

ROYAL SOCIETY TE APĀRANGI

# GENE EDITING SCENARIOS IN THE PRIMARY INDUSTRIES

AUGUST 2019



EXPLORE | DISCOVER | SHARE

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<sup>1</sup> 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.

<sup>1</sup> [royalsociety.org.nz/gene-editing](https://royalsociety.org.nz/gene-editing)

# CONTENTS

<b>Background</b>	<b>03</b>
<b>Acknowledgements</b>	<b>05</b>
<b>Primary industries in New Zealand</b>	<b>06</b>
<b>History of genetic selection in agriculture</b>	<b>06</b>
<b>Te Ao Māori</b>	<b>07</b>
<b>Use of modern gene editing techniques</b>	<b>07</b>
<b>Genomics research in New Zealand</b>	<b>08</b>
<b>Genomics and agriculture internationally</b>	<b>09</b>
<b>Regulation of gene editing in New Zealand and internationally</b>	<b>10</b>
GM Free Districts	11
Regulation of gene edited food and food products in New Zealand	11
<b>Ethical questions</b>	<b>12</b>
<b>Genetic modification, branding and economic returns</b>	<b>12</b>
<b>Scenarios for the use of gene editing in primary industries in New Zealand</b>	<b>13</b>
<b>Scenario 1: Reducing environmental impact</b>	<b>15</b>
Agricultural/environmental considerations	15
Ethical/social considerations	15
Legal considerations	16
Risks and potential benefits	16
<b>Scenario 2: Responding to insect pests and environmental stress</b>	<b>17</b>
Agricultural/environmental considerations	17
Ethical/social considerations	18
Legal considerations	18
Risks and potential benefits	19
<b>Scenario 3: Speeding up innovation</b>	<b>19</b>
Horticultural considerations	20
Ethical/social considerations	20
Legal considerations	20
Risks and potential benefits	21

<b>Scenario 4: Protecting taonga species used in the primary industries</b>	<b>21</b>
Agricultural and environmental considerations	22
Ethical/social considerations	22
Legal considerations	23
Risk and potential benefits	23
<b>Scenario 5: Providing new human health benefits</b>	<b>24</b>
Agricultural considerations	24
Ethical/social considerations	24
Legal considerations	25
Risk and potential benefits	26
<b>Implications for New Zealand</b>	<b>26</b>
<b>Appendix 1: Contributors to the technical paper</b>	<b>27</b>
<b>Glossary</b>	<b>28</b>
<b>References</b>	<b>30</b>

## 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<sup>2</sup>. 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<sup>3</sup>. 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<sup>4</sup> 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<sup>5</sup> 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.

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

<sup>3</sup> Statistics New Zealand. Goods and Services Trade by Country: Year ended June 2018. Table 4.

<sup>4</sup> [mpi.govt.nz/funding-and-programmes/primary-growth-partnership/completed-ggp-programmes/the-new-zealand-sheep-industry-transformation-project-nzstx/](http://mpi.govt.nz/funding-and-programmes/primary-growth-partnership/completed-ggp-programmes/the-new-zealand-sheep-industry-transformation-project-nzstx/)

<sup>5</sup> 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<sup>6</sup>).

## 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<sup>7</sup> 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.

<sup>6</sup> [jstor.org/stable/90008659?seq=1#page\\_scan\\_tab\\_contents](https://www.jstor.org/stable/90008659?seq=1#page_scan_tab_contents)

<sup>7</sup> 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<sup>8</sup>. 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<sup>9</sup>, 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.

<sup>8</sup> [scionresearch.com/about-us/news-and-events/news/2017/radiata-pine-genome-draft-assembly-completed](http://scionresearch.com/about-us/news-and-events/news/2017/radiata-pine-genome-draft-assembly-completed)

<sup>9</sup> [otago.ac.nz/genetics/news/otago659624.html](http://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
<i>Actinidia chinensis</i>	Kiwifruit	Food (fruit)
<i>Beta vulgaris</i>	Sugar beet	Sugar production
<i>Brassica napus</i>	Rapeseed	Oil, animal feed, biodiesel
<i>Brassica oleracea</i> var. <i>capitata</i>	Cabbage	Food (vegetable)
<i>Brassica rapa</i>	Chinese cabbage	Food (vegetable)
<i>Cajanus cajan</i>	Pigeon pea	Food (grain/pulse/bean)
<i>Carica papaya</i>	Papaya	Food (fruit, vegetable)
<i>Capsicum annuum</i>	Hot pepper	Spice
<i>Cicer arietinum</i>	Chickpea	Food (grain/pulse/bean)
<i>Citrullus lanatus</i>	Water melon	Food (fruit)
<i>Citrus clementina</i>	Clementine mandarin	Food (fruit)
<i>Citrus sinensis</i>	Sweet orange	Food (fruit)
<i>Coffea canephora</i>	Robusta coffee	Food (grain/pulse/bean)
<i>Cucumis melo</i>	Melon	Food (fruit)
<i>Cucumis sativus</i>	Cucumber	Food (vegetable)
<i>Elaeis guineensis</i>	Oil palm	Edible oil
<i>Fragaria vesca</i>	Strawberry	Food (fruit)
<i>Glycine max</i>	Soybean	Food (grain/pulse/bean)
<i>Leptospermum scoparium</i>	Mānuka	Food (honey)
<i>Malus x domestica</i>	Apple	Food (fruit)
<i>Musa acuminata</i>	Banana	Food (fruit)
<i>Oryza sativa</i> subsp. <i>indica</i>	Rice	Food (grain/pulse/bean)
<i>Phaseolus vulgaris</i>	Common bean	Food (grain/pulse/bean)
<i>Phoenix dactylifera</i>	Date palm	Food (fruit)
<i>Prunus mume</i>	Chinese plum/mei	Food (fruit)
<i>Prunus persica</i>	Peach	Food (fruit)
<i>Pyrus bretschneideri</i>	Asian pear	Food (fruit)
<i>Pyrus communis</i>	European pear	Food (fruit)
<i>Rubus occidentalis</i>	Raspberry	Food (fruit)
<i>Solanum lycopersicum</i>	Tomato	Food (vegetable)
<i>Solanum melongena</i>	Eggplant	Food (vegetable)
<i>Solanum tuberosum</i>	Potato	Food (vegetable)
<i>Sorghum bicolor</i>	Sorghum	Food (grain/pulse/bean)
<i>Theobroma cacao</i>	Cocoa	Food (grain/pulse/bean)
<i>Triticum aestivum</i>	Bread wheat	Food (grain/pulse/bean)
<i>Vaccinium corymbosum</i>	Blueberry	Food (fruit)
<i>Vaccinium macrocarpon</i>	Cranberry	Food (fruit)
<i>Vigna radiata</i>	Mungbean	Food (grain/pulse/bean)
<i>Vitis vinifera</i>	Grape	Food (fruit), beverage
<i>Zea mays</i>	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<sup>10</sup>.

