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RESEARCH ARTICLE

Clinical translation of mitochondrial replacement therapy in Canada: a qualitative study of stakeholders' attitudes

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Abstract

Mitochondrial replacement therapy (MRT) in Canada is considered a criminal offense according to article 5(1)(f) of the *Assisted Human Reproduction Act* (AHRA) (2004). The *Act* prohibits any practice that modifies the genome of "a human being or in vitro embryo such that the alteration is capable of being transmitted to descendants." We carried out 32 semi-structured interviews with clinicians, researchers, patient groups, egg donors, and members of the public to explore their attitudes toward the clinical implementation of MRT in Canada. Our interview guide was informed by the socio-ethical, legal, and scientific literature of MRT. We used a thematic analysis to identify and analyze emerging themes and sub-themes. Our findings were divided into five broad themes: (*i*) an outdated criminal ban, (*ii*) motives for using MRT, (*iii*) terminology, (*iv*) practical and theoretical risks and benefits, and (*v*) the feasibility of clinical translation in Canada. Although the public and stakeholders' views on the feasibility of foreseeable translation of MRT in Canadian clinics varied, there was consensus on conducting an overdue review of the current AHRA ban on MRT.

Key words: mitochondrial replacement therapy, genetics, ELSI, *Assisted Human Reproduction Act*, Canadian health policy

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Introduction

Mitochondria are dubbed power plants of the cell. They provide our cells with the energy that is required for their normal functioning. Mitochondrial DNA (mtDNA) contains 37 genes. These genes encode core components of the mitochondrial respiratory complexes (Russell et al. 2020). Pathogenic mutations in mtDNA lead to rare, debilitating, and progressive disorders that can be fatal in childhood, typically striking organs requiring the highest energy demands. Currently, there is no known cure for mitochondrial diseases and for the vast majority of patients, therapy is limited to symptomatic relief (NASEM 2016; Ng and Turnbull 2020).

Mitochondrial DNA deficiencies have considerable genetic and clinical heterogeneity, which provides a real challenge for any estimates of prevalence. It is estimated that 1 in 4300 people are affected by primary mitochondrial diseases (Gorman et al. 2015). Due to the challenges in predicting the degree of mtDNA mutation load, the risk of disease manifestation in future children is difficult to evaluate with predictive tests, such as preimplantation genetic diagnosis (Shoubridge and Wai 2007; Wai et al. 2008; Lee et al. 2012).

Mitochondrial replacement therapy

Mitochondrial replacement therapy (MRT), also known as nuclear genome transfer and mitochondrial donation, is a new type of in vitro fertilization (IVF) that aims to prevent the transmission of mitochondrial diseases to future generations. As mtDNA is passed down from the maternal line, MRT replaces a mother's mutated mtDNA with mitochondria from a healthy egg donor. The most prominent methods of MRT include Pronuclear Transfer (PNT) and Maternal Spindle Transfer (MST) (NASEM 2016; NHMRC 2020a). PNT requires the fertilization of a healthy donated egg and the intending mother's oocyte with the intending father's sperm. Both sets of fertilized oocytes are allowed to develop until the early zygote stage. The pronuclei of zygotes formed by the donated oocytes are then removed, discarded, and replaced by the intending parents' pronuclei. In MST, on the other hand, the transfer of parental nuclear DNA (nDNA) occurs before fertilization. This method involves removing and discarding the metaphase II spindle from the donor oocyte. The chromosome spindle complex of the intending mother will then be transferred to the enucleated healthy donor oocyte followed by fertilization with the intending father's sperm (Craven et al. 2010; Kang et al. 2016). The distinctive benefit of MRT is considered to be fulfilling the desire of having healthy, biologically related children. Since there are alternatives to having (biological) children such as egg and embryo donations as well as adoption, MRT is often regarded as less of a priority worthy of societal resources (Rulli 2016; Baylis 2017).

MRT in Canada

According to the 2004 *Assisted Human Reproduction Act* (AHRA), MRT is considered a criminal offense in Canada. The *Act* prohibits any practice that introduces heritable changes into the germline. This is applicable for both research and clinical contexts. Article (5)(1)(f) of the AHRA states that, "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" (AHRA 2004: Sec 5 (Prohibitions)). A person who violates this prohibition is punished by a fine of up to $500 000 and (or) imprisonment for up to 10 years (AHRA 2004: Sec 60 (Offences)).

