Clinical introduction of mitochondrial replacement therapy in Canada: Towards a robust national strategy

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ABSTRACT

Mitochondrial Replacement Therapy (MRT) is a new type of in vitro fertilization (IVF) that aims to prevent the transmission of mitochondrial diseases, transferred through the maternal line, by replacing mutated mitochondrial DNA with normal mitochondria from a healthy egg donor. As a result of MRT, permanent changes are made to the germline that could be passed on to future generations; thus, this so-called "three-parent IVF" is considered a form of germline genetic modification. Apart from the United Kingdom, the first country to approve MRT in 2015, only a few other countries have considered this controversial technique through public policy. In Canada, the 2004 *Assisted Human Reproduction Act* (AHRA) prohibits any practice that introduces heritable changes into the germline. As such, MRT is prohibited in both research and clinical contexts. Certain clinics in jurisdictions with less strict or non-existent regulation of health technologies are moving forward with clinical uses of MRT (i.e., Ukraine and Greece). To date, seventeen babies have been born through the use of MRT worldwide. As the progress of reproductive technologies continues to push the ethical and legal boundaries, the need for an updated AHRA that can keep up with the current and future technological advancements resonates more powerfully than ever. Considering the mounting concerns about reproductive tourism and the alternative uses of MRT, it is important to address the key issues in the MRT policy discussions and expand on the underlying ethical, legal, and policy issues surrounding MRT's clinical translation. The objective of this thesis is to contribute to the body of evidence available to Canadian policymakers on the clinical implementation of MRT and assess the relevance of the AHRA's prohibition of this technology. I aimed to (1) identify and expand on key socio-ethical and policy issues in the MRT discussion; (2) explore various stakeholders and the public's attitudes

toward the clinical translation of MRT in Canada; and (3) provide policymakers with evidence-based data and key MRT policy principles suited to the Canadian healthcare context. I conducted a review of the relevant academic sources which characterized the socio-ethical issues and scientific advancements of MRT. Next, I developed semi-structured interviews designed to assess the attitudes of Canadian stakeholders, including scientists, clinicians, patients, and egg donors, as well as the general public concerning MRT. Lastly, through the review of MRT's policy literature in combination with the results of my qualitative analysis, I proposed evidence-based policy points to consider in the clinical introduction of MRT in Canada.

RÉSUMÉ

La thérapie de remplacement mitochondrial (TRM) est un nouveau type de fécondation in vitro (FIV) qui vise à prévenir la transmission de maladies mitochondriales, transférées par la lignée maternelle, en remplaçant l'ADN mitochondrial muté par des mitochondries normales d'une donneuse d'ovule en santé. Des changements permanents sont apportés à la lignée germinale par la TRM, qui peuvent être transférées aux générations futures. Ainsi, cette soi-disant “FIV à trois parents” est considérée comme une forme de modification génétique de la lignée germinale. Hormis le Royaume-Uni, premier pays à avoir approuvé le TRM en 2015, seulement quelques autres pays ont réglementé cette technique controversée par l’entremise de leurs politiques publiques. Au Canada, la *Loi sur la procréation assistée* (2004) interdit toute pratique qui introduit des changements héréditaires dans la lignée germinale. Par conséquent, la TRM est interdite dans les contextes de recherche et clinique. Certaines cliniques dans les juridictions où la réglementation des technologies de la santé est moins stricte ou inexistante se dirigent vers l’utilisations cliniques de la TRM (l'Ukraine et la Grèce). Jusqu'à présent, seize bébés sont nés au moyen de la TRM dans le monde entier. Alors que les progrès des technologies de la reproduction continuent de repousser les limites éthiques et juridiques, la nécessité d'une Loi sur la procréation assistée à jour, capable de suivre les progrès technologiques actuels et futurs, résonne plus que jamais. Compte tenu de l'avancement du débat canadien sur la TRM et des préoccupations croissantes concernant le tourisme reproductif et les utilisations alternatives de la TRM, il est important d'aborder les principales questions dans les discussions politiques sur la TRM et de considérer les aspects éthiques, juridiques et politiques sous-jacents entourant la traduction clinique de la TRM. L’objectif de ma thèse est de contribuer au corpus d’informations dont disposent les décideurs

