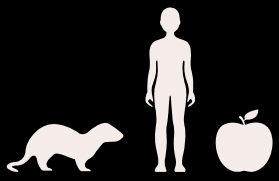
ROYAL SOCIETY TE APĀRANGI

GENE EDITING

REFLECTIONS FROM THE PANEL CO-CHAIRS

SCENARIO SUMMARIES + SCENARIOS (HEALTHCARE, PEST CONTROL AND PRIMARY INDUSTRIES)

LEGAL AND REGULATORY IMPLICATIONS



AUGUST 2019

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ROYAL SOCIETY TE APĀRANGI


TŪHURA
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TOHATOHA

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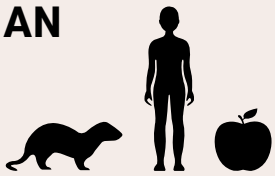
ROYAL SOCIETY TE APĀRANGI

GENE EDITING
REFLECTIONS FROM THE PANEL CO-CHAIRS

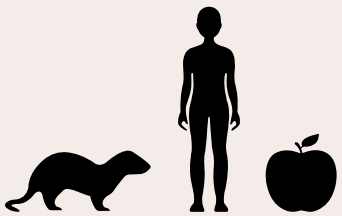
BARRY SCOTT AND DAVID PENMAN



AUGUST 2019

Nā te iahia kia titiro, ā,
ka kite ai tātou te mutunga.

You must understand the beginning
if you wish to see the end.



GENE EDITING: REFLECTIONS FROM THE PANEL CO-CHAIRS

BARRY SCOTT AND DAVID PENMAN

Random mutagenesis and selection in nature has underpinned evolution and diversity of all life and the resulting domestication of plants and animals. In modern times, advances in science and technology have allowed humankind to augment this natural process in increasingly sophisticated ways through selective breeding programmes and the use of techniques such as irradiation and chemical mutagenesis to enhance the rate of gene mutation.

The development of a number of DNA technologies, and our ability to sequence entire genomes, has opened the door to modifying specific genes to generate new traits and characteristics. The publication by Doudna, Charpentier and colleagues in 2012, demonstrating how a bacterial system for adaptive immunity called CRISPR-Cas9 could be engineered to precisely edit genomes, has set in motion a revolution in biology. It has been quite astounding how quickly laboratories around the world have adopted this new tool for applications across biology, from modifying plants, to altering insect development and potential treatment of some human diseases. The relative ease with which genomes can now be sequenced and edited has generated considerable excitement within the scientific community. However, it has also raised significant concerns about the social, legal and ethical issues raised by the use of the technology, none more so than the potential to edit genes in human embryos.

In response to these advances, many reports have been released and summits organised by academies and research organisations around the world to explain the technology, the context in which it is being used, the issues that arise for society, and the impact of these scientific advances on current regulatory frameworks. Prominent among these was the *"International Summit on Human Gene Editing"* organised by the US National Academies of Sciences and Medicine, the Royal Society (London) and the Chinese Academy of Sciences in late 2015 to discuss guidelines for the use of gene editing in humans.

These international reviews and summits have been immensely helpful in informing the public, researchers and regulatory bodies around the world, including New Zealand, and providing a framework for engaging internationally. However, New Zealand needs to have its own perspective given our unique cultural heritage and environment, the special challenges we face in maintaining our biodiversity and a viable and productive primary industry, and our unique regulatory environment. Furthermore, there has been no review of gene technologies in New Zealand since the Royal Commission on Genetic Modification held in 2001 and the subsequent amendments to the Hazardous Substances and New Organisms Act (1996). The field of genome science has advanced dramatically since then, especially the ability to sequence organism genomes and to manipulate those genomes in a very precise way.

ROYAL SOCIETY TE APĀRANGI GENE EDITING PANEL AND MĀORI REFERENCE GROUP

Royal Society Te Apārangi, as an independent science body, has a function under its Act to provide expert advice on important public issues to the Government and the community. In 2016, the Society initiated a programme of work to explore the implications of gene editing technology for New Zealand, motivated by the importance of this rapidly advancing science, the need to raise awareness of its potential applications, and to support informed discussion and debate about its implications for New Zealanders.

The first output of this programme was a short document entitled *"Gene editing. Evidence update"*, released in November 2016. This provided background on gene modification technologies and their evolution for the media, educators, policy makers and the public. Royal Society Te Apārangi then convened a multidisciplinary panel of experts, supported by a Māori reference group, to consider the social, cultural, legal and economic implications of gene-editing technologies for New Zealand. This paper outlines the approach of the panel and makes some concluding observations.

The panel was not asked to come to a view about the merits or otherwise of any particular application of gene editing. Rather, its role has been to provide information and resources that will allow others to have well informed discussions and debates. Indeed, one of the panel's main observations is that there is an urgent need for wide discussion and debate about gene editing within and across all New Zealand communities, as global research and development in applications of gene editing is continuing apace. Some countries are reviewing, or have already reviewed, their regulations in response to these developments.

The panel chose to consider the implications of the technology in parallel work streams using a range of scenarios in three areas: healthcare, environmental pest management and primary industries. The scenarios are illustrative – they are not panel recommendations for priorities for New Zealand application. They are presented in a stepped approach of increasing potential risk averseness and near and long-term benefits, to challenge and promote public engagement, and test the current regulatory regime. Each set of scenarios aimed to consider potential ethical, cultural and legal issues alongside the opportunities and potential risks and benefits. This approach proved to be a productive one for initiating a conversation with the New Zealand public.

Sitting behind the scenarios are technical papers that provide a more comprehensive overview of the research evidence base and implications for each of the three areas. These are fully referenced for readers to access the primary literature relevant to each area considered, and have been peer reviewed nationally and internationally.

New territory for Royal Society Te Apārangi was to enlist the support of a Māori Reference Group to assist the panel in capturing Māori views and approaches to assessing this technology. While the papers reflect particular ways in which some Māori would assess their use of gene editing technology, the panel observed wide diversity in views across both Māori and non-Māori communities.

PUBLIC FEEDBACK

Other innovations for Royal Society Te Apārangi in this process were the publication of material in a series of discrete work pieces over time rather than one large report, and initially publishing the scenarios in draft form to allow feedback. This enabled the panel to undertake a series of engagement workshops around the country to seek feedback and identify additional information that could be covered in the final technical papers. Senior school students attended some of these sessions and the panel invited informal comment via the Society's website. Two hui were specifically aimed at Māori communities.

This feedback process targeted testing the information in the documents for completeness and usefulness – undertaking a comprehensive national consultation was beyond the resources and mandate of Royal Society Te Apārangi and the panel. A number of themes were apparent from these interactions:

- For all three themes, there were views for and against the use of gene editing.
- In healthcare, there was an appetite to consider certain therapeutic gene-editing applications as long as it was safe enough to rule out negative side effects, and that it would enhance human health.
- In pest control, there was some appetite to consider gene drives for pest management if the benefits outweighed the risks. However, there were concerns over unintended consequences of removing species and around the risks of gene-edited pests finding their way back to their native countries.
- In the primary industries, comments on the benefits of using gene-editing technology included that it could provide a useful tool for supporting competitive advantage, and for protecting New Zealand's flora and fauna. There were concerns about unintended consequences, a need for better understanding of the relevant genetics, and that use of gene-editing technology would compromise the New Zealand brand and any "GM free" competitive advantage.
- Across all scenarios, feedback from Māori participants highlighted the importance of whakapapa and mauri, involving tangata whenua around indigenous species, protection of data, and intellectual property implications of gene editing taonga species.
- Royal Society Te Apārangi was criticised on occasions for appearing to take an advocacy position on gene editing through its publication of scenarios.
- The Society also received considerable positive feedback on undertaking the work and its use of scenarios. The society was often encouraged to lead a much wider engagement with communities given its independence and scientific standing.
- The panel has considered all the comments and incorporated additional information where possible into the final papers published.

CONCLUDING COMMENTS

The following are some closing thoughts on gene editing having explored a range of potential applications and their implications, and heard from a diverse range of interested communities.

Healthcare

Although the genetic changes proposed to achieve the outcomes in the scenarios are relatively 'simple' single-gene edits, gene editing potentially allows for multiple edits and much more complex scenarios than proposed in this discussion paper. However, the panel did not develop such scenarios, as our understanding of how multiple genes interact to determine a given trait is still rather poorly understood. Furthermore, the single gene editing scenarios developed proved to be a satisfactory approach to identifying the medical, legal and ethical considerations that need to be taken into account for implementation of gene editing approaches in healthcare.

While germline editing of embryos for research purposes is permitted in some countries, most, including New Zealand, have a ban on clinical uses of germline editing – that is changing heritable DNA. Despite these international guidelines, during the course of our work the reported editing of embryos to create two HIV-resistant babies by biophysicist He Jiankui in China this year has brought this issue into very sharp international focus. Furthermore, the fact that scientists aware of the work did not speak up highlights the need for a global framework under which human gene editing is carried out. Meanwhile, there has been a call for a global moratorium on clinical germline editing.

Pest control

This work piece provided an overview of the current state of gene drive technologies as potential solutions to the pest problems in New Zealand. Gene drives are a process that occurs naturally in some organisms, but which is greatly facilitated by deploying CRISPR-Cas.

Gene drives are a potentially useful technology for the eradication of pests given the need to widen the range of approaches if we are to achieve the goals of Predator Free 2050. However, they will not be a 'silver bullet' for pest control in New Zealand; controlling and containing pests in complex ecosystems is very challenging and will require deployment of a combination of technologies and management systems.

A number of risks and barriers, both biological and social, need to be addressed before such systems can be deployed in New Zealand. There is also growing international concern, such as expressed through the Convention on Biological Diversity and by the release of a report by the Sustainability Council in 2018 of potential negative consequences demanding that research must embrace public acceptance, cultural concerns, and legal issues before gene drives for pest control can be implemented. Furthermore, our relatively poor understanding of the reproductive biology and genetic systems of major New Zealand insect and mammalian pests, including wasps, possums, stoats and rats, precludes any rapid deployment of this technology.

Even with greater knowledge and technical ability to modify the genomes of these pest organisms, it was clear from the conversations held around these scenarios that there is a high level of risk averseness to using gene drives in the field. The challenge for New Zealand, given the significant potential for extinction of native species, is how we can achieve environmentally and socially acceptable solutions. The lack of scientific knowledge should not deter a focus on ongoing investment in long-term research in containment, to allow better understanding of the biology of New Zealand's pest organisms. This is a prerequisite for scientific breakthroughs needed to support development of acceptable solutions.

Primary industries

This paper was anticipated to be the most contentious given the history of the GM debate around crops and foods in New Zealand in the late nineties/early 2000s. The primary industries are a major part of New Zealand's economy and there are inevitable sensitivities to the impact of gene editing on offshore market perceptions in parts of the export sector. However, there is little publicly available independent evidence to inform conclusions about niche market impacts and their scope and complexity was beyond the remit and resources of the panel. Suffice to note that there are some strong views, as there have been in the past.

Although the single-gene edit scenarios proved useful for identifying issues around gene editing in the primary industries, most agriculturally important traits are determined by multiple genes rather than single genes. While gene-editing technology is sufficiently well developed to enable multiple gene edits, identifying which alleles (genotypes) to select and how they interact with one another to contribute to a particular trait (phenotype) remains a major technical challenge.

Legal and regulatory framework

Part of the panel's work was to assess the scenarios in the context of the New Zealand legal and regulatory framework. This resulted in a further paper on the regulatory system, which identifies a number of potential issues with the current framework, not the least of which is that it is becoming increasingly out of date given the advances in gene-editing technology.

The Panel would like to see a legal and regulatory system that is more future-focused and 'fit-for-purpose' by being easier to navigate, having clear and consistent definitions, and providing a better basis for assessing the risks and opportunities of particular applications of gene editing rather than focusing on the gene editing process itself. There is also an urgent need for a wide and well-informed discussion across New Zealand's diverse communities about preferences for the application of gene editing, in order to inform regulatory change.

The future

While publication of this panel's work has initiated the conversation on gene editing and identified many of the issues that arise, it is important that those conversations continue, as there are very significant social, legal and ethical issues associated with this technology. In particular, there needs to be meaningful engagement with Maori communities on the risks and potential benefits of these new DNA technologies, consistent with the principles of partnership, participation and protection enshrined in te Tiriti o Waitangi.

Many future valuable targets of gene editing will be traits, including common disease susceptibilities, which are influenced by many genes. Indeed, for some traits, thousands of independent genes have been implicated as having an impact. As single genes can also have effects on multiple different traits, there will be a fundamental need to deal with and understand the trade-offs inherent in modifying the genes for polygenic traits, with likely impacts on many other non-target traits, regardless of the precision and accuracy of the gene editing technology itself.

Genomic data is being increasingly used to study the genetic basis for human social and behavioural traits, including measures related to intelligence and educational attainment. In a future world where gene editing is routine, the potential risks in the misuse of the technology are high, and the ethical and moral challenges are manifold. Although these risks are currently remote, they will become more practically relevant as our tools for genomic manipulation become routine and precise, and cheaper to use.

Having said that, humankind has a history of successful adoption of new technologies that have the potential to enhance our health and sustain our wellbeing. Heart transplants and the introduction of IVF are two examples that were highly controversial when first proposed and which are now routinely available. Plant and animal breeding through genetic selection has made a major contribution to human wellbeing, and such innovations are never completely risk free. However, risks can be minimised and managed with well-designed, thorough, safe and transparent research programmes supported by the public. In the case of gene editing, there still needs to be a huge advance in the science and understanding of genetic architecture and the interconnectedness of different genes, if we are to realise its full potential.

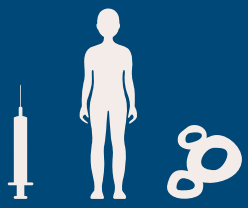
Finally, our sincere thanks to the members of the panel, the Māori reference Group, our legal advisers and all those that helped us develop and articulate the scenarios and their implications. Our hope is that the panel's work will be widely distributed and provide a useful resource for informing others' views on the implications and acceptable applications of gene editing technologies.

Ngā mihi maioha.

ROYAL SOCIETY TE APĀRANGI

GENE EDITING SCENARIOS IN HEALTHCARE

SUMMARY



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INTRODUCTION

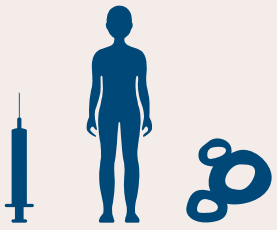
The revolution in gene editing technologies is making it easier to change genetic material, with potential benefits in many sectors including healthcare, agriculture and conservation. However, as a technology, gene editing is moving ahead of any consensus on how it should be used.

Royal Society Te Apārangi convened a multidisciplinary panel to consider the social, cultural, legal and economic implications of gene editing in Aotearoa New Zealand, incorporating Māori perspectives and broader cultural contexts.

To help you consider the potential use of gene editing in healthcare in New Zealand, this paper highlights four scenarios with different clinical outcomes, from treating disease to enhancing function and changes that would or would not be passed onto future generations:

- sickle cell anaemia
- breast and ovarian cancer
- cardiovascular disease
- improving athletic performance.

The characteristics of all living organisms are determined by their genetic material, or DNA.



WHAT IS GENE EDITING?

The characteristics of all living organisms are determined by their genetic material, or DNA. Genes are segments of DNA which provide the code for particular functions or characteristics.

Normally, when one strand of DNA is cut or damaged, it is repaired by enzymes which use the information in the other strand as a template. Gene editing uses this process but provides new repair information to change the DNA strand. By editing genes it is possible to make changes to organisms, such as changing the version of a gene from one that causes disease to one that does not.

A technique called CRISPR has increased the speed, ease and accuracy of gene editing. Modified from a system found in bacteria to cut up invading virus DNA, CRISPR is much more precise than earlier gene editing techniques. However, this ability to edit genes is, in many cases, ahead of our understanding of everything that different genes do, resulting in the possibility of unintended effects.

HOW IS GENE EDITING BEING USED IN HEALTHCARE?

Of the approximately 21,000 identified genes in the human genome so far, mutations in over 3,000 have been linked to disease. Gene-editing tools can now potentially be used to replace faulty or disease causing genes. For example, CRISPR has been used in mice to correct mutations in genes responsible for hepatitis B, haemophilia, cataracts, cystic fibrosis, and inherited Duchenne muscular dystrophy.

Gene-editing in the early stage embryo potentially allows those modifications to be passed on to future generations. Overseas, researchers have used CRISPR in human embryos to repair a gene defect that would cause a potentially deadly heart defect; modify genes responsible for ß-thalassemia, a potentially fatal blood disorder; and to modify genes in immune cells to develop increased HIV resistance.

SCENARIO SUMMARY

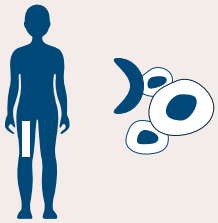
	TREATING TISSUE / ORGANS	TREATING EMBRYOS AND GAMETES
TREATING DISEASE	SCENARIO ONE | **PAGE 04** Gene editing bone marrow tissue to treat sickle cell anaemia	SCENARIO TWO | **PAGE 06** Gene editing an embryo to prevent the transmission of a cancer gene
ENHANCING CHARACTERISTICS	SCENARIO THREE | **PAGE 08** Gene editing the liver to reduce the risk of cardiovascular disease	SCENARIO FOUR | **PAGE 10** Gene editing embryos to improve athletic performance

SCENARIO ONE

GENE EDITING BONE MARROW TISSUE TO TREAT SICKLE CELL ANAEMIA

DISEASE

Sickle cell anaemia

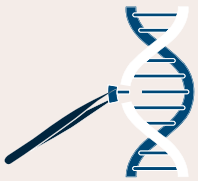


CELL TYPE

Bone marrow stem cell

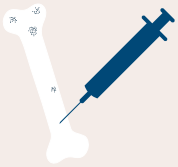
TYPE OF EDIT

Change to naturally occurring non-disease version of gene



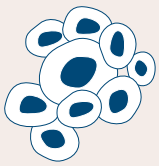
MECHANISM

Bone marrow transplant followed by viral vector and replacement stem cells



OUTCOME

Disease cured in individual



Medical considerations

Potential unintended edit of non-target areas of DNA.

Legal considerations

Edited tissue could be classed as a genetically modified organism under New Zealand law.

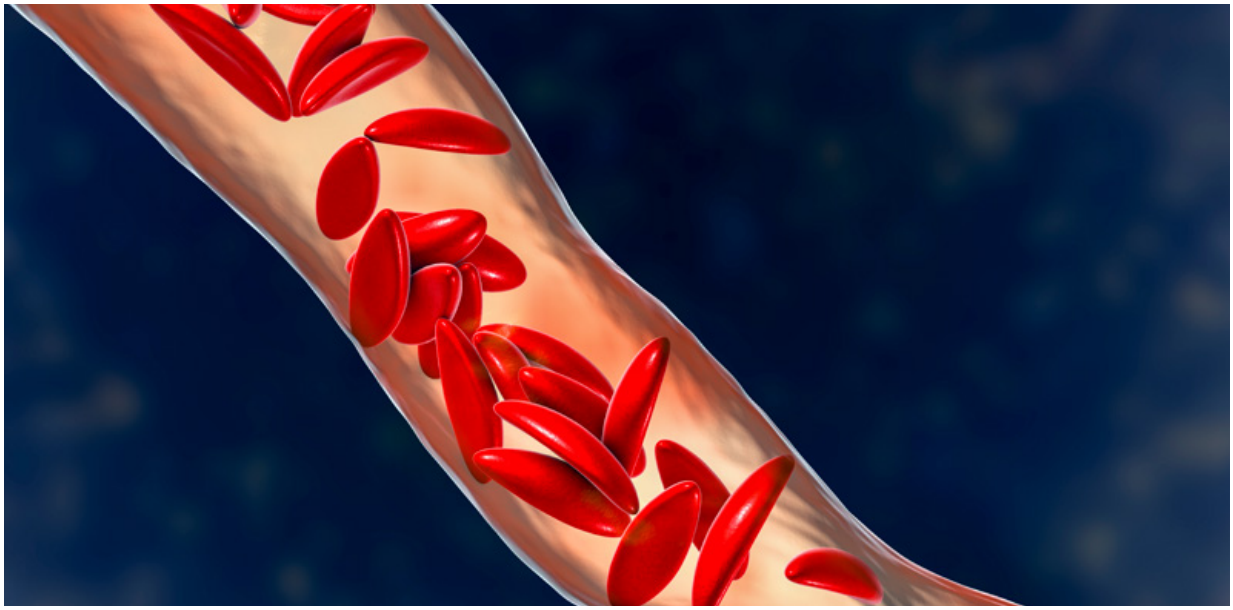
Ethical considerations

Likely to be acceptable if it provides significant benefits and has a reasonable prospect of being safe and effective. May align, or be in conflict with, Māori whakapapa.

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

Gene editing of tissues is limited largely by the ability to deliver the gene editing apparatus to the tissue cells and the efficiency of the gene editing itself.

Where editing can be performed outside the body on stem cell tissue, as with bone marrow, the technical challenges of modifying and then restoring edited cells to the patient are manageable. For other tissues, there are mechanisms that can deliver the gene editing apparatus with variable efficiency to tissues such as blood vessels, liver, eye and lung.

It is not necessary for every cell in the target tissue to be gene edited to achieve a desired clinical effect, as low levels of an otherwise absent or deficient gene product can be sufficient to cause the effects.

Risks and limitations

The frequency and consequences of unintentional editing of non-targeted genes are difficult to quantify but indications are that they are low enough to be clinically acceptable. Research is continuing to improve the efficiency of targeting.

Legal considerations

Approval of the technique by the Environmental Protection Authority (EPA), under the HSNO Act, will be required after delegation to the Director General of Health, to be assessed as a qualifying new medicine. Further, the treated tissue could be legally considered a new organism under the HSNO Act, and could require further approval by the EPA.

Ethical considerations

Gene editing of tissue to treat severe diseases controlled by a single gene is currently achievable and can be ethically acceptable if the treatment provides significant benefits to those for whom alternative therapies are limited, and if it has a reasonable prospect of being safe and effective, provided that patients are fully informed, and new treatments are subject to rigorous scientific and ethical review.

Sickle cell anaemia is a severe and debilitating disease. From that perspective, it would be hard to criticise a family wanting to use non inheritable gene editing to help afflicted people. Access to future treatment, however, would raise questions regarding public funding and equitable access to treatment.

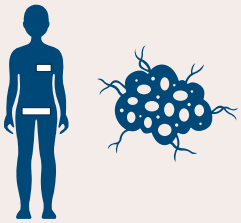
For Māori whānau, that decision may align, or be in direct conflict with, Māori values and aspirations for flourishing whakapapa into the future. The benefits of the procedure should outweigh the risks, and there should be direct benefits for participants and their communities from a Te Ao Māori perspective.

SCENARIO TWO

GENE EDITING AN EMBRYO TO PREVENT CANCER GENE PASSING TO OFFSPRING

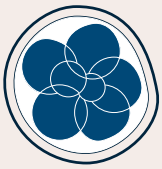
DISEASE

Breast and ovarian cancer (BRCA1 mutation)



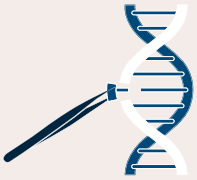
CELL TYPE

Embryos



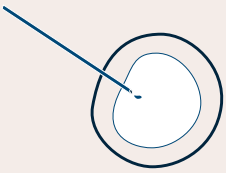
TYPE OF EDIT

Change to naturally occurring non-disease version of gene



MECHANISM

In vitro fertilisation and injection



OUTCOME

Reduced cancer risk in offspring

Medical considerations

Could also be achieved by selecting non-gene-carrying embryos through preimplantation genetic screening.

Legal considerations

A change in the law would be required under the Human Assisted Reproductive Technology Act, as it is currently prohibited.

Ethical considerations

The resulting person affected cannot consent, but considerations about the child's best interest can be made.

A 38-year-old woman with a family history of early-onset 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 variant to future generations, she proposes to employ in vitro fertilisation and to use CRISPR to revert any mutation-bearing embryos back to a version of the gene not associated with the disease.

Medical considerations

There are methods available to avoid the transmission of disease controlled by a single gene (like BRCA1) to offspring. For example, preimplantation genetic screening can be used to select an embryo not carrying the gene.

In addition, the probability of chromosome-linked disorders appearing in embryos is normally less than 100%, even when linked to the X chromosome (males only have one X chromosome). So embryos with non-disease conferring genotypes will be produced and could be selected for and re-implanted using preimplantation genetic screening.

Therefore, it is anticipated that the need to use gene editing to avoid recurrence of single gene genetic disorders in the context of IVF is likely to be very small. An exception would be where a male bearing a disease-associated mutation on his single X chromosome seeks to avoid the 100% inevitability that any daughter he conceives will be a carrier for his condition. Examples include haemophilia A and retinitis pigmentosa – a form of inherited blindness.

Although this might not affect their health, it does confer a reproductive burden. In this example, all embryos could be subject to CRISPR editing to revert the mutation-bearing gene back to a non-disease associated version.

Legal considerations

This treatment scenario would not comply with the definition of a medicine under the Medicines Act. Implanting into a human a genetically modified egg or sperm or human embryo is a Prohibited Action under the Human Assisted Reproductive Technology Act.

Ethical considerations

Gene editing an embryo will result in potential health advantages, or unintended and adverse effects, that will be inherited by future generations. This raises issues regarding 'intergenerational justice', or what we owe future generations.

Some view such changes as beyond what parents should be able to decide for their children, while others place a greater emphasis on the concepts of risk and benefits and believe that parents are morally required to undertake procedures that will enhance a child's wellbeing.

As the person who is affected cannot consent to the initiative, there is an obligation to not make a future person worse off than they would have been had the intervention not been performed.

There is an association between some disease-causing mutations in BRCA1 and Ashkenazi Jewish ancestry and it could be consistent with the values and aspirations of Ashkenazi (and other afflicted) family members to relieve their decedents of the risk of passing on this genetic condition through germline editing.

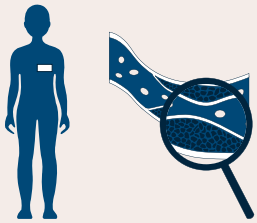
Where Māori embryos are concerned, it will be fundamental that culturally appropriate ethical processes that ensure the key values of whakapapa, tika, manaakitanga, and mana are upheld. In addition, careful consideration should be given to the pūtake or purpose of the 'manipulation' of whakapapa. It would be useful to consider the benefits of the procedure and whether those outweigh the risks. There should also be direct benefits for the participants and their communities.

SCENARIO THREE

GENE EDITING THE LIVER TO REDUCE THE RISK OF CARDIOVASCULAR DISEASE

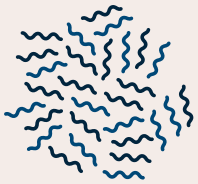
DISEASE

Lowering cholesterol (PCSK9 gene)



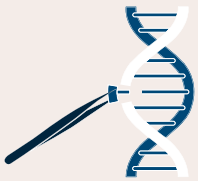
CELL TYPE

Liver tissue



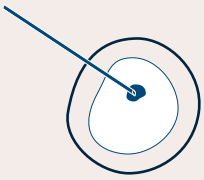
TYPE OF EDIT

Inactivation of existing gene



MECHANISM

Viral vector that targets the tissue



OUTCOME

Reduced disease risk in individual

Medical considerations

Switching off the gene may produce unintended effects.

Legal considerations

Edited tissue could be classed as a genetically modified organism. Approval by the Environmental Protection Authority under the HSNO Act required.

Ethical considerations

While this use would treat disease, targeting other genes (such as for eye colour) could confer social, rather than medical, benefits.

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 blood cholesterol.

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 (fats), have only been partially successful and have not prevented the death of several of his relatives at a young age.

Recently, he has read that naturally-arising mutations and deletions of the gene PCSK9 confer a dramatically reduced risk of heart disease by lowering blood lipid levels. Individuals with these mutations seem to have no other adverse clinical effects due to their PCSK9 genotype.

This man suggests that gene editing targeted to the liver where PCSK9 exerts its prime cholesterol lowering effect holds significant potential to prolong his life.

Medical considerations

This proposal differs 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.

Risks and limitations

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 balancing perceived risks and costs against potential benefits.

Legal considerations

This technique may be deemed a new medicine under the Medicines Act for a therapeutic purpose as long as it achieves its intended purpose. Approval by the Environmental Protection Authority will be required, after delegation to the Director General of Health, as a qualifying new medicine under the HSNO Act. The treated tissue could be legally considered a new organism under the HSNO Act.

Ethical considerations

Some would say that physiological enhancement of human characteristics to moderate disease states merges seamlessly with those that improve a person's functioning or capabilities. Whilst deleting particular genes, like those for PCSK9, can moderate disease properties, it is possible that similar, naturally-arising genomic events could confer desirable characteristics, e.g. for athletic potential or eye colour, without a medical purpose.

In this example, the enhancement aims to reduce the chances of developing a disease, and as such, it may be more similar to vaccination than, say, sports doping.

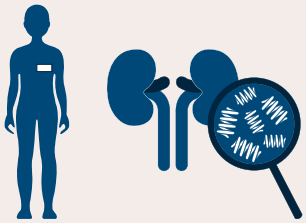
In a Māori context, careful consideration should be given to the pūtake, the purpose of the procedure, and decisions taken in full consideration of culturally appropriate ethical processes that uphold the key values of whakapapa, tika, manaakitanga, and mana. Any benefits should outweigh the risks, and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

SCENARIO FOUR

GENE EDITING EMBRYOS TO IMPROVE ATHLETIC PERFORMANCE

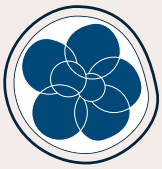
DISEASE

Increased erythropoietin production



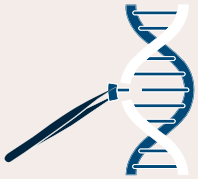
CELL TYPE

IVF in culture dish outside the body



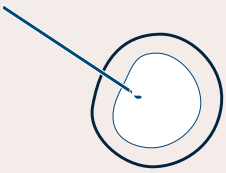
TYPE OF EDIT

Modification of gene



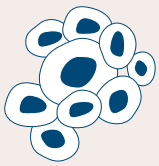
MECHANISM

In vitro fertilisation and injection



OUTCOME

Athletic enhancement in offspring



Medical considerations

Enhancing the gene may produce unintended effects.

Legal considerations

A change in the law would be required in the Human Assisted Reproductive Technology Act, as it is currently prohibited.

Ethical considerations

The resulting person affected cannot consent. Enhancements could create inequality or reinforce prejudice.

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 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 as a result.

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 a non-disease associated gene, you expect that the edited gene will exhibit unimpaired function, indistinguishable from naturally occurring genes.

When enhancements are proposed that confer new or modified functions to genes, then questions arise

and doctors would look for evidence that shows such edits produce no undesirable properties. The 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.

Legal considerations

This treatment scenario would not comply with the definition of new medicine under the Medicines Act. Implanting into a human a genetically modified gamete or human embryo is a Prohibited Action under the Human Assisted Reproductive Technology Act.

Ethical considerations

This modification seeks to move beyond human norms based on the parent's views of what contributes to an individual's well-being. Because a future child could enjoy a good quality of life without the intervention, any risks associated with making changes beyond human norms, rather than returning an individual's functioning to within human norms, carries additional significance.

Individuals are also free to choose how to live, regardless of their genetic endowment, and a future child may choose to indulge their enhanced athletic talents or may pursue other interests. Conversely, some unmodified offspring may resent their parents if they have not taken advantage of genetic interventions that they consider may enhance their life and well-being.

