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Human Germline Gene Editing: Points to Consider from a Canadian Perspective

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Please note that this document was originally created to inform the CIHR Standing Committee on Ethics at their June 2016 meeting.

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Human Germline Gene Editing: Points to Consider from a Canadian Perspective

Executive Summary

This document outlines Points to Consider about human germline gene editing and the applications of gene editing technologies in human embryos in the Canadian context. Gene editing in human germline cells is prohibited under the *Assisted Human Reproduction Act*. These Points to Consider are designed to inform future discussions in this area for research, teaching, and outreach.

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Introduction

Human gene editing is often divided into general categories:

- that which **does not** result in heritable genetic changes (i.e., changes to genes in human somatic cells),
- that which **does** result in heritable genetic changes (i.e., changes to human germ cells);
- that which **will not** be tested directly in humans (i.e., basic and preclinical research), and
- that which **will** be tested directly in humans (i.e., clinical research).

The ethical challenges raised by human gene editing in somatic cells in basic, preclinical and clinical research are addressed by existing frameworks. Such research has the potential for many therapeutic uses. In 2015, a one-year-old child in the UK with an aggressive form of acute lymphoblastic leukemia was treated with modified T-cells from donors.¹

Gene editing in the human germline causes heritable changes because it modifies the egg, sperm or embryo, passing DNA to subsequent generations. This document outlines points to consider in discussions about human germline gene editing in the Canadian context. While refraining from taking a positional stance, the CIHR Standing Committee on Ethics requested these Points to Consider to highlight relevant distinctions and considerations on this issue for CIHR and other relevant stakeholders.

Policy Context

The distinction between basic and preclinical research versus clinical research refers to modifications to germ cells that **are not** intended to be used to establish a pregnancy, versus modifications that **are** intended to establish a pregnancy. Gene editing in human germline cells is prohibited under the *Assisted Human Reproduction (AHR) Act*². This is similar to those jurisdictions signatory to the Council of Europe's "Oviedo Convention"³.

Other jurisdictions, such as the United Kingdom⁴, expressly regulate human germline gene editing in preclinical research, though the clinical use of germline gene editing is prohibited.

Canada is an outlier with respect to its strict criminal prohibition on all forms of human germline gene editing, though few jurisdictions expressly permit preclinical applications of the technologies or allow the creation of human embryos for purposes other than reproduction⁵.

Some international groups, such as the International Society for Stem Cell Research⁶, the Hinxtion⁷ Group, and the Organizing Committee of the International Summit on Human Gene Editing⁸ are recommending that basic and preclinical research be permitted with careful oversight, while the International Bioethics Committee of UNESCO⁹ calls for a moratorium on all human germline gene editing.

It is not known whether the *AHR Act* continues to reflect the values of Canadians in this respect, or if public sentiment has evolved. Recently published research on the perspective of the American public suggests that "the majority do not support gene editing in human embryos or germline cells, but the level of opposition varies depending on its goals"¹⁰, which may be a reasonable gauge of the Canadian perspective, though – to our knowledge – no data has been collected to support this inference.

On one hand, as noted by the Hinxtion Group⁷ "there is serious concern that genome editing technologies might be used in reproductive contexts long before there are data sufficient to support such use, and before the international community has had the opportunity to weigh the benefits and harms of moving forward."

On the other hand, if current prohibitions remain, Canadian researchers may fall behind on the international scene. Going forward, restrictive research policies may lead to medical tourism, as has been the case in stem cell research.¹⁷

If human germline gene editing were to be decriminalized, without being replaced by federal or provincial regulations, other options for regulation and guidance include:

- **Professional self-regulation:** Clinical practice standards could be applied to human germline gene editing, which could fall to those responsible for medical licensing standards, as well as the Canadian Medical Association (CMA), the Society of Obstetrics and Gynecology of Canada (SOGC), the Canadian Fertility and Andrology Society (CFAS), and relevant provincial and territorial partners.

- **Funding policy:** Funding organizations could outline the conditions under which they would be willing to support research that involves human germline gene editing (for example, through provisions in the *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans*).

Basic and preclinical research using gene editing in human germline cells

Basic and preclinical research using gene editing in human germline cells, specifically embryos, has the potential to:

- inform the understanding of human development;
- improve assisted reproduction technologies;
- prevent pregnancy loss;
- inform the understanding of pluripotency and placenta, and the use of that knowledge to translational stem cell research.¹¹

Most studies could make use of early embryos that are no longer needed for reproduction and would not require the creation of human embryos for research purposes.¹² The creation of human embryos for research purposes is also prohibited by the *AHR Act*, though it may be permissible for the purpose of “improving (...) assisted reproduction procedures”².

