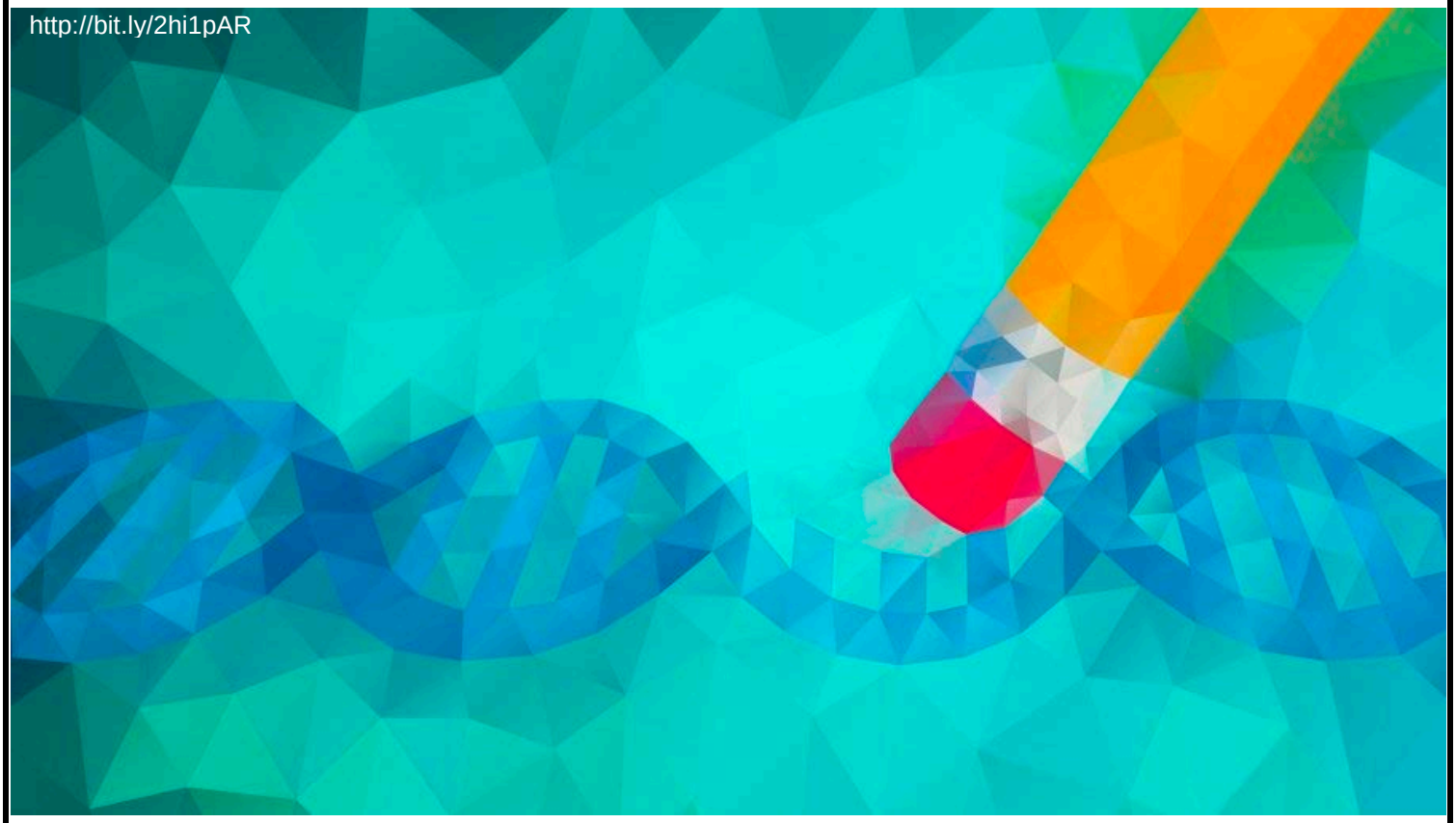
Human Genome Editing

ETHICAL AND POLICY CONSIDERATIONS

– POLICY BRIEF –



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CENTRE OF GENOMICS AND POLICY (CGP)

MCGILL UNIVERSITY AND GÉNOME QUÉBEC INNOVATION CENTRE

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GenomeQuébec

CGP Centre of Genomics and Policy
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Génome Québec

Established in 2000, Génome Québec is a private, non-profit organization with its headquarters in Montréal. Its mission is to catalyze the development and excellence of genomics research and promote its integration and democratization. Génome Québec is recognized for its assertive leadership in promoting an optimal environment conducive to the advancement of genomics research and the integration of its benefits into priority sectors for Québec. A strong culture of ethics drives its mission, providing assurance that research will be conducted within ethical guidelines acceptable to society at large.

