Brave New Genome: Gene Editing in New Zealand Healthcare

Regulating the Revolution

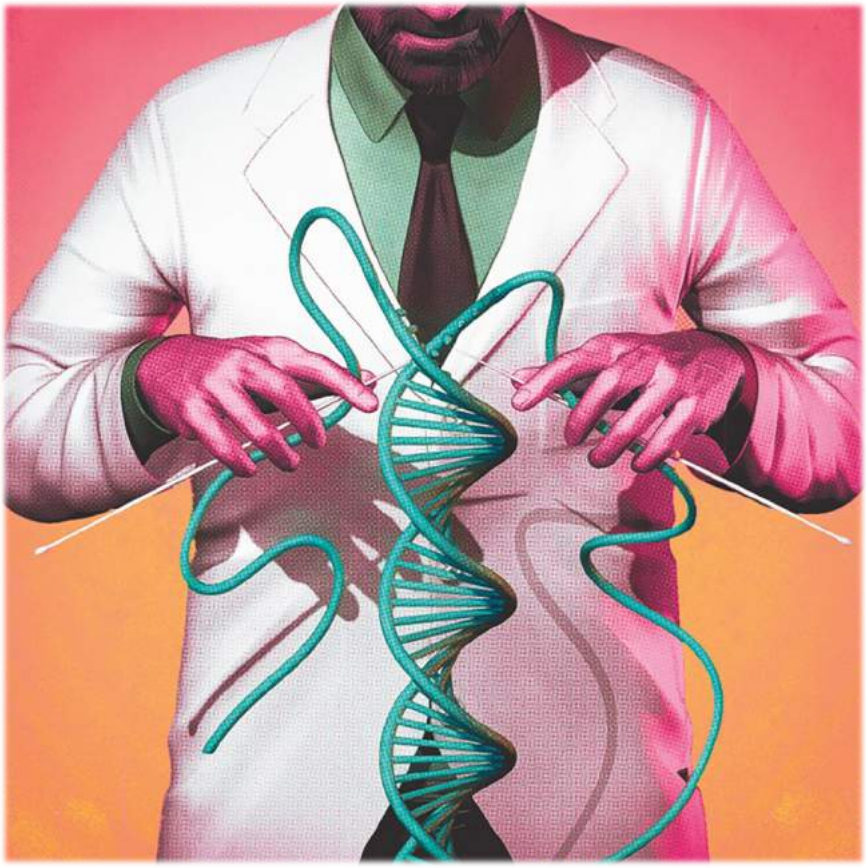

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Table of Contents

Abbreviations

ACART	Advisory Committee on Assisted Reproductive Technology
ANZTP	Australia New Zealand Therapeutic Products Authority
ATMP	Advanced therapy medicinal products
CARM	Centre for Adverse Reactions Monitoring
CAR-T	Chimeric antigen receptor T-cell therapy
CRISPR	The CRISPR-Cas9 gene editing system
ECART	Ethics Committee on Assisted Reproductive Technology
ERMA	Environmental Risk Management Authority
EPA	Environmental Protection Authority
EU	The European Union
FDA	Food and Drug Agency
GTAC	Gene Advisory Technical Committee
GMO	Genetically Modified Organism
HART Act	Human Assisted Reproductive Technology Act 2004
HDEC	Health and Disability Ethics Committee
HFEA	Human Fertilisation and Embryology Authority
HRCC	Health Research Council Committee
HSNO Act	Hazardous Substances and New Organisms Act 1996
IVF	In-vitro fertilisation
NIH	National Institutes of Healthcare
Medsafe	New Zealand Medicines and Medical Devices Safety Authority
MARC	Medicines Adverse Reactions Committee
MHRA	Medicines and Healthcare Products Regulatory Agency
NAS	National Academy of Science
PGD	Preimplantation genetic diagnosis
RAC	Recombinant DNA Advisory Committee
UK	The United Kingdom
US	The United States

INTRODUCTION

"[H]ave no doubt, this technology will — someday, somewhere — be used to change the genome of our own species in ways that are heritable, forever altering the genetic composition of human kind."

– Jennifer A. Doudna, A Crack in Creation: Gene Editing and the Unthinkable Power to Control Evolution

Five years ago, few scientists would have been familiar with the phrase 'gene editing.' However, since the dawn of its discovery, advancements have been occurring at breakneck speed, and countries compete in a molecular arms race to pioneer and commercialise the technology. In particular, the transformative CRISPR-Cas9 technology is revolutionising the field of genome editing:[1]

> *"I think it's a momentous occasion for us, but also for the field in general. Just three years ago we were talking about CRISPR-based treatments as sci-fi fantasy, but here we are."*

Able to achieve highly flexible and specific targeting, the CRISPR-Cas9 system can be modified and redirected to become a powerful tool for gene editing in broad applications such as engineering disease-resistant transgenic plants, gene therapy, human reproduction, stem cell engineering and tissue and animal disease models. My dissertation will focus on the therapeutic potential gene editing holds for humankind.

Gene editing technology has stunned the world with its rapid utilisation, sparking ethical, social and legal debate, with urgent calls for "[a] framework for open discourse on the

[1] Samarth Kulkarni, CEO CRISPR Therapeutics. Megan Molteni "CRISPR Therapeutics Plans its first clinical trial for Genetic Disease" (12 November 2017) < https://www.wired.com/story/crispr-therapeutics-plans-its-first-clinical-trial-for-genetic-disease/>.

use of CRISPR-Cas9 technology to manipulate the human genome."[2] Debate is well-founded, as gene editing holds unparalleled potential for modifying human genomes and eradicating genetic disease for good. Somatic gene editing therapies are already being used clinically. Germline human embryo research is still hotly contested and yet is also being permitted in some countries and, most significantly, germline gene editing in human reproduction is now considered likely in the near future to treat, cure and prevent genetic disease altogether.

However, amidst grandiose claims that all our genetic problems will soon disappear, there are warnings of unknown risks to human health and well-being, together with the familiar host of ethical issues surrounding the 'genetic supermarket' and fears of a dystopian future that have been subject to ongoing dispute for decades.

The unresolved ethical challenges gene editing poses means that any rules or regulations must be flexible and able to accommodate change in societal views on what uses are appropriate or inappropriate. The laws governing gene editing must be proactive, not postponed until a consensus is reached, as prolonging the technologies' implementation will only act to extend human suffering.

Chapter I explains what gene editing is, how CRISPR-Cas9 works, and examines the therapeutic potential gene editing holds.

Chapter II highlights some key ethical concerns raised and seeks to resolve them.

Chapter III outlines the current regulatory framework in New Zealand, noting the gaps that result from legislation that was enacted before gene editing was even contemplated, as well as in new proposed legislation.

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[2] Baltimore BD and others "A Prudent Path Forward for Genomic Engineering and Germline Gene Modification" (2015) Science 348 36 at 36.

Chapter IV considers the global landscape, looking at the responses to gene editing around the world by prominent scientists, authorities and organisations, before examining the international legal context and spotlighting on two major players at the forefront of the gene editing revolution.

Finally, Chapter V seeks to provide a regulatory framework that encompasses gene editing going forward.

CHAPTER I

What is Gene Editing and what Therapeutic Potential does it Hold?

A The Technology

1 Gene editing explained

Gene editing is the insertion, deletion or replacement of DNA at a specific site in the genome, or an organism or cell. It refers to the creation of sequence-specific alterations in the DNA of a cell using molecular methods that take advantage of site-directed DNA repair after strand breakage.

The gene editing process involves the generation of a double-stranded break (DSB) at the targeted DNA sequence.[3] The DSB subsequently triggers two competing DNA repair systems; homology-directed repair (HDR) or non-homologous end-joining (NHEJ).[4]

Four major platforms currently exist for inducing these site-specific DSBs: zinc finger nucleases (ZFNs), transcription activator-like effector (TALE)-nucleases (TALENs), meganucleases, and most recently, the CRISPR-Cas9 system. For the purposes of this dissertation I will focus on CRISPR-Cas9 (CRISPR). CRISPR is able to modify DNA sequences in living organisms with unprecedented precision:[5]

> "*CRISPR-Cas9 can pinpoint important but tiny gene sequences in our vast genomes, the genetic equivalent of finding a needle in a hay-stack. Once there, it can erase*

[3] Cai and others "CRISPR-mediated genome editing and human diseases" (2016) Genes & Disease 3 244 at 245.

[4] Ibid.

[5] Paul Knoepfler *GMO Sapiens: The Life-Changing Science of Designer Babies* (World Scientific Publishing Co Pte Ltd, Singapore, 2016) at 11.

> *and/or change A's, C's, G's, or T's, or even larger genomic regions, in surprisingly precise ways. CRISPR can literally re-write the genomic book inside of us*."

CRISPR has revolutionised gene editing due to this incredible accuracy, as well as its simplicity, affordability and versatility in comparison to other gene editing techniques.

2 The CRISPR-Cas 9 system

The CRISPR system is derived from genomic elements in bacteria that provide immunity against viral infection.[6] It is a bacterial defense mechanism that operates by the bacteria capturing snippets of DNA from invading viruses and using them to create DNA segments (CRISPR repeat-spacer arrays), which are then used by the bacteria to specify target sequences.

In other words, after being infected by a virus, the bacteria are able to "remember" it by having pieces of viral genes between repeated bacterial DNA sequences – these are the "clustered, regularly interspaced short palindromic repeats" from which the CRISPR name is derived. If the virus attacks again, the bacteria are able to produce DNA segments from the CRISPR array to target the viruses' DNA. The bacteria then use the Cas9 protein to cut the DNA apart, which deactivates the virus. [7]

This CRISPR-Cas9 system works similarly for gene editing purposes. Researchers create a short non-coding guide RNA (gRNA), which guides the Cas9 protein to a specific genomic locus via base pairing to the target DNA sequence.[8] Upon binding to the target sequence, the Cas9 protein induces a DSB at the site. This DSB is then repaired by the

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[6] Maeder ML and Gersbach CA "Genome-editing Technologies for Gene and Cell Therapy" (2016) Mol Ther 24 430 at 433.

[7] Cai, above n 3, at 245.

[8] Ibid.

cell's own DNA repair machinery, NHEJ or HDR. Both the gRNA and Cas9 are introduced into cells by vectors created via use of recombinant DNA technology.[9]

Extensive research is already being conducted to improve CRISPR, as this original system is somewhat clunky, unreliable and dangerous; it cannot bind at any locus in the genome, it cuts in the wrong places and has no 'off-switch.' A new wave of CRISPR has begun, using "base-editing".[10] Rather than causing breaks in DNA and the cell repairing itself with a healthy gene template, a single DNA base is changed.[11]

The explosion of gene editing technologies is truly only just beginning and CRISPR is advancing at a rapid pace. Based on progress already made, it is anticipated that the risks of CRISPR will be dramatically reduced, if not eliminated, in the near future. In Chapter II I will outline the types of risks that gene editing poses.

B The Distinction between Somatic and Germline Editing

Somatic cells contribute to the various non-reproductive cell types such as muscle, liver, eye, lung and heart cells. Gene editing that targets somatic cells would affect only the patient and are therefore similar to existing efforts to use gene therapy for disease treatment and prevention. Somatic gene editing could be used to revert an underlying genetic mutation to a variant not associated with disease, or engineer a cell so that its phenotype

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[9] Ibid.

[10] There are 50 publications using base editors from laboratories around the world, with the most successful study to date published earlier this year by Chinese researchers, which corrected 16 out of 18 embryos carrying the mutation for Marfan syndrome: Zeng and others "Correction of the Marfan Syndrome Pathogenic *FBN1* Mutation by Base Editing in Human Cells and Heterozygous Embryos" (2018) Mol Ther 26 1.

[11] Eid A "CRISPR base editors: genome editing without double-stranded breaks" (2018) Biochem J 475 1955.

differs from that of a normal cell and is better able to resist or prevent disease.[12] Both *ex vivo* and *in vivo* approaches to gene editing could be applied to treat or prevent disease, and such methods are already being used on some individuals.[13] It is also possible to undergo somatic gene editing in a foetus, but there is an increased risk of causing heritable changes to the germline.[14]

In contrast, germline cells are reproductive cells and their progenitor cells, and changes made are heritable. For a genetic alteration to be passed on to the next generation, it has to be made in (1) progenitor cells that give rise to gametes; (2) gametes themselves; or (3) in the fertilized zygote or early embryo, when all cells can still contribute to the future germline.[15]

Editing the germline of individuals carrying mutations would allow them to have genetically related children without the risk of passing on a disorder and prevent disease transmission for all subsequent generations. Germline gene editing therefore has unprecedented potential in the prevention, rather than treatment, of human genetic disease on a large scale. At the same time, this transgenerationalism makes germline gene editing more contentious. I will discuss the ethical issues relating to gene editing – but particularly germline gene editing, in Chapter II.

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[12] National Academies of Sciences, Engineering, and Medicine *Human Genome Editing: Science, Ethics, and Governance* (The National Academies Press, Washington DC, 2017) at 83.

[13] For example, in 2016 Chinese scientists injected gene edited cells into a patient to treat lung cancer: David Cryanoski "CRISPR gene-editing tested in a person for the first time" (15 November 2015) Nature News <https://www.nature.com/news/crispr-gene-editing-tested-in-a-person-for-the-first-time-1.20988>; Brian Madeaux was treated for Huntington's disease in 2017: Kate Sheridan "CRISPR: Watch How a Groundbreaking Gene-Editing Technique Cuts DNA" (15 November 2017) Newsweek <https://www.genengnews.com/gen-news-highlights/nih-commits-190m-to-somatic-gene-editing-toolstech-research/81255414>.

[14] National Academies of Sciences, Engineering, and Medicine, above n 12, at 107-108.

[15] Ibid at 240.

C The Therapeutic Potential of Gene Editing

Currently, options to treat genetic disease are limited to treating the symptoms of disease or modifying the course of disease – they do not address the underlying genetic defect. The emotional, financial, and other burdens on individual families that result from transmission of serious genetic disease can be considerable; the toll taken on an individual who inherits a genetic disorder incommensurable. Gene editing opens up new possibilities to cure genetic disease, via somatic gene editing, and prevent the transmission of disease indefinitely, via germline gene editing. I will outline the types of disorders that scientists are currently researching to be targeted by gene editing technologies and in doing so, demonstrate the broad therapeutic potential gene editing holds for the human race.

1 Monogenic disorders

Scientists estimate that over 10,000 genetically inherited diseases are caused by mutations in single genes.[16] Whilst individually many of these genetically inherited diseases are rare, collectively they affect a sizable fraction of the population, about 5-7 percent, which equates to roughly 380-530 million people.[17]

Examples where gene editing research and clinical trials are currently taking place on monogenic disorders include blood disorders (such as beta-thalassemia, sickle cell anaemia

[16] World Health Organisation "Genes and human disease: monogenic diseases" (2018) World Health Organisation <http://www.who.int/genomics/public/geneticdiseases/en/index2.html>.

[17] National Academies of Sciences, Engineering, and Medicine, above n 12, at 111.

and haemophilia),[18] cystic fibrosis,[19] Huntington's disease[20] and other neurodegenerative disorders,[21] and hereditary blindness.[22] Earlier this year a group of researchers in the US revealed that they used CRISPR-Cas9 to treat Duchenne's muscular dystrophy in mice. [23] They cut at 12 strategic "mutation hotspots", rather than fixing each mutation individually, covering the majority of the estimated 3,000 different mutations that cause this disease.[24] This technique could be applied to other genetic disorders that are caused by different mutations in multiple genes.

