ROYAL SOCIETY TE APĀRANGI

Ngā hangarau ā-ira i Aotearoa: Ōna hanganga

Genetic technologies in Aotearoa New Zealand: How they work

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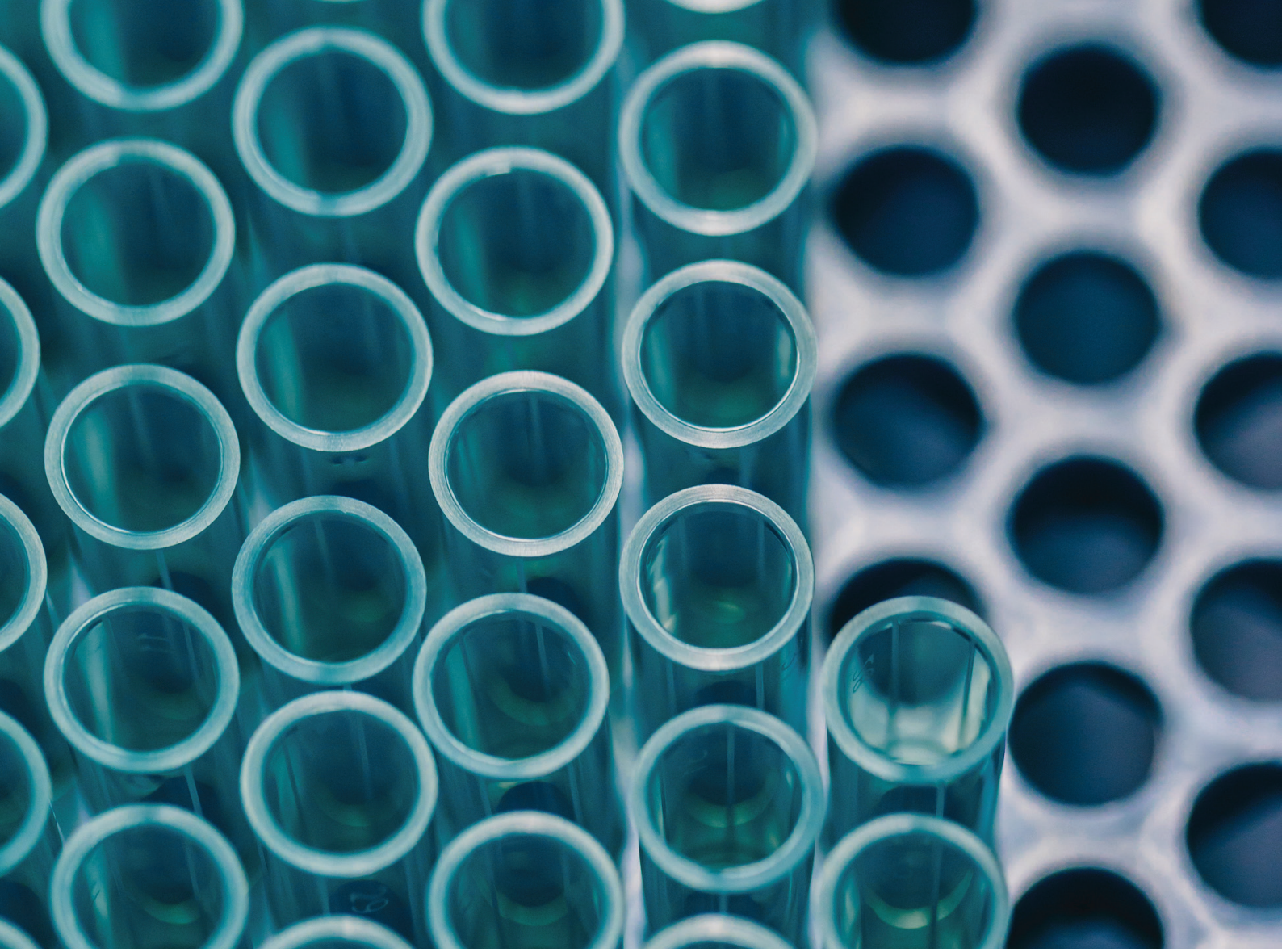

Ngā ihirangi
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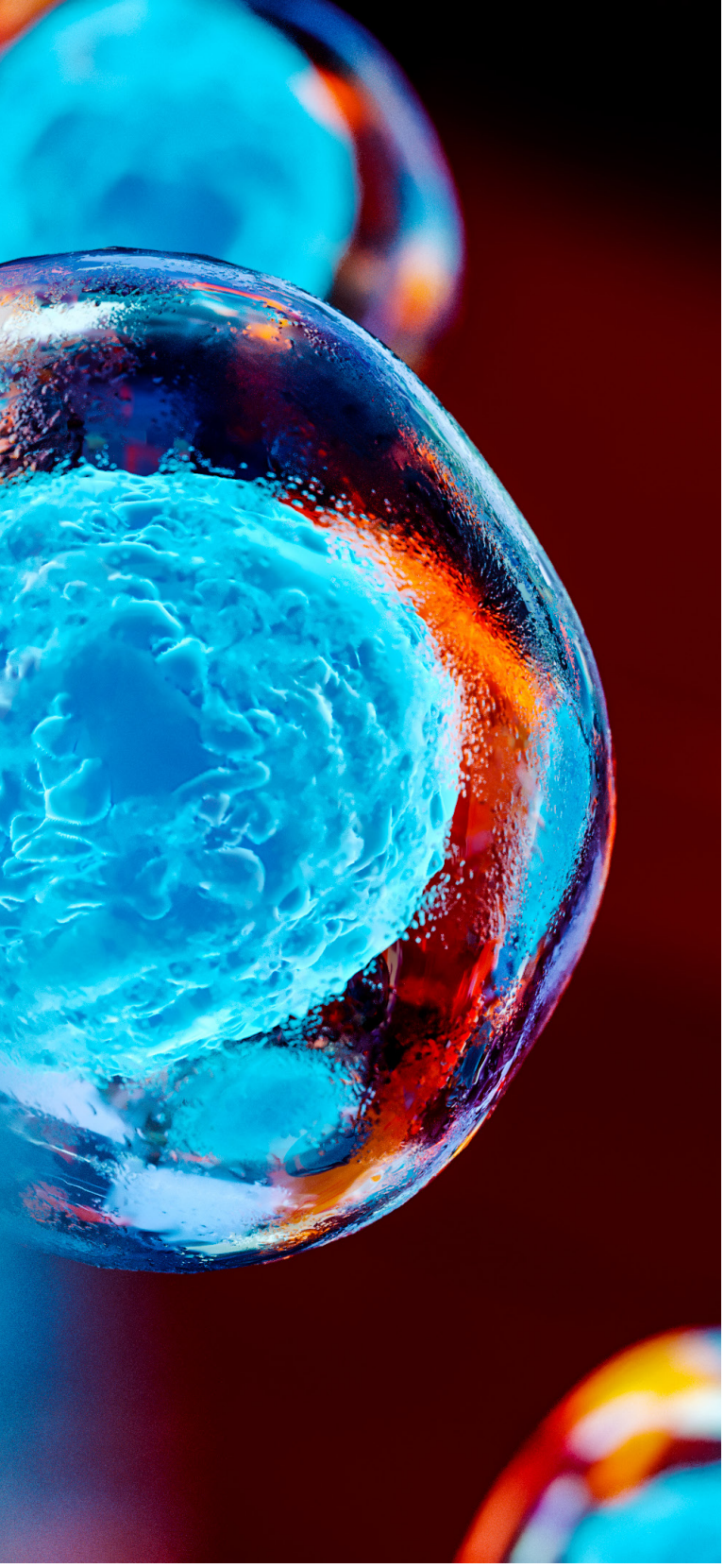