To promote a better understanding and support decision making regarding the complex issues raised by human genome editing, Génome Québec asked the Centre of Genomics and Policy to produce a Policy Brief on the subject. This document is the result of analysis and research conducted by the authors of the CGP. The views expressed herein do not necessarily reflect those of Génome Québec.

Centre of Genomics and Policy (CGP)

An integral part of the McGill University and Génome Québec Innovation Centre, the Centre of Genomics and Policy (CGP) is at the crossroads of the legal, medical and public policy fields. Within a multidisciplinary perspective and in cooperation with national and international partners, the CGP analyzes the ethical, legal and social norms that influence the many aspects involved in health prevention, protection and promotion. The CGP is currently conducting research on the ethical and legal issues involved in several areas of genomics research, including personalized health, pediatrics, cancer research, gene therapy, biobanks (population genetics) and the impact of new technologies on privacy.

About the Authors

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Table of Contents

Summary

The advent of CRISPR-Cas9, the 2015 scientific breakthrough (*Science*), gave rise to both hope for new therapies and for the prevention of genetic diseases, but also concerns regarding its potential use for enhancement or eugenic purposes (Travis, 2015).

Genome editing[1] is a way of making specific changes to the DNA of an organism. These changes can be made to either somatic cells (i.e. somatic modification) or germline cells (i.e. germline modification). Somatic modification is currently being used in the context of gene therapy, but germline modification affecting hereditary conditions is contentious (i.e. the fact that genetic alterations can be passed down to the next generation) and generally prohibited. For these reasons, our prospective analysis will primarily focus on germline modification.

The potential clinical applications of genome editing fall under three categories: a) to cure patients; b) to avoid transmission of hereditary conditions; and c) to enhance (non-medical purposes). In Canada, there is currently no regulations or guidelines particular to somatic modification for therapeutic purposes. However, gene therapy products, generally considered "biological drugs," are governed by Health Canada's *Food and Drug Regulations*, which ensure clinical safety and efficacy. Although currently covered by professionals (medical) and regulatory frameworks, the translation of somatic modifications into clinical trials for therapeutic purposes still faces certain safety challenges and hurdles (e.g., research ethics board approval). Moreover, there remains a persistent gap in public understanding that needs to be addressed.

In contrast, germline modification is criminally banned in Canada with little distinction (or clarification) made between the research or possible clinical contexts. The province of Québec has not yet developed any legislation or guidance surrounding human genome editing (either somatic or germline) even though it is the only province to have passed legislation on medically assisted reproduction. In addition, there is a lack of empirical data, qualitative or quantitative, assessing public perceptions and attitudes towards either somatic or germline human genome editing (somatic or germline).

While somatic human genome modification may soon be used in clinical trials in Québec, there has been a paucity of discussion surrounding germline modification, even at the stage of basic research. Consequently, an examination of Québec and Canadian policies surrounding genome editing technologies (with a primary focus on germline), the legislative and policy frameworks governing these technologies and their ethical, legal and social implications

[1]We suggest the use of this term within the Québec context, but this does not exclude other terms, such as gene editing, human genome modification or human genome editing.

is merited. In summary, a review of Québec and Canadian policies on genome editing technologies — and their ethical, legal and social implications — seems to be in order (Knoppers et al., 2017a; Nuffield Council on Bioethics, 2016).

Recommendations to Policymakers

Criminal bans are not a suitable instrument to regulate research on reproductive technologies. Consequently, the following actions should be considered:

1. Review the current criminal ban on germline modification.
2. Permit the modification of human germ cells in the context of basic and pre-clinical research.
3. Limit any future clinical trials involving either somatic or germline modifications to serious diseases.
4. Outline the criteria used to define a “serious” disease.
5. Monitor any future clinical trials using germline modification via rigorous oversight.
6. Encourage an inclusive approach to policymaking that recognizes a diversity of opinions and voices.
7. Include the Collège des médecins du Québec, the Network of Applied Genetic Medicine (RMGA) and the ThéCell Network in all discussions pertaining to the regulation of human genome editing.
8. Undertake a principled and pragmatic approach to discussions about the future of human genome editing.