Research objective

Currently, the United Kingdom (UK) is the first and only country to regulate the clinical applications of PNT and MST (Rhys-Evans 2020). In the UK, IVF and embryo research are regulated by the Human Fertilisation and Embryology Authority (HFEA), a regulatory agency that enforces the *Human Fertilisation and Embryology Act, 1990*. Prior to 2008, under Section 3ZA of the *Act*, permitted eggs and embryos must not have had their "nuclear or mitochondrial DNA altered" (HFEA 1990: Sec (3ZA)). In 2015, both the Upper and Lower Houses of the UK Parliament voted to pass *the Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015* (Castro 2016). Following the UK's lead, Australia appears to be on a similar path toward considering MRT's clinical implementation. Australia's 2006 *Prohibition of Human Cloning for Reproduction and Regulation of Human Embryo Research Amendment Act* prohibits introducing heritable changes into the germline (Australian Government 2006). In June 2018, the Senate Community Affairs Reference Committee, a group of members of the Australian Parliament, drafted recommendations in support of the technique (Community Affairs References Committee 2018). In January 2019, the government responded to the Senate Report indicating that MRT will be of great interest to the Australian community (Australian Government 2019). On 5 June 2020, the National Health and Medical Research Council (NHMRC) released two reports to inform the MRT debate in Australia (NHMRC 2020a, 2020b). The NHMRC reports were sent to the Federal Health Minister in March 2020. Now, Australia expects advice concerning the timing of draft legislation to be introduced in Parliament (Mito Foundation 2021).

It is particularly important to acknowledge that clinics in jurisdictions where reproductive laws may be less strict or nonexistent have been moving forward with clinical applications of MRT, notably in Ukraine and Greece (BioTexCom 2021; Darwin Life Nadiya 2021; Institute of Life 2021). While the primary aim of MRT is to prevent mitochondrial diseases from being passed on to future generations, the technique could also be used in other nontherapeutic contexts, such as "treating infertility" and lesbian motherhood where maintaining genetic ties to both mothers may be preferred (Darwin Life Nadiya 2021; Cavaliere and Palacios-González 2018). The claim that MRT may represent a new era in assisted reproduction technology as a means of solving issues of infertility is on the basis that the mitochondria in eggs are the cause of some cases of infertility. However, there is no available evidence linking mitochondria with infertility in the general population (Cecchino et al. 2018; NHMRC 2020a).

Concerns regarding reproductive tourism and the use of MRT, further highlight the importance of addressing key issues in the MRT policy discussions. Public opinion is a requirement that supports the development and implementation of policies, programs, and services designed to meet the needs and expectations of relevant stakeholders and the general public. Aside from establishing MRT's safety and efficacy, it is important to sufficiently address the implications of different germline-altering interventions. To this extent, factors such as definitions, level of evidence, risk assessments, and communication of accurate and relevant information to the public are key to establishing a favorable risk/benefit assessment. As such, we sought out to explore the attitudes of various stakeholders toward the clinical translation of MRT in Canadian clinics using a qualitative study.

Materials and methods

Data collection

Semi-structured interviews were conducted by F.N. in English and French. We conducted interviews between September 2019 and July 2020. Our interview guide was informed by the socio-ethical, legal, and scientific literature of MRT. The interview guide included open-ended questions that addressed the interview participants' perceptions, expectations, and concerns toward the clinical implementation of MRT in Canada (**Supplementary Material 1**). The guide was used to initiate discussion, but interviews were designed to explore participants' opinions and allow new themes to arise. New themes were added to the interview guide as they emerged throughout the initial interviews (Ritchie et al. 2013; Patton 2015).

We reached out to MitoCanada, Canada's not-for-profit organization focused on mitochondrial disease, and We Are Egg Donors, an international online support group for egg donors, asking them to publish our interview recruitment advertisements in their newsletters and to post on their websites and social media accounts. Mitochondrial disease clinicians and researchers across Canada were contacted via email. Members of the public with no experience of mitochondrial disease or assisted reproduction were recruited through posting in different private and public Facebook groups (e.g., student societies). Subsequent participants were identified through snowball sampling and thus recruited by suggestion of other eligible participants. Our final sample size was determined by reaching thematic saturation in data collection. Interviews were conducted both in person and over the phone. We obtained written informed consent from all participants after discussing the purpose of the research (**Supplementary Material 2**). All audio-recorded interviews were transcribed verbatim. Transcripts were deidentified and checked for accuracy.