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<sup>11</sup> 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<sup>12</sup>.

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<sup>13</sup>.

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<sup>14</sup>. 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].

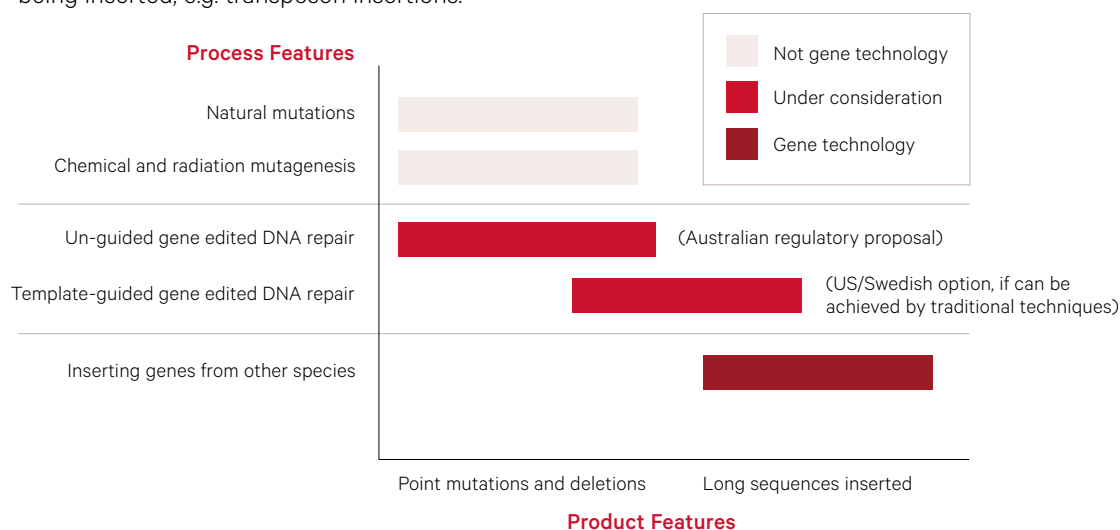
An opinion recently issued by the Advocate General of the European Court of Justice in March 2018 considered that EU GMO regulations were not applicable to certain gene edited plants and animals [50, 51]. European regulations exempt traditional mutagenesis from GM regulations, thereby plants and animals 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<sup>15</sup>

**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<sup>16</sup>, Whangarei<sup>17</sup>, Auckland<sup>18</sup> and Hastings<sup>19</sup>) 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<sup>20</sup>. 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<sup>21</sup>.

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].

<sup>10</sup> 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.

<sup>11</sup> [pioneer.com/CMRoot/Pioneer/About\\_Global/Non\\_Searchable/15-352-01\\_air\\_response\\_signed.pdf](http://pioneer.com/CMRoot/Pioneer/About_Global/Non_Searchable/15-352-01_air_response_signed.pdf)

<sup>12</sup> [fda.gov/regulatory-information/search-fda-guidance-documents/cvm-gfi-187-regulation-intentionally-altered-genomic-dna-animals](http://fda.gov/regulatory-information/search-fda-guidance-documents/cvm-gfi-187-regulation-intentionally-altered-genomic-dna-animals)

<sup>13</sup> [mainichi.jp/english/articles/20180821/p2a/00m/0na/033000c](http://mainichi.jp/english/articles/20180821/p2a/00m/0na/033000c)

<sup>14</sup> [upsc.se/documents/Information\\_on\\_interpretation\\_on\\_CRISPR\\_Cas9\\_mutated\\_plants\\_Final.pdf](http://upsc.se/documents/Information_on_interpretation_on_CRISPR_Cas9_mutated_plants_Final.pdf)

<sup>15</sup> [ogtr.gov.au/internet/ogtr/publishing.nsf/Content/reviewdiscussionpaper-hm](http://ogtr.gov.au/internet/ogtr/publishing.nsf/Content/reviewdiscussionpaper-hm)

<sup>16</sup> [fndc.govt.nz/services/the-far-north-district-plan](http://fndc.govt.nz/services/the-far-north-district-plan)

<sup>17</sup> [wdc.govt.nz/PlansPoliciesandBylaws/Plans/DistrictPlan/Documents/District-Plan-Part-E-District-Wide/GMO-Genetically-Modified-Organisms.pdf](http://wdc.govt.nz/PlansPoliciesandBylaws/Plans/DistrictPlan/Documents/District-Plan-Part-E-District-Wide/GMO-Genetically-Modified-Organisms.pdf)

<sup>18</sup> [aucklandcouncil.govt.nz/plans-projects-policies-reports-bylaws/our-plans-strategies/unitary-plan/history-unitary-plan/ihp-designations-reports-recommendations/Documents/ihp024gmos.pdf](http://aucklandcouncil.govt.nz/plans-projects-policies-reports-bylaws/our-plans-strategies/unitary-plan/history-unitary-plan/ihp-designations-reports-recommendations/Documents/ihp024gmos.pdf)

<sup>19</sup> [hastingsdc.govt.nz/our-council/news/latest-news/press-releases/article/1038](http://hastingsdc.govt.nz/our-council/news/latest-news/press-releases/article/1038)

<sup>20</sup> 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](http://fao.org/faostat/en/#data)

<sup>21</sup> [foodstandards.govt.nz/code/Pages/default.aspx](http://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<sup>22</sup> 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.

<sup>22</sup> [mpi.govt.nz/exporting/food/](https://mpi.govt.nz/exporting/food/)

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

	SCENARIO 1 <b>Reducing environmental impact</b>	SCENARIO 2 <b>Responding to pests and stress</b>	SCENARIO 3 <b>Speeding up innovation</b>	SCENARIO 4 <b>Protecting taonga species</b>	SCENARIO 5 <b>Providing new health benefits</b>
 <b>Species</b>	 <b>Douglas Fir</b>	 <b>Ryegrass endophytes</b>	 <b>Apple</b>	 <b>Mānuka</b>	 <b>Dairy cows</b>
<b>Aim</b>	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
<b>Estimated economic impact</b>	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
<b>Potential implications for trade</b>	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
<b>'Degrees of separation' from human food consumption</b>	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
<b>Estimated time to be technically possible</b>	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"<sup>23</sup> 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.

<sup>23</sup> [beehive.govt.nz/release/16m-new-funding-tackle-wilding-conifers](https://www.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<sup>24</sup>). 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)<sup>25</sup>. 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.

<sup>24</sup> 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.