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Ngā hangarau ā-ira i Aotearoa
Genetic technologies in Aotearoa New Zealand

He kupu whakataki
Introduction

Here in Aotearoa New Zealand, scientists develop world-leading gene technology innovations in research labs every day. Many imported foods contain genetically modified ingredients and we already have gene-edited New Zealanders walking amongst us – the beneficiaries of life-saving gene therapies being trialled here. Today, the potential of new genetic technologies is exploding as techniques, including ones that use machine learning and artificial intelligence (AI), rapidly improve (1–3).

Aotearoa New Zealand has a complicated history with gene technologies, which goes back over 30 years. Our current regulations are among the strictest in the world (4,5). Researchers are allowed to alter genes of approved species inside the lab, but it is extremely difficult to get approval to apply this science outside the lab (for example, growing gene-edited crops outdoors).

In 2026, the way gene technologies are regulated may be changing with a new Gene Technology Bill being considered at Parliament.

As discussion increases about expanding the use of gene technologies in Aotearoa New Zealand, so does kōrero about what this means for our unique environment, economy, culture, and te ao Māori.

This paper is one of two:

- Genetic technologies in Aotearoa New Zealand – how they work
- Genetic technologies in Aotearoa New Zealand – how they're used.

With these publications, Royal Society Te Apārangi aims to help people better understand gene technologies – and the issues surrounding them – so more communities can join these important conversations.

He aha ngā hangarau ā-ira?
What are genetic technologies?

Genetic technologies are a collection of techniques applied to DNA.

In this report, we have divided genetic technologies into two broad categories:

1. 'Reading' DNA: DNA sequencing and genomics
2. Making changes to DNA: gene editing and genetic modification.

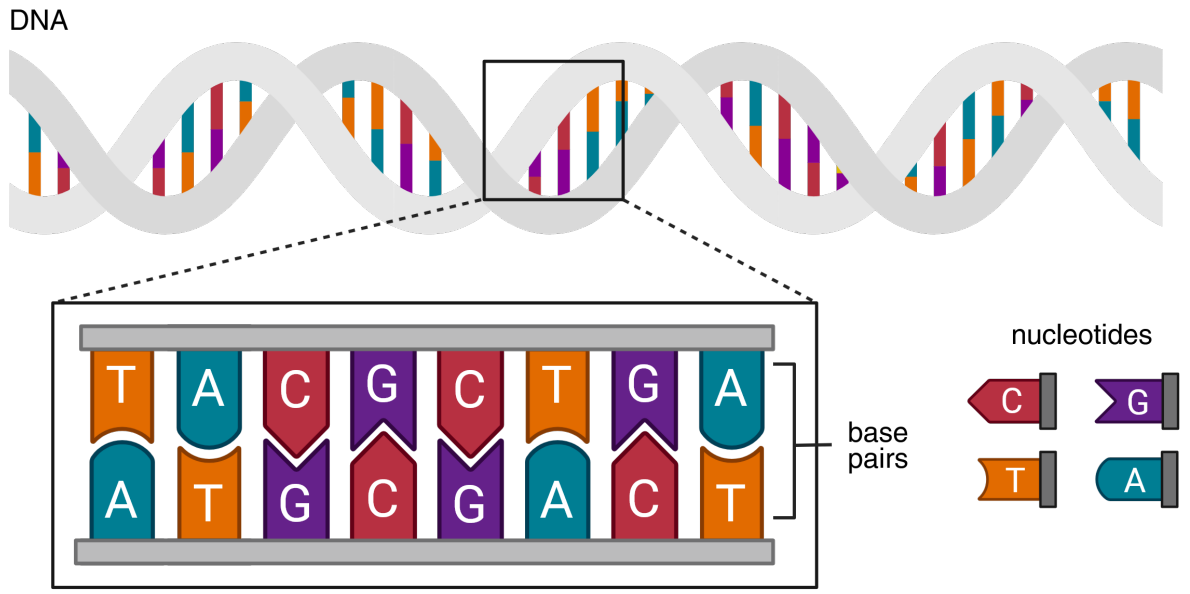
We use the term *genetic* technologies when referring to both reading and changing DNA. *Gene* technology refers to techniques for *changing* DNA, but we typically use either gene editing or genetic modification.

He aha te pītau ira?
What is DNA?

DNA is a molecule in almost all living things that carries genetic instructions used in development, general functioning, and reproduction.

DNA is collected and studied by researchers for wide-ranging reasons. These include informing the development of food varieties, gaining insights into the genetic causes of disease, and supporting conservation programmes.

FIGURE 1 | A DNA molecule consists of two strands that wind around one another to form a shape known as a double helix. The genetic instructions it carries are spelled out in nucleotides (A, T, C, G) that form base pairs that are the rungs of the DNA ladder.



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Te whakamahia: Ngā hangarau ā-ira
How they work: Genetic technologies

You don't have to be a scientist to understand the basics of genetic technologies. Read on for a brief explanation of the key points and some useful definitions.

Te whakaraupapa pītau ira
DNA sequencing

Sequencing technologies are used to 'read' the sequence of a short segment of DNA, such as a single gene; or a full genome, the complete content of an organism's genetic material.

Technologies that read DNA are already commonplace tools at work in healthcare, primary industries, and conservation here in Aotearoa New Zealand.

Examples of applications (described in our other publications) include:

- Healthcare
  - Diagnosing and tracking disease
  - Tracing genetic histories and identities for genealogy or forensics
- Farming and horticulture
  - Aiding breeding
  - Diagnosing and tracking disease
- Conservation and environment
  - Aiding breeding, eg, kākāpō
  - Monitoring water quality.

Ngā taipitopito whānui mō te whakaraupapa pītau ira
DNA sequencing in more detail

PCR (polymerase chain reaction) and DNA sequencing allow researchers and technicians to make many copies of a defined region of DNA and 'read' its sequence (spelt out in A,T,C,G nucleotides), respectively.

PCR works by cycling temperatures (from hot to cold, back and forth) to separate DNA molecules, then a DNA-copying enzyme called DNA polymerase makes a copy of a defined sequence. These cycles can make trillions of copies of the desired sequence. PCR is incredibly sensitive – a single DNA molecule can be enough to get started.