2 Multi-factorial / complex disorders

A complex disease or disorder is caused by a combination of small inherited variations in genes, often acting together with environmental factors. Complex diseases include obesity, diabetes, asthma and cancer, and could be treated using gene editing techniques by altering defective genes known to cause a predisposition to disease, to healthy variants.

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[18] Clara Rodríguez Fernández "7 Diseases CRISPR Technology Could Cure" (25 June 2018) LABIOTECH.eu <https://labiotech.eu/medical/crispr-therapeutics-clinical-trials/>

[19] Schwank and others "Functional Repair of CFTR by CRISPR/Cas9 in Intestinal Stem Cell Organoids of Cystic Fibrosis Patients" (2013) Cell Stem Cell 13 653; Firth and others "Functional Gene Correction for Cystic Fibrosis in Lung Epithelial Cells Generated from Patient iPSCs" (2015) Cell Reports 12 1385; Editas Medicine "Areas of Impact and Research: Lung Diseases" (2018) Editas Medicine <http://www.editasmedicine.com/areas-of-research/lung-diseases>.

[20] Michael Eisenstein "CRISPR Takes on Huntington's disease" (2018) Nature 557 42; Dabrowska M and others "Precise Excision of the CAG Tract from the Huntington Gene by Cas9 Nickases" (2018) Front Neurosci 12 1.

[21] Kolli and others "Application of the gene editing tool, CRISPR-Cas9, for treating neurodegenerative disease" (2018) Neurochem Int 112 187.

[22] Editas Medicine "Editas Medicine Reports Data Demonstrating Subretinal Injection of EDIT-101 Well-tolerated in Non-human Primates" (press release, 18 May 2018).

[23] Cathy Frisinger "Gene-editing alternative corrects Duchenne muscular dystrophy" (12 April 2017) UT Southwestern Medical Centre <https://www.utsouthwestern.edu/newsroom/articles/year-2017/gene-editing-alternative.html>.

[24] Ibid.

Gene editing is already being used to target cancers in several ways: correcting cancer-causing mutations and deletions and to engineer immune cells, such as chimeric antigen receptor T (CAR-T) cells for cancer immunotherapies.[25] CAR-T cell therapies have already been proven successful in treating a New Zealander, David Downs, for terminal lymphoma in the United States [26] and other CAR-T treatments using gene editing are taking place this year. [27]

In China, at least 86 people with different forms of cancer have been treated with CRISPR by deleting genes that interfere with the immune system's ability to fight cancer.[28]

3 Other forms of treatment

Gene editing can be used to treat HIV/AIDs by cutting the HIV virus out of the DNA in an infected patient's immune cells, or by making humans resistant to HIV infections.[29] Other

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[25] Wu HY and Cao CY "The application of CRISPR-Cas9 genome editing tool in cancer immunotherapy" (2018) Brief Funct Genomics ely011 1 at 1. Cart-T cell therapy works by genetically modifying the patient's own CAR-T cells to directly identify and attack their cancer cells.

[26] Malaghan Institute of Medical Research "Cancer research" (2018) Malaghan Institute of Medical Research <https://www.malaghan.org.nz/down-with-cancer>.

[27] Emily Mullin "US doctors plan to treat cancer patients using CRISPR" (17 January 2018) MIT Technology Review < https://www.technologyreview.com/s/609999/us-doctors-plan-to-treat-cancer-patients-using-crispr/>; FDA US Food and Drug Administration "FDA approval brings first gene therapy to the United States: *CAR T-cell therapy approved to treat certain children and young adults with B-cell acute lymphoblastic leukaemia"* (press release, 30 August 2017).

[28] Preetika Rana, Amy Dockser Marcus and Wenxin Fan "China, Unhampered by Rules, Races Ahead in Gene-Editing Trials (2018) Wall Street Journal <https://www.wsj.com/articles/china-unhampered-by-rules-races-ahead-in-gene-editing-trials-1516562360>.

[29] Hu W and others *"*RNA-directed gene editing specifically eradicates latent and prevents new HIV-1 infection" (2014) Proc Natl Acad Sci USA 111 11461; Li L and others "Genomic editing of the HIV-1 coreceptor CCR5 in adult hematopoietic stem and progenitor cells using zinc finger nucleases" (2013) Mol Ther 21 1259; Mandal PK and others "Efficient ablation of genes in human hematopoietic stem and effector cells using CRISPR/Cas9" (2014) Cell Stem Cell 15 643.

viral diseases such as hepatitis B, herpes simplex and human papillomavirus are also being targeted by CRISPR.[30]

CRISPR can also be used to treat causes of infertility by altering genes that cause miscarriages.[31]

Finally, CRISPR could be used to improve xenotransplantation,[32] by preventing harmful viruses being transmitted to people from animals.[33] However, I will not address the use of CRISPR for xenotransplantation any further as it remains outside the scope of this dissertation.

D Germline Editing vs Assisted Reproductive Technologies

Some researchers argue that there may never be a time when germline gene editing will offer a benefit greater than that of existing assisted reproductive technologies, such as preimplantation genetic diagnosis (PGD) and in-vitro fertilisation (IVF).[34] I will address

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[30] Dong C and others "Targeting hepatitis B virus cDNA by CRISPR/Cas9 nuclease efficiently inhibits viral replication" (2015) Antiviral Res 118 110; Kennedy EM and others "Inactivation of the human papillomavirus E6 or E7 gene in cervical carcinoma cells by using a bacterial CRISPR/Cas RNA-guided endonuclease" (2014) J Virol 88 11965; Aubert M and others "*In vitro* inactivation of latent HSV by targeted mutagenesis using an HSV-specific homing endonuclease" (2014) Mol Ther Nucleic Acids 3 e146.

[31] Fogarty NME and others "Genome editing reveals a role for OCT4 in human embryogenesis" (2017) Nature 550 67.

[32] Xenotransplantation is the process of grafting or transplanting organs or tissue between members of different species.

[33] Nunes Dos Santos RM and others "CRISPR/Cas and recombinase-based human to pig orthotopic gene exchange for xenotransplantation" (2018) J Surg Res 229 28.

[34] Lanphier and others "Don't edit the human germ line" (12 March 2015) Nature News 519 410.

the situations where, as acknowledged by scientists and bioethicists, germline gene editing can address needs not met by PGD.[35]

For parents who carry genetic disease, the key focus is not just on helping them to avoid having a child with a genetic disorder – which can be achieved using donated embryos, eggs or sperm, or by adoption – but instead, avoiding having a child with a genetic disorder that *is genetically related to them.*

Situations where PGD is not sufficient for this purpose include those where it is impossible for the prospective parents to have a genetically related child free from a specified genetic disease, and those where the likelihood of this is greatly reduced using PGD.[36] Additionally, some people object to elements of the PGD process, such as discarding affected embryos, and therefore germline gene editing is preferable.[37]

In these situations, if it were safe and efficient to use germline gene editing to correct the mutation, this alternative might be preferred by prospective parents. Given the potential severity of the conditions in question and the lack of treatment options for affected people, it seems reasonable for parents who wish to have a genetically-related child to be able to seek techniques to prevent, as far as possible, the transmission of serious genetic disorders, rather than PGD which could only minimise the potential for transmission.

I have drafted guidelines in Appendix I that would restrict the use of germline gene editing in human reproduction to purely therapeutic purposes when PGD is not effective.

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[35] National Human Genome Research Centre "Genome Editing: What are the ethical concerns about genome editing" (3 August 2017) National Human Genome Research Centre <https://www.genome.gov/27569225/what-are-the-ethical-concerns-about-genome-editing/>.

[36] National Academies of Sciences, Engineering, and Medicine, above n 12, at 114.

[37] Hampton T "Ethical and Societal Questions Loom Large as Gene Editing Moves Closer to the Clinic" (2016) JAMA 315 546; Savulescu, J and others "The moral imperative to continue gene editing research on human embryos" (2015) Protein Cell 6 476.

E Enhancement

A potential application of gene editing is enhancement - changes that go beyond restoration or protection of health; for example, build in genetic resistance or immunity to endemic diseases, tolerance for adverse environmental conditions and super-senses or super abilities.[38] Enhancement raises questions of fairness, social norms, personal autonomy, and human dignity. I will not address the issue of enhancement in detail, as this goes outside the scope of my dissertation, which is framed towards regulation in restricted therapeutic circumstances only. However, it is important to note that the term "enhancement" itself is problematic, as the question of what is 'normal' or what constitutes a 'disease' arises, and there is no bright line distinguishing therapy, prevention, and enhancement. I will address how to prohibit enhancement uses of gene editing in my final chapter.

[38] Nuffield Council on Bioethics *Genome editing: an ethical review* (Nuffield Council on Bioethics, London, 2016) at 47.

CHAPTER II
Ethical Considerations

A Introduction

A regulatory framework cannot be established without ethical considerations, because not only are ethics moral principles that govern a person's behaviour or the conducting of an activity, they are the rules or standards governing the conduct by which we live our lives. As such, they must inherently form part of any regulatory regime.

The ethical debate raised by gene editing is a vast subject, which I cannot possibly address in depth within the scope of this dissertation. However, it would not be complete without a consideration of some important issues that directly affect somatic and germline gene editing.

The possibility of germline genetic modification has been the subject of debate for many years with the rise of the idea of a "genetic supermarket" first coined by Nozick.[39] Germline gene editing is highly contentious because the resulting genetic changes are inherited by the next generation. The possibility of making heritable changes through germline gene editing moves the conversation away from individual-level concerns towards more complex technical and social concerns regarding the appropriateness of multi-generational intervention of this kind.[40]

Somatic gene editing raises less debate, as there is nothing ethically distinct from other gene therapies that currently exist, and thus the main concern is risk.[41]

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[39] Robert Nozick *Anarchy, State and Utopia* (Blackwell Publishers Ltd, Oxford, 1974).

[40] National Academies of Sciences, Engineering, and Medicine, above n 12**,** at 7; Nuffield Council on Bioethics, above n 41, at 118.

[41] Nuffield Council on Bioethics *Genome Editing: An Ethical Review* (Nuffield Council on Bioethics, London, 2016) at 118.

The ethical considerations relating to germline gene editing can be split into three categories relating to (1) the interests of the people immediately involved (prospective parents and their future children), (2) others collaterally affected and society as a whole, and (3) humanity generally.[42] As noted, I cannot address all of these and will focus on parents' reproductive rights, the welfare of future persons, eugenics and safety and risk. I will not address considerations relating to humanity broadly, such as human dignity, transgenerationalism or transhumanism,[43] or other issues such as the problem of non-identity, expressivist concerns, personal or societal financial implications such as access to health services, implications to the insurance industry and justice and equity.

Additionally, in considering all ethical issues raised by germline gene editing in substantive depth, the Nuffield Council on Bioethics concluded "that none of the considerations raised yields an ethical principle that would constitute a categorical reason to prohibit heritable genome editing interventions."[44] My central ethical thesis relies on this conclusion, together with the idea that the welfare of future persons is the outstanding moral imperative. That is, if we can prevent suffering from a serious and heritable genetic disease, we are morally obligated to do so.

[42] Nuffield Council on Bioethics, above n 38, at 58.

[43] For information on these issues, see Nuffield Council on Bioethics, above n 38, at 88-94.

[44] Ibid.

B Ethical Issues Affecting Individual Interests

1 Parents' reproductive rights

(a) Reproductive autonomy

The concept of reproductive autonomy is based on the idea of freedom to pursue procreative interests independently of any moral value.[45] The rationale is based on a fundamental presumption that the state should not interfere with the freedom of its citizens in the absence of harm to others.[46]

Germline gene editing is desirable for prospective parents who wish to have a genetically related child without the risk of the child inheriting a genetic disorder. The motivations behind the desire to have a genetically related child can be mixed – both self-regarding and other-regarding – and sometimes irrational and based on false beliefs.[47] Whatever parents' incentives or beliefs may be, the right to choose if, when and how to procreate is seen as a fundamental component of human autonomy.

Therefore, in the absence of a compelling reason not to, people have the right to control their own procreation, including the pursuit of having a genetically related child and, by extension, the use of germline gene editing for this purpose. Just as PGD was viewed as an extension of this autonomous right affording protection to prospective parents, so too is germline gene editing.

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[45] Nuffield Council on Bioethics, above n 38, at 63.

[46] Derived from John Stuart Mill *On Liberty* (Longman, Roberts & Green, London, 1869).

[47] Ibid at 61.

(b) The principle of procreative beneficence

An issue raised in a new light is whether Savulescu's 'principle of procreative beneficence' (PPB) could act as a limit on parents' reproductive autonomy by requiring that some gene editing is required to maximise the welfare of future people.[48] Under this concept, parents are morally obliged to genetically edit their children, taking away their reproductive autonomy to choose whether to use germline gene editing or not. The principle rests on the claim that if embryo A was genetically predisposed to asthma and embryo B was free from this predisposition, the parents would be morally obligated to choose B, as a predisposition to asthma would likely lead to a state of reduced well-being.[49]

However, the maximisation of welfare includes more than being disease-free and extends to an obligation on parents to enlarge or extend inherited capacities – falling into the realm of 'enhancement.'[50]

I dismiss this argument on two grounds. Firstly, the concept erodes the principle of reproductive autonomy. Savulescu admits that the PPB must be balanced with the right to autonomy in reproductive decision-making.[51] However, these two ideas appear irreconcilable in practice, as the moral obligation to maximise a child's welfare using gene editing will be overridden by parental autonomy.

Secondly, Savulescu proposed this principle with PGD in mind – where the genetic content of the possible child is confined entirely to the genetic contributions of the parental gametes. The idea of merely selecting the embryo with the combination of genes most likely to have the best life is far less onerous than holding parents morally

[48] Savulescu J "Procreative Beneficence: Why we should select the best children" (2001) 15 Bioethics 413 at 415.

[49] Ibid at 417.

[50] Walter Viet "Procreative Beneficence and Genetic Enhancement" (2018) Kriterion - J Phil 32 75 at 79.

[51] Savulescu, above n 48, at 425.

obligated to genetically alter an embryo, when this concept may not have otherwise even been considered. Further, it would be difficult to place limits on this obligation in terms of how far parents would be expected to go in terms of bestowing positional advantages.

2 The welfare of future persons

(a) Beneficence

The principle of beneficence provides that we should do what will further the welfare of an individual. Some have argued that it is unethical to withhold a technology that would eliminate devastating genetic diseases.[52] Gene editing technologies are welcome for a multitude of reasons: the wish to spare families the tragedy and burden of caring for children with deadly and devastating illnesses; compassion for the suffering of those afflicted with genetic diseases; sympathy for those couples who might otherwise forego having children, for fear of passing on heritable disorders; an interest in reducing the economic and social costs of caring for the incurable; and hopes for progress in the overall health and fitness of human society.

