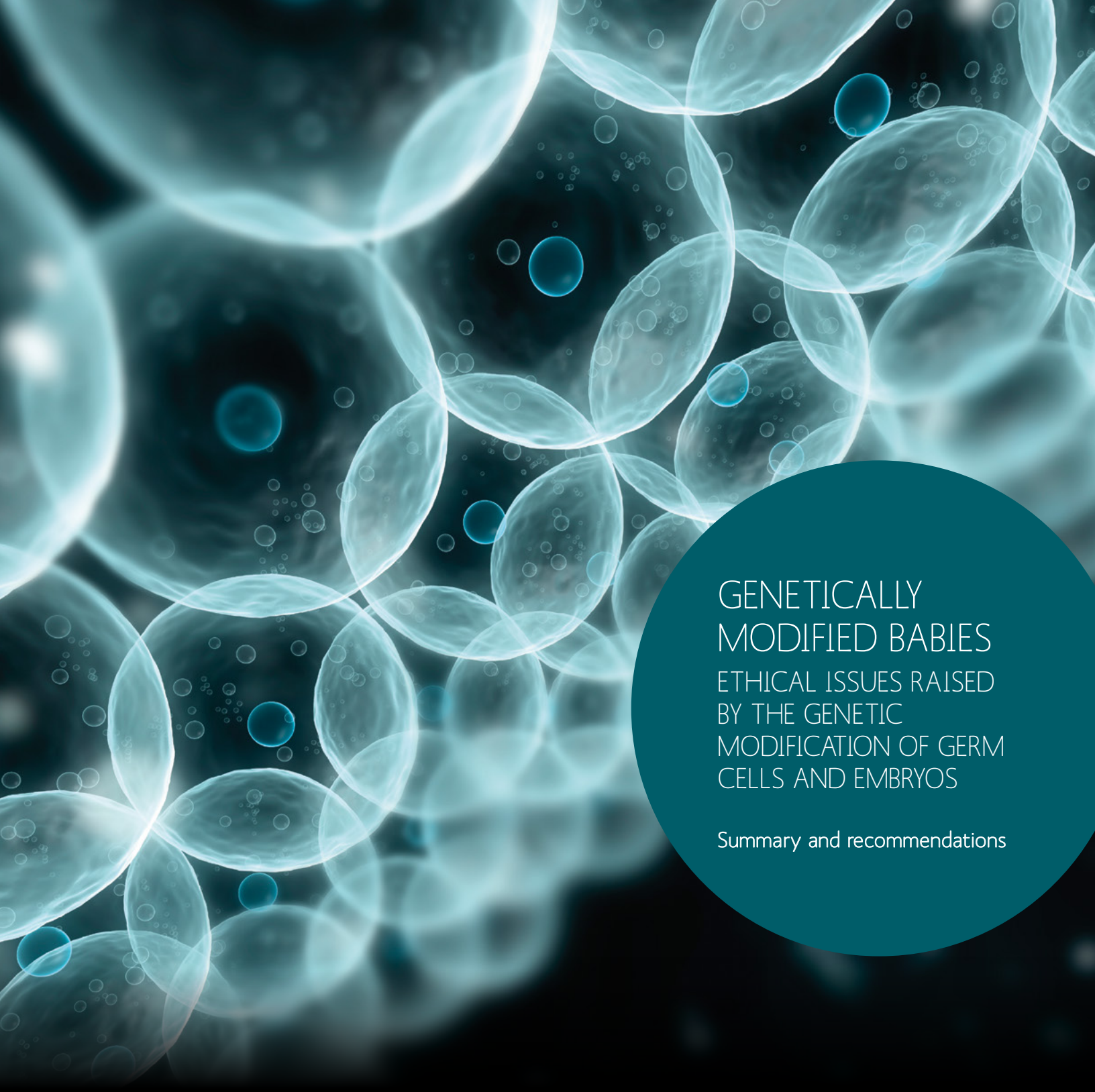

GENETICALLY MODIFIED BABIES

ETHICAL ISSUES RAISED BY THE GENETIC MODIFICATION OF GERM CELLS AND EMBRYOS

Summary and recommendations

COMMISSION DE L'ÉTHIQUE
EN SCIENCE ET EN TECHNOLOGIE

Québec

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Printing
IMPECCA image et impression

Position statement adopted at the 91st session of the
Commission de l'éthique en science
et en technologie on December 7, 2018.

Legal deposit
Bibliothèque et Archives nationales du Québec

ISBN: 978-2-550-83542-4 (Print version)
ISBN: 978-2-550-83541-7 (PDF version)

Commission
de l'éthique
en science
et en technologie
Québec

Québec City, February 18, 2019

Mr. Pierre Fitzgibbon
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Dear Sir,

I am pleased to enclose our recent position statement entitled: *Genetically Modified Babies – Ethical Issues Raised by the Genetic Modification of Germ Cells and Embryos*.

I hope it is to your satisfaction.