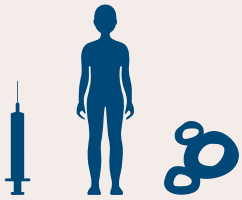
In addition, the physiological enhancement of human characteristics to improve a person's functioning or capabilities is cause for significant ethical debate. The impact of social and health inequality regarding access to potentially enhance the genetics of future generations needs to be considered to prevent uses which reinforce prejudice and worsen inequalities within and between societies.

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. 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.

ROYAL SOCIETY TE APĀRANGI

GENE EDITING SCENARIOS IN HEALTHCARE

AUGUST 2019



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ROYAL SOCIETY TE APĀRANGI

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

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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.

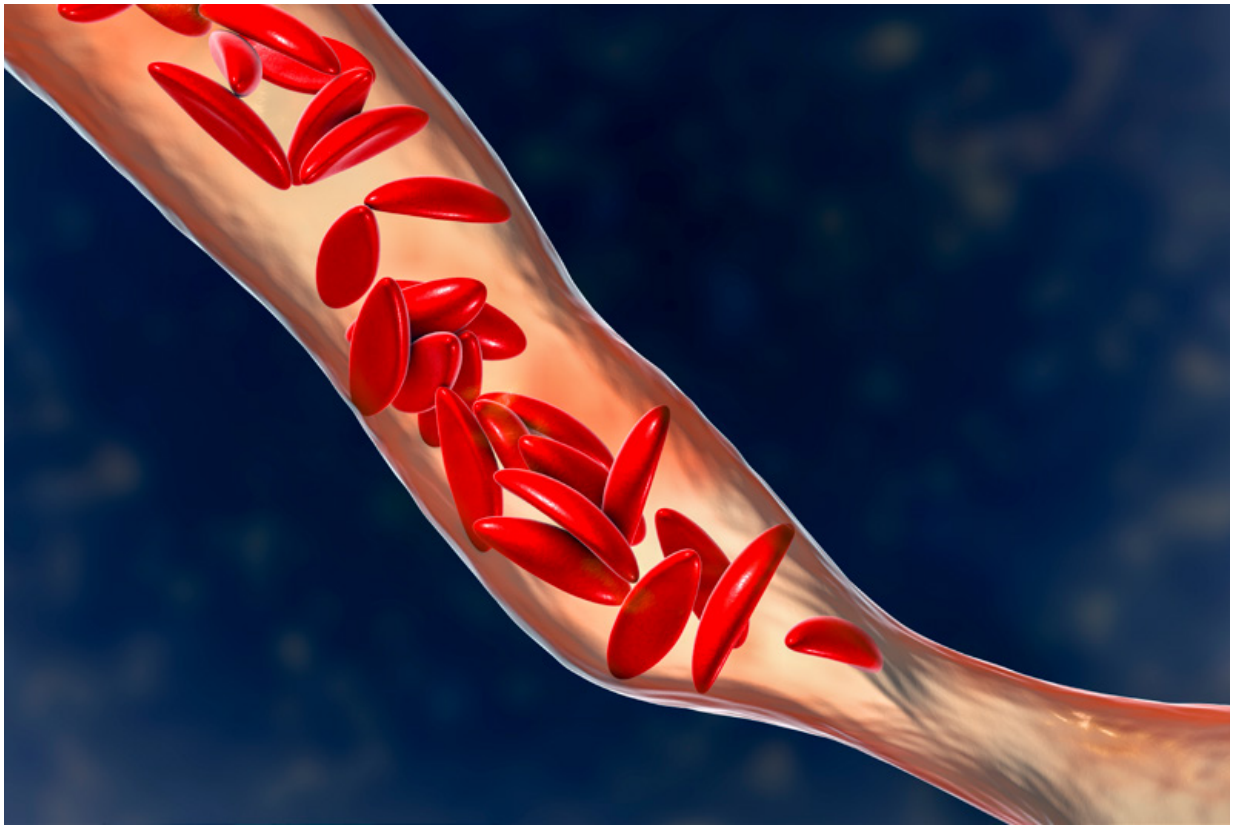
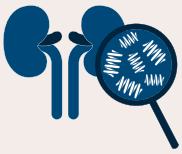


TABLE 1 | Description of four human gene editing scenarios

	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

Contributors to the technical paper

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The Society would like to thank the following experts for their valuable input in contributing to and commenting on the paper:

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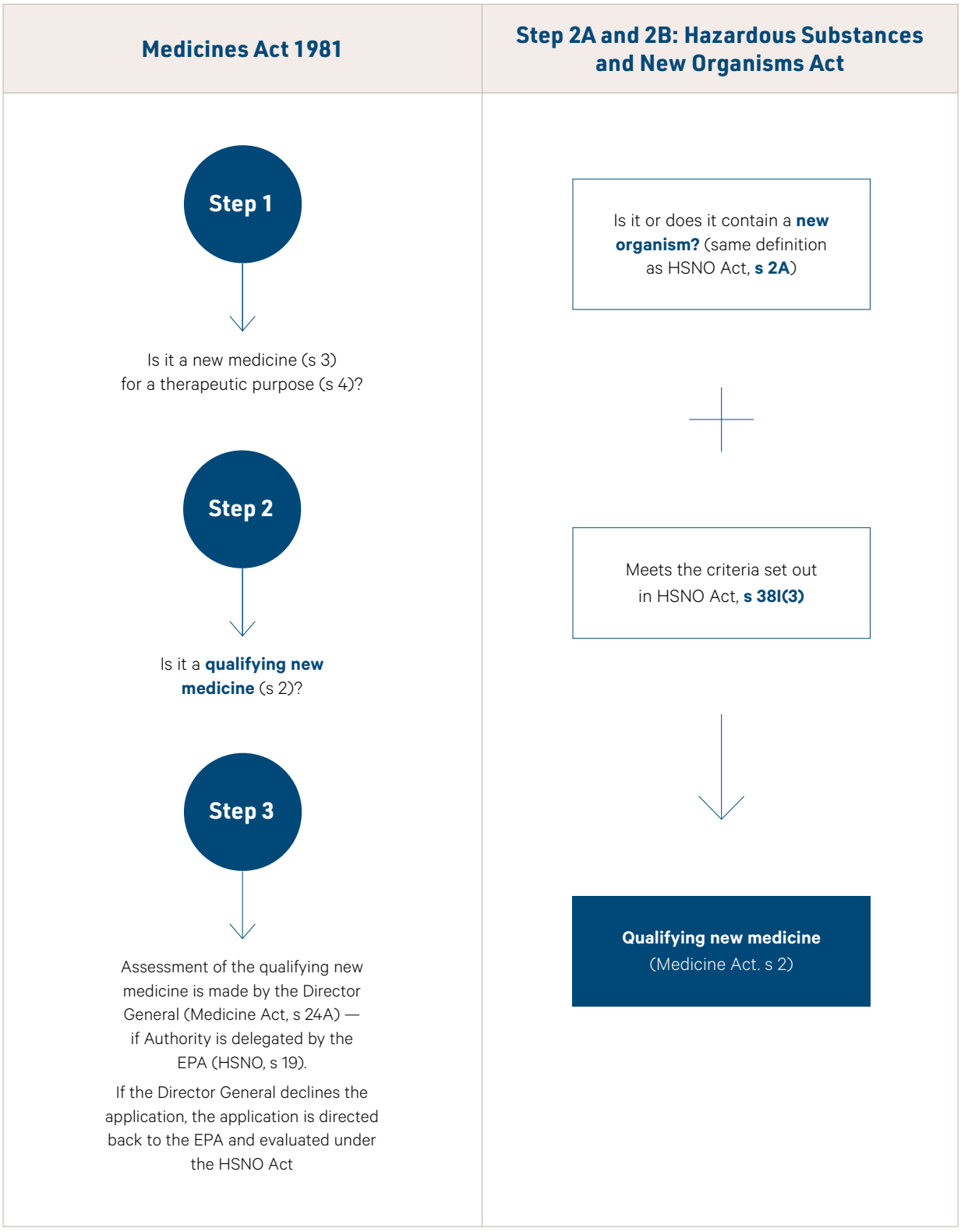
Professor Ian Alexander (University of Sydney, Australia), **Professor Rachel Ankeny** (University of Adelaide, Australia) and **Dr Sarah Chan** (University of Edinburgh, UK) provided independent international review of the paper.

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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ROYAL SOCIETY TE APĀRANGI

GENE EDITING SCENARIOS IN PEST CONTROL

SUMMARY

AUGUST 2019

EXPLORE | DISCOVER | SHARE

ROYAL SOCIETY TE APĀRANGI

INTRODUCTION

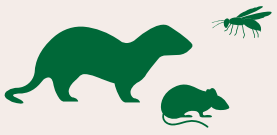
The revolution in gene editing technologies is making it easier to change genetic material with potential benefits in many sectors, including healthcare, agriculture and conservation. However, as a technology, gene editing is moving ahead of any consensus on how it should be used.

Royal Society Te Apārangi convened a multidisciplinary panel to consider the social, cultural legal and economic implications of gene editing in Aotearoa New Zealand, incorporating Māori perspectives and broader cultural contexts.

To help you consider the potential use of gene editing for pest control in New Zealand, this paper highlights three scenarios of using gene editing to create gene drives to control three types of pests:

- wasps
- possums
- rats and stoats.

The characteristics of all living organisms are determined by their genetic material, or DNA.



WHAT IS GENE EDITING?

The characteristics of all living organisms are determined by their genetic material, or DNA. Genes are segments of DNA which provide the code for particular functions or characteristics.

Normally, when one strand of DNA is cut or damaged, it is repaired by enzymes which use the information in the other strand as a template. Gene editing uses this process but provides new repair information to change the DNA strand. By editing genes it is possible to make changes to organisms, such as changing the version of a gene from one that causes disease to one that does not.

A technique called CRISPR has increased the speed, ease and accuracy of gene editing. Modified from a system found in bacteria to cut up invading virus DNA, CRISPR is much more precise than earlier gene editing techniques. However, this ability to edit genes is, in many cases, ahead of our understanding of everything that different genes do, resulting in the possibility of unintended effects.

HOW COULD GENE EDITING BE USED FOR PEST CONTROL?

Gene-editing tools have not been used to date in the conservation of wildlife, but their use in the control of non-native invasive organisms is being explored in the laboratory with the creation of sterile insects, and the use of 'gene drives'.

In 2015, researchers demonstrated how CRISPR could be used to develop gene drives, where edited genes 'drive' themselves and nearby genes through populations of organisms over many generations. In normal sexual reproduction, offspring inherit two versions of every gene, one from each parent. Each parent carries two versions of the gene as well, so chance (50:50) normally governs which particular variant of the gene that will be passed on. Gene drives ensure that the genetic changes will almost always be passed on, allowing that variant to spread rapidly through a population.

So far, gene drives are being developed in yeast, the fruit fly, mice, and two mosquito species, and could be used to drive a naturally occurring, or introduced, gene for sterility through a population.

SCENARIO ONE

INVASIVE WASPS IN NEW ZEALAND

SPECIES

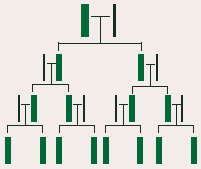
Vespula wasps

GOAL

Reduce fertility

CELL TYPE TARGETED

Germline cells (hereditary)

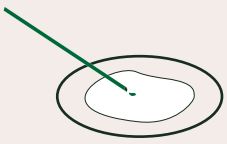


GENE EDIT

Gene switched off

MECHANISM

Embryo direct injection



OUTCOME

Pest numbers reduced

Environmental

Invasive wasps predate on native species such as caterpillars and spiders.

Technical / scientific considerations

Genetically modifying wasps has not been done before.

Legal considerations

Release of wasps with gene drives would require approval by the Environmental Protection Authority, under HSNO Act.

Ethical considerations

Risk that altered wasps could find their way back to Europe.

Two social (*Vespula*) wasps have been accidentally transported to New Zealand and become established here.

- The common wasp was first recorded in New Zealand in 1921 and became abundant in the 1970s.
- The German wasp became widespread and abundant in New Zealand after a major incursion in 1945.

They are both now distributed throughout New Zealand, with the common wasp as the dominant social wasp in beech forests.

The world's highest recorded densities of these wasps are observed in New Zealand, with up to 40 nests per hectare. Densities of workers have been observed to exceed 370 wasps per square metre of tree trunk.

The biomass of these wasps in honeydew beech forests has been estimated as similar to, or greater than, the combined biomass of birds, rodents and stoats. Their large densities exert intense predation pressure on native invertebrates. The direct economic impacts of wasps are largely associated with their predation of bees and associated hive robbing, with flow-on effects associated with lower rates of pollination in nitrogen-fixing clovers, which are important for the productivity of New Zealand pastures. In 2015, approximately 20% of beehive losses in the North Island were due to wasp attack.

Effective wasp control options currently are limited to small-scale operations involving pesticides or other chemicals (e.g. petrol). The use of toxins over large areas such as the 1 million hectares of beech forest currently overwhelmed with huge wasp numbers, is untenable. Prior attempts at biological control have been unsuccessful.

The development of a gene-drive to spread an infertility gene within the wasp population could be an additional tool that could be used to dramatically reduce their numbers.

Technical / scientific considerations

This has not been done before. It would require genetic changes, including the insertion of a CRISPR sequence into the genome of common or German wasps. Suitable genes for sterility would need to be identified.

Genetic modification of honeybees has been carried out, and given the similarities of social wasps and bees, it seems likely that this would be possible.

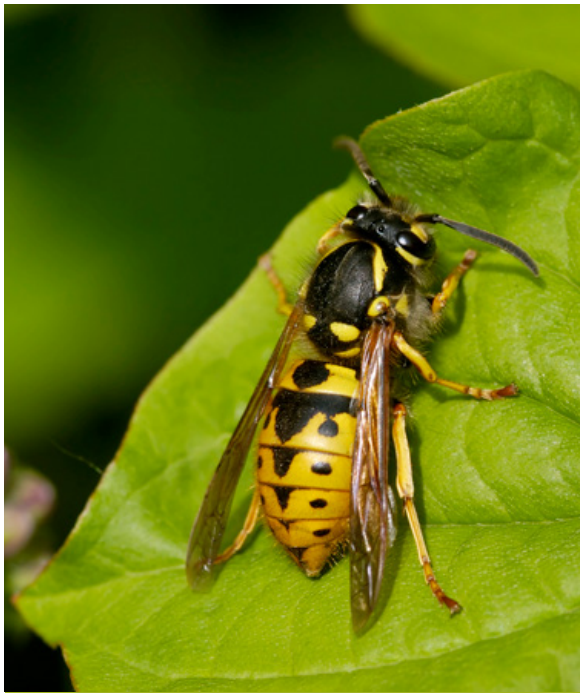
Wasps have a division of labour dependent upon whether they are reproductive or not. These features may have significant, unknown consequences for the inheritance of a gene drive system. In addition, over time resistance to the gene drive could develop in the wasp population, reducing its impact on their population.

Legal considerations

Inputs and outputs of gene drive techniques will be regulated by the Hazardous Substances and New Organisms Act (HSNO Act) if they come within the definition of an 'organism' and 'new organism' in this Act.

'Organism' is widely defined in the Act and includes a genetic structure (other than a human cell) that is capable of replicating itself. The definition of 'new organism' includes organisms belonging to species that were not present in New Zealand prior to July 1998 and Genetically Modified Organisms (GMOs).

The definition of a GMO is very broad (organisms whose genes or genetic material have been modified by *in vitro* techniques). Genetically modified animals are defined as new organisms under the HSNO Act, and therefore gene edited wasps would be classified as 'new organisms'.



Ethical considerations

While *Vespula* wasps in New Zealand are a critical pest, in their native European home areas they are valued and important components of the ecosystem.

Social wasps were not introduced deliberately to New Zealand, but have hitchhiked here, presumably in imported cargo. Given this route of introduction, any gene drive system must take into account the possibility that gene edited wasps might be transported to regions where these wasps are valued.

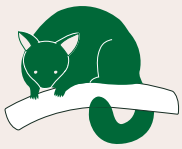
For Māori, considerations relate to various Māori values including whakapapa (of the organism, as well as the relationship/kinship between humans and other species), tika (what is right or correct), manaakitanga (cultural and social responsibility/ accountability, for example to other nations who value wasps), mana (justice and equity), tapu (restrictions), kaitiaki (guardianship) and whanaungatanga (valuing and supporting whānau).

SCENARIO TWO

BRUSHTAIL POSSUM IN NEW ZEALAND

SPECIES

Brushtail Possum

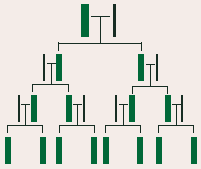


GOAL

Reduce fertility

CELL TYPE TARGETED

Germline cells (hereditary)

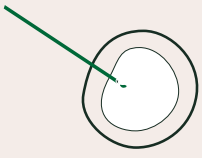


GENE EDIT

Gene switched off

MECHANISM

Egg cell direct injection



OUTCOME

Pest numbers reduced

Environmental

Possums are New Zealand's most significant mammalian pest.

Technical / scientific considerations

Genetically modifying possums has not been done before.

Legal considerations

Release of possums with gene drives would require approval by the Environmental Protection Authority, under HSNO Act.

Ethical considerations

Non-lethal means of pest control. Risk that altered possums could find their way back to Australia.

Perhaps New Zealand's most significant mammalian pest is the brushtail possum. This marsupial was first brought to New Zealand from Australia in 1837 with the aim of setting up a fur industry.

In New Zealand, the possum found an environment with few of the challenges of Australia and grew to plague proportions.

The possum eats plant matter, native birds and invertebrates, and is a carrier for bovine tuberculosis, and thus possum control is carried out for conservation and agricultural purposes.

Possum control costs the New Zealand government approximately $110 million/year, much of this spent on aerial distribution of poison baits. Other approaches, such as traps and bait stations, are also used. These methods are effective when animals are at high densities but become less effective as densities drop.

Gene drives and other genetic solutions may provide an opportunity to add another tool to the pest control 'toolbox' to achieve national eradication.

Technical / scientific considerations

Over the last twenty years knowledge of possum reproduction and genetics has increased.

One key challenge is the ability to genetically change the organism, a feat never achieved in a marsupial. To do so would require the generation of reasonable quantities (hundreds or thousands) of immature egg cells. Techniques for superovulation and implanting embryos into possums have been developed as part of a reproductive control approach to possums, and could be used to generate egg cells for manipulation.

If genetically changing possums were possible, there would be a need to identify what genes or processes should be targeted for a gene drive system. Little is known about functional genetics in marsupials. Several marsupial genomes have been sequenced, providing a resource for further genetic work, but understanding the function of marsupial genes is only making slow progress.

Over time, resistance to the gene drive could develop in the possum population, reducing its impact. The use of gene edited possums for gene drives to control wild possum populations would require very large numbers of altered animals to be bred and released (between 1 – 10% of the wild population).

Legal considerations

As for wasps, genetically modified animals are defined as new organisms under the HSNO Act, and therefore possums containing gene drive would be classified as 'new organisms'. As with wasps, risk assessments of organisms produced through gene drives are carried out under the provisions of the HSNO Act on a case-by-case basis by the Environmental Protection Authority.

Ethical considerations

From the perspective of the individual animal, some may argue that it has a fundamental right to respectful treatment, while others could argue that ecosystems and species have value in themselves and ought to be protected, even if it means violating the rights of individual animals to do it. Much hinges on the ecological impact of the removal of the pest animal.

One area of concern is around the control and containment of a possum gene drive. In Australia, brushtail possums are a protected species and an important part of many Australian ecosystems, so the spread of a gene drive that reduced possum fertility there would be most unwelcome.

To avoid such an incident we may require the means to turn off a gene drive, possibly through the introduction of a resistance gene, or the use of a 'daisy-chain' gene drive that runs out after a number of generations. However, the development of evolutionary resistance to a gene drives would also serve to diminish its impact over time.

For Māori, the ethical considerations would be similar to the previous scenario: whakapapa, tika, manaakitanga, tapu, whanaungatanga and mana. Implicit in those considerations would be the question of who stands to benefit from the introduction of a gene drive in this scenario; what the risks are to the ecosystems of other nations; and where Māori accountabilities lie in terms of the outcomes. There are also economic considerations: some Māori (and non-Māori) currently obtain income from possum control and/or fur sales. Such benefits will need to weighed against other outcomes, and are a potential consideration for Māori whose whānau are engaged in such activities (whānaungatanga).

SCENARIO THREE

STOATS AND RATS IN NEW ZEALAND

SPECIES

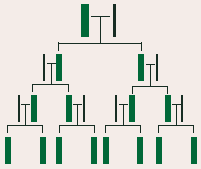
Stoats and rats

GOAL

Reduce fertility

CELL TYPE TARGETED

Germline cells (hereditary)

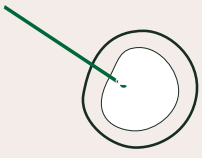


GENE EDIT

Gene switched off

MECHANISM

Egg cell direct injection



OUTCOME

Pest numbers reduced

Environmental

Rats and stoats predate on native species, such as birds.

Technical / scientific considerations

International efforts exist looking into rat gene drives, but less known for stoats.

Legal considerations

Release of rats and stoats with gene drives would require approval by the Environmental Protection Authority under HSNO Act.

Ethical considerations

Non-lethal means of pest control.
Risk that altered rats and stoats could find their way back to Europe.

Stoats are ferocious predators that do significant damage to many of our native bird populations, and have contributed to the extinction of five native species. There are three rat species in New Zealand: the ship or common rat, the Norway or brown rat and the Polynesian rat or kiore. Of the three, the ship rat is of greatest conservation concern, but they all predate native species

These pests are controlled in many different ways depending on the target species, including the widespread use of 1080 poison (sodium fluoroacetate), a metabolic poison most effective against mammalian pests. The use of this toxin remains controversial in some sections of the community, however, it is relatively cheap and able to be distributed from the air, providing a pest control tool for the rugged, heavily forested terrain that makes up much of New Zealand's conservation estate.

Other pest control measures include innovative new approaches to trapping, and the development of self-resetting traps. Current pest control measures are relatively expensive and take a lot of planning. Gene-drive solutions could provide another avenue for pest control.

Technical / scientific considerations

While New Zealand researchers have spent decades understanding the ecology, reproduction and, more recently, the genetics of possums, we are less well informed about many of these key issues for stoats.

One potentially promising avenue to explore is to harness the significant efforts made in understanding the reproduction and genetics of mink, a species valued for its fur, that is farmed in parts of the Northern hemisphere.

Unlike possums and stoats, rats are global pests and active efforts are underway to tap into international initiatives now aimed at establishing gene drive methods for the control of invasive rodents.

Rats are one of the best-studied mammals, so there is no shortage of knowledge on reproduction or genomics, although most of this knowledge comes from the Norway rat, a well-established model animal studied in laboratories that was among the first mammals to have its complete genome sequenced. Less is known about the ship rat, although it has just had its genome sequenced by a New Zealand team.

As with possums, the use of gene drives to control wild populations of rodents and stoats would likely require the breeding and repeated release of very large numbers of altered animals over large areas.

Legal considerations

As for wasps, genetically modified animals are defined as new organisms under the HSNO Act, and therefore stoats and rats containing a gene drive would be classified as 'new organisms'. As with wasps, risk assessments of organisms produced through gene drive are carried out under the provisions of the HSNO Act on a case-by-case basis by the Environmental Protection Authority.

Ethical considerations

Gene drives offer a control method that is less harmful at an individual level than conventional pest control methods, which usually involve killing the animal. However, this is dependent upon being as harmless as possible in its effects on any ecological changes the gene drive brings.

Globally, while rats are pests in many contexts, they are also important providers of key ecosystem services such as pollination or as critical elements of ecosystem food webs.

Eradicating rats in New Zealand, where our ecosystems were free of rodents up until human arrival around 800 years ago, may have few knock-on effects. However, in other parts of the globe the effects on natural systems might be very different. Rats are very good invaders, disperse well, and hybridise with closely related species, making accidental release and spread of gene drive modified rats a serious consideration.

Similarly, stoats are an important animal in northern European ecosystems, so even the prospect of such an incident will mean the need for a means to turn off any gene drive.

The key ethical considerations for Māori in this scenario will overlap with those in the previous scenario, with the exception of the kiore, which for some iwi at least, is a taonga. As such, the kiore has a whakapapa (relationship) involving humans that predates European arrival and thus is of significance for Māori. Efforts to eradicate this particular species would not be accepted by at least some hapū and iwi.

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GENE EDITING SCENARIOS IN PEST CONTROL

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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.

As a technology, gene editing is rapidly 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 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 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 current and new issues needing to be clarified or resolved
- show where gene editing applications are covered by established policies and regulations and where changes are needed
- provide a New Zealand perspective to the global discussion on this technology and identify where global consensus is important.

This paper is one 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 [1].

To help consider the implications for pest control in New Zealand, this paper[2] examines the potential impact of one particular use of gene editing, gene drives, and highlights three scenarios which raise specific considerations for three different types of pest. In particular, these case studies consider:

- the range of scientific complexities of developing a gene drive for different organisms
- the implications for the spread of animals with the gene drive to different countries.

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

[2] Derived from [2.Dearden, P.K., et al., *The potential for the use of gene drives for pest control in New Zealand: a perspective.* Journal of the Royal Society of New Zealand, 2017: p. 1-20].

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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

The last two decades have seen a substantial increase in our knowledge and ability in genetics. Researchers have now developed tools, chief among them being CRISPR,[3] to enable the manipulation of specific genes within an organism's genetic material with greater and greater precision in the modification process, and fewer and fewer unintended changes elsewhere in the genome (see box 1). With their wide availability and simplicity, these gene editing technologies are now being used to significantly accelerate research, and offer new treatments for a range of genetic diseases, while new agricultural products are beginning to be commercialised. However, alongside the development of the technology, the implementation of genetic engineering, or genetic modification, has raised ethical and values-based questions in many societies.

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)[3]. In 2012, it was discovered that, by modifying this mechanism, it was possible to target and cut any DNA sequence and edit genomes in a very precise manner [4]. 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 [5,6].

Modern advances in gene editing technologies now provide potential novel solutions for the challenges of pest control through the development of gene drives [7-10]. Much of the research on gene editing of pests published to date has concentrated on species that cause human diseases [11-15]. However, as researchers begin to understand and consider the use of gene editing techniques in pest control, more and more species are being considered as potential targets, from agricultural pests [16] to unwanted predators.

New Zealand has unique requirements when it comes to pest control [17]. New Zealand's natural and agricultural environments are beset with pest species, imported deliberately or accidentally. Pests range from mammalian omnivores such as the brushtail possum [18-21], which impact our native birds and their food sources, through to a wide assortment of predators such as rats, cats, stoats and ferrets, and insect predators such as *vespulid* wasps [22]. Weeds increasingly impact our ecosystem structure and integrity [23] and the recent discovery of the fungal disease myrtle rust threatens many native and valued plant species. Our marine and freshwater ecosystems are also threatened by pests such as sea squirts [24], koi carp [25] and invasive algae [26]. Our agricultural production ecosystems are threatened by crop and pasture pests such as leafroller moths and Argentine stem weevil [17], and weeds such as ragwort and dock. New Zealand also actively maintains a biosecurity cordon to inhibit the colonisation of our islands from new pest threats. Major biosecurity threats from pests include fruit flies (e.g. Queensland fruit fly and the Mediterranean fruit fly), the brown marmorated stink bug and lymantrid moths such as the gypsy moth.

Within our native ecosystems, intensive poisoning and trapping has been undertaken for many mammalian pests. As a result of their control, it is now known that these ecosystems rebound well after key pest suppression and removal [27-30]. In many places in New Zealand, including offshore islands [28, 29], isolatable peninsulas and predator-proofed ecosanctuaries, predators have been eradicated. The benefits of control to native wildlife have been immense, even extending outside such sanctuaries.

[3] CRISPR in this paper is being used to refer to the CRSIPR-Cas9 gene editing technique. Other gene editing techniques include Zinc-finger nucleases (ZFNs) and TALENs (transcription activator-like effector nucleases).

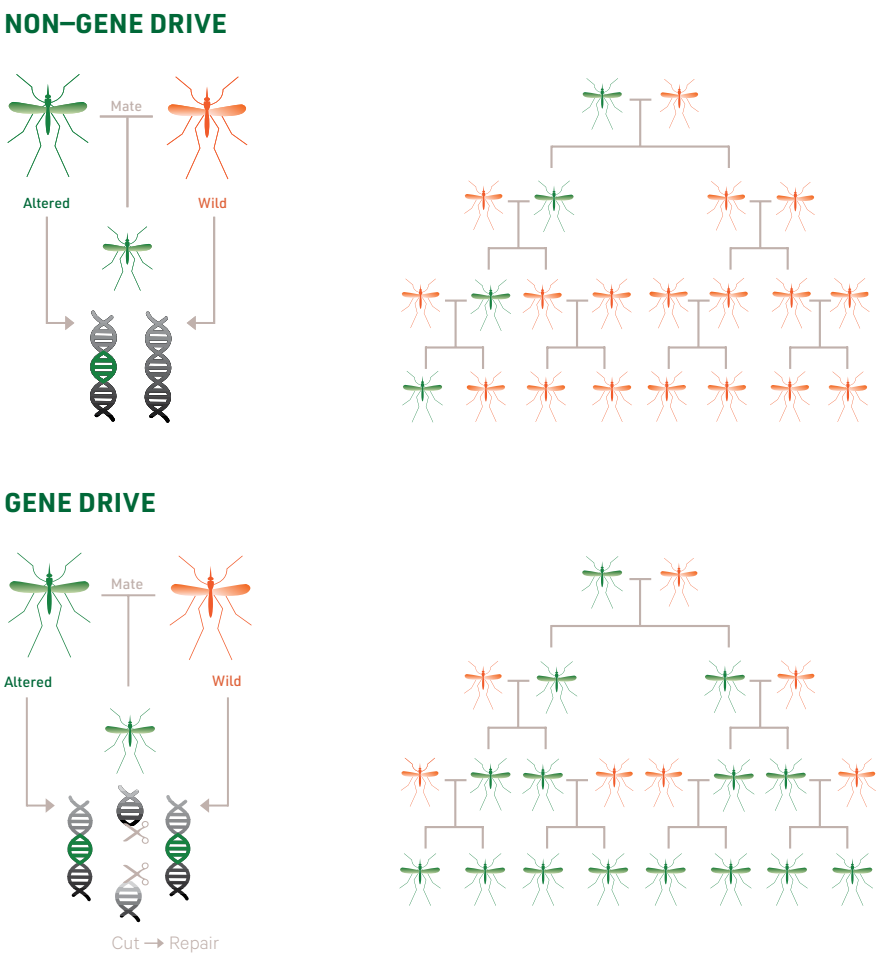
The Zealandia ecosanctuary in Wellington has increased native bird life in the surrounding city to the point that a rare native parrot, the kākā, is considered by some to be becoming a local pest species itself [31]. New Zealand agencies have cleared many offshore islands of pests, including the removal of Norway rats from the 11,000 hectares of Campbell Island. New Zealand's expertise in this area is well recognised internationally [32].

New Zealanders understand the risks they face from invasive species, both economically and environmentally. To achieve significantly reduced impacts, greater diversity will be needed in available management tools. This has been accentuated by the recently announced goal to make New Zealand predator-free by 2050, with a focus on mammalian pests in natural ecosystems, where the challenge is to achieve landscape-level eradication. New Zealand is already at the forefront of developing new pesticides, trapping technologies and biological control technologies, as well as using Trojan females and sterile insect techniques [33-35] (described below).

What are gene drives?

CRISPR gene editing can be used to create a 'gene drive' to spread a gene rapidly through generations. In sexual reproduction, one set of chromosomes is provided from each parent and combined in their offspring. If one set of chromosomes contains a 'gene drive', it will cut the partner chromosome that lacks the gene drive and copy itself onto this chromosome. In this way gene drives are a genetic system with the ability to 'drive' themselves and nearby genes through populations of organisms over many generations [1]. For example, in normal sexual reproduction, offspring inherit two versions of every gene, one from each parent. Each parent carries two versions of the gene as well, so chance (50:50) normally governs which particular variant of the gene will be passed on. But 'gene drives' ensure that a certain gene will almost always be passed on, allowing that variant to spread rapidly through a population (see Figure 1). In this way it would be possible, for example, to spread a gene that suppresses fertility in females in a pest species population.