canadiens sur la mise en œuvre clinique de la TRM et d'évaluer la pertinence de l'interdiction de cette technologie par la *Loi sur la procréation assistée*. Je visais à (1) identifier et développer les principales questions socio-éthiques et politiques dans la discussion sur la TRM; (2) explorer les attitudes de divers intervenants et du public à l'égard de l'application clinique de la TRM au Canada; et (3) fournir aux décideurs politiques des données factuelles et des principes politiques clés en matière de TRM adaptés au contexte canadien des soins de santé. J'ai effectué un examen des sources académiques pertinentes qui ont caractérisé les problèmes socio-éthiques et les progrès scientifiques de la TRM. Ensuite, j'ai développé des entrevues semi-structurées conçues pour évaluer les attitudes des intervenants canadiens, y compris des scientifiques, des cliniciens, des patients et des donneuses d'ovules ainsi que le grand public concernant la TRM. Enfin, par l'examen de la documentation sur les politiques de TRM en combinaison avec les résultats de mon analyse qualitative, j'ai proposé des suggestions pour des politiques fondés sur des données probantes à prendre en compte dans l'introduction clinique de la TRM au Canada.

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LIST OF ABBREVIATIONS

AHRA	*Assisted Human Reproduction Act*
ART	Assisted Reproductive Technology
AHR	Assisted Human Reproduction
ATP	Adenosine Triphosphate
BAC	Bioethics Advisory Committee
CBC	Canadian Broadcasting Corporation
CIHR	Canadian Institutes of Health Research
CGS-D	Canada Graduate Scholarship Doctoral Awards
CRISPR	Clusters of Regularly Interspaced Short Palindromic Repeats
CGP	Centre of Genomics and Policy
CIGM	Conditionally Inheritable Genomic Modification
COVID-19	Coronavirus Disease of 2019
CVS	Chorionic Villus Sampling
DNA	Deoxyribonucleic acid
DL-Nadiya	Darwin Life-Nadiya
DRDs	Drugs for Rare Diseases
ENMC	European Neuromuscular Centre
ELSI	Ethical, Legal, and Social Implications
ESHRE	European Society of Human Reproduction and Embryology
FDA	Food and Drug Administration
GVT	Germline Vesicle Transfer
HFEA	Human Fertilisation and Embryology Authority
HFE Act	*Human Fertilisation and Embryology Act*
HHS	Department of Health and Human Services
HGEN	Human Genetics
IVF	in vitro fertilization
ISSCR	International Society for Stem Cell Research
IRB	Institutional Review Board

IBC	International Bioethics Committee
LS	Leigh syndrome
LHON	Leber Hereditary Optic Neuropathy
MRT	Mitochondrial Replacement Therapy
mtDNA	Mitochondrial DNA
MST	Maternal Spindle Transfer
MFF	Market Forces Factor
MELAS	Mitochondrial Encephalopathy, Lactic Acidosis, and Stroke-like episodes
MERRF	Myoclonic Epilepsy with Ragged-Red Fibers
MAiD	Medical Assistance in Dying
NASEM	National Academies of Sciences, Medicine, and Engineering
NHMRC	National Health and Medical Research Council
NIH	National Institutes of Health
nDNA	nuclear DNA
PNT	Pronuclear Transfer
PND	Prenatal Diagnosis
PGD	pre-implantation genetic diagnosis
PBT	Polar Body Transfer
RNA	Ribonucleic acid
SCN	Stem Cell Network
SRQR	Standards for Reporting Qualitative Research
TCC	Trainee Communication Committee
UK	United Kingdom
US	United States

