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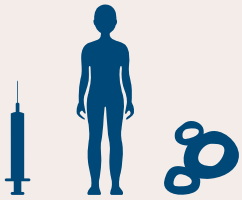
GENE EDITING SCENARIOS IN HEALTHCARE



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BACKGROUND

The revolution in gene editing technologies is making it easier to change genetic material, with huge potential benefits in many sectors including healthcare, agriculture and conservation. However, the technology to carry out gene editing and the ideas about how it might be applied are, in many cases, moving ahead of the knowledge about how to safely effect the desired changes. For example, in human health applications, gene editing could be used to treat a genetic disease, but this might accidentally disable a tumour-suppressor gene or activate a cancer-causing one. Nevertheless, around 20 human trials have begun involving removing cells from an individual's body, editing their DNA and then putting them back into the body [1].

There is a danger that gene editing technologies and their applications may move ahead of any appropriate discourse on the rights and wrongs of how they should be used. So, to explore the implications of gene editing technology for Aotearoa New Zealand, Royal Society Te Apārangi has convened a multidisciplinary panel of some of New Zealand's leading experts to consider the social, cultural, legal and economic implications of revolutionary gene editing technologies for New Zealand in order to:

- raise awareness of the scientific possibilities and associated societal issues of new gene editing technologies to inform debate
- provide information and guidance for policy makers to address new issues needing to be clarified or resolved
- show where gene editing applications are covered by established policies and regulations and where changes are now needed
- provide an Aotearoa New Zealand perspective to the global discussion on this technology, particularly where global consensus is important.

This paper is part of a series[1] considering the implications of the technology in health, pest control and agricultural situations, and is accompanied by a companion summary, and a fact sheet on how these technologies work and are being used and applied [2].

To help consider the implications for healthcare in New Zealand, this paper describes four scenarios with different clinical endpoints and highlights some points for consideration. In particular, these case studies outline:

- the possibility of treating both human tissue in individuals, and altering the genes passed on to subsequent generations, by treating embryos and gametes through IVF
- the possibility of the technology being used to both correct disease causing genes, and also modify genes in a way that changes or improves existing characteristics.

[1] royalsociety.org.nz/gene-editing

CONTENTS

Acknowledgements

The technical paper was produced by a Royal Society Te Apārangi Expert Panel, with support and advice from a Māori Reference Group. The work of the Panel has been informed by consultation with a number of experts and organisations who have provided valuable input in contributing to and commenting on the paper (Appendix 1).

Introduction

Genetic variation is the source of many visible and invisible differences between people, including health-related differences. In some instances, a genetic variant will be the chief determinant of whether or not a disease will manifest [3], while in others, genetic variants can heighten or reduce the risk of disease [3], with other genetic and environmental factors also contributing to the penetrance of clinical traits [3].

For example, in haemophilia B, a disorder of blood clotting, the presence or absence of certain genetic variants can reliably predict the likelihood of disease at the individual level [4]. By contrast, in the instance of late-onset Alzheimer's disease, the possession of certain genetic variants predicts modest elevations or reductions in risk, with wide confidence intervals, thus limiting the predictive utility of these variants in clinical settings [5].

Accordingly, genetic therapeutic approaches to mitigate diseases with a genetic component have generally focused on those diseases where the genetic variant is the chief determinant for the manifestation of the disease, and have largely attempted to replace faulty genes with functional copies. Progress in such 'gene therapy' has been slow for a number of reasons, including ineffective mechanisms for the delivery and replacement of genes and challenges in targeting delivery to the tissues of choice in a non-toxic manner [6].

Recent technological advances present the possibility of altering or removing the risk for the development of disease states by introducing specific bespoke variants into the genome of an individual [7]. These techniques, chief among them being CRISPR,[2] are able to insert, remove or replace genes or introduce new DNA sequences to 'repair' sections of the genome, at specifically targeted sites in the genome [8] (See Box 1). These technologies need not necessarily leave behind foreign gene sequences following manipulation and substantially reduce the risk of inserting a replacement gene in an unintended location compared to former gene therapy approaches. However, making the edit in the tissue, or cell, of choice remains a challenge [9].

Gene editing with CRISPR

Bacteria possess an immune system that recognises invading viral DNA and cuts it up, making the invading virus DNA inactive. This type of natural microbial immune system is known as CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats)[10]. In 2012, it was discovered that, by modifying this mechanism, it was possible to target and cut any DNA sequence and edit genomes [11]. Cells which have their DNA cut by the CRISPR nuclease will repair these cuts as 'instructed' if specific DNA repair information is provided. By altering this repair information, it is possible to change a gene of interest, for example, from one that causes disease susceptibility to one that does not [12, 13].

The technical, biological, ethical and legal considerations arising from these advances are numerous. This paper discusses the issues presented, by providing four case studies that each address different clinical endpoints. The first and second have already been shown to be achievable in human cells and at the whole organism level in mammals. The third and fourth look into the future, where the emphasis might be to enhance health and performance outcomes in a more speculative fashion.

New Zealand has a unique population and Te Tiriti o Waitangi obligations. Knowledge sharing, socialisation and mātauranga Māori incorporation in the application and development of treatments are critical pathways to democratising the new medical technologies for Māori communities and the wider population. In this context, treatment practices and practitioners in the public health system are key dissemination points for socialisation of new technologies, particularly with Māori and Pacific communities. Additional and pre-existing expertise will be needed as these new therapies are instituted, including genetic counselling, which is currently provided by Genetic Health Service New Zealand.

[2] CRISPR in this paper is being used to refer to the CRSIPR-Cas9 gene editing technique.

Human gene editing scenarios

In this document we adopt the approach of presenting four discrete scenarios to illustrate some of the range of current and potential applications of gene editing in healthcare. This approach does not preclude a comprehensive consideration of implications for all potential applications of this technology. The chosen scenarios seek to highlight the differences between editing somatic (i.e. body tissue) cells (either within the body (*in vivo*) or outside the body (*ex vivo*)) and the germline (cell types that eventually result in the formation of either egg cells or sperm), and discuss these in the light of the current evidence for the technical tractability, safety, efficacy and permissibility under New Zealand's current legal framework governing these practices. A range of clinical implications are presented from overt and severe life-limiting diseases on one hand, to perceived enhancements to existing traits conferring a functional physiological advantage to the recipient on the other.

The first case study discusses a genetic alteration to an individual's somatic cells within the precise cell type affected by a disease. This genetic alteration does not alter the individual's reproductive cells (egg or sperm cells), so the genetic variation is not transmissible to subsequent generations. Alternatively, an embryo can be genetically altered so that all cells bear the new genetic change as that embryo develops. In this case, the alteration is subsequently transmissible to future generations. This scenario is presented in case 2. The third scenario addresses the possibility of enhancement by modifying susceptibility to the development of common, but causally complex traits by gene editing. The fourth scenario portrays a futuristic possibility of parents wanting to modify their embryos to give their offspring a competitive advantage in life.

These examples cover a continuum of scenarios and highlight the blurred boundaries that may exist in considering the use of these technologies in medicine in general [14].

