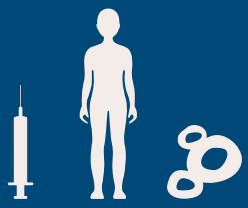
ROYAL SOCIETY TE APĀRANGI

GENE EDITING SCENARIOS IN HEALTHCARE

SUMMARY



AUGUST 2019

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ROYAL SOCIETY TE APĀRANGI

INTRODUCTION

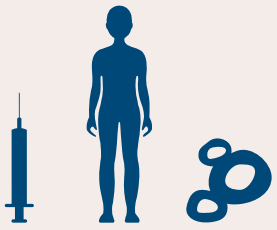
The revolution in gene editing technologies is making it easier to change genetic material, with potential benefits in many sectors including healthcare, agriculture and conservation. However, as a technology, gene editing is moving ahead of any consensus on how it should be used.

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

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

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

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



WHAT IS GENE EDITING?

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

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

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

HOW IS GENE EDITING BEING USED IN HEALTHCARE?

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

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

SCENARIO SUMMARY

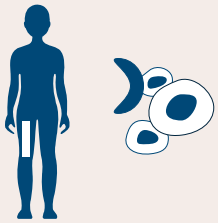
	TREATING TISSUE / ORGANS	TREATING EMBRYOS AND GAMETES
TREATING DISEASE	SCENARIO ONE | **PAGE 04** Gene editing bone marrow tissue to treat sickle cell anaemia	SCENARIO TWO | **PAGE 06** Gene editing an embryo to prevent the transmission of a cancer gene
ENHANCING CHARACTERISTICS	SCENARIO THREE | **PAGE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

SCENARIO ONE

GENE EDITING BONE MARROW TISSUE TO TREAT SICKLE CELL ANAEMIA

DISEASE

Sickle cell anaemia

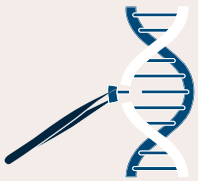


CELL TYPE

Bone marrow stem cell

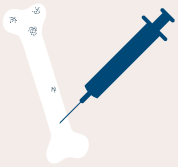
TYPE OF EDIT

Change to naturally occurring non-disease version of gene



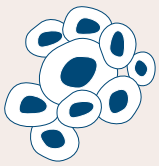
MECHANISM

Bone marrow transplant followed by viral vector and replacement stem cells



OUTCOME

Disease cured in individual



Medical considerations

Potential unintended edit of non-target areas of DNA.