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THESIS PREFACE

This is a manuscript-based thesis consisting of six chapters. Chapter 1 introduces the socio-ethical and scientific aspects of Mitochondrial Replacement Therapy (MRT). It also describes the overall objectives, hypothesis, and research questions. Chapters 2-4 are original research chapters containing manuscripts for which the thesis author is the first author. Chapter 2 is a manuscript published in *FACETS*. It covers the results of a qualitative interview study that synthesizes the attitudes from the public and key stakeholders (mitochondrial disease patients, researchers, clinicians, and egg donors) about researching and developing MRT in Canada. Chapter 3 is a manuscript under review for publication in *the Journal of Law, Medicine & Ethics*, which addresses the strengths and weaknesses of several objections against promoting MRT. Chapter 4 is a manuscript submitted to *PLOS ONE* for publication. It reviews MRT laws and policies and, in combination with the results of Chapter 2, provides policymakers with evidence-based points to consider in MRT's path to the clinic in Canada. The specific contribution of each author of the manuscripts presented in Chapters 2-4 is detailed in each Chapter's preface. Chapter 5 is a general Discussion that puts all the thesis research in context with Canada's policy framework. Chapter 6 presents the Conclusion and Future Directions.

Appendix A lists other publications to which the thesis author has contributed during her Ph.D. thesis project. Appendix B and C contain supplementary material for Chapters 2 and 4, respectively.

CHAPTER 1: INTRODUCTION

Mitochondrial Replacement Therapy (MRT) is a novel class of in vitro fertilization (IVF) that aims to prevent mitochondrial diseases by replacing mutated mitochondrial DNA (mtDNA) with normal mitochondria from a healthy egg donor. To further examine the feasibility of developing a robust strategy for the clinical translation of MRT, there is a need to identify and expand on challenges that arise from this so-called "three-parent IVF." Thus far, clinical uses of MRT raise concerns regarding reproductive tourism and unproven uses of this technique (i.e., to treat infertility), further highlighting the importance of addressing critical issues in MRT policy discussions. This introductory chapter identifies and describes the most prominent ethical challenges to implementing MRT in the clinical context. Here, I first cover the basics of mitochondrial diseases and MRT. Next, I present the identified ethical issues and thesis hypothesis and objectives.

1.1 Mitochondrial diseases

Mitochondria are membrane-bound microscopic organelles found in the cytoplasm of eukaryotic cells. They are responsible for cellular respiration and energy production in the form of adenosine triphosphate (ATP). Besides producing energy, mitochondria store calcium for cell signaling and play key roles in cell growth and death. Mitochondrial DNA is a small circular double-stranded molecule containing 37 genes. These genes encode two ribosomal RNAs, 22 transfer RNAs, and 13 proteins that are core components of mitochondrial respiratory complexes (Wolf et al. 2015; Patananan et al. 2016).

Subject to its nature, structure, and function, a given cell can house anywhere between zero (red blood cells) to thousands of mitochondria. Mitochondria have their own DNA, separate from the nuclear DNA (nDNA) (Craven et al. 2017). In humans, mtDNA is exclusively maternally inherited, and its biparental inheritance is not a common occurrence (Rius et al. 2019). However, an article published in *Proceedings of the National Academy of Sciences* in 2018 identified three unrelated multigeneration families with a high level of mtDNA heteroplasmy (mtDNA from both maternal and paternal sources) in a total of 17 individuals. The study concluded that, although the maternal inheritance of the mtDNA principle remains plausible, there are some unusual cases where mtDNA, and consequently mitochondrial diseases, could be passed to the offspring from the paternal line (Luo et al. 2018).

Harmful mutations in the mtDNA cause rare, debilitating, and progressive disorders that can be fatal in childhood, commonly impacting organs with the highest energy demands (Taylor and Turnbull 2005). Over 300 mtDNA mutations have been identified as linked to a broad phenotypic spectrum, varying from mild myopathies to deleterious multisystem syndromes. While some mitochondrial disorders only affect a single organ, such as the eye in Leber Hereditary Optic Neuropathy (LHON), most mitochondrial diseases strike several organ systems and manifest with marked neurologic, metabolic, and myopathic characteristics. Many individuals with a mutation in their mtDNA display an array of clinical features that express themselves as a distinct clinical syndrome, such as Mitochondrial Encephalomyopathy with Lactic Acidosis and Stroke-like episodes (MELAS), Myoclonic Epilepsy with Ragged-Red Fibers (MERRF), or Leigh syndrome (LS) (Schon et al. 2012; Gorman et al. 2016).

