New Zealand legislation. *Part 2: Prohibited and regulated activities.* https://legislation.govt.nz/act/public/2004/0092/latest/whole.html#DLM319311 . Retrieved on 29 January 2024.

[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. Retrieved on 28 August 2023.

2.23 In Australia, Germany, Israel, South Korea, New Zealand, and the US, there is legislation in place to prohibit heritable gene editing for clinical applications, which are similar 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, similar to the position under Singapore's Human Biomedical Research Act 2015. Singapore allows research on embryos from the time of creation to 14 days or appearance of the primitive streak, whichever is earlier. In contrast, Australian and New Zealand legislation only references the '14-day rule', whereas South Korean legislation mentions only the appearance of the primitive streak. However, German legislation does not reference either the '14-day rule' or the appearance of the primitive streak.

2.24 South Korea's laws specify that gene therapy research should only be conducted for hereditary diseases or diseases that threaten one's life 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 does 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 do not specify the need to conduct such research on embryos before 14 days or 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, and reiterated 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

[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. Retrieved on 28 August 2023.

[33] The 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. Retrieved on 28 August 2023.

[34] Ethics guidelines for human biomedical research (2021 revised edition) (2021). *Bioethics Advisory Committee*. *Annexe A, Section 5.33*. https://www.bioethics-singapore.gov.sg/publications/reports/bac-ethics-guidelines-2021. Retrieved on 31 January 2024.

[35] WHO issues new recommendations on human genome editing for the Advancement of Public Health (2021). *World Health Organization*. https://www.who.int/news/item/12-07-2021-who-issues-new-recommendations-on-human-genome-editing-for-the-advancement-of-public-health. Retrieved on 28 August 2023.

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 stated 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 support 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. Similarly, Japan has developed guidelines that recommend against the use of heritable gene editing for clinical applications.

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 (framework for governance; recommendations) aiming to help establish human (both non-heritable and heritable) gene editing as a tool for public health across the world.[37] The report on framework for governance serves to provide guidance to different groups of stakeholders to strengthen governance of the technology at the institutional, national, regional, and global levels. The Committee's report on the recommendations are for both clinical and research applications of gene editing, and include 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. Countries are encouraged to utilise the tools for governance set out in the WHO report on framework for governance and collaborate with the WHO to ensure that the recommendations of the Committee are effectively implemented.

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

2.29 The International Society for Stem Cell Research (ISSCR) Guidelines (2021) recommend the use of gene editing on germline cells for research purposes only after review and approval through 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 time for the embryo to be developed in culture beyond 14 days. The guidelines also recommend that research involving human embryos in which their nuclear genome have undergone modification are not allowed to be

[36] National Academy of Medicine, National Academy of Sciences, and the Royal Society. 2020. *Heritable Human Genome Editing*. Washington, DC: The National Academies Press. https://doi.org/10.17226/25665. Retrieved on 28 August 2023.

[37] Human genome editing: Recommendations (2021). *World Health Organization*. https://www.who.int/publications/i/item/9789240030381. Retrieved on 28 August 2023.

[38] International Society for Stem Cell Research (ISSCR) Guidelines (2021). 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. Retrieved on 28 August 2023.

transferred into or gestated in a human uterus, as these approaches are currently unsafe or raise unresolved ethical issues.

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

2.30 In Germany, the German Ethics Council published a report 'Intervening in the Human Germline' calling for an international moratorium on heritable gene editing for medical purposes in humans.[39] The report serves to encourage discussion and evaluation on 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.

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 aimed at understanding disease development to treat genetic diseases. The Guidelines, however, recommend against germline gene editing for reproductive purposes and clinical testing.[40]

VI. HNGE Guidelines that Recommend Heritable Gene Editing be Allowed on Conditions

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, if heritable gene editing applications were to be socially acceptable in the future.[36] It recommends that the use of heritable gene editing for treatment of diseases and infertility should be permitted only under the following conditions:

(i) serious monogenic diseases that cause severe morbidity or premature death;
(ii) 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 be disease-causing;

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[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. Retrieved on 28 August 2023.

[40] Public Notice of the Ministry of Education, Culture, Sports, Science and Technology (MEXT) and Ministry of Health, Labor and Welfare (MHLW) (2019). Guidelines for research using gene-altering technologies on human fertilized embryos are established as follows, and shall come into force as from the date of promulgation. https://www.lifescience.mext.go.jp/files/pdf/Overview_Human_embryo_geneome-editing_guideline2019En.pdf Retrieved on 8 February 2024.

(iii) 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

(iv) 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 recommending that human gene editing should be implemented according to appropriate evidence that is collected via well-conducted and ethically approved research studies.[41] The statement also states 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 applied to non-heritable 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 important for researchers and research institutions to adhere to these legislation and guidelines to ensure ethical and safe utilisation of gene editing technologies. These frameworks provide the necessary safeguards against potential risks from applications of gene editing technologies 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.

[41] World Medical Association (2020). WMA statement on human genome editing. https://www.wma.net/policies-post/wma-statement-on-human-genome-editing/. Retrieved on 15 March 2024.

CHAPTER 3: GENERAL ETHICAL PRINCIPLES IN HNGE

General Ethical Principles

3.1 In its deliberations on the use of HNGE in biomedical research and clinical applications, the BAC stays guided by substantive[1] and governance principles. Substantive principles include considerations on '*Respect for persons*', '*Solidarity*', '*Justice*', '*Proportionality*' and '*Sustainability*', which are discussed in greater detail as follows:

a. Respect for persons

3.2 *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. The welfare and interests of individuals are to be protected, especially when their autonomy is impaired or lacking. This principle underlies the importance of obtaining informed consent from potential research participants or those who are making decisions on behalf of them or entities in research, protection of their privacy and confidentially disclosed information, and preventing or minimising harm to them.

3.3 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. The autonomy of a person may be compromised if they are not fully informed of the possible benefits, risks, and repercussions following research and clinical applications of gene editing technologies. Individuals have the autonomy and 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 on the rights, autonomy and physical integrity of the child born as a consequence of the intervention. 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,[2] since he is unable to provide consent prior to being genetically modified.

b. Solidarity

3.4 The BAC takes the position that some measure of mutual obligation exists between the individual and society such that in specified circumstances, individual interests ought to be subordinated to achieve or promote the public good. The principle of *solidarity* reflects the moral obligations of individuals, like participants, researchers, and research institutions, to share the costs associated with research design and execution, including potential risks, in

[1] Bioethics Advisory Committee. (2022). Ethical Principles. *Bioethics Advisory Committee*. https://www.bioethics-singapore.gov.sg/who-we-are/ethical-principles/. Retrieved on 28 August 2023.

[2] 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)*, pp. 1409-1423. https://philpapers.org/rec/MINWCG. Retrieved on 26 April 2024.

return for the common good. In the context of biomedical research, acceptance of agreed social benefits is typically considered as a public good. This supports 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 also advanced as part of the public good. This would help resolve any 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 harness benefits for the society by enabling faster and accurate diagnosis of diseases or conditions in patients, introducing more targeted treatments, and allowing early prevention of the occurrence of genetic disorders. While biomedical research is important in realising long-term benefits from the applications of gene editing, it is also crucial to note that misuse and abuse of such technologies 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 disease.

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 equitably shared in society. In the event that research yields an immediate benefit that could apply to participants in the research, 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 technologies and therapies are accessible to the public according to a plausible theory of justice. However, the technologies involved may raise concerns on ensuring fair access to therapies due to the high cost incurred. As such, treatments involving the use of gene editing technologies may not be widely and readily accessible to the whole population, particularly in lower socioeconomic status groups,[3] which may lead to societal inequity issues.

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 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.

[3] Hildebrandt, C.C. and Marron, J.M. (2018) Justice in CRISPR/cas9 research and clinical applications. *Journal of Ethics | American Medical Association*. https://journalofethics.ama-assn.org/article/justice-crisprcas9-research-and-clinical-applications/2018-09. Retrieved on 28 August 2023.

3.9 When assessing the use of gene editing technologies in biomedical research or clinical purposes, 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. The stringency of any regulation or governance framework developed for research employing gene editing, including a de facto prohibition on specific research activities, must be proportionate to the risks being mitigated.

e. Sustainability

3.10 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.

3.11 In the context of human gene editing in biomedical research or clinical purposes, while gene editing technologies 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 its future generation 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 they are not misused and remain, in alignment with the United Nation (UN) Sustainable Development Goals[4].

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 though sustainability applies this to the future generations, and non-maleficence focuses on individual welfare.*

Governance Principles

3.12 In addition to the five substantive principles discussed above, the BAC has identified three governance principles as being important in the context of HNGE in biomedical research and clinical applications. These 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.

[4] United Nations. (2015). 17 Sustainable Development Goals. THE 17 GOALS | Sustainable Development (un.org). Retrieved on 19 January 2024.

I. Inclusivity

3.13 Biomedical research conducted and clinical care rendered should be representative of the population diversity in Singapore and the benefits of such research and proper clinical care should be globally accessible. The advancement of health equity through research is promoted by community engagement and participatory research. Stakeholders may be engaged through dialogues, public consultation, and consensus-building within the local community.

3.14 In the context of HNGE, benefits of research and potential clinical applications of the technology are considered a public good and need to be accessible to everyone. However, the ethical implications of HNGE could exacerbate the divergent views of technology in society, especially among groups with different social, cultural, and religious views. Hence, there is a need to carefully consider the knowledge and perspectives on HNGE informed by different social, cultural, and religious beliefs. And to also work closely with the different groups of people to facilitate 'community-engaged research', where their opinions and perspectives are considered during the conceptualisation of research plans.

3.15 Decision-makers should consider the views of all stakeholders and take them into account where possible. Appropriate stakeholders such as patients, prospective parents, and the public 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 to research design, ethical oversight or overall governance of the research and the research findings.

II. Transparency

3.16 *Transparency* relates closely to ethical responsibility and moral and legal liability for the decisions and actions arising directly from research studies 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 reporting of research helps to ensure that results are reproducible and reliable, and facilitates proper interpretation and dissemination of findings by other researchers. Transparent reporting mechanisms may also be set up to investigate concerns and possible unlawful doings, 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 [5], policymakers have to institute policies, frameworks and recommendations for research and clinical applications of technologies, including novel and upcoming ones, in a transparent way to promote public confidence. Meaningful public input with regard to the allowing or disallowing of HNGE technologies may need to be

[5] National Academies of Sciences, Engineering, and Medicine; National Academy of Medicine; National Academy of Sciences; Committee on Human Gene Editing: Scientific, Medical, and Ethical Considerations. (2017) Oversight of Human Genome Editing and Overarching Principles for Governance. *Human genome editing: Science, ethics, and governance*. Washington, District of Columbia: National Academies Press. https://www.ncbi.nlm.nih.gov/books/NBK447266/. Retrieved on 28 August 2023.

incorporated into the policy-making process, where government decisions should be subject to transparent social debate.

III. Responsible Stewardship of Science

3.17 The principle of *responsible stewardship of science* refers to the moral requirement to be prudent about the resources and having oversight of all elements responsibly, including planning, management, and decision-making in research activities in the pursuit of any emerging field in biomedical research.[6] 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 legislations should be followed when conducting research on humans, with particular attention to issues of integrity and conflict of interest. Research priorities should also be set by considering the needs of the society and in achieving maximum social and scientific benefits of research while minimising the potential risks.

3.18 In the context of HNGE in biomedical research, *responsible stewardship of science* requires that processes and outcomes of HNGE research be aligned with the values, needs, and expectations of society, as identified through 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*.

3.19 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 editing research. The group may comprise members from diverse background (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 practise appropriate caution for uncertainty and long-term risks when using gene editing technologies for 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.

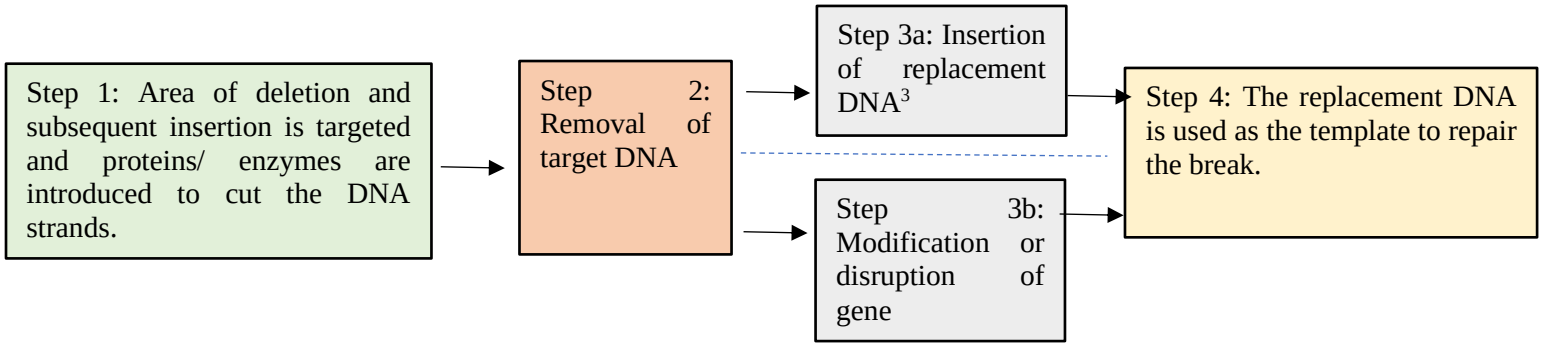
[6] Daniel P. Sulmasy (2017). Ethical Principles, Process, and the Work of Bioethics Commissions. *Goals and Practice of Public Bioethics: Reflections on National Bioethics Commissions*, special report, *Hastings Center Report* 47, no. 3 (2017), S50-S53. https://doi.org/10.1002/hast.722.