Scientific, Ethical and Legal Context

Genome editing is a technique used to make specific changes to the DNA of an organism. To this end, molecules, such as zinc finger nucleases (ZFN) and transcription activator-like effector nucleases (TALENs), are part of the biochemical agents used to introduce targeted alterations into the genetic code of an organism (Gaj, Gersbach, & Barbas, 2013). Joining these two molecules is CRISPR-Cas9 (clustered regularly interspaced short palindromic repeats), a molecular complex based on a new revolutionary technology whose effectiveness, affordability and precision have led to major scientific advances (Li, Tu, Yang, & Li, 2017).

Using an enzyme and a guide RNA, CRISPR-Cas9 complex targets a specific sequence in the genetic code resulting in the addition, deletion or alteration of a specific sequence for research purposes or to correct a disease-causing genetic mutation (Ma, Zhang, & Huang, 2014). These changes can either be made to somatic cells, meaning that the changes made will be limited to the treated individual and will not affect future offspring (i.e. somatic modification) or to germ cells, meaning that the changes are heritable and can potentially be passed on to future generations (i.e. germline modification) (NAS, 2017). Somatic modification has been deemed ethically acceptable in the context of gene therapy (even if safety concerns remain) and several clinical trials are already underway. Germline modification, however, is more contentious and generally has been prohibited (NAS, 2017).

Context Surrounding the Creation and Adoption of the *Assisted Human Reproduction Act* (2004)

In 1993, the Royal Commission on New Reproductive Technologies published a report entitled *Proceed with Care*. It recommended a federal ban on several activities and focused on the need for a regulatory framework that would ensure the safe and ethical provision of new reproductive technologies. As a result, a voluntary moratorium was introduced on nine of the practices presented in the report, including germline modification – the first step towards the current ban (Norris & Tiedemann, 2011). The decade following the publication of the Royal Commission Report paved the way for the enactment of Canada's 2004 *Assisted Human Reproduction Act* (AHRA). Debate during this decade was fuelled by fear of dystopian visions and the spectre of possible human reproductive cloning (Royal Commission, 1993). It is against this backdrop that an approach based on criminal law was adopted by the AHRA, prohibiting a wide range of activities, including the creation of embryos (s. 5 (1) (b)) and chimeras (s. 5 (1) (i)) for research purposes and germline modifications (s. 5 (1) (f)), across Canada. As such today, human genome editing for research purposes and clinical applications is addressed under a

combination of the AHRA, other Canadian regulation and legislation (where applicable), and the *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* (TCPS 2) (Social Sciences and Humanities Research Council of Canada, Natural Sciences and Engineering Research Council of Canada & Canadian Institutes of Health Research, 2014; Knoppers et al., 2017a).

Germline modification is currently prohibited under the AHRA, which states, "No person shall knowingly […] alter the genome of a cell of a human being or *in vitro* embryo such that the alteration is capable of being transmitted to descendants" (s. 5 (1) (f)). This criminal offence is flanked by sanctions ranging from a fine up to $500,000 to imprisonment for up to ten years, or both (s. 60 AHRA). The TCPS 2 defines genetic modification and reiterates the ban on germline modification set out in the AHRA (chapter 13). Worthy of note is the lack of clarity surrounding the scope of this ban. For example, should it apply to non-implantation research (Knoppers et al., 2017a)? To clinical applications? To both?

Shortly after gaining Royal Assent, the province of Québec challenged the validity of the AHRA on the grounds that the federal government had overstepped its legislative authority. In 2010, the Supreme Court of Canada ruled in favour of Québec with the result that several provisions of the AHRA were invalidated, namely regarding the creation of a federal licensing and control system, but maintaining the criminal sanctions. However, since 2010, the provinces have continued to exercise their right to regulate health including the oversight of *in vitro* fertilization clinics (*Reference Re Assisted Human Reproduction Act*, 2010).

It is interesting to note that while germline modification has been the focus of recent debate on the applications of CRISPR-Cas9, somatic modification may also require broader discussion given its current use in both the research and clinical trials contexts. Consequently, the risks and benefits associated with somatic applications require additional, explicit guidance regarding safety, traceability and quality. Moreover, given the social and contextual sensitivity of the ethical, legal and social implications, a distinction should be made between somatic modifications in an adult population versus a pediatric population. These implications will also need to be well addressed and considered when moving forward.