Yours sincerely,

Jocelyn Maclure
President of the Commission

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LIST OF ACRONYMS

Cas9	CRISPR associated protein 9
CRISPR	Clustered Regularly Interspaced Short Palindromic Repeats
DNA	Deoxyribonucleic acid
gRNA	Guide RNA
HFEA	Human Fertilisation and Embryology Authority
MST	Maternal spindle transfer
MT	Mitrochondrial transfer
mtDNA	Mitochondrial DNA
nDNA	Nuclear DNA
NASEM	National Academies of Sciences, Engineering, and Medicine
PBT	Polar body transfer
PBT1	Transfer of first polar body
PBT2	Transfer of second polar body
PB	Polar body
PB1	First polar body
PB2	Second polar body
PNT	Pronuclear transfer
RNA	Ribonucleic acid
SNP	Single-nucleotide polymorphism
TGEGCE	Targeted genome editing of germ cells and embryos

Introduction[1]

Genetic diseases are caused by gene* or chromosome* abnormalities. Some of these diseases are monogenic, meaning that they are associated with a defect in a single gene (e.g. Huntingdon's disease, pancreatic cystic fibrosis, myopathies). Approximately 10,000 monogenic diseases have been identified, and their global prevalence at birth is 10/1000. Other more complex diseases, described as polygenic, result from the combined effect of sets of genes and environmental factors (e.g. certain cancers, diabetes). Some diseases or genetic syndromes manifest at birth or in early childhood, whereas others, like Huntingdon's disease, occur later. Pathogenic mutations can affect nuclear DNA* (nDNA), or mitochondrial DNA (mtDNA). It is estimated that one person in 5,000 is a carrier of an mtDNA anomaly and one in 10,000 exhibits clinical symptoms of mitochondrial disease.

Recent developments in genetic engineering* and reproductive medicine have led to progress in genome* editing and as a result, it may eventually be possible to correct mutations responsible for diseases in humans. Applied to reproductive (germ*) cells and early embryos, these developments may allow people who are carriers of morbid mutations to give birth to unaffected children. Genetic engineering can be applied in fundamental and preclinical research (e.g. deactivation of genes to study their function [to understand embryo development], creation of disease models). Some authors also believe that it will, in the future, be necessary to use genetic modification for enhancement purposes, to help the human species resist pathogenic micro-organisms and survive in an increasingly hostile environment. Two types of technology are currently being researched and discussed extensively: targeted gene editing (e.g. CRISPR-Cas9) and mitochondrial transfer.

1. Targeted Gene Editing and Mitochondrial Transfer

Targeted gene editing involves intentionally modifying DNA in order to change specific structural or functional characteristics in an organism. Its purpose is to deactivate, modify, remove or replace genes*. When applied to germ cells and embryos at a very early development stage, modifications are genetically transmissible to descendants.

Mitochondrial transfer consists in creating an embryo with the mitochondria* of a woman other than the mother. This involves transferring the mother's nuclear DNA into a donor egg with healthy mitochondria, from which the nuclear DNA has previously been removed. These modifications are genetically transmissible by the mother.

1 In this summary, terms defined in the glossary are denoted by an asterisk (*) when they first occur in the text.

One of the main factors that might cause future parents to make use of technologies such as targeted gene editing or mitochondrial transfer is the desire to have a child who is healthy and genetically related to both parents. Otherwise, they may turn to other, less risky options such as adoption, gamete donation* or embryo donation. Preimplantation genetic diagnosis* (PGD) can allow parents to have a healthy, genetically related child, but is technically impossible for some couples. Although the desire to have a genetically related child is understandable and must be taken into consideration, the Commission nevertheless takes the view that the health and well-being of the future child is a priority, and the impacts of genetic modification technologies on society, future generations and the human species are a core concern.

Genetic modification of germ cells and embryos is prohibited in Canada, whether for research or clinical purposes. As a result, the Commission's reflections are mainly prospective in nature and are intended to support decision making concerning the future of the practice in Québec and in Canada.

2. The Ethical Analysis Framework

The Commission selected a set of ethical values and principles which it used to build an analysis framework suited to the issues raised by genetic modification of germ cells and embryos. This framework includes the following elements:

- Promotion of human health and well-being:
  - Beneficence
  - Non-maleficence
- Respect for persons:
  - Respect for autonomy
  - Non-instrumentalization of persons
  - Non-commercialization of human beings and their products
- Justice:
  - Fair distribution of risks and benefits
  - Solidarity
  - Equal opportunity
- Science as freedom of thought and as a social good
- Precaution
- Responsible resource use
- Transparency and democracy

3. Issues and Recommendations

3.1. Risks to human health

Targeted gene editing is associated with risks to the future child's health. First, it can generate unexpected phenotypic effects* because the same gene can play a role in several different phenotypic traits. Second, the intervention may trigger off-target unintentional genetic modifications with the potential to cause serious health problems. Third, the embryo may exhibit somatic mosaicism,* i.e. the embryo's cells may not all be genetically identical; some cells may be modified and others may not. Lastly, post-modification testing has some significant limitations, since some types of non-intentional modifications are difficult to detect, and even if an involuntary mutation is detected, it is not always possible to say whether or not it will have a major biological impact.