<sup>25</sup> [mfe.govt.nz/more/hazards/new-organisms/genetic-modification-new-zealand/exporting-living-modified-organisms](https://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<sup>26</sup>, 1.24 million hectares was certified by the Forest Stewardship Council in 2016<sup>27</sup>, which currently prohibits the use of GM trees<sup>28</sup>.

## 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.

<sup>26</sup> [mpi.govt.nz/news-and-resources/open-data-and-forecasting/forestry/new-zealands-forests/](https://mpi.govt.nz/news-and-resources/open-data-and-forecasting/forestry/new-zealands-forests/)

<sup>27</sup> [nzfoa.org.nz/images/stories/pdfs/Facts\\_Figures\\_2016\\_%C6%92a\\_web\\_version\\_v3.pdf](https://nzfoa.org.nz/images/stories/pdfs/Facts_Figures_2016_%C6%92a_web_version_v3.pdf)

<sup>28</sup> [nz.fsc.org/preview.national-standard-for-certification-of-plantation-forest-management-in-new-zealand-version-3-5-for-2nd-consultation.a-1341.pdf](https://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<sup>29</sup>. 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<sup>30</sup>).

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<sup>31</sup>.

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<sup>32</sup> 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)<sup>33</sup>. 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.

<sup>29</sup> HSNO Act, section 2(1).

<sup>30</sup> 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.

<sup>31</sup> [mpi.govt.nz/importing/plants/seeds-for-sowing/steps-to-importing/](http://mpi.govt.nz/importing/plants/seeds-for-sowing/steps-to-importing/)

<sup>32</sup> [epa.govt.nz/assets/Uploads/Documents/New-Organisms/Policies/155-04-09-MAF-ERMA-Std-2007.pdf](http://epa.govt.nz/assets/Uploads/Documents/New-Organisms/Policies/155-04-09-MAF-ERMA-Std-2007.pdf)

<sup>33</sup> [mfe.govt.nz/more/hazards/new-organisms/genetic-modification-new-zealand/exporting-living-modified-organisms](http://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.

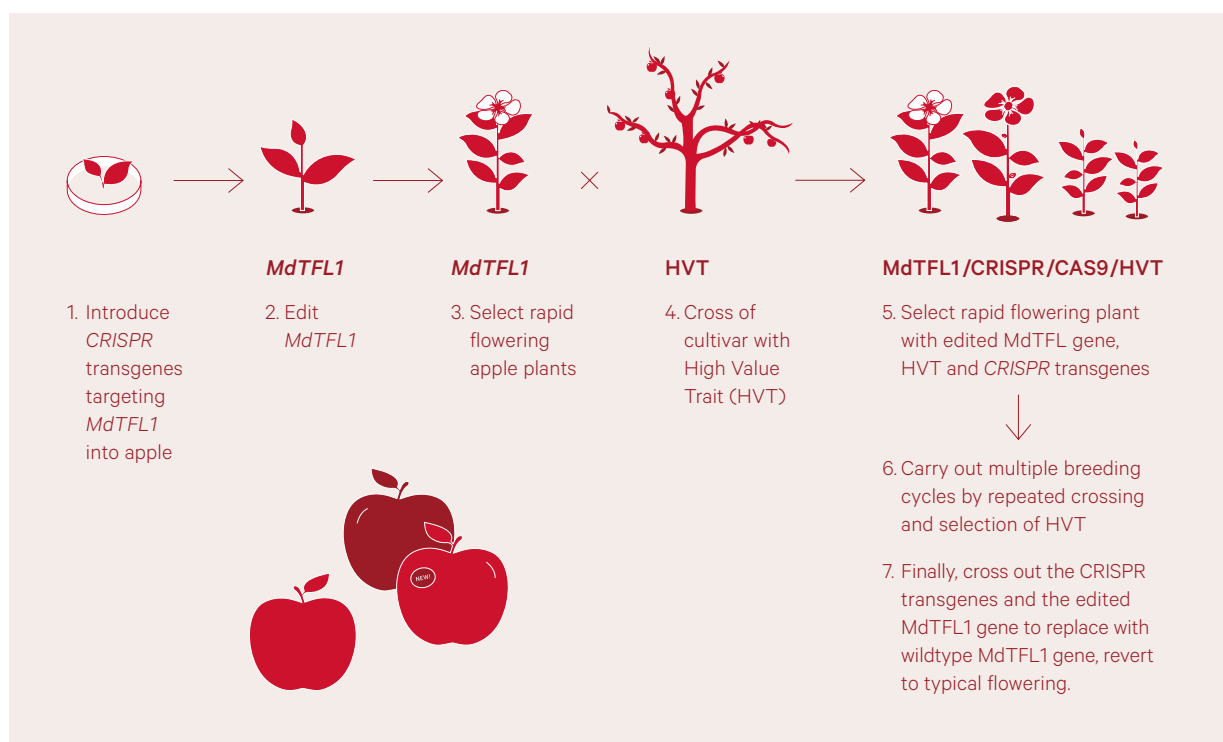
If we were to handle or export seed with endophytes considered GM in other countries, consideration would need to be given to the implication for seed exports to countries with a purity threshold of zero for GM contamination. Approval would need to be sought around the level of possible contamination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



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<sup>34</sup> 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<sup>35</sup>. Thereby, fast flowering gene edited apple trees 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<sup>36</sup>). 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.

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

<sup>35</sup> HSNO Act, section 2(1).

<sup>36</sup> 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)<sup>37</sup>. 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.

<sup>37</sup> [mfe.govt.nz/more/hazards/new-organisms/genetic-modification-new-zealand/exporting-living-modified-organisms](http://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<sup>38</sup>. 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.

<sup>38</sup> [plantandfood.co.nz/page/news/media-release/story/cracking-manukas-genetic-code-to-mitigate-myrtle-rust/](http://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<sup>39</sup>. 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].

<sup>39</sup> 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<sup>40</sup>). 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*

<sup>40</sup> 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)<sup>41</sup>. 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  $\alpha$ -lactalbumin [136] and  $\alpha$ -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.

<sup>41</sup> 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/](http://royalsociety.org.nz/gene-editing/), or contact [info@royalsociety.org.nz](mailto:info@royalsociety.org.nz).