Most sequencing technologies work by building DNA: a new strand is built against a template strand[1] – individual nucleotides are identified as they are added to the molecule. Many copies of the same DNA are sequenced at the same time to ensure accuracy.

Sequencing technology is improving rapidly, with faster and cheaper methods available all the time. For instance, the sequence for the human genome was completed in 2000 and took 13 years and 2.7 billion USD[2] (6). Today, a single human genome can be sequenced in days or even *hours* (7) for 500 USD (8) or less (9).

Sequencing populations

Sequencing technologies can be used to understand the genetics of entire populations, such as the yeast used at a brewery or all the birds in an endangered colony.

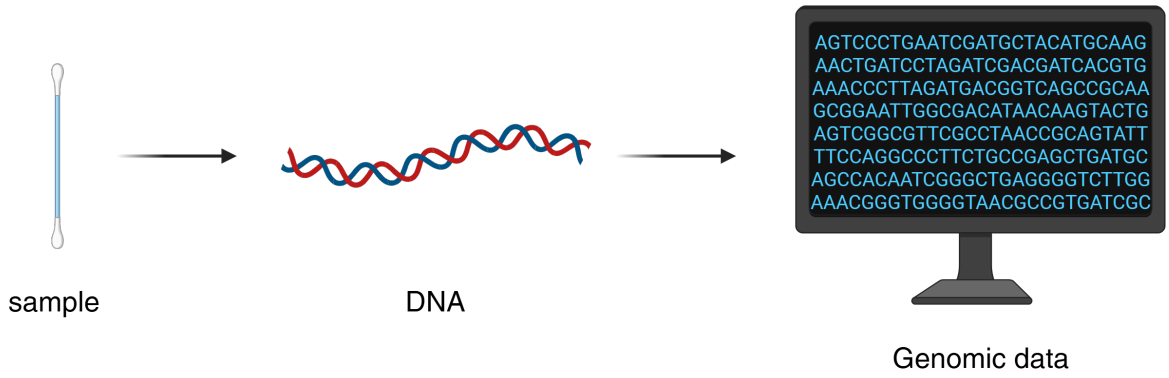
Metagenomics refers to the study of the genetics of all the organisms in an environment. This usually refers to microbial life but can also be used to sequence trace DNA from larger organisms. Metagenomics and environmental DNA (eDNA) are often used to study ecological diversity and support conservation (10). For example, DNA collected from a river that runs through farmland would have evidence of the native fish, insects, algae, and microorganisms expected of a healthy waterway, but could also have traces of invasive species and polluting bacteria from livestock upstream.

Another useful term is a variome, which is a collection of all the different genomes that exist within a population and how they differ.

1 The template strand is used to infer the sequence of complementary strand: every T is paired with an A, every C with G and vice versa.

2 This is a high-quality reference genome using DNA from multiple people.

FIGURE 2 | A simple depiction of DNA sequencing



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Te rāwekeweke ira
Gene editing

Humans have been making changes to the genes of living things for as long as we've been around. Early hunters and gatherers, then farmers, used artificial selection – choosing to breed, for example, the biggest or tastiest varieties of plants to create new varieties.

In the early 1900s, before we fully understood the underlying mechanisms of genetics, breeders of plants and animals altered DNA using X-rays, sub-atomic particles, and chemicals. These sped up mutations that led to changes in physical traits. Many such techniques are still in use but – due to their random nature – do not count as gene technology.

Nowadays, when we talk about making changes to DNA, we generally mean gene technology in a lab. Definitions of terms differ – these are the ones we use in this resource:

- Genetic modification refers to technologies that change the genome of a living organism *with the addition of foreign DNA* (from another species). Genetic modification is still the most common technique applied to plants, but is being replaced by gene editing
- Gene editing refers to technologies that change the genome of a living organism *without permanently introducing foreign DNA*. Gene editing is typically more precise than genetic modification.

For example, corn can be made resistant to the herbicide glyphosate (known as RoundUp) with changes to a single gene (11). With genetic modification, scientists take a resistant version of the same gene from another organism and use it instead of the corn gene (12). With gene editing, scientists can use CRISPR to make a small change to the corn gene to confer resistance (13).

Changing a trait by changing DNA: Apples and apples

The type of method that is used to create a new trait can have hugely different effects at the DNA level.

Scenario: an apple orchard has famously tasty apples. The owners want to grow a variant of this apple that is tasty *and* has red flesh (instead of white). A red-flesh apple exists in nature that could be cross-bred with the tasty white-flesh apple – but it tastes terrible. A single gene is responsible for the colour of the apples' flesh, but many genes contribute to taste and are not fully understood. How can the red-colour gene be transferred to the tasty apple without compromising its flavour?

There are three main approaches that could be taken to move the red-flesh gene between apples. All methods use the two parent apples (see the drawing below) to produce a red-fleshed apple, but each method differs in how many extra genes 'hitchhike' with the target gene.

FIGURE 3 | Apple scenario: parents and desired offspring

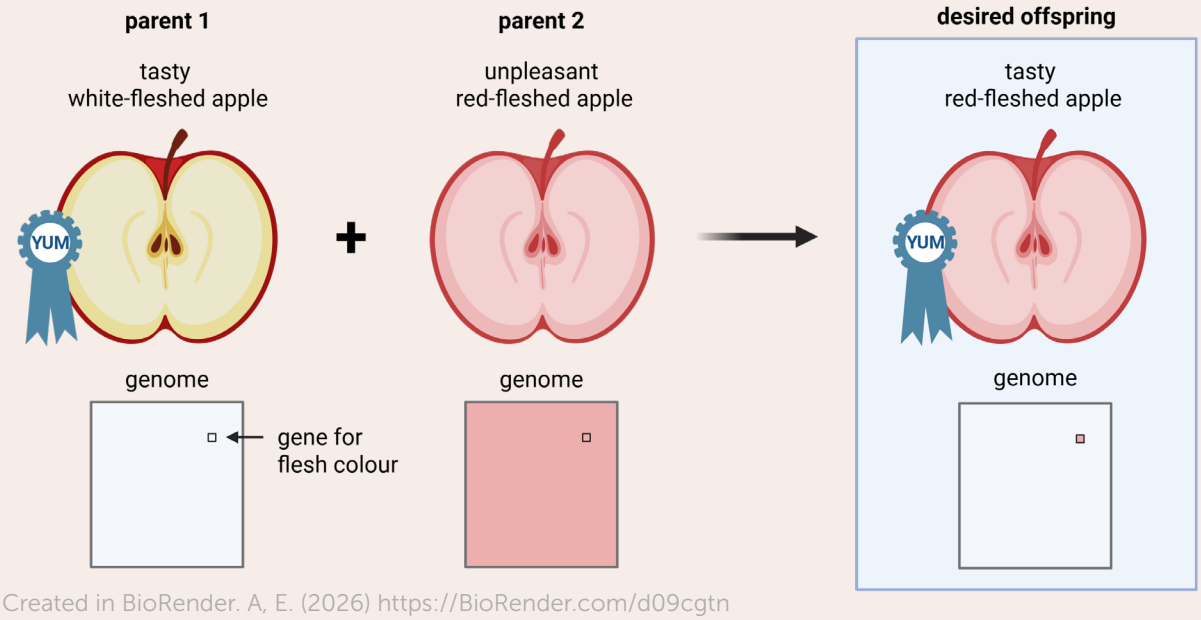

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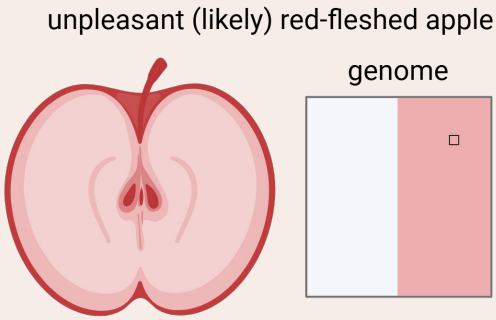
FIGURE 4 | Selective breeding



