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Article abstract

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COMMENTAIRE CRITIQUE / CRITICAL COMMENTARY (ÉVALUÉ PAR LES PAIRS / PEER-REVIEWED)

Human Genome Editing and Sickle Cell Disease in Canada: Urgent and Unresolved Ethical Considerations

Maria Klimenko[a,b], Ryan Tonkens[a,c]

Résumé
Certains pays approuvent déjà des applications thérapeutiques de l'édition du génome humain. Par exemple, le Royaume-Uni et les États-Unis ont récemment approuvé Casgevy dans le cadre d'un protocole de traitement de la drépanocytose. Le Canada doit-il suivre cette voie? Nous examinons les questions éthiques les plus importantes, mais non résolues, dans le contexte canadien, et soutenons qu'un engagement public et des délibérations beaucoup plus poussés sont nécessaires.

Mots-clés
Casgevy, équité, inclusion, éthique, édition du génome humain, justice, engagement public, drépanocytose

Abstract
Some countries are already approving therapeutic applications of human genome editing. For example, recently the United Kingdom and USA have approved Casgevy as part of a treatment protocol for sickle cell disease. Should Canada follow this lead? Here we discuss the most important, yet unresolved, ethical issues in a Canadian context, and argue that much more public engagement and deliberation is needed.

Keywords
Casgevy, equity, inclusion, ethics, human genome editing, justice, public engagement, sickle cell disease

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INTRODUCTION

Gene editing technology has been approved for use as a clinical treatment in humans. In December 2023, the United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA) approved the use of CRISPR/Cas-9 genome editing for treatment of patients over the age of 12 who have sickle cell disease; and in January 2024, the US Food and Drug Administration (FDA) also approved this treatment, which is called Casgevy™ (exagamglogene autotemcel).

After completing a procedure to extract the patient's blood stem cells from their bone marrow, Casgevy can be used to genetically modify the patient's blood stem cells, essentially replacing their adult hemoglobin with fetal hemoglobin, which reduces sickling in the blood and therefore reduces blockages that can lead to vaso-occlusive events or crises (VOCs). While these patients continue to have sickle cell disease (they are not "cured" *per se*), once the genetically edited bone marrow is transplanted, they would no longer experience VOCs, and therefore would be free of corresponding pain and other symptoms accompanying those events. In the experimental trial underpinning FDA and MHRA approval of Casgevy, 93.5% of qualifying participants reported being free from "severe VOC episodes for at least 12 consecutive months during the 24-month follow-up period." (1) According to the Vertex website, the company that developed Casgevy, this is a one-time treatment (2).

Canada is now considering approving Casgevy. In April 2024, Vertex announced that its New Drug Submission for Casgevy had been accepted for priority review by Health Canada for the treatment of patients 12 years and older with sickle cell disease with recurrent VOCs and for the treatment of patients aged 12 years and older with transfusion-dependent beta thalassemia (TDT) (3). Should Canada follow the MHRA's and FDA's lead and approve the use of human genome editing for this purpose? In this commentary, we consider some of the most important, yet unresolved, ethical issues relevant to answering this question, with the goal of contributing to deliberation on this important and pressing topic.

PATIENT SAFETY

Endorsement from the FDA and MHRA means that Casgevy has been deemed to be sufficiently safe for use in humans in the US and UK. If Canada does approve this therapeutic application of gene editing, ongoing monitoring for safety, the persistence of edited cells, and the risk of unintended harm including off-target mutations, is ethically imperative – something which is currently being done in the UK and US. Questions about who will be responsible for covering the costs of remedying unintended harms will also need to be addressed.

Casgevy is being used as one element in a larger treatment protocol, where the success of all elements is required to achieve the elimination of VOCs. In a complete ethical analysis (which is beyond the scope of this short critical commentary), the side-effects of all components of the protocol also need to be considered. For example, something not mentioned in the FDA press release is that some of the other elements in this treatment package may have serious side-effects for patients; according to the Casgevy website and informational video, "after receiving the conditioning medications [a one-time infusion after

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chemotherapy], it may not be possible for [the patient] to become pregnant or father a child", which constitutes a serious potential harm for those who undergo this treatment and who desire to become pregnant or father a child (4). Another consideration is the use of busulfan (a drug needed to achieve full myeloablation). This drug is toxic to the endothelium and significant risks exist of inducing veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) for patients with thalassemia and posterior reversible encephalopathy syndrome (PRES).