Ethical, Legal and Social Issues

A major safety and efficacy concern with genome editing generally has to do with managing and reducing mosaicisms and off-target mutations that may result from the use of CRISPR-Cas9. In addition, considerations of social justice (i.e., equitable access to the technology) and harms (e.g., new forms of discrimination, inequality and societal conflict) loom

large. The need for meaningful and substantial public engagement is also important to address. Furthermore, ethical concerns specific to germline modifications involve potential irrevocable and unforeseen risks for future generations; the preservation of human diversity and individuality; the respect for reproductive freedom and autonomy; and the protection of the well-being of children born of the technology (i.e. best interests). Despite these concerns, the international community is beginning to recognize the need for pre-implantation research in this area. In this respect, appropriate oversight mechanisms need to be implemented (NAS, 2017).

Canada has signed the *Universal Declaration of Human Rights* (General Assembly of the United Nations, 1948, art. 27) and signed and ratified the *International Covenant on Economic, Social and Cultural Rights* (United Nations Office of the High Commissioner, 1976, art. 15 (b)), which promulgate the right for all citizens "to enjoy the benefits of scientific progress and its applications." This legally actionable human right must be respected in a responsible and transparent manner. The application of this right would guarantee scientific freedom as a core principle of liberal democracies and instill the obligation for governments to ensure access to new technologies, while allowing Canadian researchers to be engaged in the international scientific community.

Issues and Evidence

Series of Workshops Organized by the Centre of Genomics and Policy (CGP) in Collaboration with the Stem Cell Network (SCN)

In 2016-2017, the CGP (McGill University), in collaboration with the SCN, organized four workshops looking at different aspects of the AHRA in order to propose amendments and revisit certain provisions based on the rapid evolution of technology and the changing societal perspectives since 2004. Indeed, the AHRA itself contained a clause mandating revision every five years, but this did not occur. During the workshops, the following topics were covered: human genome editing, mitochondrial replacement therapy, general research using human embryos and regulatory aspects (e.g., chimeras, cloning, somatic cell nuclear transfer, novel and emerging stem cell technologies) as well as pre-implantation genetic diagnosis. Each workshop brought together 21 to 30 experts on science, ethics, law, policy and medicine, as well as government observers, end users and members of the general public. The goal of these workshops was to gain insights and stimulate discussion surrounding the issue at hand within a Canadian context and to propose potential avenues forward with regard to policy recommendations and possible modifications to the Canadian regulatory framework. These discussions culminated in a set of recommendations specific to each technology (Knoppers et

al., 2017 a; Knoppers et al., 2017b; Ogbogu et al., 2018; Ravitsky et al., 2018 [in preparation]) all feeding into the final Consensus Statement, which was presented at the Till & McCulloch Meetings in November 2017 in Mont-Tremblant, Québec. For the purpose of this report, the focus will be on the first of the workshops held in August 2016 on human genome editing.

Professional Policies and Guidelines since 2015

In 2015, international discussions surrounding human genome editing, using CRISPR-Cas9, were catalyzed by the publication of two "controversial" studies performed in China. Both studies involved attempts at altering faulty genes in non-viable human embryos: one was responsible for a heritable genetic disorder; the other played a role in the prevention of human immunodeficiency virus (HIV) (Kang et al., 2016; Liang et al., 2015). Since that time, there has been an influx in the development of national and international policy statements and guidelines regarding germline modification (Appendix 1). Most of these statements resemble one another in that they are typically supportive of human genome editing (from a broad standpoint) for research purposes, as long as such research is justified and supported by ethical review and oversight to ensure both the advancement of these technologies and a better understanding of the associated safety and ethical concerns. The majority of these statements have also been supportive of a moratorium or maintaining the ban on clinical applications of germline modification called for by the International Summit on Human Gene Editing in 2015, as safety and ethical concerns still have to be addressed. The International Summit concluded that it would be "irresponsible to proceed with any clinical use of germline editing unless and until (i) the relevant safety and efficacy issues have been resolved… and (ii) there is broad societal consensus about the appropriateness of the proposed application." (Organizing Committee for the International Summit on Human Gene Editing, 2015).