FIGURE 1 | Pattern of inheritance of a gene drive in mosquito population [1]



The science behind gene drives

Scientists have been observing examples of biased inheritance generated by natural gene drive mechanisms for many years [36]. The concept of a 'synthetic gene drive' was devised around 50 years ago by Christopher Curtis, who proposed using rearrangements of genetic material to drive genes into wild species [37]. This idea was then further developed by Austin Burt in 2003, who described how gene drive systems could be an efficient means for population suppression of pest insects [38].

A gene drive is a gene which creates an enzyme which cuts both strands of DNA within a targeted area of the genome and is copied across because of naturally occurring DNA repair systems. Such DNA repair systems are a 'rescue process', whereby an organism with a double-stranded break in its DNA will try to repair that break by copying any similar sequence it can find in the cell [39]. In the case of the gene drive cut, this leads to the gene drive being copied into the gap made by the gene drive itself. This then leads to inheritance of the gene drive to all offspring and is the basis for the gene drive mechanism [38]. To be useful for population suppression, the targeted area for the gene drive should be within a gene essential for viability or fertility of the pest organism. Modelling has shown that suppression is particularly efficient if the gene drive is targeted to a gene essential for females but not males, or to a gene required for germ-cell development or reproduction in one sex [38, 40].

The implementation of this system in the past has been hampered by the difficulty in modifying the gene drive to recognise a specified site within a specific genome [41] using previous genetic modification technologies. While not a gene drive tool in its own right, the advent of CRISPR technologies [42] has given new life to the gene drive idea. CRISPR makes use of a bacterial system that allows cells to cut invasive DNA that has been encountered previously [43]. The system consists of a cutting enzyme that can be targeted to any sequence using a small RNA sequence, called a guide RNA [43]. The combination of the DNA cutting enzyme and specific guide RNA that guides the enzyme to a particular sequence provides the technology the ability to cut and target the sequence required [44-45. In bacteria, the guide sequence is derived from an invading virus or other organism. However, the guide sequence can be almost any sequence at all. Using a guide RNA to target a specific sequence in a pest genome, a gene drive mechanism created using CRISPR is easily able to target and modify a specific site in a specific gene [46].

To illustrate a gene drive system, consider the situation of a release of a few genetically modified insects that carry a dominant fluorescent protein marker gene. All the offspring from mating between the fluorescent genetically modified insects and wild type (non-fluorescent) insects will be fluorescent, as the fluorescence gene is a dominant one. Most likely these insects will mate with the numerous wild type insects in the environment. From these matings, in the absence of a gene-drive, only half of the offspring will show fluorescence because of normal patterns of inheritance. In the following generation, following Mendelian inheritance, even fewer of the population will show fluorescence because crossing with non-fluorescent wild type insects again only result in half the offspring carrying the fluorescence gene (represented in Figure 1). Now consider a release of a few insects carrying the fluorescent protein marker gene linked to a gene drive. As for the original non-gene-drive release, all the offspring from matings with wild type insects will be fluorescent, as they will carry the dominant fluorescence gene. In the genome of this first generation, the gene drive will cause a cut in the chromosome that does not contain the fluorescence gene and the insertion of a copy of the gene drive with the fluorescence gene. This repair process is likely to be near 100% efficient; all the gametes will contain a chromosome with the gene drive and the linked fluorescence gene. Thus, when the first-generation insects mate with wild type insects, all the offspring in this second generation will also be fluorescent. Further generations will continue to lead to the marker gene being driven into all offspring (see Figure 1).

Assuming that carrying the gene drive and marker gene have no negative effects on the animal's fitness in being able to pass its genes to the next generation, a 1% release could theoretically lead to 99% of the local population carrying the marker gene after just nine generations [38,40]. For population suppression, the gene drive would alter an essential gene, perhaps a gene essential for, for example, female development or fertility [38].

Evolutionary resistance to gene drives

The promise of gene drives lies in their inherent ability to rapidly spread a target gene in a very short period of time to generate a desired effect on a population. If all individuals within a population are susceptible to the gene drive, then it is predicted that it will rapidly spread. However, substitutions, insertions or deletions within the DNA targeted by the gene drive that occur during gene drive mediated DNA cutting can lead to a resistant version of the gene [8]. Most cells also have an alternative pathway for repairing double-stranded breaks, known as non-homologous end joining (NHEJ) [121]. With NHEJ, the broken ends of DNA are fused together without regard to matching similar sequences. Errors during this repair process can lead to small deletions or insertions in the genetic code, called mutations. In many cell types, this type of repair can outnumber repairs that copy similar sequences in the cell. A NHEJ mutation of the gene drive recognition site would suppress its targeting accuracy [38].

Because many resistant versions of the gene will have greater Darwinian fitness than the gene drive gene, population level resistance to the gene drive is expected to appear [8]. In fact, this is what was observed in the laboratory-based gene drive experiments on *Anopheles gambiae* mosquitos [14] and *Drosophila* [122].

In addition to the gene drive process itself generating resistant versions of the gene, it is also predicted that many pest species will harbour pre-existing genetic variations resistant to the gene drive construct. For example, measurements of genetic variation in *Anopheles gambiae* across Africa through whole genome resequencing [123] found that approximately half of the potential gene drive target sites had variants in the wild that would disrupt targeting by the gene drive construct. However, the genetic variation in invasive pests that have spread from a recent introduction of a few individuals may be much lower because of the drastic genetic bottleneck the population has gone through. For this reason, gene drives may work much better on invasive pests than on endemic populations.

How can resistance be overcome? Detailed population genomic surveys of the target pest species would need to be employed to assess variation across all potential gene drive target sites. Ideally, this would include whole genome resequencing to detect the presence of variants across potential target sites. Such data would also yield information to guide the identification of alternative target sites in the same gene or alternative genes. This approach would also have the advantage in aiding the prediction of off-target effects. Large numbers of individuals would need to be assayed, as resistant versions of genes are expected to be strongly selected for, even from very low initial frequencies [8]. Based on the population genomics results from *An. gambiae* [123], gene drives are unlikely to work unless multiple genes and multiple target sites within those genes are targeted. Increasing the number of target sites in the genome leads to a corresponding increase in the probability of off-target effects with the associated safety and ethical concerns. The use of multiple guide RNAs could also be used to target a wide range of gene variants [14]. Again, this approach requires detailed knowledge of gene variation. A further approach could be to target a conserved region of a biologically essential gene [46].

Another implication of this resistance is that intentionally releasing a resistant gene into a population could be an effective means of reversing the effects of a gene drive [124].

Scenarios for the use of gene drives for pest control in New Zealand

In view of the challenges around economically sustainable, effective nationwide pest eradication, the potential of genetic technologies, such as gene drive systems, could be evaluated. In this review, a series of scenarios is used to examine the potential from such approaches for the control of three key pests in New Zealand. All three scenarios, outlined in Table 1, are discussed in terms of the pest control opportunities they present, along with technical, social and legal ramifications.

In considering the scenarios, it should be recognised that the generation time of target organisms will substantially affect the efficacy of gene drives with regard to both the time needed to achieve population level change and for evolutionary pressures to arise that may deactivate them. On this basis, the feasibility of controlling insect pests would be higher than rodents, which in turn would be higher than for possums and stoats.

TABLE 1 | Three gene edited gene drive scenarios for pest control in New Zealand

	SCENARIO 1 **Insect**	SCENARIO 2 **Possums**	SCENARIO 3 **Rodents and stoats**
 **Species**	 **Vespine wasps, Argentine stem weevil, Australian sheep blowfly**	 **Brushtail possums**	 **Stoats and rats**
Aim	Eradication	Eradication	Eradication
Justification: Conservation, Agriculture or other	Conservation and Agriculture: Wasps attack native birds and insects and deplete critical food resources	Conservation and Agriculture: Predator of native birds and invertebrates, eats native plants, carrier of bovine TB	Conservation and Agriculture: Predator of native birds and invertebrates, eats native plants, carrier of diseases
Genetic target	Fertility or sex ratio	Fertility	Fertility or sex ratio
Nature of gene editing	Inactivation of gene	Inactivation of gene? (not yet known)	Insertion of new gene? (not yet known)
Affects target individuals or passed on to future generations	Passed on to future generations	Passed on to future generations	Passed on to future generations
Method of transmission of CRISPR gene edit: Virus, bacteria, compound, other	Direct injection into embryo	Direct injection into egg cell	Direct injection into egg cell
Are non-naturally arising genes introduced into the genome?	Yes	Yes	Yes

SCENARIO 1

Insect pests in New Zealand

Environmental rationale for control

Two colony-living social wasp species in the genus *Vespula* were accidentally imported into New Zealand and became established here. These colony-living wasps are different from the many solitary species of wasps native to New Zealand, which have evolved here with other insects and plants over thousands of years, and have never been considered a nuisance. The common wasp (*V. vulgaris* (L.)), however, was first recorded from New Zealand in 1921 and became abundant in the 1970s [22]. The German wasp, *V. germanica* (F.), became widespread and abundant in New Zealand after an incursion in 1945 [47]. These Vespine wasps are both now distributed throughout New Zealand, with the common wasp as the dominant social wasp in beech forests [48]. They are especially abundant wherever there are large quantities of honeydew produced by scale insects. This honeydew provides considerable carbohydrate food resources and is plentiful in approximately a million hectares of native beech forest [49]. The world's highest recorded *Vepsula* densities are observed in New Zealand, with up to 40 nests per hectare [50] and numbers exceeding 370 wasps per square metre of tree trunk [51]. The biomass of *Vespula* in honeydew beech forests has been estimated as similar to, or greater than, the combined biomasses of birds, rodents and stoats [52].

The extreme abundance and effects of both these wasps have resulted in them being listed among '100 of the World's Worst Invasive Alien Species' [53] and as a 'critical issue' for New Zealand entomology [54]. Their large densities exert intense predation pressure on native invertebrates. For example, vulnerable species of native caterpillars were observed to have almost no chance of surviving to become adults during times of peak wasp population densities [55]. Similarly, the probability of an orb web spider surviving until the end of a wasp season is effectively nil [56]. They are strong competitors with native predators [57], and these competitive effects over a short evolutionary period may have even altered the morphology of native species [58].

Economically, a recent analysis suggested these wasps annually cost approximately $133 million to the New Zealand economy [59]. The direct economic impacts of wasps are largely associated with their predation on bees, with flow-on effects associated with impacts on pollination (in 2015 approximately 20% of beehive losses in the North Island were due to wasp attack [60]). This economic review also suggested wasps have substantial impacts on animal health, forestry, arable farming, horticulture, tourism, human health and even traffic crashes [59]. Wasps are one of the most dangerous and lethal animals for humans, and they periodically kill New Zealanders; approximately 1,300 people per year are estimated to seek medical attention as a result of wasp stings throughout New Zealand [61, 62].

Current control options

Effective wasp control options are currently limited to small-scale operations involving pesticides or other chemicals (e.g. petrol). These pesticides may be effective on relatively small scales but the use of toxins over large areas such as the 1 million hectares of beech forest currently overwhelmed with high wasp numbers is impractical. Prior attempts at self-sustaining options that would be suitable for such large areas, such as biological control, have been unsuccessful [48, 63].

Potential future approaches

A variety of additional and 'next-generation' pest control approaches have been proposed and are being developed for wasps, funded through New Zealand's Biological Heritage National Science Challenge. These approaches include the use of the Trojan female technique, which utilises the release of females with naturally occurring mitochondrial DNA defects that cause male infertility, and is seen as a novel and humane approach for pest population control [33]. Other approaches in the National Science Challenge include gene silencing[4] technologies, the use of pheromones for mating disruption, which require annual replacement and use at each site, or biological control options [61]. These can all form part of a 'toolbox' approach that can be used in combination. The individual limitations of each approach highlight the need to expand the 'toolbox' to discover and refine new technologies based on a good biological understanding [17].

Another potential approach is the sterile insect technique, which involves the release of large numbers of sterile insects that mate with an established insect population, leading to an effective reduction in that

[4] A gene silencing pesticide uses double stranded RNA to prevent the operation of targeted genes, and is applied as a pesticide.

population. In these techniques, some of which use genetic modification to create the sterile insects, a huge number of insects must be released to ensure that matings with sterile insects are more common than those between unmodified fertile insects. The sterile insect technique has been an effective approach for eliminating screw-worm, medfly and the Mexican fruit fly [64], and has recently been used to control mosquito populations in Brazil [65]. This technology has not been used broadly in New Zealand [66], perhaps because of the large number of insects needed for release, and the large cost associated with their production. In addition, social insects have only one reproductive individual per colony and so the impact for wasps of introducing a large number of sterile males in the region is uncertain.

Technical/scientific considerations of gene drives

The development of a gene drive system in wasps using CRISPR faces a number of challenges. Current gene drive methods would require genetic modification of the common or German wasp genome, a technology not previously developed. Genetic modification of honeybees [67, 68] using CRISPR-based approaches has been carried out, and, given the similarities of social wasps and bees, it seems likely that this technical barrier will be able to be overcome. In both cases, microinjection of honeybee eggs or larvae was required to achieve transformation [67, 68]. Some understanding of the basic biology of wasp embryos will also be required for transformation to be achieved.

Another set of barriers to the development of gene drives in wasps is the nature of wasp genetics and their social organisation. Vespine wasps genetically are quite unlike other pest species already targeted by gene drive systems. These wasps, like many wasp species, have haplodiploid sex determining systems, meaning males are haploid (have one copy of their genome) and females are diploid (have two copies). Males develop, like clones, from unfertilised eggs laid by the queen. The alternative haploid and diploid generations may have significant, unknown consequences for the inheritance of a gene drive system.

The social organisation of the wasp hive, with a single queen and non-reproductive workers, is also a critical factor in the development of a gene drive for these species. Rather than the approach used in mosquitoes of trying to spread a gene drive that damages reproductive fitness in a population [11, 14], a gene drive system might fail if queens made defective by a gene drive system do not spread their genes, ensuring the gene drive will be rapidly removed from the population with little pest-control benefit.

Containing complex eusocial insect species (i.e. those with different worker castes, overlapping generations and cooperative care for their young) is challenging and so it seems likely that computer modelling will be required to assess the potential impact of a gene drive system in a vespine wasp species, and to determine the optimum efficiency of a gene-drive approach in achieving wasp extinction. Computer modelling will also be required to understand how many modified wasps might need to be released, and where, to have the most significant effect.

International considerations

While *Vespula* wasps are a critical pest in New Zealand and elsewhere, in their native European range they are valued and important components of the ecosystem. Social wasps were not introduced deliberately to New Zealand, but have hitchhiked here [47], presumably in import cargo. Given this route of introduction, the use of any gene drive system must take into account the possibility that modified wasps might be transported to regions where these wasps are valued. While New Zealand would greatly benefit from eradication of these pests, their extinction here must not mean global extinction of the entire species.

Regulatory considerations

Genetically modified organisms are defined as new organisms under the HSNO Act, and therefore wasps containing gene drive systems would be classified as 'new organisms'. Risk assessments of organisms produced through gene drive systems would be carried out under the provisions of the HSNO Act on a case-by-case basis by the Environmental Protection Authority. Importation of wasps with gene drives would also be regulated under the Biosecurity Act 1993.

Other possible insects of focus

Argentine stem weevil

Arthropod pests include such species as the Argentine stem weevil (*Listronotus bonariensis*). The Argentine stem weevil is native to Brazil, Uruguay, Argentina, Bolivia and Chile, and is a pernicious pest of pasture grasses that costs New Zealand up to $250 million per annum [69]. Biocontrol combined with endophyte-based plant resistance[5] has kept the pest in check [70], but the effectiveness of the biocontrol

agent (the parasitoid wasp *Mictroctonus hyperodae*) is decreasing, probably though genetic resistance arising from continual selection pressure [71, 72]. This is a critical problem, as it is possible that the full cost of the Argentine stem weevil may fall on New Zealand's pastoral industries. Thus, there is good reason to consider the use of genetic technologies.

Australian sheep blowfly

Despite its name, the Australian sheep blowfly is native to Africa and North America. The blowfly causes large lesions on sheep and, left untreated, can prove fatal to the animal. It has huge animal welfare implications in New Zealand and Australia. The Australian blowfly is expected to have an increasing impact, both in incidence and in geographical spread, as a result of climate change. In contrast to wasps and weevils, development of a gene drive for genetic control of the Australian sheep blowfly *Lucilia cuprina* should be relatively straightforward. This is because the technology for germline (or hereditary) modification has already been developed [73, 74]. The technology, first developed in New Zealand, has since been adapted to the New World screwworm, a blowfly that is a major pest of livestock in the Americas [75]. Further, the *transformer* gene has been shown to be essential for female but not male development [76] and thus would be a good target for a gene drive. Genetically modified strains of *L. cuprina* have been developed that produce only males, which could be used for a genetic control programme [77, 78]. However, these strains have not been adopted by the sheep industry in New Zealand or Australia because of the rearing and distribution costs of their use in an eradication campaign, and the perceived difficulty in obtaining regulatory approval. A gene drive for population suppression would be much more economical, as at least 100-fold fewer flies would need to be released [79].

New pests

Important arthropod incursion threats exist overseas that are still not present in New Zealand, but which could arrive. Species such as the Queensland fruit fly (*Bactrocera tryoni*), the brown marmorated stink bug (*Halyomorpha halys*) and the glassy winged sharp shooter (*Homalodisca vitripennis*), would have major impacts on our predominantly agricultural economy if they became established here, attacking grapes, kiwifruit, apples, citrus and stone fruit, corn and many other valuable crops. Gene drives, because of the research needed to develop them, are unlikely to be useful as first responses to a biosecurity incursion, but, given that many pest species present biosecurity risks overseas, it may be possible in the future to utilise a gene drive developed for control elsewhere. For example, gene drive systems are being developed for spotted wing *Drosophila*, a fruit fly that is a major invasive pest of soft-skinned fruits such as blueberries.[6]

SCENARIO 2
The brushtail possum

Environmental rationale for control

Perhaps New Zealand's most significant mammalian pest is the brushtail possum (*Trichosurus vulpecula*). This marsupial was first brought to New Zealand from Australia with the aim of establishing a fur industry in 1837 [80]. The possum, as it is known in New Zealand, found an environment with few of the challenges of Australia and grew to plague proportions in New Zealand forests. Along with eating native trees [20], native birds [81] and invertebrates [82], the possum is also a carrier for bovine tuberculosis [83], and thus possum control is carried out for conservation and agricultural purposes. It is indeed this latter problem that has driven most of the current programme of possum control in New Zealand. The ecology of possums in New Zealand is also well known, and has fed into computer models for exploring possum population dynamics under different control scenarios [84]. Consequently, it is possible to model the impacts of a gene drive in controlling possum populations in New Zealand.

Current control options

Possum control costs the New Zealand government approximately $110 million per year [85], much of which is spent on aerial distribution of poison baits. Other approaches, such as traps and bait stations, are also used. These technologies are effective when animals are at high densities, but become less effective as densities drop [86]. Gene drives and other genetic solutions may provide an opportunity to add to the 'toolbox' of approaches to achieve national eradication.

[5] An endophyte is a bacterium or fungus that lives with in a plant without causing disease. These endophytes can enhance resistance of host plant against insect herbivores by production of defensive compounds in the plant.

[6] swdmanagement.org/

Technical/scientific considerations of gene drives

Although valued in their native range in Australia, possums are a pest unique to New Zealand and, as such, little work has gone into the development of novel methods of possum control beyond our shores. Over about 20 years, major projects were run in New Zealand, focused on establishing immunocontraception as a tool for possum control, which uses an animal's immune system to prevent it from fertilising offspring [87]. While these projects were ultimately wound up, they did provide knowledge of possum reproduction and genetics [21] that may be useful in the era of gene editing and gene drives.

One key barrier that needs to be solved in possums, and is necessary for a gene drive, is the ability to genetically modify the organism, a feat never achieved in a marsupial. To do so would require the generation of reasonable quantities (100-1000s) of oocytes (egg cell precursors). Techniques for superovulation and implanting embryos [88, 89] into possums have been developed as part of a reproductive control approach to possums [90], and could be used to generate oocytes for manipulation.

If genetic modification of possums is possible, there will be a need to identify what genes or processes should be targeted for a gene drive system. In comparison to the mouse, little is known about functional genetics in marsupials, mainly due to the lack of a well-established model system. Several marsupial genomes have been sequenced [91], providing a resource for further genetic work, but understanding the function of marsupial genes is only making slow progress. Some potential vulnerabilities are known, particularly around reproduction, milk production and water balance, but there is still a lot of work to do to determine the viability of such targets.

With no well-established marsupial model system, the best option may be to adapt gene drives developed in mice that target genes or processes that are similar in possums. To this end, sequencing the possum genome, now underway as part of the Biological Heritage National Science Challenge, is an important and necessary first step in developing a potential gene drive.

The use of possums with gene drives to control wild possum populations would require very large numbers of altered animals to be bred and released. Depending on the modelling of the numbers of animals needed for the spread of the gene drive, taking an average density of around one possum per hectare [92, 93], it would require a quarter of a million altered possums to be distributed throughout the country for 1% of the population to be altered. This would involve successfully putting one altered possum into every 100 hectares, including rugged back country.

International considerations

One area of concern is around the control and containment of a possum gene drive. As envisaged, the gene drive would be specific to possums, likely targeted to a specific vulnerability such as fertility, with the only organisms affected being the offspring of those possums that mate with a possum possessing the gene drive. The spread of the gene drive would occur through the possum population as large numbers of gene drive possums were distributed throughout the country, and the possums disperse. This would be effective for the goal of widespread control and eradication in New Zealand. However, there would likely be an issue for Australia if a gene drive possum was to find its way or be deliberately released there, because in Australia brushtail possums are a protected species and an important part of many Australian ecosystems. The prospect of such an incident suggests the need for a means to turn off a gene drive.

Regulatory considerations

As for wasps, genetically modified possums are defined as new organisms under the HSNO Act, and, therefore, possums containing gene drive systems would be classified as 'new organisms'. As with wasps, risk assessments of organisms produced through gene drive systems are carried out under the provisions of the HSNO Act on a case-by-case basis by the Environmental Protection Authority. In addition, the Animal Welfare Act 1999 has amended the meaning of *manipulation* and includes reference to *genetic modification (section 3)*. The implications of this Act for this scenario are unclear for its use in pest management/control/eradication, as 'genetic modification' and 'biological product' are not defined in the Animal Welfare Act.

SCENARIO 3
Rodents and stoats

Environmental rationale for control

As with the environmental rationale for possums, stoats are a predominantly New Zealand problem, with the Orkney and Shetland Islands being the only

other place on the globe that shares the problem of invasive stoats [94]. Stoats (*Mustela erminea*) are ferocious predators that do significant damage to many of our native bird populations and have contributed to the extinction of five native species [95]. Rats are also a very serious pest problem. In New Zealand there are three rat species: the ship or common rat (*Rattus rattus*), the Norway or brown rat (*Rattus norvegicus*) and the Polynesian rat or kiore (*Rattus exulans*). Of the three, the ship rat is of greatest conservation concern, but all prey on native species [96].

Current control options

These pests in New Zealand are currently controlled in many different ways, depending on the target species, including the widespread use of biodegradable 1080 poison (sodium fluoroacetate), a naturally occurring metabolic poison most effective against mammalian pests [97]. 1080 is a cost-effective and safe pest control tool [98], especially when distributed by air in rugged, heavily forested terrain where trapping is not viable. However, its use remains controversial in some sections of the community [99]. Other pest control measures include innovative new approaches to trapping, including the development of self-resetting traps [100]. Technologies for identification of pests and targeted removal have also improved [101], and many of these technologies are now available to the general public.

Current pest control measures, as demonstrated by the removal of pests from large offshore islands, are effective, but they are relatively expensive and take a lot of planning [17, 102]. Given the alternatives of a broad-range poison dropped from the air, and expensive and intensive trapping campaigns, gene-drive solutions could provide another avenue for pest control [46].

Technical/scientific considerations of gene drives

While New Zealand researchers have spent decades understanding the ecology, reproduction and, more recently, the genetics of possums, researchers are less well informed about many of these key issues for stoats [103]. One potentially promising avenue to explore is to harness the significant efforts made in understanding the reproduction and genetics of mink, a related species valued for its fur that is farmed in parts of the Northern hemisphere [104, 105].

Unlike possums and stoats, rats are global pests that are implicated in food spoilage, the spread of diseases of global concern (e.g. bubonic plague) and are a key conservation threat around the globe [106]. Thus, New Zealand might not have to solve the problem alone and active efforts are underway to tap into international initiatives now aimed at establishing gene drives for the control of invasive rodents [107]. Rats are also among the best-studied mammals, so there is no shortage of knowledge on reproduction or genomics, although most of this knowledge comes from the Norway rat, a well-established lab model that was among the first mammal to have its complete genome sequenced [108]. Less is known about the ship rat, although it has just had its genome sequenced by a New Zealand team, as a legacy project from the Allan Wilson Centre, which should provide an important stepping stone towards the challenge of establishing a gene drive for rats [109].

While establishing gene drives in rats will be less challenging than for stoats and possums, there are still significant practical barriers to establishing such a system. One of these is that rats are surprisingly hard to genetically manipulate [110]. Huge efforts have gone into solving this issue, with some progress made in recent years [111, 112]. However, this may be a major challenge to the use of gene drives for controlling rats in New Zealand, and mice (also a significant pest) might be the easiest species to target in the first instance.

Several international groups are looking to develop gene drive solutions for mice. One of the most advanced is a project that aims to link a sex determining factor to a naturally occurring gene drive to produce mice that produce predominantly male offspring [113]. While feasible in theory, there are multiple questions, as yet unanswered, that may thwart the efforts to use these in the wild to achieve population control [114]. For example, researchers do not yet know if the health, survival and reproductive success of mammalian species carrying such modifications might be impaired, whether there are different versions of the gene in the target population and how frequently mutations might arise in the gene drive or its cargo gene that could disable them. Robust modelling to explore the possibilities by which gene drives may fail, need to be undertaken in a similar way to those for insect systems [8].

As with possums, the use of gene drives to control wild populations of rodents and stoats would likely require the breeding and repeated release of very large numbers of altered animals over large areas.

International considerations

Globally, while rats are pests in many contexts, they are also important providers of ecosystem services (e.g. pollination or critical elements of ecosystem food webs). Eradicating rats in New Zealand, where our ecosystems were free of rodents up until human arrival around 800 years ago, may have few knock-on effects. However, in other parts of the globe, the effects on natural systems might be very different. Rats are very good invaders, disperse well and hybridise with closely related species, making the accidental release and spread of gene drive modified rats a serious consideration. Stoats are less likely to be inadvertently spread, but they are an important animal in northern European ecosystems, so even the prospect of dispersal from New Zealand will mean the need for a means to turn off the gene drive.

Regulatory considerations

As for wasps and possums, genetically modified animals are defined as new organisms under the HSNO Act, and, therefore, stoats and rats containing gene drive systems would be classified as 'new organisms'. Risk assessment of organisms produced through gene drive systems are carried out under the provisions of the HSNO Act on a case-by-case basis by the Environmental Protection Authority. As with the use of a gene drive in possums, the implications of the Animal Welfare Act 1999 for this scenario are unclear for its use in pest management/control/eradication, as 'genetic modification', 'biological compound' and 'management' are not defined in the Animal Welfare Act.

Social, ethical and cultural considerations

An important ethical consideration for any genetic intervention is its effect on the welfare of those affected. The idea of releasing a genetically modified organism that leads to the extinction of a species, or permanently changes a species, challenges our ability to understand our rights to intervene in natural processes. Invasive species are undoubtedly a major concern in maintaining the integrity of ecosystems and a wide range of interventions are currently used in pest management. Gene editing targeting a pest organism's ability, for example, to reproduce, will provide a more specific approach than a widespread use of toxins.

In considering the possible use of gene drive technologies using gene editing, society will be challenged with a range of ethical and cultural issues, including animal welfare. While there are generic issues around the rights of target species which must be considered in any ethical approval process for research, especially mammals and birds as potential sentinel or keystone species, there are also wider concerns about potential ecosystem impacts and ethical issues.

From the perspective of an individual animal, some may argue that it has a fundamental right to respectful treatment,[7] and that these animals have a life that matters to them, and should not be treated as a mere resource (or pest) for humans. Others will support the use of gene drives because of their targeted species specificity, or support their use for insect pest control on a legal basis, as invertebrates are not covered under animal welfare statutes. Some may argue that ecosystems and species have value in themselves, and ought to be protected, even if this means harming or violating the rights of some individual animals to do it. So, individual animal rights are in tension with claims that other things in the natural environment ought morally to be protected, at an animal's expense. Much hinges on the ecological impact of the removal of the pest animal. If this is ultimately negative, then those holding this ecological view would be opposed to the use of a gene drive. Similarly, this view may attribute moral value to a species, and oppose a gene drive that would make a species extinct.

Gene drives offer an intervention that is less harmful at an individual level than conventional control of animal pests. Altering just the reproductive success of animals likely has less negative impact on the welfare of individual animals than current methods, which usually involve killing them, sometimes painfully. This, combined with the welfare improvements potentially gained by the use of gene drives, speaks in favour of their use. However, this is entirely contingent on the gene drive being as harmless as possible in its effects, both on target species and on any other species affected by the ecological changes the gene drive brings, and that there are significant benefits to others from these changes. This all depends on sound scientific knowledge about the gene drive and its effect, and our ability to control those effects. Bearing in mind that substantial ecosystem disturbances might occur in the first instance until food webs adjust, much more understanding of systems biology is needed.

[7] Regan, Tom. 2004. *The Case for Animal Rights*. Updated ed. Berkeley, Calif; London: University of California Press.

Critically, we are required to consider the ethical, societal and cultural issues from a Māori perspective. There are concerns that genetic modification, including gene editing, may be at odds with Māori tikanga (protocols), in that it may interfere with natural processes pertaining to whakapapa (genealogy) and violate the tapu (sacred restrictions) of different species. Māori communities will need to be well informed about the implications, benefits and risks associated with gene editing in pest control. Education and consultation will be central to empowering whānau (extended family), communities, hapū (kinship group) and iwi (tribe) to assess the social, moral, ethical and health considerations of gene editing within different contexts and scenarios.

For the three scenarios, in Māori terms, the ethical considerations relate to whakapapa (of the organism, as well as the relationship/kinship between humans and other species), tika (what is right or correct), manaakitanga (cultural and social responsibility/accountability, e.g. to other nations who value wasps) and mana (justice and equity) [115]. Other relevant Māori values include tapu (restrictions), tiakitanga (guardianship), and whānaungatanga (support of relatives). Implicit in those considerations would be the question of who stands to benefit from the introduction of a gene drive in this scenario; what are the risks to the ecosystems of other nations; and where do Māori accountabilities lie in terms of the outcomes [116]. In addition, broader impacts on Māori also need consideration, including any negative financial impacts on whānau that may arise, and the assurance of Māori participation in decision making regarding use of these technologies[8]. Ultimately, a decision to support a gene drive will depend on the assessed balance between benefits and harms of intervening in the natural environment. This in turn will be determined by the factors used to make the assessment. Well-informed conversations about the implications of research knowledge, along with the impact of particular views about acceptable change in a target species, will be needed across all of Aotearoa/New Zealand's diverse communities in order to determine the list of factors to consider in assessing this balance. There will need to be trust and effective communication between the public, the government and the research community if new genetic technologies are to be accepted.