Of highest importance is the ability for gene editing to alleviate suffering. Gene editing is uniquely placed, as it is not only able to cure existing individuals of genetic disease, but it also enables the prevention of heritable disorders for all subsequent generations. Germline gene editing therefore has huge potential to alleviate all forms of heritable genetic disease in the future. I argue that the principle of beneficence requires us to further the interests of those not only already suffering, but of potential children and future generations by preventing the inheritance of serious genetic disease.

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[52] James Gallagher "Embryo engineering a moral duty, says top scientist" (13 May 2015) BBC News <https://www.bbc.com/news/uk-politics-32633510>; Interview with Julian Savulescu and Margaret Somerville (Jim Brown, Canadian Broad Casting, The 180, 3 September 2015) transcript provided by the University of Oxford: Practical Ethics.

(b) Informed consent and autonomy

Some arguments against germline gene editing dispute the authority of current individuals to make decisions on behalf of future generations.[53] That is, in making germline modifications we are taking away the rights of that individual whose germline is being altered and that of future generations to make their own informed, autonomous decision. In outlining their decisions to continue not to fund germline gene editing research, the National Institutes of Healthcare (NIH) in the United States pointed to the "ethical issues presented by altering the germline in a way that affects the next generation without their consent."[54] This argument is pursued less directly in the Nature commentary, which refers to the difficulty in obtaining 'informed consent' when calling for a moratorium on gene editing.[55]

However, this issue is common to all reproductive technologies, as well as other prenatal and childhood medical interventions, and to interventions on other categories of people who lack capacity. For example, we treat people who are unable to offer consent, such as those who are unconscious, on the assumption that improving their health would benefit them. As with all interventions that create risks for individuals who cannot consent, the central question for germline gene editing is not whether the individuals who would be exposed to the risks would consent to them, but whether they will also enjoy benefits that outweigh the risks.[56]

With regards to autonomy, gene editing raises no new issues. It could be argued that germline gene editing amounts to manipulation or control of future generations by

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[53] Gyngell C, Douglas T and Savulescu J "The Ethics of Germline Gene Editing" (2017) J App Phil 34 498 at 504.

[54] Francis S Collins "Statement on NIH funding of research using gene-editing technologies in human embryos" (28 April 2015) 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>.

[55] Lanphier, above n 34.

[56] Ibid. Risks are addressed later in this chapter.

present ones, thereby reducing autonomy.[57] However, many actions of parents also intentionally influence the lives of children and this is not regarded as being a significant threat to a child's autonomy.[58] While parenting actions do not alter children's genes directly, it is difficult to see why this should be morally significant.[59] Our genes act as only one influence on our lives. Moreover, some social and environmental influences affect gene expression through epigenetic effects, and these changes can be passed down onto the next generation.[60]

C Ethical Issues Affecting Societal Interests

Reproduction, particularly where it involves biomedical technologies, takes place in a broader social and technological context. The reproduction of members of society is, at a general level, the reproduction of society and thus the production of the next generation.[61] Germline gene editing raises a number of weighty societal concerns, not only to those directly involved, but to those who may be indirectly affected by the adoption or diffusion of such practices in morally relevant ways.

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[57] Robert Sparrow "Better living through chemistry? A reply to Savulescu and Persson on 'Moral Enhancement'" (2014) J App Phil 31 23 at 26.

[58] Except in exceptional circumstances, for example cases of hyper-parenting or indoctrinating children into cults.

[59] Gyngell, above n 53, at 508.

[60] Meaney MJ "Maternal care, gene expression, and the transmission of individual differences in stress reactivity across generations" (2011) Ann Rev Neurosci 24 1161.

[61] Nuffield Council on Bioethics, above n 38, at 77.

1 Eugenics

A common objection to gene editing is the concern that gene editing may facilitate the 'consumerism' of human biology[62] through the spread of 'liberal' eugenics, (as first posited by Nozick and popularised by Agar), which is driven by the choices of individuals as opposed to the state.[63]

Many fear that if germline editing was to become common practice, eventually those that choose not to, or could not afford, the technology would be stigmatised.[64] In this sense, liberal eugenics is argued to have possibly similar socially divisive effects to the historical eugenic movement, through a combination of social pressures, reproductive autonomy and eugenic attitudes.[65]

Historic eugenic beliefs centred around improving the genetic quality of the human population and were perpetuated to the extreme by the Nazi movement.

There are, however, clear differences between how genetic technologies are used now, and historic eugenics practices, as described by Savulescu: [66]

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[62] For more detail on 'consumerisation' in healthcare see Nuffield Council on Bioethics "Medical profiling and online medicine: the ethics of 'personalised healthcare' in a consumer age" (October 2010) Nuffield Council on Bioethics <http://nuffieldbioethics.org/report/personalised-healthcare-2/what-is-personalised-healthcare>.

[63] Nozick, above n 63; Nicholas Agar *Liberal eugenics: In defence of human enhancement* (Wiley-Blackwell, Oxford, 2004).

[64] Committee on Science, Technology, and Law; Policy and Global Affairs; National Academies of Sciences, Engineering, and Medicine; Olson S (ed) "International Summit on Human Gene Editing: A Global Discussion: Meeting in Brief" (National Academies Press, Washington DC, 2016) at 4.

[65] DS King "Preimplantation genetic diagnosis and the 'new' eugenics" (1999) 25 J Medical Ethics 176 at 176.

[66] Savulescu J "Deaf lesbians, 'designer disability' and the future of medicine" (2002) BMJ 325: 771 at 772.

> *"[w]hat was wrong with the Nazi eugenics programme was that the State imposed a blueprint of perfection on couples seeking to have children by forcing sterilisation their reproductive freedom*."

There is a key ethical distinction between genetic choices today, which are not imposed through a state blueprint but driven by parental reproductive autonomy, and historical eugenics enforced sterilisation of the 'undesirable.' This separation of state influence from reproductive autonomy was tacitly accepted in the UK by the House of Commons Science and Technology Committee, stating that: [67]

> "*[i]f ensuring that your child is less likely to face a debilitating disease in the course of their life can be termed eugenics, we have no problem with its use*."

It would be unethical to prohibit parents from using gene editing to correct a lethal genetic disease such as Tay-Sachs or one that causes great suffering, such as cystic fibrosis or Duchenne's muscular dystrophy.

However, problems arise when trying to apply this statement beyond early fatal conditions. Particularly in complex diseases, such as cancer or asthma, there may be many genes of varied weight that act together to merely predispose an individual to later developing the disease, and for which there are already treatment options. The question then becomes: should parents be allowed to use gene editing to alter these types of genes, when doing so could contribute to eugenic beliefs in society? I propose in Chapter V that limits should be placed on the types of genes we allow germline gene editing to be used for, at least initially.

It is clear that concerns of a new wave of eugenics have determined to be an insufficient objection. Identical concerns of liberal eugenics have been raised with the genesis of many new genetic technologies; for example, prenatal screening and diagnostic tests with

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[67] House of Commons Science and Technology Committee (UK) *Human Reproductive Technologies and the Law* (2005) at 54.

subsequent terminations of pregnancies and the screening of embryos in the process of PGD. Approval and growing use of these technologies shows implied acceptance that the issue of liberal eugenics is not weighty enough to prevent their implementation for disease-prevention purposes.

D Safety and Risk

A fundamental objection to gene editing is the unknown health risks associated with it. Somatic gene editing poses less risk as it affects the direct individual only. Germline effects have greater potential to affect a far greater magnitude of people due to their transgenerational nature and pose greater risk as, (1) once introduced into the human population, genetic alterations would be difficult to remove and would not remain within any single community or country;[68] and (2) it will not be possible to exhaustively assess safety before birth and any problems may take years to surface due to late-onset and environmental influences.[69]

The risks posed by gene editing include incomplete editing of the cells of early-stage embryos resulting in mosaicism[70] and the unpredictability of innate immune responses in humans.[71] Of particular concern is off-target mutations, which could cause cell death and transformation and potentially result in the development of cancer or other pathologies, or result in an accumulation of random unintended mutations that may slowly lead to

[68] Committee on Science, Technology, and Law, above n 64, at 7.

[69] Lanphier, above n 34, at 410.

[70] See Committee on Science, Technology, and Law, above n 64, at 7.

[71] Carvalho M, Sepodes B and Martins AP "Regulatory and Scientific Advancements in Gene Therapy: State-of-the-Art of Clinical Applications and of the Supporting European Regulatory Framework" (2017) Front Med 4 1 at 10-11.

increasing rates of disease. [72] However, it is likely that at the current rate of improvements in gene editing techniques, these rates of off-target mutations will become negligible.[73]

A risk affecting society as a whole is that changes made to the germline will increase the frequency of genes that are beneficial to one generation, but harmful to future generations. Some genes provide protection against certain diseases but increase susceptibility to others.[74] It is highly likely there are many more gene interactions like this present, yet not known about. Therefore, current decision-makers need to consider the interests of future generations and should not reduce valuable forms of diversity.[75]

The current limits in technology do not provide a conclusive reason to completely ban use of gene editing. The principle of nonmaleficence requires that we refrain from causing harm to others. It is difficult, if not impossible, to be confident that all adverse outcomes have been identified, or to assess their likelihood of occurrence with confidence before any actual clinical use. However, in a biomedical context, there is often an inevitable risk of causing harm with any treatment and a policy that completely prioritises doing no harm over doing good would lead to an incredibly cautious and conservative approach.

Somatic gene editing is already being used in clinical trials and will continue to be improved. The uncertainties and risks associated with germline gene editing are no different from any other new medical intervention. We must continue to broaden our

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[72] Zhang F, Wen Y and Guo X "CRISPR/Cas9 for genome editing: progress, implications and challenges" (2014) Hum Mol Genet 23 40 at 43; Gyngell, above n 53, at 504.

[73] See, for example, Kleinstiver BP and others "High-fidelity CRISPR–Cas9 nucleases with no detectable genome-wide off-target effects" (2016) Nature 529 490.

[74] For example, a variant of the DARC gene (which codes for an antigen found on red blood cells) provides protection against malaria. However, this version of the gene also disposes people to be more susceptible to human immunodeficiency virus (HIV). Parents could use gene editing to provide children with the form of the gene which protects against malaria, potentially resulting in subsequent generations being decimated by HIV.

[75] Chris Gyngell and Thomas Douglas "Stocking the genetic supermarket: Reproductive genetic technologies and collective action problems" (2015) *Bioethics* 29 241 at 245.

knowledge and understanding of these risks in order to devise effective methods to overcome them.

E Conclusion

Somatic gene editing raises little concern for ethical debate and there are already substantial global evaluative and regulatory frameworks in place, as noted in Chapter IV. Assessing somatic gene editing therapies will largely come down to a risk/benefit analysis familiar to all new technologies.

On the other hand, deciding whether germline gene editing in human reproduction should be broached is pressing and ethically highly complex, and therefore is likely to be difficult to resolve. The desire of people to become biological parents and, in doing so, to secure the welfare of their children by using genome editing to influence their inherited characteristics, gives rise to a morally powerful claim. However, this must be subject to appropriate protections; namely that risks of adverse outcomes for offspring and subsequent generations should have been assessed through relevant research.

The interests of individuals must then be assessed against a broader backdrop of society's concern to safeguard the interests of people who may be made more vulnerable by gene editing and provide further constraints on the circumstances in which gene editing procedures may be used.

If the conclusion of this process is that germline gene editing should be permitted, then it is better it is available as soon as possible from a moral stance. The sooner the research is achieved, and the risks are mitigated, the sooner the therapy will become available and affected people can be treated. Prolonging the technologies' implementation would only act to extend human suffering.

CHAPTER III

The Regulatory Regime in New Zealand

There are several Acts in New Zealand, working in conjunction, that govern genetically modified organisms (GMOs) for the purposes of gene editing. For the avoidance of any doubt, the High Court ruled that gene editing techniques are techniques of genetic modification and thus fall within New Zealand statutes and regulations governing GMOs.[76]

Any treatment that is aimed at altering the genomic constitution of a person or introducing genetic material from another organism for therapeutic purposes is governed under the Hazardous Substances and New Organisms Act 1996 (HSNO Act) and the Medicines Act. These Acts work together to provide a regulatory framework for somatic gene editing therapy. I will outline the relevant regulatory bodies that would be involved in the assessment of a somatic gene editing medicine, the requirements for such a therapy to become an approved medicine, exemptions where a somatic gene editing therapy could be distributed to patients as an unapproved medicine, and the mechanisms of monitoring adverse effects.

The Human Assisted Reproductive Technology Act 2004 (HART Act) provides another level of regulation when modification is combined with an assisted reproductive technology and is therefore applicable to germline gene editing procedures followed by implantation.

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[76] *Sustainability Council of New Zealand Trust v The Environmental Protection Authority* [2014] NZHC 1067, (2014) 18 ELRNZ 331.

A Somatic Gene Editing

Approvals under the HSNO Act are required if a medicine contains a 'new organism,' which includes a GMO.[77] The Medicines Act provides additional requirements to the HSNO Act for the safe use of substances as medicines that are, or contain, new organisms.[78]

1 Regulatory bodies

There are a number of agencies involved in regulating medicines containing GMOs - as each agency regulates different aspects of product safety.

The New Zealand Medicines and Medical Devices Safety Authority (Medsafe) is responsible for assessing the quality and safety of all therapeutic products to be approved for use as a medicine on a case-by-case basis. The regulatory framework administered by Medsafe applies a number of inter-related controls that are intended to ensure that the therapeutic products available in New Zealand meet acceptable standards of safety, quality and efficacy, and performance.[79] Products are therefore expected to have greater benefits than risks.[80]

Further, if a medicine contains a new organism that has been genetically modified, both the Minister of Health and the Environmental Protection Agency (EPA) must approve its use under the HSNO Act.

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[77] Genetically modified organism is defined in s 2(1) of the Act.

[78] Medicines Act 1981, s 5A.

[79] Ibid at 7.

[80] Ibid.

This means both Medsafe and the EPA must approve a medicine containing a GMO, whereby Medsafe examines a medicine's effectiveness and safety for people, while the EPA assesses the environmental risks. [81]

2 Somatic gene editing regulatory process for approval

The step-by-step process is complicated as it alternates between the HSNO and Medicines Acts for different criteria which must be satisfied for a somatic gene editing therapy to be used on individuals. I will outline the bare-bones process and then elaborate on each requirement:

Step 1. Is it a new 'medicine' for a 'therapeutic purpose'?
Step 2. Is it a 'qualifying new medicine'?
Step 3. Are conditions for release necessary for the 'qualifying organism'?
Step 4. Assessment and approval of a qualifying organism.
Step 5. Approval of a new medicine for use.
Step 6. Provision for use of unapproved medicines.

Step 1: Is it a new 'medicine' for a 'therapeutic purpose'?

(a) <u>New medicine</u>

The definition of a new medicine is: [82]

> "*any substance or article that is manufactured, imported, sold, or supplied for administration to humans for a therapeutic purpose to achieve its principal intended*

[81] Medsafe *Guideline on the Regulation of Therapeutic Products in New Zealand - Part 1: Overview of therapeutic product regulation – Edition 1.0* (Ministry of Health, October 2014) at 13.

[82] Medicines Act 1981, s 3.

action in or on the human body by pharmacological, immunological, or metabolic means."