Data analysis

A thematic analysis was used to identify, analyze, and report themes from the data (Creswell and Creswell 2017). All interviews were conducted and systematically coded by F.N. using NVivo12 (QSR International 2020). F.N. initially organized and coded the transcripts into manageable text

segments cross-checked by M.L. Information was triangulated between sources and data saturation was sought (Ritchie et al. 2013; Patton 2015).

Ethics approval

We obtained ethics approval through the McGill Faculty of Medicine Institutional Review Board (IRB Study Number: A06-B43-19B).

Results

Participants

We conducted a total of 32 interviews (see Table 1). We reviewed emerging themes until saturation was reached. We sent email invitations for interviews to 56 individuals across Canada. Twenty-three people did not respond to the request for interview and one person declined. Twenty-three interviews were conducted over the phone and nine were conducted in person, each lasting between 45 and 200 min. Written consent was obtained for audio-recording interviews from all participants. Themes identified fell under five categories: (*i*) an outdated criminal ban, (*ii*) motives for using MRT, (*iii*) terminology, (*iv*) practical and theoretical risks and benefits, and (*v*) the feasibility of clinical translation in Canada. Table 2 summarizes the identified themes and sub-themes, along with example quotes.

An outdated criminal ban

There was consensus among all responders on the inappropriateness of banning MRT research on the basis of any fundamental principle. Participants acknowledged the underlying concept of the ban (to prevent a slippery slope toward designer babies); however, they differentiated between using MRT as a preventive tool for mitochondrial diseases and using gene editing technologies (e.g., CRISPR) to manipulate the nuclear genome to create designer babies.

Two out of eight researchers and clinicians (henceforth known as experts) believed that the criminal code should not be used to regulate scientific advancements, while others believed in having laws that are appropriately administered. Basic MRT research on human embryos is currently banned in Canada. This proves to be a hindering step in furthering MRT research.

Also, the AHRA's prohibition inadvertently encourages medical tourism practices. Two out of eight patients stated that they had considered seeking MRT abroad as a viable option. Although they acknowledged medical tourism to be fraught with costs, they claimed that they were willing to push their financial rationale and look past the economic flaws and safety concerns of this practice.

Motives for using MRT

Three sub-themes emerged across motives for using MRT.

Table 1. Research participants.

Category	Female	Male
Experts	4	4
Patients	7	1
General public	5	3
Egg donors	8	N/A

Table 2. Attitudes towards the clinical translation of MRT in Canada.

Themes	Sub-themes	Example quotes
An outdated criminal ban	—	The AHRA is an ancient ruling back in 2004, when they did not know what MRT was, so it's an antiquated law and it needs to be updated to keep up with the modern science and technology.
		I think the law should be modified all together. CRISPR-Cas9 editing is coming and if you put your head in the sand and say we're just not going to do it. It'll get done. It'll get done somewhere else and (or) it'll go underground.
Motives for using MRT	Lack of available resources for mitochondrial disease patients in Canada	We're one of the only countries in the world without a rare disease framework. So, the national government is way behind other countries like the US, the UK, and Australia. This has been stagnant for almost eight or nine years. So, if there are no champions at the national level in the government, it's not going to go anywhere.
		My aunt who has mitochondrial disease, lay in the hospital bed for 5 days with perforated ulcers and intestines, perforated! she was swelling, she was sceptic. Five days, why? Because no one knew how to treat her mitochondrial disease and they wanted to consult with every possible specialist on the planet before they removed 95% of her small intestine.
	Implications for mental health	When my son was speaking about suicide at the age of 8, I went to my paediatrician and I asked for a referral at the CLSC and I said I wanted to be seen in the hospital. He sent the referral in and I never heard from them. Meanwhile, I am dealing with an 8-year-old who is speaking about suicide and being very explicit about what he is going to do. One day passes, two day passes… and I am thinking in my head, they have got to be taking this seriously, right?
		Mitochondrial disease in my family has really affected people mentally and so my family members haven't had any children because two of my uncles who were diagnosed committed suicide and my aunt has really bad mental depression. My aunt, when she was four years old, was watching her brothers become blind for no reason because they didn't know much about it.
	Reproductive autonomy and the desire for biological kinship	For us to negate that strong feeling or the thought of wanting a biological child, I think is poor judgement, it's not taking in consideration all the aspects that it involves (financially, socioeconomically, ethically, psychologically, everything, everything, government-wise). We really have to take a multi-faceted look. If the biological or the psychological aspects of having a biological child is not included or if it's disregarded, it's like missing a piece of the pie. The understanding has to be multi-faceted, everything has to be balanced.
		This is an equal opportunity at a chance of life without disease. I believe in advancement in medicine and I want my daughter to have the opportunity to have and to carry a child of her own that will not land her in the hospital like me.
Terminology	Germline genetic modification	It's not modification. You're now assorting it, sorting it differently. If you look at human mating for example, if you picked a different partner, yes, you're selecting somebody with a different genetic make-up, but you're not manipulating your existing partner to look like some other partner. So, the process we use when we select partners that we want, that's called assortative mating. We're selecting from a pool of genes. But we're not changing the genes. So, it is an assisted reproductive technology, that's what it is.
		I don't really consider it modification. I see it as more of a pre-parent model. I don't think anyone is changing the genes per say, it's choosing parts of two eggs. My opinion is that it's more like mitochondrial donation, those are the words I would use; I would not use the words germline modification or genetic modification. I would use the word mitochondrial donation.
	Replacement therapy	It's not replacement. It is actually really nucleus transfer. It's about allowing people who have a mitochondrial disease, to produce offspring that do not have mitochondrial disease. So, it is an assisted reproductive technology.
		It's the prevention of transmission of what we know to be a pathogenic mutation. So, in that sense, I guess it depends how you define therapy.