## APPENDIX 1

### Contributors to the technical paper

#### Members of the Expert Panel

**Dr David Penman**, Director,  
David Penman and Associates

**Professor Barry Scott FRSNZ**, Professor  
of Molecular Genetics, Massey University

**Associate Professor Jane Allison**, Associate  
Professor of Computational Biology, School  
of Biological Sciences, University of Auckland

**Associate Professor Thomas Buckley**,  
Research Priority Leader/Invertebrate Systematics,  
Landcare Research

**Professor Peter Dearden**, Director, Genetics  
Otago, University of Otago

**Professor Alexei Drummond FRSNZ**, Professor  
of Computational Biology, University of Auckland

**Professor Gary Hawke FRSNZ**, Associate Senior  
Fellow, New Zealand Institute of Economic Research

**Professor Mark Henaghan FRSNZ**, Dean,  
Faculty of Law, University of Otago

**Irene Kereama-Royal**, Research Partner  
– Rangahau, Māori and Development, Unitec

**Professor Lisa Matisoo-Smith FRSNZ**,  
Professor of Biological Anthropology,  
University of Otago

**Associate Professor Susan Morton**,  
Associate Professor in Epidemiology, School  
of Population Health, University of Auckland

**Professor Richard Newcomb**, Chief Scientist,  
Plant and Food Research

**Professor Joanna Putterill**, Professor in Plant  
Molecular Genetics, University of Auckland

**Professor Stephen Robertson FRSNZ**,  
Curekids Professor of Paediatric Genetics,  
University of Otago

**Dr Phil Wilcox**, Senior Lecturer,  
Department of Mathematics and Statistics,  
University of Otago

#### Special contributors

**Dr Julie Everett-Hincks**, Legal and Scientific  
Researcher, Law Faculty, University of Otago

**Dr David Chagné**, Plant and Food Research

**Dr Jay Jayaraman**, Plant and Food Research

**Dr Goetz Laible**, AgResearch

**Dr Matthew Barnett**, AgResearch

**Dr Glenn Thorlby**, Scion

#### Society staff support

**Dr Marc Rands**, Senior Researcher,  
Royal Society Te Apārangi

**Dr Roger Ridley**, Director – Expert Advice  
and Practice, Royal Society Te Apārangi

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

**Dr Andrew Allan**, Plant and Food Research

**Tom Bruynel**, DLF seeds

**Associate Professor Julia Horsfield**, Genetics  
Otago, University of Otago

**Professor Paula Jameson**, University of Canterbury

**Julia Jones**, Primary Sector Council

**Dr Suzanne Keeling**, Beef and Lamb New Zealand

**Dr Mike King**, Bioethics Centre, University of Otago

**Dr William Rolleston**, Genomics Aotearoa

Staff from the Environmental Protection Authority,  
National Animal Ethics Advisory Committee, Ministry  
for the Environment, Ministry for Primary Industries,  
Ministry of Foreign Affairs and Trade, and the Office  
of the Prime Minister's Chief Science Advisor were  
also consulted in developing this paper.

**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

<b>Agriculture</b>	The science and art of cultivation on soil and the rearing of livestock to provide food and other products.
<b>Agrobacterium</b>	<i>Agrobacterium tumefaciens</i> is a widespread naturally occurring soil bacterium that causes crown gall, and has the ability to introduce new genetic material into the plant cell.
<b>Alkaloid</b>	A class of naturally occurring organic nitrogen-containing compounds.
<b>Aquaculture</b>	The rearing of aquatic animals or the cultivation of aquatic plants for food.
<b>Backcrossing</b>	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.
<b>Bioinformatics</b>	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.
<b>Biopsy</b>	A sample of tissue taken from the body in order to examine it more closely.
<b>Biosynthesis</b>	The formation of chemical compounds by a living organism.
<b>Clone</b>	A clone is a group of identical cells that share a common ancestry, meaning they are derived from the same cell.
<b>CRISPR</b>	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.
<b>Cryopreservation</b>	The use of very low temperatures to preserve structurally intact living cells and tissues.
<b>Cultivar</b>	A plant variety that has been produced in cultivation by selective breeding.
<b>DNA</b>	Deoxyribonucleic acid, is the hereditary material in humans and almost all other organisms.
<b>DNA marker</b>	DNA variation linked to a trait of interest (e.g. productivity, disease resistance, abiotic stress tolerance, and quality).
<b>Enzymatic hydrolysis</b>	A process in which enzymes facilitate the cleavage of bonds in molecules with the addition of the elements of water.
<b>EU</b>	European Union.
<b>Forage</b>	Food such as grass or hay for grazing animals.
<b>FDA</b>	US Food and Drug Administration.
<b>GDP</b>	Gross domestic product.
<b>Gene editing</b>	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.
<b>Genes</b>	A gene is the basic physical and functional unit of heredity. Genes are made up of DNA.
<b>Genetic modification</b>	The direct manipulation of an organism's genes using biotechnology.
<b>Genome</b>	The genetic material of an organism.
<b>Genomic selection</b>	An indirect selection process where traits of interest in an individual are predicted based on a genome-wide panel of DNA markers.
<b>Germline</b>	The cell types that eventually result in the formation of reproductive cells, sperm or pollen.
<b>Horticulture</b>	The cultivation, processing, and sale of fruits, nuts, vegetables, ornamental plants, and flowers as well as many additional services.
<b>HSNO</b>	Hazardous Substances and New Organisms Act 1996.

<b>Hybrid</b>	The result of mixing, through sexual reproduction, two animals or plants of different breeds, varieties, species or genera.
<b>Indole-diterpenes</b>	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.
<b><i>In vivo</i></b>	Carried out within the body of a living organism.
<b><i>In vitro</i></b>	Made to occur in a laboratory vessel or other controlled experimental environment rather than within a living organism or natural setting.
<b>Iwi</b>	Extended kinship group, tribe, nation, people, nationality, race.
<b>Kaitiaki</b>	Trustee, minder, guard, custodian, guardian, caregiver, keeper, steward.
<b>Kaitiakitanga</b>	Guardianship, stewardship.
<b>Mana</b>	Prestige, authority, control, power, influence, status, spiritual power, charisma.
<b>Mana Whenua</b>	territorial rights, authority and jurisdiction.
<b>Mauri</b>	Life principle, life force, vital essence, special nature.
<b>MdTFL1</b>	A gene that represses flowering in apple plants.
<b>Monoculture</b>	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.
<b>Mutagenesis</b>	A process by which the genetic information of an organism is changed, resulting in a mutation.
<b>Mutagenic agents</b>	Physical or chemical agents that change the genetic material, usually DNA, of an organism and thus increase the frequency of mutations.
<b>Neolithic</b>	The final division of the Stone Age, which began about 12,000 years ago when the first development of farming appeared.
<b>OECD</b>	Organisation for Economic Co-operation and Development.
<b>Pathogen</b>	A bacterium, virus, or other microorganism that can cause disease.
<b>RNA</b>	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.
<b>Selective breeding</b>	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.
<b>Synthetic foods</b>	Foods that have been produced or manufactured using new methods with the help of advancements in technology.
<b>Taonga</b>	Treasure, anything prized.
<b>Trait</b>	A genetically determined characteristic that can be underpinned by one or many genes.
<b>USDA</b>	United States Department of Agriculture.
<b>Whakapapa</b>	Genealogy, genealogical table, lineage, descent.
<b>Whānau</b>	Extended family, family group.
<b>Wilding conifer</b>	The New Zealand term for introduced conifers that self-sow and spread across the landscape unwanted.