This could be interpreted to exclude somatic gene editing medicines, which alter an individual's genome directly as opposed to having a secondary effect via pharmacological, immunological or metabolic means. (Although cancer immunology gene editing techniques would be included).[83]

(b) Therapeutic purpose

Therapeutic purpose is defined as: [84]

"any of the following purposes, or a purpose in connection with any of the following purposes:

(a) preventing, diagnosing, monitoring, alleviating, treating, curing, or compensating for, a disease, ailment, defect, or injury; or

(b) influencing, inhibiting, or modifying a physiological process;…"

Somatic gene editing therapy would most likely fall within (a), as it aims to prevent or cure a disease. Alternatively, it could fall under (b), as physiological processes leading to disease are altered when the underlying genetic defect causing disease is changed to code for a healthy gene. The wording here is widely framed and could include more straightforward uses of gene therapy, such as cancer immunotherapies and curing monogenic disorders such as cystic fibrosis.

It could also include therapies targeted at prevention of complex disorders, if interpreted to include cases where there is a reduced likelihood of developing disease. For example, for an individual who has a mutation in the *BRCA1* gene but has yet to develop any

[83] As outlined in Chapter I using, for example, CAR-T cell therapy.

[84] Medicines Act 1981, s 4(a).

symptoms of cancer, the mutated *BRCA1* gene could be changed to a healthy variant using gene editing to reduce the risk of the individual later developing breast cancer.[85]

Therefore, gene editing is likely to be considered for a therapeutic purpose but may not be considered a 'new medicine', as it will achieve its principal intended action by genetic means as opposed to a secondary effect.

Step 2: Is it a qualifying new medicine?

A qualifying new medicine is defined under the Medicines Act as a new medicine that is or contains a 'new organism' and meets the criteria in s 38I(3) of the HSNO Act for assessing applications of a qualifying organism.[86] New organism is given the same meaning provided for under the HSNO Act.[87]

(a) <u>New organism and organism</u>

Under the HSNO Act, a 'new organism' includes a genetically modified organism (GMO).[88] A GMO means any organism in which the genes or genetic material have been altered by *in vitro* techniques.[89] Genetically edited cells modified *in vitro* could thus be classified as a GMO to fall within the definition of "new organism". However, *in vivo* techniques fall outside this definition.

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[85] This gene has been strongly causally linked to breast cancer – a recent study estimated that about 72% of women who inherit a harmful BRCA1 mutation will develop breast cancer by the age of 80. See Kuchenbaecker KB and others "Risks of Breast, Ovarian, and Contralateral Breast Cancer for *BRCA1* and *BRCA2* Mutation Carriers" (2017) JAMA 317 2402.

[86] S 2.

[87] S 2.

[88] S 2A(1)(d).

[89] Hazardous Substances and New Organisms Act 1996, s 2.

The definition of 'organism' includes a human cell that is grown or maintained outside the human body, and a genetic structure (other than a human cell) that is capable of replicating itself, whether that structure comprises all or part of the entity.[90] Therefore somatic gene editing techniques, which may involve bacterial or viral vectors alongside human cells, fit squarely within this definition.

'Organism' does not include a human being, indicating that humans themselves cannot be classified as a GMO – a situation that would technically result, as somatic gene editing therapy alters an individual's genetic make-up.[91]

Germline gene editing on human embryos is also excluded.[92] Germline editing on unfertilised gametes would be considered an 'organism', as they are human cells. However, the human cells must be "grown or maintained outside the human body" and therefore once the use of modified gametes is contemplated for fertilisation and implantation to create a child, their regulation would fall under the ambit of the HART Act.[93]

(b) Release of a qualifying organism

The EPA must determine whether a somatic gene editing therapy meets the criteria for release of a qualifying organism per s 38I(3).

The EPA must determine that it is highly improbable that: [94]

1) the dose and routes of administration of the medicine would have significant adverse effects on the health of the public or any valued species; and

[90] Hazardous Substances and New Organisms Act 1996, s 2(1).

[91] Ibid.

[92] Regulation for research on human embryos is governed under the Human Assisted Reproduction Act instead; detail on this is provided in this Chapter under Part B.

[93] The Human Assisted Reproduction Act 2004 is discussed in Part B of this Chapter.

[94] Hazardous Substances and New Organisms Act 1996, s 38I(3).

2) the qualifying organism could form a self-sustaining population and have significant adverse effects on the health or safety of the public, any valued species, natural habitats or the environment.

It is highly unlikely that any genetically altered cells could form an undesirable self-sustaining population or have significant adverse effects on the public or any valued species.

The EPA is limited to considering only the effect of the dose and routes of *administration* of the medicine. It is explicitly prevented from considering the effects of any medicine or qualifying organism on the person being treated, with the focus of risk lying on the general public.[95]

This analysis is therefore very environmentally based; the considerations suggest that this provision is attempting to guard against genetically modified micro-organisms or vaccines which may cause harm to other species, as opposed to genetically modified human cells. This is because approval for release does not mean a qualifying medicine can be used until the medicine has been lawfully supplied for use under the Medicines Act.[96]

Step 3: Conditions for release of a qualifying organism

If the EPA determines the criteria are met for release under s 38I, it can either release the qualifying new organism outright or with controls, [97] which include:[98]

(a) controls for the distribution of the qualifying medicine:
(b) controls providing for the methods of administering the qualifying medicine:

[95] S 38I(4).
[96] S 38I(5).
[97] S 38I(1)(b).
[98] S 38K.

(c) controls concerning the persons who may administer the qualifying medicine:

(d) controls concerning the persons to whom the qualifying medicine may be administered.

These controls are important, as they establish limitations on use of potentially dangerous medicines. However, I question the appropriateness of the EPA, a primarily environmental body, to determine controls for persons or distribution and methods of administration. The role would be more appropriately governed by a medical body, such as Medsafe, and I will discuss the role of the EPA in the somatic gene editing process in more depth in Chapter V.

Step 4: Assessment and approval of a qualifying organism

The Director-General may then grant approval if he/she has the consent of the Minister of Health to do so and is acting under a designation from the EPA.[99] If the Director-General declines to grant approval because the organism is not a 'qualifying new medicine,' then he/she must provide the EPA with a copy of all information that may assist them in deciding whether to approve or decline the application under the HSNO Act.[100]

The Minister is also prevented from consenting to the distribution or sale of the medicine until the Minister receives written advice from the EPA that it has been approved for release under the HSNO Act.[101]

Step 5: Approval of a new medicine for use

The Minister's consent or provisional consent must be given before a medicine is allowed to be sold or distributed.[102]

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[99] Medicines Act 1981, s 24A.

[100] Medicines Act 1981, s 24B(a)

[101] Medicines Act 1981, s 24B(b)

[102] Medicines Act 1981, ss 20 and 23.

New medicine applications are split into three categories, based on risk.[103] Somatic gene editing therapy would fall under a New Higher-risk Medicine application (NMA-H), as it is a new multi-source biological or biotechnological medicine.[104] Medsafe assesses the applications at this stage in the process and requires an accompanying dossier of supporting quality, safety and efficacy data for all applications.[105] For NMA-H applications, applicants can choose to use the standard evaluation process, whereby Medsafe undertakes a full assessment of data provided, or an abbreviated evaluation assessment, whereby Medsafe will base its evaluation on the reports provided.[106]

Medsafe reviews this information and makes a recommendation to the Minister as to whether the medicine is approvable or otherwise.[107]

I believe this current Medsafe evaluation is sufficiently rigorous to evaluate new dangerous medicines and is thus appropriate for gene editing.

Step 6: Use of unapproved medicines

There is provision for access to unapproved medicines through exemptions from the normal product approval requirements when a medicine has not been granted Ministerial consent as in step 5.

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[103] Medsafe *New Zealand Regulatory Guidelines for Medicines - Part B: What sort of application is required? – Edition 6.16* (Ministry of Health, September 2014) at 3.

[104] Ibid.

[105] Medsafe *New Zealand Regulatory Guidelines for Medicines - Part C: Requirements for application types – Edition 6.16* (Ministry of Health, September 2014) at 3.

[106] Ibid at 15.

[107] Medsafe "Safety Information: Medsafes evaluation and approval process" (4 July 2013) Medsafe <http://www.medsafe.govt.nz/Consumers/Safety-of-Medicines/Medsafe-Evaluation-Process.asp>.

(a) Exemptions for authorised prescribers and practitioners

Authorised prescribers are permitted to procure, administer and arrange the administration of an unapproved medicine, and medical practitioners may request an unapproved medicine for the treatment of any patient under the practitioner's care.[108]

Medsafe notes that there will be medicines that are effective and safe, and approved in other countries but do not have approval in New Zealand, due to the requirement for Ministerial consent.[109] There will also be other medicines that have been approved with a particular set of indications, but for which there are other recognised indications not applied for in New Zealand.[110]

Such situations appear likely due to the burgeoning somatic gene editing clinical trials being conducted in the US, China and Europe.[111] Further, Medsafe explicitly notes that "unapproved medicines may be used for rare diseases for which there are no, or few, treatments approved in this country."[112]

(b) The clinical trials exemption

There is provision for access to unapproved medicines through a clinical trials scheme which has been approved by the Director-General of Health.[113] To be granted an exemption, the medicine must be distributed in the trial for the purpose of obtaining

[108] Medicines Act 1981, ss 25 and 29.

[109] Medsafe "Compliance: Use of Unapproved Medicines and Unapproved Use of Medicines" (22 October 2014) Medsafe <http://www.medsafe.govt.nz/profs/RIss/unapp.asp>.

[110] Ibid.

[111] As demonstrated in Chapter I when examining the therapeutic potential of gene editing.

[112] Medsafe, above n 109.

[113] Medicines Act 1981, s 30.

clinical and scientific information about the medicine concerning its safety and efficacy.[114]

The application and approval process is administered by Medsafe, who receives and processes applications and liaises with the relevant Health Research Council Committee (HRCC), along with the applicant.[115] The Director-General of Health may approve a clinical trial on the recommendation of the HRCC.[116]

The HRCC maintains the Gene Technology Advisory Committee (GTAC), a standing committee to consider clinical trial applications involving novel gene and other biotechnology therapies and make recommendations to the Director-General.[117] Thus applications involving somatic gene editing therapy clinical trials would go to GTAC.[118] GTAC's role is limited to assessing the science of applications only.[119]

It is important to note that GTAC is rarely invoked – it has only considered a handful of applications since its genesis in 1995 – indicating there has been little demand for clinical trials involving novel genetic therapies thus far in New Zealand.[120]

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[114] Medicines Act 1981, s 30.

[115] Medsafe *Guideline on the Regulation of Therapeutic Products in New Zealand - Part 11: Clinical trials – regulatory approval and good clinical practice requirements – Edition 1.4* (Ministry of Health, January 2015) at 10.

[116] Ibid.

[117] Ibid.

[118] See Gene Technology Advisory Committee *Terms of Reference* (Health Research Council, October 2015) at 1 for more detail on the types of applications GTAC considers.

[119] Ministry of Health *Operational Standard for Ethics Committees: Updated edition* (Ministry of Health, Wellington, 2006) at 13.

[120] This information comes from Ian Morrison, who has been the chair of GTAC since 1999. The committee has considered applications for xenotransplantation and most recently PEXA-VAC – a liver cancer treatment derived from a viral vaccine that has been engineered to attack cancer cells and stimulate anti-tumour immunity, for which one clinical trial has now been approved for use in New Zealand: Minister of Health *Therapeutic Products Regulation Paper 1: further policy approvals* (April 2016) at 11.

Ethics approval is then administered by the New Zealand Health and Disability Ethics Committee (HDEC).[121] The HDEC's primary role is to safeguard the rights, health and wellbeing of consumers, and research participants by providing independent ethical review of proposed research.[122]

(c) Conclusion on exemptions

These exemptions are hugely beneficial, as they not only enable patients' access to medicines they could not otherwise obtain in New Zealand, but they also enable access to a therapy without the associated costs of purchasing unsubsidised and expensive new or experimental treatments. This is true particularly in the clinical trials exemption, which may provide access for a wider range of people who would not otherwise have the means to seek treatments offered in New Zealand that are expensive, or only offered overseas and require associated travel costs.

3 Monitoring adverse effects

The Medicines Adverse Reactions Committee (MARC) is a technical advisory committee established to advise the Minister of Health on the safety of approved medicines.[123] It has narrow terms of reference and only considers cases referred to it by Medsafe to provide expert advice and consider the risk-benefit profile of a medicine when its safety is questioned.[124]

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[121] Medsafe, above n 115, at 14.

[122] Ibid at 9.

[123] Medicines Act 1981, s 8; Medsafe "Committees: Adverse Reactions Committee" (22 March 2016) Medsafe < http://www.medsafe.govt.nz/profs/MARC/TermsofReference.asp>.

[124] Ibid.

The Centre for Adverse Reactions Monitoring (CARM) is the national repository for adverse reaction reports.[125] Spontaneous reports from health professionals, pharmaceutical countries and consumers are relied upon.[126] All adverse reactions to new medicines of clinical concern are encouraged to be reported.[127] Thus CARM is also limited, in that it requires an individual to report to a health professional any adverse reactions, or to make a report themselves when they experience an adverse reaction.

While the systems of MARC and CARM may be effective to ensure the safety of conventional medicines, they are unlikely to be adequate in the context of somatic gene editing therapies that are likely to have long-term unknown effects of a varying degree. A surveillance system should be put in place requiring long-term monitoring and routine checks on all those subjected to somatic gene editing therapies – a point I will elaborate on in Chapter V.

4 The Therapeutic Products and Medicines Bill

The New Zealand Government is currently working on a new and comprehensive regulatory regime to regulate therapeutic products that will replace the Medicines Act and its Regulations.[128] The Therapeutic Products and Medicines Bill (TPM Bill) will replace and repeal the Medicines Act 1981 with the Medicines Act 2006 and create a new joint scheme with the Australian Government for the regulation of therapeutic products, the

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[125] Centre for Adverse Reactions Monitoring "Your Guide to Adverse Reaction Reporting" (September 2001) Medsafe <http://www.medsafe.govt.nz/profs/PUarticles/ADRreport.htm>.

[126] Ibid.

[127] Centre for Adverse Reactions Monitoring "Reporting" (2018) New Zealand Pharmacovigilance Centre <https://nzphvc.otago.ac.nz/reporting/>.

[128] Ministry of Health "Therapeutic products regulatory regime" (28 February 2018) Ministry of Health <https://www.health.govt.nz/our-work/regulation-health-and-disability-system/therapeutic-products-regulatory-regime>.

Therapeutic Products Act 2006.[129] The driving impetus for the Bill is the recognition that the current regime is no longer "fit-for-purpose" due to being inflexible, out of date, overly prescriptive and preventing trade of cell and tissue therapies.[130] Responsibility for regulating therapeutic products will be transferred from Medsafe to the Australia New Zealand Therapeutic Products (ANZTP) Authority as part of a move for New Zealand and Australia to harmonise their regulatory regimes.[131]

The Bill does not specifically refer to any genetic technologies or procedures. It only states that "genetically modified organisms must gain approval from ERMA" (currently the EPA) and the regulatory authority of therapeutic products before being marketed in New Zealand.[132] The interface between the Medicines Act and the HSNO Act is being examined to determine the need for two approval processes and to ensure these processes are aligned and streamlined.[133]

A notable feature of the regime is to provide a new category of therapeutic products - cell and tissue therapies (which are currently not fully regulated in New Zealand), alongside the existing categories of 'medicines' and 'medical devices.' However, the cell and tissue therapies referenced are unlikely to include genetically modified cells and tissues, as they are described as being:[134]

> *"derived from living cells and tissues of human or animal origin and include products such as skin grafts, ligaments, demineralised bone matrix, and dental-pulp derived stem cells."*

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[129] Parliamentary Library New Zealand *Bills Digest: Therapeutic Products and Medicines Bill* Bill Digest No 1467 (Parliamentary Library, Parliament Buildings, Wellington, 2006) at 1.

