

Horizon Scan

CRISPR Technologies for In Vivo and Ex Vivo Gene Editing

Key Messages

What Is the Issue?

The first therapeutics based on clustered regularly interspaced short palindromic repeats (CRISPR) technologies are entering the market. These gene-editing technologies have the potential to change treatment paradigms and may be used to treat conditions that cannot be treated or cured with current methods. This report aims to provide an overview of these technologies and their current and potential roles in health care.

What Is the Technology?

CRISPR is a novel and emerging technology, first discovered in bacterial immune systems, that can cut DNA strands and be used as a gene-editing tool. A guide ribonucleic acid (RNA) sequence leads the CRISPR-associated nuclease to the target DNA sequence where the cut is made. These edits change the function of the gene, making genes nonfunctional or replacing the coding sequence for 1 gene with another. CRISPR can also be used to increase or decrease the expression of specific genes.

What Is the Potential Impact?

CRISPR-based technologies have a variety of potential applications in health care, including:

- treating genetic diseases
- understanding the genetic mechanisms of diseases and investigating the relevance of potential drug treatments
- managing infectious diseases through detection, treatment, and elimination.

What Else Do We Need to Know?

The long-term effects of CRISPR-based therapies are currently unknown. While the first of these therapies, exagamglogene autotemcel (exa-cel) (Casgevy), is the first and only CRISPR-based therapy to receive regulatory approval anywhere internationally (e.g., US, UK), as well as in Canada in September 2024, the next viable CRISPR-based therapies are still in development, with the pivotal clinical trials not expected to be completed until at least 2027. Several ethical considerations related to the use of CRISPR-based therapies have been identified, including the implications of off-target gene modifications, a need for robust informed consent processes, and a need for ethical and legal guidelines.

Purpose and Approach

The purpose of this report is to present health care decision-makers in Canada with an overview of gene-editing technologies based on CRISPR.

To inform this report, we conducted a tailored literature search, balancing comprehensiveness and relevance, across various sources, including databases and a focused internet search conducted on May 22, 2024. These searches were supplemented with handsearching of the grey literature by the author. Content experts were consulted for input and peer review. [Appendix 1](#) provides the detailed literature search methods.

What Is the Technology and How Does It Work?

CRISPR was discovered by Dr. Jennifer Doudna and Dr. Emmanuelle Charpentier and described in their 2012 publication in the journal *Science*.¹ CRISPR is a novel and emerging technology, first discovered in bacterial immune systems, that can cut DNA and be used as a gene-editing tool. There are 2 key parts to the CRISPR technologies: a guide RNA sequence and a CRISPR-associated (Cas) nuclease. The customizable guide RNA sequence is used to direct the Cas nuclease to a target DNA sequence where the Cas nuclease binds and cuts the DNA.² CRISPR was discovered in bacterial immune systems where it was observed cutting the DNA and disabling bacteriophages that were invading the bacteria.² Drs. Doudna and Charpentier determined that the CRISPR Cas9 bacterial immune system could be repurposed as a gene-editing tool to alter DNA at specific locations in a genome.¹ CRISPR Cas9 is currently the most commonly used nuclease in gene editing.² Others include Cas12, Cas13, and Cas14. CRISPR Cas9 is guided by 2 RNAs to the DNA target and operates by creating double-stranded breaks in the DNA and leveraging cellular DNA repair mechanisms.^{1,2} Drs. Doudna and Charpentier became the first all-female team to win the Nobel Prize in Chemistry for this discovery in 2020.²

CRISPR technologies can be used to edit genes within the body (in vivo) or to edit cells that have been removed from the body (ex vivo) that are returned to the body after their editing is complete. Three common uses for CRISPR technologies include gene knockouts, gene knock-ins, and regulating gene expression. Among the various pathways involved, nonhomologous end joining (NHEJ) and homology-directed repair (HDR) are pivotal for gene editing. NHEJ is used to disrupt genes and make them nonfunctional, whereas HDR is used to insert new genes or genetic material fragments.²

Gene Knockouts

Cas9 typically repairs a double-strand break in DNA through NHEJ, which often introduces indels (i.e., insertion or deletion of 1 or more nucleotides) into the repaired region.² When these indels cause a frameshift mutation within the gene's coding region, the gene becomes nonfunctional, resulting in a gene knockout. Gene knockouts are often used in research fields such as functional genomics, pathway analysis, drug discovery, screening, and disease modelling.² Using multiple guide RNAs that target different parts of the gene ensures highly efficient gene knockout, a method that is becoming more popular. Recent research has found that genes that have been knocked out by CRISPR Cas9 may not be completely nonfunctional.³