(*continued*)

Table 2. (*continued*)

Themes	Sub-themes	Example quotes
	The sensationalized notion of a "third parent"	I don't look at it as a three-parent baby. At the basic level, I think I would look at it as a child with donated mitochondria. More like organ donation (e.g., I got into a car accident, someone donated a kidney, it's still the same person with the donated kidney, I won't look at John as "John with Joe's kidney." It's my child, it's my genetic DNA and my partner's, it's just that there is an organ donated at some point.
		So, you get headlines that call them three-parent families and things like that, but I think that's being a little dishonest because the mitochondrial genome is such a small component of the overall genome. It's the nuclear genome that's determining the traits. So, there is a lot of terms out there that one side or the other side is using that aren't really technically accurate.
Practical and theoretical risks and benefits	The notion of "sufficiently safe"	I think at this point in time, the evidence and the experience would support that MRT seems to be safe. Certainly, safer than having a kid die of MELAS syndrome for a very specific indication. It's not totally without risk, but then even other forms of in vitro fertilization are not without risk as well.
		To some extent every time people reproduce, there is mitochondria interacting with completely different nuclear genome. For example, a black woman from Batswana who has probably got an L0 haplotype has a baby with a Caucasian from Northern Sweden. Their mtDNA are about as far away as you possibly could get. I just don't buy the argument, it does not make sense.
	Health care costs in diagnostics and medical treatments	These patients will often have a high demand in the pediatric hospitals with frequent admission. They might have multiple services following them: neurology, cardiology, endocrinology, complex care because of feeding issues, we might have special education, physiotherapy involved because of the severity of the disease. So, I think there's a benefit to society from having an ability to prevent these disorders, so you're not going to end up in the long-term care facility, in the rehab center, or in the intensive care unit for one of these disorders.
		If you quantify and calculate how much money the government has spent just on my family alone in medical treatments, diagnostic and everything, I can guarantee you that that costs a lot more money than MRT could ever possibly cost one person.
	The slippery slope and deviation from a safe practice zone (i.e., treating infertility, lesbian motherhood, enhancement)	I am really opposed to MRT being explored for other causes. Mitochondrial disease is like a needle in a haystack. When you think of all the other things that could go wrong at any time, you're just going on a fishing expedition. If you know a couple has infertility or infertility problems and well, you should just do MRT and see if that helps? That, I find repulsive. I am not okay with that.
		There's no evidence that young mitochondrial genomes from young eggs are better than mitochondrial genomes from older eggs. I'm not sure that anybody really knows why eggs age, why they become less fertile. What is it about the egg that makes it more difficult to either fertilize or implant or carry the pregnancy to term and obviously the chromosomal abnormalities for sure. But, if you take that out of the equation, I'm not sure what else is there that actually impedes the process.
The feasibility of clinical translation in Canada	The demand for MRT	It is going to be very, very rare scenarios. So, we have 400–500 adults with mitochondrial disease that we follow here, of those, half are female, of those patients probably 60%–70% are either far too young or beyond reproductive year. That gives you a very narrow window, a very small number of women who would even be in this situation where MRT is something that they would consider. So, across Canada, when I start looking at the numbers, you might have 12–15 people a year who would actually qualify for moving forward with MRT.
		I don't hear a lot of demand coming from patients. The demand I'm hearing is coming from the industry. They want to be able to sell this to people. They're pretending they're fixing mitochondrial disease, they're not.