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

Gene editing technologies widely used for research

4.1 Techniques and tools developed for HNGE have evolved since inception of the technology. Nonetheless, the general steps involved in gene editing for research are similar[1] and broadly begin with targeting the area of deletion and 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 the template to repair the break and generate a healthy form of the gene. (See **Fig. 4.1** for the schematic diagram)

Figure 4.1: Schematic diagram showing the general steps involved in gene editing[2]



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 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]

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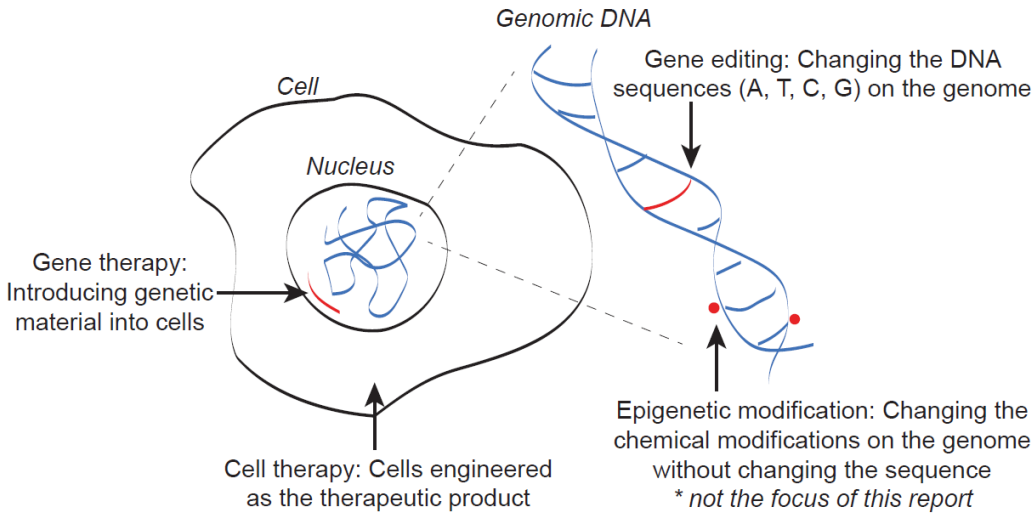
[1] National Human Genome Research Institute (2017). How Does Genome Editing Work? https://www.genome.gov/about-genomics/policy-issues/Genome-Editing/How-genome-editing-works. Retrieved on 7 September 2023.

[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)'. More will be discussed in later sections.

[4] Diane, E., Rita, C., and Joseph, L. (2011). Epigenetic Modifications: Basic Mechanisms and Role in Cardiovascular Disease. doi:10.1161/CIRCULATIONAHA.110.956839.

Figure 4.2: Schematic illustration of gene editing, epigenetic modification, and cell and gene therapy



Different types of gene editing technologies

4.3 While there are many types of gene editing technologies, such as Restricted enzymes, Cas-CLOVER,[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**).

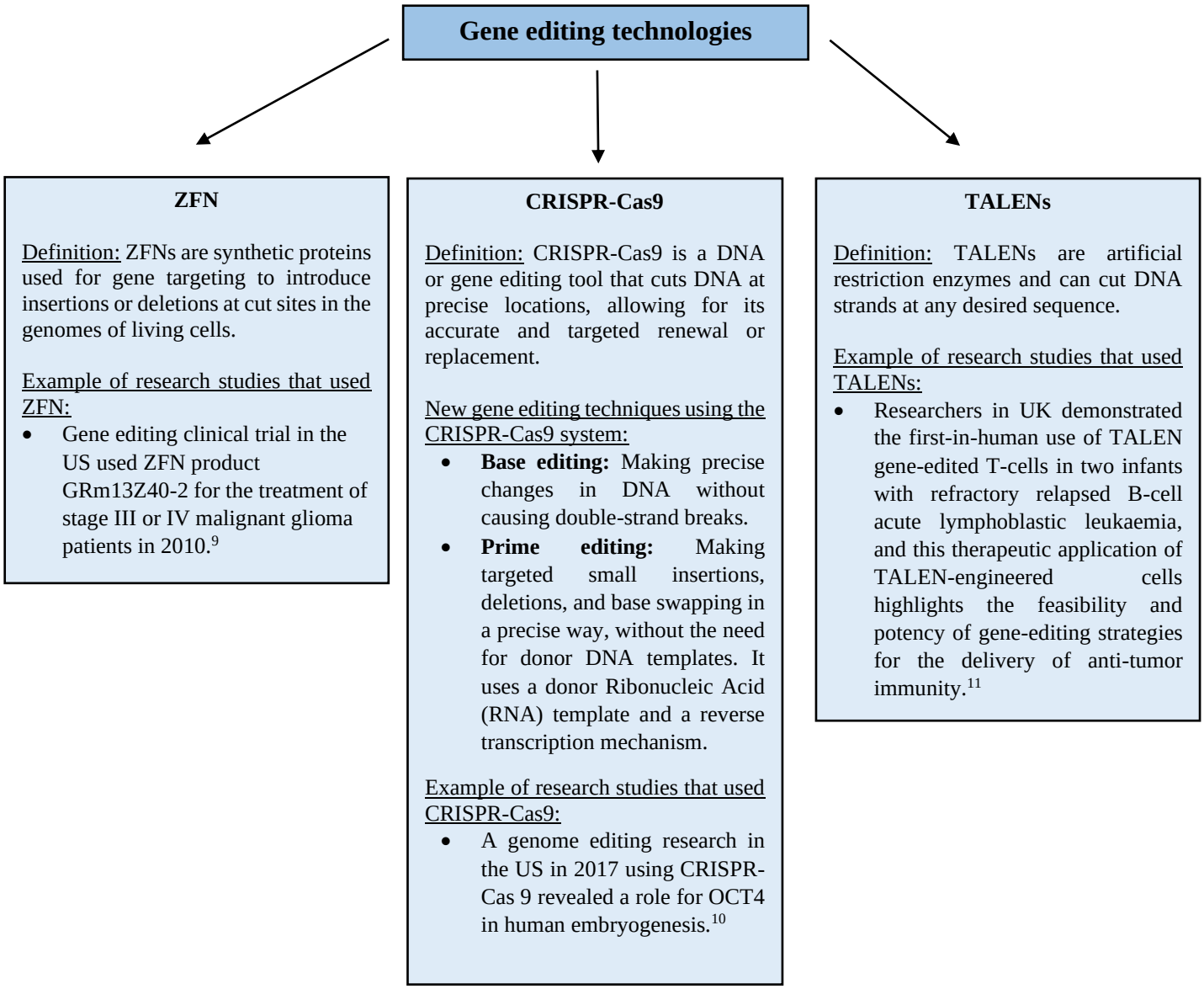
[5] Madison, B.B. *et al.* (2022). CAS-clover is a novel high-fidelity nuclease for safe and robust generation of TSCM-enriched allogeneic car-T cells, *Molecular Therapy - Nucleic Acids*, 29, pp. 979–995. doi:10.1016/j.omtn.2022.06.003.

[6] Zhao, B. *et al.* (2022). Bacterial retrons enable precise gene editing in human cells, *The CRISPR Journal*, 5(1), pp. 31–39. doi: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)*, pp. 11–27. doi:10.2174/156652311794520111.

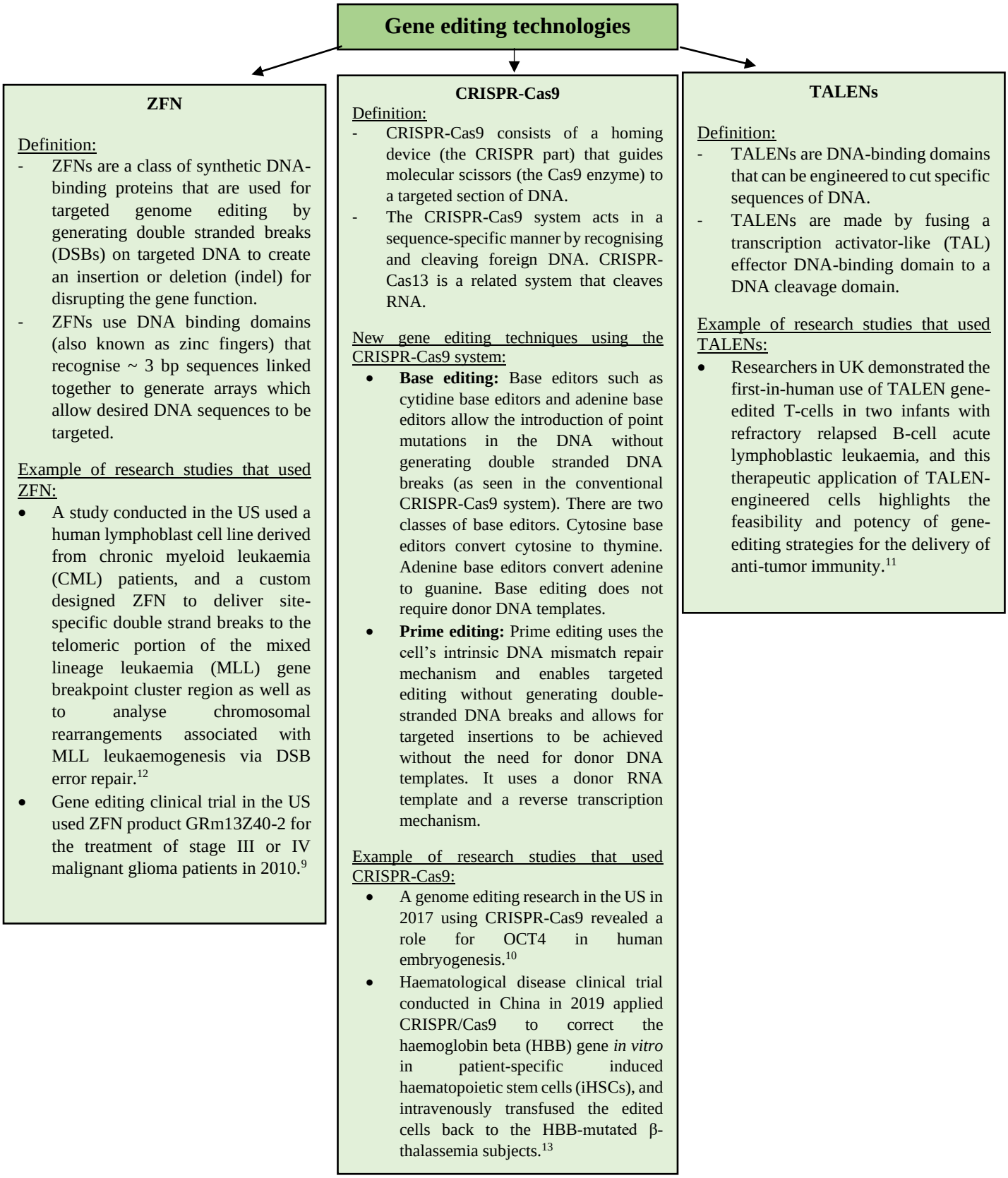
[8] This report focuses on the CRISPR-Cas9 complex as the conventional CRISPR complexes consist of the Cas9 enzyme. Cas3 and Cas12a are other examples of enzymes used in the CRISPR complexes.

Figure 4.3: Diagram of the different types of gene editing technologies in simple terms



[9] Hongyi, L. et al. (2019). Applications of genome editing technology in the targeted therapy of human diseases: mechanisms, advances and prospects. doi: 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): pp 67-73.* doi:10.10138/nature24033.
[11] National Health Service, UK (2015). World first use of gene-edited immune cells to treat 'incurable' leukaemia. https://www.gosh.nhs.uk/press-releases/world-first-use-gene-edited-immune-cells-treat-incurable-leukaemia/. Retrieved on 26 January 2024.

Figure 4.4: Diagram of the different types of gene editing technologies with more details



[12] Do, T. et al. (2012). A Zinc finger nuclease induced DNA double stranded breaks and rearrangements in MLL. *Mutat. Res. 740, pp 34 – 42*. doi: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. doi:10.1007/s00277-019-03763-2.

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) and non-homologous end-joining (NHEJ).[14] 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 less accurate in carrying out the repair of Cas9-induced DNA double strand breaks and it is difficult to control outcomes of NHEJ. 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 the patient's genetic composition with exogenous DNA.[15] 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 to treat or cure genetic diseases and can work by:

i. replacing a disease-causing gene with a healthy copy of the gene;
ii. inactivating a disease-causing gene that is dysfunctional;
iii. introducing a new or modified gene into the body to help treat a disease; or
iv. correcting disease-causing mutations.