Residual functional proteins could be generated to make up for the loss of function in a process called “knockout escaping.”³

Gene Knock-Ins

When Cas9 induces a double-strand break in DNA, cells can also repair themselves through HDR. This repair process provides an opportunity for researchers to insert new DNA, such as an entire gene, which is known as gene knock-in.² To achieve a gene knock-in, a donor template containing the desired DNA sequence flanked by homologous regions matching the cut site is required. This template, along with Cas9 and single-guide RNA, is delivered into the engineered cells.² Gene knock-ins have been used in biotechnology, enabling the production of recombinant proteins, improving immortalized cell lines, and enhancing disease modelling precision. Additionally, CRISPR knock-ins hold promise for correcting genetic mutations in cell and gene therapies for human diseases.² Gene knock-ins are more challenging than knockouts because HDR is less common than NHEJ and occurs only during specific cell cycle stages. The lower frequency of HDR typically results in lower knock-in efficiencies;² however, scientists are developing methods to overcome these challenges, such as experimental optimization, cell cycle synchronization, and treatments that enhance HDR or inhibit NHEJ during knock-in experiments.²

Regulating Gene Expression

CRISPR can also be used to regulate gene expression, meaning to control when certain genes are turned on or off in a cell.² CRISPR activation (CRISPR_a) increases the expression of a gene and CRISPR interference (CRISPR_i) decreases expression using catalytically dead Cas9 (dCas9). These gene modulators are being used for a variety of research purposes to explore future potential treatment applications, including in developmental biology, infectious disease management and prevention, functional genomics, and screening for genetic elements that mediate drug resistance.²

What Is CRISPR Used For?

CRISPR has been used as a treatment for medical conditions in 2 ways: ex vivo and in vivo gene editing.² Ex vivo gene editing, or cell therapy, involves harvesting cells from the patient, editing the cells with CRISPR while they are outside of the body (i.e., ex vivo), then returning them to the patient through an infusion.² In vivo gene editing occurs when the instructions for the CRISPR gene editor are injected directly into a patient (i.e., in vivo) with the intention that the CRISPR tool will cut out the problematic gene in the cells within the patient’s body.⁴ CRISPR can also be used to generate chimeric antigen receptor (CAR) T cells, which are used for cancer immunotherapy. Clinical trials of the safety and effectiveness of this application are currently under way.

CRISPR-based gene-editing technologies have a variety of potential clinical applications in health care, such as:⁵

- treatment for human genetic diseases (e.g., sickle cell disease, beta-thalassemia, cystic fibrosis, Duchenne muscular dystrophy, retinitis pigmentosa, cardiac disease)

- understanding the genetic mechanisms that underly cancer development and investigating the functional relevance of potential drug targets in cancer cells
- the management of infectious diseases via:
 - detection (e.g., diagnostic assays for viral detection)
 - treatment (e.g., treating diseases by directly targeting viral genomes and inhibiting viral load and replication)
 - elimination (e.g., editing the genome of viruses and parasites to disrupt their life cycle and prevent their ability to infect humans).

What Is the Evidence?

Clinical Evidence

There is well-established evidence that demonstrates the CRISPR Cas9 system is capable of inducing precise gene editing in a wide range of organisms.⁵ Ex vivo and in vivo gene editing are 2 ways CRISPR has been used to develop treatments for medical conditions.²

Ex Vivo Gene Editing (Cell Therapy)

Exagamglogene autotemcel (exa-cel), sold under the brand name Casgevy, is the first and only CRISPR-based therapy to receive regulatory approval anywhere internationally.^{6,7} Exa-cel is a CRISPR Cas9 gene-editing therapy intended to treat certain people with sickle cell disease or transfusion-dependent beta-thalassemia.^{1,8} (At the time of writing, exa-cel is undergoing reimbursement review by Canada's Drug Agency for both sickle cell disease and transfusion-dependent beta-thalassemia.) Exa-cel uses CRISPR Cas9–based gene editing to increase the amount of fetal hemoglobin in red blood cells by deleting a portion of the *BC11A* gene.⁸ The treatment involves harvesting hematopoietic stem cells from the patient, which are sent to a facility where they are modified using CRISPR Cas9. While the cells are being modified, the patient receives chemotherapy to clear out the existing stem cells in their bone marrow before their edited cells are reintroduced.⁹ As the red blood cells are regenerated, the newly edited cells replace the damaged ones, which have been observed to modify sickle cell disease and transfusion-dependent beta-thalassemia.⁸ The intervention is intended to be administered only once, with the expectation that the effects would be lifelong; however, long-term effectiveness data are not yet available.¹⁴