Community approval

Relational trust and communication between the public, government and scientists is required for new genetic technologies to be accepted. The idea of releasing a genetically modified organism that leads to the extinction of a species speaks to the darkest fears expressed about GM technology. Leading conservationists have expressed similar fears[9] reinforcing such concerns. The need to control invasive predators and pests is known; what is problematic is the way it is done and the unknown consequences on an ecosystem. While trapping and shooting are seen as acceptable by some, the use of poisons is more controversial, with protests about the use of 1080, in particular. In this environment, gene drive technologies might have a place because of their species specificity.

New Zealand regulation of the use of genetic modification for pest control

Genetic modification in New Zealand, such as using gene editing on a pest to include a gene drive, is regulated primarily by central government through the Hazardous Substances and New Organisms Act (1996) (HSNO Act). Gene drives will be regulated by the HSNO Act if they come within the definition of an 'organism' and 'new organism' in this Act. 'Organism' is defined in the HSNO Act and 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.[10] The definition of 'new organism' includes genetically modified organisms (GMOs) and organisms belonging to species that were not present in New Zealand prior to July 1998.[11] The definition of a GMO is expressly defined in supporting regulations,[12] but otherwise the HSNO Act defines GMOs as 'any organism in which any of the genes or other genetic material have been modified by in vitro techniques; or are inherited or otherwise derived, through any number of replications, from any genes or other genetic material which has been modified by in vitro techniques' (see Figure 2). The Environmental Protection Authority (EPA) can make a rapid assessment for 'low risk genetic modification'.[13]

[8] As part of this project, Māori perspectives and broader cultural contexts are being sought by the Panel in a parallel process.

[9] etcgroup.org/files/files/final_gene_drive_letter.pdf

[10] HSNO Act, s2(1).

[11] HSNO Act, s2A.

[12] HSNO Act, SR 1998/219.

[13] HSNO Act s 41(c) and SR 2003/152 r 4.

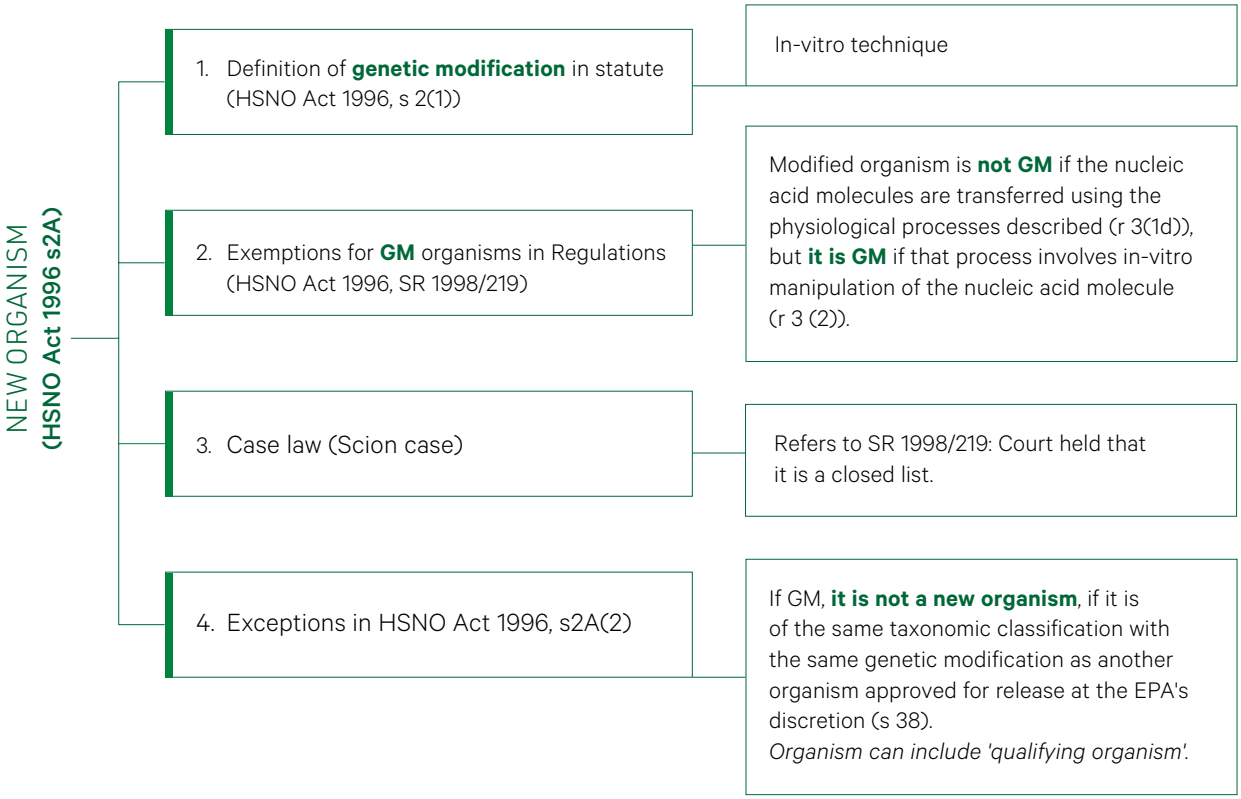
It is unlawful to import, develop, field-test and release any 'new organism' without approval from the EPA. If there is uncertainty about whether an entity is a GMO (or even an 'organism' or 'new organism'), there is a formal determination the EPA can undertake pursuant to the HSNO Act (s 26). The HSNO Act is enforced at the New Zealand border under section 28 of the Biosecurity Act 1993.

The case studies evaluated in this paper highlight a complicated regulatory framework with many 'grey' areas. The current regulatory framework may permit gene editing for pest control in containment and for release, as each application is assessed on a case-by-case basis. An application would need to be made to the EPA for approval under the HSNO Act for development and field testing in containment. Further applications would be required for release from containment, and controls may be imposed by the EPA. The HSNO Act further prescribes the mandatory assessment and decision-making process for applications, including a risk assessment of the new organism's effect on native species, biodiversity and natural habitats.[14] The EPA will decline the application if the minimum standards cannot be met.

The following legislation and associated amendments require evaluation alongside the HSNO Act, for pest control using gene editing technologies (see Figure 3):

- Animal Welfare Act 1999.
- Agricultural Compounds and Veterinary Medicines Act 1997 (ACVM Act).
- Biosecurity Act 1993 (Biosecurity Act).
- Conservation Act 1987 (Conservation Act).
- Resource Management Act 1991 (RMA).

FIGURE 2 | Summary of the process determining a new organism according to the HSNO Act



[14] HSNO Act, section 36. Minimum standards:
The Authority shall decline the application, if the new organism is likely to—
a. cause any significant displacement of any native species within its natural habitat; or
b. cause any significant deterioration of natural habitats; or
c. cause any significant adverse effects on human health and safety; or
d. cause any significant adverse effect to New Zealand's inherent genetic diversity; or
e. cause disease, be parasitic, or become a vector for human, animal, or plant disease, unless the purpose of that importation or release is to import or release an organism to cause disease, be a parasite, or a vector for disease.

HSNO Act, section 37. Additional matters to be considered:
The Authority, when making a decision under section 38, shall have regard to—
a. the ability of the organism to establish an undesirable self-sustaining population; and
b. the ease with which the organism could be eradicated if it established an undesirable self-sustaining population.

FIGURE 3 | New Zealand legislation influencing gene editing technologies in animals and organisms

NEW ZEALAND REGULATION: GENE EDITING AND GENE DRIVES IN PEST CONTROL AND PRIMARY INDUSTRIES

Guiding Principles

Culture cues and social license

Guidance from Royal Commission on GM

Cabinet Paper: Government Response to Royal Commission

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 and Federated Farmers of NZ Inc. v Northland Regional Council [2016] NZHC 2036)

Agricultural Compounds and Veterinary Medicines Act 1997

2017 Te Pūnaha Hihiko Vision Mātauranga Capability Fund

Biological Heritage National Science Challenge

Genomics Aotearoa

Pest Free New Zealand 2050

Primary Sector Science Roadmap

Treaty Partnerships

Rights to DNA data and information

Treaty of Waitangi (WAI 262)

Patents Act 2013 (ss 15, 16)

TRIPS Agreement (Art. 27)

Animal Welfare Act 1999

Te Mana Raraunga

Trade and biosecurity

Patents Act 2013 and TRIPS Agreement

(Plant Varieties: GM plants for food allergies)

Biosecurity Act 1993

National Animal Identifications and Tracing Act 2014

Animal Products Act 1999

Food Safety Authority (Australia and NZ)

Food Act 2014, s 383(3)(i)

International Treaties:

Cartagena Protocol on Biosafety to the Convention on Biological Diversity.

Nagoya-Kuala Lumpur Supplementary Protocol on Liability and Redress

Application

MPI is responsible for administering legislation that covers a wide range of sectors including **agriculture, forestry, aquaculture, biosecurity, food and fisheries**.

mpi.govt.nz/about-mpi/legislation/ for a full list.

Conservation Act 1987

Wildlife Act 1953

Biosecurity Act 1993

Animal Welfare Amendment Act (No 2) 2015

Resource Management Act 1991

Resource Legislation Amendment Act 2017

Regulatory process

There is no clear regulatory framework for specifically evaluating gene drive technologies as a method for controlling pests. However, before gene editing technology can be evaluated for use, the first step is to search legislation for a prescribed list of pests. If pests are not scheduled, then policy will need to be sought and procedure followed for assessing whether the 'target' organism can be deemed a 'pest' (Animal Welfare Act 1999, ACVM Act, RMA) or an 'unwanted organism' (ACVM and Animal Welfare Acts) for the purposes of the legislation. Note that 'pest' is defined differently in the Animal Welfare, Biosecurity and ACVM Acts.

Justification for intervention is required. Reasons may include conservation and protection of native flora and fauna, agricultural security and animal production and breeding. This will enable the correct policy to be employed from appropriate legislation. Thus, the purpose of the legislation is important (Conservation Act, ACVM Act and Animal Welfare Act). Conservation and agricultural security purposes propose a *Pest Management Plan*.

Alongside this, there is jurisdiction under the RMA for local councils to control the use of genetically modified organisms via regional policy instruments[15] and there may be implications of this on the use of gene drive pest control techniques.

Biosecurity Act

The Biosecurity Act defines a *pest management plan* as a plan to which the following apply[16]:

a. It is for the eradication or effective management of a particular pest or pests.
b. It is made under Part 5 of the Biosecurity Act.
c. It is a national pest management plan or a regional pest management plan.

The purpose of Part 5 of the Biosecurity Act, Pest Management, is to provide for the eradication or effective management of harmful organisms that are present in New Zealand by providing for:

a. the development of effective and efficient instruments and measures that prevent, reduce or eliminate the adverse effects of harmful organisms on economic wellbeing, the environment, human health, enjoyment of the natural environment and the relationship between Māori, their culture, and their traditions and their ancestral lands, waters, sites, wāhi tapu and taonga; and
b. the appropriate distribution of costs associated with the instruments and measures.

HSNO Act

The HSNO Act has been described as a comprehensive, strict and rigorous code [117] and additional amendments sought to increase restrictions following release of the organism, including reassessment (section 63), conditional release (section 38) and clarifying the meaning of genetically modified organism (Statutory Regulation 1998/219, r 3(ba)).

Regulation of genetically modified organism under the HSNO Act and RMA have been challenged in the New Zealand courts. Most notable was the Scion case,[17] which clarified the classification of gene edited organisms as 'genetically modified organisms' for the purposes of the HSNO Act.[18] The Northland Regional Council case clarified that Regional Councils control the use of genetic modification through their regional policies and district plans under the RMA.[19] Both of these cases have wide-ranging implications for New Zealand and are not limited to genetically modified crops. Central government consequently amended regulations to clarify the exemptions to the HSNO Act (EPA, HSNO Act SR 1998/219). Central government has also amended the RMA 1991 introducing a new regulation making power to prohibit or remove specified rules or types of rules by Territorial Authorities that would duplicate, overlap or deal with the same subject matter that is included in other legislation. Rules that regulate the growing of GM crops do not apply.[20]

[15] mfe.govt.nz/more/hazards/risks-new-organisms/what-are-new-organisms

[16] Biosecurity Act 1993, Part 5, section 54.

[17] *The Sustainability Council of New Zealand Trust v The Environmental Protection Authority* [2014] NZHC 1067.

[18] The High Court Judge ruled that the exemption list in the Regulations is a closed list. The conclusion was based on an interpretation of the language of the Regulation and that the regulations did not prescribe factors for the EPA to add other techniques to the list. The Judge interpreted the HSNO Act and the regulations as not implicitly giving the EPA discretionary power to add to the exemption list and ruled that the EPA could not expand the exemption list to include techniques similar to chemical mutagenesis and adding to the exemption list was a political decision, not an administrative decision.

[19] *Federated Farmers of New Zealand v Northland Regional Council* [2015] NZEnvC 89.

[20] Resource Management Act 1991, s 360D.

New Zealand has a network of legal instruments and treaties that require consideration alongside review of the HSNO Act when introducing new biotechnologies. These include the Treaty of Waitangi[21] (the Waitangi Tribunal Report recommending that Māori have a greater interest in genetic modification[22]) and the RMA (the ability of regional councils to control the use of genetically modified organisms through regional policy statements or district plans).

Agricultural Compounds and Veterinary Medicines Act 1997 (ACVM Act)

In addition to the HSNO Act, the Agricultural Compounds and Veterinary Medicines Act 1997 (ACVM Act) has possibly the greatest effect on this technology. Depending on the interpretation of 'veterinary medicine', a gene drive intervention could be regulated under the ACVM Act and thereby assessed under the Conditional Release and Release statutory provisions in the HSNO Act (potentially bypassing the Containment provision).

A veterinary medicine, according to the ACVM Act (s 2(1)), means any substance, mixture of substances or biological compound used or intended for use in the direct management of an animal.

- Note that direct management is not defined in the Act.

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

- A new organism has the same meaning in the ACVM Act and in section 2A of the HSNO Act.
- A qualifying organism means a new organism that is or is contained in a qualifying veterinary medicine (HSNO Act, s 2(1)).

Royal Commission on Genetic Modification

The 2001 Royal Commission on Genetic Modification report concluded that, 'New Zealand should preserve its opportunities by allowing the development of genetic modification whilst minimising and managing the risks involved'. The Royal Commission's overall strategy was supported by the Government. However, the Government required that research practices adhere to strict safety guidelines, including secure containment, thereby limiting discretion when determining the conditions of the research. Government also required a precautionary approach to be exercised in the operation of the HSNO Act (s 7): 'All persons exercising functions, powers and duties under this Act including, but not limited to, functions, powers, duties under sections 28A, 29, 32, 38, 45, and 48, shall take into account the need for caution in managing adverse effects where there is scientific and technical uncertainty about those effects'.

International governance

The Cartagena Protocol on Biosafety (the Biosafety Protocol) is designed to address the biosafety risks presented by GMOs when these move across borders. Established under the Convention on Biodiversity, this international treaty is founded on the principle of prior informed consent with respect to the transboundary movement of living modified organisms (LMOs). It puts a duty on an exporting party to seek prior informed consent from the destination country (Article 7). However, the procedures only work for intended movements across the border of a single nation. The protocol does not define best practice guidelines, for example, for standards for assessing effects, estimating damages or mitigating harms [77]. While these may be seen as 'gaps', it could also be argued that best practice guidelines are best left out of such rigid instruments. The related Nagoya-Kuala Lumpur

[21] NZ Law Commission (2002). *Liability for loss resulting from the development, supply, or use of genetically modified organisms*. Study Paper 14. The Law Commission looked into the issue of liability for loss resulting from GMOs and described the adverse cultural effects of GM on Māori: *'Concerns have also been raised by Māori, 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 Māori 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 Māori's ability to be kaitiaki (guardians) of their taonga and particularly their ability to care for valued flora and fauna'.*

[22] Kingsbury, A. (2011). Intellectual Property. WAI 262. NZ Law Journal, September 2011, 273.

Supplementary Protocol on Liability and Redress identifies response measures in the event of damage to the conservation and sustainable use of biological diversity resulting from living modified organisms that result from transboundary movements. It does not define rules governing liability and redress for damage, but requires Parties to either apply their existing general law on civil liability or develop specific legislation that addresses (as appropriate): damage; standard of liability (including strict or fault-based liability); channelling of liability where appropriate; and the right to bring claims.

Concerns around the potential unintended impacts of gene drives were highlighted in a US National Academies of Science review of gene drives [118] which noted:

> **"Gene drives do not fit well within the existing regulatory logic of confinement and containment because they are designed to spread a genotype through a population, making confinement and containment much more difficult (or even irrelevant) and the environmental changes introduced by release potentially irreversible. ...Research on gene drives is global. Responsible governance will need to be international and inclusive, with clearly-defined global regulatory frameworks, policies, and best practice standards for implementation."**

This will have implications for New Zealand's international social license to develop gene drives that could potentially threaten other countries' native species.

Safety mechanisms for gene drives

In their 2014 article, Esvelt and colleagues outlined a variety of uses for CRISPR gene drives in human health, agriculture and the environment [46]. Importantly, the authors noted that the potential efficiency of CRISPR gene drive systems posed a requirement for a high certainty of laboratory containment before they are deemed safe to move out of the laboratory. They suggested parallel development of a 'reversal' gene drive that would restore the original gene, but with a slightly different sequence that would not be targeted by the original guide RNA.

Although Esvelt *et al*. [46] had highlighted the need for safeguards, the ease and efficiency of the CRISPR-mediated gene drive in the fruit fly *Drosophila melanogaster* [7] was a surprise to many. These results have led to wide discussion of the risks of gene drives. Recently, scientists working on CRISPR [119] recommended a number of safeguards, including to:

1. perform gene drive experiments outside the ecological range of the organism (e.g. *Anopheles* mosquito in Boston). Consequently, if any individuals do escape the laboratory they would likely perish and/or have no potential mates
2. use a laboratory strain that cannot reproduce with wild organisms
3. have a high level of laboratory containment, using multiple substantial physical barriers. In practice, this could be a higher level of containment than is currently recommended for transgenic strains of the species of interest (i.e. for organisms containing genetic material into which DNA from an unrelated organism has been artificially introduced). For example, using air blast fans and higher precautions to prevent escape (e.g. sealing possible escape routes).

In 2016, another safety concept was developed, called the 'daisy-chain' gene drives [120], which gradually vanish after 50-100 generations. To create these gene drives that do not spread indefinitely, the gene drive is split into three or more parts to create a 'daisy chain'. Each part contains a genetic element that drives the next element in the chain so that element A can only copy and paste itself if element B is present. Element B can only copy and paste itself if element C is present. And element C, crucially, cannot copy and paste itself at all – it can only spread by normal breeding, to half of offspring. When the gene drive animals are released, they carry all three elements. Then, when they mate with their wild counterparts, all the offspring will inherit elements A and B, but only half will inherit element C. In the following generations, element B will spread rapidly and A will spread even more rapidly, but C will gradually die out. Once it does, B will start to disappear, and finally A will too. By adding more elements to the daisy chain, the gene drive could be made to persist longer in the wild. This could allow the use of gene drives locally without the worry about the risk of worldwide spread. However, getting gene drives to work is technically challenging and so chopping up the construct as part of a daisy chain may adversely affect the gene drive's performance in the environment.

Conclusion

The application of gene editing to create gene drives may offer a further opportunity to expand our arsenal for pest control in New Zealand alongside other control methods as part of an integrated management strategy, although the development of gene drives is still very much in its infancy, and possible implementation of a gene drive approach in New Zealand is still a long way off.

Generic hurdles and conditions that will need to be addressed include:

1. *scientific* – lack of information on genome of target species, number of individuals needing to be released, need for reversal mechanisms, possible spread of gene drive outside intended region
2. *social* – community opposition
3. *cultural* – Māori considerations
4. *political* – costs, governance and regulation.

All these together may make it unlikely that it would be used for more than one or two species, unless there are other significant breakthroughs.

Areas of research which could have wide benefit include genome discovery on major target pests, to open up future possibilities for control, not just gene drives.

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

Contributors to the technical paper

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Dr Joanne Daly (Senior adviser, Plant Health Australia), **Professor Ary Hoffman** (University of Melbourne, Australia), **Professor Ian Small**, (University of Western Australia), and **Dr Sue Meek** (Australian University) provided independent international review of the paper.

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ROYAL SOCIETY TE APĀRANGI

GENE EDITING SCENARIOS IN THE PRIMARY INDUSTRIES

SUMMARY

AUGUST 2019

EXPLORE | DISCOVER | SHARE

ROYAL SOCIETY TE APĀRANGI

INTRODUCTION

The revolution in gene editing technologies is making it easier to make specific changes to genetic sequences, with potential benefits in many sectors including healthcare, agriculture and conservation. However, as a technology, gene editing is moving ahead of any consensus on how it should be used.

Royal Society Te Apārangi convened a multidisciplinary panel to consider the social, cultural, legal and economic implications of gene editing in Aotearoa New Zealand, incorporating Māori perspectives and broader cultural contexts.

To help you consider the potential uses of gene editing in primary production in New Zealand, this paper highlights five scenarios and the implications that arise. In particular, these case studies consider:

- use of the technology in food and non-food items
- use of the technology in plants and animals
- use of the technology in agricultural and native species.

The characteristics of all living organisms are determined by their genetic material, or DNA.

WHAT IS GENE EDITING?

The characteristics of all living organisms are determined by their genetic material, or DNA. Genes are segments of DNA which provide the code for particular functions or characteristics. Identifying and using these different versions of genes, and the traits they create, which randomly appear and vary across populations, has been an important part of agriculture for thousands of years. By cross breeding plants with different versions of genes, and repeatedly selecting preferred plants from their offspring to serve as new parent lines, agricultural crops have been created over time with more desirable traits, such as higher yields, disease resistance, reduced toxicity and improved flavour. Much the same is true of farmed animals. Additionally, since the 1920s and 1940s, plant breeders have also used chemical mutagenic agents and radiation to generate random variations in populations from which new plant varieties could be selected.

Gene editing technologies now enable targeted changes to be made to specific gene sequences, such as directly changing the version of a gene from one that causes a plant to be susceptible to a disease to one that does not, and thereby creating a disease resistant plant.

A technique called CRISPR has increased the speed, ease and accuracy of gene editing. Modified from a system found in bacteria to cut up invading virus DNA, CRISPR enables much more efficient and precise changes to be made to gene sequences. However, this ability to edit genes is, in many cases, ahead of our understanding of everything that genes do.

HOW COULD GENE EDITING BE USED IN PRIMARY INDUSTRIES?

Gene editing techniques have been recently developed that enable more targeted and precise genetic changes than have ever been possible before in crop and livestock breeding. This now allows for continuous improvement of crops and livestock without introducing deleterious versions of genes from crossing and recombination, nor requiring time-consuming plant and animal breeding to restore the original desired genetic background. In a plant breeding context, gene editing can rapidly generate improved plant varieties with no trace of foreign DNA.

Earlier DNA modifications via gene transfer techniques pioneered in the 1970s have resulted in a range of genetically modified (GM) crops grown by 24 countries worldwide, covering 10% of the world's arable land. Half of New Zealand's domestic food supply in 2013 was imported and food ingredients derived from 88 lines of genetically modified lines of canola, corn, potato, rice, soybean, sugar beet and lucerne (alfalfa) are approved for use in Australia and New Zealand. These GM food lines are not currently grown in New Zealand and none have been derived from gene editing technologies to date. There are no GM plants currently grown out of containment in New Zealand.

SCENARIO ONE

REDUCING ENVIRONMENTAL IMPACT

SPECIES

Douglas fir trees

PROBLEM

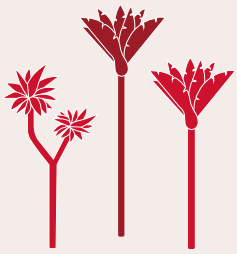
Wilding trees (trees growing outside tree plantations)

GENE EDIT

Use gene editing to make future planted trees sterile

OUTCOME

Protect environment and save money on conservation efforts



Agricultural and environmental considerations

Wilding conifers overwhelm native landscapes and are expensive to control.

Ethical and social considerations

Forests are thought of being free of human influence, but there are also obligations to protect the environment.

Legal considerations

Gene edited pines would require approval by the Environmental Protection Authority under the HSNO Act.

Risks and potential benefits

New trees may be more expensive, but could prevent new wildings, and reduce pollen allergy.

Wilding conifers come from the seeds of exotic conifer species such as Douglas fir and are an unintended consequence of forestry, agriculture (shelter-belts) and erosion control plantings in New Zealand.

Wildings currently occupy large tracts of conservation land in New Zealand because they are difficult and costly to control. It is critical that management of new plantings of wilding-prone species includes strategies to prevent the generation of new wilding populations in the conservation estate.

Gene editing could be used to create sterile trees for plantation to prevent new plantation forestry from generating new wilding conifers. CRISPR could be used to target and inactivate genes for cone initiation or development. This edit would prevent reproduction by producing sterile trees, and would also eliminate pollen production. Tissue culture would therefore be required to propagate new trees for plantations.

Agricultural and environmental considerations

Wood derived from Douglas fir is economically important. However, if wilding conifers become established outside the plantation areas they can overwhelm native landscapes, compete with native plants, and reduce native insect and bird populations. They also have a huge impact on our economy by removing valuable water out of catchments, adding costs to farming and conservation, and impacting on tourism and recreational opportunities.

Ethical and social considerations

Forests have an emotive and aesthetic value for many people and a place in history, mythology and identity. Forests, unlike agricultural fields and paddocks, may be seen as 'uncultivated' – even though they are, in fact, in many cases both cultivated and intensively managed. So, concerns about genetic modification may be rooted in concerns about the purity, or freedom, of wilderness, and a belief that wild nature needs to be free of human influence. On the other hand, there could be a kaitiaki (guardian) obligation to reduce the environmental impact of wilding pines, which this technology could support, and intergenerational justice considerations to prevent the need to remedy the impact of wilding pines falling on future generations. Prevention of wilding pines would also protect the purity of surrounding wilderness from human influence.

Legal considerations

Gene edited wilding-prone species are likely to be deemed genetically modified, and a new organism under the HSNO Act. Gene edited wilding-prone species designated new organisms must be developed and field tested in containment. Subsequent approvals need to be sought from the Environmental Protection Authority for release from containment and conditional release. The CRISPR gene editing system may be deemed an agricultural compound for the purposes of the Agricultural Compounds and Veterinary Medicines Act.

According to the Cartagena Protocol on Biological Diversity (an international agreement), gene edited wilding conifers and their seeds (but not logs or sawn timber) would meet the definition of a living modified organism (LMO), if it possessed a novel combination of genetic material. As such, a business seeking to import or export modified conifers would need to comply with the Imports and Exports (Living Modified Organisms) Prohibition Order 2005.

Risks and potential benefits

The primary benefits would be through prevention of environmental, social and economic damage caused by new wildings, but would not address existing wildings. The ability to plant stock that does not generate wildings would remove the risk from future plantings and allow control operations to focus on existing wildings. Prevention of pollen production by sterile trees would mitigate problems associated with pollen allergy and the seasonal nuisance created by large pollen clouds from planted forests. It is predicted that preventing cone development will boost growth and increase wood production by redirecting energy and nutrients to increased vegetative growth. In terms of risks, the availability and cost of the new trees could be more restrictive and expensive than conventional varieties, and some argue that using gene edited trees is a risk to our national 'pure' brand. In addition, most of New Zealand's plantation forest is certified by the Forest Stewardship Council, which currently prohibits the use of GM trees.

SCENARIO TWO

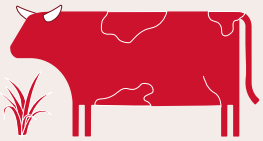
RESPONDING TO INSECT PESTS AND ENVIRONMENTAL STRESS

SPECIES

Ryegrass

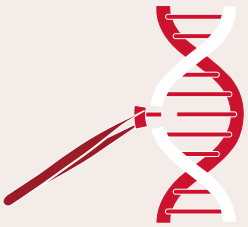
PROBLEM

Beneficial fungi in grass can deter insect pests eating the grass, helping it survive environmental stress, but can also make livestock sick



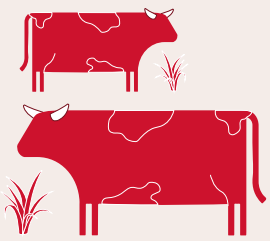
GENE EDIT

Edit the beneficial fungi's genes to maintain pest deterring chemicals while reducing chemicals harmful to livestock



OUTCOME

Healthier stock, pest control and growth, to help survival in adverse conditions, such as drought



Agricultural and environmental considerations

New fungi could provide added protection to the grass growing in the field, and healthier stock.

Ethical and social considerations

Public perceptions of gene edited fungi, versus improved animal welfare benefits.

Legal considerations

Gene edited fungi may be classed as living modified organisms under the Cartagena Protocol.

Risks and potential benefits

Difficulties in managing GM/non-GM seed contamination for export.

Perennial ryegrass is the most important forage crop grown in New Zealand pastoral agricultural systems. Important to the persistence of this crop in the field is the presence of a beneficial fungus that lives inside the grass, known as an endophyte ('living inside').

These fungi produce a range of chemicals in the grass that reduce the amount of grass that insects and mammals will eat, thereby helping the grass to endure environmental stresses. However, some of the chemicals that the fungi produce to prevent being eaten are detrimental to livestock health under certain environmental conditions, resulting in animal welfare issues and causing production and financial losses to the farmer.

Gene editing could be used to selectively delete genes in the fungi that produce the chemicals detrimental to mammals, creating strains of fungi that completely lack the ability to synthesise these chemicals while still synthesising the anti-pest chemicals that do not affect mammals. Alternatively, the fungi could be modified to produce chemicals with unique protective properties, or to introduce genes that confer new benefits, such as drought tolerance, improved grass quality or provide health benefits to the grazing livestock.

Agricultural and environmental considerations

Most proprietary ryegrass seed currently sold in New Zealand contain endophytes because of the added protection the presence of this organism confers to grass when grown in the field. The health of these grasses in the field will depend on both the biology of the grass and the biology of its associated beneficial fungus.

Ethical and social considerations

The main social consideration would be acceptability of using forage seed in agriculture containing gene edited fungi, and the perception of risk from modified fungal chemicals. There would be reduced risk from the fungi's chemicals for the grazing animals, with resulting animal welfare benefits.

Legal considerations

Gene edited fungi would be deemed genetically modified, and a new organism under the HSNO Act. Perennial ryegrass containing gene edited fungi must be developed and field tested in containment. Subsequent approvals need to be sought for conditional release and release from containment, from a ministry approved facility. The gene editing system may be deemed an agricultural compound for the purposes of the Agricultural Compounds and Veterinary Medicines Act.

According to the Cartagena Protocol, gene edited fungi may meet the definition of a living modified organism (LMO), depending on the genetic change made. As such, a business seeking to import or export modified ryegrass endophytes, or ryegrass products (such as hay, silage or nuts to be used as animal feed) with viable endophytes would need to comply with the Imports and Exports (Living Modified Organisms) Prohibition Order 2005.

Risks and potential benefits

Forage seed is widely traded both within and outside New Zealand. While there are good tracking systems in place it would be difficult to control movement of all seed. This would lead to the risk of inadvertent movement of seed containing modified fungi to a region or country where it is regulated differently from the source of origin. Seed containing fungi with minor edits would be difficult to distinguish from naturally occurring strains, and procedures would need to be put in place to account for possible contamination of GM and non-GM seed exports, for countries with purity thresholds for GM contamination.

SCENARIO THREE

SPEEDING UP INNOVATION

SPECIES

Apple

PROBLEM

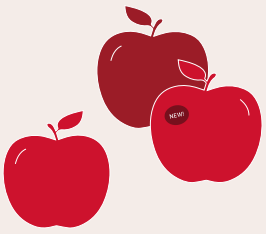
Breeding new varieties of apple takes a long time as new trees can take up to five years to fruit

GENE EDIT

Gene edit introduced to allow a rapid flowering tree from which new varieties can be developed

OUTCOME

New cultivars and varieties produced more quickly for economic advantage



Horticultural considerations

Modified genes could be removed by conventional plant breeding.