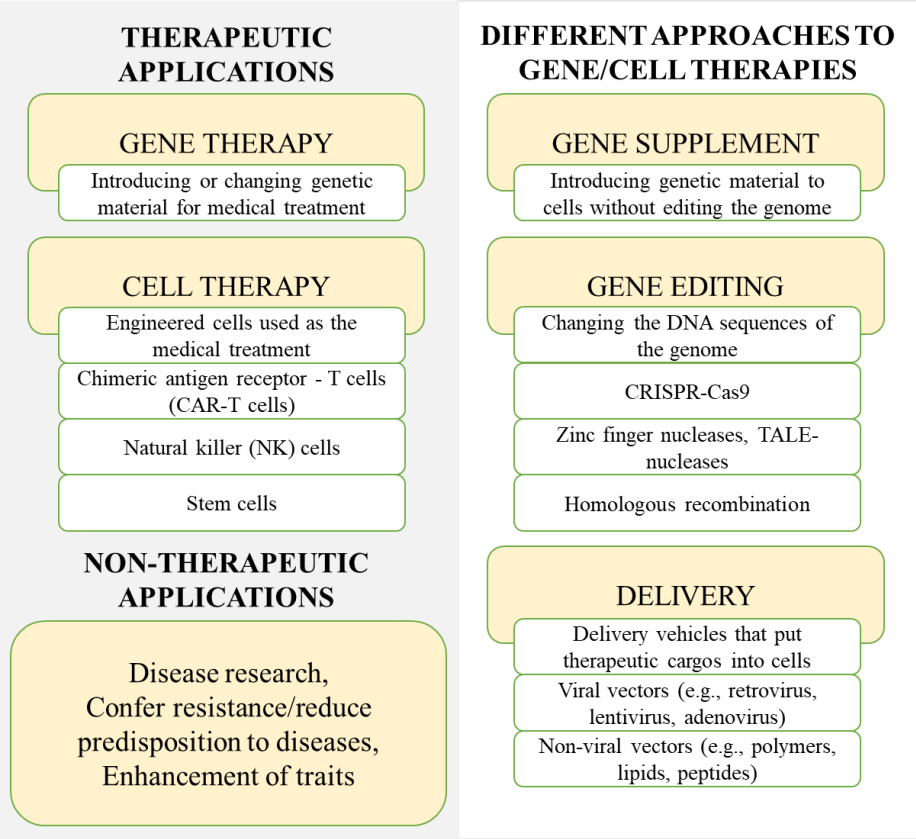
Gene therapy may be performed *in vivo*, in which the therapeutic gene is directly delivered to cells inside the patient's body, or *ex vivo*, in which the therapeutic gene is inserted into cells outside the body before being introduced into the body. *Ex vivo* gene therapy is also a form of cell therapy.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

4.6 **Cell therapy** refers to the introduction of new cells into a patient's body to grow, replace or repair damaged tissue in order to treat a disease.[16] The treatment regimen may employ cells from the patients' 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

[14] Li, H., Yang, Y., Hong, W. *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). doi:10.1038/s41392-019-0089-y.
[15] U.S. Food and Drug Administrative (2018). What is gene therapy? https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/what-gene-therapy. Retrieved on 7 September 2023.
[16] AstraZeneca (2023). Harnessing the Power of Cell Therapy https://www.astrazeneca.com/r-d/next-generation-therapeutics/cell-therapies.html. Retrieved on 7 September 2023.

introduce beneficial edits in targeted stem cells. Gene-edited stem cells are currently and increasingly investigated as a new therapeutic modality. 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.[17]

Figure 4.5: Schematic diagram showing different applications of gene editing, gene therapy, and cell therapy[18]



Similarities and differences between gene therapy and gene editing

4.7 Gene editing is employed in gene therapy where both targets 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 both gene editing and gene therapy are 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 to correct the protein produced by the DNA and restore proper cellular function.[19] 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.

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

[18] The non-therapeutic applications of gene editing stated in the schematic diagram are examples and not exhaustive.

[19] NHS England (2023). What are Genome Editing and Gene Therapy? https://www.genomicseducation.hee.nhs.uk/blog/what-are-genome-editing-and-gene-therapy/. Retrieved on 26 January 2024.

Gene therapy is solely used for therapeutic purposes, while gene editing has applications beyond therapeutics, such as understanding disease development, conferring resistance, and reducing predisposition to diseases, enhancement of traits, as well as other non-therapeutic applications of technology underlying human gene editing.

Similarities and differences between cell therapy and gene editing

4.8 Both 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, and 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 The inception of gene editing technologies 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 made using chimeric gene editing tools (e.g., ZFNs, TALENs, and CRISPR-Cas9) are powerful methods to assess gene function as well as precisely manipulate cellular behaviour and function. In particular, developments in gene editing technologies have been leveraged on 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 technologies have been used in research for various purposes and indications. Some examples of research conducted using gene editing technologies 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 production of proteins harbouring aberrant functions which result 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 target tumour cells specifically. This area of research is also receiving much attention in the pursuit of more effective treatment modalities in cancer.

b. Neurodegenerative Diseases

5.4 Neurodegenerative diseases (NDs), such as Alzheimer's, Huntington's, and Parkinson's diseases, are debilitating conditions with 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

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

[2] Dimitri, A., Herbst, F. and Fraietta, J.A. (2022) 'Engineering the next-generation of car T-cells with CRISPR-Cas9 gene editing', *Molecular Cancer*, 21(1). doi: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). doi:10.1016/j.ymthe.2019.10.009.

(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 tool to develop ND models for interrogating disease mechanisms as well as 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 external environmental factors. Gene-editing technologies have also been used to probe the mechanisms of hereditary eye diseases.[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] They found that the correction of the causative mutation in RPGR via CRISPR-Cas9 reverses ciliopathy and rescues photoreceptor loss by restoring gene expression, 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 touted to be beneficial in the study of human embryo development and understanding of birth defects. In the context of gene editing technologies, research involving human embryos may be carried out to potentially discover and develop new treatments for genetic or complex diseases, enhance longevity for healthy individuals by delaying ageing and 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 miscarriage. By doing so, the underlying genetic causes of these maladies may be established to facilitate the finding of new treatments.

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

[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). doi: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). doi: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* . doi: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), pp. 1267–1281. doi: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. Retrieved on 23 January 2024.
[9] Addie, S. *et al.* (2020) Stem Cell–Based Models of Human Embryos, *Examining the state of the science of Mammalian Embryo Model Systems: Proceedings of a workshop*. Washington, DC: The National Academies Press. https://www.ncbi.nlm.nih.gov/books/NBK560186. Retrieved on 23 January 2024.

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 should 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] The 14-day rule defines that biomedical research is allowed only in early human embryo development.[11] The rule 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. In view that there could potentially be further research development in gene editing for human embryos, there would 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 conduct large scale stakeholder (e.g., legislators, medical practitioners, and scientists) and public engagement to ensure that all views from the scientific and public communities are taken into consideration 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 to study early human development.

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

5.10 Rapid and accurate methods to diagnose diseases are equally and increasingly important to detect the onset of symptoms and allow 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 enables 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] Singapore (2017) 'No. S 622 Human Biomedical Research (Restricted Research) Regulations'. https://sso.agc.gov.sg/SL/HBRA2015-S622-2017. Retrieved on 23 January 2024.
[11] Blackshaw, B. P., & Rodger, D. (2021). Why we should not extend the 14-Day rule. *Journal of Medical Ethics, 47(10)*, pp. 712–714. doi: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), pp. 67–73. doi:10.1038/nature24033.
[13] Zhang, Z. *et al.* (2023). Functional nucleic acid-based biosensors for virus detection, *Advanced Agrochem*, 2(3), pp. 246–257. doi: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 done near a patient/person outside of the clinical laboratory setting) by untrained personnel to be done at home. Broadly, CRISPR-Cas9 diagnostics may be categorised into two classes, six types and several subtypes based on evolutionary relationships. While applications of CRISPR as diagnostics are mostly still in development, three notable ones 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 was developed in 2017 by the Broad Institute.[14] The 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 has 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.

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

5.13 In 2018, a CRISPR-based diagnostic method, DETECTR, that 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 identification of new drug targets and biomarkers presents an avenue in precision medicine.[17] This is particularly relevant for studies involving cancer 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 not only be used in high-throughput screening to discover novel

[14] Gootenberg, J.S. *et al.* (2017). Nucleic acid detection with CRISPR-CAS13A/C2C2, *Science*, 356(6336), pp. 438–442. doi: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/ Retrieved on 6 October 2023.
[16] Chen, J.S. *et al.* (2018). CRISPR-CAS12A target binding unleashes indiscriminate single-stranded DNase activity, *Science*, 360(6387), pp. 436–439. doi:10.1126/science.aar6245.
[17] Xing, H. and Meng, L. (2019). CRISPR-Cas9: A powerful tool towards precision medicine in cancer treatment, *Acta Pharmacologica Sinica*, 41(5), pp. 583–587. doi:10.1038/s41401-019-0322-9.

therapeutics but also in elucidating pathways driving drug resistance in cancer cells, and ultimately leading to the development of personalised treatments for patients.

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

5.15 Gene editing has been explored for its potential application in raising or conferring resistance of individuals to diseases. This could be achieved by altering genes commonly found in the general population to variants that are known or anticipated to be beneficial, thereby enhancing certain traits of the individual. For instance, the β-globin (HBB) gene involved in the genetic blood disorder beta-thalassaemia was first modified in zygotes in 2015.[18] However, findings from the 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 area of treating diseases, there are possibilities for the 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 could be illustrated by the experiment conducted by He Jiankui in China that led to the birth of genetically enhanced babies.[19] He used CRISPR-Cas9 to modify the CCR5 gene in human embryos with the intention to produce human babies with increased resistance to HIV infections. CCR5 is a co-receptor expressed on the surface of immune cells involved in signalling and coordination of immune responses, and it acts like a 'door' that allows the HIV entrance into the cell, therefore playing an essential role in HIV pathogenesis. Mutation in CCR5 gene locks "the door" which prevents HIV from entering into 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 the possible health risks to the babies in the future, which led to criticisms for his risky conduct of ethically contentious and medically unjustified procedure[22] (see Chapter 12 'Genetic Enhancement and the Effects on Society' 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 for the purpose of enhancing specific traits would need to be clearly evaluated before the technology is approved for widespread use.

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

[19] Normile, D. (2018). CRISPR bombshell: Chinese researcher claims to have created gene-edited twins. https://www.science.org/content/article/crispr-bombshell-chinese-researcher-claims-have-created-gene-edited-twins Retrieved on 6 October 2023.

[20] Julia, P. (2013). HIV resistant mutation. https://www.nature.com/scitable/blog/viruses101/hiv_resistant_mutation/#:~:text=The%20mutation%20causes%20the%20CCR5,from%20entering%20into%20the%20cell Retrieved on 6 October 2023.

[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 Retrieved on 16 October 2023.

[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 Retrieved on 16 October 2023.

[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), pp. 581–588. doi:10.1007/s10815-016-0710-8.

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

5.17 Gene editing strategies developed or are being studied in clinical trials are largely for lethal diseases that are typically associated with single nucleotide variants (SNVs) and are relatively low in prevalence within the general population. Polygenic 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 in the Rice University developed the "drive and process" (DAP) array, which is a streamlined CRISPR-based technology that is able to correct dozens of errors at the same time 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 will be conducted for their gene therapy, VERVE-101.[26] The 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 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 treatment of diseases is widely studied for its potential to correct aberrant genetic mutations with high 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 the mutations for treatment of diseases, which are discussed as follows:

a. Human Immunodeficiency Virus (HIV)

[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, pp. 135–152. doi: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 Retrieved on 6 October 2023.
[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*. https://ir.vervetx.com/news-releases/news-release-details/verve-therapeutics-doses-first-human-investigational-vivo-base Retrieved on 6 October 2023.

5.20 HIV is a major public health concern, where millions are infected and many die from its complications every year.[27] However, there is no effective vaccine and 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 challenging primarily due to the 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 to achieve a functional HIV cure. For example, a research conducted in the US in 2014 studied the NHEJ-mediated 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 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

[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 Retrieved on 6 October 2023.

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

[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), pp. 901–910. doi:10.1056/nejmoa1300662.

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

[31] Sagar, D. *et al.* (2005). Molecular origin of polyglutamine aggregation in neurodegenerative diseases, *PLoS Computational Biology*, 1(3), p. 30. doi: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). doi: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*. doi:10.1101/2023.01.20.524978.

expression by precisely editing survival motor neuron 2 (SMN2), possibly delivering 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. β-thalassaemia

5.23 β-thalassaemia is a genetic blood disorder caused by β-chain deficiency in haemoglobin production. The standard treatment for β-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 diseases.[35] Gene editing applied to β-thalassaemia can treat the disease 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 β-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. The study however 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 for the treatment of β-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 for β-thalassaemia.

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

5.24 This section will only discuss 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 would be discussed in-depth in the subsequent chapters (i.e., from Chapters 6 to 10).

a. Conventional treatments

[34] Mahajan, R. (2019). Onasemnogene Abeparvovec for spinal muscular atrophy: The Costlier Drug Ever, *International Journal of Applied and Basic Medical Research*, 9(3), p. 127. doi:10.4103/ijabmr.ijabmr_190_19.