Mitochondrial transfer is also associated with risks to the future child's health. First, when the mother's nDNA is transferred to the donor's healthy cell, a minute quantity of the mother's defective mitochondria is involuntarily carried over. Subsequently, as the cells are divided and ovocytes* are produced, a small percentage of the defective mitochondria may grow to a pathological threshold. Second, some research has suggested that there is potential for incompatibility between the mother's nuclear DNA and the mitochondrial DNA of another person. In addition, very little is known about the interactions between the mitochondria of the mother and the donor within the cell. Lastly, post-modification testing has some significant limitations; it is not possible to draw definitive conclusions about the future health of the child from the embryo's mitochondrial genetic information.

In accordance with the principle of promoting human health and well-being (**beneficence, non-maleficence**), Table 1 lists a set of elements that must be assessed by researchers to ensure that the benefits for the people concerned are maximized and the risk of harm is minimized:

Table 1 – Scientific Standards

Standards for Preclinical Research (First: animal models; Second: germ cells and human embryos less than 14 days old, not transferred to the uterus)

- Assess the safety of embryo cell harvesting techniques.
- Assess the representativeness of the harvested embryo cells.
- Assess the validity of genetic data sequencing and interpretation techniques.
- Assess the safety and efficiency:
  - Criteria
    - Success of targeted editing.
    - Assess each nuclease-guide-target-dose combination (TGE).
    - Absence of unintentional mutations (TGE).
    - Acceptable level of heteroplasmy* (MT).
    - Absence of unintentional epigenetic modifications.
    - Absence of mosaicism.
  - Method
    - Give priority to complete sequencing.
    - Test on several different animal models.
    - Test several different tissues (postnatal animal tissues).
- Assess potential structural damage to the cell during core transfers in MT.
- Conduct longitudinal postnatal monitoring (animal).

Standards for clinical research

- Assess the effectiveness of each intervention (preimplantation, prenatal and postnatal)
  - Criteria
    - Success of the targeted modification.
    - Absence of unintentional mutations (TGE).
    - Acceptable level of heteroplasmy (MT).
    - Absence of unintentional epigenetic modifications.
    - Absence of mosaicism.
  - Method
    - Give priority to complete sequencing.
    - Test several different tissues.
- Set up an electronic registry for longitudinal cohort monitoring.

Given the scientific uncertainty surrounding the safety and effectiveness of genetic modification of germ cells and embryos,

Given the risks to the future child's health,

[1] the Commission recommends that the Gouvernement du Québec make representations to Health Canada in order to maintain the ban on all clinical research and clinical applications to humans.

Given the scientific uncertainty surrounding the safety and effectiveness of genetic modification of germ cells and embryos,

Given the priority ascribed to studies using animal models as part of responsible scientific research,

Given the lack of animal model-based preclinical research into the genetic modification of germ cells and embryos,

[2] the Commission recommends that the research funding agencies support more animal model-based preclinical research into the genetic modification of germ cells and embryos.

Given the scientific uncertainty surrounding the safety and effectiveness of genetic modification of germ cells and embryos,

Given the risks to the future child's health,

in the event that Health Canada decides to allow clinical applications of genetic modification of germ cells and embryos,

[3] the Commission recommends that the Gouvernement du Québec make representations to Health Canada to ensure that a set of stringent scientific conditions be met before proceeding (see Table 1 on preclinical and clinical standards);

[4] the Commission recommends that the Ministère de la Santé et des Services sociaux set up an electronic register in order to conduct longitudinal medical monitoring of children who have undergone genetic modification (TGE and MT). Monitoring should be mandatory until the person concerned is able to give consent (14 or 18 years of age, as determined by a research ethics committee), after which the free, informed and ongoing consent of the person must be obtained.

3.2. Scarcity of germ cells and embryos for research

Preclinical research into genetic modification of germ cells and embryos requires access to numerous ovocytes and single cell embryos (zygotes*). However, these cells are rare. If Health Canada decides to allow this type of research, ethically justified and socially acceptable ways of obtaining these cells would be required.

It has been suggested that compensation for ovocyte providers would help reduce the shortage. This is a controversial option that contravenes the principle **non-commercialization** of the human body and its products, and also creates the risk that certain groups of women would be exploited (**autonomy, non-maleficence**). Given the absence of a social consensus on the question of remuneration for ovocyte providers, the Commission proposes other avenues.

With regard to single cell embryos, permitting the creation of embryos for research purposes, as other countries have done (e.g. Netherlands, Belgium, Sweden, Israel, Japan, China) would help solve the problem of scarcity. However, this option is controversial in Canada. The Commission therefore proposes that the law should not be changed until a certain social consensus has been reached on this issue.

Given the importance of having access to human ovocytes for fundamental research into reproduction and preclinical research into the genetic modification of germ cells and embryos,

Given the scarcity of human ovocytes,

Given the absence of a social consensus on the question of remuneration for ovocyte providers,

If Health Canada decides to allow preclinical research into the genetic modification of germ cells and embryos,

[5] the Commission recommends that the funding agencies finance research designed to develop methods of obtaining human ovocytes (e.g. from somatic cells*, cultivation of surgical eggs until maturity). These methods would be in addition to other sources of ovocytes, such as local donations, imports and recovery of unused cryopreserved eggs.