[130] Minister of Health *Therapeutic Products Regulation Paper 1: Context and Overview* (April 2016) at 3.

[131] Therapeutic Products and Medicines Bill 2006 (103-1) (explanatory note) at 1.

[132] Therapeutic Products and Medicines Bill 2006 (103-1) at 103-104.

[133] Minister of Health, above n 120, at 11; Minister of Health, above n 130, at 9.

[134] Minister of Health, above n 130, at 2.

The medicines category is defined similarly to the current definition of 'medicine' in the Medicines Act as working "primarily through pharmacological, immunological or metabolic means".[135] An additional qualifier has been added that the medicine "comprises of substances that interact with human physiological and pathological processes".[136] Once again, this could be interpreted to exclude somatic gene editing techniques, especially as somatic gene editing therapies aimed at reverting a mutated gene associated with disease to a healthy variant will not interact with physiological or pathological processes itself. The gene editing therapy itself is not influencing these processes, but the change of an underlying genetic defect may have secondary effects on physiological or pathological processes.

Therefore, there is no specific provision made in the Bill, as it currently stands, for new biotechnologies involving genetic modification – an issue I will address further in Chapter V.

B Germline Gene Editing Regulation

1 Implantation of a genetically altered embryo or gametes

(a) Three categories of procedures

The HART Act divides assisted reproductive technologies into three categories; prohibited procedures (which are banned completely),[137] regulated procedures and established procedures.[138] Regulated procedures are those that fall within the definition

[135] Ibid.
[136] Ibid.

[137] Schedule 1.

[138] An 'established procedure' is defined in section 5 of the HART Act 2004 to be any procedure, treatment or application declared to be an established procedure under section 6. Section 6 allows the Governor-

of an 'assisted reproductive procedure,'[139] but are not specifically prohibited or established. Regulated procedures are only able to proceed with the prior approval in writing of the Ethics Committee on Assisted Reproductive Technology (ECART) on a case-by-case basis.[140]

The Advisory Committee on Assisted Reproductive Technology (ACART) recommends which procedures should be approved, and develops policies and guidelines for regulation which are issued to ECART.[141] ECART has a mandatory requirement to act in accordance with any guidelines issued by ACART,[142] and may not grant approval until it is satisfied that the activity proposed is consistent with the relevant guidelines.[143] In the absence of guidelines, ECART will not approve a procedure until ACART provides direction on the issue.

Therefore, regulated procedures require ACART to create guidelines and advice, which are then issued to ECART, who assess applications on a case-by-case basis.

(b) Definition of assisted reproductive procedure

Assisted reproductive procedure is defined as a procedure for the purpose of assisting human reproduction that involves:[144]

(a) the creation of an in vitro human embryo; or
(b) the storage, manipulation, or use of an in vitro human gamete or an in vitro human embryo; or

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General, following the recommendation of the Minister after advice tendered by the advisory committee, to declare certain procedures as established procedures.

[139] S 5.

[140] Human Assisted Reproduction Technology Act 2004, s 16(1)

[141] Human Assisted Reproduction Technology Act 2004, s 35.

[142] Human Assisted Reproduction Technology Act 2004, s 29(a).

[143] Human Assisted Reproduction Technology Act 2004, s 19(2).

[144] Human Assisted Reproduction Technology Act 2004, S 5.

(c) the use of cells derived from an in vitro human embryo; or

(d) the implantation into a human being of human gametes or human embryos;

Germline gene editing could fall under any of the latter three of these and therefore would be considered an assisted reproductive procedure.

(c) Germline gene editing prohibited

It is currently a prohibited action to implant into a human a genetically modified human embryo or gamete.[145] The HART Act does not define these terms and does not refer to the HSNO Act for the definition of "genetically modified". However, it can be assumed that germline gene editing on an embryo or gamete would be considered genetic modification and therefore be prohibited.

2 Germline gene editing research on human embryos

It is also important to note that it is an offence to conduct human reproductive research that uses or creates a human gamete or a human embryo without gaining prior approval from ECART or the ministerial ethics committee.[146] Further, it is an offence to allow an *in vitro* embryo to develop beyond fourteen days gestation.[147] ECART considers applications for embryo research under guidelines issued to it by ACART.[148] However, these guidelines only allow research using non-viable human embryos, and thus ECART is unable to grant

[145] Human Assisted Reproductive Technology Act 2004, s 8(1) and Schedule 1(8).

[146] Human Assisted Reproductive Technology Act 2004, ss 16 and 19.

[147] Human Assisted Reproductive Technology Act 2004, s 9.

[148] See National Committee on Assisted Human Reproduction *Guidelines for Research on Gametes and Non-viable Embryos* (2005).

ethics approval that uses viable human embryos.[149] Further, human embryo research cannot be approved by ministerial ethics committees due to a lack of specific guidelines.[150]

As a result, human embryo research that can be undertaken overseas in countries like Australia, the United Kingdom and the United States cannot be conducted in New Zealand. The issues surrounding uncertainty and the lack of clear guidelines defining embryo research are outside the scope of this dissertation. This may act as a significant barrier to progressing scientific research that requires use of embryos in New Zealand. I will argue in Chapter V that New Zealand needs to improve its research capabilities.

C Conclusion

The position New Zealand takes on human embryo research is restrictive and requires greater analysis into the laws governing this, together with the socio-ethical concerns that arise from extending the law. As such I will not cover this topic in any depth.

Germline gene editing for the purposes of implantation is prohibited and therefore legislative change would be required before its application in New Zealand.

New Zealand's system for somatic gene editing therapies appears fairly robust with the dual roles of Medsafe and the EPA assessing risks to the individual, and to the public and environment more broadly. International standards must be conformed to in several stages of the procedure and there are mechanisms for control, including those that the EPA may impose on release of a qualifying new medicine. Provision for access to unapproved medicines enables patients to gain access to new medicines in several ways, which are necessary to ensure New Zealanders are not at a disadvantage compared to other countries with more extensive involvement in the development of new medicines.

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[149] Ibid.

[150] Human Assisted Reproductive Technology Act 2004, ss 16 and 19. See University of Auckland "Government called on to define law on embryo research" *Targeted News Service* (22 June 2018).

There are several areas of weakness however, notably the fact that genetically modified excludes *in vivo* techniques of modification, and the current adverse monitoring system is inadequate to effectively monitor the complex and unknown risks associated with altering an individual's genome directly.

More broadly, the mechanisms under the Medicines and HSNO Acts require jumping back and forth for definitions, steps and requirements. The process for somatic gene therapy to gain approval is therefore confusing, and calls into question whether the mechanisms are actually effective. The TPM Bill recognises the fact that the current Medicines Act is out of date; however, it does not appear to address novel genetic technologies specifically and at this stage much is left up in the air about how it will interplay with the HSNO Act. In Chapter V I will make recommendations on how to rectify these problems, focusing on a proactive approach to emerging biotechnologies.

It would therefore be beneficial to examine approaches other countries take in regulating somatic gene editing technologies, as well as their positions on germline gene editing. This could also then inform a way forward for New Zealand in considering what gene editing uses we want to allow and what we want to restrict.

CHAPTER IV
Global Considerations

A Global Response to Gene Editing

An International Summit on Gene Editing was held by the National Academy of Sciences, Engineering and Medicine (NAS) in December 2015 to allow all stakeholders and official authorities an opportunity to define what ethical, legal and political issues were emerging as the technology became more proliferate. The summit was followed by a consensus study convened by the NAS, which issued its report in December 2017. The NAS Report focused on the scientific underpinnings of human-gene editing technologies and the clinical, ethical, legal and social implications of their use.[151]

The study endorsed the use of somatic cell gene editing in human clinical medicine.[152] The NAS Report further concluded that the oversight of somatic gene editing could rely on the evaluative and regulatory frameworks developed for gene therapy.[153] Thus, the oversight of gene editing in human somatic cells to date has not required the establishment of new regulatory authorities beyond those established for gene therapy transfer oversight.[154]

In respect to germline gene editing, the scientific community reacted to the first reports of gene editing on human embryos in 2015 with a series of cautionary statements. A call for an immediate voluntary moratorium on any gene editing experiments with human embryos was published by a number of prominent scientists.[155] This was followed by another seminal publication of the views of eighteen scientists, organised by Jennifer Doudna,[156]

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[151] National Academies of Sciences, Engineering, and Medicine, above n 12.

[152] Ibid at 110.

[153] Ibid at 159.

[154] Kane EM "Human Genome Editing: An Evolving Regulatory Climate" (2017) Jurimetrics 57 1 at 11.

[155] Lanphier, above n 34.

[156] An original pioneer of CRISPR who first identified the nuclease's ability as a gene editing tool.

calling for a prohibition on the clinical application of germline genome modification and for more discussion on the use of gene editing on human embryos.[157]

In contrast, an endorsement of gene editing research on human embryos emerged from an international bioethics consortium.[158] More recently, a position statement issued by a coalition of professional genetics organisations not only supported genome editing on human embryos but went further to recommend public funding of such experiments.[159]

This support of gene editing research on human embryos is in no way support for its application to human reproduction. The position statement further went on to say it is "inappropriate" to use germline genome editing in human reproduction.[160] The NAS International Summit concluded it would be "irresponsible" to conduct any clinical germline gene editing at present until technical and safety issues were resolved and societal consensus was reached,[161] a sentiment acknowledged by others.[162] The NAS Report did not, however, call for a prohibition on the use of genome editing in human reproduction - stating that such trials should be approached with caution, noting that caution does not mean they must be prohibited.[163] The Nuffield Council addressed human reproduction as an issue that should be urgently addressed in its ethical review,[164] and in its follow up report

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[157] Baltimore, above n 2. Note: many of the authors were organisers of the NAS International Summit held in 2015; Lundberg AS and Novak R "CRISPR-Cas Gene Editing to Cure Serious Diseases: Treat the Patient, Not the Germ Line" (2015) Am J Bio 15 38.

[158] Chan S and others "Genome Editing Technologies and Human Germline Genetic Modification: The Hixton Group Consensus Statement" (2015) Science 36 348.

[159] Ormond KE and others "Human Germline Genome Editing" (2017) Am J Hum Genetics 101 at 167.

[160] Ibid at 172.

[161] Committee on Science, Technology, and Law, above n 64, at 7.

[162] Araki M and Ishii T "International regulatory landscape and integration of corrective genome editing into in vitro fertilisation" (2014) Rep Biol End 12 at 10; International Society for Stem Cell Research "The ISSCR Statement on Human Germline Genome Modification" (press release, 19 March 2015).

[163] National Academies of Sciences, Engineering, and Medicine, above n 12**,** at 189.

[164] Nuffield Council on Bioethics, above n 41, at 115-116.

on genome editing and reproduction it stated it could envisage circumstances where germline genome editing should be permitted.[165]

The various reports and recommendations made by a growing number of prominent bodies demonstrate that the global discussion on ethical limitations now needs to move on past the theoretical into action and ensure that mechanisms are devised for the regulation of this revolutionary technology.

B International Law and Regulation: a brief overview

No international treaty explicitly governs genome editing in humans. However, there are relevant treaties in international law, particularly human rights law, that highlight general international principles underlying conventions which have become essential elements of global norms and aspirations.[166] These treaties encompass the rights of dignity and integrity to humanity, and either prohibit or strongly discourage germline editing at this time. Eugenic practices "aimed at the selection of persons" are also specifically prohibited in the Charter of Fundamental Rights of the European Union – although this is aimed at historical eugenic practices and it is doubtful whether this practice could apply to 'liberal eugenics' (as outlined in Chapter II). [167]

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[165] Nuffield Council on Bioethics, above n 38, at 154.

[166] Universal Declaration on the Human Genome and Human Rights UNESCO 29 C/17 (adopted 11 November 1997); Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine 164 ETS (opened for signature 4 April 1997, entered into force 1 December 1999); For more in-depth explanation of these prohibitions and rights see: Nuffield Council on Bioethics, above n 38, at 120-127.

[167] Charter of Fundamental Rights of the European Union 2000/C 364/01 (entered into force 1 December 2009), art 3(2).

C The Current State of Laws

There are three key players at the forefront of gene editing research and technology: the United States (US), the United Kingdom (UK) and China. In order to glean the best approach for regulating gene editing in New Zealand, I will analyse the current laws and regulations in the US and UK. The US and China are both considered research and market leaders in gene editing and have similar stances on regulation, although China has conducted more somatic gene editing clinical trials on humans.[168] I will only look to the US's regulatory regime however, as it has a more restrictive approach to clinical trials and is therefore likely to be more relevant for the purposes of providing direction for New Zealand. In contrast, the UK provides an example of a more conservative approach and tends to align more closely with overarching ideas and laws in New Zealand.

1 The United States

(a) Somatic gene editing regulation

In the US, proposed somatic genome editing protocols and clinical trials have been absorbed into the pre-existing regulatory framework for gene therapy.[169] All applications for clinical experiments must be approved by the Food and Drug Agency (FDA) and reviewed by the National Institutes of Health (NIH).

The FDA defines somatic cell therapy and gene therapy in broad terms, allowing the application of gene editing of somatic cells to be subject to FDA regulations.[170] The

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[168] Rana above n 28.

[169] Kane, above n 154**,** at 10.

[170] Centre for Biologics Evaluation and Research *Guidance for Industry: Guidance for Human Somatic Cell Therapy and Gene Therapy* (US) March 1998 at 3. Somatic cell gene therapy is defined as: "the administration to humans autologous allogeneic or xenogeneic living cells which have been manipulated or processed *ex vivo;"* gene therapy is defined as: "a medical intervention based on modification of the

FDA's centre for Biologics Evaluation and Research has a well-established programme in place to evaluate gene therapy products.[171] Once the FDA approves a gene therapy product for public sale, it requires companies to monitor its use, report any adverse events and give public warnings as appropriate.[172] The FDA also advises researchers to follow up with participants in gene therapy trials for as long as fifteen years after the end of the trial to discover and deal with any delayed ill effects.[173] As noted, New Zealand has no long-term surveillance scheme in place for gene therapies and would strongly benefit from a similar system, with a specialised body in place to govern this.

The NIH's Recombinant DNA Advisory Committee (RAC) considers ethical implications and offers advice to the NIH on whether to approve gene-editing proposals that seek government funding. [174] While the NIH is responsible for overseeing some gene-transfer research studies, its oversight and review are limited to the projects and institutions it funds.

Several commentators have remarked that this regulatory regime is sufficient for using CRISPR to edit somatic cell genes, since no new safety or ethical issues are raised, and the FDA and NIH are well positioned to regulate applications.[175]

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genetic material of living cell. Cells may be modified *ex vivo* for subsequent administration to humans or may be altered *in vivo* by gene therapy given directly to the subject. When the genetic manipulation is performed *ex vivo* on cells which are then administered to the patient, this is also a form of somatic cell therapy."