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

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

5.25 While gene editing offers new and promising strategies to the treatment of severe diseases which lack effective cures in most cases, the technology is still in development and requires deep scrutiny prior to approval for widespread clinical applications. 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 heritable gene editing.

5.26 Conventional treatments are generally regarded to be safe for clinical use and had demonstrated good clinical efficacy given that 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 in patients who have developed resistance to treatments (e.g., chemotherapy resistance in cancer), and hence, 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 her foetus' health, and primarily consists of prenatal screening and prenatal diagnosis.[37] Screening tests are used to identify the likelihood of abnormalities 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 may also choose not to undergo any prenatal testing for such abnormalities.

5.28 Prenatal testing assures parents of the foetus's condition and allows them to obtain information about the possibility of predispositions for certain genetic conditions to 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 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 therapeutic termination of 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 it is dependent on the

[37] Mayo Clinic (2022). Prenatal testing: Is it right for you? https://www.mayoclinic.org/healthy-lifestyle/pregnancy-week-by-week/in-depth/prenatal-testing/art-20045177 Retrieved on 6 October 2023.
[38] Women's Health Institute. (2023). The benefits of prenatal testing. https://www.whisanantonio.com/the-benefits-of-prenatal-testing/ Retrieved on 6 October 2023.
[39] Sparks T.N. (2021). The current state and future of fetal therapies. *Clinical Obstetrics and Gynecology*, 64(4): 926-932. doi:10.1097/GRF.0000000000000651.
[40] Bringman, J.J. (2014). Invasive prenatal genetic testing: A Catholic healthcare provider's perspective, *The Linacre Quarterly*, 81(4), pp. 302–313. doi:10.1179/2050854914y.0000000022.

specific type of test employed, such procedures are generally accompanied with an increased risk of miscarriage and other pregnancy complications. For instance, the rate of miscarriage with amniocentesis is about 1 in 200, and carries 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 of 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 available tests such as non-invasive prenatal testing (NIPT) which are non-invasive, these tests are primarily used 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.

5.30 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[45] 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.[46] 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.

c. Adoption

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

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[41] March of Dimes (2017). Amniocentesis. https://www.marchofdimes.org/find-support/topics/planning-baby/amniocentesis Retrieved on 6 October 2023.

[42] National Health Service (NHS) UK. (2023). Chorionic Villus Sampling: Complications. https://www.nhs.uk/conditions/chorionic-villus-sampling-cvs/risks/. Retrieved on 25 January 2024.

[43] Ghidini, A. *et al.* (1993). Complications of fetal blood sampling, *American Journal of Obstetrics and Gynecology*, 168(5), pp. 1339–1344. doi: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. doi:10.3390/diagnostics13152570.

[45] Tan, T. (2015). Combined first trimester screen or noninvasive prenatal testing or both, *Singapore Medical Journal*, 56(01), pp. 1–3. doi:10.11622/smedj.2015001.

[46] Ministry of Health Singapore (2004). Guidelines on termination of pregnancy. https://www.moh.gov.sg/docs/librariesprovider4/default-document-library/(2)_guidelines-on-termination-of-pregnancy.pdf Retrieved on 6 October 2023.

5.32 Adoption provides couples, who are unable to produce children that are genetically healthy, an opportunity to complete their family. However, it 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 primarily used to prevent or reduce the 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 for 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 that 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 known genetic, structural, or other abnormality identified during prenatal testing.[49]

5.34 However, the procedure is also accompanied by 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 chance of a viable embryo to be successfully implanted is subjected 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) is 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

[47] Brodzinsky, D.M. (2011). Children's Understanding of Adoption: Developmental and Clinical Implications, *Professional Psychology: Research and Practice*, 42(2), pp. 200–207. doi:10.1037/a0022415.
[48] Beriwal, S., Impey, L. and Ioannou, C. (2020). Multifetal pregnancy reduction and selective termination, *The Obstetrician & Gynaecologist*, 22(4), pp. 284–292. doi:10.1111/tog.12690.
[49] Rochon, M. and Stone, J. (2022). Multifetal pregnancy reduction and selective termination, *UpToDate*. https://www.uptodate.com/contents/multifetal-pregnancy-reduction-and-selective-termination Retrieved on 6 October 2023.
[50] Weiran, Z. *et al*. (2021). Retained placenta creta after selective fetal reduction in twin pregnancy: a case report. https://mednexus.org/doi/full/10.1097/FM9.0000000000000117. Retrieved on 25 January 2024.
[51] Miremberg, H. *et al.* (2023). Adverse outcome following selective termination of presenting twin vs non-presenting twin, *Ultrasound in Obstetrics & Gynecology*, 61(6), pp. 705-709. doi: 10.1002/uog.26170.
[52] Mastenbroek, S. *et al.* (2011). Embryo selection in IVF, *Human Reproduction*, 26(5), pp. 964–966. doi:10.1093/humrep/der050.
[53] Elpida, F. (2007). Preimplantation genetic diagnosis: present and future, *Journal of assisted reproduction and genetics*, 24(6), pp: 201 – 207. doi: 10.1007/s10815-007-9112-2.

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 without the inherited genetic disorder. However, embryo selection is limited and may not be a feasible option in situations where all or majority of embryos are affected from 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 sufficiently healthy to lead to successful pregnancy, or when one or both parents are affected by genetic condition(s), which may prevent or affect 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 has 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.

g. Intrauterine foetal gene therapy

5.39 Gene editing technologies 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 currently not available for clinical use, it might be a possible 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, therefore making foetal gene therapy a promising alternative to heritable gene editing. However, similar to other genetic modifying technologies, foetal

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

gene therapy may cause insertional mutagenesis, oncogenesis, genetic mutation transfer from mother to child and foetal disruption.

5.41 The applications of HNGE stretches 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 research groups aforementioned are largely preliminary and necessitate further studies to determine the long-term safety and efficacy of gene editing technologies. Studies pertaining to the difference in idiosyncratic effects due to individual genetic variations should also be taken into consideration. Therefore, until the safety and efficacy of HNGE technologies are demonstrated in pre-clinical studies and in clinical trials approved under regulated clinical trial framework, the current established methods would be preferred to treat or prevent diseases in individuals and future offsprings.

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

6.1 Targeted modifications to nuclear DNA and gene editing technologies have the potential to prevent, treat, or 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] Such technologies could 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 to individuals and the society, 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 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. This phenomenon may occur when gene editing is conducted on embryos beyond the single-cell stage (i.e., after significant DNA replication and cell division take place)[3]. It 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 increased risk of birth disorders and genetic diseases, given that there are no current non-destructive method to determine 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 be inflicted with severe genetic diseases that could be more fatal than 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 (if permitted in the future):

a. Proportionality

[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). doi:10.1038/s41392-019-0089-y.

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

[3] National Academies Press (US). (2020). Heritable Human Genome Editing. Chapter 2: The State of Science. https://www.ncbi.nlm.nih.gov/books/NBK565923. Retrieved on 26 October 2023.

[4] Lamas-Toranzo, I. *et al.* (2019) Strategies to reduce genetic mosaicism following CRISPR-mediated genome edition in bovine embryos. *Scientific Reports*, 9(1). doi:10.1038/s41598-019-51366-8.

6.3 The principle of *proportionality* requires researchers to ensure that 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 technologies for treatment of diseases, conferring resistance, enhancement of traits, or for treatment of infertility. With the lack of sufficient safety and efficacy data for interventions employing heritable gene editing, the existence 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 on 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 mother. Therefore, heritable gene editing for treatment of diseases, conferring resistance, enhancement of traits or for infertility should be considered only if scientific and technological advancements are able to reduce mosaicism or mitigate the effects of mosaicism.

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 its future generations. Given that gene editing technologies have the potential to 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. This may potentially compromise 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 would be important to validate the safety and efficacy of gene editing technologies before they are used for clinical applications involving heritable gene editing.

c. Solidarity

6.5 The principle of *solidarity* maintains that benefits harnessed from research and applications of HNGE involving altruistic participation from individuals should extend to the society and that risks should be minimised. Given that heritable gene editing for treatment of diseases, conferring resistance, enhancement of traits or for infertility have the possibility to result in chromosomal mosaicism and miscarriages, research participants and people undergoing such procedures may be exposed to harm that could also affect the future generations. The

[5] Mehravar, M. et al., Shirazi, A., Nazari, M., & Banan, M. (2019). Mosaicism in CRISPR/cas9-mediated genome editing. Developmental Biology, 445(2), pp 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). doi:10.1186/s12920-022-01187-y.

[7] Sina, A, and Jennifer, F.K. (2021). Pregnancy and Neonatal Outcomes after Transfer of Mosaic Embryos: A Review. *Journal of Clinical Medicine*, 10(7). doi:10.3390/jcm10071369.

principle of *solidarity* and consideration of the public good deserve greater consideration in making sure that advances in HNGE become shared benefits.[8] Hence, heritable gene editing should not be conducted until they are proved to be safe and beneficial to the research participants and the society.

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. This is known as off-target effects. The ability to reduce the frequency of unwanted changes and the ability to detect off-target mutations when they occur have both progressed in recent years, where 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 (heritable or non-heritable) still harbour the possibility of causing DNA deletions and rearrangements which can eventually lead to genome instability and disruption of the functional genes.[9] As such, this may result in aberrant cell cycles, unprecedented changes in gene expression and regulation.[10] Risk of further complications such as development of cancer and allergic reactions, would be dependent on the type 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 applications:

a. Proportionality

6.7 The principle of *proportionality* provides that the risks of clinical applications involving HNGE are not disproportionate to their benefits by minimising the harm to individuals and future offspring while maximising 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 result in harmful consequences for

[8] John, J. M, Benjamin, C., et. al. (2017). Ethical Issues of CRISPR technology and gene editing through the lens of solidarity. British Medical Bulletin, 122, pp 17 – 29. doi; 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), pp. 406–416. doi: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/. Retrieved on 26 October 2023.
[11] National Hearth, 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. Retrieved on 1 November 2023.

healthy gene function[12] and affect the health and well-being of patients undergoing clinical trials on non-heritable gene editing[13]. These consequences could outweigh the benefits of non-heritable gene editing, such as 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 on 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 would be essential for further studies on non-heritable gene editing to be conducted to fully understand the unintended consequences of HNGE.

b. Sustainability

6.8 The principle of *sustainability* provides that clinical applications of HNGE should ensure that adverse effects or harm rendered by the use of the technology are not perpetuated to future generations. Although heritable gene editing holds promise in preventing and treating debilitating inherited diseases, and enabling infertile couples to conceive children, a study at Oregon Health and Science University reveals 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 well-being. In another research, by researchers at Columbia University, that aimed at fixing defective DNA in human embryos using CRISPR-Cas9, it was found that the editing caused unintended changes, such as loss of an entire chromosome in more than 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 done safely. Therefore, more research would need to be conducted to develop methods to mitigate off-target effects and other unintended mutations as a result of heritable gene editing on human embryos before gene-editing established pregnancy can be deemed safe.

c. Responsible stewardship of science

6.9 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 bear in mind the ethical guidelines governing its application. This includes setting research

[12] PHG Foundation (2023). Somatic genome editing: ethics and regulation. https://www.phgfoundation.org/briefing/somatic-genome-editing-ethics-regulation. Retrieved on 26 October 2023.

[13] Li, H., Yang, Y., Hong, W., Huang, M., Wu, M., & Zhao, X. (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), pp. 268–282. doi:10.1016/j.gendis.2023.02.027.

[15] Erik, R. (2023). Study reveals limitations in evaluating gene editing technology in human embryos. https://news.ohsu.edu/2023/03/07/study-reveals-limitations-in-evaluating-gene-editing-technology-in-human-embryos#:~:text=In%20addition%2C%20the%20study%20reveals,harmful%20changes%20in%20the%20genome. Retrieved on 26 October 2023.

[16] Associated Press. (2020). Lab tests show risks of using CRISPR gene editing on embryos. https://www.statnews.com/2020/10/29/lab-tests-show-risks-of-using-crispr-gene-editing-on-embryos/. Retrieved on 26 October 2023.

priorities while considering the needs of the 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 existing errors arising from HNGE. For instance, gene editing tools with greater precision, such as base editors, have been investigated in preclinical disease models to determine their editing efficiencies and accuracy.[17] Patients undergoing gene editing interventions should be made fully aware of the potential risks prior to receiving the treatment, and their informed consent should be obtained prior to the procedure. Given that the off-target effects can now be sensitively and comprehensively quantified,[18] patients should be informed of the potential off-target risks, including the probability and level of risk involved (from low to extremely high severity) during genetic consultation.

6.10 HNGE has been postulated to advance medicine significantly given its potential to offer novel methods of curing diseases, enhancing traits, conferring resistance, and treating infertility. However, it is clear that the current state of the technology is largely in the nascent stage that is lacking in both safety and efficacy data. Therefore, the risks entailed largely outweigh the benefits perceived from the use of gene editing technologies, which compromise on the principle of *proportionality*. With the current understanding of gene editing tools, it is difficult to ascertain that future generations of individuals receiving the treatment would be free of harm, which places the principles of *sustainability* and *solidarity* into question. Nonetheless, research in HNGE have continued to improve the precision of gene editing technologies to ensure *responsible stewardship of science*.