3.3. From the desire for a genetically related child to the future child's medical needs

The desire for a healthy child who is genetically related to both parents is one of the main reasons why aspiring parents would turn to genetic modification of germ cells and embryos. There are less risky options than genetic modification for mutation carriers (e.g. adoption, gametes donations), but these options involve sacrificing the genetic relationship, in whole or in part. Prenatal genetic diagnosis (PND) and preimplantation genetic diagnosis (PGD) can help some couples who are carriers of mutations to have children who are genetically related to both parents, but this option is not technically possible for all couples.

Some people believe the desire for a genetically related child is not sufficient to justify investments of resources in research, development and supply of genetic modification technologies for germ cells and embryos. On the other hand, others believe the desire to have genetically related children is a need that engenders certain rights. The Commission has already stated its opinion of this: it does not believe the "right to a child" exists, nor does it believe that the State is bound to meet all the demands for medically assisted procreation.

One might think that, if genetic modification technologies are not available, people who want a genetically related child but for whom PGD and PND are not options would turn to other solutions in which the genetic connection would be wholly or partially sacrificed, or would simply not have children. However, ethicists point out that these people may also decide to conceive a child naturally in spite of the risks. In these cases, the consequence may well be the birth of a child affected by a genetically transmissible disease. Given the existence of this possibility, the genetic modification of germ cells and embryos can be justified on the basis of the future child's medical needs (**beneficence**).

Given that a couple's desire to have a genetically related child is understandable, but is not a medical need or a right,

the Commission believes the desire to have a genetically related child does not create an obligation for society to develop and offer genetic modification services for germ cells or embryos.

Given that, for some people, the genetic relationship with the child is essential,

Given that PNG and PND are not technically possible as choices for some carriers of pathogenic mutations and that these couples may decide to conceive children naturally in spite of the risks,

Given the risks to the health of the future child in these situations,

the Commission believes the genetic modification of germ cells and embryos can be regarded as medically justified care where the child may be born affected by a serious genetic disease and there are no other reproductive or therapeutic options.

3.4. The ethically justified nature of potential applications

3.4.1. Medical indications

Many potentially serious risks are associated with genetic modification of germ cells and embryos. These risks must be justified by substantial benefits for the future child (**beneficence, non-maleficence**). The children who would benefit the most from these interventions are those who have a significant chance of being born affected by a very serious genetic disease with a high likelihood of manifestation, for which there is no available reproductive or therapeutic option. In these cases, some ethicists believe the use of genetic modification to prevent the disease is a moral responsibility arising from the principles of **beneficence** and **equal opportunity**. The risks associated with the intervention are harder to justify in the case of low penetrance* diseases and are not justified for treatment of unaffected carriers or to increase the chance of successful fertilization.

Given that the benefits for the child must exceed the risks associated with the genetic modification of germ cells or embryos (beneficence and non-maleficence),

if Health Canada decides to permit clinical applications,

[6] the Commission recommends that this type of intervention be used solely for very serious, high penetrance diseases, where there are no other reproductive or therapeutic options available.

Stigmatization of people affected by genetic diseases and their families

In liberal societies, respect for personal **autonomy** means that a couple can decide to have a child who has a significant chance of being affected by a genetic disease. Having said this, when a preventive medical technology is available, genetic disease carriers may come under strong social pressure to use it. This currently seems to be the case for some prenatal tests, for example. Pressure such as this is contrary to the principal of parental autonomy and should be minimized.

The fact of identifying certain serious medical conditions as valid indications for genetic modification may also result in more social prejudice and intolerance for the people who suffer from these diseases. Prejudice and intolerance can lead in turn to stigmatization and discrimination against the people concerned and their families, which is contrary to the principle of **non-maleficence**. There may also be more pressure on the parents to use the technologies.

Given that the availability of genetic modification technologies for germ cells and embryos may result in future parents who are carriers of serious genetic diseases being pressured to use them, contrary to the principle of autonomy

Given that the identification of certain medical conditions as valid indications for genetic modification may increase social intolerance of people affected by those diseases,

if Health Canada decides to permit clinical applications,

[7] the Commission recommends that the Ministère de la Santé et des Services sociaux ensure that existing support and information programs (e.g. genetic counselling processes) should allow couples to make free and informed decisions;

[8] the Commission recommends that the Gouvernement du Québec establish or improve programs designed to meet the needs of people suffering from genetic diseases and their families, to fight stigmatization and discrimination against them, and to promote their integration into society.

Equal access and distribution of resources

If germline genetic modification is eventually recognized as an approved, available health care for serious diseases, there is a risk that it would lead to the creation of two classes of citizens: those who have the financial means to use it, and those who do not. The idea of equitable access to heal care is based on a number of values and principles. The first of these is **solidarity**, or the need to support the most vulnerable and disadvantaged members of society and reduce inequalities in health and access to care. Inequitable access to genetic modification technologies would hinder **equal opportunity** since it would allow certain people to enjoy good health while for others, the range of opportunities available to them would be significantly reduced. Therefore, if a germline genetic modification technology is approved as a means of preventing serious disease, it should be included as needed in the universally-available healthcare basket.