Method 1: Selective breeding

Selective breeding, when compared to other methods, is a simpler way to get a tree with red-fleshed apples. However, offspring from the cross would carry half the genes of each parent and likely inherit many undesirable genes (eg, bad taste).

Back-crossing (breeding the red offspring with the tasty apple) would eventually lead to a tasty, red-fleshed apple, but it would take many generations.

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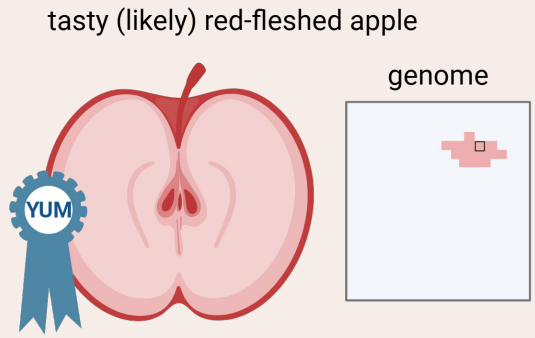
FIGURE 5 | Genetic modification



Method 2: Genetic modification

Genetic modification would use genetic tools to move the red-flesh gene into the new apple's genome, but it's hard to avoid bringing some other DNA. Sometimes you can't control where the new gene goes, and this can cause problems.

The offspring apple will likely taste good, though, because most of its genes are from the tasty parent.

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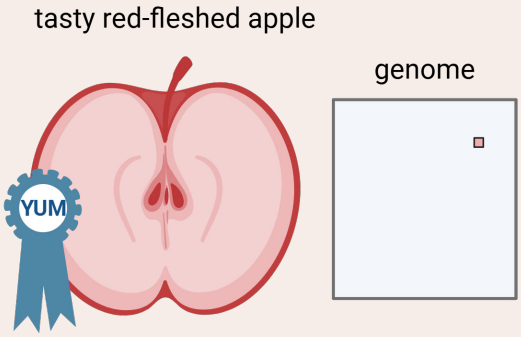
FIGURE 6 | Gene editing



Method 3: Gene editing

Gene editing using CRISPR (explained below) would make small changes required for red-fleshed apples to the tasty apple's genes, without adding DNA from another variety of apple. Apples will have red flesh and taste exactly like the tasty parent.

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Te rāwekeweke ira mā te CRISPR
Gene editing using CRISPR

Gene editing is the main focus of this resource and we concentrate on the technique CRISPR (clustered regularly interspaced short palindromic repeats).

If you want to learn about other techniques used for gene editing and genetic modification, please see our previous publications (14–19).

He aha te CRISPR?
What is CRISPR?

CRISPR is a scalpel-precise method to cut DNA in exactly the target location. CRISPR uses an enzyme called Cas9 to cut DNA at a position encoded by the scientist. This technique allows scientists to edit DNA, write DNA, move DNA, and much more.

CRISPR has been a game changer for gene technology – it is vastly more accurate and efficient at gene editing than previous techniques. Scientists adapted CRISPR from a process found in nature. It originally formed part of a bacterial immune system (20,21).

Te whakamahia: CRISPR
How it works: CRISPR

CRISPR is short for CRISPR/Cas system. It has two main components:

- Cas9[3], a site-directed nuclease (DNA cutting enzyme): DNA-specific molecular scissors that can only cut when instructed
- guideRNA (gRNA), the cutting instructions for Cas9: the gRNA binds Cas9 and DNA that exactly matches the RNA sequence[4]. gRNA can be 'programmed' by scientists to cut at a desired position.

How CRISPR works in nature

When a bacterium has a viral infection (yes, bacteria get sick too), it creates a biological memory of the virus so the immune system can recognise the virus next time and defend against it (20,21). CRISPR is named after the sequences that encode these biological memories in a bacterial genome.