Mitochondrial DNA deficiencies have significant genetic and clinical heterogeneity, making prevalence estimates a real challenge (Alston et al. 2016). Estimates range from 1 in 200 individuals harboring a potentially disease-causing mtDNA mutation to 1 in 4300 people affected by primary mtDNA-related diseases (Craven et al. 2017; Thompson et al. 2020; Gorman et al. 2015). There is no cure for inherited mitochondrial diseases, and for most patients, treatment is limited to symptomatic relief and the early detection of symptoms (Ng and Turnbull 2020).

1.2 Mitochondrial Replacement Therapy (MRT)

Given the absence of efficient treatments and the extremely disabling phenotypes in many patients, preventing the transmission of mutations in the mtDNA is an important goal for affected families. For those who hope to have healthy children, egg and embryo donation and adoption are amongst available choices (Baylis 2013). For families with mitochondrial diseases who wish to have healthy genetically related children, Mitochondrial Replacement Therapy (MRT) is a possible alternative (Craven et al. 2018). MRT is a new kind of in vitro fertilization (IVF) that proposes to prevent mitochondrial diseases by substituting mutated mtDNA for normal mitochondria from a healthy egg donor. Methods of MRT include Pronuclear Transfer (PNT), Maternal Spindle Transfer (MST), Polar Body Transfer (PBT), and Germline Vesicle Transfer (GVT) (NHMRC 2020a). In PNT, the intending mother's oocytes and healthy donated eggs are fertilized simultaneously with the intending father's sperm. Both sets of fertilized oocytes are left to develop until the early zygote stage, where the pronuclei are visible. The pronuclei of zygotes from donated oocytes are removed, discarded, and replaced by the intending parents' pronuclei (Craven et al. 2010). In MST, the transfer of parental nDNA occurs before fertilization. This technique requires

removing and discarding the metaphase II spindle from the donor oocyte. The chromosome-spindle complex will be removed from the intending mother's oocyte and transferred to the enucleated donor oocyte, followed by fertilization with the intending father's sperm (Kang et al. 2016).

Proof of concept studies for PNT and MST in rodents, non-human primates, and human embryos have existed for over thirty years. Groundbreaking research since 1984 has indicated that both procedures are compatible with the development of embryos and, in the case of rodents and non-human primates, can create healthy offspring (McGrath and Solter 1984; Shoubridge and Wai 2007; Tachibana et al. 2009; Kang et al. 2016; Craven et al. 2010). PBT and GVT, on the other hand, are emerging techniques that have not been validated in the clinical context yet. Research suggests these techniques are not currently as improved as MST and PNT (NHMRC 2020a; Tang et al. 2019).

1.3 Policy developments

The United Kingdom (UK) is the first and only country to regulate PNT and MST's clinical applications (*Mitochondrial Donation Regulations 2015*). Following the UK's lead, Australia appears to be on a similar path toward considering the clinical implementation of MRT (Mito Foundation 2021). CHAPTER 4 describes MRT policy developments in the countries as mentioned earlier and other jurisdictions in detail.

1.4 Researching and developing MRT: Ethical issues

Debates on the ethics of introducing new reproductive technologies are pivoted on the requirement of balancing possible benefits and risks and the reproductive freedom of prospective parents. Many challenges to the implementation of MRT in the clinical context have emerged in the literature. Common issues among assisted reproductive technologies include human dignity, informed consent, and the destruction of embryos (Dupras et al. 2018). Risks and benefits, the slippery slope toward germline genetic modification, and the implications of having a third genetic contributor are among the most cited issues regarding promoting MRT. Issues that require further exploration are the use of MRT as a preventive tool versus in other contexts, the importance of addressing the interest in genetic kinship, and the significance of establishing MRT's status.

1.4.1 Risks and benefits

1.4.1.1 Safety and Efficacy

Concerns over human germline modification techniques are primarily related to safety and efficacy limitations. While advances in MRT development might indicate readiness for clinical translation, there have been extensive debates about potential risks for future generations. In MRT, the presence of donor mtDNA adds a third DNA source that would be passed on to both sexes in the first generation (Wolf et al. 2015). This has ignited intense debates about potential risks for future generations (Fogleman et al. 2016; NASEM 2016; Nuffield 2012).