Legal considerations

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

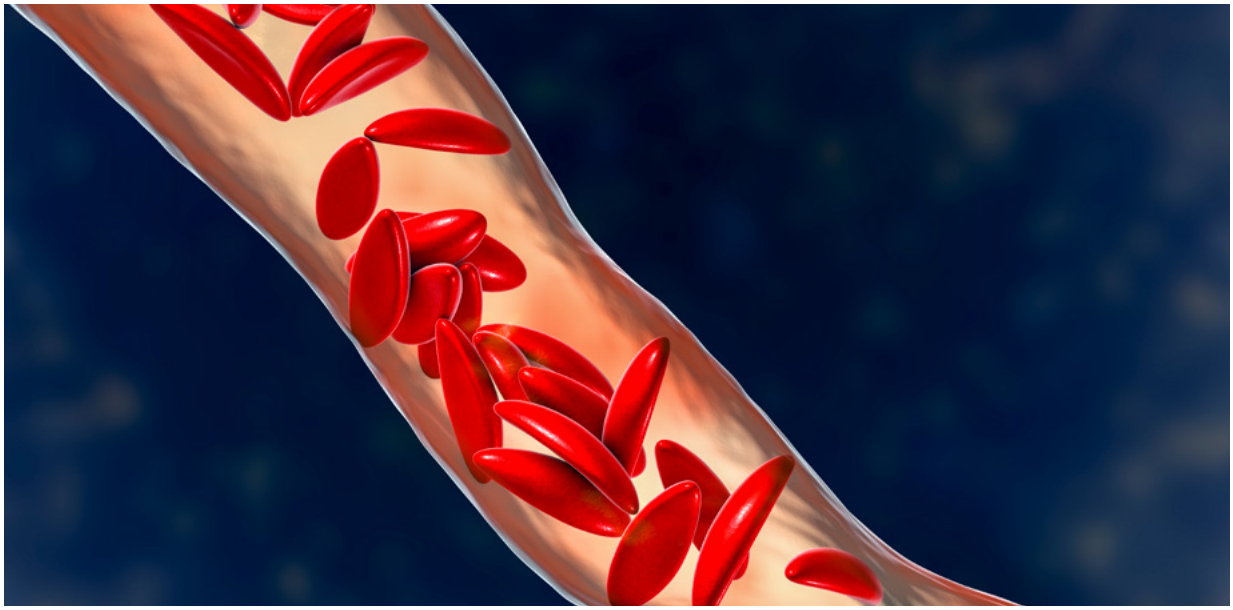
Ethical considerations

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

An 18-year-old woman has sickle cell anaemia, caused by a common genetic mutation that can lead to strokes, blindness, skin ulcers, thrombosis and many other complications, as sickle shaped blood cells don't deliver oxygen to tissues in the body as normal blood cells would.

After recurrent admissions to hospital for treatment of sickling of her red blood cells, she requests definitive treatment of her disease using gene editing. The treatment is to remove bone marrow using standard techniques and treat this removed tissue using CRISPR that will alter one or both of her sickle cell anaemia-causing HBB genes turning it back into a non-disease causing version. The remaining bone marrow will be removed and treated by chemotherapy. The removed and altered bone marrow will then be delivered back to her as per standard bone marrow transplant procedures.

Since this procedure uses her own tissues, immune suppression will not be required and, as long as transplanting is successful and gene editing sufficiently efficient, the chance of her developing complications from her sickling blood cells will be eliminated permanently (but not for any children she may have in the future).



Medical considerations

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

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

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

Risks and limitations

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

Legal considerations

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

Ethical considerations

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

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

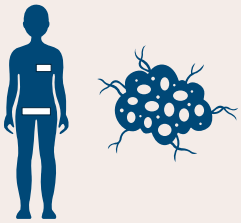
For Māori whānau, that decision may align, or be in direct conflict with, Māori values and aspirations for flourishing whakapapa into the future. The benefits of the procedure should outweigh the risks, and there should be direct benefits for participants and their communities from a Te Ao Māori perspective.

SCENARIO TWO

GENE EDITING AN EMBRYO TO PREVENT CANCER GENE PASSING TO OFFSPRING

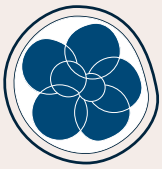
DISEASE

Breast and ovarian cancer (BRCA1 mutation)



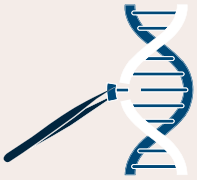
CELL TYPE

Embryos



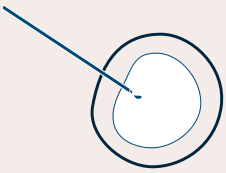
TYPE OF EDIT

Change to naturally occurring non-disease version of gene



MECHANISM

In vitro fertilisation and injection



OUTCOME

Reduced cancer risk in offspring

Medical considerations

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

Legal considerations

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

Ethical considerations

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

A 38-year-old woman with a family history of early-onset bilateral breast and ovarian cancer wants to eliminate the risk of transmitting this condition to future generations.

She, and many of her relatives, have undergone genetic analysis which has identified a mutation in the BRCA1 gene that is commonly observed amongst Ashkenazi Jewish women with a similar family history, worldwide.

This woman has not yet had a diagnosis of cancer, but is aware that to reduce her risk of getting cancer, she could have a double mastectomy and have her oviducts and ovaries removed.

Aware of these considerations and determined not to transmit her disease-conferring gene variant to future generations, she proposes to employ in vitro fertilisation and to use CRISPR to revert any mutation-bearing embryos back to a version of the gene not associated with the disease.

Medical considerations

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

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

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

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

Legal considerations

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

Ethical considerations

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

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

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

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

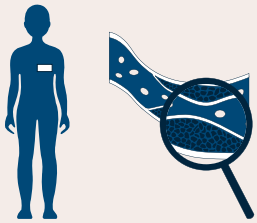
Where Māori embryos are concerned, it will be fundamental that culturally appropriate ethical processes that ensure the key values of whakapapa, tika, manaakitanga, and mana are upheld. In addition, careful consideration should be given to the pūtake or purpose of the 'manipulation' of whakapapa. It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

SCENARIO THREE

GENE EDITING THE LIVER TO REDUCE THE RISK OF CARDIOVASCULAR DISEASE

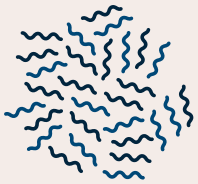
DISEASE

Lowering cholesterol (PCSK9 gene)



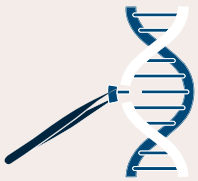
CELL TYPE

Liver tissue



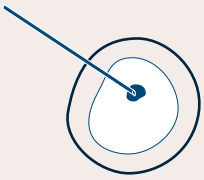
TYPE OF EDIT

Inactivation of existing gene



MECHANISM

Viral vector that targets the tissue



OUTCOME

Reduced disease risk in individual

Medical considerations

Switching off the gene may produce unintended effects.