[171] Melillo TR "Gene Editing and the Rise of Designer Babies" (2017) Vand J Transnat'l 50 757 at 773.

[172] Gutmann A and Moreno JD "Keep CRISPR Safe: Regulating a Genetic Revolution" (2018) Foreign Aff 97 171 at 174.

[173] Ibid at 173.

[174] Barnett SA "Regulating the Human Germline Modification in Light of CRISPR" (2017) U Rich L Rev 52 553 at 579; Robert Califf and Ritu Nalubola "*FDA's Science-based Approach to Genome Edited Products"* US Food and Drug Administration Department of Health & Human Services (18 January 2017) <https://blogs.fda.gov/fdavoice/index.php/2017/01/fdas-science-based-approach-to-genome-edited-products/>.

[175] Grant EV "FDA Regulation of Clinical Applications of CRISPR-CAS Gene-Editing Technology" (2016) Food Drug LJ 71 608 at 608; Kane, above n 154, at 21; Gutmann and Moreno above n 172, at 174.

(b) Germline gene editing regulation

Unlike New Zealand, the US lacks any official prohibition on human germline gene editing. However, there are indirect sources of resistance that reduce the possibility that germline genome editing could be used in human reproduction. Shortly after the news spread of Chinese researchers' gene editing experiments, the NIH issued a statement that it would 'not fund any use of gene editing technologies in human embryos,' and noted there were multiple legislative and regulatory prohibitions on such work.[176]

Such prohibitions include the RAC's formal refusal to consider any protocols for germline alteration, and the Dickey-Wicker amendment, which acts as a ban on federal funding for most human embryo research.[177]

The FDA also enacted legislative prohibition on its ability to review any proposals for clinical trials involving gene editing on human embryos.[178] However, technically the FDA has no authority to regulate this type of research, as gametes and embryos are not "human subjects".[179] This effectively allows for germline editing experimentation as long as embryos are not placed *in utero* or aimed at the development of a 'product' subject to its approval.[180] Further, based on the vital Separation of Powers Doctrine in the US, some states are looking to their laws and guidelines to see if it is permissible to fund research of gene editing on human embryos.[181]

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[176] Collins, above n 54.

[177] Balanced Budget Downpayment Act I H.R.2880, s 128 (US); Melillo, above n 171, at 772. The amendment prohibits the Department of Health and Human Services from using funds for both "the creation of a human embryo or embryos for research purposes" and "research in which human embryos are destroyed, discarded, or knowingly subjected to risk of injury or death greater than that allowed for research on foetuses in utero."

[178] Kane, above n 154**,** at 8

[179] Barnett, above n 174, at 578.

[180] Ibid.

[181] Ibid.

Since there is no government agency that regulates privately funded projects, it is not illegal to implant a genetically modified embryo if done through private institutions.[182]

Therefore, there are significant gaps in regulations and funding that can be exploited to enable germline gene editing research on embryos or gametes, although implantation is highly unlikely to be approved. In comparison, New Zealand has a more straightforward approach, in that embryo research is only allowed in limited circumstances. This is a benefit in the sense that the approach is not governed by agencies making determinations on what is appropriate for a contentious technology – Parliament would have to make legislative changes, which commands more authority and aligns with public opinion. However, the downfall is that the US will continue to be a strong leader in this field, while New Zealand must rely on the research of others to formulate views and move forward.

2 The United Kingdom

For somatic gene therapy, the United Kingdom's approach is not unlike the United States', but it has more centralised and intensive regulatory control over therapies that involve gametes and embryos.

(a) Somatic gene editing regulation

Somatic gene editing is regulated under the advanced therapy medicinal products (ATMP) legal framework, which has its foundations in EU law.[183]

[182] Melillo, above n 171, at 774.

[183] Council Regulation 1394/2007, 2007 O.J. (L 324) 121 (EC).

An ATMP is any of the following intended for human use: a gene therapy medicinal product; a somatic cell therapy medicinal product; or a tissue-engineered product.[184] Each of these could contain gene edited cells. Thus, unlike New Zealand, the UK has clear legislation encompassing gene editing, which has broadly framed categories that could easily incorporate new genetic biotechnologies.

ATMPs that are placed on the market in the EU must have a marketing authorisation, and the ATMP Regulation establishes a tailored regime for the evaluation and granting of marketing authorisations for ATMPs, managed by the European Medicines Agency (EMA).[185] The manufacture of ATMPs in the United Kingdom also needs to be authorised by the UK Medicines and Healthcare Products Regulatory Agency (MHRA).[186]

A third regulator, the UK Human Tissue Authority[187] also licenses the procurement, testing, processing, storage, distribution, and import/export of tissues and cells intended for human application, subject to a range of qualifications and exceptions.[188]

There are two ways in which ATMPs may be made available in the UK without marketing authorisation. The "hospital" exemption is specific to ATMP's and may be relied upon for an ATMP that is custom-made to meet individual medical prescription for a patient.[189] The "specials" exemption may apply to any medicinal product, and similarly may apply where the ATMP has been created for an individual medical prescription for a patient.[190] Hospitals require a license from the MHRA to rely on either exemption.

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[184] Council Regulation 1394/2007, 2007 O.J. (L 324) 121 (EC), art. 2(1)(a).

[185] Davies JL "The Regulation of Gene Editing in the United Kingdom" (2016) SciTech 13 14 at 15.

[186] Ibid.

[187] Acting under the Human Tissues Act 2004 (UK).

[188] Davies, above n 185, at 17.

[189] Ibid at 15.

[190] Ibid.

As gene editing cells are created for specific individuals, it is likely these exemptions will be relied upon to allow the therapeutic use of gene-edited somatic cells without the need for further regulation.[191] In this sense, the UK framework is very similar to the exceptions provided for in the Medicines Act, which will also likely be relied on to allow use of somatic gene therapies in New Zealand – at least initially.

(b) Germline gene editing regulation

The Human Fertilisation and Embryology Act 2008 governs the Human Fertilisation and Embryology Authority (HFEA), which develops standards and regulates all research involving human embryos by requiring researchers to obtain a license in order to perform any such experiment.[192] Unlicensed research or treatment, or activity outside the terms of a license, is a criminal offense.[193] To be licensed, clinics must meet safety and quality assurance standards, offer counselling to patients, monitor birth outcomes and the well-being of children conceived through the new technologies, and generally provide personnel and systems that allow for ongoing compliance monitoring.[194]

Under the previous 1990 Act, alteration of the genetic structure of an embryo was prohibited unless Parliament enacted specific regulations – which it never did.[195] The removal of this prohibition has paved the way for researchers using the licensing scheme to gain permission to edit human embryos genetically.[196] This research license allows for the keeping, use and storage of embryos for a period of three years, with the option

[191] Ibid.

[192] Barnett, above n 174, at 584.

[193] Davies, above n 174, at 15.

[194] National Academies of Sciences, Engineering, and Medicine, above n 12, at 58.

[195] Human Fertilisation and Embryology Act 2008, c.22, Explanatory Notes 65.

[196] Melillo, above n 171, at 776.

of renewal, for the purpose of developing treatments for serious disease or other serious medical conditions.[197]

Although China was the first to use CRISPR for gene editing, this licensure approval represents the first endorsement worldwide of research of this kind by a national regulatory authority, and many scholars believe that it has established a strong precedent for this type of research.[198] With the HFEA governing applications for licenses, alongside ethics approval required for all gene editing research,[199] there are strong mechanisms of control in place and New Zealand should look to the UK as a research regime to strive towards.

Whilst germline gene editing on embryos for research is permitted, the use of modified embryos for pregnancy is banned in the Act, with the 2008 amendment outlining that only permitted embryos or gametes may be transferred to a woman, which excludes those whose nuclear or mitochondrial DNA or cells have been altered.[200] The HFEA also reiterated the prohibition that research can never involve placing non-permitted embryos or gametes in a woman [201] and the explanatory notes to the amendment acknowledge that the limitation on implantation "ensures embryos created by artificial gametes or genetically modified gametes could not be placed in a woman."[202]

The UK has therefore responded to gene editing in a very different way than the US. It has specifically enacted a scheme which will govern gene editing, along with other gene therapies, whereas the US utilises regulatory bodies to govern regulation of somatic gene therapies. Further, the specific approval of germline gene editing research in

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[197] Human Fertilisation and Embryology Authority License Committee – minutes (14 January 2016) at 1.18.

[198] Callaway E "UK scientists gain license to edit genes in human embryos*"* (2016) Nature 530 18.

[199] Ibid at 2.2

[200] Human Fertilisation and Embryology Act 2008, c.22, ss 3(2), 3(5)(4)(c).

[201] Ibid at 1.19.

[202] Ibid 29

human embryos is revolutionary. However, the UK takes a similar approach to New Zealand in specifically prohibiting use of germline gene editing in human reproduction.

3 Conclusion

The UK and the US have relied on existing mechanisms to regulate somatic gene editing. The US has a clear oversight mechanism in place using various regulatory bodies. The UK also has a system utilising regulatory bodies, together with the ATMP legislation gained from the EU. It would be worthwhile to consider a similar approach in New Zealand, whereby new legislation is enacted targeted at broadly regulating gene therapies, as discussed in Chapter V.

It is of interest to note that the US EPA and the UK equivalent are not involved in the application process, indicating there is no consideration of release into the environment and broader impacts on public health and safety as there is by the EPA in New Zealand. Both the US and the UK rely on a system of several medical authorities to regulate different aspects of the gene therapy application process. This calls into question what role the EPA should have in moving forward with our regulatory regime and whether its considerations are necessary.

The US and UK both permit embryo research (albeit in different ways). New Zealand arguably has an overly restrictive approach to embryo research and would benefit from looking to the UK as providing a model system for regulation.[203] However, in depth-analysis of embryo research remains outside the scope of this dissertation, so I will go no further than tentatively suggest reform in this area.

All three countries align on their views in respect to prohibiting implantation of a genetically altered gamete or embryo. Both New Zealand and the UK have explicit legal

[203] University of Auckland, above n 150.

prohibitions in statute, whereby the US has attempted to ban germline gene editing but has left loopholes that could potentially be exploited to get around this.

Chapter V
Forging a Path Forward: Insights and Recommendations

A Introduction

This chapter begins by providing an overview of social views and attitudes surrounding gene editing. I then recommend that New Zealand takes a more proactive approach to regulating emerging genetic biotechnologies. The rapid development of the genetics field has resulted in an unprecedented uptake of novel genetic technologies that will continue to stretch legal boundaries. In this new era of emerging technology, descriptive dissociation threatens to render current legal mechanisms obsolete unless new ways of formulating legislation are adopted to guard against this.

I outline that there are two options that could be taken for regulating somatic gene editing therapy; one leaving the current procedures in place and another suggesting that new legislation is enacted to broadly regulate gene therapies. These options are discussed in more detail, and recommendations are made to improve several aspects of regulation.

Finally, I address germline gene editing as it applies to human reproduction – that is, editing in an embryo or gametes followed by implantation using IVF. This includes that use should not be permitted until risks of adverse outcomes have been thoroughly assessed, and only then on a case-by-case basis, under a set of guidelines issued by ACART and applied by ECART and within the context of a carefully monitored study with comprehensive follow-up arrangements in place.

B Social Views and Attitudes

The Royal Society of New Zealand has put in place a multi-disciplinary panel to consider the social, cultural, legal and economic implications of gene editing in healthcare and provided a discussion paper for members of the public to send feedback on.[204]

The aim is to enable New Zealanders to come to an informed opinion on how they feel about the use of gene editing, which will then inform how the technology will be regulated in New Zealand.[205] This approach aligns with the numerous reports stressing the importance of reaching social consensus, such as the NAS Report and the Nuffield Council on Bioethics report. The results of this discussion are not yet available but will be vital in determining the stance New Zealand will take. A global survey on attitudes to gene editing indicates that a majority of individuals agree that both somatic and germline gene editing should be used in children and adults to cure life-threatening or debilitating disease.[206] This provides a solid indication that when limited to therapeutic purposes of a certain gravity, gene editing is acceptable.

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[204] See Royal Society of New Zealand "The use of gene editing in healthcare: discussion paper (17 November 2017) <https://royalsociety.org.nz/assets/Uploads/The-use-of-gene-editing-in-healthcare-discussion-paper.pdf>; Royal Society of New Zealand "Gene editing in a Healthcare Context: technical paper" (December 2017) <https://royalsociety.org.nz/assets/Uploads/Gene-editing-in-healthcare-technical-paper.pdf>.

[205] Royal Society of New Zealand "New Zealanders encouraged to consider potential uses of gene editing" (news report, 19 December 2016).

[206] McCaughey T and others "A Global Social Media Survey of Attitudes to Human Genome Editing" (2016) Cell 18 569 at 571. In regard to somatic gene editing, 59% responded they agreed with its use in children or adults to cure life-threatening or debilitating disease. Surprisingly, for germline gene editing applications, a larger portion (63%) agreed that it should be used on embryos to prevent life-threatening and debilitating disease.

C An Adaptive Regime for Emerging Biotechnology

In a broad sense, New Zealand needs a regulatory system that can better respond to rapid changes in biotechnology. Today's innovation-driven global economy accelerates the biotechnology revolution and furthers the need for flexible and adaptable laws. As seen in the US and UK, flexibility is made possible by implementing the use of adaptable regimes, combined with agencies or bodies that are given authority to determine the safety, ethics and appropriateness of gene editing technologies. New Zealand has the potential to achieve regulation of this calibre but needs to strengthen and streamline existing regulatory bodies and processes to accomplish this.

Existing gaps need to be filled and legislation updated to prevent the regulatory disconnect seen in the Medicines Act. A more flexible approach is required so that our laws can encompass and better respond to new biotechnologies, such as gene editing, which was not contemplated, nor envisaged to be within humanity's reaches, at the time of legislative drafting. As seen in the US, private institutions are able to exploit regulatory lacunae to avoid prohibitions on germline gene editing embryo research.

As Gregory Mandel noted “the early stages of an emerging technology’s development present a unique opportunity to shape its future.”[207] New Zealand has the opportunity to determine how gene editing can be used to positively shape our medical future and benefit those who most desperately seek access to new therapies and treatments. Rather than reactively responding to the legal challenge’s gene editing poses, we should act proactively to determine a regime which is adaptive enough to apply to gene editing and other new emerging genetic biotechnologies.

[207] Mandel GN “Regulating Emerging Technologies” (2009) Law Inn Tech 1 75 at 92.

D Somatic Gene Editing

There are two options to govern how New Zealand could approach somatic gene editing therapies:

Option 1 Leave the current system as it is, with the Medicines Act 1981 (soon to be replaced by the Therapeutic Products Act 2006 and the Medicines Act 2006[208]) and HSNO Act providing a framework for regulating genetically modified medicines. Strengthen and amend existing frameworks to ensure emerging genetic biotechnologies are provided for.

Option 2 Create a new legislative regime designed specifically to regulate current and emerging genetic biotechnologies, including somatic gene editing therapy.

I will explain in more detail how each option would work and its merits and weaknesses, before turning to specific recommendations.