The first issue concerns mtDNA carryover and its potential implications. Carryover in MST embryos and embryonic stem cell lines has been reported to be below 1% in rhesus monkeys and human oocytes. Similarly, PNT in human zygotes has been reported to contain little mtDNA carryover (Tachibana et al. 2013; Lee et al. 2012; Craven et al. 2010). In most patients with mtDNA diseases, a threshold of 60% or higher of mutated mtDNA must be reached for the clinical manifestation of the disorder; as such, it has been reported to be unlikely that low mtDNA carryover during MRT would be problematic in the future (Fogleman, et al. 2016; Lee et al. 2012; Paull et al. 2013). Nevertheless, there remains a concern that in a few cases, the level of mutated mtDNA could increase during pregnancy and result in children affected by mitochondrial diseases. Therefore, the consensus surrounding MRT is that the technique can reduce the risk of mtDNA disease, but it *does not* guarantee prevention (Craven et al. 2018; Hyslop et al. 2016).

The next issue is the possible incompatibility between the nDNA and mtDNA from the egg donor. It has been reported that some mtDNA haplotypes could affect cell growth and reproduction and provide a selective advantage for cells with maternal mtDNA (Wallace and Chalkia 2013). Evaluating compatible donor mtDNA haplotypes has been suggested to avoid reversion to mutant mtDNA (NASEM 2016). Research studies that have proposed possible interactions between the nDNA and the mtDNA have been reportedly performed using highly inbred animal models. The potential risks of nuclear-mitochondrial incompatibility are believed to be very low in humans (Eyre-Walker 2017).

Another concern is that manipulation of the eggs or zygotes during MRT may cause epigenetic changes that result in developmental or health problems in the resulting children (Craven et al.

2010; Wang et al. 2014). So far, no significant differences in gene expression between genome-exchanged and unmanipulated cells have been reported (NHMRC 2020a; NASEM 2016).

As stated in the UK's scientific reports (2011-2016), there will always be some risks and uncertainties associated with the use of MRT in humans until it is implemented in the clinical context. Thus, MRT is highly recommended to be initially used as a risk reduction treatment for carefully selected patients (HFEA 2011-2016).

1.4.1.2 Harms to egg donors

Harms to egg donors are among existing objections to MRT. There are associated physical and psychological risks for egg donors, such as pain and cramping, ovarian hyperstimulation, mood changes, possible infertility, or damage to the ovaries associated with egg donation (Woodruff 2017). Moreover, egg donors might accept undue risks to their health because of financial need, even when informed of the potential risks, brings about concerns over the possible "coercion and exploitation" of underprivileged persons and minorities. According to some critics, that is reason enough to oppose techniques similar to MRT (Baylis 2013). Fear of potential harms to egg donors, according to others, is not a plausible reason for resisting the inclination for MRT, or any other assisted reproductive technology, as an appropriate MRT regulatory framework would significantly limit the likelihood of coercion and exploitation of egg donors (Palacios-González and Cavaliere 2018).

1.4.2 MRT and the slippery slope toward germline genetic modification

The issue with crossing the germline barrier, as MRT allegedly does, is that it will open the floodgates and enable other germline interferences. In the context of germline genetic modification techniques for the prevention of disease, there is a possibility for potential adverse events, such as eugenic practices and unacceptable genetic enhancements. Thus, the notion of a slippery slope is believed to be inherent in the context of all human germline genetic modification techniques (Newson and Wrigley 2017; Walton 2017). In this light, several international treaties and instruments have discussed and/or taken a stance on human genetic modification regarding (1) possible opposition with human dignity, (2) limited application (somatic editing for preventive, diagnostic, or therapeutic purposes), and (3) restriction on clinical applications of germline editing clinical trials. For example, Article 24 of the *Universal Declaration on the Human Genome and Human Rights* states that "germ-line interventions" could be "contrary to human dignity" (UNESCO, *Universal Declaration on the Human Genome and Human Rights* 1997), and Article 13 of the Council of Europe's *Convention on Human Rights and Biomedicine* expresses that "an intervention seeking to modify the human genome may only be undertaken for preventive, diagnostic or therapeutic purposes and only if its aim is not to introduce any modification in the genome of any descendants" (*Convention on Human Rights and Biomedicine* 1997). Furthermore, according to Article (9)(6) of the 2001 *European Union Directive on Clinical Trials*, "no gene therapy trials may be carried out which result in modifications to the subject's germline genetic identity" (Official Journal of the European Communities 2001). While acknowledging these stances, the nDNA could be regarded as fundamental to a person's genetic identity in ways that the mtDNA is not. The deemed importance of this distinction is proposed to be that, compared to

