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Gene Editing in a Healthcare Context

Royal Society Te Apārangi Gene Editing Panel

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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 well 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, or will soon, involving removing cells from an individual's body, editing their DNA and then putting them back into the body [1].

Gene editing is also in danger of moving ahead of any consensus on the rights and wrongs of how it should be used. So to explore the implications of gene editing technology for New Zealand, the 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 to:

- Raise awareness of the scientific possibilities and associated public 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 of papers[1] considering the implications of the technology in health, pest control, and agricultural situations, and is accompanied by a companion discussion paper inviting public feedback, 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 tissues in individuals, as well as 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 a disease will manifest or not [3], while in others, genetic variants can heighten or reduce the risk of disease [3], with other genetic and environmental factors also being partially determinative [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 (genetic therapy) [7]. These techniques, chief amongst them being CRISPR[2], are able to insert, remove or replace genes or introduce new DNA sequences to 'repair' sections of the genome, at predetermined 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, inducing the edit in the tissue and cell of choice, remains a challenge [9].

Box 1: 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 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 CRISPR 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 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.

The first case study discusses a genetic alteration to an individual's somatic (i.e. body tissue) cells within the main organ system 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

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

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 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 the therapy-enhancement continuum 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 (PCKS9 mutation)*	*Enhances* erythropoietin *production to increase athletic performance*
Genetic therapy 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

Human gene editing scenarios

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 don't 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 [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 therapeutic approaches, such as bone marrow transplantation, have been optimised, and the result of the treatment in the avoidance of substantial morbidity, including strokes and premature death, represent substantial clinical inducements. The mutation leading to sickle cell anaemia is common to millions of people world-wide and hence developing standard approaches could be economically and therapeutically attractive to health services.

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 treat mutations that underpin immune based and haematological disorders [18]. 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) [19].

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

On the whole, somatic gene editing to treat severe, single-gene diseases is a technically achievable option and can be medically justifiable, considering the anticipated risks and benefits. The concept of disease severity is already incorporated into oversight guidelines for assisted reproductive technologies, specifically those citing the grounds for performing preimplantation genetic diagnosis, although a formal definition has not been arrived at [20, 21], and could be used for gene editing. Sickle cell anaemia is a severe and debilitating disease. From that perspective, it would be hard to deny a family access to non-inheritable gene editing to help affected people. For Māori whānau, that decision may align, or be in direct conflict with, Māori values and aspirations for 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 [22].

Legal considerations

From a regulatory perspective:

- Assessment and approval of the technique as a ‘qualifying new medicine’ is legislated by the Medicines and HSNO Acts.
- The technique will likely be captured under the Medicines Act as a new medicine for a therapeutic purpose.
- The treated tissue could be considered a new organism, as defined by the Hazardous Substances and New Organisms Act 1996 (HSNO Act). Genetic therapy is undertaken outside the body, however the viral vector with the CRISPR mechanism is developed in-vitro.
- The procedure will be evaluated for release as prescribed in s 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 Environmental Protection Authority (EPA) unless the EPA chooses to delegate authority to the Director General of Health.

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 amongst Ashkenazi Jewish women with a similar family history worldwide. 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.

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 [23]. 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 subsequent on-going propagation through subsequent generations (e.g. through preimplantation genetic diagnosis). 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.

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 editing to revert the mutation-bearing embryos back to the non-mutated version.

Ethical considerations

While accepting that the indications for germline (or hereditary) genomic editing using *in vitro* reproductive technologies might not be as numerous as first perceived, the ethical considerations surrounding gene editing in this reproductive context require consideration. Any genetic manipulation of an embryo clearly has to proceed with the understanding that the person who is affected is the individual who develops from that embryo and that they cannot consent to the initiative. Where that manipulation is of the germline, this could also impact on their reproductive health, and could lead to the transmission of modified genes, which may have undefined biological effects for some genes. Currently, medical decisions are made for children prior to the age when consent is practicable. In this situation, decisions are made about the child's welfare by considering the child's best interests; choosing the least burdensome alternative; and considering the child's future. This removal of their autonomy is, however, in conflict with currently held ethical views underlying the prohibition of modification of the human germline (genetic material passed on in reproduction) [20, 21].