1 Option one

Option one is easier from a legislative point of view – the development of the TPM Bill can continue and nothing substantive needs to be altered. Under this option I recommend:

- Amend the definitions of 'genetically modified organism' in the HSNO Act and 'medicine' in the Medicine Act to better provide for gene editing.
- Ensure the new Therapeutic Products and Medicines Acts are proactive, rather than reactive by specifically encompassing gene editing and other emerging genetic biotechnologies.

[208] Therapeutic Products and Medicines Bill 2006 (103-1) (explanatory note) at 1.

- Strengthen existing regulatory bodies to ensure those most appropriate are being utilised at each stage of the development of a somatic gene editing therapy, from research through to clinical trials and finally, dissemination as a medicine.

This approach aligns with the numerous reports and statements made globally as well as the approaches taken by the UK and the US which suggest somatic gene editing can be regulated under current gene therapy regulatory oversights.

I also believe the role of the EPA should be examined, as to whether this body is appropriate to regulate gene therapies. The UK and US systems of regulation all rely on medical bodies for expertise at different stages of the process, from clinical trial assessment to marketing and distribution. It seems unusual that an environmental body would be given such strong input into a medical approval process.

2 Option two

Option two provides a more radical approach but follows suit with the forward-thinking ATMP legislation in Europe and the UK. In providing a comprehensive regime aimed solely at gene therapies, New Zealand would not only establish itself as a world leader, but also promote and encourage researchers and institutions to undertake more work in this area. A regime purposely addressing genetic biotechnologies would also provide clear guidance for researchers and practitioners and still be framed to allow for flexibility to capture new technologies within its ambit.

This approach aligns with the Health Committee's recommendations made when reviewing New Zealand's clinical trial system, that New Zealand should invest more in its scientific infrastructure to help drive economic growth.[209] New Zealand's economy and environment means it has a strong foundation to promote itself as similar to countries leading the

[209] Report of the Health Committee *Inquiry into improving New Zealand's environment to support innovation through clinical trials* (June 2011) at 23.

development of biotechnologies, such as the US, UK and the European Union, who conduct sound clinical trials in respect to safety and quality, while also being able to offer a relatively cost-effective environment.[210]

Whilst New Zealand may not currently be considered a major player in the field of genetic scientific research and development, this area is a rapidly growing field and development is starting to progress. For example, the Malaghan Institute is currently developing cancer immunotherapy treatments, including the cutting-edge CAR-T cell immunotherapy and is set to become the first institute in New Zealand to conduct a clinical trial using this innovative therapy 'in the near future.'[211] A New Zealander, David Downs, was successfully treated for terminal lymphoma after travelling to the US to take part in a clinical trial for CAR-T cell therapy.[212] If development in this sector were encouraged, more New Zealanders would have access to novel, potentially life-saving, treatments.

3 Recommendations

(a) The definition of genetically modified

For the purposes of the HSNO Act, GMOs only include *in vitro* techniques, unless expressly provided otherwise by regulations.[213] This definition should be modified to include *in vivo* techniques as follows:

> *Genetically modified organism means, unless expressly provided otherwise by regulations, any organism in which any of the genes or other genetic material—*
>
> *(a) have been modified by in vitro or in vivo techniques; or*

[210] Ibid.

[211] Malaghan Institute of Medical Research "Cancer research" (2018) Malaghan Institute of Medical Research <https://www.malaghan.org.nz/what-we-do/car-t-cell/>.

[212] Ibid.

[213] S 2.

> *(b) are inherited or otherwise derived, through any number of replications, from any genes or other genetic material which has been modified by in vitro or in vivo techniques*

Alternatively, if option two was followed, the definition under the HSNO Act could remain the same and under new legislation governing gene editing therapies, provision could be made to include *in vivo* as well as *in vitro* techniques explicitly. This new definition in an alternative act would not create inconsistencies with the HSNO Act due to the qualification in the definition of 'genetically modified' which provides that other regulations may expressly alter the HSNO definition.[214]

(b) The definition of medicine

The current definition of the Medicines Act and the proposed description under the TPM Bill could both be interpreted to exclude somatic gene editing techniques, in that they modify the genome directly rather than acting by pharmacological, immunological or metabolic means.[215] Therefore, this definition should be altered to be more inclusive of gene editing techniques:

> *Medicine means any substance or article that achieves, or is likely to achieve, its principal intended action in or on the human body by pharmacological, immunological, metabolic or **genetic** means and comprises of substances that interact with human physiological, pathological and **genetic** processes.*

(c) Regulating gene editing under the Therapeutic Products and Medicines Bill

As the TPM Bill is currently being developed, the timing is ideal to accommodate somatic gene editing therapy. It has already been noted that the processes under the

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[214] Genetically modified organism is defined in s 2.

[215] For the current definition of medicine, see s 3 of the Medicines Act 1981 and for the proposed definition under the TPM Bill, see Minister of Health, above n 130**,** at 9.

current Medicines Act and HSNO Act need to be streamlined and that the new therapeutics regulator and the EPA should work together to ensure the application process for therapeutic products containing new organisms is efficient and effective.[216]

However, as noted in Chapter III, the proposed TPM Bill does not address genetic technologies and contains no reference to GMOs. The current categories of therapeutic products (medicines and cell and tissue therapies) appear to exclude gene editing. I suggest that a new category of therapeutic products is created to regulate genetic biotechnologies, including a broad range of gene therapies alongside somatic gene editing. This category could be described as follows:

> *"Genetic therapies are derived from a combination of human cells and tissues and other organisms and work by:*
>
> *(a) Altering the genome; or*
>
> *(b) Modifying, supplying or blocking genes or gene products; or*
>
> (c) *Modifying the genetic make-up of cells or structures for the purposes of immunotherapy;*
>
> *to treat, cure, prevent or reduce the risk of the development of a genetic disease, disorder or condition."*

This would capture a broad range of gene therapies and somatic gene editing, together with genetic technologies used to create immunotherapies, such as those based on cancer and HIV.

(d) A New Genetic Monitoring Agency

A new genetic monitoring agency or authority should be formulated for a number of purposes.

[216] Minister of Health, above n 130, at 9.

A centralised adverse effects system should be designed to monitor and collate any adverse reactions to gene therapies. The current adverse effects system, or MARC and CARM, is designed for the surveillance of conventional medicines by monitoring serious effects only and relies on spontaneous reporting. Medicines relying on genetic processes are different, in that many of the risks and long-term effects are largely unknown. The interactions of genetic processes with other genes, other physiological processes, the patient's own immune system and the environments, are highly complex. An agency that monitors not only serious side-effects, but routinely monitors all other aspects of human health is important for the health and safety of individuals who have undergone any form of genetic treatment.

This agency should ensure there are routine check-ups by health professionals and long-term surveillance of individuals to ensure that monitoring captures a full range of adverse reactions, ranging from minor to serious, alongside other processes in the body that are altered in any way – even though there may be no negative effect.

The agency should monitor medicines on all individuals who have undergone genetic treatment, whether as part of a clinical trial or from an approved medicine.

(e) Research and the Role of GTAC

As explained when outlining my proposal for option two, there are huge benefits in investing more in scientific infrastructure and research. In the inquiry into clinical trials, the Health Committee stated that:[217]

> *"We believe that the investment that New Zealand makes in research and development, including the clinical trial industry, is low relative to the OECD average."*

[217] Report of the Health Committee, above n 209, at 23.

The TPM Bill acknowledges its support of the development of clinical trials in New Zealand:[218]

> *"Clinical trials conducted within a robust regulatory framework offer social and economic benefits. For example, they attract and help retain high-quality, innovative clinicians, academics, and scientists; and bring investment and employment opportunities. New Zealand's high-quality infrastructure makes it a desirable location for clinical trials and the new regime aims to facilitate New Zealand-based trials under a robust regulatory regime."*

The Minister for Health has proposed that the new TPM Bill covers trials of all therapeutic products (medical devices, cell and tissue therapeutic products and, under my proposal, genetic products), rather than be limited only to medicines.[219]

As part of this process I recommend that more weight should be given to the involvement of GTAC in the clinical trial process. GTAC is made up of well-established scientists and therefore is best-placed to determine the scientific accuracy of applications for clinical trials of experimental new genetic biotechnologies. While the new ANZTP Authority under the TPM Bill could assess applications for medicines that have already established their safety, quality and efficacy with research and clinical trial data, GTAC should stay in place to assess clinical trial applications.

Further, provision should be made for the ANZTP Authority to call upon GTAC to provide expert advice on the science of applications for medicines that involve genetic biotechnologies.

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[218] Minister of Health, above n 133, at 3.

[219] Ibid.

E Germline Gene Editing in Human Reproduction

Currently, germline gene editing combined with an assisted reproductive technology is not yet feasible, nor is it politically, ethically or socially acceptable, as seen by the large body of reports outlined in Chapter IV, part A. However, the potential germline gene editing has in alleviating suffering *en masse*[220] for generations cannot be blindly ignored out of fear. The way that technology is being driven by scientifically innovative countries like China and the US means that studies using germline editing are already being conducted on non-viable and viable human embryos. The Nuffield Council has envisaged circumstances in which heritable gene editing interventions should be permitted.[221] Therefore, a proactive regime for New Zealand should at least be contemplated and prepared for such an eventuality.

1 Changes needed for germline gene editing to be allowed

The prohibition on implanting a genetically modified gamete, human embryo, or hybrid embryo needs to be removed.[222] Then germline modification for implantation would fall into the 'regulated activity' category, as it would be classed as an ART.

However, ECART would still be unable to accept any applications for germline gene editing followed by implantation without any guidelines issued to it by ACART. I will make suggestions on what such guidelines should include later in this chapter and include my recommended guidelines in Appendix 1.

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[220] In a group, altogether.

[221] Nuffield Council of Bioethics, above n 38, at 154.

[222] Schedule 1(8).

Another issue that remains is that "genetically modified" is undefined in the HART Act. The HART Act should therefore be amended to provide its own definition of genetically modified, or alternatively, to refer to the definition in the HSNO Act. I would suggest the definition as:

> *Genetically modified means any organism in which the genes or genetic material have been artificially modified using in vitro or ex vivo techniques and includes modification to germline and/or somatic cells.*

This definition includes *in vitro* and *ex vivo* techniques but excludes *in vivo* on the basis that extension of any direct genetic modification of embryos developing inside a woman's womb would be a step too far (at this point in time) in terms of risk and would then also fall outside the scope of being an 'assisted reproductive procedure.' Both germline and somatic cells are referenced for the avoidance of any doubt.

2 Regulation of germline gene editing in human reproduction

(a) General suggestions

(i) Regulatory oversight mechanisms

- Germline gene editing should only take place where there is a stringent oversight system, able to limit uses to specified criteria and prevent extension to uses other than preventing a serious disease or condition.
- ECART should refer to another agency where expert advice is required on the safety, efficacy and scientific soundness of any particular application. I suggest that this agency be GTAC, as it is well-positioned to provide scientific expert advice since it already provides such advice for clinical trial applications involving novel gene or biotechnologies.

(ii) Long-term surveillance system

There should be comprehensive plans in place for long-term, multigenerational follow-up, similar to that in the US which enables surveillance of up to fifteen years. This could be governed by the same agency as I suggested for somatic gene editing.

(iii) Reassessment and public involvement

There should be continued reassessment of both health and societal benefits and risks of germline gene editing in human production by ACART and any other relevant bodies. There should also be broad ongoing participation and input by the public, using similar mechanisms to the current Royal Society inquiry as outlined previously.

(b) Suggested guidelines on germline gene editing in reproduction

The suggestions contained in the guidelines are derived from the growing body of reports on germline gene editing, most notably the NAS and the Nuffield Reports.[223] I have compiled these suggestions to create a set of principles, requirements and preconditions that would need to be met before such a procedure could proceed. The guidelines I have suggested are intended to be the first step in germline gene editing in human reproduction only – later extensions on what is allowable could be made as the reliability of the technology improves and social attitudes change.

I have emphasised the importance of informed consent in this situation, as the prospective parents need to be able to adequately understand the long-term implications of their decision - that future generations will be affected by the change in relation to the unknown risks that may be present.

Other important requirements include: seriousness of the disease, with scientific research strongly supporting (1) that a mutant gene is causally associated with disease,

[223] National Academies of Sciences, Engineering, and Medicine, above n 12**;** Nuffield Council on Bioethics, above n 38.

and (2) that reversion is to a proven healthy variant; the desirability of the prospective parents for genetically-related offspring must be present; and an absence of reasonable alternatives in that PGD will not or is very unlikely to be successful. I have outlined the specific genetic circumstances where these situations arise in Appendix I.

These restrictions are necessary, at least in the near future, to reduce the likelihood of stigmatisation and discrimination.

Finally, enhancement is prohibited. As previously noted, the line between enhancement and therapeutic use is blurred. There may be no clear definition of enhancement that can be used practically in situations like this. Thus, ECART will need to determine whether an application is considered to be for therapeutic purposes, or whether it crosses into the sphere of enhancement.

CONCLUSION

"The power to control our species' genetic future is awesome and terrifying. Deciding how to handle it may be the biggest challenge we have ever faced."
– Jennifer A. Doudna, A Crack in Creation: Gene Editing and the Unthinkable Power to Control Evolution

No longer is genetic modification of the human genome confined to the realm of science fiction. The rapid development of the genetics field has resulted in an unprecedented uptake of novel genetic technologies that will continue to stretch legal boundaries. This new era of emerging technology threatens to render current legal mechanisms obsolete unless new ways of formulating legislation are adopted to guard against this.

Whilst the ethical issues surrounding gene editing are complex to say the least, we cannot allow this to stifle research and movement. The Nuffield Council on Bioethics summarises the importance of progress and development in the face of ethical difficulties:[224]

> "*It is also preferable for ethical reflection to shape the course taken rather than to appear as a final hurdle to 'overcome' when the research has already been accomplished, resources committed, and hopes and fears piqued…. Addressing this issue now will help to meet concerns that research and technology development is rushing ahead of public debate and allow such debate to influence the development of the technology, distinguish acceptable from unacceptable aims, and reduce the uncertainty and ambiguity under which researchers and potential beneficiaries live."*

New Zealand is in desperate need of an update to its regulations governing medicines.

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[224] Ibid at 116.

The current Medicines Act is out of date, which is recognised by the proposed TPM Bill, but the legislation does not go far enough to address innovative genetic technologies such as somatic and germline gene editing.

Further, monitoring agencies responsible for scrutinising new gene therapies need to be better provisioned to deal with the different spectrum of risks genetic technologies pose. The role of the EPA should be seriously considered within this framework and others such as GTAC, who have expert knowledge in the field of genetics, should be given more prominent roles.

Development of a well-regulated framework, which accounts for ethical concerns and remains open to change, is the only way forward. The United Kingdom and the United States provide examples of powerhouses taking proactive approaches to gene editing and other biotechnologies. Their forward-thinking regulatory systems allow for growth and yet still provide reasonable constraints.

The growth of scientific research and clinical trials should be encouraged in New Zealand, due to the economic benefits they offer. In particular the rules surrounding embryo research, which are currently restrictive, should be reviewed in more depth to determine if New Zealand should take a new stance on this issue - which is ethically charged and complex in its own right.