nuclear genetic modification, MRT is unlikely to alter the identity of the future person, does not introduce foreign components into the gene pool, and is less likely to be used for human enhancement (Scott and Wilkinson 2017).

1.4.3 The implications of having a third genetic contributor

There are several relevant ways in which the connection between genes and biological origins might determine identity. Dependent on what sense of identity is being assigned (e.g., genetic, numerical, or qualitative), it becomes clear that various issues regarding personal and social characteristics are raised by MRT (Nuffield 2012; NASEM 2016). MRT involves heritable genetic changes that, technically, affect one's genetic identity. One's genetic heritage may have profound implications for their personal identity; however, an individual's essence and identity extend also to include family dynamics, cultural narratives, and the reality of illness and disability, all of which shape one's narrative/social identity (Scully 2016). As for numerical identity (in contrast to qualitative identity), the question is whether MRT creates a new and numerically different child vs. affecting the features of a present child. If X and Y are numerically identical, it conveys that they are identical. If X and Y are qualitatively identical; however, it does not necessarily mean that they are identical but could be. If X and Y are numerically identical, they share all qualities; thus, they are qualitatively identical (Morrison 2021; Maverick Philosopher 2017). Considering this, since MRT is disruptive to an egg or zygote's integrity and continuity, it can be argued that it will be creating a numerically distinct individual (Liao 2017). Also, the development of qualitative properties through epigenetic interactions/changes could be identity-affecting (Wrigley et al. 2015).

The UK reports conducted by the Department of Health strongly dismissed the idea of a mitochondrial donor as a third parent. These reports concluded that children born using MRT have DNA from three people but that "the genes contributing to personal characteristics and traits come solely from the nuclear DNA" and that "the donated mitochondrial DNA will not affect those characteristics" (Department of Health 2014, 15-16). Also, according to the UK reports, since the nDNA from the parents provides most of the child's total genetic material (>99.9%), the contribution of the mitochondrial donor is quantitatively negligible to identity-forming characteristics (Department of Health 2014). How personal and identity-determining characteristics are defined in this context, though, is not clear.

Some critics call the UK reports' depiction of reality "unfortunate" since they imply that MRT babies are entirely of the intending parents' genetic makeup. According to these scholars, it is important to address the fact that children may challenge the idea of having only two parents later in life. Currently, the UK legislation grants access to non-identifying information relating to egg donors in case adult children born as a result of MRT were to seek them one day (HFEA 2021). This is, according to critics, "regrettable" and may cause "serious long-term psychological distress in the prospective children" and prevent them from developing a healthy sense of identity (MacKellar 2017, 136).

If identity-shaping features are considered physical characteristics and personality traits, one argument focuses on the fact that the mtDNA's primary function is to provide the cells with the energy required for normal functioning; therefore, it would not be considered identity altering in

nature. In this respect, the nDNA is regarded as fundamental to a person's identity in ways that the mtDNA is not. This is because MRT does not introduce foreign components into the gene pool and is less likely to be used for human enhancement (Scott and Wilkinson 2017). On the contrary, based on available evidence, some scholars challenge the view that MRT does not raise the same ethical issues as the modification of the nDNA. According to these critics, mitochondria are more than responsible for just the production of cellular energy; thus, they may have a relevant effect on our characteristics and identity. This results from a particular association between the nDNA and the mtDNA (Gómez-Tatay et al. 2017; Bredenoord et al. 2011).