The pivotal clinical trials (CLIMB-111, CLIMB-121, and CLIMB-131) of exa-cel for sickle cell disease and transfusion-dependent beta-thalassemia are ongoing, with plans to follow the enrolled patients to evaluate their longer-term outcomes after receiving treatment.¹⁰⁻¹² The manufacturer presented interim results of these studies at the Annual European Hematology Association Congress in June 2024.¹⁰ These interim results are summarized here and were not critically appraised for this report. (A critical appraisal of the available clinical trial results will be included in our reimbursement reviews for exa-cel, which are anticipated to be available for public feedback in November 2024.)³⁰ The manufacturer presented interim results for 46 patients with sickle cell disease and 56 patients with transfusion-dependent beta-thalassemia with at least 16 months

of follow-up data. The longest patient follow-up was more than 5 years since receiving treatment.¹⁰ In the CLIMB-121 trial, enrolled patients with sickle cell disease were reported to experience an average of 4.1 (± 3.0) vaso-occlusive crises per year before treatment, with 59% (26 of 44) having had 3 or more vaso-occlusive crises per year for the previous 2 years.¹¹ The sponsor reported that, following treatment, 92.3% (36 of 39) of the patients with sickle cell disease included in the long-term follow-up data were free from vaso-occlusive crises for at least 12 months, with a mean duration of 27.9 months.¹⁰ Vaso-occlusive crises occur when circulation is limited by the sickled red blood cells, which causes organ injury and pain.¹³ Of patients with at least 16 months of follow-up, 97.4% (38 of 39) were reported to be free from hospitalizations related to vaso-occlusive crisis for at least 12 consecutive months.¹⁰

People with transfusion-dependent beta-thalassemia require monthly transfusions and iron chelation. In total, 94.2% of patients (49 of 52) were reported to be transfusion independent for at least 12 consecutive months, with a mean duration of 31.0 months.¹⁰ Patients in both disease groups reported sustained and meaningful improvements in their quality of life, including physical, emotional, social and/or family, and functional well-being, and overall health status. After their participation in the pivotal studies, patients will be asked to enrol in the long-term, open-label CLIMB-131 study, which aims to follow these patients for up to 15 years after their treatment with exa-cel.¹⁰

In Vivo Gene Editing

In 2020, a CRISPR gene therapy was injected directly into a patient's eye as a potential treatment for hereditary blindness. They were the first person to receive the treatment with the intention that the CRISPR tool would cut out the gene causing blindness and thus restore the patient's vision.⁴ Subsequently, the initial results of a phase I and II open-label, single-ascending-dose study were published in 2024.¹⁵ Study participants who were aged 3 years or older with *CEP290*-associated inherited retinal degeneration caused by a homozygous or compound heterozygous IVS26 variant received a subretinal injection in their worse eye. No serious adverse events were observed in the 14 participants and no dose-limiting toxic effects were recorded.¹⁵ Four of the 14 participants achieved clinically meaningful improvements in best corrected visual acuity.¹⁵ We did not critically appraise the results summarized for this report; however, based on these trials, there are no data on comparative effectiveness or safety relative to existing treatments, nor long-term data.

Clinical Safety and Long-Term Effects

CRISPR causes double-stranded breaks in DNA, which may result in indels that could cause large deletions and chromosomal instability. Newer techniques, such as base editing and prime editing, induce only single-strand breaks and therefore lower levels of indels.²² These newer techniques may more precisely correct base substitutions in genetic diseases and reduce the risk of off-target edits. Off-target edits are a key risk associated with gene editing. These can occur when the Cas nuclease cuts at unintended genetic sites, which could result in unknown consequences to an individual's health. There are also unknown effects to the individual that result from the editing of their genes and the consequences these gene edits may have on them in the future.²¹ There is also little known about the interactions edited genes may have with unedited genes and whether those interactions may impact biological functions and pathways.²¹

Regulatory Status

Exa-cel is the only CRISPR-based therapeutic to gain regulatory approval anywhere internationally. It was first approved for use by the US FDA and the UK Medicines and Healthcare products Regulatory Agency for those with sickle cell disease or transfusion-dependent beta-thalassemia in late 2023 and early 2024. As of September 25, 2024, exa-cel was granted market authorization by Health Canada for the same patient groups.^{6,7} The drug also received conditional authorization from the European Medicines Agency in 2024.