## References

1. Journeaux, P., et al., *Analysis of Drivers and Barriers to Land Use Change*. 2017, Ministry for Primary Industries: Wellington, New Zealand.
2. Pacher, M. and H. Puchta, *From classical mutagenesis to nuclease-based breeding – directing natural DNA repair for a natural end-product*. Plant J, 2017. **90**(4): p. 819-833.
3. Nuffield Council on Bioethics, *Genome editing: an ethical review*. 2016, Nuffield Council on Bioethics: London, UK.
4. Khoury, C.K., et al., *Origins of food crops connect countries worldwide*. Proceedings of the Royal Society of London B, 2016. **283**(1832): p. 20160792.
5. Hake, S. and J. Ross-Ibarra, *The natural history of model organisms: genetic, evolutionary and plant breeding insights from the domestication of maize*. Elife, 2015. **4**: p. e05861.
6. Matsuoka, Y., *Evolution of polyploid Triticum wheats under cultivation: the role of domestication, natural hybridization and allopolyploid speciation in their diversification*. Plant and cell physiology, 2011. **52**(5): p. 750-764.
7. Jain, S.M., *Major mutation-assisted plant breeding programs supported by FAO/IAEA*. Plant Cell, Tissue and Organ Culture, 2005. **82**(1): p. 113-123.
8. ISAAA, *Global Status of Commercialized Biotech/GM Crops in 2017: Biotech Crop Adoption Surges as Economic Benefits Accumulate in 22 Years, in ISAAA Brief 53*. 2017. Ithaca, NY.
9. Royal Society, *GM plants: Questions and answers*. 2016, Royal Society of London. p. 40.
10. Doudna, J.A. and E. Charpentier, *Genome editing. The new frontier of genome engineering with CRISPR-Cas9*. Science, 2014. **346**(6213): p. 1258096.
11. Schiml, S. and H. Puchta, *Revolutionizing plant biology: multiple ways of genome engineering by CRISPR/Cas*. Plant Methods, 2016. **12**: p. 8.
12. Kleinstiver, B.P., et al., *High-fidelity CRISPR-Cas9 nucleases with no detectable genome-wide off-target effects*. Nature, 2016. **529**(7587): p. 490-5.
13. Gao, F., et al., *DNA-guided genome editing using the *Natronobacterium gregoryi* Argonaute*. Nature Biotechnol, 2016. **34** (7), p. 768.
14. Abudayyeh, O.O., et al., *C2c2 is a single-component programmable RNA-guided RNA-targeting CRISPR effector*. Science 2016, **353** (6299): aaf5573.
15. Zetsche, B., et al., *Cpf1 is a single RNA-guided endonuclease of a class 2 CRISPR-Cas system*. Cell, 2015. **163**(3): p. 759-71.
16. Woo, J.W., et al., *DNA-free genome editing in plants with preassembled CRISPR-Cas9 ribonucleoproteins*. Nat Biotechnol, 2015. **33**(11): p. 1162-4.
17. National Academies of Sciences Engineering and Medicine, *Genetically Engineered Crops: Experiences and Prospects*. 2016, Washington, DC: The National Academies Press. p. 420.
18. Voytas, D.F. and C. Gao, *Precision genome engineering and agriculture: opportunities and regulatory challenges*. PLoS Biol, 2014. **12**(6): p. e1001877.
19. Dominguez, A.A., W.A. Lim, and L.S. Qi, *Beyond editing: repurposing CRISPR-Cas9 for precision genome regulation and interrogation*. Nat Rev Mol Cell Biol, 2016. **17**(1): p. 5-15.
20. Kosicki, M., K. Tomberg, and A. Bradley, *Repair of double-strand breaks induced by CRISPR-Cas9 leads to large deletions and complex rearrangements*. Nature Biotechnology, 2018. **36** (8), p. 765.
21. Scheben, A., et al., *Towards CRISPR/Cas crops – bringing together genomics and genome editing*. New Phytol, 2017. **216**(3): p. 682-698.
22. Shukla, V.K., et al., *Precise genome modification in the crop species *Zea mays* using zinc-finger nucleases*. Nature, 2009. **459**(7245): p. 437-41.
23. Curtin, S.J., et al., *Targeted mutagenesis for functional analysis of gene duplication in legumes*. Methods Mol Biol, 2013. **1069**: p. 25-42.
24. Jiang, W., et al., *Demonstration of CRISPR/Cas9/sgRNA-mediated targeted gene modification in *Arabidopsis*, tobacco, sorghum and rice*. Nucleic Acids Res, 2013. **41**(20): p. e188.
25. Li, T., et al., *High-efficiency TALEN-based gene editing produces disease-resistant rice*. Nat Biotechnol, 2012. **30**(5): p. 390-2.
26. Shan, Q., et al., *Targeted genome modification of crop plants using a CRISPR-Cas system*. Nat Biotechnol, 2013. **31**(8): p. 686-8.
27. Wendt, T., et al., *TAL effector nucleases induce mutations at a pre-selected location in the genome of primary barley transformants*. Plant Mol Biol, 2013. **83**(3): p. 279-85.
28. Wang, X., et al., *Generation of gene-modified goats targeting *MSTN* and *FGF5* via zygote injection of CRISPR/Cas9 system*. Sci Rep, 2015. **5**: p. 13878.
29. Carlson, D.F., et al., *Production of hornless dairy cattle from genome-edited cell lines*. Nat Biotechnol, 2016. **34**(5): p. 479-81.