Ethical and social considerations

Food labelling will be important to enable consumers to make informed choices.

Legal considerations

Even though modified genes are removed in the final apple, the apples would be considered GM under the New Zealand HSNO Act.

Risks and potential benefits

New traits could be rapidly introduced into prized apple varieties. Checks for off-target gene edits would need to be made.

The speed with which new apple varieties with high-value traits can be produced is limited by the long juvenile period in apple, often up to five years before the plants are able to flower and then fruit. Thus plant breeding, which typically involves multiple cycles of sexual crossing and selection to produce improved varieties with desirable fruit characteristics, is a very slow process.

New Zealand has benefited from a long-term selection and breeding programme. Increasing threats from pests and diseases and rising consumer expectations for new varieties means that much of the research effort in breeding new fruit tree varieties is focused on reducing breeding cycle time. Even small improvements in breeding speed can deliver significant returns sooner or can provide a timely solution to the industry if a new disease or pathogen strikes, or with changing climate conditions.

A gene editing approach could knock out an apple gene that represses flowering, thus reducing the breeding cycle in apple to eight months. With the shorter breeding cycle, the desirable characteristics could be introduced through conventional, and now faster, plant crossing. Once a suitable apple variety had been produced, the modified flowering gene could be removed by conventional plant crossing. There would be no fast-flowering modifications in the final plant.

Horticultural considerations

Potentially, crosses using the edited flowering gene line could be developed and field tested in containment, but permission would be needed to release the plants which no longer contained the modified gene. This would have implications for horticulture producer boards, who would be required to ensure the GM status is known to New Zealand and international consumers.

Ethical and social considerations

Although gene edited plants might be analytically indistinguishable from traditionally bred plants, the fact that a technical procedure, which might be perceived as unnatural, or affecting the apple's purity, is involved in producing new plants, may be of concern to some people. For consumers to have the freedom to make such a choice, labelling (either voluntary or compulsory) will be important. Consequently, tracing an auditable chain of custody becomes imperative for that purpose.

Legal considerations

The gene edited fast-flowering apple trees, and subsequently conventionally crossed versions, would be deemed genetically modified, and a new organism in New Zealand under the HSNO Act. The gene edited fast-flowering apple trees would be developed and field tested in containment, and following plant crossing, the resulting version without the fast-flowering gene would still need to be approved by the Environmental Protection Authority for release from containment and conditional release. This would be because the HSNO Act defines *genetic modification* as any organism in which any of the genes or other genetic material are inherited, or otherwise derived, through any number of replications, from genetic material which has been modified by *in vitro* techniques.

Since gene edited apples contain viable seeds, gene edited apples would meet the definition of a living modified organism (LMO) in the Cartagena Protocol, and therefore exports would be legally bound to the Imports and Exports (Living Modified Organisms) Prohibition Order 2005. The gene editing technique may also be deemed an agricultural compound for the purposes of the Agricultural Compounds and Veterinary Medicines Act.

Risks and potential benefits

The primary beneficiaries of the proposed scenario would be apple breeders as they would be able to rapidly introduce traits into prized plant varieties through rapid breeding cycles and help New Zealand remain competitive in international markets. Indirectly this would then benefit growers and consumers depending on the traits that were modified. As the resulting cultivars would no longer contain the edited flowering gene, the only risks would be off-target effects, that is genetic changes that might occur in other parts of the genome as a result of the gene editing and might have negative effects. Genetic sequencing would, however, be able to identify if any off-target effects had occurred.

SCENARIO FOUR

PROTECTING TAONGA SPECIES USE IN THE PRIMARY INDUSTRIES

SPECIES

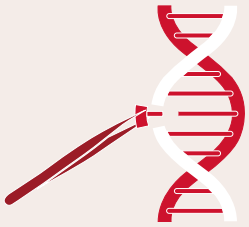
Mānuka

PROBLEM

Vulnerability to disease

GENE EDIT

Increased disease resistance



OUTCOME

Protect taonga species and allow mānuka honey industry to thrive

Agricultural and environmental considerations

Disease resistance would need to be introduced into a range of mānuka varieties, while ensuring growth is not affected.

Ethical and social considerations

Active engagement with Māori collectives would be needed on whether this approach is appropriate and useful.

Legal considerations

As taonga, mānuka need to be preserved and sustainably managed under the Resource Management Act, the National Parks Act and the Biosecurity Act.

Risks and potential benefits

Mānuka would be protected from disease, but honey from gene-edited mānuka could be considered unnatural.

Extracts of leaves and bark from mānuka have been used by Māori, and in modern day medicine, for treatment of a wide range of ailments. Mānuka is found throughout New Zealand and grows in many different habitats.

Mānuka is insect and bee pollinated and recently a burgeoning business has developed from the harvesting and niche marketing of mānuka honey, which in 2016 was worth up to $148 per kilogram. However, the potential arrival of new plant diseases, such as myrtle rust, raises considerable concern about the potential threat to mānuka and other members of the Myrtaceae family (e.g. kānuka, pōhutukawa and rātā). While there may be uncertainty about the future impact of pathogens on this group of highly valued native species, plans are in place to collect seed to deposit in seed collections and research is underway to find ways to mitigate the impact of future disease.

Gene editing could be used to switch off genes in mānuka that make the plant susceptible to infection, or to add genes found in different mānuka plant varieties that offer resistance to infection. Such genes would first need to be identified.

Agricultural and environmental considerations

If only a limited range of mānuka ecotypes/provenances are gene edited then there is the potential that these disease-resistant types will have increased fitness and may spread throughout the country. This spread could potentially affect the genetic diversity of the species in New Zealand. One solution would be to cross breed disease-resistant, gene edited mānuka from a wide range of origins before release. Gene-edited mānuka could also result in resistance to many microbes, including beneficial ones. This could be managed by research on the growth of resulting gene edited mānuka lines, under differing environmental conditions, prior to field release.

Ethical and social considerations

Gene editing a valued native species would require active engagement, participation by, and ongoing consultation with, Māori collectives on whether this approach is appropriate and useful for Māori as kaitiaki (guardian). Māori worldview perspectives, Māori cultural norms and other holistic considerations, including environmental, social and economic benefits and risks, would be considered during these decision making processes to ensure adequate protections are adhered to and to maintain balances and protocols. Ultimately, Māori would consider whether the whakapapa (relationship), mauri (life force), and mana (justice and equity) of the mānuka, and of the Māori themselves, are not adversely impacted or irreversibly destroyed. Products derived from gene edited disease-resistant mānuka could preserve jobs in regions such as East Cape and Northland, due to the maintenance of a thriving and resilient mānuka honey and oils industry. Māori communities could also actively lead and contribute to research efforts.

For some, gene edited disease-resistant mānuka will be seen as enabling the responsibilities of kaitiakitanga (guardianship) by contributing to long term conservation of the species and maintaining ecosystems where mānuka is an integral species. It could be seen to have a positive impact by conserving species interconnected with other species (human, game animals, bees, beneficial fungi). However, for others, there may be opposition to the use of the technique, as gene editing mānuka may alter, or impact, the mauri, or essential life force of mānuka, or its natural properties. The economic interests of Māori and other producers are also likely to be negatively impacted if gene editing is poorly perceived by consumers of mānuka honey products.

Some may also argue that there is a special value in animals and plants that live without the influence of people – nature is wild and should exist without human influence. Therefore, even though disease-resistant mānuka can be created through use of this technology, this replacement would be a cultural artefact, which does not have the natural value of the original. Others, however, argue that humans and nature cannot be separated in this way, and that efforts in restoring nature are valuable for nature itself, as well as any benefits for humans. Moreover, the alternative of not doing anything to help mānuka survive disease challenge, may also risk losing mānuka completely.

Legal considerations

Mānuka are tāonga (precious) species, are native to New Zealand and, therefore, a matter of national importance to be preserved, sustainably managed and protected, under the Resource Management Act, the National Parks Act and the Biosecurity Act. Gene edited mānuka trees would be deemed genetically modified, and a new organism, under the HSNO Act. The gene edited mānuka would be developed and field tested in containment, and then an application made to the Environmental Protection Authority for release. Release allows the new organism to move within New Zealand free of any restrictions other than those imposed by the Biosecurity and Conservation Acts.

The gene editing system may be deemed an agricultural compound for the purposes of the Agricultural Compounds and Veterinary Medicines Act. According to the Cartagena Protocol, gene edited mānuka would meet the definition of a living modified organism (LMO) resulting from modern biotechnology if it possessed a novel combination of genetic material, but the honey from the mānuka would not likely be classified in this way.

Risks and potential benefits

The economic benefits of protecting mānuka in this way would be to allow continued production of mānuka-derived products, such as oils and honey, and to protect mānuka plants from new pathogens. Economic risks may include the perception by some of gene edited mānuka as unnatural, which could negatively affect the New Zealand honey industry. Such campaigns may be triggered nationally and globally by competitors to the mānuka honey industry.

SCENARIO FIVE

PROVIDING NEW HUMAN HEALTH BENEFITS

SPECIES

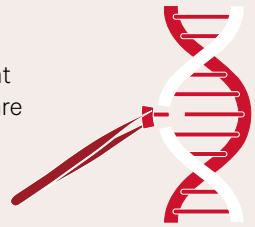
Cow

PROBLEM

Milk is a nutritious food but some people are allergic to milk proteins

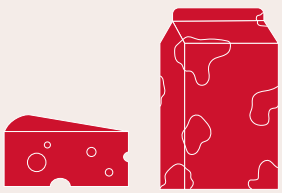
GENE EDIT

Remove gene for protein that some people are allergic to



OUTCOME

Allergen removed, and increased market for dairy products



Agricultural considerations

New traits could be rapidly introduced into prize breeds.

Ethical and social considerations

Views on genetic modification would be weighed against the advantages of reduced allergen levels.

Legal considerations

The milk from gene edited cows would require approval from Foods Standards Australia New Zealand.

Risks and potential benefits

Would allow sufferers of this milk allergy to drink milk, but would not remove all milk allergens.

With its high nutritional value and potential for a safe and secure food supply, humans have embraced cows' milk as a major source of nutrition to promote human health and wellbeing. But the consumption of cows' milk is not universally tolerated and can cause allergic reactions, ranging from mild to life-threatening symptoms, particularly in infants.

Cows' milk contains the milk protein beta-lactoglobulin, which has no equivalent in human milk or anywhere else in the human body. It can raise a strong immune reaction resulting in high levels of antibodies in people with allergies against this protein. Total elimination of beta-lactoglobulin from cows' milk is the safest option to minimise the allergenic potential and produce a milk that could provide a valuable source of nutrition for those consumers that currently cannot eat or drink dairy products from cows due to an allergic immune response against beta-lactoglobulin.

A gene editing approach could eliminate the allergy-causing protein from cows' milk by disrupting the gene in cows responsible for its production. This can be achieved by introducing a small deletion that disrupts that gene. In cows, this can be done by introducing the beta-lactoglobulin-specific CRISPR gene editor into one-cell cow embryos. The only change to the genome will be a deletion in the beta-lactoglobulin gene, allowing the appearance of the desirable traits within a single generation.

Agricultural considerations

Gene editing in animals has not merely accelerated research but made research possible that had been previously unfeasible. Because the generation interval in most commercial animals is long (typically three to four years) and their reproductive rates are often low (for example, one offspring per generation in cattle, although as many as 15 in pigs), the cross breeding strategies that are used so effectively in plant breeding are considerably less productive in most livestock. On the other hand, the method of reproduction, which allows the manipulation of embryos, makes animals more responsive to gene editing.

The New Zealand dairy industry is presently based on bulk milk production. The beta-lactoglobulin-free milk would be a high value, speciality product with health benefits for only a defined group of people. It would, therefore, require a separate supply/value chain. Meat from the gene edited dairy cows would also enter the food chain. Beta-lactoglobulin free milk would have an additional benefit of improved processing efficiency in milk factories as the beta-lactoglobulin protein fouls the heat exchanges in milk processing plants.

Ethical and social considerations

People's interactions with food, and being able to choose what they eat in response to personal allergies, is important. There will be social and ethical issues around people's views on genetic modification of animals and the milk and meat produced from such animals, which will need to be weighed against the advantages of reduced allergen levels. Some people may have ethical concerns around the disruption of species boundaries, or the nature, or mauri, of the animals modified, and the welfare of animals used in the research and development.

Legal considerations

Gene edited cows and their offspring would be deemed genetically modified, and a new organism in New Zealand under the HSNO Act. The gene edited cows would be developed and field-tested in containment, and an application made to the Environmental Protection Authority for release. The Animal Welfare Act covers the use of animals in research, with the gene editing procedure for beta-lactoglobulin-free milk requiring animal ethics approval. The gene editing machinery used to make milk free from beta-lactoglobulin may be deemed an agricultural compound for the purposes of the Agricultural Compounds and Veterinary Medicines Act.

To eventually make beta-lactoglobulin-free milk available for people affected by milk protein allergies, the milk would require both regulatory approval according to the Food Standards Australia New Zealand (FSANZ) standard for 'Food produced using gene technology', and safety assessment to demonstrate the product is safe to eat. It is likely that other products from culled dairy cows, such as meat used for burger patties, will also need to be assessed by FSANZ, and labelled as a food derived from genetic modification. Food sold in a café, restaurant or takeaway is exempt from these labelling requirements.

Gene edited cows, gametes (sperm) and embryos (but not milk or meat) would meet the definition of a living organism and a living modified organism (LMO) resulting from modern biotechnology under the Cartagena Protocol, unless it can be shown through bovine genomic sequencing that this deletion is naturally occurring in other breeds or populations of cow. Exporters would need to comply with the Imports and Exports (Living Modified Organisms) Prohibition Order 2005.

Risks and potential benefits

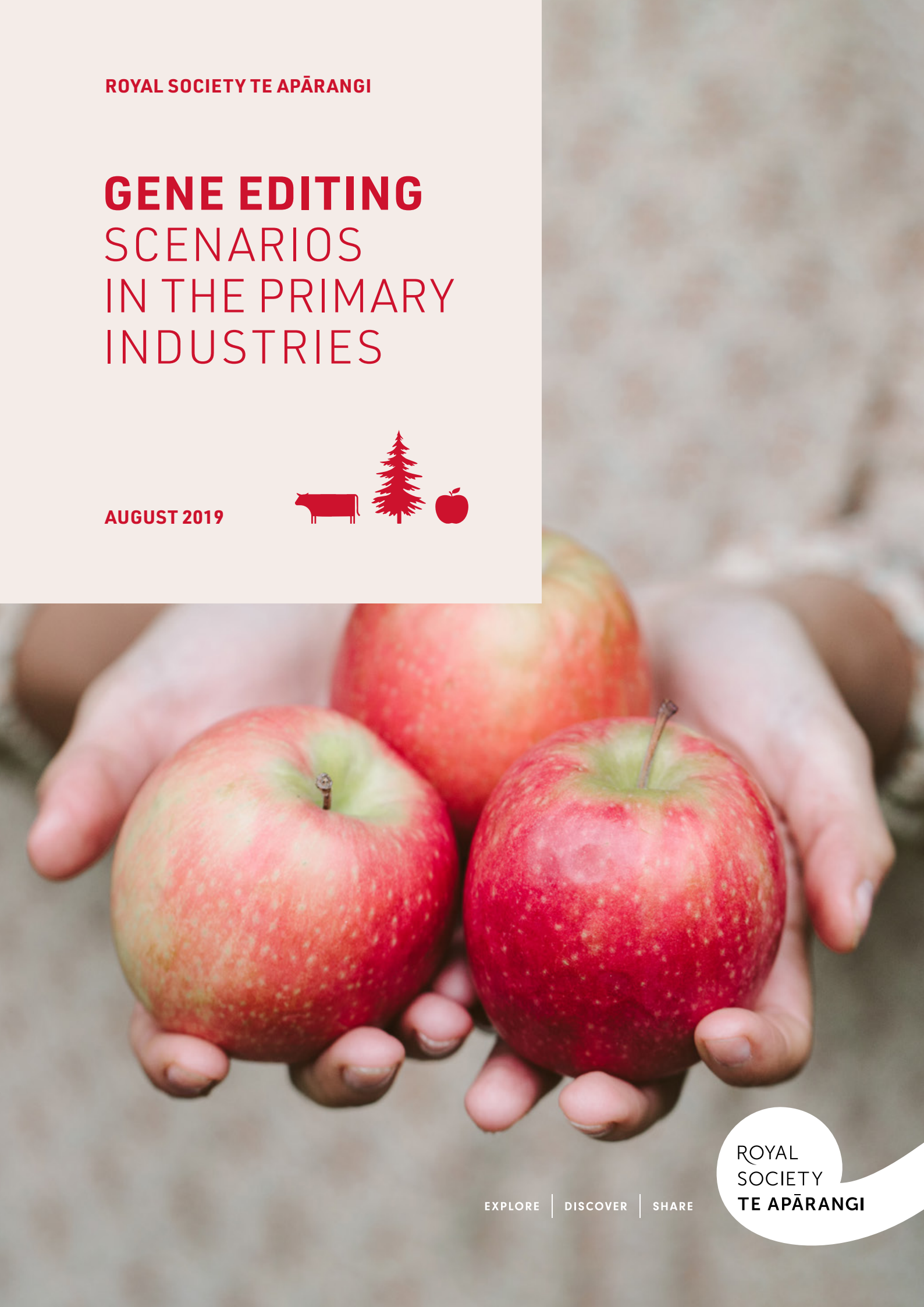
The benefit of this milk would be to provide a high quality protein source to sufferers of beta-lactoglobulin milk allergies and in particular infants, who are otherwise unable to consume cow's milk. While beta-lactoglobulin is a major cows' milk allergen, some people will have allergic reactions not only to beta-lactoglobulin but to other milk proteins, or will be lactose intolerant. Care is therefore needed when promoting the milk as 'allergen free', and tolerance to any substitute milk needs to be appropriately assessed.

Taupo, New Zealand

ROYAL SOCIETY TE APĀRANGI

GENE EDITING SCENARIOS IN THE PRIMARY INDUSTRIES

AUGUST 2019



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ROYAL SOCIETY TE APĀRANGI

Taupo, New Zealand

BACKGROUND

A revolution in gene editing technologies is making it easier to change genetic material. This has implications for 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 our understanding and regulatory frameworks, and any consensus on the rights and wrongs of how it should be used.

To explore the implications of gene editing technology for New Zealand, Royal Society Te Apārangi has convened a multidisciplinary panel of some of New Zealand's leading experts to consider the implications of gene editing technologies for New Zealand to:

- Raise awareness of the scientific possibilities and associated public issues of gene editing technologies to inform debate
- Provide information and guidance for policy makers to address current and new issues that need to be clarified or resolved
- Show where gene editing applications are covered by established policies and regulations and where changes are needed
- Provide a New Zealand perspective to the global discussion on this technology and identify where global consensus is important.

This paper is one of a series[1] produced by the panel considering the implications of the technology in health, pest control, agriculture and forestry, and is accompanied by a companion summary, and a fact sheet on how these technologies work and are being used and applied [1].

To help consider the implications for primary production in New Zealand, five scenarios in which gene editing might be used are highlighted, and the implications that might arise are identified. These case studies consider:

- uses of the technology within and outside the human food chain
- use of the technology in agricultural plants and animals
- what the potential harms and benefits are.

The panel was not able, however, to undertake an economic cost/benefit export analysis for the different scenarios.

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

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Acknowledgements

This technical paper was produced by a Royal Society Te Apārangi Expert Panel, with support and advice from a Māori Reference Group, who ran a huihuinga with whānau Māori in Wellington in October 2018 to seek Māori views on gene editing in the primary industries. The work of the Panel has been informed by consultation with several experts and organisations who have provided valuable input in contributing to and commenting on the paper (Appendix 1). Stakeholder workshops were also held in Hamilton, Napier and Dunedin to seek feedback on the gene editing in primary industries scenarios in October 2018. These consultation processes helped inform the Panel's work, but could not be fully comprehensive in their collection of views.

Primary industries in New Zealand

New Zealand, unlike many OECD countries, has an economy and self-image that are closely linked to land and sea-based managed ecosystems and the natural environment. New Zealand's productive capacity has flourished through the introduction of plants and animals, and the managed ecosystems they create are critical to our economy. Over 60% of New Zealand, inclusive of off-shore islands, is used for agricultural production, including forestry [1].

In 2017, agriculture, forestry and their respective products contributed $24 billion to the New Zealand economy, almost 10% of GDP[2]. Of New Zealand's top 25 exports in 2018, 12 were agricultural and forestry products, representing 21% of all New Zealand exports, with 51% of these to China, 19% to the EU, 10% to the US, 13% to Australia, 4% to United Arab Emirates, and 4% to Malaysia[3]. However, New Zealand's primary industries are under pressure from a changing climate, impacts on the environment, new pests and pathogens, innovations in synthetic foods, competition from other countries' exports and changing market access.

History of genetic selection in agriculture

The success of our agriculture, horticulture, aquaculture and forestry industries has been helped by our ability to identify, select and breed desirable traits into commercial species. New traits generally arise within a population through spontaneous mutation of genes within the genome of the organism. By selecting for those desirable traits, be they single gene mutations or highly polygenic combinations, animal and plant breeders are able to concentrate these traits within the population; a process known as selective breeding [2]. This process of selective breeding started as early as the Neolithic period, when early farmers started selecting individual plants and animals with superior traits or performance [3, 4].

In the absence of any knowledge of genetics this would have been a very time consuming and laborious process. Nevertheless, some of the results from this selective breeding were spectacular, such as the selection of maize and wheat. In the case of maize, it is now known that as few as five genetic changes account for the major differences in the size of the flower head (or ear/cob) in comparison with that of its ancient ancestor, teosinte [5], while we know that wheat is a complex hybrid of three different species [6]. Current breeding approaches of crop plants and animals[4] involve a variety of methods to accelerate and refine the selective breeding process. These include selection based on appearance, the use of mutagenic agents, the use of DNA markers in approaches such as genomic selection, marker assisted selection[5] and backcrossing and, in the last 35 years, genetic modification involving the insertion of genes from related and unrelated species. This has come to be referred to as genetic modification (GM), though conventional breeding also results in varieties that are modified genetically compared to their varietal ancestors.

The discovery of X- and gamma-rays and, in the 1920s the demonstration that they were highly mutagenic, provided a new tool (*radiation induced mutagenesis*) for plant breeders to generate mutations at a higher rate and so create a wider range of variants from which to select for new traits. However, because of the random nature of the changes, generating mutants with desirable traits, or without undesirable ones, remained a challenge.

Likewise, experiments in the 1940s demonstrated how certain chemicals such as ethylmethanesulfonate could be used as mutagenic agents (*chemically-induced mutagenesis*) to increase the mutation rate to generate random variation in the population from which new plant cultivars could be selected. While the radiation and chemically-induced mutagenesis techniques used over the last 75 years [7] have been useful tools for generating variation within a genome as part of conventional breeding, the position and number of induced changes cannot be controlled. Mutagenesis results in many genetic changes requiring time consuming screening and selection processes to identify those few organisms which carry beneficial mutations.

[2] Statistics New Zealand. National accounts (industry production and investment): Year ended March 2017. Table 2 (Agriculture, Forestry & Logging, Food manufacturing, Wood & paper manufacturing).

[3] Statistics New Zealand. Goods and Services Trade by Country: Year ended June 2018. Table 4.

[4] mpi.govt.nz/funding-and-programmes/primary-growth-partnership/completed-pgp-programmes/the-new-zealand-sheep-industry-transformation-project-nzstx/

[5] Screening for genetic markers to identify whether offspring contain a gene of interest.

Early DNA modification methods were developed in the 1970's, and by the 1980's gene delivery systems such as *Agrobacterium* enabled the transfer of novel genes into plants. However, the ability to target the gene to a specific site in the genome or to modify specific genes remained very difficult.

Genetically modified (GM) plant crops, made using DNA modification and gene insertion methods, are now used in production systems for some of the major commodity crops including soybean, corn, canola, cotton, potato, squash, alfalfa, papaya, and sugar beet [8]. This generation of GM crops typically involves the introduction of genes from another species that, for example, confer resistance to insect pests or resistance to specific herbicides to manage weeds. The production area of GM crops is significant and growing. Currently, 24 countries grow GM crops, accounting for 10% of the world's arable land, covering 189 million hectares [8, 9]. While there are many examples of GM technology being used to generate transgenic animals for research and commercial developmental purposes, there is currently only one example of a genetically modified farm animal in commercial food production (GM salmon[6]).

Te Ao Māori

Like many other cultures, pre-European Māori practiced selective breeding, as evidenced by cold-adapted kumara varieties and tribal narratives. This history of food harvesting and production in Aotearoa New Zealand and their holdings in land and fish-quota have led Māori, in the modern era, to have significant interests in New Zealand's primary sector and, in some cases, direct interests in commercial plant and animal breeding programmes. One example of Māori involvement in plant breeding is the Ngai Tahu-owned company ProSeed, which produces commercial quantities of seed from radiata pine and other tree species. Indirectly, virtually all of the commercially grown non-indigenous species are of interest to Māori entities involved in primary production. Moreover, because Māori have kaitiaki rights under the Article 2 of the Treaty of Waitangi, commercial production systems are of interest to Māori on land over which mana whenua iwi ostensibly have rights. Māori also assert kaitiaki rights over indigenous species, including genetic resources, although this is not currently recognised in New Zealand law. The long histories of interaction with indigenous species that have led to specialised knowledge of many indigenous plants and animals, in addition to the emotional and spiritual connections with indigenous biota within a broader whakapapa context, further underpin the significance of indigenous species to Māori.

Use of modern gene editing techniques

The recent development of gene editing tools such as CRISPR[7] that enable a broad scope of more precise changes in the genome are enabling rapid advances in microbe, plant and animal research and breeding. These genetic modification techniques use gene repair mechanisms to insert, remove, replace or modify genes at predetermined sites in the genome [10] (See Box). The precision of gene editing technologies has been improving over the last 10 years, substantially reducing the frequency of changes in random locations and in some cases not using, or leaving behind, foreign gene sequences following manipulation [11-16]. In plants, this has resulted in a significant improvement over past genetic engineering technologies [11], which either used bacteria or viruses, or involved coating small metal particles with the DNA, and then 'shooting' the particles into cells, to transfer the DNA to random sites in the genome [17]. In animals, gene editing technology has also resulted in major improvements in accuracy [18, 19], although as observed for plants, unintended changes can still occur [20]. With modern gene sequencing, any unintended insertions can be identified and, if undesirable, can be eliminated from the breeding programme.

Gene editing can include everything from adding a new, long sequence of DNA (e.g. multiple foreign genes), to cutting a specific DNA site to cause small, random changes, to changing a single nucleotide to create a version of the gene that already exists in nature. Hence, some gene editing events will be indistinguishable from naturally occurring variation or variation induced by mutagenesis, while other events will be more similar to the insertion of new engineered genes using older GM technology.

[6] jstor.org/stable/90008659?seq=1#page_scan_tab_contents

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

There are now a number of research examples of the effectiveness of this approach in improving plant traits (e.g. drought tolerance, disease resistance, fruit ripening, grain number and size within the major crop species [21-27]) and animal traits (e.g. angora coat length, increased meat yield, lack of horns and disease resistance [28-32]). This new technology can use existing variation within the plant or animal population or introduce gene sequences equivalent to those in related species. Such an approach has an advantage over traditional breeding methods by, in some cases, enabling continuous improvement of elite cultivars and breeds, without potentially introducing deleterious versions of genes from crossing and recombination or requiring time-consuming plant and animal breeding to restore the original elite genetic background. In a plant breeding context, gene editing can in some cases rapidly generate improved cultivars with no trace of 'foreign' DNA. There is also considerable potential for domestication of new crops that are better adapted to more extreme climate, soil and nutrient conditions [21]. Gene editing is a powerful new breeding tool: it relies on information about the genome of the species; requires bioinformatics tools to interrogate the DNA sequence of the genome; as well as knowledge of the genes that underpin traits of interest and understanding of the impact that gene editing-induced modifications have on the target gene and other genes and characteristics. Applying these relies on overcoming important non-trivial obstacles.

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)[20]. In 2012, it was discovered that, by modifying this mechanism, it was possible to target and cut any DNA sequence and edit genomes in a very precise manner [21]. 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 [22].

For some species there are still major technical barriers to getting the enzymatic machinery into the cell nucleus to make the desired edits, and then turning edited cell lines into adult plants and animals. More generally, our understanding of many important traits means that we do not know which genes to target, and it is likely that for some traits with complex genetic architectures gene editing may be of limited use since many changes in particular combinations will be required.

Genomics research in New Zealand

An important first requirement for gene editing is to first have a knowledge of the gene sequence(s) to be edited. Several New Zealand Crown Research Institutes (CRIs) have been involved in programmes to sequence and improve our knowledge of the genomes of crop plants and domesticated animals of importance to New Zealand's primary production systems. Examples include AgResearch's involvement in sequencing the sheep genome [33] and improving ryegrass genetics [34], Plant & Food Research in sequencing the genomes of apple, pear and kiwifruit [35-37], and Scion's ongoing efforts in sequencing the very large genome of radiata pine[8]. Further, functional genomics research is also being undertaken to identify the genes that underpin important traits in these plants and animals.

The new Ministry of Business, Innovation and Employment's advanced genomics platform, Genomics Aotearoa[9], is providing advanced genome sequencing and bioinformatics capabilities across New Zealand's universities and CRIs, to keep New Zealand crop and animal production at the forefront of technology and land efficiency, respond to pests and diseases, and improve human health. These capabilities are likely to be applied to a range of New Zealand-grown species such as cattle, sheep, radiata pine, ryegrass, apples and kiwifruit. While this information will be critical for conventional breeding scenarios, it will provide some of the underpinning information, such as genome sequences and annotation, needed to implement gene editing.

Genomics Aotearoa is working with Māori to ensure work in this area takes into account Treaty of Waitangi obligations, and to develop culturally informed guidelines for the application of genomics in indigenous species.

[8] scionresearch.com/about-us/news-and-events/news/2017/radiata-pine-genome-draft-assembly-completed

[9] otago.ac.nz/genetics/news/otago659624.html

Genomics and agriculture internationally

Table 1 lists the crop plant species used for food for which genome sequences are available [35, 37-42]. This number is growing as the cost of genome sequencing reduces, and the speed with which it can be accomplished accelerates.