Within the United States (U.S.), although no national ban exists, the National Institutes of Health (NIH) has stated that it will not provide funding for any research involving the use of genome editing technologies on human embryos (Collins, 2015). Yet, the 2017 report entitled "Human Genome Editing: Science, Ethics and Governance" of the National Academies of Sciences, Engineering and Medicine (hereinafter the NAS Report) maintains that basic research (3.1) on human genome editing (germline modification) as well as somatic genome editing research (4.1) should be allowed to proceed under existing regulatory processes for human gene therapy (NAS, 2017). It purports that clinical trials involving human genome editing of somatic cells should be limited to treatment and preventive purposes (4.2). The report situates such trials within the existing regulatory frameworks and ethical norms that currently govern

somatic gene therapy and its clinical applications. It also notes that the technical context and intended use of somatic gene editing should be evaluated. With regard to germline modification, it is the first report to adopt a more progressive approach, stating that clinical trials may be a possibility in the limited context of treating or preventing serious diseases, provided that specific safety criteria are met and rigorous oversight is in place (5.1). The report does, however, conclude that genome editing should not be used for non-medical purposes at this time (6.1-6.2), while emphasizing the importance of public discussion and debate to explore the social impacts and inform policy for uses other than treatment or prevention of disease. Interestingly, the American Society of Human Genetics (Ormond et al., 2017), as well as the European Society of Human Genetics (ESHG) and the European Society of Human Reproduction and Embryology (ESHRE) (de Wert et al., 2018) also support this same direction of allowing "cautious" pre-clinical research on germline modification. This is also the position taken by the CGP/SCN workshops, as we shall see below.

Scientific Progress

Research using genome editing has been on the rise with China leading the way in terms of volume of studies and with the U.S. leading in terms of successful results. As mentioned above, it was the published research of two Chinese teams that triggered the international policy debates (Kang et al., 2016; Liang et al., 2015). Both of these studies used non-viable human embryos, which were subsequently destroyed. The results, however, were not as positive as anticipated given the higher-than-expected number of off-target mutations and mosaicism. Recently, it has been announced that another team of Chinese scientists will be moving forward with the first human clinical trial using CRISPR (i.e. somatic modification) (Le Page, 2017). In the United Kingdom (UK), the Human Fertility and Embryology Authority (HFEA) approved the first research licensing application for human embryo genome editing at the blastocyst stage back in 2016. This was a licence application for research purposes only with the aim of better understanding non-implantation and miscarriages (Cressey, Abbott, & Ledford, 2015). In Sweden, research has been undertaken in healthy human embryos, which is a first, in the hopes of understanding what role certain genes play and potentially uncovering new information about infertility, miscarriages and human embryonic stem cells (Stein, 2016). Similar to the approach taken in the UK, Japan has granted approval to a research team to use genome editing on fertilized human eggs for research purposes, but not clinical applications. The purpose of the study being to identify the genes involved in the early growth phase and

ultimately to develop treatments for congenital diseases (Gallego, 2016; Japan panel greenlights gene editing of human eggs for basic study, 2016).

In June 2016, the Advisory Committee of the NIH approved the first clinical trial using CRISPR-Cas9 in the U.S. (Begley, 2016; Kaiser, 2016; Kulkarni, 2016); its goal being to assess the safety of CRISPR use in humans. Most recently dominating the media, however, have been the results from a study aimed at correcting a genetic mutation causing a common and deadly heart disorder (Ma et al., 2017). This study, the first to use CRISPR-Cas9 to successfully correct genes in human embryos, represents a breakthrough for the evaluation of the safety and efficacy of genome editing in viable human embryos, albeit, in the research context. The findings generated by the study are important as they begin to address the relevant safety and efficacy issues related to germline modification and its potential future therapeutic applications. The potential to repair mutations and perhaps one day, with germline modification, to prevent the reproductive transmission of heritable diseases is an exciting and promising possibility, especially for severe monogenic diseases (Pruden, 2017; Servick, 2017a). However, as with any "first of" study, it has been met with scepticism (Servick, 2017b) and further research is needed to confirm the safety of this technology before a move to the clinical context for germline modification can even be considered. Following this study, we can expect that other researchers will attempt to replicate the results in order to further demonstrate/confirm the safety and efficacy of the technology for the repair of genetic mutations in human embryos.

Public Perceptions

Over the past two decades, the criminal ban on genome editing has generally resulted in a lack of ongoing public debate on the issue – until the advent of CRISPR that is. Thus, over the past two years, there has been a sudden, exponential increase in media coverage of human genome editing, often associated with phrases like "editing humanity," "DNA revolution," "eugenics is back," "engineering the human race," and "the end of life as we know it." These terms tend to both reveal the social representations of genome editing and to perpetuate the current hype, thereby exacerbating the fears surrounding the technology.