3 This stands for CRISPR-associated protein 9.

4 RNA, ribonucleic acid, is a single-stranded nucleic acid with multiple important functions in the cell.

FIGURE 7 | A simple depiction of CRISPR in action

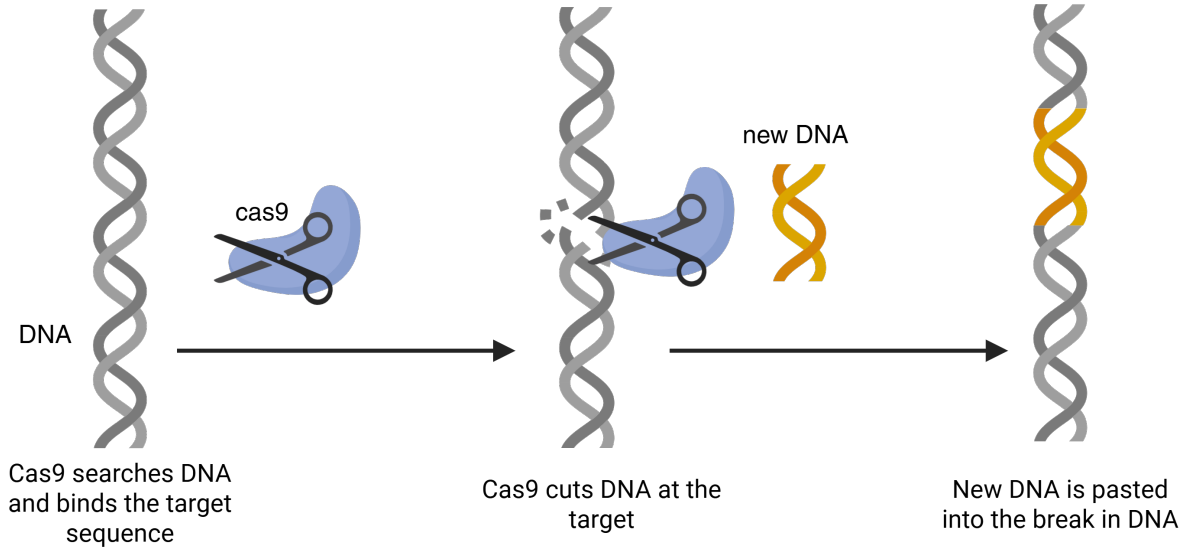

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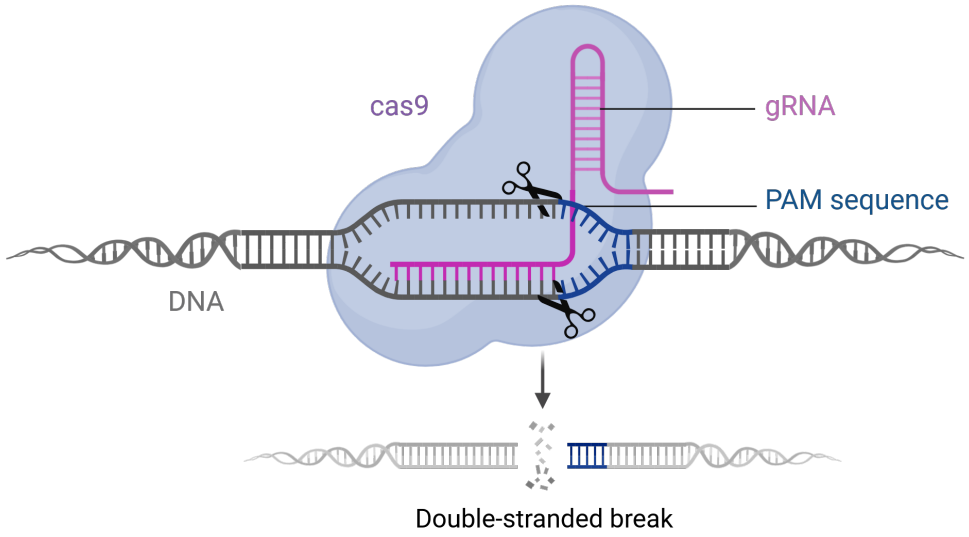
FIGURE 8 | CRISPR requires gRNA recognition and a PAM site after the gRNA binding site



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After an infection, a bacterium incorporates a piece of the virus's DNA into its own genome, bordered by the CRISPR sequences. This DNA template is then used to make a gRNA that is used to check DNA in the cell. If the gRNA is a perfect match for the DNA (base pairing with a complementary DNA sequence), it signals to Cas9 to come and destroy the invading viral DNA (21,22).

Cas9 will only bind and cut DNA if:

- gRNA recognises and binds the DNA: this means the DNA matches a genetic record of a previous infection
- There is a PAM (protospacer adjacent motif) site after the gRNA: this is a safety check to confirm the DNA is an invader and not the bacterium's own record. A PAM site is a 2–6 base pair sequence following the gRNA binding site which is only present in invading DNA (22).

These rules for cutting stop Cas9 from indiscriminately chopping up the bacterium's own DNA.

The bacterium typically contains multiple sequence records of a given invader, which leads to the viral DNA being cut in multiple places and destroyed before it can kill the cell.

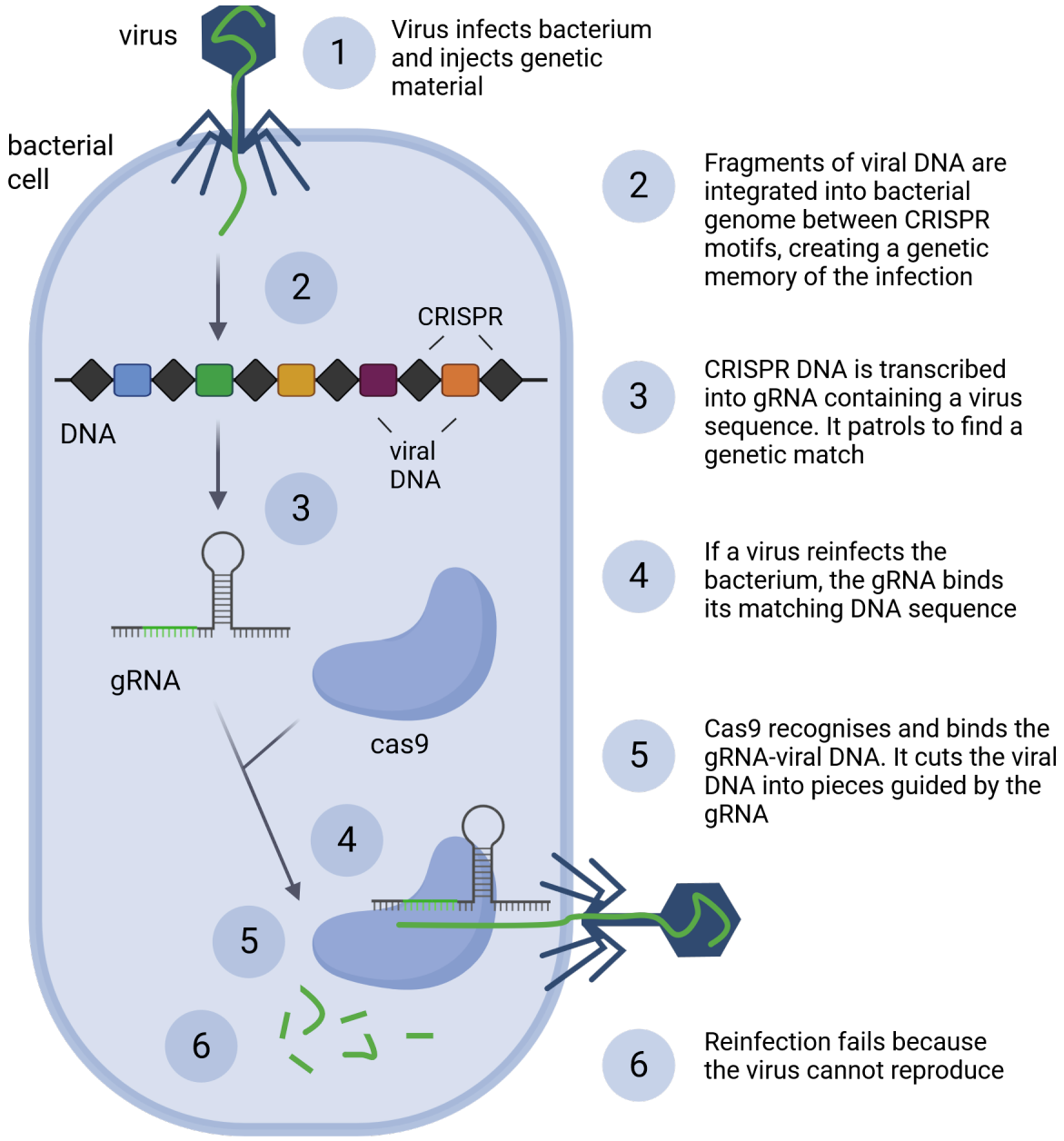
Early uses of CRISPR in biotechnology

CRISPR is highly programmable. Lab researchers can create their own gRNAs to direct Cas9 to cut almost any region of DNA they desire. This level of precision was groundbreaking. Previous gene editing and genetic modification technologies were often limited by strict DNA sequence recognition requirements of nucleases and other DNA cutting enzymes.