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

[18] 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). doi:10.1126/sciadv.abo7676.

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 its early development, which raises concerns regarding the 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 to manage 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 approved for use.[1,3] Notable ones that have been granted the Regenerative Medicine Advanced Therapy (RMAT) designation by the FDA for accelerated approval include, *inter alia*, exagamglogene autotemcel (exa-cel) for sickle cell disease (SCD) and transfusion-dependent beta thalassaemia (TDT).[2] This same treatment was approved by the UK and is sold under the brand name '*Casgevy*', and is meant to prevent episodes of excruciating pain that are typical of sickle cell disease and free people with beta thalassaemia from regular blood transfusions.[3] Another treatment that is granted accelerated approval by the FDA is CRISPR-modified chimeric antigen receptor T (CAR-T) cells that targets cancer cells for leukaemia and lymphoma, bringing hope to afflicted patients who otherwise do not have 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 remain to be sufficiently addressed even in preclinical studies.[4] As such, unforeseeable repercussions could arise years after patients received treatment from non-heritable gene editing clinical trials and may result in undesirable biological consequences or side effects. For instance, off-target modifications resulting from the treatment of gene editing could trigger activation of cancer-causing genes and affect the

[1] Henderson, H. (2023). CRISPR clinical trials: A 2023 update. *Innovative Genomics Institute (IGI)*. https://innovativegenomics.org/news/crispr-clinical-trials-2023/ Retrieved on 17 November 2023.
[2] 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 Retrieved on 17 November 2023.
[3] Emily, M. (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/. Retrieved on 21 November 2023.
[4] Doudna, J.A. (2020). The promise and challenge of therapeutic genome editing, *Nature*, 578(7794), pp. 229–236. doi:10.1038/s41586-020-1978-5.

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 the risks of HNGE technologies are not disproportionate to its benefits, by minimising the harm to individuals and future offspring while maximising benefits using non-heritable gene editing. 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, 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.

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 largely unknown long-term effects of gene editing technologies, 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 gaining short term benefits. Appropriate measures, such as establishing guidelines for evaluating off-target effects[7] and risk assessments,[8] should be taken by researchers to anticipate and/or manage uncertainties and long-term consequences associated with non-heritable gene editing to ensure *responsible stewardship of science*. Patients should be fully informed of the risks and proper informed consent should be taken prior to participating in clinical trials or receiving any treatment of non-heritable gene editing.

7.6 Given that the long-term safety of non-heritable gene editing has not been fully established, it is essential for researchers and physicians to conduct long-term follow-up on patients and participants of clinical trials evaluating new therapeutic modalities for non-heritable gene editing. This would help to mitigate the risk of any delayed adverse event occurring due to

[5] Teboul, L. et al. (2020) 'Variability in genome editing outcomes: Challenges for research reproducibility and clinical safety', Molecular Therapy, 28(6), pp. 1422–1431. doi: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*. Available at: https://smer.se/wp-content/uploads/2022/04/smer-2022_1_english_summary_webb.pdf. Retrieved on 17 November 2023.
[7] Ishii, T. (2016). Somatic Genome Editing for Health: Disease Treatments and Beyond. *Curr Stem Cell Rep* 2, 313–320. https://doi.org/10.1007/s40778-016-0061-5.
[8] Bittlinger, M. *et al.* (2022). Risk assessment in gene therapy and somatic genome-editing: An expert interview study. *Gene and Genome Editing*, 3–4, p. 100011. doi:10.1016/j.ggedit.2022.100011.

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 up to 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 poses the following ethical challenges:

i. Experimental approaches commonly employed in clinical trials such as randomised controlled trials are usually not suitable for long-term monitoring.[12] This is because subjects randomly assigned to a particular treatment regimen for prolonged periods (e.g., five or more years) or to a placebo group may choose to opt out of the study in the event a better treatment becomes available, or may decide to switch therapy for other reasons such as poor prognosis or treatment-related side effects.[13]

ii. The use of placebo may become less ethical and relevant for trials with increased study durations, especially in situations where patients with dilapidating conditions, such as cardiovascular diseases or cancer, are placed in the placebo control group.[14] Clinical trials carried over a longer duration also necessitates an open label study design where both researchers and participants are aware of the treatment being administered. Otherwise, researchers may conduct an uncontrolled trial (without a placebo group), with all participants receiving the same treatment if there is no standard of care, and might reap results that are insufficient to establish efficacy of the intervention.[12] Nonetheless, 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.

iii. As the duration of a study increases, the number of research subjects in the study may decline further. It was reported that in four participants drop out on average, citing reasons such as fear of side effects, study procedures,

[9] Meredith, L. (2022). Long-term follow-up studies: Gene therapy products, protocols and potential issues. https://www.Precisionformedicine.com/blogs/long-term-follow-up-studies-gene-therapy-products-protocols-potential-issues/. Retrieved on 21 November 2023.
[10] Hacein-Bey-Abina, S. *et al.* (2008). Insertional oncogenesis in 4 patients after retrovirus-mediated gene therapy of SCID-X1. *Journal of Clinical Investigation*, 118(9), pp. 3132–3142. doi:10.1172/jci35700.
[11] (2021). Gene therapy needs a long-term approach. *Nature Medicine, 27, 563*. Doi:10.1038/s41591-021-01333-6.
[12] Herbert, R.D., Kasza, J. and Bø, K. (2018) Analysis of randomised trials with long-term follow-up, *BMC Medical Research Methodology*, 18(1). doi: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 Med Res Methodol* 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), pp. 1121–1124. doi:10.1359/jbmr.2003.18.6.1121.

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

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, clinical applications of heritable gene editing raise significantly more concern pertaining to the safety and long-term consequences of its use.[16] 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.[17]

7.8 Mutations introduced to genes may interact with inherent gene variants present within an individual and effect unprecedented biological outcomes.[18] 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 called 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 occur during natural cellular processes such as cell division, or due to environmental factors such as exposure to ultraviolet radiation from the sun or smoking.[19] While heritable gene editing can present prospective parents the opportunity to have a biological child without passing on a genetically-heritable disease, the current technology still lacks the ability to predict how these exogenous genetic alterations may interact with existing gene variants within the child. The difficulty in anticipating and in turn, mitigating possible side effects arising from the intrinsic genetic interaction as well as that with the environment could expose the 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 suggests the unpredictability of the long-term consequences.

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 only performed on a small group

[15] Poongothai, S. *et al.* (2023). Strategies for participant retention in Long Term Clinical Trials: A participant – centric approaches. *Perspectives in Clinical Research*, 14(1), p. 3. doi:10.4103/picr.picr_161_21.
[16] Almeida, M. and Ranisch, R. (2022). Beyond safety: Mapping the ethical debate on Heritable genome editing interventions. *Humanities and Social Sciences Communications*, 9(1). doi:10.1057/s41599-022-01147-y.
[17] Rubeis, G. and Steger, F. (2018). Risks and benefits of human germline genome editing: An ethical analysis. *Asian Bioethics Review*, 10(2), pp. 133–141. doi:10.1007/s41649-018-0056-x.
[18] Mani, R. *et al.* (2008). Defining genetic interaction. *Proceedings of the National Academy of Sciences*, 105(9), pp. 3461–3466. doi:10.1073/pnas.0712255105.
[19] 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/. (Retrieved on 10 November 2023).

of cells.[20] The current ability to perform quality control experiments on only a subset of cells means that the precise effects of genetic modification to 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 for years even 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 21% increase in their mortality rate. The CCR5 gene has been widely demonstrated to be involved 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,[21] 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 above considerations, researchers are advised to consider the following ethical principles when conducting heritable gene editing for 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 of gene editing technologies are put to good use to improve health outcomes, and to acknowledge the difficulties and uncertainties along with the benefits of heritable gene editing for clinical applications (if permitted in the future). Researchers also have the 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 of the gene editing technologies, 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 the future offspring. The use of heritable gene editing can only be considered safe for clinical applications following further research studies to prove the safety and efficacy of gene editing technologies.

b. Sustainability

7.12 The principle of *sustainability* provides that research and applications of HNGE should ensure that adverse effects or harm rendered from gene editing technologies are not passed down to future generations. Given that the long-term consequences of the heritable gene editing cannot be predicted or mitigated until the birth of the modified child, any of its clinical applications would infringe the principle of *sustainability* as the welfare of the offspring and future generations are likely compromised when exposed to serious side effects.

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

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

7.13 Intergenerational monitoring, which refers to long-term follow-up studies of research participants and their descendants, could help researchers to 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.[22] One example of intergenerational monitoring in biomedical research would be the Framingham Heart Study examining the natural history, risk factors, and prognosis of cardiovascular, lung, and other diseases. The study began recruitment of research subjects in 1948, and enrolled the second and third generation of the original subjects in 1971 and 2002 respectively. The follow-up studies included clinical and laboratory assessments of cardiac structure and function.[23] However, intergenerational monitoring in clinical trials, 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 appropriate consent of the participants.[24] 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 management of risks associated with heritable gene editing and communication of any adverse findings with subjects on whom intergenerational monitoring is carried out.[22] The waiver could apply to certain key aspects of the child's life as well as its 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.[22]

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

[22] Cwik, B. (2019). Intergenerational monitoring in clinical trials of germline gene editing. *Journal of Medical Ethics*, 46(3), pp. 183–187. doi:10.1136/medethics-2019-105620.
[23] 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), 1328-35. doi:10.1093/aje/kwm021.
[24] Ranisch, R., Trettenbach, K. and Arnason, G. (2022). Initial heritable genome editing: Mapping a responsible pathway from basic research to the Clinic. *Medicine, Health Care and Philosophy*, 26(1), pp. 21–35. doi: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[25] as well as modifying the genes associated with infertility in germ cells.[26] 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, and studies have revealed that several genes are indispensable for male fecundity.[27] However, preclinical studies have yet to establish the safety of these gene editing technologies in mammalian models and humans, apart from rats.[28] Hence, heritable gene editing is still considered to be unsafe for clinical use to treat male/female infertility as they can be exposed to unwanted side effects such as mutagenesis.[29] 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 researchers to ensure risks of heritable gene editing for infertility are not disproportionate to its benefits by minimising the harm to individuals and future offspring. Given the lack of safety data on current gene editing technologies for treatment of infertility in humans, clinical 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 other 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 the alternatives to HNGE).

7.17 Hence, while non-heritable and heritable gene editing hold tremendous promise for addressing genetic disorders and advancing medical science, the long-term safety and efficacy remain a paramount concern. The safety and ethical issues necessitate a cautious and well-regulated approach to ensure the responsible application of gene editing technologies until these concerns are addressed in the future. Rigorous research, ongoing

[25] 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), 10401-10436. doi:10.1073/pnas.1506974112

[26] Hall, S.S. (2016). The first tinkering with human heredity may happen in the infertility clinic. *Scientific American*. Available at: https://www.scientificamerican.com/article/the-first-tinkering-with-human-heredity-may-happen-in-the-infertility-clinic1/. Retrieved on 17 November 2023.

[27] Soojin, P, Keisuke, 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),* pp 195 to 204. doi:10.1093/biolre/ioaa084.

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

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

monitoring, and clear ethical guidelines are imperative to mitigate risks and uphold the wellbeing of individuals. It would also be important to consider the potential benefits from the advancements in HNGE and risks as well as ethical considerations to ensure the long-term safety and efficacy of the technology.

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

8.1 Human embryos have been used by researchers on 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. 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] However, the use of embryos in gene editing research raises several ethical issues. This chapter provides an overview on 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, the application of relevant ethical principles of *respect for persons*, *justice, proportionality*, and *transparency*, and recommendations to manage the ethical issues.

A. 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 originated because the primitive streak 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 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 at the time when the rule was implemented, with scientific advancement, maintaining physiologically normal embryos in culture beyond 14 days is becoming a foreseeable reality[5]. Hence, there has been continuing pressure to modify the rule. For example, many UK scientists are calling for the current 14-day limit on embryo research to be doubled to 28-days, so that they can study the

[1] Liang, P. *et al.* (2015). CRISPR/Cas9-mediated gene editing in human Tripronuclear zygotes. *Protein & Cell*, 6(5), pp. 363–372. doi:10.1007/s13238-015-0153-5.
[2] Ethics guidelines for human biomedical research (2021 revised) (2021). Bioethics Advisory Committee Singapore. https://www.bioethics-singapore.gov.sg/publications/reports/bac-ethics-guidelines-2021/. Retrieved on 8 December 2023.
[3] Insoo, H, Amy, W, and Josephine, J. (2016). Embryology policy: Revisit the 14-day rule. Nature 533, pp. 169 – 171. doi:10.1038/533169a.
[4] John, B, and Annelien, L. (2018). Should the 14-day rule for embryo research become the 28-day rule? *EMBO Molecular Medicine, 10:e9437*. doi: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. Retrieved on 7 November 2023.

unexplored areas of early human development. This 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 seven to 14 days is still in the early stages[7]. In addition, most discoveries to date have been within the first seven days, where researchers have been using gene editing technologies 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. Therefore, the BAC's position on this issue remains unchanged even for gene editing research.