Further to this point, others argue that the egg donor presents an embryo with the mtDNA and an essential environment for its growth. Although it has been presented that the mtDNA counts for less than 0.1 percent of the entire genome (Taylor et al. 2001), some scholars declare that this small amount is critical enough. After all, a child without mtDNA-related disease is born because of healthy mtDNA from a donor. A disease-free life narrative would substantially impact one's development and identity (Haimes et al. 2015). Others argue that one needs to be more than a genetic contributor to be a parent. They believe that the quantitatively negligible mtDNA from a mitochondrial donor saves one from disease and suffering and that complaining about an identity crisis by healthy children in the future is unlikely. This argument is taken a step further, stating that only those condemned to a life of pain and illness would have something to complain about and blame those who are against the clinical introduction of MRT (Harris 2015; Harris 2016).

1.5 Underexplored areas

Finally, three critical areas regarding MRT appear to require further exploration: (1) The tension between the applications of MRT, (2) the importance of addressing genetic kinship, and (3) the significance of establishing the status of MRT.

1.5.1 The use of MRT as a preventive tool versus in other contexts (i.e., infertility and lesbian motherhood)

A key area regarding MRT that appears to require further exploration is the tension between the possible applications of MRT. While the primary purpose of MRT is to prevent mitochondrial diseases, the technology could also be used in other contexts, such as "treating infertility" and lesbian motherhood, where maintaining genetic ties to both mothers may be preferred (Palacios-González and Cavaliere 2018; Cavaliere and Palacios-González 2018). The claim that MRT may represent a new era in assisted reproductive technology as a means of solving infertility issues is that the mitochondria in eggs are the cause of some cases of infertility (Coghlan 2016). Although there is no available evidence linking mitochondria with infertility in the general population, clinics in jurisdictions such as Greece and Ukraine are moving forward with clinical applications of MRT to "treat infertility" (Nadiya clinic 2021; Institute of Life 2021; Cecchino et al. 2018). CHAPTER 4 discusses the details of MRT's clinical applications.

1.5.2 Genetic kinship

While avoiding the risk of severe mitochondrial diseases, it has been argued that prohibiting the clinical applications of MRT would be denying future children the benefit of a substantial genetic relationship with their gestational mothers (Cohen et al. 2019; Adashi and Cohen 2017). According to some critics, however, the sole value of MRT rests in having healthy, genetically related children. Therefore, the technique has limited social value (Rulli 2016). CHAPTER 3 explores the notion of MRT and the legitimacy of genetic kinship in more detail.

1.5.3 Establishing the status of MRT

There is no consensus in the research community on the status (i.e., category of inheritable modification occupied by the technique) of MRT so far. According to some scholars, MRT does not precisely meet the requirements of the established narrow categories of somatic or germline modification techniques. As such, a novel account is required to define it. Newson and Wrigley propose "Conditionally Inheritable Genomic Modification (CIGM)" as a subcategory of inheritable modification for classifying MRT. This division be a non-exclusive, inheritable modification class that, unlike other genetic modification techniques, recognizes the unique pattern of the mtDNA inheritance (i.e., matrilineal transmission) (Newson and Wrigley 2017). However, others believe that this theoretical attempt at separating MRT from other germline genetic modifications is incorrect. These scholars state that germline modification techniques introduce heritable changes in gametes or embryos. In this sense, changes are made to the germline through MRT that would be transmitted to future generations (Gómez-Tatay et al. 2017). CHAPTER 4

focuses on the status of MRT and describes the UK, the US, and Australia's approaches in attempting to classify the technology.

1.6 Canada

In Canada, Assisted Human Reproduction (AHR) and related research is regulated by the *Assisted Human Reproduction Act* (AHRA) (2004). Article 5(1)(f) of the AHRA prohibits any practice that introduces heritable changes into the germline: "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." (*Assisted Human Reproduction Act*, Section 5 (Prohibited Activities)). As such, MRT is prohibited in both research and clinical contexts. This prohibition can inadvertently encourage medical tourism practices, and its relevance has been questioned by several Canadian experts (Knoppers et al. 2017b).