All four scenarios, outlined in Table 1, will be discussed and considered on their merits in terms of the therapeutic opportunities they present, along with their ethical and legal ramifications.

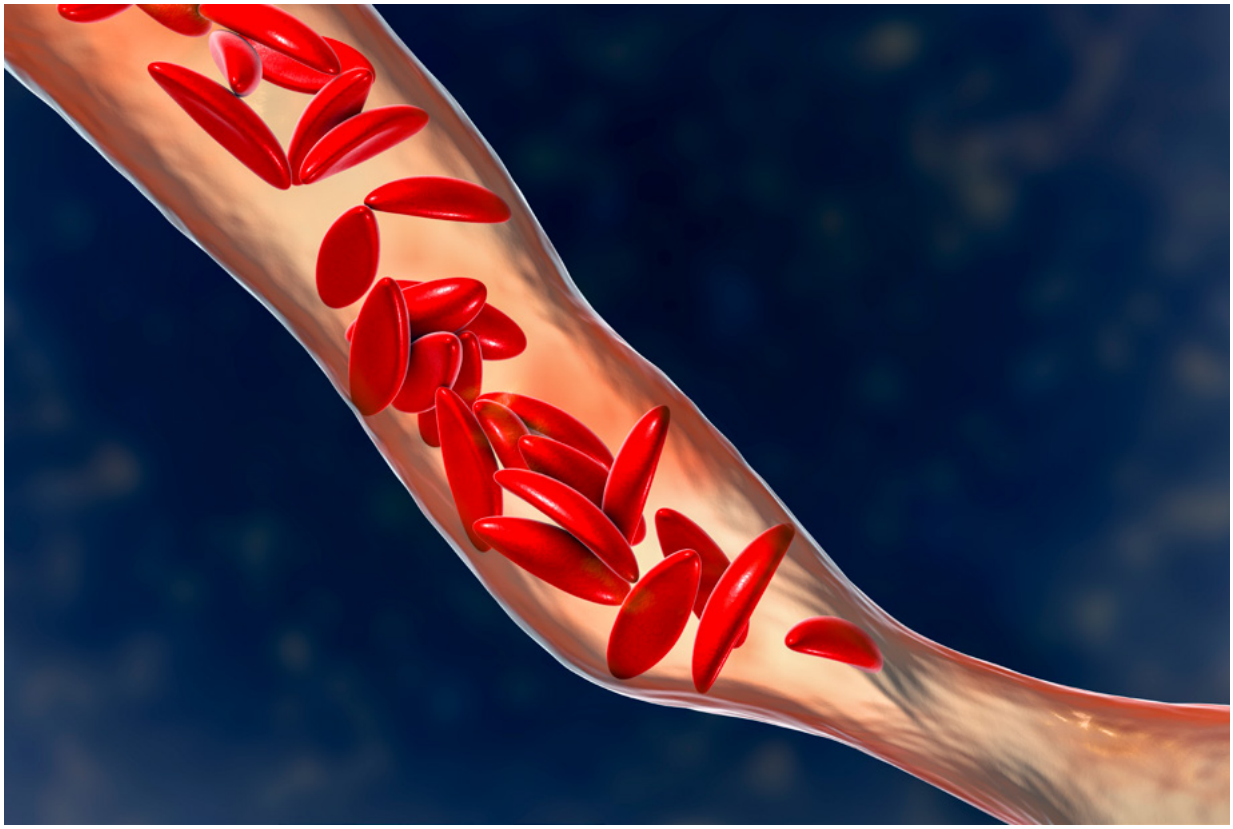
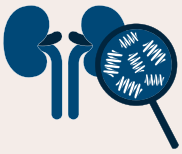


TABLE 1 | Description of four human gene editing scenarios

	SCENARIO 1 **Body (somatic) tissue genetic therapy**	SCENARIO 2 **Hereditary genetic therapy**	SCENARIO 3 **Body (somatic) tissue genetic enhancement**	SCENARIO 4 **Hereditary genetic enhancement**
				
Disease/ phenotype	**Sickle cell anaemia (monogenic disease)**	**Breast and ovarian cancer (BRCA1 point mutation)**	**Improve cardiovascular health (PCSK9 mutation)**	**Enhances erythropoietin production to increase athletic performance**
Genetic treatment applications	*In vitro*, in a controlled environment, on tissue outside the body	*In vitro*, in a controlled environment, on cells outside the body	*In vivo*, on the whole tissue within the body	*In vitro*, in a controlled environment, on cells outside the body
Nature of editing	Modification back to non-disease version	Modification back to non-disease version	Inactivation	Modification
Mechanism for transmission of CRISPR	Bone marrow transplantation followed by viral vector and replacement in stem cells	Embryo – direct injection or transfection of CRISPR mechanism	Viral vector targeted to the liver	Embryo – direct injection or transfection
Are non-naturally occurring sequences introduced into the genome	No	No	No	Yes

SCENARIO 1

Sickle cell anaemia: Body tissue genetic therapy

An 18-year-old woman has sickle cell anaemia, caused by a common genetic mutation that can lead to strokes, blindness, skin ulcers, thrombosis and many other complications, as sickle shaped blood cells do not deliver oxygen to tissues in the body as normal blood cells would. After recurrent admissions to hospital for treatment of sickling of her red blood cells, she requests definitive treatment of her disease using gene editing. The treatment is to remove bone marrow using standard techniques and treat this removed tissue using CRISPR that will alter one or both of her sickle cell anaemia-causing HBB genes, turning it back into a non-disease causing version. The remaining bone marrow will be removed and treated by chemotherapy. The removed and altered bone marrow will then be delivered back to her as per standard bone marrow transplant procedures. Since this procedure uses her own tissues, immune suppression will not be required and, as long as transplanting is successful and gene editing sufficiently efficient, the chance of her developing complications from her sickling blood cells will be eliminated permanently (but not for any children she may have in the future).

Medical considerations

Ambitions to adopt body tissue gene editing are limited largely by the differences in the types of mutations that can cause disease, the ability to deliver the editing mechanism to the cells of relevance and the efficiency of the gene editing itself. Where editing can be performed outside the body, as with bone marrow, the technical challenges of modifying and then restoring edited cells to the patient are solvable and can be very efficient [15]. For other targeted tissues, four decades of gene therapy research has resulted in a number of mechanisms that can deliver CRISPR and the target genes with variable efficiency to tissues such as blood vessels, liver, eye and lung. Importantly, it is not necessary for every cell in the target tissue to be gene edited to achieve a clinical effect, since low levels of an otherwise absent or deficient gene product can be sufficient to restore adequate physiological function in many instances [16].

The frequency and impact of off-target effects of editing (unintentional editing of non-targeted areas of the genome with unknown, unpredictable or unintended consequences) are difficult to quantify, but indications are that they are low enough to be approaching thresholds of clinical acceptability and are being continually improved [17]. The scale and invasiveness of the procedures are likely to be accepted because commonly used treatments, such as bone marrow transplantation, have been optimised and the result of the treatment in the avoidance of substantial illness, including strokes and premature death, represent substantial clinical inducements. The mutation leading to sickle cell anaemia, although very rare in the New Zealand context, is common to millions of people world-wide and, hence, developing standard approaches could be economically and therapeutically attractive to health services. Clinical trials have begun to demonstrate proof of principle for somatic cell gene editing for sickle cell anaemia [18].