B. 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 other couples with fertility difficulties;[9]

b. embryos created specifically for the purpose of research using gametes procured specifically for research studying 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 benefit from such research.[2] However, the Human Biomedical Research (Restricted Research) Regulations 2017 only allows surplus embryos created in assisted reproduction treatment to be used for biomedical research, following approval from the IRB[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 With regard to the use of oocytes or embryos in biomedical research, the BAC's position is that specific and personal consent from the donors must be obtained before any oocyte or

[6] Michelle, R. (2023). Scientists: Allow forbidden 28-day embryo experiments. BBC News. https://www.bbc.co.uk/news/health-67204553. Retrieved on 2 November 2023.
[7] Bruce, P., and Daniel, R. (2021). Why we should not extend the 14-day rule. https://pubmed.ncbi.nlm.nih.gov/34112721/. Retrieved on 24 January 2024.
[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. Retrieved on 24 January 2024.
[9] Machado, C.S. (2020). The fate of surplus embryos: Ethical and emotional impacts on assisted reproduction. *JBRA Assisted Reproduction*. doi:10.5935/1518-0557.20200015.
[10] Human Biomedical Research (Restricted Research) Regulations 2017 (2017). https://sso.agc.gov.sg/SL/HBRA2015-S622-2017. Retrieved on 8 December 2023.

embryo is used for research. The potential donors should be provided with sufficient information and time to make an informed decision.[2] In particular, consent for donation of surplus oocytes or embryos should be kept separate from the consent of treatment for women undergoing fertility treatments. 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 the 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, there may be limited availability of gametes with desired genotypes or genetic profiles.[11] If a scientist becomes interested to study gene mutations in oocytes for a given disease-causing gene, or to correct a specific gene mutation, it is essential to obtain oocytes with the desired genotype.[12] For such oocyte gene editing research, researchers may have to procure oocytes from women, which raises ethical issues as described below.

Issue 1: Risks involved in 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 has to undergo stimulation of her ovaries through multiple hormone injections. Thereafter, the oocytes are collected under mild anaesthesia via special needle attached to an ultrasound vaginal probe. Such ovarian stimulation carries some health risks, as it 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 be life-threatening if severe, although such cases are rare.[14] Such risk for 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 the 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 of oocyte procurement in healthy donors.[15]

[11] Emilia, N. & Heidi, C. (2020). Ethical issues related to research on genome editing in humans. *Computational and Structural Biotechnology Journal*, *18*, pp 887 – 896. doi: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. doi: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. Retrieved on 1 March 2024.
[14] Donation of Human Eggs for Research. (2008). *Bioethics Advisory Committee Singapore*. https://www.bioethics-singapore.gov.sg/files/publications/reports/donation-of-human-eggs-for-research-full-report. Retrieved on 24 January 2024.
[15] Ma, H. et al. (2017). Correction of a pathogenic gene mutation in human embryos. *Nature, 548(7668)*, pp. 413–419. doi:10.1038/nature23305.

Other potential risks could also be psychological in nature, including anxiety, mood swings, and post-donation adjustment.[16]

8.11 With the scarcity of human embryos and gametes, particularly oocytes that are available for biomedical research, this generates various concerns. These concerns would include the risk of exploitation through commercialisation of eggs as an unintended consequence of substantial compensation amounting to an inducement,[14] which 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 loss of time and earnings.[14] However, in such cases, it would be difficult to determine a level of compensation that will 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 the above considerations, researchers are advised to consider the following ethical principles when procuring oocytes for the purpose of HNGE research studying 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 respecting their rights to make their own decisions and ensuring that 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 impinged on. It is also important that there are safeguards to protect oocyte donors and ensure that there is no coercion or undue influence on their decision to donate. 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 maintain donation as an altruistic act done without inducement. The Act, however, allows for the reimbursement of any reasonable expenses incurred by a person 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 fairly reciprocate individuals' contribution to HNGE research, and that researchers and their institutions shoulder some responsibility for the welfare of participants in the event of adverse outcomes arising directly from their

[16] National Academies Press. (2007). Assessing the Medical Risks of Human Oocyte Donation for Stem Cell Research: Workshop Report. https://nap.nationalacademies.org/read/11832/chapter/3. Retrieved on 24 January 2024.
[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).* Pp 37 – 44. doi: 10.1016/j.scr.2007.09.003.
[18] Singapore Human Cloning and Other Prohibited Practices Act. (2004). https://sso.agc.gov.sg/Act/HCOPPA2004. Retrieved on 8 December 2023.

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, only if the eggs were obtained 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 or the quality of the eggs obtained, as it is not payment for the eggs.[14] This also applies 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 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, it is less clear as to whether compensation for loss of time and earnings to donors are permitted and there should be more clarity provided by the relevant regulatory authority on the stance. The relevant regulatory authority 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, the relevant regulatory authority should determine an appropriate compensatory amount for these donors based on the time spent as a result of the procedures required to obtain the eggs for research. The authority may need to review current legislation to determine whether legislative amendments are required to implement any proposal for compensation.[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 the medical care when required.[14] This also applies for gene editing research in embryos or germline cells.

c. Proportionality

8.16 The principle of *proportionality* requires researchers to ensure the risks of HNGE research are not disproportionate to its 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 (even risk of death), it would be important for researchers to weigh the benefits of procuring oocytes solely for gene editing research against the risks 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.

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, and it might be possible that not all gamete donors are adequately informed of this aspect of research and its implications.[11] For example, the informed consent forms used in the study on heterozygous MYBPC3 mentioned above did not explicitly mention about the genome sequencing aspect of the research. Inadequate information and understanding of what research participation entails undermines consent for research and may cause subsequent withdrawal of consent and loss of trust, if donors find out that they have not been informed of genomic sequencing. Genomic sequencing could also lead to a breach of privacy and confidentiality of donors' genomic data. For example, genomic sequencing can query nearly all protein-coding regions of the human genome at once, including most genes believed to have roles in disease. For researchers to glean meaning from these data, they must be accompanied by phenotypic and demographic information. This increases the likelihood that data may be linked back to individuals who contributed the data, even when de-identified. Hence, breaching the confidentiality of donors' genomic data. In addition, researchers may share these data in biorepositories and databases, which may lead to misuses of genetic information, that relate to risk 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 helps to 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. 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 confidentiality of disclosed information to minimise harm to them. Therefore, it is important for researchers to ensure that data obtained from genome sequencing during gene editing research on human embryos are not misused, and ensure the security of data storage, so that the privacy and confidentiality of embryo or gamete donors are not breached.

8.20 The ethical considerations surrounding oocyte procurement and 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

[19] Leila, J; Julie, C, et. Al. (2014). Research participants' attitudes towards the confidentiality of genomic sequence information. *European Journal of Human Genetics,* 22, pp. 964-968. doi:10.1038/ejhg.2013.276.

imperatives of informed consent and potential consequences are paramount, and this could be achieved when researchers and research institutions prioritise respect for the autonomy and well-being of oocyte donors, as well as ensure transparency in the research process.

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. These technologies can also be potentially used for enhancing specific traits. However, as with many new modalities in medicine, gene editing technologies would give rise to concerns of inequitable access by those who are in need but cannot afford them. This affects particularly the low and middle income countries, where there is insufficient funding and support for healthcare and 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 remains in much debate pertaining 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 relevant to 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 market exclusivity granted by patents.[3] It is estimated that in 2016, gene therapies have an average cost of between 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, which 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 are due 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, and the costs are set higher to maximise return on investments for these companies. Nonetheless, it is possible that gene editing interventions may be scaled up and made accessible to more people at affordable

[1] Mohiuddin, A.K. (2019). Affordability issues of biotech drugs in low- and middle-income countries. *Juniper Online Journal of Public Health*, 5(1). doi: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), pp. 1–11. doi:10.1038/s41431-017-0024-z.
[3] Muigai, A.W. (2022). Expanding global access to genetic therapies. *Nature Biotechnology*, 40(1), pp. 20–21. doi:10.1038/s41587-021-01191-0.
[4] Marsden, G. *et al*. (2017). Gene Therapy: Understanding the science, assessing the evidence, and paying for value. *Institute for Clinical and Economic Review*. Report from the 2016 ICER Membership Policy Summit. https://icer.org/assessment/gene-therapy-2016/. Retrieved on 8 December 2023.
[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. Retrieved on 8 December 2023.
[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/. Retrieved on 8 December 2023.

costs in the longer term as these technologies advance and become increasingly prevalent following the availability of generics after the expiry of patents.[3] In addition, the Rare Disease Fund in Singapore has expanded in end 2023 to cover CTGTPs, which would help to mitigate the high costs involved for patients.[7] However, gaining equal access to HNGE technologies-based gene therapies may still pose challenges for the economically disadvantaged population. This 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 equitably shared in society. While therapeutic interventions employing gene editing may subsequently become affordable with greater scale of production, the current high cost of the technology may deny the less advantaged in the society access to such medical treatments.[8] This would further aggravate problems in healthcare equity since the benefits of gene editing technologies would not be equally accessible to all and thereby compromise the principle of *justice*.

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 everyone within the society. If medical treatments employing gene editing are costly, individuals with lower socioeconomic status would not be able to access them despite their needs.[9] As such, this inequity in access to medicine may be conceived as differential treatment especially if those that are denied access belong to minority populations, which would not be inclusive. 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 more urgent, and will require appropriate planning for costs and infrastructural needs for gene therapy treatments.[10] Currently, the European Union (EU) is undergoing discussions to update its pharmaceuticals legislation, where one of the objectives is to create a balanced system for pharmaceuticals in the EU that promotes

[7] Ministry of Health (2023). Rare Disease Fund. https://www.moh.gov.sg/news-highlights/details/rare-disease-fund. Retrieved on 9 February 2024.
[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), pp. 874–882. doi:10.2105/ajph.2023.307315.
[9] Hildebrandt, C. and Marron, J. (2018). Justice in CRISPR/cas9 research and clinical applications. *AMA Journal of Ethics*, 20(9). doi:10.1001/amajethics.2018.826.
[10] 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. Retrieved on 8 December 2023.

affordability for health systems, including advanced therapy medicinal products (ATMPs), while rewarding innovation.[11]

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.[12] However, it was perceived that more clinical trials were funded and conducted in the United States of America, Europe and United Kingdom than in Asia.[13] This was observed in the low participation of Asians in clinical trials, according to a 2020 analysis of global participation in clinical trials conducted by the FDA.[14] It was reported that out of 292,537 clinical trial participants globally, 76% were white, 11% were Asians, 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 frequency present in different ethnic populations.[15] Some populations may respond better to specific drugs that result in better clinical outcomes. Therefore, design of clinical trials for HNGE research should consider the following principles:

a. Justice

9.6 The principle of *justice* provides fairness and equality for all individuals, where benefits harnessed from research and clinical applications of HNGE should be equitably shared in society. Sufficient Asian representation in research or clinical trials for gene editing will allow us to gain insights and extrapolate trends that are specific to the Asian population. If there is insufficient representation of Asians, it may not be possible to garner insights

[11] European Parliamentary Research Service (EPRS). (2023) *Revision of the EU pharmaceutical legislation. Initial Appraisal of a European Commission Impact Assessment*. https://www.europarl.europa.eu/RegData/etudes/BRIE/2023/747464/EPRS_BRI(2023)747464_EN.pdf. Retrieved on 8 December 2023.

[12] 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/. Retrieved on 8 December 2023.

[13] Number of clinical trials by year, country, who region and Income Group (1999-2019) (Mar 2020) (2020) *World Health Organization*. 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. Retrieved on 8 December 2023.

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

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

relevant to the Asian demographics to tailor customised healthcare for this population.[16] As a result, the population may not have equal access to or yield maximum benefits from the technology or research, undermining the principle of *justice*.

b. Inclusivity

9.7 The principle of *inclusivity* maintains that research and applications involving HNGE should be representative of population diversity and the benefits of such research should be globally accessible. To encourage more Asian participation in clinical trials for gene editing technologies, researchers can strengthen recruitment and engagement strategies to communicate the benefits of participating in biomedical research. This is so that the demographics of trial participants take into consideration the principle of *inclusivity* and consider the various genomic profiles of a multi-ethnic society like Singapore. Researchers should also improve access to information about clinical trials involving gene editing to promote 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 collects information of clinical trials using human gene editing technologies. In accordance with the principles of *transparency* and *inclusivity*, the HGE registry aims at making information about clinical trials using gene editing technologies easily accessible to all interested stakeholders, including the public.[17]

9.8 Developing new biotechnologies in unchartered grounds requires channelling of substantial funds and resources into the domain. Given the early stage of the HNGE technology, careful consideration to the eventual delivery of resultant therapies and prudent allocation of resources should be established. This is so that equitable access to healthcare by the population is ensured, following the principles of *justice* and *inclusivity* so that benefits reaped from 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 the diversity of Singapore's population. This would enable insights on clinical outcomes relevant to the local demographics to be harnessed for use so that the principles of *justice* and *inclusivity* are maintained.