Funding of technology access in the health system (inclusion in the healthcare basket) must also reflect the principles of **responsible resource allocation.** Since resources are limited and needs are potentially unlimited, decisions must be made about priorities. A number of questions must be addressed: Does the funding of genetic modification technology for a given indication constitute an efficient use of resources (cost-benefit ratio)? What is the opportunity cost of this funding – in other words, which other research and health care must be set aside to pay for the funding? What else could have been done with the resources? What budgetary impact does the inclusion of this technology have on public finances? Does the fact of funding these expensive technologies threaten the public health care system's sustainability? These questions are addressed in the analyses of the technological assessment agencies tasked with making recommendations to governments concerning public funding for the technologies.

Given that solidarity promotes equal access to care,

Given that equal access fosters equal opportunity,

Given that it is the role of decision-makers to allocate resources efficiently and responsibly,

if Health Canada decides to permit clinical applications,

> **[9] the Commission recommends that the Gouvernment du Québec include these application in the State-funded healthcare basket, provided the agency responsible for assessing the technologies finds that the cost-benefit ratio, the opportunity cost and the budgetary impact are all acceptable.**

3.4.2. Creation of "designer" babies and capacity enhancement

Some people object to genetic modification of germ cells and embryos because they are concerned that allowing research into and medical applications of these technologies would open the door to more controversial uses (the "slippery slope" argument). Targeted genome editing could eventually be used to allow parents to select the characteristics of their unborn child, including the physical or psychological traits (personality traits, eye colour, gender, cognitive ability, physical strength, etc.) desired for aesthetic reasons, performance and so on. Another controversial use would be the application of targeted genome editing to enhance the child's biological capacities beyond the level needed for good health and even beyond the current limits of the human body.

Some authors have suggested that, if safe and effective technologies are eventually available, parents should in fact be given maximum flexibility to choose the genetic characteristics of their children, under the principle of **parental autonomy**. With regard to the specific use of genetic modification technologies for capacity enhancement, some people think this is not only permissible but also necessary if the human species is to resist pathogenic micro-organisms and survive in an increasingly hostile environment (**beneficence**). Some even go so far as to suggest that parents would have a moral duty to their unborn children to use available technologies for capacity enhancement.

Other ethicists have called for public discussion of the fundamental ethical questions raised by the creation of designer babies and capacity enhancement. First, some critics suggest that this type of application would be contrary to the principle of **non-instrumentalization** of children, because its main aim would be to meet social standards and satisfy parental preferences as opposed to meeting the needs of the unborn child. In addition, by designing a child according to their preferences, parents could significantly reduce the range of possibilities available to the child. The parents' decisions concerning genetic modification must respect the child's right to an open future (**autonomy**); in other words, a future that offers a variety of potential life plans.

Second, parental genetic modification choices may stem from prejudices and discriminatory social norms (e.g. lookism, racism, ableism), whether because the parents have internalized these norms or because they do not want their future child to be stigmatized or discriminated against. In these cases, individual choices would actually reinforce and exacerbate these norms, leading to even more discrimination and stigmatization, contrary to the principle of **non-maleficence**.

Third, given that genetic modifications may give certain children an advantage over others, some people believe this would be contrary to the principle of **equal opportunity**. Because genetic modification technologies would probably be more easily available to couples with greater financial means, the genetic benefits for children who are already privileged would increase social and economic inequality.

Given that the benefits for the child must exceed the risks associated with the genetic modification of germ cells and embryos,

Given the absence of a social consensus on the subject of genetically transmissible modifications for non-medical reasons or to enhance capacities,

if Health Canada decides to permit clinical applications,

the Commission reiterates recommendation [6] to limit this type of intervention to very serious, high penetrance diseases, where there are no other reproductive or therapeutic options available;

[10] the Commission recommends that only those modifications that would bring back a mutation to a normal human allele* (i.e. a dominant allele within the population) be used.

3.5. The Intergenerational Nature of the Impacts of Genetic Modification of Germ Cells and Embryos

Genetic modifications of germ cells and early embryos are transmissible to descendants. The risks associated with these modifications therefore affect not only the target embryo, but also future generations and the genetic heritage of the human race as a whole. Some of the risks associated with this type of intervention are potentially very serious and irreversible. According to certain ethicists, risks with the potential to cause severe, irreversible damage to the human race or the environment are morally unacceptable and require the application of the precautionary *principle* or *approach*.

Under the precautionary approach (as defined by the Commission in previous opinions), applied to the genetic modification of germ cells and embryos, a number of measures must be applied. The first of these is the adoption of exceptionally high scientific standards to determine the safety and effectiveness of genetic modification of germ cells and embryos. A second measure, if Health Canada decides to permit clinical interventions, would be to restrict these interventions to a very small number of patients (as identified in recommendation 6), in order to minimize the impacts on the human gene pool. A final measure would be required for MT in particular. Since mitochondria are transmitted by the mother only, the technique could initially be applied only to male embryos, to prevent the modification from being transmitted to descendants. This measure could be applied until MT techniques have been shown to be safe.