TABLE 1 | List of agricultural crops that have had their genome sequenced

Scientific name	Common name	Economic importance
Actinidia chinensis	Kiwifruit	Food (fruit)
Beta vulgaris	Sugar beet	Sugar production
Brassica napus	Rapeseed	Oil, animal feed, biodiesel
Brassica oleracea var. *capitata*	Cabbage	Food (vegetable)
Brassica rapa	Chinese cabbage	Food (vegetable)
Cajanus cajan	Pigeon pea	Food (grain/pulse/bean)
Carica papaya	Papaya	Food (fruit, vegetable)
Capsicum annuum	Hot pepper	Spice
Cicer arietinum	Chickpea	Food (grain/pulse/bean)
Citrullus lanatus	Water melon	Food (fruit)
Citrus clementina	Clementine mandarin	Food (fruit)
Citrus sinensis	Sweet orange	Food (fruit)
Coffea canephora	Robusta coffee	Food (grain/pulse/bean)
Cucumis melo	Melon	Food (fruit)
Cucumis sativus	Cucumber	Food (vegetable)
Elaeis guineensis	Oil palm	Edible oil
Fragaria vesca	Strawberry	Food (fruit)
Glycine max	Soybean	Food (grain/pulse/bean)
Leptospermum scoparium	Mānuka	Food (honey)
Malus x domestica	Apple	Food (fruit)
Musa acuminata	Banana	Food (fruit)
Oryza sativa subsp. *indica*	Rice	Food (grain/pulse/bean)
Phaseolus vulgaris	Common bean	Food (grain/pulse/bean)
Phoenix dactylifera	Date palm	Food (fruit)
Prunus mume	Chinese plum/mei	Food (fruit)
Prunus persica	Peach	Food (fruit)
Pyrus bretschneideri	Asian pear	Food (fruit)
Pyrus communis	European pear	Food (fruit)
Rubus occidentalis	Raspberry	Food (fruit)
Solanum lycopersicum	Tomato	Food (vegetable)
Solanum melongena	Eggplant	Food (vegetable)
Solanum tuberosum	Potato	Food (vegetable)
Sorghum bicolor	Sorghum	Food (grain/pulse/bean)
Theobroma cacao	Cocoa	Food (grain/pulse/bean)
Triticum aestivum	Bread wheat	Food (grain/pulse/bean)
Vaccinium corymbosum	Blueberry	Food (fruit)
Vaccinium macrocarpon	Cranberry	Food (fruit)
Vigna radiata	Mungbean	Food (grain/pulse/bean)
Vitis vinifera	Grape	Food (fruit), beverage
Zea mays	Maize	Food (grain/pulse/bean)

Regulation of gene editing in New Zealand and internationally

Gene editing is considered genetic modification under current law and regulation in New Zealand. This means all uses of the technology must be approved by the Environmental Protection Authority and any releases into the environment are subject to public consultation through a series of hearings. Experience has shown that these hearings can be protracted and expensive.

Many other countries are also grappling with how to define and regulate gene edited plants and animals, given that many (but not all) gene edited organisms will be indistinguishable from those generated by traditional plant and animal breeding processes [43]. For instance, one approach to accelerate plant breeding uses gene editing to reduce time to flowering. This typically involves an intermediate generation of GM plants where the gene editing machinery is inserted to shorten the time to flowering, speeding up the breeding process (see the apple breeding scenario). The inserted genes, as well as the edited target, are later removed by conventional crossing with non-GM plants, so that no foreign genetic material or edited genes remain in the resulting crop [16, 44]. In addition, not all countries are subject to the same international obligations, which has a bearing on the kinds of domestic regulations they have in place[10].

The USA chose to use existing regulatory frameworks to manage genetically modified plants and animals; principally the USDA for plants, the EPA for environmental releases and the FDA for food and animals. The FDA has, for example, co-opted its regulations designed for animal drugs to regulate GM animals. In 2016, USDA approved the cultivation and sale of a gene edited mushroom and waxy corn[11] without regulation [45]. More recently, the USDA stated that under its biotechnology regulations, it will not regulate, nor has any plans to regulate, plants that could otherwise have been developed through traditional breeding techniques, as long as they are developed without the use of a plant pest as the donor or carrier and they are not themselves a plant pest [46, 47]. The FDA on the other hand has indicated in draft guidance released in 2017 that animals with 'intentionally altered DNA' (i.e. which are gene edited) would likely continue to be considered and regulated as GMOs[12].

In August 2018, an expert committee in Japan recommended that only gene editing which involves foreign genes should be regulated and that gene editing that involves switching off or deleting genes already present in the genetic code of organisms should not require government approval[13].

Coming to a similar conclusion, the Swedish Board of Agriculture has decided that plants mutated by CRISPR that do not contain any foreign DNA sequences, are exempted from GM legislation[14]. Canada has also decided to regulate on a case-by-case basis focusing on the risks associated with the outcome of the modification (new traits) rather than the process used to generate the change [48]. This trait-based approach is in line with their regulation of other forms of genetic modification and is analogous to the regulation of new medical products, in that it takes into account the context in which the product will be applied [49].

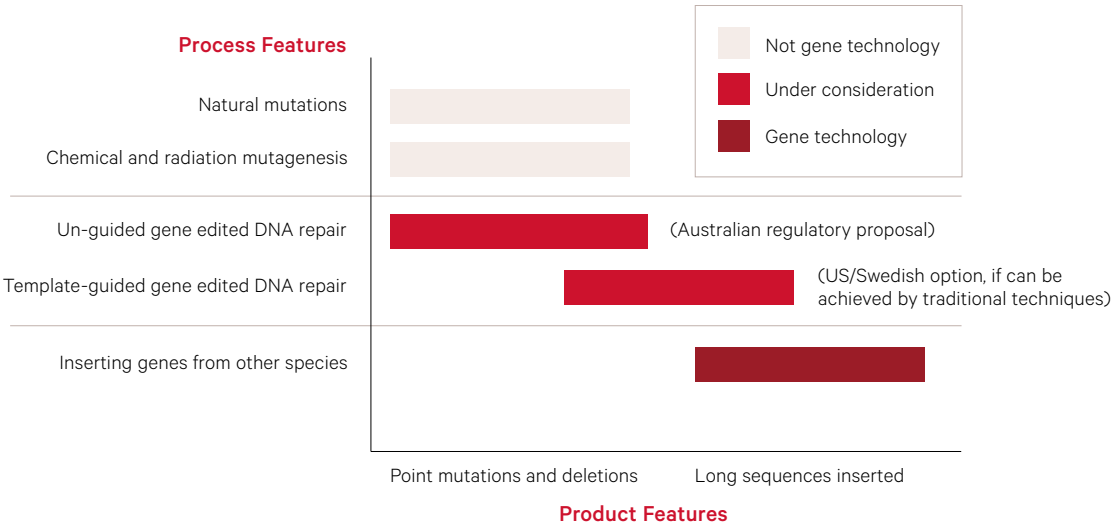
An opinion recently issued by the Advocate General of the European Court of Justice in March 2018 considered that EU GMO regulations were not applicable to certain gene edited plants and animals [50, 51]. European regulations exempt traditional mutagenesis from GM regulations, thereby plants and animals possessing novel traits produced by radiation or chemical mutagens are not regulated as GMOs. The European Advocate General suggested that the mutagenesis exemption should not be confined to mutagenesis techniques such as radiation and chemical mutagens, as they were understood in 2001 when the original European GMO Directive was drafted, but should also include new techniques that induce mutations, such as the gene editing tools Zinc finger nucleases, TALENs and CRISPR [46, 52]. However, in July 2018, the Court of Justice of the European Union provided its judgement that organisms created through new gene editing techniques are not covered by the Directive's 'mutagenesis exemption' and are thereby subject to the same rigorous risk assessment, product development and trade requirements as transgenic plant varieties [53].

In Australia, a technical review of the Australian Gene Technology Regulations 2001 was initiated in October 2016 [54]. Under proposed recommendations, gene editing, without introduced templates to guide genome repair, would not be regulated as GMOs as the repairs would be guided by the cell's normal repair processes. Similarly, organisms modified by introduced RNA that blocks gene expression (RNAi) would not be deemed GMOs, provided the RNA does not give rise to any change in the genome sequence.

Figure 1 outlines these different approaches.

FIGURE 1 | Comparison of international regulatory scenarios for gene editing[15]

Note: Natural mutations can also involve long sequences being inserted, e.g. transposon insertions.



GM-Free Districts

At the time of writing several councils (Far North[16], Whangarei[17], Auckland[18] and Hastings[19]) have, or are consulting on, restrictions on the use of genetic modification in the environment, under the Resource Management Act 1991, while exempting medical and veterinary uses. This restriction would include those organisms that may have been approved for release by The Environmental Protection Authority (EPA).

Regulation of gene edited food and food products in New Zealand

Half of New Zealand's domestic food supply in 2013 was imported[20]. Food standards for regulation of food and food products sold in Australia and New Zealand are set by the independent regulatory agency, Food Standards Australia New Zealand (FSANZ). The current policy is that all food produced using gene technology cannot be sold unless it has been assessed and listed in Schedule 26 of Section 1.1.1-10 of the New Zealand (Australia New Zealand Food Standards Code) Food Standards 2002.

To date, 88 varieties of genetically modified canola, corn, potato, rice, soybean, sugar beet, and lucerne (alfalfa) are approved for use in foods in Australia and New Zealand. None of these have been derived from gene editing, and none are currently grown in New Zealand[21].

However, in response to the development and application of a number of new breeding techniques, including gene editing, FSANZ is undertaking a review of the Food Standards Code to assess its application to food products of new breeding techniques, and to consider the definitions of '*food produced using gene technology*' and '*gene technology*' [55].

[10] Neither Canada, Australia nor the US are bound by the Cartagena Protocol as the US is not a party to the Protocol, and Canada and Australia have not ratified the agreement. The EU, New Zealand, China and Japan have ratified the agreement.

[11] pioneer.com/CMRoot/Pioneer/About_Global/Non_Searchable/15-352-01_air_response_signed.pdf

[12] fda.gov/regulatory-information/search-fda-guidance-documents/cvm-gfi-187-regulation-intentionally-altered-genomic-dna-animals

[13] mainichi.jp/english/articles/20180821/p2a/00m/0na/033000c

[14] upsc.se/documents/Information_on_interpretation_on_CRISPR_Cas9_mutated_plants_Final.pdf

[15] ogtr.gov.au/internet/ogtr/publishing.nsf/Content/reviewdiscussionpaper-htm

[16] fndc.govt.nz/services/the-far-north-district-plan

[17] wdc.govt.nz/PlansPoliciesandBylaws/Plans/DistrictPlan/Documents/District-Plan-Part-E-District-Wide/GMO-Genetically-Modified-Organisms.pdf

[18] aucklandcouncil.govt.nz/plans-projects-policies-reports-bylaws/our-plans-strategies/unitary-plan/history-unitary-plan/ihp-designations-reports-recommendations/Documents/ihp024gmos.pdf

[19] hastingsdc.govt.nz/our-council/news/latest-news/press-releases/article/1038

[20] FAOSTAT, Commodity Balances -Livestock and Fish Primary Equivalent & Commodity Balances – Crops Primary Equivalent. Food and Agriculture Organization of the United Nations, Rome, Italy. fao.org/faostat/en/#data

[21] foodstandards.govt.nz/code/Pages/default.aspx

Ethical questions

As noted by the Nuffield Council on Bioethics [3], food production is one of the necessities of human life, and is also a matter of deep social significance, often rooted in cultural, ethnic, religious and social practices, such as fairness, freedom, harm/benefit, and sanctity or purity [56]. Many of the resulting questions relating to genomic manipulation of foods that we eat are common to both plants and animals and involve complex moral, political and scientific considerations.

Opinions on genetic modification are often dependent on an individual's broader worldview [57]. For some, genetic modification of plants and animals is not wrong according to their ethical principles. This could perhaps be because they see gene editing as a logical continuation of selective breeding; an ethically permissible practice that humans have been carrying out for years; or because of views that human life is more important than animal/plant life. There can also be a belief that if, for example, gene editing creates animals or plants that help to develop new human medicines or which have positive outcomes for the environment, then we may have an ethical obligation to create and use them.

For others, genetic modification may go against their ethical principles in a variety of ways [58]. For example, costs may be seen to outweigh benefits because of the perception that the ultimate cost is the violation of species integrity and disregard for the inherent value of plants and animals. Some may view a plant or animal's whakapapa as something that cannot or should not be altered, and therefore altering the whakapapa would be ethically wrong. Others may simply see genetic modification as wrongfully exaggerating an imbalance of power between humans and nature, in effect 'playing god'. In addition, there may be those who feel strongly opposed to certain applications of genetic modification, but more accepting of others. For example, recent evidence suggests that some individuals may be more accepting of biomedical applications than those relating to food production [59, 60].

In a recent UK study on the potential uses for genetic technologies [61], the contexts that moderated public acceptability of pursuing UK research into genetic technologies included applications that:

- Promote equitable access to genetic technologies as they are developed
- Prioritise collective welfare
- Enable the science to develop further and knowledge of future applications to be extended
- Provide cheaper health interventions
- Prioritise positive and reduce negative environmental impacts
- Have benefits to society that outweigh risks to human health, animal welfare and the environment
- Alleviate suffering
- Use transparent processes.

Applications that were unacceptable to many were those which:

- Edit out difference and create a monoculture
- Prioritise individual and/or corporate wealth
- Drain currently over-stretched healthcare resources
- Enable humans, plants or animals to be weaponised
- Are introduced with insufficient safety monitoring or measures
- Restrict freedom to choose whether they should be applied or not, e.g. enforced genetic screening
- Reduce biodiversity or harm the ecosystem and related food chains
- Contaminate plants or animals not grown or reared using genetic technologies
- Are not sufficiently regulated and equally are so over-regulated as to stifle scientific progress.

There is also an entanglement between technology and big business in agriculture. The opposition to the use of these genetic technologies is often associated with the concern around ownership of food resources.

Genetic modification, branding and economic returns

Successful branding depends on consumer beliefs and responses rather than on analysis [62, 63]. For example, consumer food choice is more strongly influenced by branding and price than by nutritional quality. While consumer choice may change in response to information, the process of informing can be a very long one [64].

There are a range of views about the desirability of genetically modified (GM) crops and animals in New Zealand [65-67], which may have relevance to gene editing. Social science and public policy research suggests that if the choices of individuals are independent, the choice over the use of GM crops and animals can be left to individuals in the relevant market. However, when the actions of one producer constrain the reasonable choices of other producers, there might be a case for public intervention [68-70]. This would be the case if there is a feasible intervention, and the intended consequences of the intervention generate an increase in public welfare [71]. Clearly, these balances need to be considered with gene edited crops and animals, at least at a national level.

An important characteristic of New Zealand foods is that they generally aim for 'premium' status[22] in export markets, often with a focus on naturalness. If the presence of genetic modification affects acceptability as a premium product, there might be a case for public intervention to protect certain producers from the actions of others, around the use of genetically modified organisms. This is especially relevant in the case of genetic modification because while export markets might vary in their reactions to genetic modification [72], it is unlikely that geographic regions of New Zealand could be differentiated in international markets. This is particularly true for New Zealand products as government agencies and exporters promote the country's products in some respects using New Zealand as a brand.

To be in New Zealand's economic interests, a market premium is required for 'GM-free' produce, however that might be defined, and this should be weighed against any applications of GM which may have to be foregone. Furthermore, even if all these links were substantiated, the appropriate policy response is not obvious. That requires further analysis of the options of 'GM-free' and 'not GM-free', with the inclusion of GM produce not resulting in the exclusion of New Zealand from major markets. If GM products are also able to command premiums for their qualities, such as nutritive and health values or environmental benefits, and retain access to major markets, the attractiveness of a GM-free brand is diminished [73]. But gene editing technology may cause reconsideration of the concept of 'GM-free'. For example, small CRISPR-directed edits could produce outcomes both possible by, and indistinguishable from, those achieved with conventional breeding (albeit faster and more cheaply).

While there is no systematic analysis of being GM-free, the overall position could be considered similar to organic produce which has attracted a minority of consumers and of producers [74] who can co-exist with other producers, even if not always entirely harmoniously [75], with concerns around contamination from herbicides and pesticides from nearby fields. The biggest differences with GM are probably in the extent to which producers are interdependent, and some entrenched philosophical differences between some producers who want to use GM and their opponents. For New Zealand to remain innovative and environmentally sustainable in the primary sector, the loss of the advantages provided by gene editing technology may be a risk.

Scenarios for the use of gene editing in primary industries in New Zealand

The sustainability of global primary production systems faces many challenges from issues such as climate change, invasive pests, diseases and weeds, and increasing and ever-changing consumer demands. Because New Zealand's economy is strongly linked to primary production, we have been at the forefront in addressing these challenges through improving management systems, biosecurity measures and being responsive to changing consumer attitudes. Genetic selection and breeding have also been important approaches, but the relative imprecision, long time frames and slow uptake create a lag in the realisation of benefits. Gene editing technologies, such as CRISPR, have the potential to increase precision while reducing some societal concerns about previous approaches to genetic modification.

Five scenarios have been selected to illustrate the potential of using gene editing to reduce environmental impacts, improve productivity, protect taonga species, help animal welfare and improve human health. The five scenarios, outlined in Table 2, are not being advocated by the Panel, but are put forward as examples for discussion in terms of potential opportunities, risks and concerns, along with possible agricultural, environmental, ethical, societal and legal ramifications. The timeline for possible application of these scenarios varies from near term to long term.

[22] mpi.govt.nz/exporting/food/

TABLE 2 | Five primary industries' gene editing scenarios and associated issues

	SCENARIO 1 **Reducing environmental impact**	SCENARIO 2 **Responding to pests and stress**	SCENARIO 3 **Speeding up innovation**	SCENARIO 4 **Protecting taonga species**	SCENARIO 5 **Providing new health benefits**
						
Species	**Douglas Fir**	**Ryegrass endophytes**	**Apple**	**Mānuka**	**Dairy cows**
Aim	Reduce weediness in agricultural and conservation land	Provide field persistence to ryegrass by protection from pest herbivory and environmental stress	Speed up breeding of high value plant cultivars	Provide disease resistance	Remove allergen from milk
Estimated economic impact	Government currently spends $15M/yr on wilding pine control	Currently, endophytes in ryegrass contribute about $200M/yr	Rapid breeding of high value cultivars	Potentially high if mānuka is susceptible to new disease	Potential new markets for milk in Asia
Potential implications for trade	Export logs may be considered genetically modified in some markets, with conditions on exports	New endophyte may be considered genetically modified in some markets, with conditions on exports, but new qualities could be attractive to customers	New varieties would be considered a GM crop in New Zealand, but might not be in other markets	New varieties could be perceived as producing GM honey	New milk could reach new markets overseas, but could be considered GM by some consumers
***'Degrees of separation'* from human food consumption**	Not consumed by humans or any other vertebrate animal	Consumed by animals, that are then consumed by humans	Cultivar of apple without transgene, but from gene edited parents, consumed by humans	Honey derived from plant with gene edited genome consumed by humans	Milk and meat from gene edited cows consumed by humans
Estimated time to be technically possible	10 years	Within 5 years	Within 5 years	10 to 20 years	Now

SCENARIO 1

Reducing environmental impact

Wilding conifers are derived from the seeds of exotic species such as *Pseudotsuga menziesii* (Douglas fir) and are an unintended consequence of plantation forestry, agriculture (shelter belts) or erosion control plantings in New Zealand. Wildings currently occupy large tracts of conservation land in New Zealand because they are difficult and costly to control [76]. It is critical that management of new plantings of wilding-prone species includes strategies to prevent the generation of new wilding populations in the conservation estate.

A gene editing approach that modifies genes involved in the sexual reproductive process of conifers is an option to prevent the production of wildings. Targets include genes essential for cone initiation or development that would be deactivated (modified) to produce sterile trees [77]. There are promising candidate target genes but these would require research and testing to establish their role in conifer reproduction [78-82]. Once identified, gene editing could be used to target and inactivate these genes, to prevent reproduction [83].

Increasingly, conifers that are planted are not derived from seeds, but are reproduced via tissue culture. In this clonal forestry route, clones for planting are derived from a single embryo taken from cones that were produced by crossing two trees with desirable traits. These embryogenic cells can be preserved by cryopreservation and can also be propagated to ultimately produce huge numbers of trees [84]. To identify the best clones, cells are recovered from cryopreservation and the trees produced can be tested for their properties. The best performing ones, the 'production clones', can then be mass-produced from the cells remaining in cryopreservation.

Once good clonal lines are identified, it would be intended to gene edit cells recovered from cryopreservation and then use the same tissue culture techniques as used in clonal forestry. Each original production clone would need to be edited independently, but this would fit in with the current production programme, where each clone is propagated independently by tissue culture and not via crossing. While the production method would be the same as is currently being used for clonal forestry, there would be an extra gene editing step early in the process. The additional costs are thus mainly associated with developing the gene editing and sterility technology, rather than production of the edited trees.

As per current practice, there would need to be a number of different production clones to mitigate the dangers of planting a monoculture [85]. The number required would be decided by the forestry company using already established procedures.

Agricultural and environmental considerations

When wilding conifers become established outside the plantation areas, they overwhelm native landscapes, compete with native plants, and reduce native insect and bird populations [86, 87]. They also have a huge impact on our economy by removing valuable water out of catchments, adding costs to farming and conservation, and impacting on tourism and recreational opportunities. In 2016, the government declared wildings to be "the most significant weed problem New Zealand faces"[23] and added a further $4M per year to the existing $11M spent annually on their control. There are also economic and regulatory barriers in place to prevent planting of wilding-prone species in potentially productive areas where there is a risk of spread. However, because wood derived from Douglas fir is economically important, the complete removal of Douglas fir is not ideal, so moves to minimise harmful effects from wilding are critical.

Ethical and social considerations

Forests have an emotive and aesthetic value for many people and a place in history, mythology and identity [88]. Forests, unlike agricultural fields and paddocks, may be seen as 'uncultivated' – even though they are, in fact, in many cases both cultivated and intensively managed. Concerns about genetic modification may be rooted in concerns about the purity, or freedom, of wilderness, and a belief that wild nature needs to be free of human influence [89].

There could, however, be a kaitiaki obligation to reduce the environmental impact of wilding pines, which this technology could support, and intergenerational fairness considerations to prevent the impact of wilding conifers falling on future generations to remedy. Prevention of wilding conifers would also protect the purity of surrounding wilderness from human influence.

[23] beehive.govt.nz/release/16m-new-funding-tackle-wilding-conifers

Legal considerations

Gene editing wilding-prone species is a hypothetical example that aims to target the germline cells using an *in vivo* cell application gene editing technique to inactivate genes and thus enabling male and female plant sterility. Genetically modified organisms are *new organisms* under the Hazardous Substances and New Organisms Act 1996 (HSNO Act). The CRISPR gene editing system is initiated *in vitro*, thereby classifying it as an *in vitro* technique for the purposes of genetically modified organisms. Thereby, gene editing wilding-prone conifer species would be deemed to be *genetic modification* in statute (HSNO Act, section 2(1) and section 2A(2)(b)) and by regulation and case law (SR 1998/219 and Scion Case[24]). The Environmental Protection Authority (EPA) may, on application by any person, determine whether any organism is a new organism (HSNO Act, section 26) and the determination must be issued by notice in the *Gazette*.

Wilding-prone conifer species that are new organisms must be developed and field-tested in containment (HSNO Act, section 27). Subsequent approvals need to be sought for release from containment and conditional release. The EPA can decline the application if the organism fails to meet the minimum standards (HSNO Act section 36), or the adverse effects outweigh the benefits, or insufficient information is available to enable the EPA to assess the adverse effects of the organism (HSNO Act, sections 37 and 38).

The National Parks Act 1980, the Reserves Act 1977 and the Resource Management Act 1991 (RMA) would need to be considered and applied as these statutes legislate for the introduction of biological organisms using ministerial authority. Douglas fir is not native to New Zealand and therefore is not to be preserved according to section 5 of the National Parks Act 1980. Tools or mechanisms to reduce the population of wilding pines will promote the protection of indigenous flora and fauna (RMA, section 6).

New Zealand logs and conifer products are exported. The role of the Agricultural Compounds and Veterinary Medicines Act 1997 (ACVM Act) is to prevent or manage risks associated with the use of agricultural compounds in primary produce, as they may pose a risk to trade or to agricultural security (ACVM Act, sections 4(a)(i) and (iii)).

The CRISPR gene editing system may be deemed an *agricultural compound* for the purposes of the ACVM Act (sections 2(1)(i) and (ii)) if it meets the definition for a *biological compound* (section 2(1)) or a biological compound declared to be an agricultural compound for the purposes of the ACVM Act by Order in Council (section 2(1)(b)(iii)). The scheme of the ACVM Act (section 4a) enables integration with the Biosecurity (regulation of unwanted organisms) and HSNO Acts (regulation of new organisms).

The Cartagena Protocol on the Convention on Biological Diversity is an international agreement that aims to ensure an adequate level of protection in the field of safe transfer handling and use of *living modified organisms* (LMOs). Article 1 of the Protocol states that this is in accordance with the precautionary approach contained in Principle 15 of the Rio Declaration on Environment and Development. According to the definition of a LMO in the Cartagena Protocol, gene edited wilding-prone conifers or seeds (but not logs or sawn timber) would be considered *living organisms*, and gene edited wilding-prone conifer species would likely meet the definition of a LMO resulting from modern biotechnology if it possessed a novel combination of genetic material. This would result in the requirement for seed or sapling export to comply with the procedures for transboundary movement of LMOs intended for direct use as food or feed, or for processing (Article 11)[25]. New Zealand importers and exporters are legally bound by the Imports and Exports (Living Modified Organisms) Prohibition Order 2005 (SR 2005/12).

Risks and potential benefits

The primary benefits derived from using conifers gene edited to be sterile in plantation forestry would be through prevention of environmental, social and economic damage caused by new wildings, but this would not address existing wildings. The ability to plant stock that does not generate wildings would remove the risk from future commercial forestry plantings and allow control operations to focus on existing wildings.

Prevention of pollen production would mitigate problems associated with pollen allergy and the seasonal nuisance created by large pollen clouds from planted forests.

[24] The HC Judge ruled that the exemption list is a closed list; that plants created with genetic techniques ZFN-1 and TALENs are genetically modified organisms.

[25] mfe.govt.nz/more/hazards/new-organisms/genetic-modification-new-zealand/exporting-living-modified-organisms

It is predicted that preventing cone development will boost growth and increase wood production by redirecting energy and nutrients to increased vegetative growth [90]. This would have a substantial economic impact as it is estimated that 10–15% of a tree's energy is used for cone production [91, 92].

The gene edited trees would be sterile and would not contain foreign DNA, but the availability and cost of the new trees could be more restrictive and expensive than conventional varieties, and some argue that using gene edited trees is a risk to our national brand. Of New Zealand's 1.71 million hectares of planted plantation forest[26], 1.24 million hectares was certified by the Forest Stewardship Council in 2016[27], which currently prohibits the use of GM trees[28].

SCENARIO 2

Responding to insect pests and environmental stress

Perennial ryegrass (*Lolium perenne*) is the most important crop grown in New Zealand, being the dominant pasture grass in livestock production [93]. Important to the persistence of this crop in the field is the presence of a beneficial fungus (*Epichloë festucae*) that lives inside the grass [94] and is therefore known as an endophyte ('living inside'). These fungi produce a range of secondary metabolites that provide bioprotective benefits for the grass host in natural ecosystems such as protection from being eaten by insects and mammals, as well as providing protection from environmental stresses such as drought [95]. However, some of the chemicals that the fungi produce, including alkaloids (e.g. ergovaline) and indole-diterpenes (e.g. lolitrem B), are detrimental to grazing livestock under certain environmental conditions, resulting in welfare, production and financial losses to the farmer [96]. To overcome issues of mammalian toxicity, a number of novel beneficial fungi have been selected which retain the beneficial ability to protect the grasses from being eaten by insects but have also lost the ability to synthesise the mammalian toxins [97]. Molecular analysis of these strains show that the loss of this capability is due to deletion or inactivation of key genes in the biosynthetic pathways for these compounds [98]. While the selection and transfer of these novel fungi into the most productive ryegrass cultivars has brought significant benefits to the farmer and the forage industry in New Zealand, further advances are limited by identification of and selection for natural variation of the fungi found in seed collections [99].

Identification of the genes required for the synthesis of fungal alkaloid toxins, combined with an understanding of the individual steps in the biosynthetic pathways, has created the opportunity to breed these fungi through various genetic techniques [100-103]. With the advent of gene editing technology it is now easier to selectively delete single or multiple genes in these alkaloid toxin biosynthetic pathways to generate strains that either completely lack the ability to synthesise mammalian toxins or accumulate intermediates with unique bioprotective properties [93]. There is also the potential to introduce genes sourced from other organisms that confer new protective properties, such as drought tolerance, alter the herbage quality and/or provide health benefits to the grazing livestock.

In this scenario there is no genetic alteration of the grass, only of the fungus that lives within it. While the fungi colonise the grass seed and pass from generation to generation, they do not colonise pollen so are not wind dispersed [104]. Foreign genes may be present or absent in the final edited strain depending on the nature of gene editing carried out. Such genetic manipulations have the potential to generate beneficial fungal strains with novel protective properties, thereby enhancing persistence in the field as well as conferring animal welfare benefits. These novel beneficial fungi could be readily developed either in New Zealand or overseas.

Agricultural and environmental considerations

Most proprietary ryegrass seed currently sold in New Zealand contains endophyte because of the added protection the presence of this endophyte confers on the host in the field. Ryegrass and other introduced grasses (non-native) to this country are very widely distributed across New Zealand. Many grass species are highly adapted to a range of environmental conditions. Persistence of temperate grasses in the field will be dependent on both grass and endophyte genotypes.

[26] mpi.govt.nz/news-and-resources/open-data-and-forecasting/forestry/new-zealands-forests/

[27] nzfoa.org.nz/images/stories/pdfs/Facts_Figures_2016_%C6%92a_web_version_v3.pdf

[28] nz.fsc.org/preview.national-standard-for-certification-of-plantation-forest-management-in-new-zealand-version-3-5-for-2nd-consultation.a-1341.pdf

Grass cultivars containing these novel fungi have been estimated to contribute around $200M per year to the New Zealand economy [97].

Ethical and social considerations

The main social consideration would be acceptability of using forage seed in agriculture containing gene edited endophytes, and the perceptions of risks from the chemicals from the new gene edited fungi. There would be reduced risk from the endophyte's chemicals for the grazing animals, with resulting animal welfare benefits.

Legal considerations

Gene editing *Epichloë festucae* is a hypothetical example that aims to inactivate the toxicity genes using an *in vivo* cell application technique. Genetically modified organisms are *new organisms* under the HSNO Act. The CRISPR gene editing system is initiated *in vitro*, thereby classifying it as an *in vitro* technique for the purposes of genetically modified organisms[29]. Consequently, gene edited *Epichloë festucae* would be deemed *genetically modified* in statute (HSNO Act, section 2(1) and section 2A(2)(b)) and by regulation and case law (SR 1998/219 and Scion Case[30]).

According to the HSNO Act (section 25(1)) no new organism shall be imported, developed, field-tested, or released otherwise than in accordance with an approval issued under the HSNO Act. Importation of non-genetically modified ryegrass seed with a new endophyte into New Zealand also needs to meet the Import Health Standard, Seeds for Sowing (155.02.05) and may require a phytosanitary certificate to meet biosecurity requirements[31].

Perennial ryegrass (*L. perenne*) containing new organisms (gene edited *Epichloë festucae*) must be developed and field-tested in containment (HSNO Act, section 27), in a Ministry for Primary Industries' approved[32] facility. Subsequent approvals need to be sought for release from containment and conditional release. Where the EPA receives an application under section 40 of the HSNO Act to develop a genetically modified organism in containment, the EPA may make a rapid assessment of the adverse effects of developing that organism (HSNO Act, section 42(1) and 42(A). The EPA can decline the application if the organism fails to meet the minimum standards in section 36, or the adverse effects outweigh the benefits, or insufficient information is available to enable the EPA to assess the adverse effects of the organism (HSNO Act, sections 37 and 38).

The purpose of the proposed gene editing scenario is to improve animal welfare and animal production by removing endophyte mammalian toxicity of the fungi and improving drought tolerance of the grass. Gene edited *Epichloë festucae* will likely be deemed an *agricultural compound* if it meets the definition for a *biological compound* used in the direct management of plants and animals as a feed for animals (ACVM Act, subsections 2(1)(ii),(iii) and (vi)). The ACVM Act's role is to prevent or manage risks to animal welfare associated with the use of agricultural compounds (ACVM Act, section 4(a)(ii)). The scheme of the ACVM Act (section 4a) enables integration with the Animal Welfare Act 1999 and HSNO Acts (regulation of new organisms).