While competent and informed patients should be left to make decisions about their own health (and about their family building goals), it is important to highlight that safety approval of this new gene editing technology does not address the potential risks of the other treatment elements involved. And even assuming that Casgevy is sufficiently safe and effective for use in humans, other ethical considerations also need to be addressed.

INCLUSION AND PUBLIC ENGAGEMENT

Has the decision to allow this clinical treatment for sickle cell disease and thalassemia been informed by meaningful public engagement, including discussion about the research, development, and potential implementation of therapeutic applications of human genome editing into health care systems more generally? To our knowledge, no such public engagement has been conducted in Canada. If not, then there is good reason for Health Canada to not approve such treatment at this time.

One reason why public engagement is ethically imperative in this context is because it is public tax dollars that are funding public health care systems in Canada, and those systems are in place to meet the health needs of citizens, grounded in their right to access health care (e.g., *Canada Health Act*). Another reason why inclusive public engagement is important is to make sure that existing inequalities are not perpetuated. Moreover, meaningful public engagement will reveal whether Canadians are interested in having this treatment available in the first place and, if so, where access to this new treatment ranks in the list of priorities for Canadians, relative to other options for allocating funding. Lastly, the decision about whether to include human genome editing in the public health care system is a decision that will affect all Canadians. For example, because of the potential transformative nature of gene editing technology and because people will then have to *choose* whether to use gene editing technology, this should be a decision that all Canadians have a *reasonable* opportunity to inform. Once one or more applications of gene editing are approved, then it would be more difficult to halt the gene editing enterprise.

EQUITY

Sickle cell disease affects approximately 1 in 4200 people in Ontario, Canada (5). Over 6000 Canadians have sickle cell disease, and "approximately 100,000 people in the U.S., most commonly in African Americans" (1). The prevalence of thalassemia, the other hemoglobinopathy, is not known in the Canadian population but is likely to be increasing due to immigration. Prevalence can range from less than 1% to 40% in individuals from sub-Saharan Africa, Southeast Asia, Mediterranean countries, the Middle East, and the Indian subcontinent (7).

One ethical reason in favour of approving this new treatment in Canada is that it promotes the interests of populations who have traditionally been, and continue to be, marginalized and disadvantaged. Conversely, medical treatments that help only those who are in relative positions of power, or those who have the most privilege within society, are likely to be inequitable. Using cutting-edge health care technologies to serve the interests of those most well-off in society would be considered unfair on standard egalitarian accounts of social justice and the fair distribution of resources and opportunities within society, since they are not attached to positions in society that are open to everyone (i.e., being wealthy and powerful), and are not to the benefit of everyone, including those who are the least well-off. In this case, using gene editing to help people of colour and who also have a rare and devastating disease is consistent with the ethical principle of equity.

ACCESS AND AFFORDABILITY

At the same time, however, Casgevy and the larger treatment protocol that it is a part of is extremely expensive; Vertex has assigned it a listing price of 2.2 million USD. Other costs, such as autologous stem cell transplantation and extended hospitalization, must be considered on top of the treatment cost. Indeed, according to a recent *New York Times* article, the chief scientific officer for Vertex has said that a "medicine that is so resource-intensive as this is may not be appropriate in many places where the amount of resources for health care is more limited." (8)

At such a high price point, Casgevy is unlikely to be accessible to many Canadians who would benefit most from this therapy. Indeed, the issue is amplified once we consider the *global* distribution of health care resources: The majority of people in the world who have sickle cell disease live in Sub-Saharan Africa and are unlikely to be able to afford this expensive treatment, or to have access to the medical infrastructure and other resources required for administering this treatment protocol (9). Keeping the earlier point about equity in mind, currently this kind of treatment for sickle cell disease will only be accessible to relatively affluent people, and most likely those with relative ease of access to trained medical professionals and medical institutions who have the requisite resources (e.g., hospital beds, staff, and equipment for the conditioning medicine and stem cell transplant procedures, etc.). Thus, while equitable in some ways, this treatment raises concerns about *fairness* in light of existing injustices in access to health care.