Given that genetic modifications of germ cells are transmissible to future generations and would alter the human gene pool,

Given the scientific uncertainty regarding the safety and effectiveness of genetic modifications to germ cells and embryos,

Given that the health risks associated with these modifications are potentially serious and irreversible,

if Health Canada decides to permit clinical applications of genetic modifications to germ cells and embryos,

the Commission reiterates recommendation [3] that the Gouvernement du Québec make representations to Health Canada to ensure that a set of stringent scientific conditions be met (see Table 1 on preclinical and clinical standards);

[11] the Commission recommends the adoption of exceptionally high scientific standards applicable to preclinical testing of the safety and effectiveness of genetic modifications to germ cells and embryos;

the Commission reiterates recommendation [6] to limit this type of intervention to very serious, high penetrance diseases, where there are no other reproductive or therapeutic options available, in order to limit the target population and the scope of any impacts on the human gene pool;

[12] the Commission recommends that mitochondrial transfer be applied initially to male embryos only, to avoid transmission of the modification to future generations.

3.6. Offshoring of Research and Medical Tourism

If a specific jurisdiction restricts preclinical research and clinical trials, they may be moved offshore, i.e. to countries with less stringent regulations. Stricter regulations may therefore hinder the development of local expertise, cause scientific opportunities to be missed and encourage leading-edge researchers to leave (**scientific freedom**). In addition, evidence of technical safety and effectiveness may be of lesser quality when studies are carried out in countries where scientific oversight is less rigorous (**responsible science**).

Clinical trials are often moved to developing countries where populations are more vulnerable and less protected. As a result, citizens in these countries are more likely to be exploited and to agree to take part in clinical trials that expose research subjects to significant risks (**non-maleficence**; **autonomy**). In addition, these populations rarely benefit from the outcomes of the research, raising questions about distributive justice. At the other end of the scale, more strictly regulated countries provide greater protection for their populations and can take advantage of knowledge developed elsewhere (**fair distribution of risks and benefits**).

When access to certain health technologies is restricted, citizens may be tempted to travel to countries with fewer or no rules in order to obtain them (medical tourism). Medical tourism exposes patients to potentially serious health risks (**non-maleficence**). In addition, when they go home they are taken into charge by the health system in their country of origin, and the medical follow-up they require can sometimes be very costly.

Scientific offshoring and medical tourism can be addressed by harmonizing regulations among countries. An international organization such as the United Nations could be tasked with further standardizing the regulatory framework.

Given the phenomena of research offshoring and medical tourism,

Given the risks associated with medical tourism for parents and future children,

Given the scientific uncertainty surrounding the safety and effectiveness of genetic modification of germ cells and embryos,

the Commission strongly discourages patients from going abroad to undergo genetic modification of germ cells or embryos;

[13] the Commission recommends that Québec's Ministère de la Santé et des Services sociaux support organizations that raise patients' awareness of the risks associated with reproductive medical tourism;

[14] the Commission recommends that the Gouvernement du Québec ask the Government of Canada to work actively, within the framework of international organizations, to harmonize the regulations governing transmissible genetic modifications in different countries.

3.7. Mitochondrial Transfer and the Child's Identity

Given that MT involves using part of the genome (mtDNA) of a third person for conception, ethicists have questioned the potential impacts of this technique on the child's personal identity. Will someone who knows he or she was conceived from three genetic contributors have a confused representation of the self and experience difficulty with social relationships? Might these people develop an ambiguous perception of their identity, or might they experience inner or interpersonal conflicts that are detrimental to their well-being?

The implications of biological donations vary according to the people concerned and the products received: blood, tissue, gametes, embryos, organs from living donors (e.g. kidney), organs from deceased donors, and so on. Since the practice is new, it is difficult to predict the consequences of gametes donations for the construction of identity. Given the characteristics of mtDNA, it is reasonable to think that mitochondrial donations would have less impact than gametes donations, for example. In MT, the DNA contribution is minimal (37 genes) compared to what the child receives from the biological parents (20,000 – 30,000 nDNA genes). In addition, unlike nDNA, mtDNA is not associated with the phenotypical features normally involved in the construction of identity (e.g. physical appearance, personality traits). It is for this reason that some people believe mitochondrial donations are more comparable to organ donations than to gametes donations in this respect.

MT could have indirect impacts on a child's identity by changing the family dynamics. The fact that the child was conceived from the genetic material of three people may affect family relationships: the sense of belonging to an atypical family, confusion regarding origins, and so on. However, experience of and research into other forms of assisted procreation and family structures tends to show that family connections are flexible enough to adjust to different configurations without causing significant psychological damage.

Parents who use MT will have to decide whether or not they will tell their child that he or she was conceived in this way and therefore has donor mitochondria. In the case of gametes donations (nDNA), research shows that it is better to tell the child earlier, rather than later, that he or she was conceived with donor gametes, so as to minimize distress (**non-maleficence**). Even so, some parents may prefer to keep details of the child's conception secret. Should **parental autonomy** prevail in these circumstances? Is the child entitled to know the truth about how he or she was conceived?

