BRAVE NEW WORLD

Are we ready for human germline gene editing?

In April 2015, scientists in China shocked the world with the news that they used an exciting new tool called CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) to alter the genes of non-viable human embryos. Their published paper ignited an urgent need for a global discussion about the ethics of editing the human genome. We are at the dawn of a brave new world where designer babies will be possible, but is it right to tinker with the master code of humanity?

Genome modification has been around since the 1970s, but in the last few years, the CRISPR innovation has allowed researchers to cut precisely targeted sections of DNA and paste in new pieces. CRISPR allows for simpler, faster and cheaper research: what used to take millions of dollars and years to accomplish now costs about $2,000 and takes a few weeks. Thousands of labs around the world are using the tool to hunt for new treatments for people living with debilitating conditions caused by genetic mutations. For example, Dr. Ronald Cohn uses CRISPR extensively in his research program at The Hospital for Sick Children in Toronto to develop targeted treatments for children with Duchenne muscular dystrophy.

Gene editing of somatic cells, as with Cohn's research, can only impact people who receive the treatments. But using CRISPR to edit human eggs, sperm or embryos produces

Current Reproductive Technologies in Canada[6]

In vitro fertilization (IVF) includes:
- Ovarian stimulation and egg retrieval
- Sperm collection
- Fertilization and embryo culture
- Embryo transfer
- Progesterone supplementation
- Pregnancy test

Artificial insemination uses donor sperm to help women achieve a pregnancy. Two lab technologists work together to transfer specimens to cryopreservation tanks and document inventory to ensure safety, accuracy and compliance with Health Canada regulations.

Preimplantation genetic diagnosis/screening (PGD/PGS) involves testing embryos before implantation by IVF. Embryos showing these conditions or chromosomal abnormalities associated with IVF failure or miscarriage are discarded rather than implanted:
- Cystic Fibrosis
- Hemophilia
- Huntington's disease
- Marfan syndrome
- Muscular Dystrophy
- Thalassemia
- Tay-Sachs Disease
- Spinal Muscular Atrophy
- Sickle Cell Anemia
- Down Syndrome
- Edwards Syndrome

germline changes that are passed down to descendants, raising a host of ethical questions and considerations. The edits might be ideal to prevent a child from inheriting a devastating genetic condition like Huntington's disease, but where do we draw the line between disease prevention and human enhancement to optimize offspring for traits like intelligence, eye colour or height? Will this new technology be available to everyone who wants to have children? Will it disenfranchise people living with disabilities?

Françoise Baylis, PhD, a professor at Dalhousie University in Halifax, Nova Scotia and Canada's Research Chair in Bioethics and Philosophy says, "If we're talking about changing the species, surely that's worth having a conversation. The question is, who decides, and why do you think you should decide?"

In December 2015, leading scientists and bioethicists from around the world convened at the International Summit on Human Gene Editing in Washington, D.C., to discuss these ethical issues and outline a framework for how the global scientific community should move forward. At the conclusion of the Summit, the panel released a consensus statement with four recommendations.

Two of the points apply to reproductive medicine. "Intensive basic and preclinical research is clearly needed and should proceed, subject to appropriate legal and ethical rules and oversight, on:

(i) technologies for editing genetic sequences in human cells;
(ii) the potential benefits and risks of proposed clinical uses, and
(iii) understanding the biology of human embryos and germline cells.

If, in the process of research, early human embryos or germline cells undergo gene editing, the modified cells should not be used to establish a pregnancy; and Clinical Use – Germline… 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, based on appropriate understanding and balancing of risks, potential benefits, and alternatives, and

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(ii) there is broad societal consensus about the appropriateness of the proposed application. Moreover, any clinical use should proceed only under appropriate regulatory oversight…"[1]

Baylis, the only Canadian on the Summit's organizing committee, says it's critical to pay attention to the part of the statement that says, "unless and until there is a broad societal consensus." She says, "The issues with this technology should not be reduced to safety and efficacy alone to justify moving forward."

On their own, the issues are nowhere near resolved. Baylis says, "We don't know what safety and efficacy mean yet. For example, do you have to believe it's reversible for it to be considered safe and effective?" Researchers in China successfully produced the first twin baby monkeys with specific genetic mutations in January 2014. In their experiment, they disrupted three genes in 180 single-cell monkey embryos. Of the 83 embryos implanted, 10 pregnancies resulted, one of which led to the birth of the twins with two genetic mutations[2]. It was a compelling demonstration of genetic engineering, but we are a long way from knowing if experiments like these will be successful in the long term and if the results might translate to humans.