Similar approaches to those considered in this case study are being developed for gene editing to modify immune cells to combat cancers and infectious diseases as well as to treat mutations that underpin immune based and haematological disorders [19]. Targeting of organs, such as the liver, could conceivably be treated in a similar way to restore function or produce a key protein (e.g. factor IX in haemophilia B) [20].

More technically challenging will be diseases where the build-up of a toxic protein, as in, for example, alpha-1-anti-trypsin deficiency or amyloidosis, requires the modification of a gene back to a non-disease-associated version in many cells in a target tissue, rather than just a few. Efficient delivery of the CRISPR carrying machinery to the target tissue in sufficient numbers will be the major challenge to treat these types of diseases.

Ethical considerations

In this scenario, the goal of gene editing is to restore the function of a single gene to enable the individual to experience the same health and well-being that people without sickle cell disease enjoy. Accordingly, somatic gene editing to treat severe, single-gene diseases could be ethically acceptable if a number of conditions are met, such as the proposed treatment conferring significant benefits to the individual, and it having a reasonable prospect of being safe and effective.

However, there are also other relevant considerations in the context of new biomedical technologies, primarily the obligation to 'first of all do no harm'. The risks of new medical interventions are often hard to quantify in advance (such as the risk of off-target effects), and the likelihood of benefit may be uncertain. If it is unclear whether there is a reasonable prospect of a beneficial outcome, there is an ethical duty to not make life worse for that patient. Nevertheless, the potential of somatic gene editing therapies to confer significant benefits to those for whom alternative therapies are limited, creates a weighty reason to enable access to therapy, provided that patients are fully informed, new treatments are subject to rigorous scientific and ethical review, and researchers meet minimum standards of responsible research and innovation.

Another relevant ethical factor in this context is whether the cost involved in developing and providing this therapy is a justifiable use of public research funds, as it may divert funds from other health priorities (unless private funding is available for research and development). Determining whether this research should be pursued using public funds would need to take into account the severity of the illness, the benefits of the treatment, the number of people affected by the condition and any other relevant considerations, such as whether the condition disproportionately affects certain (potentially marginalised) groups. Similarly, access to future treatment would raise questions regarding public funding and equitable access to treatment.

For Māori whānau, that decision may align or be in direct conflict with, values and aspirations for a flourishing whakapapa into the future. As an ethical guideline for Māori, the benefits of the procedure should outweigh the risks, and there should be direct benefits for participants and their communities from a Te Ao Māori perspective [21].

Legal considerations

Assessment and approval of the application of the CRISPR gene editing system in this way as a *qualifying new medicine* is legislated by the Medicines Act 1991 and Hazardous Substances and New Organism Act (HSNO) 1996 (section 2). The gene editing system will likely be captured under the Medicines Act as a new medicine for a therapeutic purpose. Gene editing of somatic tissue is undertaken *ex vivo* (outside the body), the viral vector with the CRISPR mechanism is developed *in-vitro* and thus the modified human cells are defined as a genetically modified organism under the HSNO Act (Section 2). Thereby the treated tissue could be considered a *new organism*, as defined by the HSNO Act 1996 (HSNO Act, section 2 A). The procedure will be evaluated for release as prescribed in s38I(3) of HSNO Act. It is highly improbable that administration of the medicine will have significant adverse effects on the public and form a self-sustaining population. Application approval as a *qualifying new medicine* under the HSNO Act would need to be sought from the Environmental Protection Authority (EPA) after delegation from the Director General of Health. The Therapeutic Products Bill is currently under development. It would repeal and replace the Medicines Act 1981 and regulate all therapeutic products across their lifespan (including cell and tissue therapeutic products, and clinical trials).[3]

SCENARIO 2
BRCA1 breast and ovarian cancer gene: Hereditary genetic therapy

A 38-year-old woman with a family history of early-onset, frequently bilateral, breast and ovarian cancer wants to eliminate the risk of transmitting this condition to future generations. She, and many of her relatives, have undergone genetic analysis, which has identified a mutation in the *BRCA1* gene that is commonly observed among Ashkenazi Jewish women with a similar family history worldwide. In New Zealand around 5% of women with breast cancer will have a similar single causative genetic variant predisposing them to this clinical outcome. This woman has not yet had a diagnosis of cancer but is aware that, to reduce her risk of getting cancer, she could have a double mastectomy and have her oviducts and ovaries removed. Aware of these considerations, and determined not to transmit her disease-conferring gene to future generations, she proposes to employ *in vitro* fertilisation (IVF) and to use CRISPR to revert any mutation-bearing embryos back to a version of the gene not associated with the disease. Although, on average, half of her embryos will not bear the mutation (as only one of her two chromosomes carries the mutation), maximising her number of embryos is a priority, hence her desire to correct the mutation-bearing embryos, in addition to utilising those embryos that do not have the mutation.

[3] Information about the Bill is available at health.govt.nz/our-work/regulation-health-and-disability-system/therapeutic-products-regulatory-regime

Medical considerations

Many discussions on the use of gene editing in medicine focus on the use of this technology in the production of 'designer' babies by using IVF [22]. As indicated by this case, the genetics of most disorders controlled by a single gene are such that other options exist to avoid the transmission of a disease-associated version of a gene to offspring with its propagation through subsequent generations (e.g. through preimplantation genetic diagnosis, or adoption). The chances of offspring carrying the disease-associated gene are less than 100% (with rare exceptions – see below), meaning that embryos without the disease will be produced and could be selected for and re-implanted using preimplantation genetic diagnosis. Therefore, the need to use gene editing in avoiding the recurrence of these disorders in the context of IVF is likely to be very small, but if gene editing was used on the embryos with the disease, it could increase the number of viable embryos that could be used for re-implantation. Although the feasibility of germline gene editing in humans has been demonstrated for a paternally transmitted monogenic disorder [23], legal and ethical considerations preclude any further demonstration of proof of principle for this approach to disease risk remediation. Additionally, successfully targeted embryos were only obtained in this study using specific conditions and only at certain stages of the fertilisation event, possibly presenting the prospect that the technique may still be quite inefficient.

Exceptions might exist, as illustrated in the scenario where a male bearing a mutation on his single X chromosome that does not preclude him reproducing (examples include haemophilia A and retinitis pigmentosa – a form of inherited blindness) seeks to avoid the 100% inevitability that any daughter he conceives will be a carrier for his condition. Although this might not affect his daughter's health, it does confer a reproductive burden – something the father might seek to reasonably obviate for his prospective daughters. In this example, all embryos could be subject to CRISPR directed editing to revert the mutation-bearing embryos back to the non-mutated version.