CHOICE OF TARGET APPLICATION FOR THERAPEUTIC GENE EDITING

It is understandable that developers of therapeutic applications of human gene editing technology will want to focus on monogenetic diseases, such as sickle cell disease, since these are better understood (at present) and relatively more straightforward to target, compared to polygenetic diseases. At the same time, health research dollars are finite, and where such dollars get allocated should be a matter of debate and public conversation, with all key stakeholders in the discussion. Our contention here is that it would be ethically responsible to steer Canada's decision about whether to participate in the gene editing enterprise via inclusive and sustained public discussion and debate, compared to the decision being dominated by market pressures. In the case of Casgevy, it seems as though private profit maximization ideals are leading (or are at least heavily influencing) decisions about where to aim limited research and development resources (money, time, human resources), without explicit attention being given to where such resources could actually do the most *good*.

Many jurisdictions are experiencing a crisis-level shortage of health care professionals, including access to family physicians. Is it ethically appropriate to fund research on gene editing to treat sickle cell disease (for relatively affluent people who can afford the treatment) under conditions where, for example, there continues to be boiling water advisories in many communities across Canada, and ongoing suffering from unmet needs to help cure tuberculosis in places like Nunavut? While Casgevy certainly holds the promise of benefit to the people in Canada who have sickle cell disease and who can afford the treatment, and who have access to the requisite health care professionals and infrastructure, there are of course *many* more people suffering in different ways. Unless all such needs can be met simultaneously, difficult decisions will need to be made about prioritization. Our contention is that such decisions should not be left to private corporations to make on their own, without other stakeholders being involved, including the public and representatives from key socio-political institutions.

POTENTIAL IMPACTS ON REPRODUCTIVE AUTONOMY

It is possible that Casgevy and other gene editing therapies will become more widely available, and perhaps even be used earlier on in the human life cycle. For example, it may be possible to use a version of such technology on human embryos, to prevent hereditary and other non-communicable diseases. We have seen the latest advancements in the application of gene editing therapies to embryos, such as the story of a Chinese woman giving birth to genetically modified twin girls in 2019, regardless of the current laws that exist to prevent incidents of this nature (10); in Canada, genetic modification of human embryos for reproductive purposes is currently illegal (11).

Multiple ethical considerations arise regarding the impact on reproductive autonomy in women and people who can have children. The voluntary participation of women in carrying genetically modified embryos may introduce societal pressures due to the potential benefits (i.e., chronic disease prevention), potentially limiting or even compromising reproductive autonomy. If some women choose not to undergo the procedure, despite its safety and anticipated benefits, they may experience marginalization and their reproductive rights may be impacted. Additionally, if a woman decides to abort a pregnancy involving a genetically modified embryo, the principle of autonomy must be upheld to the highest standard. The right to abortion must play a role in ethical discussions involving reproductive autonomy in the context of gene editing. Lastly, there will be a certain level of involvement from third parties, such as clinical staff, government entities, and others at various stages of a woman voluntarily carrying a genetically modified embryo. To preserve the reproductive rights of women, the extent of third-party involvement or control must be discussed in order to safeguard women's reproductive rights.

As therapeutic applications of gene editing continue to advance and become more widely available for earlier phases in the human life cycle, consideration and discussion around women's reproductive rights are imperative.

TRUTH AND RECONCILIATION IN CANADA

The Truth and Reconciliation Commission of Canada (TRCC) has implored all Canadians and Canadian governments and institutions to work towards reconciliation (12). Two of the Commission's *Calls to Action* in the context of "Health" are:

> …to establish measurable goals to identify and close the gaps in health outcomes between Aboriginal and non-Aboriginal communities […] Such efforts would focus on indicators such as: infant mortality, maternal health, suicide, mental health, addictions, life expectancy, birth rates, infant and child health issues, chronic diseases, illness and injury incidence, and the availability of appropriate health services (Call to Action #19);

and,

> …to provide sustainable funding for existing and new Aboriginal healing centres to address the physical, mental, emotional, and spiritual harms caused by residential schools, and to ensure that the funding of healing centres in Nunavut and the Northwest Territories is a priority (Call to Action #21).