[16] 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), pp. 646–649. doi:10.1007/s10903-021-01142-6.

[17] World Health Organisation (WHO). 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. Retrieved on 8 December 2023.

CHAPTER 10: GENETIC ENHANCEMENT AND THE EFFECTS ON SOCIETY

10.1 Gene editing is playing an increasing part in various therapeutic applications to treat and prevent diseases. Recent advances have increased the possibility that gene editing can also be used for purposes that go beyond therapies and medical interventions discussed in the previous chapters. Such 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. This chapter discusses the ethical issues involved in applications of gene editing technologies for genetic enhancement, and the application of relevant ethical principles of *proportionality, sustainability, justice, inclusivity, transparency, and responsible stewardship of science.*

10.2 Enhancing features of the human body is not an unfamiliar concept.[1] Biomedical technologies, such as drugs and surgical techniques, are increasingly being 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 different biomedical techniques that promise dramatic effects. One such technique is the brain-machine interfacing, which some predict may allow human brains to be connected directly to computers to improve our information processing abilities.[2] Given the incremental use and progress in scientific technology, many forms of enhancements are broadly accepted by the society today and seen as efforts to improve the lives of people with disabilities.[1] While many of the current methods used for physical, functional or mental enhancements only affect the individuals and not future generations, this would not be the case if gene editing technologies are used for genetic enhancements.

10.3 An international survey was conducted by Pew Research Center in 20 countries from October 2019 to March 2020 across Europe, Russia, the Americas, and the Asia-Pacific on the view towards specific circumstances where gene editing may be used.[3] 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 comes to specific applications of human gene editing, including showing wide support for therapeutic uses.[3] A demographically representative sample of 1,501 people in Singapore, which included people of different genders, ages, education backgrounds, and regions, found that although 29% of the people responded that gene editing to change a baby's genetic characteristics and make the baby more intelligent would be appropriate, 62% responded that such applications would be

[1] Masci, D. (2016). Human enhancement, Pew Research Center Science & Society. https://www.pewresearch.org/science/2016/07/26/human-enhancement-the-scientific-and-ethical-dimensions-of-striving-for-perfection/. Retrieved on 28 December 2023.
[2] University of Oxford. (n.d.). Enhancement. https://www.practicalethics.ox.ac.uk/enhancement/. Retrieved on 16 May 2024.
[3] Funk, C. et al. (2020). Biotechnology research viewed with caution globally, but most support gene editing for babies to treat disease, Pew Research Center Science & Society. https://www.pewresearch.org/science/2020/12/10/biotechnology-research-viewed-with-caution-globally-but-most-support-gene-editing-for-babies-to-treat-disease/. Retrieved on 4 January 2024.

considered as a misuse of technology. While support for the notion was conceivably low, it was still substantially greater than the median support level of 14% in other surveyed countries.[3] In the same survey, 68% of the people responded that it would be appropriate to use gene editing to change a baby's genetic characteristics to treat a serious disease or conditions that the baby would have at birth, while 22% responded that such applications would be considered as misuse of technology.[3] As such, the local perspectives towards the applications of gene editing technologies are largely supportive if they are used for therapeutic purposes, but not for genetic enhancement.

10.4 The primary ethical concern with permitting heritable gene editing for the purpose of enhancement is that heritable gene editing may affect future generations. This is because any changes made to the genes of germline cells or embryos will be permanent and passed down to future generations. Hence, future offsprings may be subject to any unintended consequences or negative impacts that may arise as a result of genetic enhancement, which might compromise their wellbeing (discussed in the later part of this chapter).

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

10.5 Heritable gene editing, if permissible in future, will be employed in genetic enhancement where germline cells or human embryos are genetically modified to acquire advantageous features.[4] Although the perceived risks associated with gene editing technologies (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 be more justifiable as there is a clear medical need. However, risks involved in the applications of gene editing that goes beyond addressing medical conditions, may be less justifiable when the goals are not directly related to health improvement. Therefore, researchers, research institutions and IRBs are advised to consider the following ethical principle for applications of gene editing for enhancement if they are permitted in the future:

a. Proportionality

10.6 The principle of *proportionality* requires that risks of research and applications of gene editing technologies are not disproportionate to their benefits by minimising the harm to individuals and future offspring while maximising benefits. Gene editing for therapeutic purposes often target well-understood genetic mutations, reducing the likelihood of unintended consequences. In addition, severe illnesses caused by genetic disorders such as blood cancers and lymphomas often lack effective treatment options, and gene editing provides an alternative life-saving therapy. For such applications of gene editing, the risks involved may be proportionate to their benefits. On the other hand, heritable gene editing for genetic enhancement may involve manipulating multiple genes to achieve the desired traits, and the intricate interplay of genes in complex traits makes it challenging to accurately predict and control the outcomes.[4] Genetic enhancement to confer resistance to diseases or

[4] Cwik, B. (2019). Moving beyond "therapy" and "enhancement" in the ethics of gene editing. *Cambridge Quarterly of Healthcare Ethics, 28(04)*, pp. 695–707. doi:10.1017/s0963180119000641.

for enhancement of cognitive abilities, are often speculative and may be risky, especially since enhancement is not intended for medical purposes and may be passed down to future generations. Therefore, researchers are advised to weigh the benefits against the risks of applications of gene editing for enhancement should they be permitted in the future.

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

10.7 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.[5] While heritable gene editing for the purpose of enhancement could help to select for desirable traits by correcting natural biological variants, gene editing technologies may be misused and abused for purpose of creating 'designer babies' by removing unwanted genes.[6] 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 the genetically modified and unmodified individuals and exacerbate social inequities.[7] This may lead to the potential for establishing programs for design and preferential reproduction of "more desirable" and "better" kinds of human beings which borders on eugenics[5]. 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. Justice

10.8 The principle of *justice* encompasses the general principles of fairness and equality for all individuals and implies that access to the benefits of research and clinical applications involving gene editing technologies should be equitably shared in society. The high costs of gene editing would mean that only a small group of wealthy individuals may gain access to technologies for the purpose of enhancement.[8] This could affect the distribution of perceived advantages and disadvantages of genetic enhancement among people. As a result, the selected or desirable traits would be concentrated within a privileged wealthy group and could subject future generations to discrimination.[6] This may exacerbate and reinforce existing social division and inequality. Protecting the interests of future generations is important, particularly those who are vulnerable to discrimination or social inequities like individuals with disabilities or from lower-income backgrounds. This must be considered as a collective and shared responsibility of both the research community and the public. If permitted, the current generation's decisions to use gene editing technologies to enhance the traits of their future child could affect subsequent offspring. Given that applications of gene

[5] Friedmann, T. (2019). Genetic therapies, human genetic enhancement, and … eugenics?, *Gene Therapy*, 26(9), pp. 351–353. doi:10.1038/s41434-019-0088-1.
[6] Sufian, S. and Garland-Thomson, R. (2021). The Dark Side of CRISPR, Scientific American. https://www.scientificamerican.com/article/the-dark-side-of-crispr/. Retrieved on 15 January 2024.
[7] Lau, P.L. (2023). Evolved eugenics and reinforcement of "othering": Renewed Ethico-legal perspectives of genome editing in reproduction, *BioTech*, *12(3)*, pp. 51. doi:10.3390/biotech12030051.
[8] Muigai, A.W. (2022). Expanding global access to genetic therapies, *Nature Biotechnology*, *40(1)*, pp. 20–21. doi:10.1038/s41587-021-01191-0.

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. Researchers, scientists and the society should also develop a strong sense of stewardship of environmental, biological, and social factors to ensure the well-being and interests of future generations are not compromised if such applications of gene editing technologies are permitted in the future.

b. Inclusivity

10.9 The principle of *inclusivity* maintains that benefits of research and clinical applications involving gene editing technologies are considered a public good and should be accessible to everyone within the society. Gene editing technologies for genetic enhancement, if permitted in the future, can promote inclusivity by providing individuals with the opportunity to enhance traits such as intelligence, physical strength, or disease resistance, hence reducing disparities that arise from natural genetic variations. This could lead to a more inclusive society where everyone has access to means to improve themselves, regardless of their initial genetic makeup. However, potential applications of gene editing technologies for genetic enhancement could also create disparities among those who cannot afford or access such enhancements. Therefore, it would be important to ensure equitable access to these technologies for genetic enhancement to prevent widening existing inequalities. If the use of gene editing technologies for genetic enhancement is permitted in the future, research and governance frameworks should be established by research institutions and relevant regulatory authorities to ensure such technologies are accessible to the public. Researchers and scientists should ensure that the benefits of applications of gene editing technologies for genetic enhancement are made available to everyone, to prevent widening of social disparity.

10.10 In view of the potential discrimination that may arise from the use of gene editing technologies for enhancement, initiatives or programmes to foster inclusion and support for people who are vulnerable to discrimination (e.g., individuals with disabilities or developmental needs) should be developed and implemented. Social inclusion can also be promoted by eliminating discriminatory practices, educating the public and developing inclusive workplace policies to 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 engender an inclusive environment.

c. Transparency

10.11 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 may not disclose research methods, analysis, 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, it would be important for researchers, research institutions and approving authorities to ensure that reporting mechanisms are in place to prevent misuse or abuse of gene editing technologies for enhancement.

Issue 3: Shift in attitudes and behaviours towards reproductive choices

10.12 Heritable gene editing for enhancement purposes could lead to undesirable societal expectations and change the perception of conventional reproductive choices among future generations. This is because reproductive technologies offer a more certain way to select the characteristics of the next generation than 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 otherwise have been born with the conditions for which screening is available.[9] With the availability of prenatal screening technologies, parents now have the choice to selectively reproduce only healthy children (i.e., children with no genetic diseases or conditions), and terminate pregnancies that are diagnosed with 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).[9] If gene editing technologies were to become more common and widely utilised, this could bring into question the choices of people who refuse to use such technologies. A shift in behaviours and expectations may affect the evaluation of the responsibilities of prospective parents towards their future children. This could put pressure on prospective parents to have children using gene editing technologies to secure commonly accepted conventional outcomes.[10] 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

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

b. Responsible stewardship of science

[9] Nuffield Council on Bioethics (2018). Genome editing and human reproduction: social and ethical issues. https://www.nuffieldbioethics.org/publications/genome-editing-and-human-reproduction. Retrieved on 4 January 2024.

[10] 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. Retrieved on 4 January 2024.

10.14 The principle of *responsible stewardship of science* refers to 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 technologies should always be aligned with society's values and perceptions to ensure responsible 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 technologies for enhancement may not be in alignment with society's values and perceptions as they may lead to undesirable expectations that could harm the society.

Issue 4: Reduction of genetic diversity in human population

10.15 Heritable gene editing could contribute to the reduction or even elimination of some serious inherited diseases from a population. However, variants associated with disease might also be associated with other beneficial characteristics, which would also be lost.[10] These beneficial characteristics that are lost might be important for survival.[6] For example, the Chinese scientist, He Jiankui, disabled the C-C chemokine receptor 5 (CCR5) gene to confer resistance to HIV in human embryos which resulted 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, and it was also found that humans who lack this protein are more susceptible to severe encephalitis and even death as compared to other people when infected with West Nile Virus.[11] 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 gene editing for enhancement if permitted in the future:

a. Proportionality

10.16 The principle of *proportionality* requires that risks of research and clinical applications involving gene editing technologies for enhancement are not disproportionate to their benefits by minimising harm while maximising benefits to individuals and future offspring. There is an obligation for researchers to reduce potential harm or limit to reasonable risks to individuals and future offspring and maximise 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 which may be vital for survival. Hence, causing the potential risks of such applications of gene editing (e.g., more susceptible to viral infections that may be fatal) to be disproportionate to the potential benefits (i.e., to be resistant to a particular disease).

10.17 Applications of gene editing technologies for genetic enhancement have potential benefits of enhancing cognitive, physical, and functional abilities as well as increased resistance to diseases. Nonetheless, such applications of gene editing technologies raise many ethical implications and profound questions on fairness, societal norms, and unintended consequences, which will require careful consideration. Therefore, applications of gene

[11] 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. Retrieved on 2 January 2024.

editing technologies for genetic enhancement should only be considered after careful public consultation and social debate, as well as when the safety and efficacy of such applications have been 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, the current state of HNGE technology is 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 only a small group of privileged people and in doing so exacerbate social inequality.[4] In the event 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 further 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 on the governance and framework tools for HNGE that should be put in place at the following respective levels:

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

11.3 Policies and practices in place for HNGE research should be regularly reviewed by institutions to manage risks and maximise potential benefits that may arise 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

[1] World Health Organization (2021). Human genome editing: A framework for governance, World Health Organization. https://www.who.int/publications/i/item/9789240030060. Retrieved on 10 January 2024.
[2] Furtado, R.N. (2019). Gene editing: the risks and benefits of modifying human DNA, *Revista Bioética*, 27(2), pp. 223–233. doi:10.1590/1983-80422019272304.
[3] Davies, B. (2019). The technical risks of human gene editing, *Human Reproduction, 34(11)*, pp. 2104–2111. doi:10.1093/humrep/dez162.
[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)*, pp. 874–882. doi:10.2105/ajph.2023.307315.
[5] Sufian, S. and Garland-Thomson, R. (2021). The Dark Side of CRISPR. *Scientific American*. https://www.scientificamerican.com/article/the-dark-side-of-crispr/. Retrieved on 10 January 2024.

scientific research community and other parties (e.g., government bodies, experts, and general public) within society – was critical to establishing an effective regulatory system.[6] This is because perceptions on the use of HNGE may vary among individuals, 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 conduct of 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 it 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 to 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 on HNGE should implement guidelines and put in place robust systems to understand, monitor, and minimise or to mitigate the relevant risks and their impact on research subjects and patients undergoing clinical trials. This may be done by considering the anticipated limitations of the proposed technology and comparison with available standards for safety and efficacy studies.[1] An example would be the "Cellular & Gene Therapy Guidances" published by US FDA for industry, FDA reviewers, and FDA staff.[11]

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[6] Aikyo, T., Kogetsu, A. and Kato, K. (2023). Stakeholder involvement in the governance of human genome editing in Japan, *Asian Bioethics Review*, 15(4), pp. 431–455. doi: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-. Retrieved on 10 January 2024.