Ethical considerations

In this scenario, the objective of gene editing is to enable a future child to live a life without an increased risk of developing BRCA1-related breast cancer. However, it must be noted that editing a single gene does not eliminate the risk of developing breast or ovarian cancer completely. Any future child born still has the 'ordinary' risk of developing non-BRCA1 breast cancer.

While gene editing an embryo created by IVF similarly enables a future person to enjoy the same health enjoyed by the majority of others without the BRCA1 mutation, two significant factors distinguish this example from the first scenario. First, there is an alternative and relatively safe means of avoiding having a child with a BRCA1 mutation in the form of Preimplantation Genetic Diagnosis (PGD). PGD involves testing embryos for the mutation, and avoiding transfer of embryos that carry the BRCA1 mutation.

Second, the gene edit will be inherited by future generations. While this may confer a health advantage for future generations, any unintended and potentially adverse effects caused by the gene editing procedure may also be transmitted to future generations. This raises issues regarding what has been called 'intergenerational justice', which is essentially the question of what we owe future generations.

For some individuals, conducting germline gene therapy crosses an ethical line and fails to demonstrate respect for the dignity of the person who is subsequently born [24]. For those who hold this view, the fact that germline gene therapy alters an individual's genome, distinguishes it from other health interventions parents' consent to on behalf of their child, based on the parents' conception of what is in the child's best interests. On this account, permitting a procedure that will cause permanent changes in a prospective child's genome is beyond the sphere of parental autonomy (or in this case reproductive liberty) that parents should enjoy. Other people hold different views, and may place greater emphasis on the concepts of risk and benefits.

A harm-based approach would balance the risk of the gene editing procedure against the disadvantages of living with a BRCA1 mutation. On this account, if the risks of germline gene editing are worse than living with BRCA1 mutation, it is clearly not ethically justifiable to permit gene editing for the condition. However, if the intervention is low risk and there will be tangible benefits to the future child's health and well-being, some consider that prospective parents should have the right to make choices in the interests of their future child's health. Indeed some ethical commentators have gone so far as to suggest that the principle of 'procreative beneficence' morally requires prospective parents to undertake procedures that will enhance a future child's well-being [25].

Because this scenario involves a procedure performed on an embryo that is intended to be implanted in a woman, the interests of the future person who will be born must be considered. In the context where an essentially 'elective' procedure is performed, a minimal obligation is to not make a future person worse off than they would have been had that intervention not been performed. If the procedure is conducted and the child is harmed in the sense of being made worse off than if the intervention had not been performed, it constitutes a 'preconception' harm. Such a harm crystallises at birth. The potential for preconception harms imposes scientific limits on this type of treatment, unless it involves a serious condition where the putative risks of therapy are outweighed by tangible benefits, taking into account the unknown risks.

There is an association between some BRCA1 pathogenic variants and Ashkenazi Jewish genealogy and it could be consistent with the values and aspirations of Ashkenazi (and other affected) family members to relieve their descendants of the risk of passing on this genetic condition through germline editing. Where Māori embryos are concerned, culturally appropriate ethical processes [21] will be fundamental to ensure the key values of whakapapa, tika, manaakitanga and mana are upheld. In addition, careful consideration should be given to the pūtake or purpose [26] of the 'manipulation' of whakapapa. As for Scenario 1, the benefits of the procedure should outweigh the risks, and there should also be direct benefits for participants and their communities.

Legal considerations

Assessment and approval of the application of CRISPR gene editing system in this way as a *qualifying new medicine* is legislated by the Medicines and HSNO Acts. The procedure will likely not meet the definition of *new medicine* under sections 3(1)(a)(i) and 3(1)(c)(vi) of the Medicines Act 1981. Genetic treatment is undertaken on the embryo outside the body; however, the CRISPR mechanism is developed *in-vitro* and thus the modified human cells are defined as a genetically modified organism (HSNO Act, section 2). The procedure results in the creation of a *new organism*, as defined by the HSNO Act (section 2A). The procedure will be evaluated for release as prescribed in section 38I(3) of HSNO Act. It is highly improbable that administration of the new organism will have significant adverse effects on the public and form a self-sustaining population. Approval will be sought from the EPA after delegation from the Director General of Health. However, this procedure will likely be deemed a Prohibited Action under section 8 (and Schedule 1) of the Human Assisted Reproductive Technology Act 2004 (HART), as it involves implanting a genetically modified egg or human embryo into a human. Importantly, *genetically modified* is not defined in the HART Act and the Act does not refer to the HSNO Act for definition.

SCENARIO 3
Introduction of a genetic variant to improve cardiovascular health: Body tissue genetic enhancement

A 35-year-old male presents with a request to undergo gene editing to reduce his risk of developing cardiovascular disease. He has a family history of death in the fourth and fifth decades of life from coronary artery disease in association with elevated concentrations of blood lipids (fats). Despite attempts by several members of his family to define the basis for their predisposition to this trait, no determinative genetic or lifestyle factor has been identified. Furthermore, efforts to alter established risk factors, such as the prescription of drugs to control blood lipids, have only been partially successful and have not prevented the death of several of his relatives at a young age.

Recently, naturally arising mutations that eliminate gene function of the *PCSK9* locus have been shown to lead to a dramatic lowering of blood lipids with a resulting reduction in the risk of cardiovascular disease. The man is aware that individuals with these mutations seem to have no other adverse clinical complications due to their *PCSK9* genotype. This man suggests that a gene editing viral vector targeted to the liver, where *PCSK9* exerts its prime lipid-lowering effect, holds significant potential to prolong his life. The technical basis for this treatment is currently being established [27].

Medical considerations

This case introduces another level of complexity to the discussion on what place gene editing might take in medicine. This proposal differs fundamentally from the previous two scenarios in that the plan is not to revert the genomic sequence back to 'normal' but instead to induce a change in the genome to enhance or improve a physiological function. While such genotypes may have occurred naturally in other individuals, the proposal to induce them in a genome could be seen as an enhancement. In this respect, an enhancement could be conceptualised as the modification of a gene such that a new haplotype[4] is created for the purposes of producing an anticipated and desirable phenotypic[5] effect. While the proposed modification occurs naturally, introducing it through gene editing might lead to it interacting with other genes to produce adverse effects. Predicting such side effects for a given individual is very difficult, so the decision to proceed along these lines would be a matter of balance of perceived risks against potential benefits. As was the case in Scenario 1, any concerns about the inheritance of the gene editing effects are removed, as this proposal targets only the liver. Proof of concept for this approach has been achieved in mouse models, but published data in humans has not emerged at the present time [28].

Ethical considerations

In this context, the objective of the intervention is to reduce the risk of developing cardiovascular disease by introducing a mutation that is associated with (beneficial) lipid-lowering effects. In other words, its aim is to exploit a known mutation for its beneficial effects to subvert the individual's familial risks so that he may experience the same cardiovascular health that other people enjoy. The modification is only sought for the associated intrinsic value of enhancing long-term cardiovascular health.

Much of the ethical consideration in this context concerns the safety and efficacy of the treatment. As well as having the potential for off-target effects, introducing the known mutation may have unknown side effects due to pleiotropy (multiple gene effects), which means that obtaining fully informed consent to the procedure may be challenging.