One of the Commission's recommendations is that the Ministère de la Santé et des Services sociaux set up an electronic register for longitudinal monitoring of children who have undergone genetic modification. Monitoring should be mandatory until the child is able to give consent for research (14 or 18 years of age, depending on the level of monitoring risk as assessed by the research ethics committee), after which the free, informed and ongoing consent of the person being monitored must be obtained (**research subject's autonomy**). To give consent, however, the person must first be familiar with the circumstances of his or her birth. Therefore, if the authorities eventually decide to allow MT, the Commission recommends that the children concerned be informed before the age at which they can consent to research.

Given that mitochondrial DNA accounts for a tiny portion of an individual's genome,

Given that mitochondrial DNA is not associated with the phenotypical traits normally involved in the construction of identity,

the Commission feels that mitochondrial transfer will probably have negligible impacts on the future child in terms of self-representation and social relationships;

the Commission invites researchers to continue to research the potential impacts of reproduction technologies on identity and social relations.

3.8. Education and Public Participation

Science and technology policies should be based on a certain level of social consensus and public participation. This will ensure that the process is more democratic and is perceived as being more valid by the general public. In addition, it should be possible to subject decisions concerning science and technology to a democratic examination as a means of ensuring accountability of decision-makers. This will also require transparency, meaning that scientists, regulatory agencies and governments must share relevant information with the stakeholders concerned (**transparency** and **democracy**).

Hence, it is important to involve the general public and engage in democratic dialogue on the issues raised by the modification of germ cells and embryos. In the past, debate on genetics issues has often been limited to specialists. If citizens are to take part, plain language must be used and, because public opinions are dependent to some extent on the quality of the information provided, it should be as objective and accurate as possible.

If a true dialogue is to take place, participatory approaches should be used, and methods designed simply to convey information or "sell" the technology should be set aside. Information must be provided, of course, but it is important to go even further by giving citizens the opportunity to express their opinions, and by including as many different views as possible. So far, very little seems to be have been done in this respect.

Different types of public activities can be organized: conferences, plays, scientific exhibitions, videos, forums, workshops, communications via the traditional media and the social media, public consultations and so on. Organizations with expertise in public information and participatory debate should be involved in this process. Scientific studies into public attitudes, beliefs and preferences may also be useful.

Given the need to involve the general public in the debate leading to the development of public policies on major social issues,

Given the need to obtain a certain level of social consensus before allowing the use of ethically and socially controversial technologies,

[15] the Commission recommends that the Ministère de la Santé et des Services sociaux support organizations with expertise in public education and consultation, so that they can organize interactive activities for the general public on the genetic modification of germ cells and embryos (e.g. scientific exhibitions, public consultations and debates, plays, etc.);

the Commission invites social science researchers to carry out studies of public attitudes, beliefs and preferences regarding the modification of germ cells and embryos.

Conclusion

Canadian federal law on assisted procreation prohibits all forms of human genetic modification that may be transmissible; in other words, any genetic modification of germ cells and early embryos. However, that law may eventually be changed. In this position statement, the Commission has adopted a pragmatic approach that consists in identifying the conditions in which germline genetic modification could be ethically justified, and proposes a set of recommendations that it believes will help ensure that these conditions are met.

GLOSSARY

Allele: Alleles are different versions of the same gene*.

Alternative splicing: A mechanism by which the same gene* can give rise to several different variants of a protein*. It increases the number of proteins synthesized from a limited number of genes.

Amino acid: Organic compound forming part of a protein*. The amino acid sequence* is determined by DNA and confers the specific functions of the protein. The genome of living organisms encodes 22 amino acids.

Chromosome: The condensed form of DNA* during cellular division. Each chromosome is composed of one very long nuclear DNA molecule. In humans, the 46 chromosomes in a cell are linear in shape and are divided into 23 X-shaped pairs.

Cytoplasm: The internal environment of a cell, excluding the nucleus. It contains different structures that perform one or more specific functions. These structures include organites (mitochondria*, endoplasmic reticulum, vacuoles) and ribosomes.

Deletion: Genetic mutation* causing loss of DNA* fragments ranging from a single nucleotide to a group of several genes.

DNA (deoxyribonucleic acid): Macromolecule present in almost all cellular organisms. It is composed of nucleotides* and contains genetic information allowing for the development, functioning and reproduction of living beings.

DNA is found in cell nuclei (nADN) and in the mitochondria* (mtADN). Nuclear DNA is composed of two strands rolled together to form a double helix. Mitochondrial DNA is circular.

Embryo: An organism in the early stages of development from fertilization (union of an egg and a sperm cell, cf. zygote*) to the fetal stage (roughly 8 weeks for human beings).

Epigenetic: A mechanism (e.g. methylation*) that regulates gene* activity by promoting or preventing gene expression. It allows for different expressions of the same genetic sequence*.

Gamete: A reproductive cell: ovocytes for women and sperm cells for men.

Gametogenesis: Process by which reproductive cells (gametes*) are formed. In women, ovogenesis produces ovocytes. In men, spermatogenesis produces sperm cells.

Gene: A specific segment of a DNA* sequence that has the potential to be transcribed into RNA* and then into protein*.

Genetics: Sub-discipline of biology that studies heredity, i.e. the transmission of features and traits from one generation to the next.

Genome: All the genetic material of an indivual or species contained in DNA*.