It should be noted that fertility clinics are increasingly freezing embryos for future reproductive use at the blastocyst stage (day 5), rather than at an earlier stage (day 2)¹³, which subsequently limits the stage of development that can be studied. Thus, once earlier-stage embryos that have been frozen and are no longer needed for reproduction are no longer available, it may become necessary to create embryos in order to undertake such research.

Further, using single cell embryos (approximately 1 day-old, which would have to be created for research purposes) will be required for other studies (e.g., preclinical research on germline gene editing)¹² to control against mosaicism (i.e., where not all cells are modified).

Creating human embryos for research purposes in Canada would require changes to the *AHR Act*.

Clinical research using gene editing in human germline cells and potential subsequent clinical use of such cells

The primary benefit of using germline gene editing in humans is the prospect of disease prevention, particularly in monogenic dominant diseases, such as Huntington’s, or in recessive diseases where the parents are aware that they are carriers of a monogenic disease.

Germline gene editing could also have the potential to improve the efficiency of the procreation of “saviour siblings”: embryos chosen for transfer based on a match to the sibling could be

corrected to be disease-free should they also inherit genetic disease, potentially requiring fewer *in vitro* fertilization cycles to achieve pregnancy¹⁴.

There are important limitations of this approach to disease prevention:

- Avoiding devastating genetic diseases can be addressed by genetic testing and counselling of ALL couples to identify and assess risk. Most couples are unaware that they carry a genetic disease until an affected child is born.¹⁵
- Most Mendelian diseases can be prevented by undergoing *in vitro* fertilization and pre-implantation genetic diagnosis to select unaffected embryos.¹⁵ The others, while compelling, are extremely rare, presenting challenges in terms of development (e.g., determining acceptable clinical trial design)¹⁶, affecting the cost of treatment, and possibly raising questions of resource allocation.
- Due to the cost of gene editing techniques and the lack of public funding for them, clinical uses will likely be limited to those with the means to use them.

Further, the statement issued by the Organizing Committee of the International Human Gene Editing Summit⁸ enumerates the following concerns about the clinical application of human germline gene editing:

- *the risks of inaccurate editing (such as off-target mutations) and incomplete editing of the cells of early-stage embryos (mosaicism);*
- *the difficulty of predicting harmful effects that genetic changes may have under the wide range of circumstances experienced by the human population, including interactions with other genetic variants and with the environment;*
- *the obligation to consider implications for both the individual and the future generations who will carry the genetic alterations;*
- *the fact that, once introduced into the human population, genetic alterations would be difficult to remove and would not remain within any single community or country;*
- *the possibility that permanent genetic ‘enhancements’ to subsets of the population could exacerbate social inequities or be used coercively; and*
- *the moral and ethical considerations in purposefully altering human evolution using this technology.*

Hype is also emerging as a concern that can lead to medical tourism and costly unproven treatments¹⁷.

There is general consensus that the technology is not “sufficiently developed to consider human genome editing for clinical reproductive purposes at this time”⁷. However, while some argue that clinical uses of human germline gene editing should never proceed, the Hinxton Group and the Organizing Committee of the International Human Gene Editing Summit argue that it could eventually proceed “only under appropriate regulatory oversight”⁸. Their respective statements raise several points to consider should clinical uses of human germline gene editing be decriminalized in Canada:

- Much more preclinical research is needed;

- Extensive consultations with various stakeholder groups are needed to determine if this would be a suitable approach and at what point it might become appropriate;
- “As with most emerging biomedical technologies, human genome editing raises substantial concerns about justice and equity, such as questions about for whom treatments are developed and who will have access. (...) Attention should be paid to how applications are prioritized and based on what criteria, such as magnitude and frequency of need, nature of the genetic change being made, anticipated feasibility, and the presence of accepted alternative approaches—all of which bear directly on the risk/benefit analysis and the justification for any given use.”⁷

Conclusion

These Points to Consider can inform future discussions with respect to subsequent activities (e.g., issues scan, consultation with researchers, public engagement) in this area as well as future approaches towards the use of gene editing in humans.

For more information about Ethics at CIHR and the Standing Committee on Ethics, please visit <http://www.cihr-irsc.gc.ca/e/2891.html>, or contact ethics-ethique@cihr-irsc.gc.ca.

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