In a Māori context, careful consideration should be given to the pūtake, the purpose [26] of the procedure, and decisions taken in full consideration of culturally appropriate ethical processes that uphold the key values of whakapapa, tika, manaakitanga and mana. Any benefits should outweigh the risks, and the outcome should benefit the Māori community [21].

Legal considerations

Assessment and approval of the application of CRISPR gene editing system in this way as a *qualifying new medicine* is legislated by the Medicines and HSNO Acts. The gene editing system will likely be captured under the Medicines Act (section 2) as a *new medicine* for a therapeutic purpose, as long as it achieves its intended action. Genetic treatment is undertaken on whole tissue within the body, however the viral vector with the CRISPR mechanism is developed *in-vitro* and thus the modified human cells meet the definition for a genetically modified organism in section 2 of the HSNO Act. The treated tissue could be considered a *new organism*, as defined by the HSNO Act. The procedure will be evaluated for release as prescribed in section 38I(3) of HSNO Act. It is highly improbable that administration of the medicine will have significant adverse effects on the public and form a self-sustaining population. Approval will be sought from the EPA after delegation by the Director General of Health (HSNO Act, section 19).

[4] A haplotype is a set of DNA variations that tend to be inherited together.

[5] Phenotypic effects relate to the observable characteristics of an individual.

SCENARIO 4

Introduction of a genetic variant to improve prospective offspring: Hereditary genetic enhancement

A couple using fertility services ask for heritable gene editing of their prospective offspring. The couple are in good health without any known predispositions to disease. They are both actively involved in competitive endurance athletic events. They are aware that it has recently become possible to edit genes, using IVF plus gene editing, to increase erythropoietin levels in the bloodstream. They are also aware that increased erythropoietin production increases red blood cell mass, oxygen carrying capacity and, consequently, athletic performance. Their reasoning in requesting this genetic enhancement for their embryos is that it will enhance their athletic capability over a broad range of sports and pastimes and contribute to their offspring living more accomplished and fulfilled lives.

Medical considerations

While gene editing can, in principle, be directed to any genomic location to produce a wide range of alterations, it is difficult to predict the resulting effects. When reverting a disease associated mutated gene back to the non-disease associated gene, the edited gene will exhibit unimpaired function, indistinguishable from naturally occurring genes. However, when enhancements are proposed that confer new or modified functions to genes, then substantial questions arise, and evidence would be needed that show such edits produce no undesirable properties. This level of confidence in the results of the procedure is unlikely to approach that of Scenarios 1 and 2 where genes are restored to a functional state. It is clear that the editing process will seldom reach levels of 100% efficacy, particularly when targeting body tissue cells in situ. It is unclear what the biological effects will be of deliberately inducing populations of cells with different genotypes in one individual. Substantial evidence exists to suggest that all humans have populations of cells with different genotypes and that reservations and concerns about the effects of inducing further populations of cells with different genotypes at yet another site through the use of gene editing, as for instance in Scenario 1, may not result in adverse outcomes [29].

Ethical considerations

The modification sought in this context involves alterations 'beyond human norms' based on the parents' views of what contributes to a future individual's 'well-being' and flourishing [30]. There are two ethically relevant aspects of the parental objectives in this scenario. First is the belief that enhanced athleticism is an intrinsic good and will make their future children better off than they would otherwise have been. The second ethically relevant aspect is the parental objective to enable the future child to enjoy a competitive advantage over others who will (presumably) not be similarly genetically advantaged.

Although the intervention involves alteration beyond human norms, this alone does not mean that such a choice is morally wrong, but it does attract additional ethical considerations. Firstly, an intervention to bring about alterations beyond human norms involves a different risk-benefit ratio compared with an intervention that seeks to return an individual's functioning to within human norms. Because a future child could enjoy a good quality of life without the intervention, any risks associated with the intervention necessarily assume a greater significance. Other ethical considerations include the implications of the intervention for the future individual that is born, its effect on the parent-child relationship and the implications for society in general.

For some, the problematic aspect of parents choosing to alter the genes of future children arises from parents seeking control over the trajectory of their future child's life [31]. Parents who 'design' or 'manufacture' their child's talents may have significant expectations regarding their offspring's potential and subsequent life choices. Such a future child may resent the parents who are responsible for their 'talents' and feel pressured to live up to and/or conform to parental expectations. However, parental expectations may be true of all children, whether modified or not. Ultimately, individuals are free to choose how they live, regardless of their genetic endowment. In the given scenario, a future child may choose to indulge her enhanced athletic talents or may pursue other self-regarding interests. Conversely, some 'unmodified' offspring may resent their parents if they have not taken advantage of germline interventions that they consider may have enhanced their life and well-being.

In the context of reproductive genetic enhancements, similar concerns regarding pressure to engage in technology and the potential subsequent shift in genetic and reproductive 'norms' previously discussed in Scenario 2 arise. Philosopher Michael Sandel states [32]:

> **It is sometimes thought that genetic enhancement erodes human responsibility by overriding effort and striving. But the real problem is the explosion, not the erosion, of responsibility. As humility gives way, responsibility expands to daunting proportions. We attribute less to chance and more to choice. Parents become responsible for choosing, or failing to choose, the right traits for their children.**

A concern often raised in relation to enhancement beyond human norms is that it risks exacerbating existing inequalities, creating a divide between the genetic 'haves' and 'have nots'. Although this kind of treatment would not realistically be supported by public funding, the question as to whether potentially increasing inequality alone is a reason to prohibit such a treatment depends upon the likelihood of instrumental benefits accruing to individuals in the short term and to society in the long term if enhancement technologies were to become safe, effective and affordable in the future [33].

However, if enhancements are only sought so that an individual obtains a positional advantage over others, the cost-benefit analysis alters significantly. Enhancements that confer a competitive advantage for an individual over other 'unmodified' individuals risks encouraging a genetic 'arms race'. In this case, an increasing number of prospective parents may want to ensure the competitive benefits of enhancement for their offspring. However, any competitive advantage may be short lived, as the 'enhanced' ability becomes the new norm. This is potentially counter-productive, as it increases the number of people exposed to the risks of enhancement, while no single individual is better off as a result [34].

As in the previous scenario, any procedure involving Māori embryos requires strict adherence to culturally appropriate ethical processes that ensure the key values of whakapapa, tika, manaakitanga and mana are upheld [21]. Once again, careful consideration should be given to the pūtake or purpose of the 'manipulation' of whakapapa, benefits should outweigh risks and there should be direct benefits to the Māori community.