The Summit consensus statement outlined some of the anticipated risks, which include inaccurate editing that could cause off-target mutations, incomplete editing of early-stage embryos that could lead to mosaicism, a condition where cells in the same person have different DNA, and the difficulty of predicting how engineered genetic changes will interact with the environment[1]. Arthur Leader MD, FRCSC, founder of the Ottawa Fertility Centre and professor of obstetrics, gynecology and reproductive medicine at the University of Ottawa, says, "We still don't have enough knowledge to know what the downstream linkages are. You may be replacing a page in the book, but it may in fact change the whole story."

Baylis says, "the reality of the science is that ultimately, it's only going to happen in conjunction with an IVF clinic, putting the material back into women to reproduce. We need to remember to pay attention to the women who will be participants in this research as they are the ones who will be pregnant and give birth. Even before that, they are the sources of the raw material. It's not all that easy to get access to women's eggs, and yet we talk about it as if they're all lying around for people to pick up."

Broad societal consensus will be a difficult bridge to cross, given the different regulatory environments around the world. The United Kingdom's Human Fertilisation & Embryology Authority (HFEA) is very progressive. On January 14, 2016, developmental biologist Kathy Niakan of the Francis Crick Institute in London, received regulatory permission to modify human embryos using CRISPR/Cas9 gene editing

Three-Parent Babies

Mitochondrial DNA replacement therapy (MRT) is another new gene modification technology that leading ethicists, scientists and legal experts around the world are currently discussing. It prevents passing down a mitochondrial disease from mother to child. Mitochondrial diseases affect the mitochondria, tiny energy-producing structures found outside the nucleus of every body cell. MRT involves inserting the nucleus from the mother's egg cell into a donor's egg where the nucleus has been removed. IVF either before or after MRT produces an embryo that has genetic material from three parents.

Ethical issues include potential harms to egg providers, offspring, and future generations, and society as a whole.[7] Illegal in Canada under the AHRA, MRT was approved in the U.K. in October 2015. In the U.S., the approach is more cautious. In February 2016, the Institute of Medicine's Committee on the Ethical and Social Policy Considerations of Novel Technologies for the Prevention of Maternal Transmission of Mitochondrial DNA Diseases recommended that the FDA consider initial clinical investigations subject to certain conditions including limiting investigations to women who are at risk of passing on a serious mitochondrial disease to their offspring, the mutation is known to cause disease and the disease is predicted to be severe; and only male embryos will be transferred for gestation to avoid introducing germline changes until more is known.

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for research purposes. The HFEA approved her application with the requirement that the embryos will not be transferred to a woman's womb for implantation[3]. Niakan's research goal is to use CRISPR to determine which genes drive growth processes in early embryonic development, which could shed light on future infertility treatments. The approval process included a parliamentary vote and a lengthy review by the HFEA[4].

In Canada, we have a whole different regulatory framework. Currently, there are three reproductive technologies permitted in Canada under the *The Assisted Human Reproduction Act (AHRA)*: in vitro fertilization (IVF), artificial insemination and preimplantation genetic diagnosis/screening (PGD/PGS) to screen embryos for inherited diseases. (See sidebar on page 22 for more information.) Gene editing of eggs, sperm or embryos is explicitly prohibited under (AHRA: 2004; revised 2012) Section 5(1) f: *No person shall knowingly alter the genome of the cell of a human being or an in vitro embryo such that the alteration is capable of being transmitted to descendants.*

Leader says, "What's allowable in the U.K. is much broader than in Canada because they have a framework in place. The HFEA is satisfied that process for ethical oversight is in place and what goes on in lab clinics can be managed within that framework as long as you balance the consideration of the needs of science, ethics, and the impact of both on society. In Canada, we are left with prohibitions and no framework to proceed, until the legislation is revised at some future date." Baylis says that an outright ban is how most people are reading the act, however, she sees a wrinkle: "You could argue, and nobody has yet, whether 'capable' means you intended to transfer the embryo. If you don't intend to put it into a woman, then it could never be transmitted to descendants, and you are not affecting the germline."

Until the legislation changes in Canada, the prohibition on human gene editing means that Canadian researchers will miss out on a chance to participate in breakthrough research that could increase knowledge about treating and preventing serious diseases and illnesses as well as the causes of miscarriage, and developing new infertility treatments and more effective techniques for contraception, says Leader. In the meantime, medical laboratory technologists and scientists who wish to pursue research in reproductive medicine using these new technologies will have to go outside Canada or practice on non-humans.

The Summit's organizing committee concluded that there is a global need for an ongoing forum for the discussion of the ethics of human genome editing. Even though each jurisdiction will decide how to proceed with their different regulatory frameworks, "the human genome is shared among all nations."[1] Even though in Canada we are not currently participating directly, we will no doubt all be affected by how this brave new world unfolds.

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