[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. Retrieved on 10 January 2024.

[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).

[11] U.S. Food & Drug Administration. Cellular & Gene Therapy Guidances. Cellular & Gene Therapy Guidances | FDA. Retrieved on 11 January 2024.

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 constantly reviewed and revised. National policies should be developed after 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, to make 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 differing stakeholders in society.

11.8 In this regard, a study assessing the national governance capacity of the development on non-heritable gene editing technologies in eight geographically, socially, economically, and culturally diverse countries, found that generally 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 responsibilities for biosafety and research ethics are allocated.[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 consultation would be desirable to address the shortcomings of inadequate information available, short timelines for responses, and the lack of awareness from the public on the consultation processes. The study also found a lack of information on enforcement or organisations that actively monitor for non-compliance, which may suggest that while there are governance measures that exist in theory, the practice may actually differ.

II. Tools and Approaches to Strengthen Existing Research Governance

11.9 Various approaches and tools, such as self-regulation by professional bodies, development of guidelines, conduct of ethics and training courses, reinforcement of institutional practices, establishment of HNGE registries and implementation of whistle-blowing mechanisms, could be introduced to fortify existing research governance frameworks. We turn to examine each of these below.

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 functions as an important deterrent to scientific misconduct. Professional self-regulation may rely on ethical codes developed by advisory committees[13] which may include representatives from patient

[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.

[13] Conley, J. M., Davis, A. M., Henderson, G. E., Juengst, E. T., Meagher, K. M., Walker, R. L., Waltz, M., & Cadigan, J. (2020). A New Governance Approach to Regulating Human Genome Editing. *North Carolina journal of law & technology*, *22(2)*, pp. 107–141.

groups, public interest groups, advocacy organisations and civil society. Professional societies can also develop professional guidelines for the sector, setting out best practices, standards and ethical considerations in HNGE research. Such guidelines have the flexibility to be reviewed regularly in response to the rapidly evolving field of gene editing technologies, in contrast with legislative approaches.

11.11 However, professional self-regulation may give rise to potential conflicts of interest,[14] as the party setting down 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, 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 understand public concerns and needs, thereby ensuring that information is conveyed accurately to prevent any distortion of public perceptions and expectations about 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 technologies, 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 regularly revised and updated to keep pace with the changes and developments in HNGE research, technologies, and legislation.

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[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*. doi:10.3389/frma.2022.775336.

[15] World Health Organisation (2021). Human genome editing: recommendations. https://apps.who.int/iris/bitstream/handle/10665/342486/9789240030381-eng.pdf?sequence=1. Retrieved on 10 January 2024.

11.15 In addition, annual reporting requirements, declaration mechanisms, processes for self-monitoring of HNGE research may be put in place by institutions. These mechanisms may also be used to keep track of achievements and other outcomes achieved from 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 updated with the latest trends and developments of HNGE, and remain informed and competent 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 on 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 central global database that assimilates information pertaining to clinical trials for human gene editing technologies.[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 on 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

[16] World Health Organisation. Human genome editing registry, *World Health Organization*. 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). Retrieved on 10 January 2024.

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

[18] Basic research is a type of scientific research with the aim of improving scientific theories for better understanding and prediction of natural or other phenomena.

submissions for fundamental and pre-clinical research and avoid abuse by businesses seeking to prematurely commercialise gene editing technologies. 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 treatment safety 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] Such non-heritable gene editing clinical trial registries could help to prevent selective publication and reporting of research outcomes, reduce unnecessary duplication of research effort, and enable access to patients and the public on 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 are considering approval of new research studies of similar work or scope.

(iii) Non-heritable gene editing clinical applications

11.20 For treatments employing non-heritable gene editing technologies carried out under the hospital exemption rule (i.e., innovation salvage therapy cases) but fall outside the scope of clinical trials, data may not always be made publicly available. Setting up open-access registries of such treatments could help facilitate access to treatment strategies and data, provide evidence on 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 whistleblowing mechanisms to be introduced [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 on illegal, unregistered, unethical, or unsafe HNGE research.[21]

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[19] US Food and Drug Administration. Long term follow-up after administration of human gene therapy products. 2020. https://www.fda.gov/media/113768/download. Retrieved on 10 January 2024

[20] Delaye, F. (2021). Genome editing: WHO banks on whistleblowers, *Geneva Solutions*. https://genevasolutions.news/global-health/genome-editing-who-banks-on-whistleblowers. Retrieved on 11 January 2024.

[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. https://apps.who.int/iris/bitstream/handle/10665/345331/WHO-SCI-RFH-2021.05-eng.pdf. Retrieved on 10 January 2024.

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 on unethical HNGE research from outside an institution, a new reporting mechanism can be set up through the establishment of a confidential portal, website, or hotline, which will allow individuals to report anytime and from anywhere. Follow-up procedures should be put in place to investigate any information provided and to demonstrate that action has been taken where appropriate.[1] A two-stage investigation 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 through national legislation, in consultation with the relevant research institutions or funding agencies, 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., researcher or a member of the public) for reporting on unethical HNGE research. Individuals reporting on such incidents should have their identities kept confidential, and should be provided with the 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 on for reporting unethical experiments, establishing a system supported by WHO may send a signal to the world that reporting of unethical experiments is a responsibility of researchers globally.

III. Governance Framework for Heritable Gene Editing (for Treatment of Diseases, Conferring Resistance, Enhancement of Traits, and Infertility) and Gene Editing in Embryos or Germline Cells for Research Purposes

11.25 Heritable gene editing calls for greater attention in the establishment of proper governance frameworks, since any genetic modifications made may be passed down to successive generations. In particular, heritable gene editing for the treatment of diseases, conferring resistance, enhancement of traits, and to treat infertility 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 exacerbate social implications such as inequity and undesirable social expectations. In comparison, gene editing in embryos or germline cells for research purposes is of lower risk, as research conducted on germ line cells do not affect future generations. Therefore, the extent of oversight in developing governance and framework tools should be corroborated with the extent of risks and sensitivity involved, whether for

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

clinical applications of heritable gene editing or research activities for 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.

CHAPTER 12: CONCLUSION

12.1 Applications of gene editing in human biomedical research have advanced developments in genetics, disease modeling and therapeutics. The increasing use of gene editing in clinical applications holds promise for treating genetic disorders, infertility, enhancing personalised medicine and improving health outcomes. While these technologies have the potential to confer resistance to diseases and enhancement of traits in the future, they may also bring along unintended consequences and long-term effects on individuals and future generations. Hence, it would be important to review the issues holistically and 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, and developed recommendations to guide the responsible use of such technologies. These recommendations consider the ethical implications that may arise from such uses, and the potential benefits and risks to individuals and future generations. The objectives of BAC's recommendations are not only to encourage more ethical debates on genetic enhancements and discussions 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 shape policies to balance scientific progress with ethical considerations and facilitate decision making.

12.3 In this advisory report, the BAC recommends that researchers, research institutions, IRBs, and healthcare professionals consider the five substantive principles of (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. BAC's recommendations for the safe and ethical use of gene editing technologies are summarised as follows (refer to chapter 6 to chapter 10 for detailed discussion on these recommendations):

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

12.4 For any research 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 prior to the 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 of clinical trials involving non-heritable gene editing. This is to mitigate the risk of any delayed adverse event occurring due to the treatment. It would also be important for researchers and research institutions to take

appropriate measures, such as establishing guidelines for evaluating off-target effects and risk assessments, to anticipate and manage uncertainties and long-term consequences associated with non-heritable gene editing.

b. Gene editing on germline cells or embryos for research

12.6 The BAC does not recommend any gene editing research on human embryos after the 14th day. Creation of human embryos solely for research purposes can only be justified when there is strong scientific merit and potential benefit from such research. In future, if there is stronger evidence of scientific merit for conducting gene editing research on human embryos after the 14th day, the BAC may reconsider this position following public consultation and stakeholder engagement. The BAC 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 and any potential data that may be collected and their implications. Donors should also be given sufficient time to express 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 safeguard the security of data storage.

12.7 With regard to compensation of women undergoing oocyte procurement for gene editing research, the BAC recommends that the relevant regulatory authority provide a clearer stance on whether compensation for loss of time and earnings should be allowed, given that the 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 setting a limit on the amount of compensation to avoid any inducement.

c. Heritable gene editing for clinical applications

12.8 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 consent, autonomy and inequality issues. 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. Hence, more research would need to be conducted to determine whether clinical applications of heritable gene editing are considered safe and ethical before they can be recommended in the future.

12.9 Nonetheless, if and when the risks involved in the applications of gene editing technologies 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 for diseases where 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 by 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, including potential societal impacts and international implications.

12.10 The governance of research and clinical applications of gene editing technologies is important and serves to uphold ethical principles, foster responsible innovation and promote ethical advancement of such technologies. The BAC's recommendations aimed at governing the ethical and responsible use of gene editing technologies are summarised as follows (refer to chapter 11 on 'Governance and Framework Tools for HNGE' for 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 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 to mitigate the risks and their impacts 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 technologies and comparison with available standards for safety and efficacy studies.

c. The BAC recommends that governments and policy makers should constantly review and revise legislations and guidelines pertaining to the application 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 the conduct of stakeholder consultations with the scientific community and patient advocates, and that feedback are sought from the general public so that policies pertaining to HNGE are aligned with societal values.

d. The BAC recommends for different approaches and tools to be introduced to enhance existing research governance frameworks for HNGE, such as self-regulation by professional bodies, development of guidelines, conducting of ethics and training courses, reinforcement of institutional practices, setting up of HNGE registries, and implementing 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 for 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 should be subject to a more stringent governance.

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

a. Guidance from international organisations

12.12 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 also prevents disparities in regulatory approaches, fostering a unified stance on responsible gene editing. As the field of gene editing is continuously evolving, BAC's recommendations should keep abreast with the latest international guidelines and recommendations, while tailoring them to fit the local context.

b. International governance and collaborations

12.13 International governance and collaborations on HNGE are important as they encourage for 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 promoting international ethical standards in gene editing.[2] In addition, it would be important for policymakers and organisations developing recommendations and guidelines pertaining to gene editing technologies to work together with international institutions and bodies interested in the field of gene editing, such as the 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 technologies. Sharing of information on laws and legislations relevant to gene editing, as well as engaging in

[1] World Health Organization (2021). Human genome editing: A framework for governance. https://www.who.int/publications/i/item/9789240030060. Retrieved on 17 January 2024.
[2] Shampa, G; Soumya, G, et. al. (2023). Balancing potential benefits and ethical considerations of gene editing. doi:10.1016/S0140-6736(23)01084-X.

collaborative international governance and oversight of gene editing, will enable better alignment of ethical standards.

c. Continuous stakeholders and public engagement

12.14 Stakeholders and public engagement are and should continue to play an important part of research and clinical applications of gene editing technologies and its advancement. These engagements are crucial for ethical and transparent decision-making, and help to ensure diverse perspectives are considered, and 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 that HNGE progresses to serve the public's interests.

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

12.15 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 technologies, and enhances the public's knowledge on 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 technologies, and enables them to make informed decisions about supporting or participating in gene editing research or in clinical trials involving gene editing technologies. In addition, public education clarifies any misperceptions regarding gene editing, and it equips individuals with the knowledge to discern legitimate scientific advancements from potential misconceptions or fraudulent activities. This reduces the likelihood of individuals' participation in unethical or questionable clinical trials involving gene editing technologies.

12.16 In conclusion, the ethical landscape surrounding gene editing requires academics, researchers, healthcare professionals, IRBs, and research and healthcare institutions to consider the ethical principles highlighted in this report when using gene editing technologies for research or clinical applications. With further advancements in gene editing technologies, it would be important to balance the potential benefits with the associated risks, 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 technologies.

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 protein found in the nucleus of most living cells, carrying genetic information in the form of genes.

Clinical Ethics Committees (CECs) – Hospitals are required under the 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 – DNA, or deoxyribonucleic acid, 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 8 weeks of gestation, the embryo becomes known as a foetus.

Extra-chromosomal DNA (abbreviated 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 behavioral 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 anemia, 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, 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.