Legal considerations

Assessment and approval of the application of CRISPR gene editing system in this way as a qualifying new medicine is legislated by the Medicines and HSNO Acts. The gene editing system will likely not meet the definition of new medicine under sections 3(1)(a)(i) and 3(1)(c)(vi) of the Medicines Act 1981. Genetic treatment is undertaken on the embryo outside the body, however the CRISPR mechanism is developed in-vitro on human cells, thereby meeting the definition for genetically modified organism in section 2 of the HSNO Act. The procedure results in the creation of a new organism, as defined by the HSNO Act (section 2A). The procedure will be evaluated for release as prescribed in section 38I(3) of HSNO Act. It is highly improbable that administration of the new organism will have significant adverse effects on the public and form a self-sustaining population. Approval will be sought from the EPA after delegation by the Director General of Health (HSNO Act, section 19). However, this procedure will likely be deemed a Prohibited Action under section 8 (and Schedule 1) of the HART Act 2004, as it involves implanting a genetically modified egg or human embryo into a human being. Importantly, genetically modified is not defined in the HART Act and does not refer to the HSNO Act for definition.

Social considerations

Implications for the healthcare system

Decisions about gene editing in human health would be guided by the same considerations as other New Zealand health procedures, starting with the general intention to provide cost-effective treatments, and a comparison with existing therapeutic approaches. For example, in the future, enhancement options for body tissues, such as the liver to better detoxify in adverse environments, could be promoted as an anti-cancer strategy.

Social issues for the healthcare system to consider will include [35] ensuring that all health research related to the development of gene editing approaches is subject to ethical oversight, such as research ethics committees, and remains public, ensuring oversight and transparency. It will equally be important to ensure against uses which reinforce prejudice and narrow the definitions of normality, and naturally occurring heterogeneity, in our societies. Allied to this point, it will be important to safeguard

against uses which worsen inequalities within and between groups or members of the community, as unequal access and cultural differences affecting uptake could create large differences in the relative incidence of a given condition by region, ethnic group or socioeconomic status. Similarly, equity of access to the benefits conferred by this technology should be ensured.

Māori cultural considerations

From a Māori perspective, there are concerns that genetic modification, including gene editing, is at odds with, or interferes with, natural processes pertaining to whakapapa. Māori communities will need to be well informed about the implications, benefits and risks associated with gene editing in healthcare. Education and consultation will be central to enabling whānau, communities, hapū and iwi to assess the social, moral, ethical and health considerations of gene editing within different contexts and scenarios. As part of this project, Māori perspectives and broader cultural contexts are being sought by the Panel in a parallel process.

New Zealand Regulation of Human Gene Editing

In New Zealand, any treatment that is aimed at altering the genomic constitution of a person or introducing genetic material from another organism for therapeutic purposes would be regulated primarily by the Hazardous Substances and New Organisms Act 1996 (HSNO Act). This is a non-exclusive code for new organisms, limited to new organisms identified post 1998 and genetically modified organisms developed using in vitro techniques. An added level of regulation is imposed when the modification is made in the reproductive context (e.g. pre-implantation genetic modification of embryos) governed by the HART Act. Restrictions on specified biotechnical procedures, referring primarily to xenotransplantation, are regulated by the Medicines Act 1981 (Medicines Act).

In relation to medicines that are or contain new organisms, the requirements of the Medicines Act are additional to the requirements of the HSNO Act,[6] and ethics review by Health and Disability Ethics Committees or the Ethics Committee on Assisted Reproductive Technology is required for medical research involving genetically modified organisms before being reviewed for the HSNO Act. It is important to note that in the event of an inconsistency between the provisions of the Medicines and HSNO Acts, the Medicines Act and its regulations prevail over the HSNO Act (Medicines Act 1981, s 110). A summary of the New Zealand regulatory framework as it applies to human gene editing for health treatments is provided in Appendix 2.

In New Zealand there is a vast network of legal instruments that require consideration alongside the HSNO and Medicines Acts: the Accident Compensation Act 2001; public and private law remedies [36]; NZ Bill of Rights Act 1990 and the right not to be deprived of life (s 8); the Treaty of Waitangi[7] and the Waitangi Tribunal Report recommending that Māori have a greater interest in genetic modification [37]; the future role of the Human Research Council, Genetic Technology Advisory Committees and Institution Research Committees; the Resource Management Act 1991 and the ability of regional councils to control the use of genetically modified organisms through regional policy statements or district plans. These points, along with others, are listed and presented in Figure 1.

[6] Medicines Act 1981, s 5A.

[7] The Law Commission looked into the issue of liability for loss resulting from GMOs and described the adverse cultural effects of GM on Maori: *'Concerns have also been raised by Maori, which arise from a different belief structure. Although the basis for many of the Māori cultural objections to genetic modification vary among iwi, they are usually based around impacts on whakapapa, mauri, kaitiakitanga and rangatiratanga. The traditional Maori worldview considers all parts of the natural world to be related through whakapapa. Genetic modification risks interfering with such relationships, and threatens the sanctity of mauri (life principle) and wairua (spirit) of living things. Concluding that genetic modification may affect Maori's ability to be kaitiaki (guardians) of their taonga and particularly their ability to care for valued flora and fauna'*. NZ Law Commission (2002).

[8] HSNO Act s2(1).

HSNO Act

The HSNO Act's purpose is to protect the environment and health and safety of people and communities by preventing or managing the adverse effects of hazardous substances and new organisms. The HSNO Act was never intended to include human beings as new organisms. However, an 'organism' is defined in the HSNO Act as including a human cell[8] (grown or maintained outside the human body). 'Organism' also includes a genetic structure (other than a human cell) that is capable of replicating itself, whether that structure comprises all or part of the entity.[9] The gene editing technique can involve multiple 'organisms' (bacteria, virus, human cells, etc.).

Medicines Act

The Medicines Act refers to the HSNO Act for the definition of new organism and for determining and assessing a qualifying new medicine (Medicines Act, section 2). It is through these terms, defined in section 2, that the Medicines Act and the HSNO Act interact. In particular, a qualifying new medicine is defined in the Medicines Act, section 2, as a new medicine that:

a. is or contains a new organism; and
b. meets the criteria set out in section 38I(3) of the Hazardous Substances and New Organisms Act 1996, in that it is highly improbable that administration of the medicine would have significant adverse effects on the public and form a self-sustaining population.

The Medicines Act was amended in 2005, with the following biotechnical procedures repealed and subsequently provided for in the HART Act as prohibited actions in Schedule 1: cloned human organism, cloning procedure, genetically modified embryo, genetically modified gamete and germ cell genetic procedure. The HART Act does not define these terms and does not refer to the HSNO Act for definition.

The Medicines Act is now 36 years old and at the time of drafting the scenarios in this paper were not considered possible and are therefore not explicitly regulated. All therapeutic products involving genetic modification that are put forward to Medsafe for approval for use as a medicine, are assessed on a case-by-case basis. A replacement of the Medicines Act is currently being drafted and designed to enable regulation of advancements in genetic technology in health. By the time the scenarios discussed are to be considered for approval, they will likely be under new legislation. The scenarios are therefore a snapshot of how these could be regulated today but not necessarily in the future.

Any law that New Zealand wants to incorporate needs to be consistent and harmonious with other laws domestically and internationally. International law on gene editing and genetic modification is still evolving and is open to debate. Many countries are reviewing how to regulate the new technology and whether regulation should differ for somatic and germline treatments.