There is an association between *BRCA1* and Ashkenazi Jewish genealogy but 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 [22] that ensure the key values of whakapapa, tika, manaakitanga, and mana are upheld, will be fundamental. In addition, careful consideration should be given to the pūtake or purpose [24] of the 'manipulation' of whakapapa. As for Scenario one, the benefits of the procedure should outweigh the risks, and there should also be direct benefits for participants and their communities.

Legal considerations

From a regulatory perspective:

- Assessment and approval of the technique 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.
- The procedure results in the creation of a new organism, as defined by the HSNO Act. Genetic therapy is undertaken on the embryo outside the body, however the CRISPR mechanism is developed in-vitro.
- The procedure will be evaluated for release as prescribed in s 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 Environmental Protection Authority (EPA) unless the EPA chooses to delegate authority to the Director General of Health.
- 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.

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 4th and 5th 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 [25].

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 occured 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[3] is created for the purposes of producing an anticipated and desirable phenotypic[4] 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 transgenerational effects are removed as this proposal targets only the liver.

Ethical considerations

Some would say that physiological enhancement of human phenotypes to reduce disease states or avoid their development altogether merges seamlessly with traits that ostensibly improve a person's functioning or capabilities. Whilst deleting particular genes, like those for *PCSK9,* can moderate disease properties [26, 27], it is possible that changing other naturally-arising variants in genes could confer 'desirable' phenotypic traits, e.g. for athletic potential [28] or eye colour [29], without a medical purpose. This distinction has been cause for significant ethical debate in the past in other contexts [14] and the use of gene editing to this end, at least in instances where it is somatic genetic

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

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

alterations that are being induced, is qualitatively no different. There's much to be said about how and where we would want to draw that line, however, in this example the enhancement aims to reduce the chances of developing a disease, and as such, it may be seen as more akin to vaccination than, say, sports doping.

In a Māori context, careful consideration should be given to the pūtake, the purpose [24] 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 [22].

Legal considerations

From a regulatory perspective the procedure:

- Assessment and approval of the technique as a 'qualifying new medicine' is legislated by the Medicines and HSNO Acts.
- The technique will likely be captured under the Medicines Act as a new medicine for a therapeutic purpose, as long as it achieves its intended action.
- The treated tissue could be considered a new organism, as defined by the HSNO Act. Genetic therapy is undertaken on whole tissue within the body, however the viral vector with the CRISPR mechanism is developed *in-vitro*.
- The procedure will be evaluated for release as prescribed in s 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 Environmental Protection Authority (EPA) unless the EPA chooses to delegate authority to the Director General of Health.

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 is has recently become possible to edit genes 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, you expect that 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 may not result in adverse outcomes [30].

Ethical considerations

As with case study 2, any genetic manipulation of an embryo has to proceed with the understanding that the person who is affected cannot consent to the initiative. This removal of their autonomy sits at the core of the ethical prohibition of modification of the human germline [31]. Currently, medical decisions are made for children prior to the age when consent is practicable. In this situation, decisions are made about the child's welfare by considering the child's best interests; choosing the least burdensome alternative; and considering the child's future. In addition, the physiological enhancement of human characteristics to improve a person's functioning or capabilities has been cause for significant ethical debate [32]. The potential impact of social and health inequality around access to the potential to enhance the genetics of future generations needs to be considered [20, 21].

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 [22]. 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

From a regulatory perspective the procedure:

- Assessment and approval of the technique as a 'qualifying new medicine' is legislated by the Medicines and HSNO Acts.
- The technique will likely not meet the definition of new medicine under sections 3(1)(a)(i) and 3(1)(c)(vi) of the Medicines Act.
- The procedure results in the creation of a new organism, as defined by the HSNO Act. Genetic therapy is undertaken on the embryo outside the body, however the CRISPR mechanism is developed in-vitro.
- The procedure will be evaluated for release as prescribed in s 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 Environmental Protection Authority (EPA) unless the EPA chooses to delegate authority to the Director General of Health.
- 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.

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 in future be promoted as an anti-cancer strategy.

Social issues for the healthcare system to consider will include [33]:

- Ensuring health research is subject to ethical oversight, such as research ethics committees, and remains public, ensuring oversight and transparency.
- Ensuring against uses which reinforce prejudice and narrow definitions of normality in our societies
- Ensuring against uses which worsen inequalities within and between societies, 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

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. Training and specialist advisers will be needed for these new medical therapies, including genetic counselling, which is currently provided by Genetic Health Service New Zealand.