Germ (cell): The cells of an organism that convey genetic information to descendants during reproduction and that form the germline. The germline includes germinal stem cells (spermatogonia and ovogonia) that mature into gametocytes and subsequently into gametes*.

Heteroplasmy: The presence of several types of mitochondrial DNA (mtDNA) in a cell, tissue or individual.

Intracytoplasmic sperm injection (ICSI): An in-vitro fertilization technique in which a single sperm cell is injected into an egg to fertilize it.

Methylation: Epigenetic* process in which certain nucleobases (nucleotide* components) in the DNA* are altered by the addition of a methyl group. Methylation of DNA affects gene expression.

Mitochondria: Structures (organites) contained in cells. They contain DNA* that is separate from nDNA. They produce cellular energy and play a role in regulating the cell's metabolism. They also play a role in apoptosis processes, immune response, synthesis of certain hormones and calcium regulation.

Mitotic spindle: A structure that segregates chromosomes* during cellular division.

Mosaicism: Coexistence of two or more populations of cells with different DNA in the same organism.

Mutation: Alteration of the DNA* causing changes to nucleotides* and their sequences*.

Nucleotide: An organic molecule making up the strands of DNA* or RNA*. Nucleotides are composed of a nucleobase or nitrogen base (adenine [A], cytosine [C], guanine [G] or thymine [T], uracil [U]), a sugar (deoxyribose/ribose) and a phosphate group. The order in which the nucleotides succeed one another along a DNA strand is known as the sequence* and constitutes the genetic information.

Ovocyte: Female germ cell* at the development stage situated between the germ stem cells and fertilization.

Ovogenesis: cf. gametogenesis.

Penetrance: The probability that an allele* is manifested in the phenotype*. Where 100% of the allele carriers express it phenotypically, penetrance is complete. Conversely, if not all the allele carriers exhibit the corresponding phenotypical trait, penetrance is incomplete.

Phenotype: The set of morphological, anatomical and physiological characteristics of an individual (hair colour, eye colour, shape of face, height, etc.).

Pleiotropy: The mechanism by which a single gene* determines several different phenotypical* features.

Polar body: Tiny cell formed during development of the ovocyte (ovogenesis) and expelled during cellular division (meiosis).

Preimplantation diagnosis (PID): Genetic diagnosis of an embryo obtained by in-vitro fertilization before it is transferred to the mother's uterus. It allows for selection of an embryo that is not affected by the screened disease.

Prenatal diagnosis: Medical examination to detect a disease in the embryo or fetus during pregnancy.

Pronucleus: Male or female nucleus in a fertilized egg (zygote*) before fusion.

Protein: Macromolecule composed of amino acids* that plays a structural (e.g. cell cytoskeleton, tissue elasticity) or functional (e.g. metabolism) role.

RNA (ribonucleic acid): RNA is a molecule composed of a sequence* of nucleotides. The RNA sequence is determined by the DNA nucleotide sequence. RNA is formed from DNA by an enzyme that copies the sequence in a process known as transcription*. RNA can be functional (non-coding RNA, e.g. transfer RNA, ribosomal RNA, micro RNA), or can play a role in protein synthesis* (messenger RNA).

Sequence: The order of nucleotides* along a DNA* or RNA* strand, making up the genetic information.

Somatic (cell): An organism's cells, excluding the germ cells* and the cells of an embryo at the very early stages of development.

Totipotent (cell): Stem cells that can develop into any type of cell. In humans and large mammals, they make up the embryo during the development phase extending from the single cell zygote* to an 8-cell embryo (approximately days 3 to 4).

Transcription: The mechanism that allows for RNA synthesis based on the genetic information contained in a gene*. It involves reproducing the sequence* of the DNA* segment in the RNA sequence.

Zygote: An undivided cell (egg) obtained by combining the male and female gametes* (fertilization). This is the first life stage of a human being.

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Recent developments in genetic engineering and reproductive medicine have led to progress in gene editing. It may eventually be possible to correct mutations responsible for diseases in humans. Applied to reproductive (germ) cells and early embryos, these developments may allow people who are carriers of morbid mutations to give birth to unaffected children. Two types of technology are currently being researched and discussed extensively: targeted gene editing (e.g. CRISPR-Cas9) and mitochondrial transfer (sometimes referred to as creation of "three-parent babies").

In this position statement, the Commission addresses the ethical issues raised by the genetic modification of germ cells and embryos. It attempts to answer some fundamental questions, such as: What are the risks to the health of the future child and for future generations? What criteria could be used to assess the safety and effectiveness of these technologies? What types of applications could be justified from an ethical standpoint? What indirect effects could the various types of potential applications have for certain groups and society as a whole? The Commission makes a set of recommendations concerning the measures required to address the ethical issues raised by these new technologies.

This opinion and the Commission's other publications are available at: **www.ethique.gouv.qc.ca**

The mission of the Commission de l'éthique en science et en technologie is twofold. On the one hand, it consists in informing, raising awareness, gathering opinions, fostering reflection and organizing debates on the ethical issues raised by developments in science and technology. On the other, it consists in proposing general guidelines for use by stakeholders in their decision-making.

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