There is the potential for medical tourism and this is not a new challenge, as evidenced by the example of international commercial surrogacy, regulated on an ad hoc basis rather than by comprehensive and dedicated legislation. New Zealand takes into consideration the best interests of the child and will likely accept the outcome of a person coming into New Zealand. It is likely that gene edited people would be viewed in the same way.

[9] HSNO Act, s2(1).

FIGURE 1 | Summary diagram of legal instruments affected by and influencing human gene editing

NEW ZEALAND REGULATION: HUMAN GENE EDITING – TREATING AND PREVENTING DISEASE

Guiding Principles

Culture cues and social license

Guidance from Royal Commission on GM

Cabinet Paper: Government Response to Royal Commission

Treatment accessibility and customs entry

Human Assisted Production Technology Act 2004 (Schedule 1, Prohibited actions s 8)

Human Tissue Act 2008

Accident Compensation Act 2001 (s 32 Treatment Injury re immune response to vector or transgene and 'off target' (and 'on target') editing and expression)

Health Professionals Competence Assurance Act 2003 (re-Certification)

Resource Management Act 1991 *(Local regulation of GMOs for Hospitals and Research. Case law: Federated Farmers NZ v Northland Regional Council [2015] NZEnv89)*

Rights to DNA data and information

The new Therapeutic Products regulatory regime is set to replace the Medicines Act 1981 and its Regulations.

health.govt.nz/our-work/regulation-health-and-disability-system/therapeutic-products-regulatory-regime

Te Mana Raraunga

Research

Hazardous Substances and New Organisms Act 1996 (HSNO) (non exclusive code for GMOs; limited to *new organisms*; *in vitro*)

(Case law: The Sustainability Council of NZ Trust v EPA [2014] HC 1047) Medicine Act* *amended – GMO transferred to HSNO*

2017 Te Pūnaha Hihiko Vision Mātauranga Capability Fund

Genomics Aotearoa

Treaty Partnerships

Public (and Private) Funding

Institution Research Committees (ISBC)

Guidance from International Regulators:

- Canada, Australia, USA, UK, EU, China
- Product c.f. technology/process approach (mechanistic/basic research; clinical use – somatic; clinical use – germline)
- Risk assessment: Autologous c.f. non-autologous
- World Health Organisation

Application

HDC Code of Health and Disability Services

Consumers Rights Regulations 1996

Treaty of Waitangi

Patents Act 2013 (ss 15, 16)

TRIPS Agreement (Art. 27)

Legal status of embryos (CRISPR technologies c.f. Prenatal Genetic Diagnosis)

NZ Bill or Rights Act 1990 (Right not to be deprived of life, s8)

Human Rights Act 1993, re discrimination provisions.

Implications for New Zealand

To explore these issues for New Zealand, the Royal Society Te Apārangi established an expert panel to consider the implications of gene editing technologies for New Zealand society. The intention of the Panel was to raise public awareness of the technologies and their uses, and provide insight and advice on the future implications associated with the application of these new technologies for New Zealand.

For more information and resources about gene editing, visit the Society's web pages: **royalsociety.org.nz/gene-editing/**, or contact **info@royalsociety.org.nz**.

APPENDIX 1

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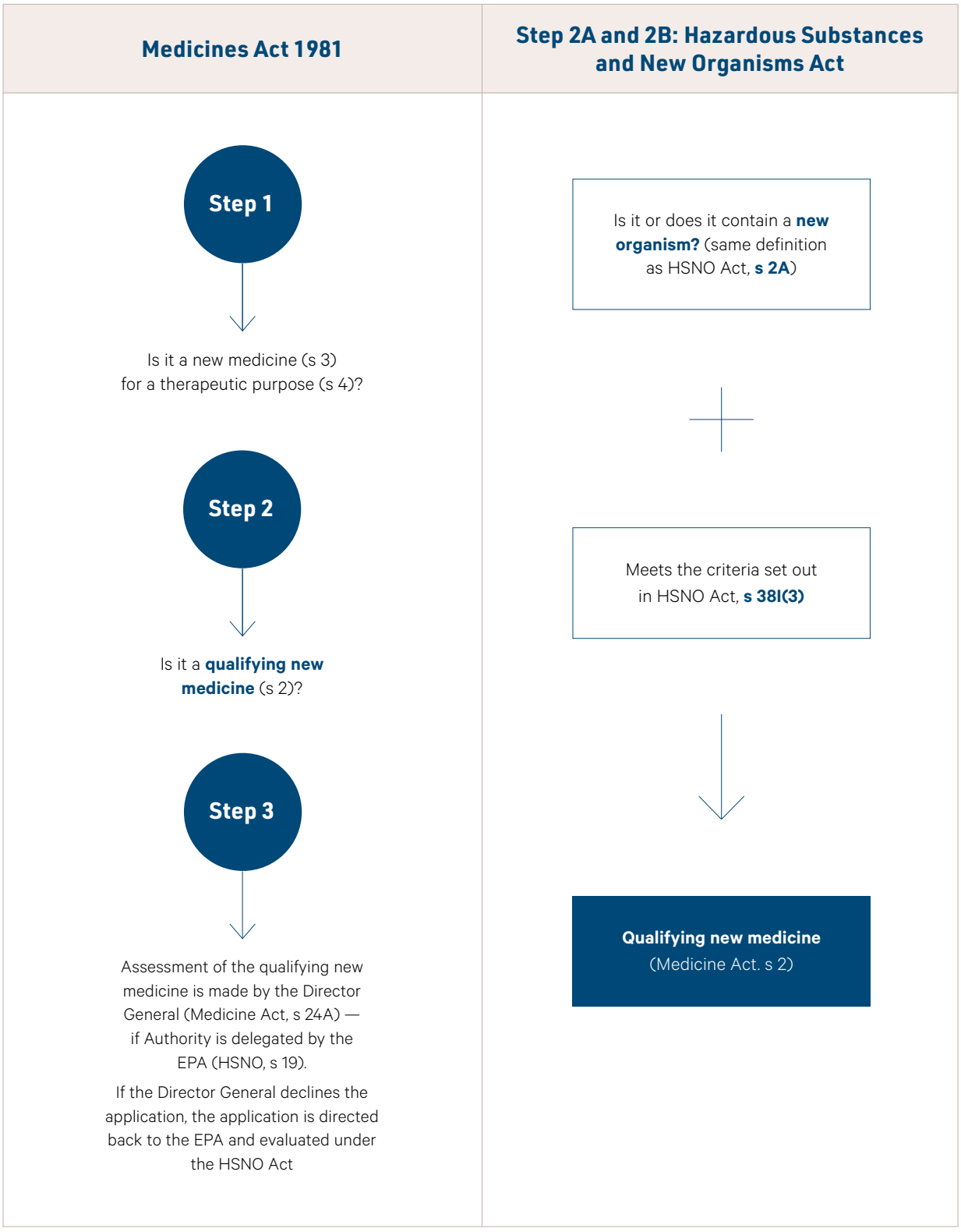
APPENDIX 2

The New Zealand regulatory framework as it applies to human gene editing for health treatments

The following diagram presents a summary of the regulatory process, followed by a detailed description of each of the steps.