Whilst germline gene editing as part of human reproduction is not yet acceptable, its potential cannot be ignored. It is imperative that New Zealand prepares for this eventuality and contemplates what purposes that fall outside circumstances of strict therapeutic use, or beyond therapeutic use, we want to allow or restrict in the near future.

Gene editing has untold power to reshape the biosphere and who can say what the future will hold – but to prepare for this looming reality it is imperative New Zealand takes a proactive stance and makes the most of opportunities to benefit from this technology. CRISPR could vastly improve our lives – so long as we do not lose control of it.

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APPENDIX I

Germline Gene Editing in Human Reproduction Guidelines

Preamble

Germline gene editing in reproduction, that is, implantation of a gamete or embryo that has been modified using germline gene editing techniques, is not an established procedure and must be submitted to ECART for approval.

Other than what is provided for in these guidelines, sex selection of embryos is an offence under the HART Act.

1. *HART Act Principles*

When considering an application for germline gene editing in reproduction, ECART must be guided by the principles of the HART Act.[225]

2. *Overarching ethical principles to govern germline gene editing in human reproduction*
    (a) The technology should intend to secure, and be consistent with, the welfare of the child who may be born as a consequence of interventions using germline gene editing.
    (b) It should not increase the likelihood of social division, discrimination or disadvantage and uphold ideas of social justice and solidarity.

3. *Informed consent*

    Prospective parents should be informed by a competent medical professional of the nature of germline gene editing – that it affects not only the prospective child but all subsequent future generations. In particular, the possibility of long-term risks and uncertainties should be explained. Only once the

prospective parents understand these issues can they be determined as agreeing to the procedure with informed consent.

4. *Restrictions surrounding the genetic disorder/disease*

   Genome gene editing in human reproduction should only take place for the purposes of treating or preventing serious disease or disability. The following restrictions should also be in place:

   (a) Restriction to editing genes that have been convincingly demonstrated to cause or strongly predispose to that disease or condition; and

   (b) Restriction to converting such genes to versions that are prevalent in the population and are known to be associated with ordinary health with little or no evidence of adverse effects.

5. *Risks and Safety*

   (a) The availability of credible preclinical and/or clinical data on risks and potential health benefits of the procedures.

   (b) The risks of adverse clinical outcomes for individuals involved must be thoroughly assessed.

6. *Necessary pre-conditions that must be met:*

   (a) The prospective parents must strongly desire to have a genetically related child. If there is no overriding wish for the child to be genetically related to both parents, then adoption or sperm, egg or embryo donation might be considered.

   (b) The absence of reasonable alternatives must be proved

      (i) In particular PGD applicability should be assessed, and reasons provided as to why PGD cannot be the solution.

(ii) Situations acceptable for genome editing are those where it is the only option available to have a genetically related child while excluding a specific condition.

(iii) Other situations where it is possible, but very difficult, to achieve the birth of a genetically related child with desired characteristics using alternative approaches may also be acceptable.

7. *Enhancement Prohibited*

(a) Germline gene editing should only be used for prevention of a serious disease or condition, that is for therapeutic purposes. Uses that do not prevent any serious disease or condition and are focused on improving, increasing or otherwise modifying the human condition for purely enhancement purposes are prohibited.

(b) Enhancement purposes include:

(i) Building resistance or immunity to a disease

(ii) Increasing tolerance to environmental conditions; or

(iii) Enhancing senses or abilities.

(c) Determinations should be made on a case-by-case basis as to whether any application is for enhancement purposes.

Schedule 1: Situations in 6(b)(ii)

Situations acceptable for genome editing are those where it is the only option available to have a genetically related child while excluding a specific condition, are very rare.[226] Such situations include, but are not limited to:

(1) Dominant genetic conditions, where one or both of the prospective parents carries two copies of the disease-causing gene;

[226] In these cases, all resulting embryos will be affected.

(2) Recessive genetic conditions where both of the prospective parents carry two copies of the disease-causing gene;
(3) Y chromosome defects; [227]
(4) Inversions and deletions of chromosome segments.

Schedule 2: Situations in 6(b)(iii)

Situations where it is possible, but very difficult, to achieve the birth of a genetically related child with desired characteristic using alternative approaches include, but are not limited to:

(1) where the aim is to exclude predispositions to complex disease in which there is a significant risk of later morbidity or mortality requiring intrusive or invasive treatment, or where later treatment would or might be ineffective.
(2) where there is a need to increase the number of available embryos with desired characteristics, including:
    (a) dominant genetic conditions where both parents are heterozygous for the predisposing variant;[228]
    (b) where one parent is heterozygous for the predisposing variant and the other carries the common variant;
    (c) recessive genetic conditions where one parent is homozygous and one heterozygous;[229]
    (d) X-linked disorders.[230]
(3) Where the aim is to select for multiple characteristics that are inherited independently.[231]

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[227] Which are passed on from fathers to sons automatically.

[228] On average 25 percent of embryos will be unaffected.

[229] On average 50 percent of embryos will be unaffected.

[230] Males are hemizygous (as they only carry one X chromosome) and are therefore more likely to be affected by X-linked recessive mutations.

[231] For example, instances of co-dominance - where combinations of specific alleles in two or more genes cause a disease

APPENDIX II
Glossary of Terms

All terms are adapted from the Iowa Institute of Human Genetics[232] and the National Academies of Sciences, Engineering and Medicine.[233]

Allele—An alternate form of a gene at a given locus or location in the genome. Each locus has two alleles, one inherited from each parent.

Autosomal Dominant—A disease caused by a gene not on a sex chromosome. The phenotype/disease/trait is expressed by individuals who have one copy of the gene variant. Individuals with an autosomal dominant condition have a 50% chance of passing the gene variant to offspring with each pregnancy.

Autosomal Recessive—A disease caused by a gene not on a sex chromosome. The phenotype/disease/trait is expressed by individuals who have inherited two genetic variants at the same locus or gene. Most often one changed copy of the gene is inherited from each parent.

Base pair—Two complementary nucleotides (adenine, thymine, guanine, or cytosine) in double-stranded DNA. A unit of measure of DNA sequence length.

Base pairing—The process of binding separate DNA sequences by base pairs.

Cas9 (CRISPR Associated Protein 9)—A specialized enzyme known as a nuclease that has the ability to cut DNA sequences. Cas9 makes up part of the "toolkit" for the CRISPR/Cas9 method of genome editing.

Chromosome—A structure found in every cell of the body that contains DNA. Humans have 46 chromosomes, 22 pairs of autosomes, and 2 sex chromosomes which we inherit from our parents.

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[232] Iowa Institute of Human Genetics "Glossary of Terms and Abbreviations" (2018) University of Iona Health Care: Carver College of Medicine <https://medicine.uiowa.edu/humangenetics/community/humangenetics/humangenetics/humangenetics/resources/glossary-terms-and-abbreviations>.

[233] National Academy of Sciences, Engineering and Medicine, above n 12, at 293-309.

Clinical trial—A supervised and monitored experimental test in patients of a newly developed clinical application to ensure minimization of risk and optimization of efficacy. Clinical trials are required before a treatment is approved for general use.

CRISPR (Clustered Regularly-Interspaced Short Palindromic Repeats)—A naturally occurring mechanism found in bacteria that involves the retention of fragments of foreign DNA, providing the bacteria with some immunity to viruses. The system is sometimes referred to as CRISPR/Cas9 to denote the entire gene-editing platform in which RNA homologous with the targeted gene is combined with Cas9 (CRISPR Associated Protein 9), which is a DNA-cutting enzyme (nuclease) to form the "toolkit" for the CRISPR/ Cas9 method of genome editing.

DNA—Deoxyribonucleic acid – a molecule composed of two chains which coil around each other to form a double helix. DNA codes genetic information in all prokaryotic and eukaryotic organisms, and in some virus, for the transmission of inherited traits. The information in DNA is made up of base pairs.

Dominant — A pattern of inheritance of a gene or trait in which a single copy of a particular allele (gene variant) confers a function independent of the nature of the second copy of the gene in a diploid cell of an organism.

Double-strand break (DSB)—A break in the DNA double helix in which both strands are cut, as distinct from a single-strand break or "nick."

Embryo—An animal in the early stages of growth and differentiation that are characterized by cleavage (cell division of the fertilized egg), differentiation of fundamental cell types and tissues, and the formation of primitive organs and organ systems; the developing human individual from the time of implantation to the end of the eighth week after conception, after which stage it becomes known as a foetus.

Enzyme—A protein that acts as a biological catalyst, speeding up chemical reactions.

Epigenetic effects—Changes in gene expression that occur without changing the DNA sequence of a gene; for example, in the epigenetic effect called genomic imprinting, chemical molecules called methyl groups attach to DNA and alter the gene's expression.

Ex vivo—Latin: "out of the living"; outside an organism.

Exogenous—Introduced or originating from outside a cell or an organism.

Fertilisation—The process whereby male and female gametes (sperm and egg) unite.

Gamete—A reproductive cell (egg or sperm). Gametes are haploid (having only half the number of chromosomes found in somatic cells—23 in humans), so that when two gametes unite at fertilization, the resulting one- cell embryo (zygote) has the full number of chromosomes (46 in humans).

Gene—A functional unit of heredity that is a segment of DNA in a specific site on a chromosome. A gene typically directs the formation of a protein or RNA molecule.

Gene editing—A technique that allows researchers to alter the DNA of cells or organisms to insert, delete, or modify a gene or gene sequences to silence, enhance, or otherwise change the gene's characteristics.

Gene editing—A technique that allows researchers to alter the DNA of cells or organisms to insert, delete, or modify a gene or gene sequences to silence, enhance, or otherwise change the gene's characteristics.

Gene therapy—Introduction of exogenous genes into cells with the goal of ameliorating a disease condition.

Genome—The complete set of DNA that makes up an organism. In humans, the genome is organized into 23 pairs of homologous chromosomes.

Germ cell (or germline cell)—A cell at any point in the lineage of cells that will give rise to sperm or eggs. The germline is this lineage of cells. Eggs and sperm fuse during sexual reproduction to create an embryo. In so doing, the germline continues into the next generation.

Guide RNA (gRNA)—Short segments of RNA used to direct the DNA- cutting enzyme to the target location in the genome. gRNA segments contain the region of homology to the target sequence (usually 20 bases), and a sequence that interacts with the nuclease (e.g., Cas9). gRNAs used in genome editing are synthetic and do not occur in nature.

Hemizygous / Hemizygote—An individual with only one allele present for a particular gene.

Heritable genetic change—Modifications to genes that could be passed down through generations.

Heterozygous / Heterozygote—An individual with two different alleles at a given location/locus in the human.

Homologous recombination—Recombining of two like DNA molecules, including a process by which gene targeting produces an alteration in a specific gene.

Homology-directed repair (HDR)—A natural repair process used to repair broken DNA, which relies on a DNA "template" with homology to the broken stretch of DNA. This usually occurs during or after DNA synthesis, which provides this template. In genome editing via HDR, the DNA template is synthesised or made by recombinant DNA techniques, and usually contains regions of exact homology to the target locus at each end, with the desired alteration contained within the middle.

Homozygous / Homozygote — An individual who has two identical alleles at a given location/locus in the human genome, one on each chromosome of a pair.

Implantation—The process by which an embryo becomes attached to the inside of the uterus (7-14 days in humans)/

In utero—Latin: "in the uterus."

In vitro—Latin: "in glass"; in a laboratory dish or test tube; in an artificial environment.

In vitro fertilization (IVF)—An assisted reproduction technique in which fertilisation is accomplished outside the body.

In vivo—Latin: "in the living"; in a natural environment, usually in the body of the subject. This term is often also used to refer to events in "living" cells in culture.

Locus (pl. loci) —A specific position of a gene or DNA marker on a chromosome.

Mitochondrial transfer (or mitochondrial replacement)—Novel procedures designed to prevent the maternal transmission of mitochondrial DNA (mtDNA) diseases.

Mitochondrion (plural, Mitochondria)—A cellular structure in the cytoplasm that provides energy to the cell. Each cell contains many mitochondria. In humans, a single mitochondrion contains 37 genes on a circular mitochondrial DNA, compared with about 35,000 genes contained in the nuclear DNA.

Mutation—A change in a DNA sequence. Mutations can occur spontaneously during cell division or can be triggered by environmental stresses, such as sunlight, radiation, and chemicals.

Nonhomologous end joining (NHEJ)—A natural repair process used to join the two ends of a broken DNA strand back together. This is prone to errors where short indels (usually of two to four base pairs of DNA) are introduced.

Off-target effect—A direct or indirect, unintended, short- or long-term con- sequence of an intervention on an organism other than the intended effect on that organism.

Preimplantation genetic diagnosis (PGD)—Before an in vitro–fertilized embryo is implanted in a woman's uterus, it can be screened for specific genetic mutations that are known to cause particular genetic diseases or for chromosomal abnormalities. One or more cells are removed from the preimplantation embryo for testing and the surviving embryo that is implanted is one that is not carrying the genetic abnormality.

Recessive—A recessive allele of a gene is one whose effects are masked by the second allele present in a diploid cell or organism, which is referred to as dominant.

Recombinant DNA—A recombinant DNA molecule is made up of DNA sequences that have been artificially modified or joined together so that the new genetic sequence differs from naturally occurring genetic material.

Recombination—The process, natural or engineered, in which two pieces of DNA undergo breakage and reunion to generate a new combination of DNA segments.

Somatic cell—Any cell of a plant or animal other than a reproductive cell or reproductive cell precursor. Latin: soma = body.

Sex-linked trait/disorder—A trait due to a gene alteration on the X or Y chromosome.

T cells—Types of white blood cells that are of crucial importance in the immune system. They cooperate with other immune cells in killing infected or cancerous cells but can also participate in inflammation or in autoimmunity when they become activated against an organism's own cells or tissues.

Target sequence—Specific sequence of DNA bases within the genome that is the target of genome-editing tools. For CRISPR/Cas9 methods this will be a 20 nucleotide sequence

that the gRNAs are designed to recognize (i.e., they will contain a complementary sequence of the same length).

Transcription Activator-Like Effector Nuclease (TALEN)—A class of engineered restriction enzymes generated by the fusion of a transcription activator-like effector DNA-binding domain (that binds to a specific DNA sequence) to a DNA-cleavage domain (nuclease) to be used as a genome- editing tool. TALENs followed zinc finger nucleases and preceded CRISPR/Cas9 as genome-editing tools.

Transhumanism—A class of philosophies of life that seek the continuation and acceleration of the evolution of intelligent life beyond its currently human form and human limitations by means of science and technology, guided by life-promoting principles and values (More, 1990).

Variant—Genes have many variants in a population that can differ some- what in function, some being advantageous and some being deleterious or non-functional.

Vector—A vehicle that transfers a gene into a new site (analogous to insect vectors that transfer a virus or parasite into a new animal host). Vectors used in molecular cell biology and genetic engineering include plasmids and modified viruses engineered to carry and express genes of interest in target cells. The most clinically relevant viral vectors for gene transfer include retroviral, lentiviral, adenoviral, and adeno-associated viral vectors.

Zinc finger nuclease (ZFN)—A class of engineered enzymes generated by the fusion of zinc finger DNA-binding domains to a DNA-cleavage enzyme (usually FokI) that can be used as a genome-editing tool One of the first and a reliable method of genome editing.