Gene edited endophytes of exported perennial ryegrass species would meet the definition of a *living organism* in the Cartagena Protocol to the Convention on Biological Diversity. However, it may not meet the definition of a *living modified organism* (LMO) if the endophyte does not possess a novel combination of genetic material, for example, if the CRISPR technique is used to delete a nucleotide using a sequence that is already present in the species' population. If it is deemed an LMO, it would need to comply with the procedure for transboundary movement of LMOs intended for direct use as food or feed, or for processing (Article 11)[33]. New Zealand importers and exporters are legally bound by the Imports and Exports (Living Modified Organisms) Prohibition Order 2005 (SR 2005/12). If ryegrass products such as hay, silage or nuts to be used as animal feed were to contain viable endophytes, the product would be deemed a LMO and therefore would be subject to the Cartagena Protocol and gene editing regulation in the import country. If the endophytes were not viable, the product would be subject to the importing country's laws and regulations on gene edited animal feed products.

[29] HSNO Act, section 2(1).

[30] The HC Judge ruled that the exemption list is a closed list; that plants created with genetic techniques ZFN-1 and TALENs are genetically modified organisms.

[31] mpi.govt.nz/importing/plants/seeds-for-sowing/steps-to-importing/

[32] epa.govt.nz/assets/Uploads/Documents/New-Organisms/Policies/155-04-09-MAF-ERMA-Std-2007.pdf

[33] mfe.govt.nz/more/hazards/new-organisms/genetic-modification-new-zealand/exporting-living-modified-organisms

Risks and potential benefits

Introduction of edited endophytes with novel bioprotective benefits into forage grasses will provide protection to the host from various environmental and biological stresses, leading to greater persistence in the field and potential benefits to the forage industry. Endophytes that have been edited to prevent the synthesis of harmful toxins provide welfare benefits and production benefits to the grazing livestock. On the other hand, some consideration is needed of the ecology of the fungus and the impact of the introduced traits on wild populations.

Forage seed is widely traded both within and external to New Zealand. While there are good tracking systems in place it would be difficult to control movement of all seed. This would lead to the risk of inadvertent movement of seed containing modified endophyte to a region or country where it is regulated differently to the source of origin. Seed containing endophyte with minor edits would be difficult to distinguish from naturally occurring strains.

If we were to handle or export seed with endophytes considered GM in other countries, consideration would need to be given to the implication for seed exports to countries with a purity threshold of zero for GM contamination. Approval would need to be sought around the level of possible contamination risks for exports of seed with non-GM endophyte.

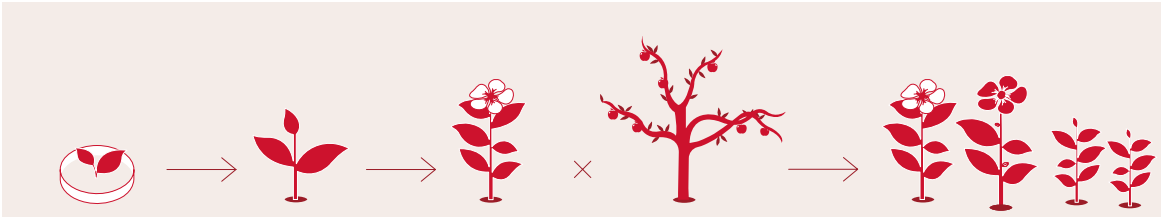
SCENARIO 3

Speeding up innovation

The speed with which new apple varieties with high value traits can be generated is limited by the long juvenile period in apple, often up to 5 years before the plants are able to flower and then fruit [105]. Thus, plant breeding, which typically involves multiple cycles of sexual crossing and selection to produce improved varieties with desirable fruit characteristics, is a very slow process. New Zealand has benefited from long-term selection and breeding programmes but increasing threats from pests and diseases, and rising consumer expectations for new varieties, means that much of the research effort in breeding new fruit tree varieties is focused on reducing breeding cycle time. Even small improvements in breeding speed can deliver significant returns sooner or can provide a timely solution to the industry if a new disease or pathogen strikes, or with changing conditions due to climate change [106].

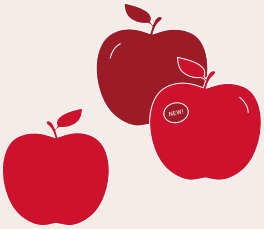
In apples, previous research has demonstrated substantial reductions in the time to flowering are possible through genetic modification. Initial research using the overexpression of a gene from silver birch (*BpMADS4*) has been able to reduce the breeding cycle in apple to a single year [107-109]. Using this technology, researchers were able to

FIGURE 2 | Using CRISPR and flowering gene *MdTFL1* in rapid breeding (fast-track breeding approach)



MdTFL1 | ***MdTFL1*** | **HVT** | **MdTFL1/CRISPR/CAS9/HVT**

1. Introduce *CRISPR* transgenes targeting *MdTFL1* into apple
2. Edit *MdTFL1*
3. Select rapid flowering apple plants
4. Cross of cultivar with High Value Trait (HVT)
5. Select rapid flowering plant with edited MdTFL gene, HVT and *CRISPR* transgenes
6. Carry out multiple breeding cycles by repeated crossing and selection of HVT
7. Finally, cross out the CRISPR transgenes and the edited MdTFL1 gene to replace with wildtype MdTFL1 gene, revert to typical flowering.



integrate fire blight resistance into an elite cultivar through five crosses within seven years to generate a plant that, while carrying the desirable fire blight resistance trait, no longer carried the *BpMADS4* transgene [107]. A similar reduction in the juvenile period in apple has been achieved using antisense technology[34] to reduce the expression of the apple's flowering gene *MdTFL1*, thus bringing the plants into flower and fruit much more rapidly [110, 111]. Therefore, rather than overexpressing a foreign gene, a similar outcome was achieved by turning an apple gene off.

Gene editing could be used to obtain the same rapid flowering phenotype for use in rapid breeding, with a guide RNA targeting and knocking out the gene that represses flowering using CRISPR technology [112]. This would result in an apple that flowers almost constantly and is able to be crossed every eight months. Once the desirable characteristics have been combined through rapid crossing, the modified flowering gene and gene editing machinery could be removed by conventional plant crossing, restoring the typical flowering pattern and leaving no modifications in the final plant [113] (See Figure 2).

Horticultural considerations

The proposed scenario speeds up the apple breeding cycle with the resulting plants not containing any transgene or the gene edited version of the new flowering gene. Potentially, crosses using the edited flowering gene line could be developed and field-tested in containment, and permission then sought to release from containment the subsequently produced plant that would no longer contain the modified gene. This would have implications for horticulture producer boards, to ensure the GM status is known for New Zealand and international consumers.

Ethical and social considerations

As noted by the Nuffield Council on Bioethics [3], although gene edited plants might be analytically indistinguishable from traditionally bred plants, the fact that a technical procedure, which might be perceived as unnatural, or affecting the apple's purity, is involved in producing these new plants, may be of concern to some people [114]. This is arguably a matter for consumers rather than producers, since it allows consumers to exercise choices about the kinds of producers and production systems they wish to support through their purchasing. For consumers to have the freedom to make such a choice, labelling (either voluntary or compulsory) may be particularly important. Consequently, tracing through an auditable chain of custody becomes imperative for that purpose. The fact that it is only the tree flowering that is being altered using gene editing, rather than the apple, and that this edit will not be present in the cropping variety, may change people's views.

Legal considerations

Gene editing the apple *MdTFL1* gene is a hypothetical example that aims to enable continuous flowering using an *in vivo* cell application and clonal propagation techniques. Out-crossing breeding techniques are then used to remove the edited version of the *MdTFL1* apple gene along with the CRISPR machinery, to restore normal flowering. The primary purpose of gene edited apple trees is to rapidly breed high value cultivars to increase production and develop new varieties for consumers.

Genetically modified organisms are *new organisms* under the HSNO Act. The CRISPR gene editing system is initiated *in vitro*, thereby classifying it as an *in vitro* technique for the purposes of genetically modified organisms[35]. Thereby, fast flowering gene edited apple trees would be deemed genetically modified in statue (HSNO Act, section 2(1) and section 2A(2)(b)) and by regulation and case law (SR 1998/219 and Scion Case[36]). It is unclear whether the out-crossed apple tree for release to orchardists, with the fast flowering gene removed by conventional plant crossing, would meet the definition of genetic modification according to section 2(1)(b) of the HSNO Act. The EPA may, on application by any person, determine whether or not the out-crossed apple tree is a new organism and the determination must be issued by notice in the *Gazette* (HSNO Act, section 26). The EPA may revoke or reissue a determination issued by it under section 26(6) if it receives further information. According to the HSNO Act (section 25(1)) no new organism shall be imported, developed, field-tested, or released otherwise than in accordance with an approval issued under the HSNO Act.

[34] Antisense technology uses synthetic single stranded strings of nucleic acids that bind to RNA and thereby alter or reduce expression of the target RNA.

[35] HSNO Act, section 2(1).

[36] The HC Judge ruled that the exemption list is a closed list; that plants created with genetic techniques ZFN-1 and TALENs are genetically modified organisms.

The gene edited apple tree would be developed and field-tested in containment and, following out-crossing, the progeny lacking the edited gene may be released. Release would allow the new organism to move within New Zealand free of any restrictions other than those imposed by the RMA, Biosecurity and Conservation Acts. Evaluation by the EPA under the provisions of the HSNO Act would determine whether the new organism would be released free of any restrictions, released with controls (conditional release), restricted to containment or released under special emergency conditions. Gene edited apple trees must be developed and field-tested in containment (HSNO Act, section 40). The EPA can decline the application if the organism fails to meet the minimum standards in section 36, or the adverse effects outweigh the benefits, or insufficient information is available to enable the EPA to assess the adverse effects of the organism (HSNO Act, sections 37 and 38). Note that the restriction on the importation of a new organism in New Zealand does not apply to biological material of the organism that cannot, without human intervention, be used to reproduce the organism (HSNO Act, section 25(5)), for example apple juice.

The ACVM Act's role is to prevent or manage risks to trade in primary produce and risks to public health associated with the use of agricultural compounds (ACVM Act, subsections 4(a)(i) and 4(a)(ia)). The gene edited apple tree may be deemed an *agricultural compound* for the purposes of the ACVM Act (sections 2(1)(ii) and (vii)) if the CRISPR system meets the definition for a *biological compound* (section 2(1)) *and* the biological compound is declared to be an agricultural compound for the purposes of the ACVM Act by Order in Council (section 2(1)(b)(iii)). The scheme of the ACVM Act (section 4A) enables integration with the Biosecurity and HSNO Acts (regulation of new organisms).

Since gene edited apples contain viable seeds, gene edited apples would meet the definition of a *living modified organism* (LMO) resulting from modern biotechnology in the Cartagena Protocol on Biological Diversity if it possessed a novel combination of genetic material. This would result in the requirement to comply with the procedure for transboundary movement of LMOs intended for direct use as food or feed, or for processing (Article 11)[37]. New Zealand importers and exporters are legally bound by the Imports and Exports (Living Modified Organisms) Prohibition Order 2005.

Risks and potential benefits

The primary beneficiaries of the proposed scenario would be apple breeders as they would be able to rapidly introduce traits into elite cultivars through more rapid breeding cycles. This could benefit growers and consumers, both directly and indirectly, depending on the traits incorporated. As the resulting cultivars no longer contain the edited flowering gene, the risks would be 'off target effects', that is genetic changes that might occur in other parts of the genome as a result of the gene editing and might have negative effects. Genome sequencing would, however, be able to identify if any off target effects had occurred. It is worth noting that the risk of off target effects is also associated with chemical mutagenesis, where backcrossing cannot easily be used to remove unwanted DNA changes that are not required for the new phenotype, as would be the case in apple.

SCENARIO 4
Protecting taonga species used in the primary industries

Mānuka (*Leptospermum scoparium*), which Captain Cook called the tea tree, has a rather variable form ranging from flat creeping varieties and small shrubs to tall trees. Extracts of leaves and bark were traditionally prepared and used by Māori, and are still used in modern day medicine, for healing purposes for a wide range of ailments. Mānuka is found throughout New Zealand and grows in many different habitats. It is an early coloniser of ecosystems and fulfils an important role in stabilising soils on steep erosion-prone hillsides. Mānuka is bee pollinated and has very small wind-blown seeds, which ensure widespread dispersal. Recently a burgeoning business has developed from the harvesting and niche marketing of mānuka honey, which in 2016 could command prices of $148 per kilogram [115]. However, the arrival of new plant diseases, such as myrtle rust, raises considerable concern about the threat to mānuka and other members of the Myrtaceae family (e.g. kānuka, pōhutukawa and rātā)[116, 117]. While there is uncertainty about the impact of a new disease on this group of highly valued native species, plans are in place to collect seed to deposit in germplasm collections and research is underway to find ways to mitigate the impact of diseases should they become established in our forests.

[37] mfe.govt.nz/more/hazards/new-organisms/genetic-modification-new-zealand/exporting-living-modified-organisms

At present little is known about natural resistance to pathogens within mānuka. Plant & Food Research have established populations of mānuka that could be used to map genes that confer tolerance/resistance to different pathogens. In addition, the mānuka genome has been sequenced, providing a crucial resource for identifying possible susceptibility and/or resistance genes to inform future breeding programmes and conservation efforts across mānuka provenances, as well as to provide potential targets for gene editing[38]. One of the first challenges to overcome in order to gene edit mānuka would be development of a delivery system to introduce the CRISPR machinery. A very common method that is used in plants is *Agrobacterium*-mediated transfer, but this methodology has yet to be developed in mānuka. Three possible approaches of gene editing that might provide resistance to disease in mānuka include:

- the deletion of a susceptibility gene,
- editing an existing gene to match an allele known to drive resistance, or
- the introduction of a resistance gene from another species.

In the first two approaches, the resulting organism would not contain any foreign genes whereas in the last approach it would.

These scenarios involve gene editing of a valued indigenous species and would therefore require active engagement, participation by, and ongoing consultation with, Māori collectives on whether this approach is appropriate and useful for Māori as kaitiaki. Māori worldview perspectives, Māori cultural norms and other considerations, including environmental, social and economic benefits and risks, would be considered during these decision-making processes to ensure adequate protections are adhered to and to maintain balances and protocols. Ultimately, Māori would consider whether the whakapapa, mauri, and mana of the mānuka, and of Māori themselves, are not adversely impacted or irreversibly destroyed [118].

Agricultural and environmental considerations

If only a limited range of mānuka ecotypes/provenances are gene edited, then there is the potential that these disease resistant types will have increased fitness and may spread throughout the country. This spread could potentially affect the genetic diversity of the species in New Zealand. One solution would be to cross breed disease-resistant, gene edited, mānuka from a wide range of provenances before releasing.

Gene edited mānuka could result in resistance to many microbes, including beneficial ones [119], [120]. This can be managed by research on the growth of resulting gene edited mānuka lines, under differing environmental conditions, prior to field release.

Ethical and social considerations

Products derived from gene edited disease-resistant mānuka could preserve jobs in regions such as East Cape and Northland, due to the maintenance of a thriving and resilient mānuka honey and oils industry. Māori communities could become actively involved in leading and being part of the research efforts.

For some, gene edited, disease-resistant mānuka will be seen as enabling the responsibilities of kaitiakitanga by contributing to long-term conservation of the species and maintaining ecosystems where mānuka is an integral species. It could be seen to have a positive impact by conserving species interconnected with other species (human, game animals, bees, beneficial fungi). However, for others, there may be opposition to the use of the technique, as gene edited mānuka may alter, or impact, the mauri or essential life force of mānuka, or its natural properties [121]. Some may also argue that there is a special value in processes and organisms that live without the influence of human agency – nature is wild and should exist without human influence. Thus, even though it seems like mānuka is helped through use of this technology, and other species too, potentially, this is in fact their replacement with a cultural artefact, which does not have the natural value of the original [122, 123]. Others argue that humans and nature cannot be separated in this way, and that efforts in restoring nature are valuable for nature itself, as well as any benefits for humans [124]. Moreover, the alternative of not doing anything to help mānuka survive disease challenge, may risk losing mānuka completely.

The economic interests of Māori and other producers are also likely to be negatively impacted if gene editing is poorly perceived by consumers of mānuka honey products.

[38] plantandfood.co.nz/page/news/media-release/story/cracking-manukas-genetic-code-to-mitigate-myrtle-rust/

Legal considerations

Mānuka is a taonga species, native to Aotearoa New Zealand and therefore a matter of national importance to be preserved, sustainably managed and protected (RMA sections 5 and 6, National Parks Act 1980 (section 5), Biosecurity Act section 54, the Wai 262 Claim and Article 2 of the Treaty of Waitangi). The purpose of gene editing would be to provide mānuka with disease resistance to aid in its preservation and support a growing export honey industry.

Gene edited mānuka trees would be deemed *genetic modification* in statute (HSNO Act, section 2(1) and section 2A(2)(b)) and by regulation and case law (SR 1998/219 and Scion Case). Genetically modified organisms are *new organisms* under the HSNO Act, and therefore a gene edited mānuka tree would likely be deemed a new organism for the purposes of the HSNO Act[39]. According to the HSNO Act (s 25(1)) no new organism shall be imported, developed, field-tested, or released otherwise than in accordance with an approval issued under the HSNO Act.

Gene edited mānuka would have to be developed and field-tested in containment (HSNO Act, section 27), but to achieve their purpose, the gene edited trees would need to be released. Approval for release would need to be sought from the EPA (sections 34, 34A and 38A). Release would allow the new organism to move within New Zealand free of any restrictions other than those imposed by the Biosecurity and Conservations Acts (HSNO Act, section 2(1)).

Evaluation by the EPA under the provisions of the HSNO Act would determine whether the new organism (gene edited mānuka tree) will be released free of any restrictions, released with controls (conditional release), restricted to containment or released under special emergency conditions. The EPA would decline the application if the organism failed to meet the minimum standards in section 36, or the adverse effects outweigh the benefits, or insufficient information is available to enable the EPA to assess the adverse effects of the organism (HSNO Act, sections 37 and 38).

The ACVM Act's role is to prevent or manage risks to trade in primary produce and risks to agricultural security associated with the use of agricultural compounds (ACVM Act, section 4(a)(i)). Primary produce is defined as *"any plant or animal, or any derivative of any plant or animal, intended for sale" (ACVM Act, section 2(1)).* Mānuka honey would likely be deemed *primary produce* and therefore subject to risk assessment by MPI in relation to trade. Gene edited mānuka may be deemed an *agricultural compound* for the purposes of the ACVM Act (subsections 2(1)(ii) and (vii)) if the gene edited product meets the definition for a *biological compound* (section 2(1)) *and* the biological compound is declared to be an agricultural compound for the purposes of the ACVM Act by Order in Council (section 2(1)(b)(iii)). The scheme of the ACVM Act (section 4A) enables integration with the Biosecurity (regulation of unwanted organisms) and HSNO Acts (regulation of new organisms).

Gene edited mānuka would meet the definition of a *living modified organism* (LMO) resulting from modern biotechnology under the Cartagena Protocol on Biological Diversity if it possessed a novel combination of genetic material, but the honey from the mānuka would not be classified in this way.

Risk and potential benefits

The economic benefits of protecting mānuka in this way would be to allow continued production of mānuka-derived product, such as oils and honey, should a new pathogen become established, and to protect mānuka plants from new pathogens. Economic risks may include the perception by some of gene edited mānuka as unnatural, which could negatively affect the New Zealand honey industry. Such campaigns could be triggered nationally and globally by competitors to the mānuka honey industry.

There is a risk that the disease resistance conferred by the gene edit may be short-lived, especially if the gene edit takes the form of targeting a single gene whose product may be negatively affecting the pathogen (a resistance gene). For example, selection pressure may favour pathogens with mutations that can get around the resistance afforded by this single gene. This might necessitate ongoing selection and breeding. However, a significant advantage of gene editing is that it is possible to target susceptibility genes. These would be genes that are required for pathogens to establish disease in the mānuka plant. Studying resistant mānuka lines can lead to the discovery of such genes and editing them would likely result in durable on-going resistance [125].

[39] Refer to HSNO Act section 2A. Please note the exceptions in section 2A(2).

SCENARIO 5

Providing new human health benefits

Cows have evolved to provide milk as a balanced source of nutrition to support the early life of calves. Recognising its high nutritional value and potential for a safe and secure food supply, humans have embraced cows' milk as a major source of nutrition to promote human health and wellbeing. But the consumption of cows' milk is not universally tolerated and can cause allergic reactions, ranging from mild to life-threatening symptoms, particularly in infants. Cows' milk contains the milk protein beta-lactoglobulin that has no equivalent in human milk or anywhere else in the human body, and constitutes a major cows' milk allergen. It can raise a strong immune reaction resulting in high levels of anti-beta-lactoglobulin antibody in people with allergies against this protein. Different processing technologies, including enzymatic hydrolysis, are current strategies to mitigate the allergenic properties of milk proteins. Besides being expensive, such processing also risks exposing previously hidden parts of proteins that may be novel triggers for allergic reactions or that cause the milk to taste bitter. Elimination of beta-lactoglobulin from cows' milk could be a safe option to minimise the allergenic potential and produce a milk that could provide a valuable source of nutrition for those consumers that currently cannot eat or drink dairy products from cows due to an allergic immune response against this protein [126].

The precision and efficiency of gene editing makes it now possible to simply eliminate the allergy-causing protein from cows' milk by disrupting the gene responsible for its production in cows [127]. This can be achieved by designing gene editing tools that target the gene for beta-lactoglobulin to introduce a small deletion that disrupts the reading frame of the encoded milk protein. In cows, this can be done by introducing the beta-lactoglobulin-specific gene editor into one-cell cow embryos [128, 129]. In this approach, the embryos are cultured *in vitro* for seven days until they reach an early embryonic stage called a blastocyst. Typically, a small biopsy will be taken from the embryos and used to confirm the intended edit before the embryos are transferred to recipient cows for development to term and production of live gene edited calves. Potentially, the only change to the genome will be the small deletion in the beta-lactoglobulin gene, allowing the direct introduction of specific desirable traits within a single generation.

Agricultural considerations

The Nuffield Council on Bioethics [3] has identified that gene editing of animals and plants has not merely accelerated research, but made research possible that was previously unfeasible [130]. Because the breeding interval in most commercial animals is long (typically many months) and their reproductive rates are often low (for example, one offspring per generation in cattle, although as many as 15 in pigs), the backcrossing strategies that are used so effectively in crop breeding are considerably less productive in most livestock. On the other hand, the embryo transfer mode of animal reproduction enables embryological micromanipulation, makes animals more responsive to certain forms of editing, and can be applied to traits already known [131].

The New Zealand dairy industry is presently based around bulk production. The beta-lactoglobulin-free milk would be a high value, specialty product with health benefits for only a defined group of people. It would, therefore, require separation from the supply and value chain. It is important to note that meat from gene edited dairy cows would also enter the food chain. Beta-lactoglobulin free milk would have a benefit of improved processing efficiency in milk factories, as beta-lactoglobulin fouls the heat exchanges in milk processing plants [132, 133].

In terms of beta-lactoglobulin's function in dairy cows, the whey protein may be an important source of amino acids for calves [134], so there may be a need to ensure that the gene edited calves' diets are sufficiently supplemented to replace the missing protein.

Ethical and social considerations

People's interactions with food and being able to choose what they eat is important. There will be social and ethical issues around people's views on genetic modification of animals and the milk produced from such animals, which will need to be weighed against the advantages of reduced allergenicity. Some people may have ethical concerns around the disruption of species boundaries, or the nature, or mauri, of the animals modified, and the welfare of animals modified, including during the research and development for the modification process [135].

Legal considerations

Gene editing of the bovine beta-lactoglobulin gene would be done by introducing a beta-lactoglobulin-specific gene editor into single-cell embryos.

Gene edited beta-lactoglobulin dairy cow embryos, and the milk producing adult cows resulting from the gene edited embryos, would be deemed *genetically modified* in statute (HSNO Act, section 2(1)) and section 2A(2)(b)) and by regulation and case law (SR 1998/219 and Scion Case[40]). The progeny of adult gene edited dairy cows also meet the definition of genetic modification according to section 2(1)(b), as they "are inherited or otherwise derived, through any number of replications, from any genes or other genetic material which has been modified by *in vitro* techniques".

The gene edited and genetically modified embryo and adult dairy cow will likely be deemed a *new organism* for the purposes of the HSNO Act (section 2A). According to the HSNO Act (section 25(1)) no new organism shall be imported, developed, field-tested, or released otherwise than in accordance with an approval issued under the HSNO Act (HSNO Act, section 27). Gene edited beta-lactoglobulin dairy cows would have to be developed and field-tested in containment (HSNO Act, section 39), and released to the wider dairy industry as part of the conventional farming production system. Approval for release would need to be sought from the EPA (sections 34, 34A and 38A). Release would allow the new organism to move within New Zealand free of any restrictions other than those imposed by the Biosecurity and Conservations Acts (HSNO Act, section 2(1)).

Evaluation under the provisions of the HSNO Act would determine whether the new organism (a gene edited dairy cow) will be released free of any restrictions, released with controls (conditional release), restricted to containment or released under special emergency conditions. The EPA would decline the application if the organism fails to meet the minimum standards in section 36, or the adverse effects outweigh the benefits, or insufficient information is available to enable the EPA to assess the adverse effects of the organism (HSNO Act, sections 37 and 38).

Animals used in gene edited beta-lactoglobulin dairy cow research are subject to Part 6 of the Animal Welfare Act, which legislates the use of animals in research, testing and teaching and provides the circumstances under which animals can be manipulated. The purpose of Part 6 is to ensure that the use of animals for research purposes is confined to cases in which there is good reason to believe that the findings of the research or testing will enhance the maintenance or protection of human health and welfare (Section 80(1)(a)(ii)); or the production and productivity of animals (section 80(1)(a)(iv)). Research, testing and teaching must only occur when, along with other conditions, the anticipated benefits of the research outweigh the likely harm to animals (section 80(1)(b)). There are restrictions on who can manipulate animals (section 82). The term manipulation includes the breeding or production of an animal using any breeding technique (including genetic modification) that may result in the birth or production of an animal that is more susceptible to, or at greater risk of pain or distress during its life as a result of the breeding or production (section 3(1B)). In this scenario, and in any other breeding approach, the association of the gene edited beta-lactoglobulin gene on other genes in the cattle genome may not be known. There are also restrictions on carrying out research (section 83) whereby no person may carry out any research unless it has been first approved by an animal ethics committee appointed by the code holder.

To eventually make beta-lactoglobulin-free milk available for people affected by milk protein allergies, the milk would require both regulatory approval according to the Food Standards Australia New Zealand (FSANZ) standard for food produced using gene technology, which would include evidence that the product is safe to eat. Meat products from the gene edited animals and their progeny would also need to be approved for human consumption by FSANZ and would have to be labelled as a food derived from genetic modification. Food sold in a café, restaurant or takeaway is exempt from the labelling requirements.

The ACVM Act's role is to prevent or manage risks to public health, risks to trade in primary produce and risks to animal welfare associated with the use of agricultural compounds and veterinary medicines (ACVM Act, subsections 4(a) (i), (ii) and (iii)). The scheme of the ACVM Act (section 4A) enables integration with the Animal Welfare Act, Animal Products Act, Food Act and HSNO Acts (regulation of new organisms). The gene editing system used to eliminate beta-lactoglobulin from cow's milk may be deemed an *agricultural compound* for the purposes of the ACVM Act (subsections 4(a)(i),(ii) and (iii)) if it meets the definition for a *biological*

[40] The HC Judge ruled that the exemption list is a closed list; that plants created with genetic techniques ZFN-1 and TALENs are genetically modified organisms.

compound (section 2(1)(a)(ii); intended for use in the direct management of animals for the purposes of promoting animal productivity and performance) and the biological compound is declared to be an agricultural compound for the purposes of the ACVM Act by Order in Council (section 2(1)(b)(iii)).

Gene edited cows, gametes (sperm) and embryos (but not milk or meat) would meet the definition of a *living organism* and a *living modified organism* (LMO) resulting from modern biotechnology under the Cartagena Protocol on Biological Diversity. This would result in the requirement to comply with the procedure for transboundary movement of LMOs intended for direct use as food or feed, or for processing (Article 11)[41]. New Zealand importers and exporters are legally bound by the Imports and Exports (Living Modified Organisms) Prohibition Order 2005 (SR 2005/12).

Risk and potential benefits

The benefit of this milk would be to provide a high-quality protein source to sufferers of milk allergies, in particular infants, who are otherwise unable to consume cows' milk.

Some consumers, however, may prefer alternative milks that don't contain the allergy-causing milk proteins from dairy animals, but which aren't a product of gene editing, such as those from other ruminant species, or plant based 'milks'. While beta-lactoglobulin is a major cows' milk allergen, some people will have allergic reactions not only to beta-lactoglobulin but to other milk proteins such as α-lactalbumin [136] and α-casein [137]. Lactose intolerance is another, unrelated, reason for adverse reactions associated with milk consumption. Where there is allergy or intolerance to cows' milk, care is needed, and tolerance to any substitute milk must be appropriately assessed [138]. There is a risk that people with milk allergies not solely caused by beta-lactoglobulin might suffer adverse health effects from other allergens when drinking a beta-lactoglobulin free milk. Hence, labelling would need to say 'beta-lactoglobulin free' to avoid risks of legal liability associated with any claims around a product being 'less allergenic', if this doesn't prove to be the case.

[41] mfe.govt.nz/more/hazards/new-organisms/genetic-modification-new-zealand/exporting-living-modified-organisms

Implications for New Zealand

To assist the public discussion, Royal Society Te Apārangi is publishing a number of papers that outline scenarios for the use of gene editing in pest management and healthcare, alongside this one on the primary industries.

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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The Society would like to thank the following experts for their valuable input in contributing to and commenting on the paper:

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Professor Jonathan Jones (University of Norwich, UK), **Professor Ottoline Leyser** (University of Cambridge, UK), and **Professor Steve Swain** (CSIRO, Australia) provided independent international review of the paper.

The Society would like to give special mention to the contribution of **Dr Barry Smith** (Te Rarawa, Ngāti Kahu), who chaired the Society's Gene Editing Panel Māori Reference Group from 2017– 19. Barry helped highlight relevant parts of mātauranga and identify where interpretation of a study in mātauranga and western-based knowledge systems may be different, and advised on how to share information in a way that recognises cultural context and constructively informs and supports Māori community discussion on these technologies. He also took part in a number of hui with communities across New Zealand to hear people's views.

Glossary

Agriculture	The science and art of cultivation on soil and the rearing of livestock to provide food and other products.
Agrobacterium	*Agrobacterium tumefaciens* is a widespread naturally occurring soil bacterium that causes crown gall, and has the ability to introduce new genetic material into the plant cell.
Alkaloid	A class of naturally occurring organic nitrogen-containing compounds.
Aquaculture	The rearing of aquatic animals or the cultivation of aquatic plants for food.
Backcrossing	A crossing of a hybrid with one of its parents or an individual genetically similar to its parent, to achieve offspring with a genetic identity which is closer to that of the parent.
Bioinformatics	The development and application of computational methods in biology, biotechnology and medicine, taking advantage of rapidly expanding databases including those related to biodiversity, genomics, proteomics and structural biology.
Biopsy	A sample of tissue taken from the body in order to examine it more closely.
Biosynthesis	The formation of chemical compounds by a living organism.
Clone	A clone is a group of identical cells that share a common ancestry, meaning they are derived from the same cell.
CRISPR	Clustered Regularly Interspaced Short Palindromic Repeats, which are the hallmark of a bacterial defense system that forms the basis for CRISPR-Cas9 gene editing technology.
Cryopreservation	The use of very low temperatures to preserve structurally intact living cells and tissues.
Cultivar	A plant variety that has been produced in cultivation by selective breeding.
DNA	Deoxyribonucleic acid, is the hereditary material in humans and almost all other organisms.
DNA marker	DNA variation linked to a trait of interest (e.g. productivity, disease resistance, abiotic stress tolerance, and quality).
Enzymatic hydrolysis	A process in which enzymes facilitate the cleavage of bonds in molecules with the addition of the elements of water.
EU	European Union.
Forage	Food such as grass or hay for grazing animals.
FDA	US Food and Drug Administration.
GDP	Gross domestic product.
Gene editing	A type of genetic modification using a group of technologies that allow genetic material to be added, removed, or altered at particular locations in the genome.
Genes	A gene is the basic physical and functional unit of heredity. Genes are made up of DNA.
Genetic modification	The direct manipulation of an organism's genes using biotechnology.
Genome	The genetic material of an organism.
Genomic selection	An indirect selection process where traits of interest in an individual are predicted based on a genome-wide panel of DNA markers.
Germline	The cell types that eventually result in the formation of reproductive cells, sperm or pollen.
Horticulture	The cultivation, processing, and sale of fruits, nuts, vegetables, ornamental plants, and flowers as well as many additional services.
HSNO	Hazardous Substances and New Organisms Act 1996.