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 Human Assisted Reproductive Technology Act 2004 (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[5], 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 NZ 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; revisiting public and private law remedies [34]; NZ Bill of Rights Act 1990 and the right not to be deprived of life (s 8); the Treaty of Waitangi[6] and the Waitangi Tribunal Report recommending that Maori have a greater interest in genetic modification [35]; the future role of the Human Research Council, Genetic Technology Advisory Committees and Institution Research Committees; the legal status of embryos; 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.

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[7] (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[8]. The gene editing technique involves 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.

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[5] Medicines Act 1981, s 5A.

[6] 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 Maori 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).

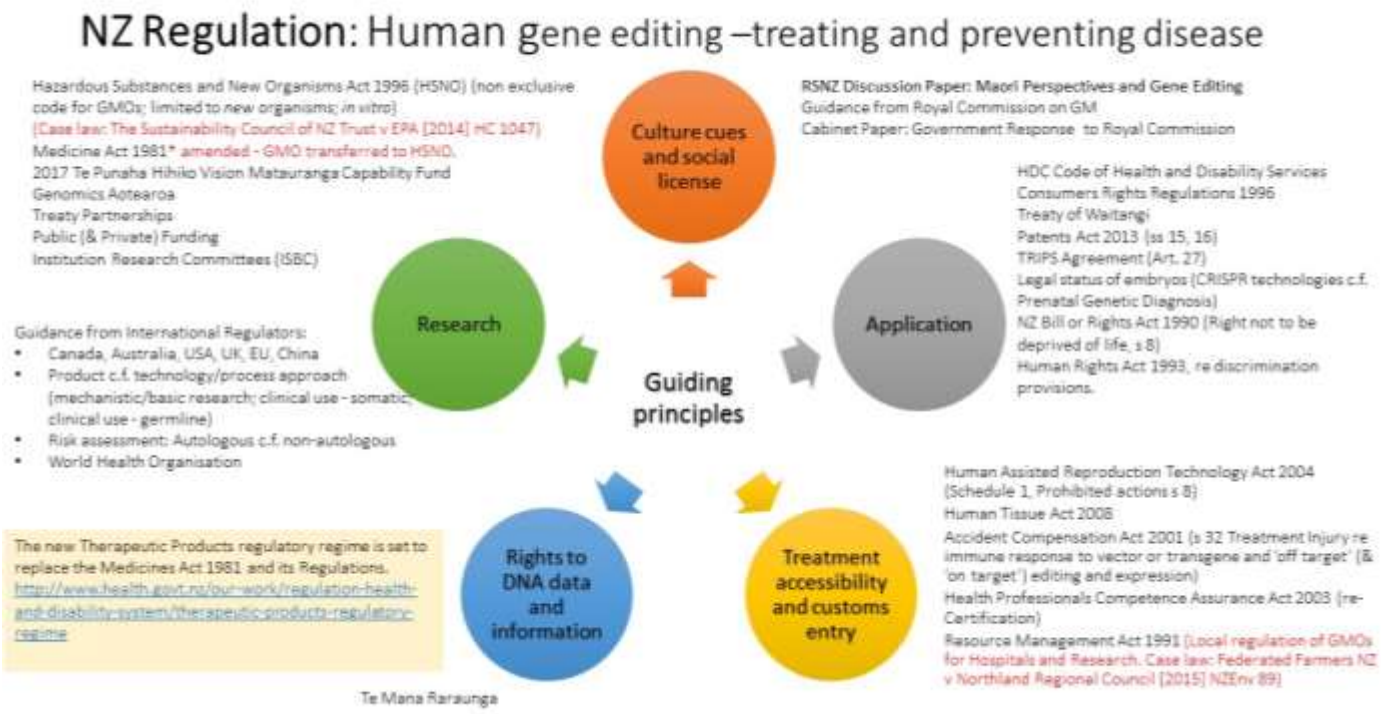
[7] HSNO Act s2(1)

[8] HSNO Act, s2(1)

The Medicines Act was amended in 2005, with the following biotechnical procedures repealed and subsequently provided for in the Human Assisted Reproduction Technologies Act 2004 (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.

Figure 1. Summary diagram of legal instruments affected by and influencing human gene editing.