30. Whitworth, K.M., et al., *Gene-edited pigs are protected from porcine reproductive and respiratory syndrome virus*. Nat Biotechnol, 2016. **34**(1): p. 20-2.
31. Lillico, S.G., et al., *Mammalian interspecies substitution of immune modulatory alleles by genome editing*. Sci Rep, 2016. **6**: p. 21645.
32. Lyall, J., et al., *Suppression of avian influenza transmission in genetically modified chickens*. Science, 2011. **331**(6014): p. 223-6.
33. Jiang, Y., et al., *The sheep genome illuminates biology of the rumen and lipid metabolism*. Science, 2014. **344**(6188): p. 1168-1173.
34. Barrett, B., et al., *Breaking through the feed barrier: options for improving forage genetics*. Animal Production Science, 2015. **55**(7): p. 883-892.
35. Pilkington, S.M., et al., *A manually annotated Actinidia chinensis var. chinensis (kiwifruit) genome highlights the challenges associated with draft genomes and gene prediction in plants*. BMC genomics, 2018. **19**(1): p. 257.
36. Velasco, R., et al., *The genome of the domesticated apple (Malus× domestica Borkh.)*. Nature genetics, 2010. **42**(10): p. 833.
37. Chagné, D., et al., *The draft genome sequence of European pear (Pyrus communis L.'Bartlett')*. PloS one, 2014. **9**(4): p. e92644.
38. Thottathil, G.P., K. Jayasekaran, and A.S. Othman, *Sequencing crop genomes: a gateway to improve tropical agriculture*. Tropical life sciences research, 2016. **27**(1): p. 93.
39. Chagné, D., et al., *Simple sequence repeat (SSR) markers for New Zealand mānuka (Leptospermum scoparium) and transferability to kānuka (Kunzea spp.)*. New Zealand Journal of Crop and Horticultural Science, 2017. **45**(3): p. 216-222.
40. VanBuren, R., et al., *Sequence and Analysis of the Black Raspberry (Rubus occidentalis) Genome*, in *The Genomes of Rosaceous Berries and Their Wild Relatives*. 2018, Springer. p. 185-197.
41. Li, X., et al., *De novo sequencing and comparative analysis of the blueberry transcriptome to discover putative genes related to antioxidants*. Gene, 2012. **511**(1): p. 54-61.
42. Verde, I., et al., *The high-quality draft genome of peach (Prunus persica) identifies unique patterns of genetic diversity, domestication and genome evolution*. Nature genetics, 2013. **45**(5): p. 487.
43. Whelan, A.I. and M.A. Lema, *Regulatory framework for gene editing and other new breeding techniques (NBTs) in Argentina*. GM Crops Food, 2015. **6**(4): p. 253-65.
44. Ainsworth, C., *Agriculture: A new breed of edits*. Nature, 2015. **528**(7580): p. S15-6.
45. Waltz, E., *Gene-edited CRISPR mushroom escapes US regulation*. Nature, 2016. **532**: p. 293.
46. *A CRISPR definition of genetic modification*. Nature Plants, 2018. **4**(5): p. 233-233.
47. Waltz, E., *Gene-edited CRISPR mushroom escapes US regulation*. Nature, 2016. **532**(7599): p. 293.
48. Smyth, S.J., *Canadian regulatory perspectives on genome engineered crops*. GM Crops Food, 2017. **8**: p. 35-43.
49. Hunter, J. and G. Duff, *GM crops-lessons from medicine*. Science, 2016. **353**(6305): p. 1187.
50. Abbott, A., *European court suggests relaxed gene-editing rules*. Nature. 2018. **19**
51. Bobek, M., *Case-law of the Court of Justice of the European Union*. 2018. Opinion of Advocate General Bobek. Case C-528/16. Luxembourg.
52. Court of Justice of the European Union., *According to Advocate General Bobek, organisms obtained by mutagenesis are, in principle, exempted from the obligations in the Genetically Modified Organisms Directive*, in *Press Release No 04/18*. 2018, Court of Justice of the European Union: Luxembourg.
53. Court of Justice of the European Union, *Organisms obtained by mutagenesis are GMOs and are, in principle, subject to the obligations laid down by the GMO Directive.*, in *PRESS RELEASE No 111/18*, Court of Justice of the European Union, Editor. 2018: Luxembourg.
54. Department of Health Office of the Gene Technology Regulator, *Technical Review of the Gene Technology Regulations 2001-2017-18 Amendment Proposals Consultation*, Department of Health Office of the Gene Technology Regulator, Australian Government, Editor. 2018.
55. Food Standards Australia New Zealand, *Consultation paper. Food derived using new breeding techniques*, Food Standards Australia New Zealand, Editor. February 2018.
56. Graham, J., et al., *Moral Foundations Theory: On the advantages of moral pluralism over moral monism*. 2016. In: Gray K, Graham J, editors. *The Atlas of Moral Psychology: Mapping Good and Evil in the Mind*. New York: Guilford Press.
57. Ormandy, E.H., J. Dale, and G. Griffin, *Genetic engineering of animals: Ethical issues, including welfare concerns*. The Canadian Veterinary Journal, 2011. **52**(5): p. 544.
58. Blancke, S., et al., *Fatal attraction: the intuitive appeal of GMO opposition*. 2015. **20**(7): p. 414-418.
59. Schuppli, C.A. and D.M. Weary, *Attitudes towards the use of genetically modified animals in research*. Public understanding of science, 2010. **19**(6): p. 686-697.
60. Garas, L.C., J.D. Murray, and E.A. Maga, *Genetically engineered livestock: ethical use for food and medical models*. Annu Rev Anim Biosci, 2015. **3**: p. 559-75.