One thing is certain, there is a lack of data on public perceptions towards genome editing in Québec. Only a few quantitative studies evaluating public perceptions have been published and most are U.S. centred. Findings from one of the initial surveys conducted by the Pew Research Center show that Americans are rather conservative when it comes to genome editing, with more than 50% of respondents opposed to the idea of genetic enhancements that would give babies a much-reduced disease risk, would improve cognitive abilities, or would

much improve physical abilities (Funk, 2017; Funk, Kennedy, & Podrebarac Sciupac, 2016). In contrast to this study, others demonstrate greater support for the use of genome editing in certain circumstances (Blendon, Gorski, & Benson, 2016; McCaughey et al., 2016; Scheufele et al., 2017; Weisberg, Badgio, & Chatterjee, 2017). Generally, participants seem comfortable with the use of genome editing in humans to treat disease (i.e. somatic modification) or to prevent a life-threatening or debilitating disease in future generations (i.e. germline modification), but oppose the use of the technology to enhance non-disease characteristics (i.e. genetic enhancement). Religion, risk, ethnicity, political affiliation and gender are factors that appear to influence the views of participants. This trend may be indicative of a change in public attitudes towards a more positive, albeit cautious, view of human genome editing.

Comparative Legal Analysis

The CGP conducted a comparative legal and policy analysis of six different reproductive technologies – including germline modification and human somatic gene therapy – across a sample of 16 countries to get a global snapshot of the spectrum of policy and legislative approaches (from restrictive to permissive) (Isasi, Kleiderman, & Knoppers, 2016). See Appendix 2.

International Approaches: The *Universal Declaration on the Human Genome and Human Rights* refers to the principles of dignity, diversity and equality, and supports the concept of the human genome as a symbol of humanity's heritage (art. 1, United Nations Educational, Scientific and Cultural Organization, 1997). Yet it does not specifically single out genome editing as a practice that is contrary to human dignity. In 2015, UNESCO's International Bioethics Committee (IBC) published its Report on Updating its Reflection on the Human Genome and Human Rights in which it recommends a moratorium on human germline modification until concerns about its safety and efficacy have been addressed (International Bioethics Committee, 2015).

Europe: The *Oviedo Convention*, however, specifically prohibits germline modification stating, "an intervention seeking to modify the human genome may only be undertaken for preventive, diagnostic or therapeutic purposes and only if its aim is not to introduce any modification in the genome of any descendants" (art. 13, Council of Europe, 1997). It also mentions the need for public debate surrounding emerging technologies (art. 28). In its Statement on Genome Editing Technologies, the Council of Europe refers back to the *Oviedo Convention* as providing the necessary principles to guide discussions surrounding genome editing, while agreeing to

undertake the examination of the ethical and legal issues stemming from genome editing technologies (Committee on Bioethics, 2015).

In May 2016, the European Union (EU) revised its *Clinical Trials Regulation* (EU No 536/2014) and maintained the view that gene therapy trials that result in alterations to an individual's germline should continue to be prohibited (the European Parliament and the Council of the European Union, 2014). In addition, most European countries prohibit germline modifications (e.g., Belgium, France, Germany, the Netherlands). Germany has adopted a broad bottom up ban on germline modifications that extends to both research (i.e. embryo research) and reproductive purposes (*The German Embryo Protection Act*, 1990). In France and the Netherlands, the bans are more specific in scope, clearly prohibiting germline modifications for reproductive purposes and requiring intent on the part of the individual, without prohibiting research *per se* (*Act containing rules relating to the use of gametes and embryos*, 2002; Code civil, 1804). As is the case in China, the United Kingdom has adopted a more permissive approach to germline modifications. It bans such modifications for reproductive purposes, but regulates research purposes via a licensing process overseen by the Human Fertilization and Embryology Authority (*Human Fertilization and Embryology Act*, 1990).

North America: The United States does not have federal legislation or guidance surrounding genome editing. However, the NIH has stated that it would not provide funding for research involving the use of genome editing technologies in human embryos.

Mexico: In Mexico, the *Penal Code of the Federal District of Mexico* (2002) prohibits germline modifications for purposes other than to treat or prevent serious diseases (Isasi et al., 2016).

Australia/New Zealand: Similar to Canada, Australia has made germline modification a criminal offence as stipulated in article 15 of the *Prohibition of Human Cloning for Reproduction Act 2002* and the *Regulation of Human Embryo Research Amendment Act 2006* (2006). It is punishable by imprisonment for up to 15 years. However, the *Act* adds the notion of intent to the mix, meaning that to be considered a criminal offence, genome editing must involve the intent to pass on a modification to future generations. To date, no legislation or policy documentation on genome editing has been adopted in New Zealand.