FIGURE 2 | Regulatory process summarised for determining and assessing a qualifying new medicine



STEP 1:
Is it a medicine for a therapeutic purpose?

Section 3 of the Medicines Act specifies that a medicine means any substance or article that:

- is manufactured, imported, sold, or supplied wholly or principally for administering to one or more human beings for a therapeutic purpose[10] and achieves, or is likely to achieve, its principal intended action in or on the human body by pharmacological, immunological, or metabolic means; and
- includes any substance or article that is manufactured, imported, sold, or supplied wholly or principally for use as a therapeutically active ingredient in the preparation of any substance or article that falls within paragraph (a); or of a kind or belonging to a class that is declared by regulations to be a medicine for the purposes of this Act.

STEP 2
Is it a qualifying new medicine?

The Medicines Act defines a *qualifying new medicine* as a *new medicine* that is or contains a new organism and meets the criteria set out in section 38I(3) of the HSNO Act.

- A qualifying organism means a new organism that is or is contained in a *qualifying new medicine*.
- A new organism has the same meaning as in section 2A of the HSNO Act.

STEP 2A
Is the organism new?

Genetically modified organisms are new organisms under the HSNO Act(s 2A(2)(b)) and s 2. Organisms not deemed genetically modified are provided for under statutory regulation (SR 1998/219(r 3)) and include organisms that result from mutagenesis that uses chemical or radiation treatments that were in use on or before 29 July 1998. The CRISPR-Cas gene editing system is developed *in vitro*,[11] thereby classifying it as an '*in vitro* technique' for the purposes of genetically modified organisms.[12] This determination is based on the initial organism, not the resulting organism.

[10] In s 4 of the Medicines Act 1981, therapeutic purpose means 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; or*
c. *testing the susceptibility of persons to a disease or ailment; or*
d. *influencing, controlling, or preventing conception; or*
e. *testing for pregnancy; or*
f. *investigating, replacing, or modifying parts of the human anatomy.*

[11] Ceasar, S. A., Rajan, V., Prykhozhij, S. V., Berman, J. N. & Ignacimuthu, S. (2016). Insert, remove or replace: A highly advanced genome editing system using CRISPR/Cas9. *Biochimica et Biophysica Acta (BBA) - Molecular Cell Research*, 1863, 2333-2344.

[12] HSNO Act, s 2(1).

STEP 2B

Does it meet the criteria set out in section 38I(3) of the HSNO Act?

Section 38I of HSNO Act prescribes the assessment of applications for release of qualifying organisms.

- If the Authority does not approve an application under this section, the Authority must assess and determine the application under s 38.
- If the Authority receives an application under s 34 that relates to a qualifying organism, the Authority may –
    - make a rapid assessment of the adverse effects of importing for release or releasing from containment the qualifying organism; and
    - approve the importation for release or release from containment of the qualifying organism with or without controls.
- The Authority or the responsible chief executive may determine that a qualifying organism is or is contained in a qualifying medicine only if satisfied that, taking into account all the controls that will be imposed (if any), it is highly improbable that –
    - the dose and routes of administration of the medicine would have significant adverse effects[13] on the health of the public; or any valued species; and
    - the qualifying organism could form an undesirable self-sustaining population and would have significant adverse effects on the health and safety of the public; or any valued species; or natural habitats; or the environment.

STEP 3

Assessment and approval of a qualifying organism

Assessment of a qualifying medicine for approval, appears to be primarily under the regulation of section 24A of the Medicines Act. The Director General may grant approval under section 38I of the HSNO Act for the release of a *qualifying new medicine* if the Director General has the consent of the Minister to do so and is acting under a delegation from the EPA given under s 19 of the HSNO Act.

If the Director General declines to grant an approval because the new organism is not a *qualifying new medicine*, then the Director General must inform the EPA that the *new medicine* is not a *qualifying new medicine* and provide the EPA with a copy of all information that may assist the EPA in deciding whether to approve or decline the application under the HSNO Act.

[13] HSNO Act, s 2(1) specifies what is included under 'effect'.

Glossary

Amyloidosis	A rare disease that occurs when a substance called amyloid builds up in your organs.
Chromosomes	A thread-like structure of nucleic acids and protein found in the nucleus of most living cells, carrying genetic information in the form of genes.
CRISPR	Clustered Regularly Interspaced Short Palindromic Repeats, which are the hallmark of a bacterial defence system that forms the basis for CRISPR-Cas9 gene editing technology.
DNA	Deoxyribonucleic acid, the hereditary material in humans and almost all other organisms.
Ex vivo	Carried out on cells outside the normal, living organism.
Hapū	Kinship group, clan, tribe, subtribe.
In vivo	Carried out within the body of a living organism.
In vitro	Made to occur in a laboratory vessel or other controlled experimental environment rather than within a living organism or natural setting.
IVF	In vitro fertilisation, a fertility treatment technique where embryos are introduced directly into the uterus.
Iwi	Extended kinship group, tribe, tribal federation, nation, people, nationality, race.
Gametes	A sex, or reproductive, cell containing only one set of dissimilar chromosomes, or half the genetic material necessary to form a complete organism.
Genes	A gene is the basic physical and functional unit of heredity. Genes are made up of DNA.
Genetic variants	Genetic differences between individuals in a population, and between populations. This variation arises through genetic mutation and is important, as it provides the diversity within and between populations required for natural selection.
Genome	The genetic material of an organism.
Germline/Germ cell	The cell types that eventually result in the formation of either egg cells or sperm.
Haematological	Pathological conditions primarily affecting the blood or blood-producing organs.
HART	Human Assisted Reproductive Technology Act 2004.
HSNO	Hazardous Substances and New Organisms Act 1996.
Immunological	Relating to the structure and function of the immune system (that part of the body that fights off infection).
Lipid	Another word for fat-like substances found in your blood and body tissue. A lipid is chemically defined as a substance that is insoluble in water and soluble in alcohol, ether and chloroform.
Mana	Prestige, authority, control, power, influence, status, spiritual power, charisma.
Manaakitanga	Hospitality, kindness, generosity, support; the process of showing respect, generosity and care for others.
Metabolic	Relating to, or deriving from, the whole range of biochemical processes that occur within living organisms.
Morbidity	Refers to having a disease or a symptom of disease, or to the amount of disease within a population.

Pharmacological	The science of drugs, including their composition, uses and effects.
Preimplantation genetic diagnosis	A procedure used in conjunction with IVF to test early human embryos for serious inherited genetic conditions and chromosomal abnormalities before they are transferred to the uterus.
Somatic	Cells of the body in contrast to the germline cells.
Te Tiriti o Waitangi	Treaty of Waitangi.
Therapeutic	Relating to the healing of disease.
Tika	Truth, correctness, directness, justice, fairness, righteousness, right.
Trait	A genetically determined characteristic.
Whakapapa	Genealogy, genealogical table, lineage, descent.
Whānau	Extended family, family group.
Xenotransplantation	The process of grafting or transplanting organs or tissues between members of different species.

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