(*continued*)

Table 2. (*concluded*)

Themes	Sub-themes	Example quotes
	Coverage and equity of access	I think this inequality between provinces in access to innovative treatments is an issue. People in Ontario have better access to some innovative treatments than those living in other provinces. So, that's why I think there has to be decision making at the federal levels so that there is consistency across Canada. I think it should be similar to the management of approving new innovative treatments like enzyme replacement therapy. However, it should be a process that involves all provinces accepting the same legal framework, if at all possible. That may be impossible given the federal nature of governance in Canada.
		I'm not sure it's fair to deny people access to this if that's what they want to do. It's a different issue whether the government should cover it because what you're really talking about is, should the government be covering something that is an assisted reproductive technology? You're not covered universally in all provinces for IVF. So then, if you say that's the case, then this would not be treating anything differently, you just pay for it yourself.
	The notion of "serious" mitochondrial disease	That's a difficult one and that is so open to interpretation because unlike an on and off switch with the nuclear genome where you get Down syndrome or you don't get Down syndrome; it is very idiosyncratic, so if you got Deschene, for example, you know, + or − two years you are going to be in a wheelchair like around 11 years old, whereas with mitochondrial disease, with MELAS syndrome, if you got 95% heteroplasmy, you are probably going to have seizures and strokes and die as an infant. If you have 70% heteroplasmy you are probably going to have seizures and strokes and hearing loss when you are in your 60s. So, it's a very difficult decision.
		I think it is difficult to precisely quantify that. So, I think in general, severe conditions are mitochondrial mutations or conditions that can lead to significant functional impairment rather than mitochondrial disorders that may cause early deafness or diabetes at a later age in life. However, in mitochondrial disorders, it's not necessarily the genetic variants that causes the severity, it's the mutant load in a particular tissue. So, one genetic variant present in the woman that is only merely causing her a migraine and muscle aches may cause early death and significant neurological disease in a future child if the mutation load is severe.
	Open donation	I think it's important that I'm around if people have questions or they just want to meet me way, way down the line. I think that's important.
		To me, the legality of it, having to be anonymous, that in itself seems kind of unethical. I think that you should give people a choice. I don't really think that's the government's decision as to whether there's emphasis put on the third genetic contributor. That should be up to the parents. I don't think there's any reason to take the emphasis off a third person being involved. Like, what's the problem?

Note: AHRA, *Assisted Human Reproduction Act*; MRT, mitochondrial replacement therapy; CLSC, Centre local de services communautaires; MELAS, Mitochondrial Encephalopathy, Lactic Acidosis, and Stroke-like episodes

Lack of available resources for mitochondrial disease patients in Canada

All experts believed Canada's general approach to managing rare disease, in both research and practice, to be defective. The most frequent reasons appeared to be lack of suitable funding for research and health care, insufficient amount of rare disease specialists, and costly treatments. According to the experts, there are considerable differences in delivery of rare disease care across different provinces and territories, both in terms of availability of drugs for rare diseases (DRDs) and coverage. More importantly, there is no universal system of efficacy evaluation for DRDs. For example, although Health Canada takes charge in approving a drug, individual provinces decide whether to have it on the provincial drug plans and formularies. Experts also noted that the protocol and standard of care that physicians follow does not distinguish between the complexity of the disease.

According to experts, the current health care framework is not conducive to the extended time and care that complex mitochondrial diseases require.

All experts and patients reported that the length of time it took to receive a mitochondrial disease diagnosis ranged from 6 months to 10 years. Participants commented that this was likely due to the lack of knowledge by health care providers about rare disease and mitochondrial disease specifically. All patients raised the concern of being overlooked by the health care system. According to patients, the uncoordinated and inefficient care they were receiving was caused by the lack of a rare disease care system in Canada. All patients were also eager to see more awareness in emergency rooms (i.e., from triage nurses) about rare disease. As nurses are considered the first point of care in the hospital, a more comprehensive understanding of mitochondrial disease would make patients' frequent visits to the emergency room less troublesome.

Finally, two out of eight experts pinpointed the lack of effective collaborative efforts amongst Canadian researchers working in rare diseases. Additionally, to all experts, the education of medical students did not seem to foster a lot of understanding or appreciation of rare diseases.

Implications for mental health

There was consensus amongst patients that inherited mitochondrial diseases had exposed them and their families to immense emotional and physical distress. All patients with no children asserted that having a family history of mitochondrial disease was the reason why they had put their family-making plans on hold. A few patients reported suicide attempts amongst diagnosed family members. Procedural anxiety and suicidal thoughts as a result of mitochondrial disease were reported in children as young as 8 years old.