Implications for New Zealand

To explore these issues for New Zealand, the Royal Society Te Apārangi has established an expert panel to consider the implications of gene-editing technologies for New Zealand society. The intention of the Panel will be 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 further information

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

Appendix 1: Contributors to the technical paper

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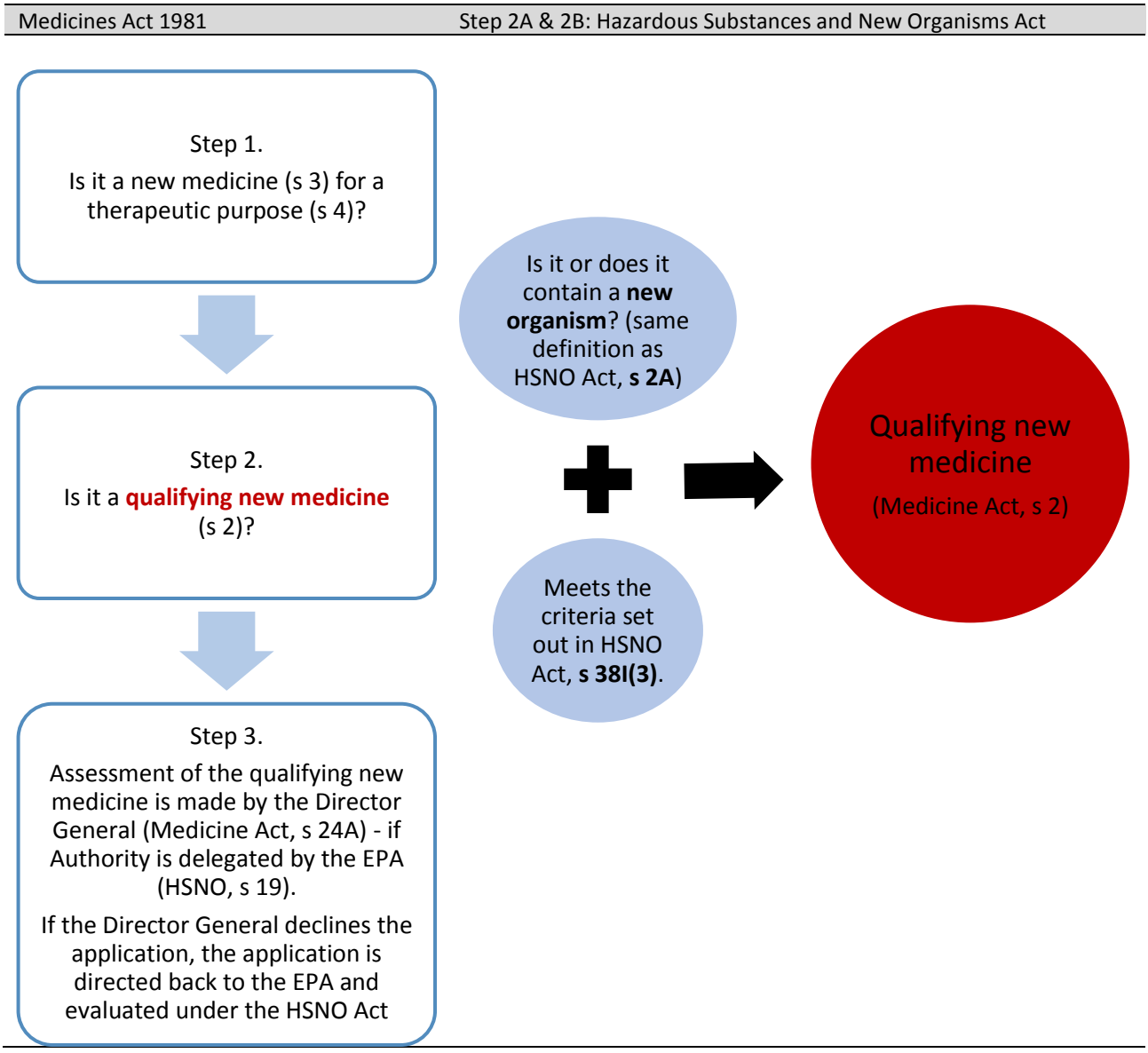
Appendix 2: The New Zealand regulatory framework as it applies to human gene editing for health treatments

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

Figure 3. 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[9]; and achieves, or is likely to achieve, its principal intended action in or on the human body by pharmacological, immunological, or metabolic means; and

[9] 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:

- 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*[10], thereby classifying it as an '*in vitro* technique' for the purposes of genetically modified organisms[11]. This determination is based on the initial organism, not the resulting organism.

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[12] 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

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(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.

[10] 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.

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

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

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.

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