Middle East: Like France and the Netherlands, Israel has specifically prohibited reproductive applications of germline modifications, while adopting a more permissive approach to research applications. The *Prohibition of Genetic Intervention (Human Cloning and Genetic Manipulation of Reproductive Cells) Law 5759-1999* (1999) sets out a moratorium on "using reproductive

cells that have undergone a permanent intentional genetic modification (Germ Line Gene Therapy) in order to cause the creation of a person" section 3 (2). However, an exception does exist whereby a licence to conduct a prohibited genetic intervention may be obtained, provided that "human dignity will not be prejudiced" (section 5).

Asia, South America and Africa: China has adopted a more permissive approach towards genome editing, which covers research for reproductive purposes, while not explicitly prohibiting clinical translation (Isasi et al., 2016). Singapore and Japan both have guidelines in place banning germline modifications as there is a lack of evidence to support the safety and efficacy of the technology (Bioethics Advisory Committee - Singapore, 2015; Ministry of Health Labour and Welfare, 2002). South Korea's *Bioethics and Safety Act* states, "no gene therapy shall be applied to an embryo, ovum, or fetus." (art. 47 (2)). Research on gene therapy may be conducted provided it meets the following two conditions: 1) be "research on a therapy for a hereditary disease, Acquired Immune Deficiency Syndrome (AIDS), or any other disease that threatens one's life or causes a severe disability"; 2) be "research on a therapy where there is no applicable therapy at present or the effect of a gene therapy is expected to be significantly better than other therapies". (art. 47 (1) (*Bioethics and Safety Act, 2013)*. In India, the the Indian Council of Medical Research's *Ethical Guidelines for Biomedical Research on Human Participants* prohibit germline modification for both therapeutic and enhancement purposes (Indian Council of Medical Research, 2006). In addition, somatic modification for therapeutic purposes may only be considered for the prevention or treatment of serious or life-threatening diseases, and provided that the following considerations have been taken into account: risk of harm, availability of counselling, future consequences and ethics approval.

Efficacy of Existing Approaches

There is currently no Canadian or Québec legislation or guidance (other than the AHRA) pertaining specifically to human genome editing. In Québec, the Commission de l'éthique en science et en technologie du Québec (CEST) is undertaking the preparation of a guidance document that will outline a set of recommendations to be considered when discussing human genome modification. In 2010, the CEST published a position statement entitled: "Ethics and Assisted Procreation: Guidelines for the Donation of Gametes and Embryos, Surrogacy and Preimplantation Genetic Diagnosis" that focused on issues within the realm of assisted reproduction (Commission de l'éthique, de la science et de la technologie, 2010). Québec is the only province or territory in Canada to have passed legislation on the clinical and research

activities associated with human reproduction in its *Act respecting clinical and research activities related to procreation* (2010; O'Neill & Blackmer, 2015).

Ironically, the current outright criminal bans on germline modification of the last decades (including in Canada) have actually foreclosed and silenced public debate as the issues were presumed to have been "settled." Thus, the suitability of criminal law as a policy tool for science and societal responses to actual or future technologies must be put back into question. It is only natural that a society's initial reaction is one of fear of the unknown, particularly surrounding disruptive technologies. As such, it should come as no surprise that the immediate response has been to prohibit rather than to regulate.

In 1982, the Law Reform Commission of Canada noted that criminal law should only be used for "conduct which is culpable, seriously harmful, and generally conceived of as deserving of punishment," and that it should be "an instrument of last resort" (*The criminal law in Canadian Society*, 1982). In the context of science, criminal prohibitions are considered to be suboptimal policy tools as they are "inflexible, stifle public debate, and hinder responsiveness to the evolving nature of science and societal attitudes" (Caulfield, 2002). In contrast, moratoria allow for a time-limited halt on any research, until further evidence is collected on the safety, efficacy and ethical implications of the technology that is to be regulated. That being said, both bans and moratoria "may offer the illusion of finality and safety while halting research required to move forward and validate innovation" (Knoppers et al., 2017a).

In considering the regulatory approach in Québec, article 10 of its *Act respecting clinical and research activities relating to assisted procreation* states that "in order to raise the quality, safety and ethical standards of assisted procreation activities, the Collège des médecins du Québec draws up guidelines on assisted procreation and ensures that they are followed." Consequently, it would be advisable to include the Collège des médecins du Québec and other groups, such as the Network of Applied Genetic Medicine (RMGA) and ThéCell Network, in any and all discussions on regulating genome editing. In addition, it may be reasonable to consider a role for the Stem Cell Oversight Committee (SCOC) of the Canadian Institutes of Health Research (CIHR), whose current mandate includes reviewing human stem cell research applications to ensure compliance with the TCPS 2 (2014) and providing advice to the CIHR Governing Council concerning the ethical, scientific and legal issues surrounding human stem cell research and potential clinical translation. In this respect, foreseeing a regulatory role for SCOC would be a possible solution. Its mandate could be expanded to include oversight and possible licensing mechanisms and processes for genome editing research to be evaluated on a case-by-case basis.