Reproductive autonomy and the desire for biological kinship

While not all participants saw MRT as a worthy cause to spend societal resources on, the notion of biological kinship was universally considered an individual "choice." Seven out of eight patients stated that they wanted their children to be genetically related to both them and their partners. Others stated that they would not consider MRT as their first option and that having a biological tie to their children was not an important issue. All patients with affected children stated that they would have wanted their children to experience life without a serious, progressive disease. The conventional egg and embryo donation, like adoption, was not interpreted as incompatible with motherhood as all participants believed that the desire for biological children is a personal matter. Participants also expanded on the reality of adoption in Canada, claiming that even under the best of circumstances, it could take years for the process of adoption to be successful. Although participants believed MRT to be an expensive journey, they argued that it could be more affordable as compared with adoption.

Terminology

Three sub-themes were discussed under terminology.

Germline genetic modification

Six out of eight experts did not consider MRT a germline genetic modification technology since the technique does not attempt to change the genes in either the nucleus or mitochondria. Others expanded on the idea that there is no getting around the fact that MRT is germline genetic manipulation, as the content of the maternal germline would be changed through the technique. However, these participants stated that the manner and implications of MRT as a germline modifying technique is quite distinct from those of manipulating the nuclear genome. The most preferred description of the technique appeared to be "assisted reproduction" and "mitochondrial donation."

Replacement therapy

Three out of eight experts believed "mitochondrial replacement therapy" to be a misleading description of the technology since the technique is not a therapeutic intervention for people who have mitochondrial diseases. Rather, it is a form of IVF that involves the manipulation of egg cells to give women affected by mitochondrial diseases the opportunity to have healthy biologically related children. Others believed "therapy" to be an appropriate account of the technique as MRT is a "therapeutic approach" that allows women with maternal mitochondrial diseases to procreate.

The sensationalized notion of a "third parent"

There was consensus amongst all participants that egg donors should not be considered third parents as the mitochondrial genome only accounts for a small component of the overall genome (<0.1%) (Wolf et al. 2015) and that the prospective children would largely have the genetics of the intending parents. There was consensus among egg donors that the "three-parent" terminology takes into consideration only the biological concept of being a parent while widely neglecting the social concept of a parent who raises a child. All egg donors made a clear distinction between a parent and an egg donor. Further, the egg donors did not differentiate their stance between donating their eggs to be used in the conventional IVF and donating their eggs to be used in the context of MRT.

Practical and theoretical risks and benefits

Three sub-themes emerged across the practical and theoretical risks and benefits.

The notion of sufficiently safe

Five out of eight experts indicated that key aspects of MRT require further investigation, for example through studies looking at early developmental and epigenetic changes. Others believed that the current experience of other countries (i.e., the UK) and evidence support MRT to be sufficiently safe (HFEA 2016). Potential risks of MRT were deemed minor when compared with the outcomes of having children affected by severe cases of mitochondrial disease: strokes, seizures, persistent vegetative state, and death. However, two out of eight experts felt offering MRT to patients at this time would still be too early because of the number of unknowns within the field (e.g., the nuclear-mitochondrial interactions). There was consensus among the experts on the necessity of conducting long-term follow ups of every birth that occurs through the use of MRT to understand the lasting implications of this technique.

In addition, five out of eight experts considered the concept of a nuclear and mitochondrial mismatch to be a theoretical risk. Mitochondrial haplotype matching is based on the concern that mitochondrial genetic variances in certain populations may not be safe to mix with nuclear genes from other populations (Wallace and Chalkia 2013). However, most responders believed this not to be a practical risk as biological experiments with cross-ethnic children and mixed races have turned out to be perfectly healthy.

Health care costs in diagnostics and medical treatments

Although mitochondrial disease patients do not comprise a large segment of the population, they do account for a large number of patient visits. According to the experts, mitochondrial disease patients often have significant needs in hospitals. Several experts stated that every year around 30% of all health care costs in Canada are attributed to admissions of patients with underlying genetic disorders and that promoting preventive technologies like MRT carries a societal benefit.