Early uses of CRISPR in biotechnology involved breaking genes (creating knockouts) or inserting genes. In short, when Cas9 cuts DNA (creating what is called a double-stranded break), the repair is rarely perfect and the gene sequence is disrupted. This can be a useful function of CRISPR, with genes being intentionally broken or the break used to insert a new sequence – provided by the researcher – guided into place with matching DNA sequences at either end.

Limitations of CRISPR include this tendency to break genes (less useful when you don't want to), and issues with accuracy (does Cas9 cut in the correct place?), precision (does Cas9 make the correct edit?), timing (changes can only be fully incorporated in actively dividing cells), and delivery (CRISPR is bulky and can be difficult to get into cells).

FIGURE 9 | CRISPR in nature



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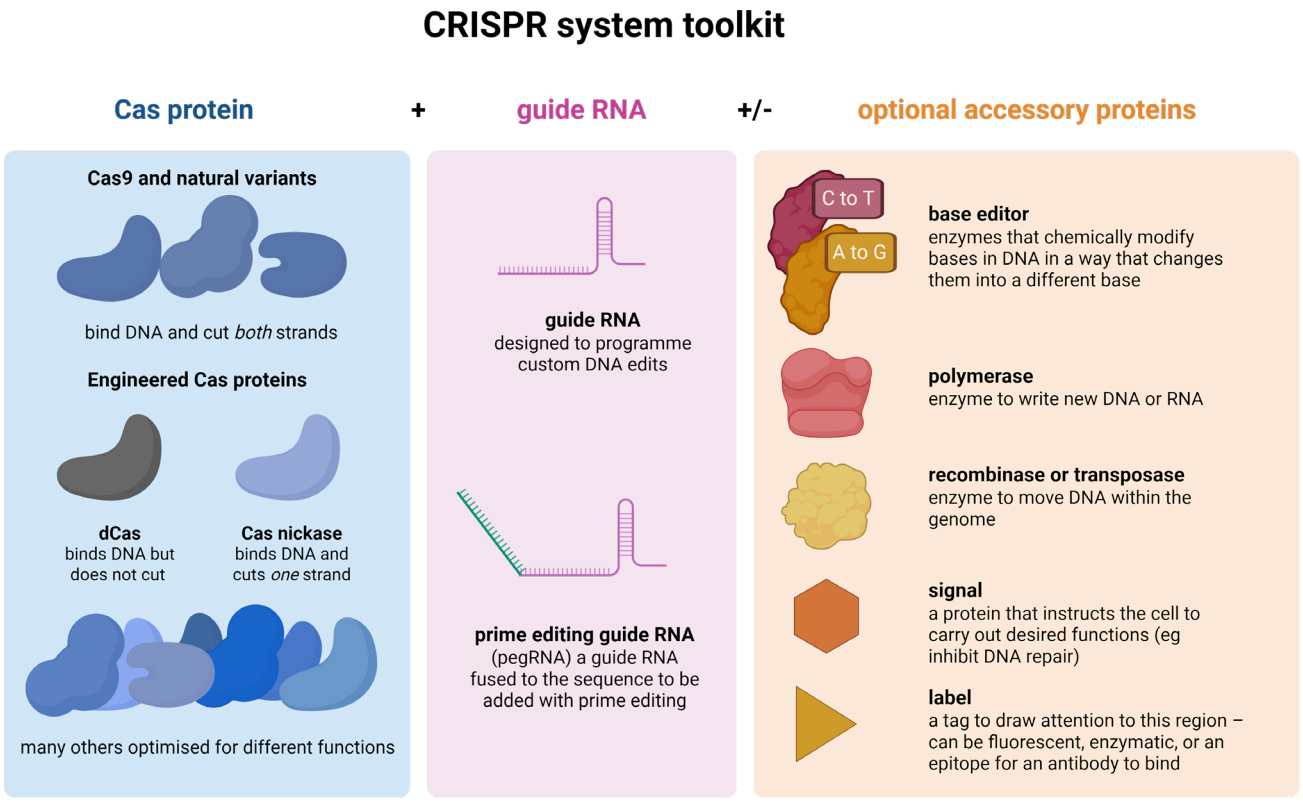
Advances in CRISPR gene editing

A lot has changed since the world learnt about CRISPR in 2012. CRISPR rapidly became an everyday tool in molecular biology, leading to big advances in medicine, primary industries, and many other applications. Co-discoverers Jennifer A. Doudna and Emmanuelle Charpentier shared the Nobel Prize for Chemistry in 2020 (23,24), a commendation that typically takes decades. CRISPR has been the focus of many innovations. Many of the technology's limitations have been addressed by engineering the system to improve accuracy and efficiency (25). An edited organism's genome sequence can be checked.

CRISPR has also been adapted to perform many new molecular tasks (25,26). Sometimes the Cas protein itself is engineered to acquire a new function and other times it acts as a vehicle to deliver a specialised enzyme. Modified Cas proteins are still summoned to DNA when gRNA binds the target sequence, but new functions once they arrive can include the following:

- Cutting only one strand of DNA (known as nicking or creating a single-stranded break) with an engineered Cas nickase (27)
- Chemically changing the DNA bases to edit the sequence (base editors) (28–31)

FIGURE 10 | CRISPR system toolkit



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- Inserting new DNA in small (prime editors) (32) or large segments (recombinases among others) (33). Making large rearrangements (34–36)
- Activating or repressing a gene through transcription regulation (ie, mRNA synthesis; mRNA interference) (37–40)
- Making transient changes by editing mRNA with RNA-targeting Cas proteins (RNA base editing (41))
- Changing the three-dimensional structure of the DNA (chromatin) for large scale gene regulation, also known as epigenome editing (42–46)
- A switch to regulate DNA editing in response to signals either inside or outside the cell (47–52)
- A fluorescent tag as a useful glowing label to see the target region of DNA in a living cell (27,53–57).

These and other components make up our ever-expanding CRISPR toolbox and can be modified and combined to fit the gene editing task at hand.

Two CRISPR technologies in particular have been vital for gene editing: base editing and prime editing (58,59). Both avoid double-strand DNA breaks (which are harder to control) and give more freedom in choosing the location and nature of DNA edits. Base and prime editing can be used in non-dividing cells, such as heart and muscle cells (traditional CRISPR can only incorporate changes into cells that are actively growing, like skin cells) (28).

Base editing

A base editor can substitute a single base/nucleotide to another (58,59). Base editors are comprised of several functional pieces fused together, including:

- An engineered Cas nickase protein that binds and cuts one strand of DNA
- A customisable gRNA
- A base editing domain
- Sometimes, a signal domain (28,58,59).

The Cas nickase uses gRNA to read and bind DNA at the intended edit site. Once in place, the base editing domain makes the desired

change but only in one DNA strand. The result is a mismatch – the new base no longer follows base pairing rules with its partner. The solution to this is the Cas nickase, which makes a cut on the unedited strand to summon cellular repair machinery. DNA repair enzymes will find the mismatch and assume that the base on the cut DNA is the wrong one, and "fix" it to pair with the edited base.