61. Van Mil, A., H. Hopkins, and S. Kinsella, *Potential uses for genetic technologies: dialogue and engagement research conducted on behalf of the Royal Society*. 2017: Hopkins Van Mil: Creating Connections Ltd, London, UK.
62. Peter, J.P., J.C. Olson, and K.G. Grunert, *Consumer behavior and marketing strategy*. 1999. McGraw-Hill, London, UK.
63. Keller, K.L. and D.R. Lehmann, *Brands and branding: Research findings and future priorities*. Marketing science, 2006. **25**(6): p. 740-759.
64. Nikolova, H.D. and J.J. Inman, *Healthy choice: the effect of simplified point-of-sale nutritional information on consumer food choice behavior*. Journal of Marketing Research, 2015. **52**(6): p. 817-835.
65. Chikazhe, T.L., *New Zealand public attitudes towards genetically modified food*. 2015, Lincoln University, Christchurch, New Zealand.
66. Brunton, C., *Genetically Modified Organisms Survey: Results prepared for Auckland Regional Council*. 2009, Colmar Brunton: Auckland, New Zealand.
67. Small, B. *An investigation of the social sustainability of genetically modified rye grass forage in New Zealand*. In *Proceedings from the 17th Australian Society of Agronomy Conference: Building Productive, Diverse and Sustainable Landscapes*. 2015. p. 20-24.
68. Sen, A., *Poverty and famines: an essay on entitlement and deprivation*. 1981: Oxford Clarendon Press.
69. Mill, J.S., *On liberty*. 1859, London: J. W. Parker and Son. 207 p.
70. Arrow, K.J., *Social choice and individual values*. Vol. 12. 2012: Yale University Press.
71. Shaw, R. and C. Eichbaum, *Public policy in New Zealand: Institutions, processes and outcomes*. 2008: Pearson Education New Zealand.
72. Knight, J.G., A. Clark, and D.W. Mather, *Potential damage of GM crops to the country image of the producing country*. GM crops & food, 2013. **4**(3): p. 151-157.
73. Nesbit, S., *An updated look at New Zealand's comparative advantage*. Occasional Paper, 2011. **11**.
74. Jones, G. and S. Mowatt, *National image as a competitive disadvantage: the case of the New Zealand organic food industry*. Business History, 2016. **58**(8): p. 1262-1288.
75. Lyons, K. and G. Lawrence, *Institutionalisation and resistance: organic agriculture in Australia and New Zealand*, in *Food, Nature and Society*. 2017, Routledge. p. 81-100.
76. Froude, V.A., *Wilding conifers in New Zealand: beyond the status report*. Report prepared for the Ministry of Agriculture and Forestry, Pacific Eco-Logic, Bay of Islands, 2011. **44**.
77. Strauss, S.H., et al., *Genetic engineering of reproductive sterility in forest trees*. Molecular Breeding, 1995. **1**(1): p. 5-26.
78. Vázquez-Lobo, A., et al., *Characterization of the expression patterns of LEAFY/FLORICAULA and NEEDLY orthologs in female and male cones of the conifer genera Picea, Podocarpus, and Taxus: implications for current evo-devo hypotheses for gymnosperms*. Evolution & development, 2007. **9**(5): p. 446-459.
79. Moyroud, E., et al., *A link between LEAFY and B-gene homologues in Welwitschia mirabilis sheds light on ancestral mechanisms prefiguring floral development*. New Phytologist, 2017. **216**(2): p. 469-481.
80. Englund, M., et al., *Morphological "primary homology" and expression of AG-subfamily MADS-box genes in pines, podocarps, and yews*. Evolution & Development, 2011. **13**(2): p. 171-181.
81. Melzer, R., Y.-Q. Wang, and G. Theißen. *The naked and the dead: the ABCs of gymnosperm reproduction and the origin of the angiosperm flower*. In *Seminars in cell & developmental biology*. 2010. **21**(1):118-28.
82. Silva, C.S., et al., *Evolution of the plant reproduction master regulators LFY and the MADS transcription factors: the role of protein structure in the evolutionary development of the flower*. Frontiers in plant science, 2016. **6**: p. 1193.
83. Yin, K., C. Gao, and J.-L. Qiu, *Progress and prospects in plant genome editing*. Nature plants, 2017. **3**(8): p. 17107.
84. Hargreaves, C. and M. Menzies, *Organogenesis and cryopreservation of juvenile radiata pine*, in *Protocols for Micropropagation of Woody Trees and Fruits*. 2007, Springer. p. 51-65.
85. Burdon, R. and J. Aimers-Halliday, *Risk management for clonal forestry with Pinus radiata—analysis and review. 1: Strategic issues and risk spread*. New Zealand Journal of Forestry Science, 2003. **33**(2): p. 156-180.
86. Pawson, S.M., et al., *Density-dependent impacts of exotic conifer invasion on grassland invertebrate assemblages*. Journal of Applied Ecology, 2010. **47**(5): p. 1053-1062.
87. Harding, M., *South Island wilding conifer strategy*. 2001: Department of Conservation, Christchurch, New Zealand.
88. Hall, C., *GM technology in forestry: lessons from the GM food 'debate'*. International Journal of Biotechnology, 2007. **9**(5): p. 436-447.
89. United Nations Food and Agriculture Organisation, *Forests and Genetically Modified Trees*. 2010, Food and Agriculture Organisation of the United Nations: Rome, Italy.
90. Santos-del-Blanco, L. and J. Climent, *Costs of female reproduction in a conifer tree: a whole-tree level assessment*. Journal of Ecology, 2014. **102**(5): p. 1310-1317.



91. Cremer, K., *Relations between reproductive growth and vegetative growth of Pinus radiata*. Forest Ecology and Management, 1992. **52**(1-4): p. 179-199.
92. Kramer, R.D., S.C. Sillett, and A.L. Carroll, *Structural development of redwood branches and its effects on wood growth*. Tree physiology, 2014. **34**(3): p. 314-330.
93. Johnson, L.J., et al., *The exploitation of epichloae endophytes for agricultural benefit*. Fungal Diversity, 2013. **60**(1): p. 171-188.
94. Schardl, C.L., *Epichloë festucae and related mutualistic symbionts of grasses*. Fungal Genet Biol, 2001. **33**(2): p. 69-82.
95. Tanaka, A., et al., *Fungal endophytes of grasses*. Curr Opin Plant Biol, 2012. **15**(4): p. 462-8.
96. Fletcher, L., B. Sutherland, and C. Fletcher, *The impact of endophyte on the health and productivity of sheep grazing ryegrass-based pastures*. Ryegrass endophyte: an essential New Zealand symbiosis. Grassland Research and Practice Series, 1999. **7**: p. 11-17.
97. Johnson, L.J., et al., *The exploitation of epichloae endophytes for agricultural benefit*. Fungal Diversity, 2013. **60** (1): 171-188.
98. Young, C.A., et al., *Indole-diterpene biosynthetic capability of Epichloë endophytes as predicted by ltm gene analysis*. Applied and Environmental Microbiology, 2009. **75**(7): p. 2200-2211.
99. Gundel, P.E., et al., *Symbiotically modified organisms: nontoxic fungal endophytes in grasses*. Trends in plant science, 2013. **18**(8): p. 420-427.
100. Panaccione, D.G., et al., *Elimination of ergovaline from a grass-Neotyphodium endophyte symbiosis by genetic modification of the endophyte*. Proceedings of the National Academy of Sciences (USA), 2001. **98**: p. 12820-12825.
101. Young, C.A., et al., *Molecular cloning and genetic analysis of a symbiosis-expressed gene cluster for lolitrem biosynthesis from a mutualistic endophyte of perennial ryegrass*. Molecular Genetics and Genomics, 2005. **274**: p. 13-29.
102. Fleetwood, D.J., et al., *A complex ergovaline gene cluster in epichloë endophytes of grasses*. Applied and Environmental Microbiology, 2007. **73**(8): p. 2571-2579.
103. Florea, S., et al., *Chromosome-End Knockoff Strategy to Reshape Alkaloid Profiles of a Fungal Endophyte*. G3 (Bethesda), 2016. **6**(8): p. 2601-10.
104. Christensen, M.J., and Voisey, C.R. *The biology of the endophyte/grass partnership*. In *6th International Symposium on Fungal Endophytes of Grasses*. 2007. Grasslands Research and Practice Series, Christchurch, New Zealand.
105. Kotoda, N., et al., *Antisense expression of MdTFL1, a TFL1-like gene, reduces the juvenile phase in apple*. Journal of the American Society for Horticultural Science, 2006. **131**(1): p. 74-81.
106. Yamagishi, N. and N. Yoshikawa, *A New Plant Breeding Technique Using ALSV Vectors to Shorten the Breeding Periods of Fruit Trees*. In *Genetic Engineering-An Insight into the Strategies and Applications*. 2016, In Tech, London, 47-61.
107. Schlathölder, I., et al., *Generation of advanced fire blight-resistant apple (Malus x domestica) selections of the fifth generation within 7 years of applying the early flowering approach*. Planta, 2018; **247**(6): 1475-1488.
108. Flachowsky, H., et al., *Application of a high-speed breeding technology to apple (Malus x domestica) based on transgenic early flowering plants and marker-assisted selection*. New Phytol, 2011. **192**(2): p. 364-77.
109. Kathleen, W., et al., *Integration of BpMADS4 on various linkage groups improves the utilization of the rapid cycle breeding system in apple*. Plant Biotechnology Journal, 2015. **13**(2): p. 246-258.
110. Kotoda, N., et al. *The break-through in the reduction of juvenile phase in apple using transgenic approaches*. In *International Society for Horticultural Science (ISHS)*. 2003. Leuven, Belgium.
111. Kotoda, N., et al., *Antisense expression of MdTFL1, a TFL1-like gene, reduces the juvenile phase in apple*. Journal of the American Society for Horticultural Science, 2006. **131**: p. 74-81.
112. Igarashi, M., et al., *Biotechnology and apple breeding in Japan*. Breeding science, 2016. **66**(1): p. 18-33.
113. Wolt, J.D., K. Wang, and B. Yang, *The regulatory status of genome-edited crops*. Plant biotechnology journal, 2016. **14**(2): p. 510-518.
114. Araki, M. and T. Ishii, *Towards social acceptance of plant breeding by genome editing*. Trends in plant science, 2015. **20**(3): p. 145-149.
115. Ministry for Primary Industries, *Apiculture. Ministry for Primary Industries 2016 Apiculture Monitoring Programme*. 2016. p. 1-16. Wellington, New Zealand.
116. Carnegie, A.J. and J.R. Lidbetter, *Rapidly expanding host range for Puccinia psidii sensu lato in Australia*. Australasian Plant Pathology, 2012. **41**: p. 13-29.
117. Carnegie, A.J., et al., *Impact of the invasive rust Puccinia psidii (myrtle rust) on native Myrtaceae in natural ecosystems in Australia*. Biol Invasions, 2016. **18**: p. 127-144.
118. Hudson, Maui, et al. "Indigenous perspectives and gene editing in Aotearoa New Zealand." *Frontiers in bioengineering and biotechnology*. 2019; 7:70.
119. Liu, J., et al., *Arbuscular mycorrhizal symbiosis is accompanied by local and systemic alterations in gene expression and an increase in disease resistance in the shoots*. The Plant Journal, 2007. **50**(3): p. 529-544.
120. Schrey, S.D. and M.T. Tarkka, *Friends and foes: streptomycetes as modulators of plant disease and symbiosis*. Antonie Van Leeuwenhoek, 2008. **94**(1): p. 11-19.