The slippery slope and deviation from a safe practice zone (i.e., treating infertility, lesbian motherhood, enhancement)

All experts were opposed to MRT being explored for other causes (i.e., infertility) due to the currently available poor evidence linking mitochondria with infertility in the general population. Seventeen out of 32 responders believed that MRT, if proven to be safe and effective, could be an opportunity worth exploring by women experiencing infertility as well as by lesbian couples to give both mothers a genetic contribution to their child. Improving oxygen consumption as a possible alternative of MRT in the context of sports (enhancement) was considered unethical and inappropriate by all responders.

The feasibility of clinical translation in Canada

Four sub-themes emerged across the feasibility of clinical translation.

The demand for MRT

Experts considered the number of women who would qualify to move forward with MRT across Canada to be quite rare, with only around 12–15 women being eligible per year. All experts asserted that there are enough qualified clinicians in Canada who would be able to deal with this small number of potential applicants. They also stated that MRT would have to be done in a tertiary care center, as a part of a very comprehensive team approach, in around six or seven facilities across Canada.

Coverage and equity of access

Sixteen out of 32 participants raised concerns in regard to the issue of inequality between provinces and territories in accessing innovative treatments. They stated that if MRT were to be approved in Canada, there must be decision-making at the federal level accepted by the provincial governments. Families affected by mitochondrial disorders may already be under significant financial burdens due to having an affected child. So, in the case that MRT were to only be made available in a few provinces, only those with the resources to travel would have access to the technique.

Twenty-one out of 32 participants believed that MRT should be funded by the government while others believed that the technology should follow the same path as IVF in Canada. As various areas of the health care system are in dire need of reform, most participants questioned the legitimacy of holding governments responsible for funding assisted reproduction. Since IVF is not universally covered in all provinces across Canada, a majority of participants believed that MRT should not be treated any differently.

The notion of "serious" mitochondrial disease

According to all experts, applying the labels of "serious" and "severe" mitochondrial diseases to identify MRT-eligible cases are open to interpretation. Because of challenges in predicting the degree of heteroplasmy (the ratio of mutant and wild type mtDNA molecules within a cell) transmitted (Hahn and Zuryn 2019), the risk of disease manifestation in future children is difficult to evaluate (Shoubridge and Wai 2007; Wai et al. 2008; Lee et al. 2012). As childhood death qualifies as a severe mitochondrial disease, the act of defining a serious mitochondrial disease proved to be complicated, according to the experts. Some raised examples of short stature, intellectual disability, and late-onset seizures, all of which significantly impact one's quality and quantity of life. A serious mitochondrial disease could be considered a condition that shortens the life span, or is expected to shorten the life span, and (or) has a major impact on the functional and intellectual capacity of an individual. Experts also believed it beneficial to have an oversight committee, similar to the advisory body for coordinating organ transplantation in Canada, requiring at least two clinicians in agreement to identify MRT-eligible cases.

Open donation

Three out of eight egg donors were in support of open donation, as they believed prospective children had the right to choose if they wanted to access their genetic history and contact all of their genetic contributors. A few egg donors considered legally regulated anonymous egg donations to be unethical and a by-product of the heteropatriarchal family structure of two parents. These egg donors asserted that the disclosure of the egg donors' information to future children to be solely a parental decision and not imposed by law.

Discussion

The concept of MRT research appeared to be widely supported by the participants. Experts, key stakeholders, and the public had different and sometimes skeptical views on the foreseeable clinical translation of MRT in Canada. Nonetheless, there was consensus on the need to undertake an evidence-based review of the current AHRA ban on MRT and the importance of recognizing reproductive autonomy in the MRT debate. There was also consensus amongst participants on the lack of support for mitochondrial disease patients in the current Canadian health care system. This suggests that Canada has much room to improve upon in regard to their training of experts and the funding of research for mitochondrial diseases.

The general consensus was that failing to address the AHRA ban on the research and safe clinical practice of new reproductive technologies, such as MRT, could fall short of providing society with the access to breakthrough scientific innovations. This will then prompt Canadians to seek MRT in jurisdictions with no established regulations, further exposing them to the associated risks and shortcomings of unregulated practices around the world. The potential dangers of medical tourism could further put a strain on the Canadian health care system.

MRT is often categorized and thus regulated as germline genetic modification. Although there is no general consensus in the research community on the status of MRT so far, there have been attempts at separating the technique from the field of germline genetic modification. The supposed normative significance of distinguishing MRT from impermissible germline modifying techniques are proposed to be that (*i*) with MRT, there is no direct modification or editing of the nDNA or the mtDNA sequence, (*ii*) mitochondria are responsible for solely the production of cellular energy and only accounts for <0.1% of the genome, and (*iii*) mtDNA is only transferred through the maternal line so male offspring do not transmit any changes (Gómez-Tatay et al. 2017).