Base editing domains – also known as nucleotide deaminases – exist in nature and have been co-opted and modified for biotechnology (29,30). They are enzymes that chemically alter DNA bases adenine (A) and cytosine (C) in a way that makes the cell recognise them as guanine (G) and thymine (T), respectively[5]. This type of change is known as a transition and occurs within the same class of DNA bases[6] but not between them. Changes between classes are called transversions and these are harder to achieve.

The first base editors could make specific transitions with cytosine base editors (C to T) (29,30,60) and adenine base editors (A to G) (31,61). Cytosine base editors have an extra component in addition to the Cas nickase, gRNA, and base editing domain: a signal protein that discourages/inhibits cell repair mechanisms from "fixing" the edited base back to the original (61)[7].

Recently, researchers have developed base editors for each of the possible transitions and transversions (26,62,63). Base editors have also been engineered to introduce intentionally random mutations (for mutagenesis) (64), an important tool in research and synthetic biology. RNA base editors specifically target RNA for edits intended to be temporary (41,65).

Base editors have a range of limitations, including being finnicky about where they edit; sometimes editing the wrong 'off-target' sequence; and a bulky size that can be difficult to get into cells. Solutions can be engineered to all of these limitations (66,67) and scientists weigh up the pros and cons of different approaches for each project.

5 Deamination converts adenine to inosine, and cytosine to uracil.

6 Adenine and guanine are both purines; cytosine, thymine, and uracil (in RNA) are pyrimidines.

7 A comparable signal protein is not necessary for adenine base editors because the repair process that targets A to G edits is slower (28).

Prime editing

A prime editor can precisely perform any small edit, including substitutions, deletions and insertions. They are comprised of:

- An engineered Cas nickase protein
- A customisable prime editing guide RNA (pegRNA)
- A reverse transcriptase domain (32,58,68).

The Cas nickase in a prime editor acts in a similar way as it does in a base editor: it locates the editing site and nicks one DNA strand (69). The pegRNA is an instruction molecule of two parts: like gRNA, it contains the directions to guide Cas to the editing site, but it also has the template for the exact edit to be carried out there (26).

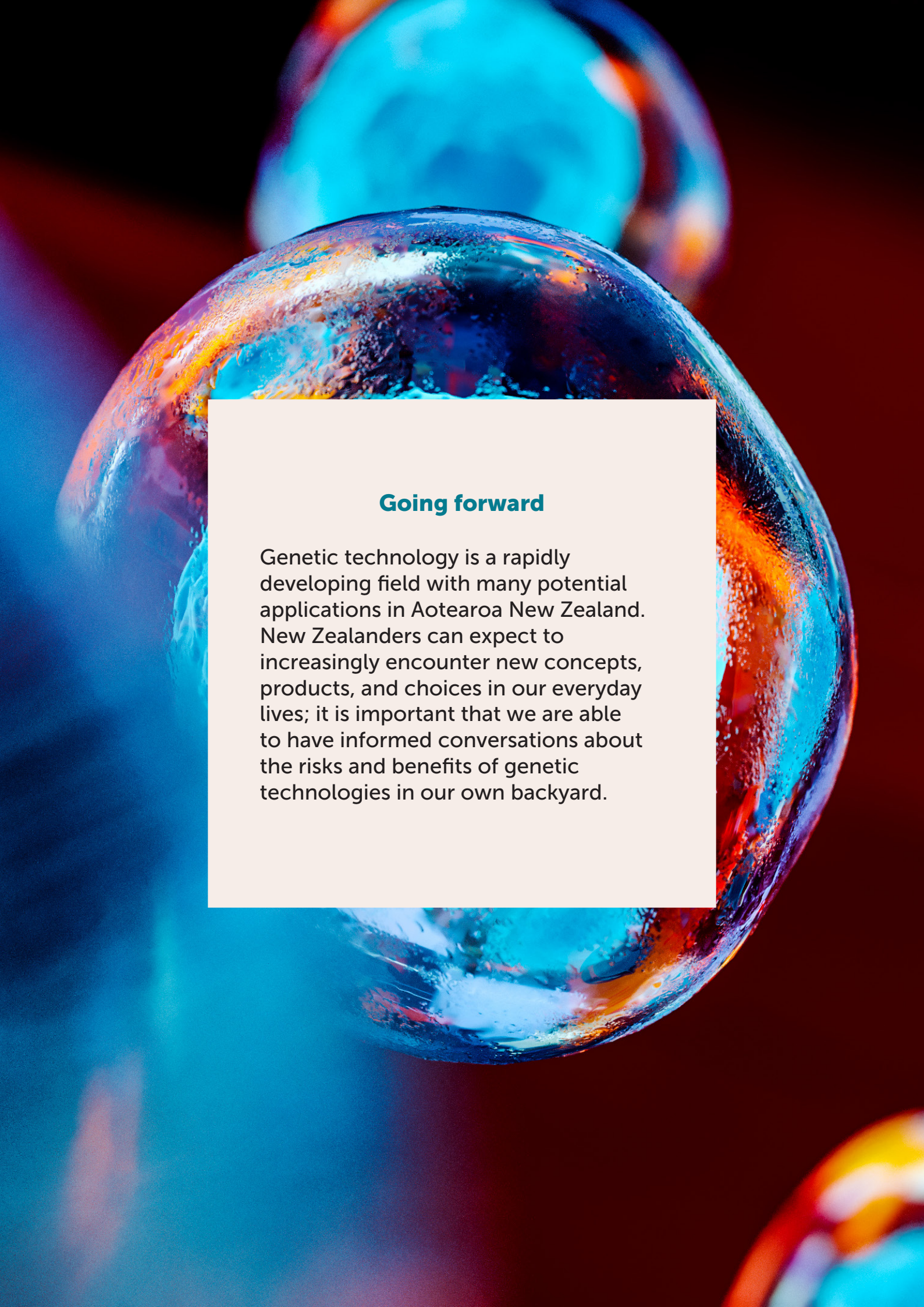
The reverse transcriptase domain is key to prime editors' functionality. Reverse transcriptases are enzymes taken from nature[8] and use RNA templates to write DNA, in the opposite direction to the typical process of transcription. Engineered reverse transcriptases are used routinely in molecular biology.

In prime editing, the Cas nickase uses the guiding portion of the pegRNA to find and bind the correct DNA editing site. The nickase cuts the target DNA strand and the reverse transcriptase domain uses the template portion of the pegRNA to write new DNA (26,58)[9]. The new DNA strand is patched to the old using existing DNA repair processes in the cell.

Prime editors are more versatile and precise than base editors. Prime editing allows a greater range of DNA edits and is less restricted by sequence contexts. Errors and off-target effects are minimal (26). However, at time of writing, prime editors are not very efficient and are still a developing technology (58,68,71).