What Does It Cost?

There is currently no publicly listed price for exa-cel; however, the cost of treatment with exa-cel has been reported as US\$2,200,000 for a 1-time treatment.^{17,18} It is possible that the cost in Canada may be different than what has been reported in US sources. Chemotherapy is required before receiving the treatment and will contribute to the overall treatment cost.¹⁸ Additionally, those receiving treatment are also required to be admitted to the hospital for approximately 1 month, which would add to the overall treatment cost. The cost is expected to be the same for both sickle cell disease and transfusion-dependent beta-thalassemia.

Ethical Considerations

The literature identifies several ethical considerations associated with the application of CRISPR-based therapies. While a range of ethical issues have been identified related to CRISPR applications more broadly, including their uses in germline modifications (i.e., those that can be passed on to the next generation)¹⁹⁻²¹ or agricultural settings,^{5,19} these are beyond the scope of this review. As identified in the overview of clinical evidence, the long-term safety and effectiveness of CRISPR-based therapies are unknown because of a lack of long-term data. Uncertainties also remain related to the potential risks of off-target effects and other unintended consequences of these therapies.^{20,21} These uncertainties have implications for patients who may be exposed to these long-term uncertainties and risks, and for health systems, where decisions must be made to invest in these therapies with potentially uncertain outcomes. Robust informed consent conversations with patients, caregivers, and providers and shared decision-making regarding these uncertainties can support autonomous decision-making. At the policy level, it has been recommended that researchers develop a set of ethical and legal guidelines and best practices to guide the use of CRISPR technologies in creating human disease models and therapies.¹⁹

Access to CRISPR technologies may be limited by patient eligibility criteria and inequities related to how these technologies are funded, distributed, and used. Other infrastructural requirements needed to access CRISPR technologies, such as travel to reach treatment facilities in urban centres and wraparound care and supports to access these technologies, may also limit equitable access across population groups.

Related Developments

There are technical limitations to the widespread implementation of CRISPR technologies.⁵ Editing inherited epigenetic modifications can be challenging because of its complex nature and our lack of understanding of the interplay between epigenetic markers and how they influence gene expression.⁵ It has also been reported that it is difficult to gain proficiency with the technology while maintaining an adequate safety profile.¹⁴

Clinical Therapeutics

The concept of using gene therapies, including those created using CRISPR-based techniques, is being studied for a range of diseases, and most of the available information outlines the preclinical and discovery phases of this research. Gene-editing treatments for genetic diseases caused by single gene mutations will have earlier clinical applications than those caused by multiple gene mutations because of the complexity of gene interactions for diseases caused by multiple mutations. Experience from the development of therapeutics for genetic diseases caused by single gene mutations will inform the therapy's development and extension to more complex genetic disorders. In this review we identified overview articles that describe the progress of this research in cardiovascular disease and osteoarthritis. We have not critically appraised this evidence.

Cardiovascular Disease

Ganipineni and colleagues (2023)²⁴ conducted a clinical review of the use of CRISPR technologies in cardiovascular disease, in particular its use for dilated cardiomyopathy, which is a major cause of heart failure. Currently available therapies focus on slowing disease progression and managing symptoms, and cardiac transplant is currently the only available curative treatment.²⁵ The hope is that gene therapies will be developed that will be able to reverse cardiac damage.²⁵

CRISPR system applications that have been studied in dilated cardiomyopathy include:²⁶

- ex vivo gene editing for disease and therapeutic modelling
- in vivo gene editing for disease modelling.

The authors of the literature review determined that gene editing has shown some promise when developing precise genotype-specific therapeutic strategies; however, limitations remain. The mechanics of delivering CRISPR Cas9 to human cardiomyocytes using viral vectors is a challenge as the vectors can potentially cause an immune response or other adverse reactions.²⁵ Unintended gene targeting, or off-target edits, is another limitation. The genes involved in dilated cardiomyopathy are complex and have multiple functions, and CRISPR Cas9 has been observed to, at times, target the wrong part of the genome and result in unintended effects that could be benign or harmful, depending on which area has been targeted.²⁵ A phase III clinical trial is currently under way for a CRISPR-based therapy for familial amyloid cardiomyopathy and is anticipated to be completed at the end of 2027.¹⁴

Osteoarthritis

Jia and colleagues (2024)²⁴ systematically reviewed current studies on CRISPR-based technologies for the improvement of cell deterioration, inflammation, and cartilage damage associated with osteoarthritis. The researchers estimated that between 40% and 60% of osteoarthritis is gene related and hypothesized that gene therapy might provide a viable treatment option.²⁴ There are currently no treatments available to cure osteoarthritis. Lifestyle modification and pain management are the main management options and existing drug therapies that are recommended to manage symptoms usually have dose-dependent toxicity.²⁴ The concept of using CRISPR applications to target the genes believed to be associated with the osteoarthritis inflammation process and the cartilage repair process has been investigated.