Legal considerations

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

Ethical considerations

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

A 35-year-old male presents with a request to undergo gene editing to reduce his risk of developing cardiovascular disease. He has a family history of death in the fourth and fifth decades of life from coronary artery disease in association with elevated blood cholesterol.

Despite attempts by several members of his family to define the basis for their predisposition to this trait, no determinative genetic or lifestyle factor has been identified. Furthermore, efforts to alter established risk factors such as the prescription of drugs to control blood lipids (fats), have only been partially successful and have not prevented the death of several of his relatives at a young age.

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

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

Medical considerations

This proposal differs from the previous two scenarios in that the plan is not to revert the genomic sequence back to 'normal' but instead to induce a change in the genome to enhance or improve a physiological function. While such genotypes may have occurred naturally in other individuals, the proposal to induce them in a genome could be seen as an enhancement.

Risks and limitations

While the proposed modification occurs naturally, introducing it through gene editing might lead to it interacting with other genes to produce adverse effects. Predicting such side effects for a given individual is very difficult, so the decision to proceed along these lines would be a matter of balancing perceived risks and costs against potential benefits.

Legal considerations

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

Ethical considerations

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

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

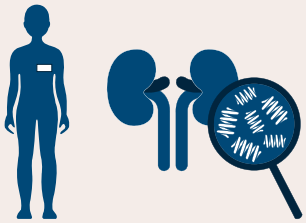
In a Māori context, careful consideration should be given to the pūtake, the purpose of the procedure, and decisions taken in full consideration of culturally appropriate ethical processes that uphold the key values of whakapapa, tika, manaakitanga, and mana. Any benefits should outweigh the risks, and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

SCENARIO FOUR

GENE EDITING EMBRYOS TO IMPROVE ATHLETIC PERFORMANCE

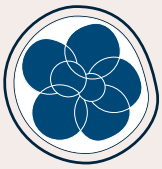
DISEASE

Increased erythropoietin production



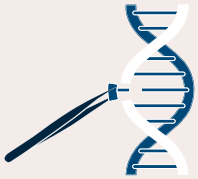
CELL TYPE

IVF in culture dish outside the body



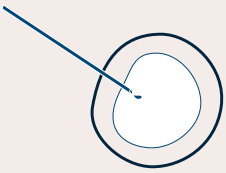
TYPE OF EDIT

Modification of gene



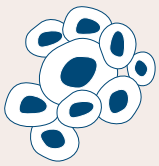
MECHANISM

In vitro fertilisation and injection



OUTCOME

Athletic enhancement in offspring



Medical considerations

Enhancing the gene may produce unintended effects.

Legal considerations

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

Ethical considerations

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

A couple using fertility services ask for heritable gene editing of their prospective offspring. The couple are in good health without any known predispositions to disease. They are both actively involved in competitive endurance athletic events.

They are aware that it has recently become possible to edit genes to increase erythropoietin levels in the bloodstream. They are also aware that increased erythropoietin production increases red blood cell mass, oxygen carrying capacity and consequently athletic performance.

Their reasoning in requesting this genetic enhancement for their embryos is that it will enhance their athletic capability over a broad range of sports and pastimes and contribute to their offspring living more accomplished and fulfilled lives as a result.

Medical considerations

While gene editing can, in principle, be directed to any genomic location to produce a wide range of alterations, it is difficult to predict the resulting effects. When reverting a disease associated mutated gene back to a non-disease associated gene, you expect that the edited gene will exhibit unimpaired function, indistinguishable from naturally occurring genes.

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

and doctors would look for evidence that shows such edits produce no undesirable properties. The level of confidence in the results of the procedure is unlikely to approach that of scenarios 1 and 2 where genes are restored to a functional state.

Legal considerations

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

Ethical considerations

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

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

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

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

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For further information on the use of gene editing in healthcare, a reference paper on the topic prepared by the Panel is available on the Royal Society Te Apārangi's web page along with a fact sheet on the technology, and links to relevant panel discussions chaired by RNZ's Kim Hill: **royalsociety.org.nz/gene-editing**

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