The concern with crossing the germline barrier, as MRT purportedly does, is that it will open the floodgates and allow other germline interventions to take place. In this regard, existing prohibitions on MRT in countries like Canada that legislate research and clinical applications of assisted reproductive technology tend to generally prevent people from altering the DNA of the gametes and embryos intended to be used to create a pregnancy (Singapore Statutes Online 2005; Australian Government 2006; Ministry/Agency: Ministry of Health and Social Affairs 2006). These prohibitions are mainly in place to prevent so-called "designer babies" that would be made to have specific desirable genetic traits. The AHRA defines genome as "the totality of the deoxyribonucleic acid sequence of a particular cell" (AHRA 2004: Sec 2 (Interpretation and Application)), which includes mtDNA. Thus, establishing consensus on the status of MRT seems to be one of the primary steps toward discussing the clinical translation of MRT in Canada.

In identifying the challenges of clinical implementation of MRT, the obvious question addresses the legitimacy of using this technique to fulfill the desire of having and raising healthy, biologically related children. It has been argued that the interest in having genetically related children is broad and strong and that MRT extends the reproductive freedom of women (Ishii and Palacios-González 2017;

Schaefer and Labude 2017). However, since the technology is neither a cure nor a therapeutic intervention for those with mitochondrial diseases, the value of MRT rests solely in having healthy, biologically related children. In this sense, the desire to use MRT may not appear to be a priority worth allocating societal resources toward, because alternatives exist, such as egg and embryo donation, as well as adoption (Rulli 2016; Baylis 2017). A majority of patients (seven out of eight) did not consider the alternatives to MRT viable options. Respect for individuals' autonomy, as a fundamental bioethical principle, guides the process of reproductive rights, which needs to be considered and addressed in greater detail in assessing the risks and benefits of MRT.

Limitations

As with most qualitative research, we cannot assert that our findings are universal. Except for those from the general public, our participants belong to categories of individuals who are already likely to have a positive bias toward the clinical implementation of MRT. As bioethicists' perspectives are already reflected in the literature to a great extent (Baylis 2013, 2017, 2018), we sought to talk to Canadians who had not been heard in the MRT debate. A greater variety of health technology evaluation expert perspectives (e.g., economists) could also further help enrich this debate.

As we aimed to talk to stakeholders and experts across Canada, we relied on phone interviews 70% of the time, which may have served as a limitation in the study design as we were unable to assess body language and nonverbal cues. We were also not able to collect data in all provinces and territories. However, due to the nature of mitochondrial expertise in Canada (an already scarce commodity), there is not a very large pool of experts to choose from. This affects the number of individuals who have a suspicion of or an established diagnosis of mitochondrial diseases, which was the patient inclusion criteria in our study. Also, we were not able to collect data on Indigenous peoples affected by mitochondrial diseases. There is a glaring inequality in accessibility and availability of health services between Indigenous communities and the rest of Canada due to socioeconomic status and geographical location as well as discrimination and stereotyping. How the Indigenous community perceive the emerging reproductive technology needs to be considered and addressed in greater detail in considering the clinical translation of MRT in Canada.

Conclusion

Because clinics in jurisdictions where laws are less strict or nonexistent are moving forward with clinical applications of MRT, efforts must be made to consider what the clinical translation of this technology would look like from a scientific, ethical, and policy perspective for Canada. This study takes the first step in focusing on the Canadian perspective on MRT and invites the possibility of future work to further the discussion. Additional work is needed to engage the greater public in exploring the need for a revised AHRA in regard to furthering research in the field of new reproductive technologies. Deliberative engagements will allow for discussions of both the potential and uncertainty of MRT providing a critical reflection on the strengths and weaknesses of current governmental strategies. Advocating for the needs of mitochondrial disease patients is a necessary next step to spread awareness in the community about the lack of a Canadian rare disease care system. This could further help policymakers outline elements to be considered in a robust national MRT strategy.

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Author contributions

FN conceived and designed the study. FN performed the experiments/collected the data. FN and ML analyzed and interpreted the data. FN and YJ contributed resources. FN, ML, and YJ drafted or revised the manuscript.

Competing interests

Yann Joly is an editorial board member.

Data availability statement

All relevant data are within the paper and in the Supplementary Material.

Supplementary materials

The following Supplementary Material is available with the article through the journal website at doi:10.1139/facets-2020-0062.

Supplementary Material 1

Supplementary Material 2

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