Canada has made a commitment to "achieving reconciliation with Indigenous peoples through a renewed, nation-to-nation, government-to-government, and Inuit-Crown relationship based on recognition of rights, respect, co-operation, and partnership as the foundation for transformative change," (13; cf. 14,15).

If funding is being used for developing new applications of gene editing technology *instead of* meeting these Calls to Action, then it is fair to ask governments (and researchers, private drug companies, health care organizations, etc.) to explain their justification for this decision. And, if finite health care research dollars are being allocated towards gene editing *instead of* towards closing "the gaps in health outcomes between Aboriginal and non-Aboriginal communities", then the Calls to Action in the category of "Health" are being circumvented and will remain unmet (12).

Nothing here is meant to conclude that the gene editing enterprise in Canada is necessarily or unavoidably inconsistent with truth and reconciliation, or that the two are mutually exclusive. As discussed above, forming a meaningful and inclusive discussion is imperative. At the time of writing, there has not been public engagement about human gene editing and its relationship to truth and reconciliation, and yet Health Canada is considering approval of therapeutic gene editing and therefore by extension considering whether to begin embarking on the gene editing enterprise. After having meaningful discussions about the prospect of therapeutic applications of gene editing, it *may* turn out that some people support this venture and believe they could benefit from such new medical tools. However, we *first* need to ask the questions in order to know their answers.

RESPONSIBILITY FOR POOR (GENETIC) HEALTH

Canada currently does not have any protections in place for people who choose not to participate in the gene editing enterprise, including those who will choose not to use safe, effective, and affordable therapeutic gene editing technology (16). In the context of Casgevy, this issue is perhaps less urgent compared to future treatments, since Casgevy is not (currently) affordable and therefore not accessible. However, it is worth raising this class of concern here, to begin important discussion in this area. If a person with sickle cell disease or thalassemia chooses to forgo a gene editing treatment protocol, and subsequently requires health care after experiencing VOCs, then their need for health care would have been avoidable, and therefore it may be thought that their need is self-caused. Because of this, it may be tempting to give such people lower priority in access to (scarce, stretched) medical resources, compared to people who have not caused their own need. Or else, one can reasonably imagine parents of a child with sickle cell disease being discriminated against or otherwise harmed for their decision to forgo Casgevy treatment for their child (or their decision to conceive a child with a risk of having sickle cell disease, etc.). The state has been known to intervene paternalistically into the decision making of parents in cases where those decisions are deemed to be harmful to the child and the reasons upon which the parental decision are based are seen as being irrational. A host of ethical issues emerge in this area, which have received very little attention up until now in the context of human genome editing – they will need to be answered if Canada decides to permit gene editing treatments like Casgevy. At the very least, protections will be needed for people who choose to forgo safe and effective therapeutic gene editing, and who choose not to participate in the gene editing enterprise.

ALTERNATIVE TREATMENTS AVAILABLE

In Canada, alternative treatments for symptoms of sickle cell disease currently exist, most notably haploidentical stem cell transplantation and hydroxyurea. Haploidentical stem cell transplantation is the most prominent treatment option for patients with sickle cell disease. This treatment has a high disease-free survival of >90% (17), but there is also the risk of graft-versus-host disease due to partial immune compatibility between donor and recipient (17). While hydroxyurea is not a one-time treatment like Casgevy (it must be taken daily in pill form) and cannot prevent long-term complications, it does not have any known significant side effects and has been effective in reducing symptoms for many people (19). However, hydroxyurea only delays fatality due to chronic irreversible systemic microvascular organ damage (mainly of the heart, kidney, and lung) (19). Further, existing treatments are (currently) less expensive than the treatment protocol involving Casgevy, making them more accessible to disadvantaged populations, and hydroxyurea also has the benefit of not requiring additional health care professionals or infrastructure (hospital rooms, transplant teams, etc.). Because of this, they seem less likely to contribute to the exacerbation of existing health inequalities (locally or globally), and do not require vast amounts of funding which could be used for other purposes.

A complete ethical analysis of Casgevy should include a comprehensive discussion of the benefits and harms compared with existing alternative treatments, and preferably include consultation with the public and key stakeholders, including people who have sickle cell disease.

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