The main areas of focus for potential future gene therapies for osteoarthritis include:²⁴

- engineering undifferentiated adult stem cells to give them the ability to repair inflammation or differentiating differentiated adult stem cells into chondrocytes to repair damaged cartilage
- editing the mitochondrial DNA of damaged chondrocytes to treat osteoarthritis by inhibiting and regulating immune processes
- modulating the inflammatory pathways of osteoarthritis to improve or possibly reverse the damaged cells to maintain the cellular lifespan.

Diagnostic Testing

In addition to being a treatment for medical conditions, CRISPR can also be used as the base for diagnostic tests. CRISPR Cas12 and Cas13 are often used in diagnostic assays.²⁷ In their systematic review and bibliometric analysis, Leta and colleagues (2024)²⁷ identified 580 different CRISPR-based diagnostic assays that target 170 pathogens, with around 72% of those assays being developed for point-of-care testing. CRISPR Cas12 and Cas13 demonstrated collateral nucleic acid cleavage activity, a characteristic that has been used to develop diagnostic tests that are specific, sensitive, fast, and portable.²⁷ The majority of the tests identified in the review used a lateral flow assay to display the results. Lateral flow assays detect the presence of antibodies or antigens in a liquid sample. The sample is drawn through a conjugate pad and, if present, the target of the test will bind to the immunoreagent and a line will appear to indicate a positive result.²⁸ A familiar example of a lateral flow assay is a simple 2-line pregnancy test or at-home tests for COVID-19. Lateral flow assays do not require complicated equipment, which makes them suitable for point-of-care testing.²⁷ Multiplex assays that can detect more than 1 pathogen using a single test can be of great use in detecting and differentiating between infectious diseases; however, at the time of drafting this report, there appears to be limited development of these tests using CRISPR technologies.

During the COVID-19 pandemic, emergency use authorization was granted by the US FDA to several CRISPR-based diagnostic tests. These include the Sherlock CRISPR SARS-CoV-2 lab-based test kit^{2,27} and the Accula SARS-CoV-2 test.²⁷ The Lucira Check It COVID-19 test kit was authorized for use in both the US and Canada. There does not appear to be much publicly available information about the real-world performance or use of these tests.

Looking Ahead

Although the first CRISPR-based therapeutic is now available to treat patients in some countries, including Canada, it is unlikely that a rush of new CRISPR-based gene therapies will follow its entry to the market. Other therapeutics are in the works, but they remain in the early phases of clinical development. Based on the information available about the clinical trials that are currently under way, the next phase III trials of viable CRISPR-based therapies (for the treatment of familial amyloid cardiomyopathy) are anticipated to be completed at the end of 2027.¹⁴ There are more than 20 phase II trials ongoing for CRISPR-based therapies, including for cancers and cardiovascular disease, with the earliest safety trial set to be complete in December 2025.^{14,18}

CRISPR-based therapies may represent a paradigm shift in health care by providing management options or curative treatment for conditions that previously had no cure or limited options for treatment. Looking ahead, balancing the hope for these therapies with the uncertainty that remains about their long-term safety and effectiveness, and ethical and other considerations, will be critical. Long-term follow-up studies of the recipients of CRISPR-based therapies will further understanding of how these treatments impact human health in the long term.

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Appendix 1: Methods

Note that this appendix has not been copy-edited.

Literature Search Strategy

An information specialist conducted a literature search on key resources including MEDLINE, the Cochrane Database of Systematic Reviews, the International HTA Database, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search approach was customized to retrieve a limited set of results, balancing comprehensiveness with relevancy. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. Search concepts were developed based on the elements of the research questions and selection criteria. The main search concept was CRISPR. Search filters were applied to limit retrieval to health technology assessments, systematic reviews, and meta-analyses. The search was completed on May 22, 2024, and limited to English-language documents published since January 1, 2019. Internet links were provided, where available.

Selection Criteria

One author screened the literature search results and reviewed the full text of all potentially relevant publications. Publications were considered for inclusion if the intervention was related to CRISPR-based technologies. Grey literature was included when it provided additional information to that available in the published studies.



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