Recommendations

Criminal bans are not a suitable instrument to regulate research on reproductive technologies. Consequently, the following actions should be considered:

1. Review Canada's criminal ban on germline modification in order to consider different approaches and policy tools to address the promises and challenges of human genome editing.
2. Permit the modification of human germ cells in the context of basic and pre-clinical research in Québec and Canada. There is a scientific and societal value in promoting research, including research that may involve germline modification techniques in human embryos or gametes prior to the stage of implantation[2].
3. Limit any future clinical trials involving either somatic or germline modifications to serious diseases, and only consider germline modification as a "last" resort (i.e. when no other reasonable alternatives exist), as recommended by the National Academies of Sciences, Engineering and Medicine in their 2017 Report.
4. Outline, clearly and objectively, the criteria/attributes to be used to define a "serious" disease. This determination is not only a medical one. It should remain sensitive to and take into account the perspectives of relevant stakeholders, including affected individuals, their families and communities.
5. Create a rigorous oversight system should germline modification proceed to clinical trials one day.
6. Encourage an inclusive approach to policymaking that recognizes a diversity of opinions and voices. However, policymakers should remain cautious regarding the use of data about public perceptions of emerging technologies. Perhaps Québec can play an instrumental role in initiating and encouraging the provinces to start discussions on how to move this forward in Canada.
7. Include the Collège des médecins du Québec, the Network of Applied Genetic Medicine (RMGA) and the ThéCell Network in all discussions pertaining to the regulation of human genome editing (e.g., in the development of guidelines and best practices).

   At a federal level, it may be the Stem Cell Oversight Committee (reconstituted as a regulatory body) that would be best placed to develop oversight and possible licensing mechanisms and processes for the use of genome editing in a research context.

[2] Pulled from Knoppers et al., 2017a.

8. Undertake a principled and pragmatic approach to discussions about future advances in human genome editing, including possible transition to the clinical context[2].

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Appendix 1: Summary of Policy Recommendations on Germline Modification

This table draws from research published in the following articles:

a) Ormond et al. 2017. Human germline genome editing. *The American Journal of Human Genetics*, *101* (2), 167-176

b) Isasi, R., Kleiderman, E., & Knoppers, B. M. (2016). Editing policy to fit the genome? *Science*, *351* (6271), 337-339.

	Basic research should be permitted	**Preclinical research** should be permitted	**Clinical applications** should not currently be permitted	**Clinical applications** could be considered if… 1) Safe and efficiency 2) Social consensus 3) Monitoring 4) Medical justification	Encourage **public participation**
Académie nationale de médecine [France]	X	X	X	1	X
Academy of Medical Science, Medical Research Council, Wellcome Trust, Association of Medical Research Charities, Biotechnology and Biological Sciences Research Council [United Kingdom]	X	X	X	1	X
ACMG			X	1, 2	X
ASHG	X	X	X	1, 2, 3, 4	X
ASGCT and JSGT [United States and Japan]	X		X	1, 2	X
EASAC [national]	X	X	X	1, 2	X
EGE [national]	moratorium		X	1, 2, 3	X
Hinxton Group [United Kingdom]	X		X	1, 2, 3	X
International Summit on Human Gene Editing	X	X	X	1, 2, 3	X
ISSCR [international]	X		X	1, 2	X
Leopoldina Nationale Akademie der Wissenschaften [Germany]	X	X	X	1	X
NAS [United States]	X	X	X	1, 2, 3, 4	X
NIH [US]	No funding		X		
UNESCO [international]			X	1	X

Reference for Appendix 1:

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(Jointly written and affirmed by the National Society of Genetic Counselors (NSGC), Canadian Association of Genetic Counsellors (CAGC), International Genetic Epidemiology Society (IGES), Association of Genetic Nurses and Counsellors (AGNC)).

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Appendix 2: Worldwide Normative Approaches Regarding Genetic Technologies

Image taken from Isasi, R., Kleiderman, E., & Knoppers, B. M. (2016). Editing policy to fit the genome? Science, 351 (6271), 337-339.