121. Royal Commission on Genetic Modification, *Report of the Royal Commission on Genetic Modification*. 2001. Wellington, New Zealand.
122. Katz, E., *Nature as subject: Human obligation and natural community*. Vol. 70. 1997: Rowman & Littlefield.
123. Rolston III, H., *Is there an ecological ethic?* *Ethics*, 1975. **85**(2): p. 93-109.
124. Katz, E. and A. Light, *Environmental pragmatism*. 2013: Routledge. 368p, London.
125. Delmotte, F., et al., *Combining selective pressures to enhance the durability of disease resistance genes*. *Frontiers in plant science*, 2016. **7**: p. 1916.
126. Wei, J., et al., *Cattle with a precise, zygote-mediated deletion safely eliminate the major milk allergen beta-lactoglobulin*. *Scientific Reports*, 2018. **8**(1): p. 7661.
127. Tan, W., et al., *Gene targeting, genome editing: from Dolly to editors*. *Transgenic Res*, 2016. **25**(3): p. 273-87.
128. Wei, J., et al., *Efficient introgression of allelic variants by embryo-mediated editing of the bovine genome*. *Sci Rep*, 2015. **5**: p. 11735.
129. Wei, J., et al., *Cattle with a precise, zygote-mediated deletion safely eliminate the major milk allergen beta-lactoglobulin*. 2018. **8**(1): p. 7661.
130. Tan, W.S., et al., *Precision editing of large animal genomes*. *Adv Genet*, 2012. **80**: p. 37-97.
131. Whitelaw, C.B.A., et al., *Engineering large animal models of human disease*. *The Journal of pathology*, 2016. **238**(2): p. 247-256.
132. Bansal, B. and X.D. Chen, *Fouling of heat exchangers by dairy fluids-a review*. 2005. ECI Symposium Series, Volume RP2: Proceedings of 6th International Conference on Heat Exchanger Fouling and Cleaning -Challenges and Opportunities, Editors Hans Müller-Steinhagen, M. Reza Malayeri, and A. Paul Watkinson, Engineering Conferences International, Kloster Irsee, Germany.
133. Singh, H.J.L.L., *Interactions of milk proteins during the manufacture of milk powders*. 2007. **87**(4-5): p. 413-423.
134. Kontopidis, G., C. Holt, and L. Sawyer, *Invited review:  $\beta$ -lactoglobulin: binding properties, structure, and function*. *Journal of dairy science*, 2004. **87**(4): p. 785-796.
135. Thompson, P.B., *Ethics and the genetic engineering of food animals*. *Journal of Agricultural and Environmental Ethics*, 1997. **10**(1): p. 1-23.
136. Wüthrich, B. and S.G.O. Johansson, *Allergy to cheese produced from sheep's and goat's milk but not to cheese produced from cow's milk*. *Journal of Allergy and Clinical Immunology*, 1995. **96**(2): p. 270-273.
137. Spuerger, P., et al., *Allergenicity of alpha-caseins from cow, sheep, and goat*. *Allergy*, 1997. **52**(3): p. 293-8.
138. Rodríguez del Río, P., et al., *Allergy to goat's and sheep's milk in a population of cow's milk-allergic children treated with oral immunotherapy*. *Pediatric Allergy and Immunology*, 2012. **23**(2): p. 128-132.



Taupo, New Zealand

## ROYAL SOCIETY TE APĀRANGI

11 Turnbull Street, Thorndon, Wellington 6011  
PO Box 598, Wellington 6140, New Zealand


**Phone** +64 4 472 7421


**Email** [info@royalsociety.org.nz](mailto:info@royalsociety.org.nz)

### Whakapā mai **Connect with us**

 [RoyalSocietyNZ](https://www.facebook.com/RoyalSocietyNZ)

 [@royalsocietynz](https://twitter.com/royalsocietynz)

 [royalsociety.org.nz](http://royalsociety.org.nz)

 [royalsocietynz](https://www.instagram.com/royalsocietynz)

---

**Print ISBN:** 978-1-877264-41-2

**Digital ISBN:** 978-1-877264-35-1

Except for figures and the Royal Society  
Te Apārangi logo, expert advice papers  
are licensed under a Creative Commons  
3.0 New Zealand Licence.

**Published August 2019**