Hybrid	The result of mixing, through sexual reproduction, two animals or plants of different breeds, varieties, species or genera.
Indole-diterpenes	A structurally diverse group of secondary metabolites with a common cyclic diterpene backbone derived from geranylgeranyl diphosphate and an indole group derived from indole-3-glycerol phosphate.
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.
Iwi	Extended kinship group, tribe, nation, people, nationality, race.
Kaitiaki	Trustee, minder, guard, custodian, guardian, caregiver, keeper, steward.
Kaitiakitanga	Guardianship, stewardship.
Mana	Prestige, authority, control, power, influence, status, spiritual power, charisma.
Mana Whenua	territorial rights, authority and jurisdiction.
Mauri	Life principle, life force, vital essence, special nature.
MdTFL1	A gene that represses flowering in apple plants.
Monoculture	The agricultural practice of producing or growing a single crop, plant, or livestock species, variety, or breed in a field or farming system at a time.
Mutagenesis	A process by which the genetic information of an organism is changed, resulting in a mutation.
Mutagenic agents	Physical or chemical agents that change the genetic material, usually DNA, of an organism and thus increase the frequency of mutations.
Neolithic	The final division of the Stone Age, which began about 12,000 years ago when the first development of farming appeared.
OECD	Organisation for Economic Co-operation and Development.
Pathogen	A bacterium, virus, or other microorganism that can cause disease.
RNA	Ribonucleic acid: a class of single-stranded molecule that can be transcribed from DNA and therefore contains a linear sequence of nucleotide bases that is complementary to the DNA strand from which it is transcribed.
Selective breeding	Also known as artificial selection, where humans select only individual plants and animals with desirable traits to reproduce. New traits often arise by bringing together genetic variation in new combinations. Thus these individuals may be the result of repeated cycles of controlled crossing and selection of offspring.
Synthetic foods	Foods that have been produced or manufactured using new methods with the help of advancements in technology.
Taonga	Treasure, anything prized.
Trait	A genetically determined characteristic that can be underpinned by one or many genes.
USDA	United States Department of Agriculture.
Whakapapa	Genealogy, genealogical table, lineage, descent.
Whānau	Extended family, family group.
Wilding conifer	The New Zealand term for introduced conifers that self-sow and spread across the landscape unwanted.

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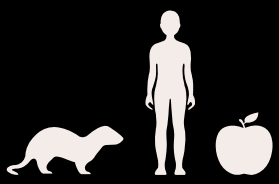
Taupo, New Zealand

ROYAL SOCIETY TE APĀRANGI

GENE EDITING
LEGAL AND REGULATORY IMPLICATIONS

AUGUST 2019



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RATIONALE

Genetic technologies such as gene editing are developing quickly and their cost is rapidly falling. This is creating new approaches in health care, environmental management and food production, which have reached a point that challenges existing legal, regulatory and risk assessment systems, with some applications raising ethical concerns around the world.

Aotearoa New Zealand needs to ensure that its regulatory framework is able to accommodate these technological developments, while protecting our unique environment and indigenous and cultural heritage. The status of Māori as tangata whenua of Aotearoa, the principles of Te Tiriti o Waitangi/ the Treaty of Waitangi, and kaitiakitanga guardianship, also create a unique context in which New Zealand's regulatory framework needs to sit. Without regulatory reassessment, New Zealand risks being unprepared for both the new technologies' benefits, and the risks and challenges they bring.

As a global citizen, Aotearoa New Zealand also has an ethical obligation to share and contribute to global knowledge and understanding of the opportunities and risks that using these technologies present. New Zealand cannot leave this to other nations. Other countries and regions, such as USA, Europe, Australia and Japan, are currently reviewing their regulatory systems to ensure they keep pace with technological change and provide an appropriate level of oversight.

Alongside this, New Zealand industries, research communities, as well as local and central government, need to work together to raise awareness and assist New Zealand's diverse communities to understand the real risks and opportunities these new technologies bring, in order to inform any changes.

The Royal Society Te Apārangi Gene Editing Panel recognises that its competence does not extend to the whole of regulation design and writing. However, the Panel's mandate does include examining and deliberating on the research evidence, the implications of gene editing technologies, and identifying the issues which might need a policy response. With this in mind, the Panel has examined the current New Zealand legal and regulatory environment, informed by its analysis of, and stakeholder reaction to, a range of scenarios demonstrating possible future applications of gene editing techniques[1].

[1] royalsociety.org.nz/major-issues-and-projects/gene-editing-in-aotearoa/; Everett-Hincks J.M & Henaghan R.M (2019) Gene editing pests and primary industries – legal considerations. New Zealand Science Review, Vol 75 (2-3).

SUMMARY OF FINDINGS

1 Defining genetic modification

The Panel considers that New Zealand's statutory provisions and regulations around genetic modification need to account for an increasingly nuanced view, and reflect the modern reality that organisms cannot be simply categorised as 'genetically modified' or 'not-genetically modified'. This is also essential to support a constructive and meaningful conversation within New Zealand communities on their preferences for the use of these new gene technologies.

2 Regulatory complexity and consistency

The Panel considers that the development of a shared set of definitions across the regulatory system would be a useful first step to enabling a constructive debate and determining the degree of public support for use of genetic technologies for different applications. Clearer pathways for making decisions would also enable more efficient and effective navigation of the regulatory system across agencies and Acts. In future-proofing regulations, government should also seek to ensure that statutory provisions take into account Māori cultural views.

3 International regulation and enforcement

The Panel considers that the potential trade and regulatory enforcement impacts from different treatment of gene editing technologies in different countries need to be investigated to ensure that New Zealand's regulations continue to be fit-for-purpose, both domestically and internationally. New Zealand could also consider the recommendations from the Australian Office for the Genetic Technology Regulator and Food Standards Australia New Zealand reviews.

4 Making regulation proportionate to risk

The Panel considers that addressing issues such as definitions, complexity and inconsistency in the current legislation, and accommodating the advances in gene technologies, would be more effectively achieved with a risk-tiered approach where regulatory burden is commensurate with risk. This would support public confidence in decision-making and provide greater flexibility and adaptability to accommodate further scientific and technological changes in future.

5 Community engagement

The Panel considers that regulation needs to be informed by wide engagement with the public. Current information and culturally appropriate education resources about new genetic technologies and their application should be shared widely and feedback sought on public attitudes and ethical views.

6 Capacity and capability

The Panel considers that there should be ongoing development and support for the necessary capacity and capability within communities, the research sector and central and local government, to support effective engagement and decision-making around new biotechnologies. While some applications of gene technologies may be unacceptable or not feasible at this time, it is important that New Zealand has the means to assess developments and opportunities as they arise in future.

BACKGROUND

Since the dawn of life, the diversity of biology has been based upon genetic change. Random genetic mutations in nature have underpinned evolution and the diversity of plants, microbes, fungi and animals we now observe, and upon which humans depend for survival. Advances in science and technology have led to increasingly sophisticated plant and animal breeding programmes to select for favourable characteristics. Techniques such as irradiation and chemical mutagenesis have been used to induce mutation and thus increase opportunities to introduce favourable characteristics or remove unfavourable characteristics. These random mutagenesis techniques have led to many of the crops we eat today, which are not legally defined as genetically modified, but have a long history of safe use.

As the science and technology has advanced further, the potential for targeted and deliberate modifications in specific genes, or introducing genes from one species into another, has led to community concerns about the risks and the ethical implications of these advances. These techniques enable more efficient means to modify an organism in a targeted way, and accelerate the rate at which organisms can be modified. This is a cause for concern if the modifications overstep society's acceptance of the changes, as in the recent example of a scientist in China using genetic modification to modify human babies' heritable DNA. However, new techniques also enable a more precise means to achieve certain outcomes, because they reduce the risk of unwanted mutations that feature in random mutagenesis techniques.

In 2000, the New Zealand government responded to public concerns with its Royal Commission on Genetic Modification (GM) in the face of polarized views. The Royal Commission's main recommendation in 2001, that "*New Zealand should preserve its opportunities by allowing the development of genetic modification whilst minimising and managing the risks involved*", remains the basis for the Hazardous Substances and New Organisms Act 1996 (HSNO Act) and regulatory framework, following its subsequent amendments, nearly two decades on.

The science and its application to genetic manipulation has continually advanced since then, with powerful gene editing tools such as Zinc-finger nucleases, TALENs and now CRISPR-Cas being developed[2]. CRISPR-Cas, in particular, has brought much greater precision in altering genetic traits, and at a rapidly decreasing cost. These and other advances in the future will continue to open doors to a much wider range of potential applications, from addressing genetic diseases in humans to managing the environment, and accelerating conventional plant and animal breeding programmes.

These advances and potential new applications are challenging regulatory frameworks around the world. New Zealand needs to ensure that its legal and regulatory framework is future-proofed as technology continues to evolve, and is informed by constructive debate about whether these applications are acceptable to New Zealand communities.

Māori communities are taking a keen interest in these new technologies and how they might be applied within their cultural context. Attitudes to genetic modification and other genetic technologies have been partially surveyed or expressed in various fora, such as *Te Mata Ira: Guidelines for Genomic Research with Māori*. Various ethical and operational frameworks have been developed as a result to facilitate better engagement with Māori communities about such technologies[3].

[2] CRISPR-Cas (Clustered Regularly Interspaced Short Palindromic Repeats), TALENs (transcription activator-like effector nucleases).

[3] At the regulatory level in New Zealand, the HSNO Act sets out the statutory process for analysing and deciding on applications. The Environmental Protection Authority, (EPA) uses a risk/benefit assessment process that involves a dedicated Māori operational policy team (Kaupapa Kura Taiao). The EPA's statutory Māori Advisory Committee, Ngā Kaihautū Tikanga Taiao (Ngā Kaihautū), may provide advice from a Māori perspective to assist an EPA decision-making committee to understand Māori views. Advice from Ngā Kaihautū does not detract from, or seek to substitute in any form, the distinct perspectives of iwi, hapū and/or whānau, but aims to ensure those perspectives have been sought and considered by the EPA. In addition, some research institutions have developed internal processes and procedures for consultation on research (e.g. University of Otago, and Scion via the Te Aroturuki process). However, these processes have been ad hoc and voluntary, and therefore have not always been uniformly implemented. As background, see Hudson M. et. Al (2019) Indigenous Perspectives and Gene Editing in Aotearoa New Zealand. Front Bioeng. Biotechnol. 7:70.

Regulatory framework

The Panel makes the following observations based on its analysis of the current legal and regulatory framework.

Defining genetic modification

Many countries and regions, including Canada, USA, Australia, UK and Europe, are grappling with how to define and regulate gene edited plants, microbes, fungi and animals in response to new gene editing technologies. As in other countries, gene editing technology now has the potential to leapfrog New Zealand's regulations and legislation and its ability to support the previous recommendations of the Royal Commission on Genetic Modification in terms of securing the opportunities while managing risks.[4]

The HSNO Act is the primary means of regulating genetically modified organisms in New Zealand.[5] In the two decades since its enactment, there have only been minor amendments to the Act. The HSNO Act defines *genetic modification*[6] and provides regulations for when organisms *are not* genetically modified.[7] A number of New Zealand's statutes and Local Government unitary plans now include the term *genetic modification* but do not define it.

The definitions of genetic modification in the HSNO Act, appear to no longer be fully 'fit for purpose.' For example:

- The use of gene editing technologies, including CRISPR-Cas, are deemed *genetic modification* under current legislation, and the resulting organisms are, therefore, classed as *new organisms*. By contrast those generated by random mutagenesis, which results in many more gene alterations in addition to the desired change, do not count as *new organisms*. It does not make scientific sense for organisms with genetic changes that are already found in their population to be considered *new organisms* under the HSNO Act.
- CRISPR-Cas can be applied using *in-vivo* (within the body of an organism) techniques, thereby no longer fitting the legislative definition relying on *in-vitro* (within a laboratory vessel) manipulation[8]. This possibility was not envisaged when the legislation was developed, yet it now opens the door to new treatments for cancer and other health conditions.
- Gene editing can involve deleting genes already present in the genetic code of organisms, guided by the cell's own normal repair processes[9].
- Genetic modification cannot be detected in some situations because it is not practically possible to distinguish some simple gene edits from naturally occurring mutations, or those induced by irradiation or chemical mutagenesis.
- Organisms can be modified in containment, but produce offspring through cross breeding that are free of the gene editing machinery and genetic modifications made whilst in containment (null segregants). (E.g. a fast flowering gene used to speed up reproduction rates and thereby reduce the time needed to create new plant varieties through conventional plant breeding methods)[9].

The Panel notes that the intentional deletion of even a single gene base-pair is considered a genetic alteration, and gene editing techniques provide a continuum of change that starts at the scale of natural mutations, and ends with the future possibility of creating synthetic organisms.

1

The Panel considers that New Zealand's statutory provisions and regulations around genetic modification need to account for an increasingly nuanced view, and reflect the modern reality that organisms cannot be simply categorised as 'genetically modified' or 'not-genetically modified'. This is also essential to support a constructive and meaningful conversation within New Zealand communities on their preferences for the use of these new gene technologies.

[4] Royal Commission on Genetic Modification. 2001. Ministry for the Environment. *mfe.govt.nz/sites/default/files/media/Hazards/Royal%20Commission%20on%20GM%20in%20NZ-Final.pdf*

[5] *Federated Farmers of New Zealand v Northland Regional Council* [2015] NZEnvC 89, [2015] NZRMA 217 at [47].

[6] HSNO Act, section 2(1) *genetically modified organism* means, unless expressly provided otherwise by regulations, any organism in which any of the genes or other genetic material—

a. have been modified by *in vitro* techniques; or

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

[7] Hazardous Substances and New Organisms (Organisms Not Genetically Modified) Regulations 1998 (SR 1998/219) <legislation.govt.nz/regulation/public/1998/0219/latest/DLM255889.html>.

[8] Royal Society Te Apārangi (2017) Gene editing in a healthcare context.

[9] Royal Society Te Apārangi (2018) Gene editing in the primary industries.

Regulatory complexity and consistency

The Panel's analysis of various scenarios against current legislation and regulation highlighted the legislative complexity around the use of gene editing in New Zealand. For example:

- The purpose of the HSNO Act is to protect the environment and health and safety of people and communities, and it was never intended for new organisms to include human beings. Human cells, outside of the human body, are deemed *human tissue* and are regulated by the Human Tissue Act 2008. The HSNO Amendment Act 2003 added the term human cell in a transitional provision. As a result, *organism* is defined in the HSNO Act as including a *human cell* (grown or maintained outside the human body). If gene editing were to be used in New Zealand to treat a patient's bone marrow to create blood cells that target the patient's cancer cells, the resulting blood cells, if genetically modified outside the body, would be classified as a new organism according to the HSNO Act.
- If gene editing were to be used to develop and administer a gene drive[10] to rid New Zealand's conservation estate of possums, it would require the navigation of multiple pieces of legislation with different regulatory authorities (see Appendix A). For example, animal ethics approval (Animal Welfare Act 1999) during development, EPA approval for the new organism (HSNO Act 1996, section 27), the Biosecurity Act 1993 if the organism is imported (to minimize inadvertent importation of pests or diseases) or is, in itself, likely to be a pest and, in some territorial authorities a plan change and/or a resource consent under the Resource Management Act 1991 (RMA). A gene drive organism could be incorporated into, or controlled by, pest management plans (RMA and Biosecurity Act) or conservation management plans (Conservation Act 1987, Wild Animal Control Act 1977, Marine Reserves Act 1971, Reserves Act 1977, Marine Mammals Protection Act 1978).
- The joint food regulatory system with Australia includes a Standard for the regulation of food produced using gene technology, which is now under review. This means the food products of genetically modified organisms are regulated separately to the organisms themselves.

Currently, the legal and scientific definitions are not harmonised across Acts and regulatory frameworks, meaning that there is no shared common language with which to engage with communities. Debates are likely to be confused by this lack of harmony. For example, the use of *human* versus *human cell* (or embryo); *animal* excluding and including invertebrates (such as the honeybee); *pest* versus *unwanted organism*; and *biological product* versus *biological compound*.

Such complexity may also limit the ability to provide coordinated and timely responses to the big environmental and societal challenges such as biosecurity threats; new and invasive diseases (to plants, animals and humans); medical trials; and regional and national climate change challenges to valued flora, fauna and primary produce.

In some cases, necessary definitions are missing. For example, *genetic modification* is not defined in the Human Assisted Reproductive Technology 2004 (HART) and Animal Welfare Acts, nor do they refer to the HSNO Act for definition.

The provisions that acknowledge the importance and protection of taonga Māori and consideration of the Treaty of Waitangi, or recommendations of the WAI 262 Report[11], are also inconsistent, may not go far enough (i.e. *take into account* rather than *recognise and provide for*), and in some cases are completely absent from these Acts.[12]

2

The Panel considers that the development of a shared set of definitions across the regulatory system would be a useful first step to enabling a constructive debate and determining the degree of public support for use of genetic technologies for different applications. Clearer pathways for making decisions would also enable more efficient and effective navigation of the regulatory system across agencies and Acts. In future-proofing regulations, government should also seek to ensure that statutory provisions take into account Māori cultural views.

International regulation and enforcement

Internationally, New Zealand is part of a global trading and standards environment. Other countries and regions such as USA, Europe, Australia and Japan are already considering what changes may be needed to their systems to effectively regulate new genetic technologies like gene editing. International agreements to which New Zealand is a party, such as the Cartagena Protocol[13] that regulates the movement of genetically modified organisms (GMOs) between countries, also contain different definitions of genetic modification to those found in the HSNO Act.

In Australia, a scientific and technical review of the Australian Gene Technology Regulations 2001 was initiated in October 2016, by the Office for the Genetic Technology Regulator (OGTR)[14], which defines what constitutes gene technology and genetically modified organisms for the purposes of the Gene Technology Act 2000. The review resulted in the exemption of gene editing using site directed nucleases without introduced templates to guide genome repair (SDN-1) from regulatory oversight, from October 2019. As the repairs would be guided by the cell's normal repair processes, organisms modified using SDN-1 cannot be distinguished from conventionally-bred animals or plants, and there is no evidence that they pose safety risks that warrant regulation.

Food Standards Australia New Zealand (FSANZ) is also undertaking a review of the Food Standards Code to assess its application to food products derived from new genetic technologies, and to consider the definitions of "food produced using gene technology" and "gene technology". Half of New Zealand's domestic food supply is imported[15] and therefore any amendments to the Food Standards Code may have implications for trade.

Because it is not practically possible to distinguish some simple gene edits from naturally occurring mutations, or those induced by irradiation or chemical mutagenesis, the enforcement of GMO regulations at the New Zealand border may become impractical and compliance very difficult under the current regulatory environment.

3

The Panel considers that the potential trade and regulatory enforcement impacts from different treatment of gene editing technologies in different countries need to be investigated to ensure that New Zealand's regulations continue to be fit-for-purpose, both domestically and internationally. New Zealand could also consider the recommendations from the Australian OGTR and FSANZ reviews.

[10] Gene drives are a genetic system that ensure the genetic modification will almost always be passed on, allowing that variant to spread rapidly through a population. In this way it would be possible, for example, to spread a gene that suppresses fertility in females in a pest species population.

[11] The Waitangi Tribunal concluded in the WAI 262 Report "*that the law and policy in respect of genetically modified organisms does not sufficiently protect the interests of kaitiaki in mātauranga Māori or in the genetic and biological resources of taonga species*" (Ko Aotearoa Tenei, Chapter 2; The Genetic and Biological Resources of Taonga Species, page 86).

[12] All persons exercising powers and functions under the HSNO Act are to *take into account* the relationship of Māori and their culture and traditions with their ancestral lands, water, sites, waahi tapu, valued flora and fauna, and other taonga (section 6(d)) and the Treaty of Waitangi (section 8).

[13] The Cartagena Protocol to the Convention on Biological Diversity in accordance with the precautionary approach contained in Principle 15 of the Rio Declaration on Environment and Development, is an international agreement that aims to ensure an adequate level of protection in the field of safe transfer handling and use of *living modified organisms* (LMOs). Particular attention is given to LMO resulting from biotechnology that may have adverse effects on the conservation and sustainable use of biological diversity, considering risks to human health and specifically focusing on transboundary movements (Article 1).

[14] Australian Government Department of Health, Office of the Gene Technology Regulator ogtr.gov.au/internet/ogtr/publishing.nsf/Content/reviewregulations-1

[15] FAOSTAT, Commodity Balances -Livestock and Fish Primary Equivalent & Commodity Balances – Crops Primary Equivalent. Food and Agriculture Organization of the United Nations, Rome, Italy. fao.org/faostat/en/#data

Making regulation proportionate to risk

The current regulatory framework for GMOs is *process*- rather than *outcome*-based, i.e. focusing on the process used to introduce the genetic traits rather than what the trait is and what its impacts might be. This may result in inconsistent regulatory outcomes, where like products (in terms of their characteristics and potential risk) are not treated equally under regulations. For example, CRISPR can be used to generate a wide range of traits that can also be generated by less precise, yet unregulated technologies and practices (i.e. conventional breeding, or chemical and radiation mutagenesis).

The question of whether GMO regulation should be based on the process or the outcome, or a hybrid of both, is currently being debated in other countries, with different jurisdictions adopting different approaches. New Zealand has a largely process-based approach, along with the European Union, whereas Canada has adopted a 'novel product'-based approach and the United States has implemented a hybrid system.

The Panel's view is that process-based regulatory systems, which are premised on a binary system of 'modification', will become increasingly obsolete and unsustainable, as the potential for genetic changes becomes more sophisticated with new technologies, in comparison with existing conventional mutagenesis approaches.

For example, there are genetic technologies exempt from regulation listed in HSNO's 'Organisms Not Genetically Modified' Regulations that were in use before July 1998, such as chemical and irradiation mutagenesis. However, they do not include CRISPR-Cas technology because it was developed after July 1998, even though the outcome sought may be the same. Furthermore, a High Court decision in 2014[16] stated that the exemption list was an exclusive list, not a list of examples for guidance, and it could not be interpreted to include other techniques that were similar to chemical mutagenesis.

A risk-tiered regulatory approach, for example one similar to that supported by the Australian Legislative and Governance Forum on Gene Technology in its recent review of the National Gene Technology Scheme[17], would give more flexibility to make regulation proportionate to risk in response to changing technologies. It would allow risk assessment to be consistently applied across industries and products where the outcomes are the same and support public confidence in decision-making about which research and applications are appropriate in New Zealand. It would also attract investment to implement and commercialise the results of successful research. A risk-tiered approach could also reflect the history of safe use, with the regulatory burden reducing or increasing as more is known, uncertainty is reduced, and the level of risk with different approaches is better understood.

4

The Panel considers that addressing issues such as definitions, complexity and inconsistency in the current legislation, and accommodating advances in gene technologies, would be more effectively achieved with a risk-tiered approach where regulatory burden is commensurate with risk. This would support public confidence in decision-making and provide greater flexibility and adaptability to accommodate further scientific and technological changes in future.

[16] Reference case: The Sustainability Council of New Zealand Trust v The Environmental Protection Authority [2014] NZHC 1067, (2014) 18 ELRNZ 331.

[17] Legislative and Governance Forum on Gene Technology Forum. 2018. health.gov.au/internet/main/publishing.nsf/Content/ohp-gene-tech-oct18-comm.htm

Community engagement principles and education

Informed discussion and engagement within New Zealand's diverse communities is a vital part of determining preferences and public acceptance for the use of any new gene technologies. When engaging with communities about regulatory change, the Panel proposes that consideration be given to adopting the following principles:

- **The uniqueness of Aotearoa/New Zealand** valuing our uniqueness, and making decisions tailored to our environment, and indigenous and cultural heritage.
- **The Treaty of Waitangi/Te Tiriti o Waitangi** adopting the principles of partnership, reciprocity, participation, autonomy, active protection, and mutual benefit enshrined in the Treaty of Waitangi as the basis for engagement and regulatory co-design between tangata whenua and the Crown, on Māori rights and interests, and their special relationship with their taonga.
- **Sustainability** sustaining and regenerating our unique but fragile environment for generations to come.
- **Being part of a global family** safeguarding those things that are uniquely ours, while sharing in and contributing to global developments.
- **The well-being of all** meeting the needs of all New Zealanders to ensure positive educational, health and social outcomes whilst reducing and avoiding inequalities.
- **Freedom of choice** recognising our diverse cultures and beliefs.
- **Participation and māramatanga/understanding** ensuring effective systems of consultation and engagement between the Crown and Māori communities, with understanding and informed consent.
- **Transparency and openness** committing to openness and sharing of information in ways that are accessible and understandable to all citizens and enable informed decision-making based on māramatanga.

The Panel's view is that there is wide disparity in community understanding of new genetic technologies and applications and, for many, the potential applications of the technologies is moving ahead of their understanding. There is a need to close this gap through wide and deep engagement with communities, and acknowledge that this needs to be done in a way that recognises the partnership between the Crown and Māori.

5

The Panel considers that regulation needs to be informed by wide engagement with the public. Current information and culturally appropriate education resources about new genetic technologies and their application should be shared widely and feedback sought on public attitudes and ethical views.

Capacity and capability

Effective decision-making around new biotechnologies will rely on best-practice skills and knowledge within communities, the research system and regulatory bodies. The range of considerations needed to make decisions has widened considerably since the original development of the HSNO Act and the EPA. Examples include mātauranga Māori, types of regulation and risk assessment, molecular biology, genetics, bioinformatics, environmental management, ecological and production systems modelling, and financial and economic assessment. Educating our younger generations now is critical for our future sustainability within a globally connected economy.

Decision-making on the impact of these technologies will increasingly need to assess and manage outcome risk. While some outputs of gene editing technologies will be similar to those that already exist using traditional technologies, other outputs may be unlike anything that exists today. Organisms will need to be evaluated in their environmental and social contexts and horizon scanning will be required to keep abreast of regulatory and biosecurity challenges.

6

The Panel considers that there should be ongoing development and support for the necessary capacity and capability within communities, the research sector and central and local government, to support effective engagement and decision-making around new biotechnologies. While some applications of gene technologies may be unacceptable or not feasible at this time, it is important that New Zealand has the means to assess developments and opportunities as they arise in future.

For further information

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**.

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The Society would like to thank the Gene Editing Māori Reference Group and the following people for their valuable comments and feedback on the paper:

Tom Bruynel, DLF Seeds

Thomas Chin, New Zealand Plant Breeding and Research Association

Dr William Rolleston, Genomics Aotearoa

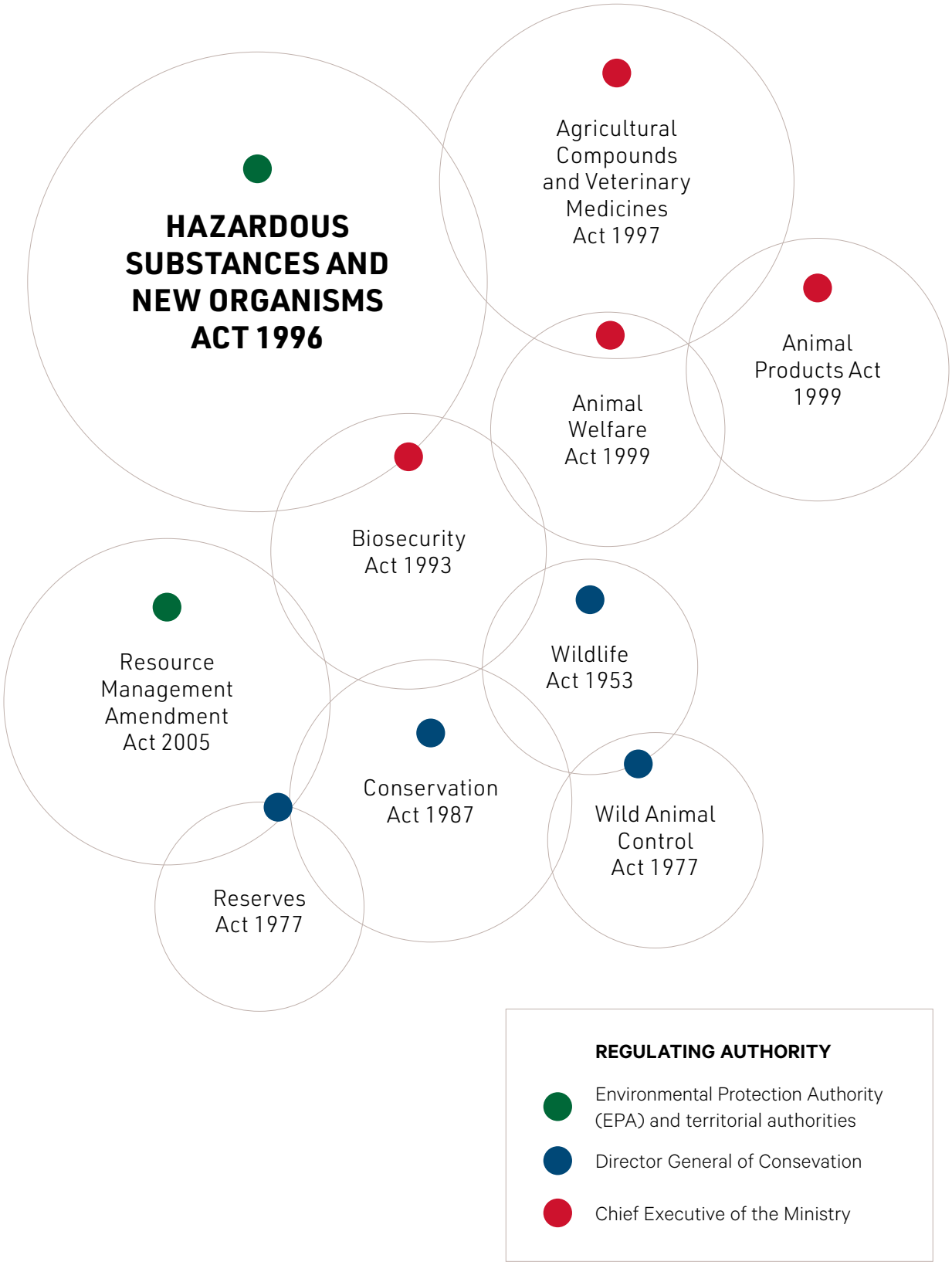
Professor Jeroen Vanderheijden, School of Government, Victoria University of Wellington

Staff from the Environmental Protection Authority, Food Standards Australia New Zealand, Ministry for the Environment, Ministry for Primary Industries, Ministry of Foreign Affairs and Trade, Ministry of Business, Innovation and Employment, and the Office of the Prime Minister's Chief Science Advisor were also consulted in developing this paper.

Professor Ian Small (University of Western Australia) and **Dr Sue Meek** (Australian National University) provided independent international review of the paper.

APPENDIX A

Legislation and regulatory authorities involved in administering a gene drive to rid New Zealand's conservation estate of possums



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Print ISBN: 978-1-877264-44-3
Digital ISBN: 978-1-877264-45-0

Published August 2019