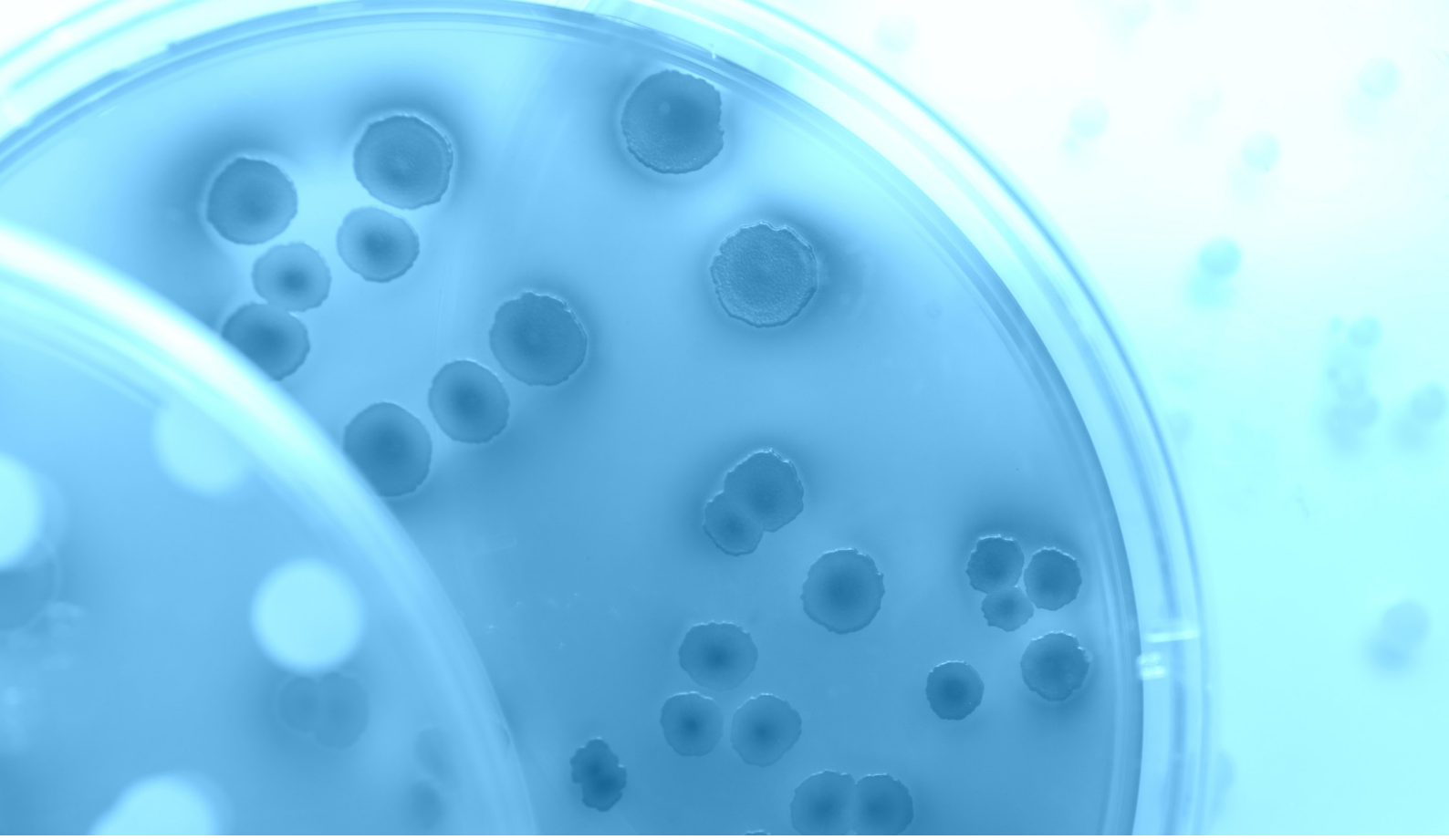
8 Reverse transcriptase enzymes are used by retroviruses to convert their RNA genomes to DNA and hide in their host genomes (70). HIV is an example of a retrovirus.

9 A more detailed description can be found in (69).



Going forward

Genetic technology is a rapidly developing field with many potential applications in Aotearoa New Zealand. New Zealanders can expect to increasingly encounter new concepts, products, and choices in our everyday lives; it is important that we are able to have informed conversations about the risks and benefits of genetic technologies in our own backyard.



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- Professor Andrew Allan (Bioeconomy Science Institute; University of Auckland Waipapa Taumata Rau)
- Professor Stephen Robertson (University of Otago Ōtākou Whakaihu Waka; Curekids).

Conflicts of interest:

Professor Black is a member of the Māori Focus Group, which supports Ministry of Business, Innovation and Employment (MBIE) to identify and understand Māori rights and interests for inclusion in policy advice to Government regarding gene technology. Professor Black is also participating in a research programme with MBIE, weaving cultural authority into developing gene drives for pest wasps.

Professor Wilcox co-chairs Te Ira Tātai Whakaheke Charitable Trust whose mission is to ensure culturally safe use of genomics in Māori healthcare. Professor Wilcox also co-leads the He Kākano and Rakeiora projects, is Deputy Director of Maurice Wilkins Centre, and is co-chair (Māori) of Rare Diseases of New Zealand (RDNZ) research network leadership group.

Professors Allan and Robertson are members of the Technical Advisory Group which provides technical advice to MBIE on up-to-date gene technology regulation.

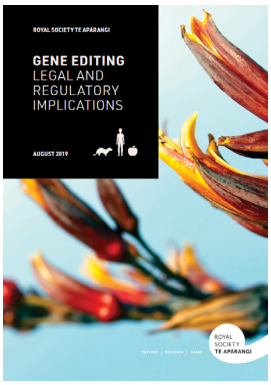
Read more

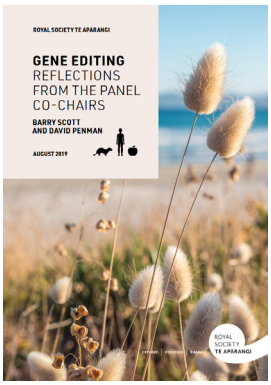
Read about practical applications for genetic technologies in:

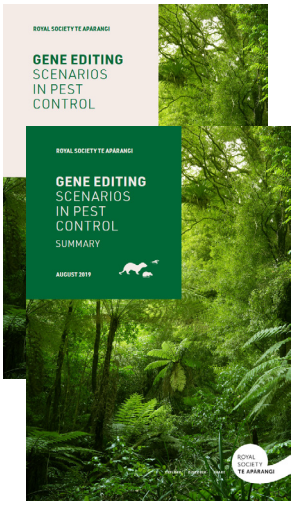
- Genetic technologies in Aotearoa New Zealand – how they're used
- Full content is available on the Society's webpage

Our previous publications on genetic technologies include:

- Gene editing: Legal and regulatory implications
- Gene editing: Scenarios in healthcare
- Gene editing: Scenarios in primary industries
- Gene editing: Scenarios in pest control
- Gene editing: Reflections from the panel co-chairs.







Ngā tohutoro
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