1.7 Objective, hypothesis, and research questions

As reproductive technologies continue to redefine ethical and legal boundaries, there is a need for an updated AHRA that can keep up with current and future advancements of assisted reproductive technology. This thesis project aims to contribute to the body of evidence available to policymakers on the clinical implementation of MRT in Canada and assess the relevance of the AHRA's prohibition of this technology.

Under the AHRA, MRT is categorized and regulated as germline genetic modification. When the AHRA came into force in 2004, the concept of germline genetic modification in the context of MRT was not yet explored. I hypothesized that this is among MRT policy issues that create a strong need for engaging stakeholders and reaching consensus on the status of MRT in a robust national biotechnology strategy.

With this objective and hypothesis in mind, I aimed to:

(1) Identify and expand on key socio-ethical and policy issues in the MRT discussion.
(2) Explore key stakeholders and the public's attitudes toward the clinical translation of MRT in Canada.
(3) Provide policymakers with evidence-based data and key policy points to consider in MRT's clinical translation in Canada.

CHAPTER 2: Clinical translation of mitochondrial replacement therapy in Canada: a qualitative study of stakeholders' attitudes

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Preface

Exploring public views about new assisted reproductive technologies can address the influence of socio-cultural factors upon stakeholders' motives for using these techniques. In this manuscript, the knowledge produced through the review of MRT's literature was used to develop semi-structured interviews designed to assess the attitudes of the public and key stakeholders (researchers, clinicians, patients, and egg donors (so-called "third parents")) regarding MRT.

Author contributions:

- Forough Noohi designed the study and the interview guide, conducted and transcribed half of the interviews verbatim, initially organized and coded all transcripts into manageable text segments, and systematically coded them using NVivo12. She obtained the ethics approval from McGill, wrote the manuscript and managed its submission, revisions, and contact with the editor.
- Miranda Li transcribed the other half of the interviews verbatim and cross-checked the coded manuscripts produced by FN.
- Yann Joly read and revised the manuscript.
- All authors read and approved the final manuscript.

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

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2.1 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

2.2 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).

2.2.1 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).

2.2.2 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)).

2.3 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.

2.4 Materials and Methods

2.4.1 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 (Patton 2015; Ritchie et al. 2013).

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.

2.4.2 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 (Patton 2015; Ritchie et al. 2013).

2.4.3 Ethics approval

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

2.5 Results

2.5.1 Participants

We conducted a total of 32 interviews (see Table 2.1). We reviewed emerging themes until saturation was reached. We sent email invitations for interviews to 56 individuals across Canada. 23 people did not respond to the request for interview and one person declined. 23 interviews were conducted over the phone and 9 were conducted in person, each lasting between 45 to 200 minutes. 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 2.2 summarizes the identified themes and sub-themes, along with example quotes.

2.5.2 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 in order 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.

2.5.3 Motives for using MRT

Three sub-themes emerged across motives for using MRT.

Table 2.1: Research participants.

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

Table 2.2: 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 days passes… and I am thinking in my head, they have got to be taking this seriously, right?

Themes	Sub-themes	Example quotes
		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

Themes	Sub-themes	Example quotes
		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.
	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

Themes	Sub-themes	Example quotes
		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.

Themes	Sub-themes	Example quotes
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.
	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.

Themes	Sub-themes	Example quotes
	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

2.5.3.1 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.

2.5.3.2 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.

2.5.3.3 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.

2.5.4 Terminology

Three sub-themes were discussed under terminology.

2.5.4.1 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."

2.5.4.2 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.

2.5.4.3 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.

2.5.5 Practical and theoretical risks and benefits

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

2.5.5.1 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.

2.5.5.2 Healthcare 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.

2.5.5.3 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.

2.5.6 The feasibility of clinical translation in Canada

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

2.5.6.1 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.

2.5.6.2 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.

2.5.6.3 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**.**

2.5.6.4 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.

2.6 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 (G´omez-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.

2.7 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; Baylis 2017; Baylis 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 for seventy percent 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.

2.8 Conclusion

Since clinics in jurisdictions where laws are less strict or non-existent 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. Further 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 mitochondrial donation 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

2.10 References

Assisted Human Reproduction Act, S.C. 2004, c. 2. Section 2 (Interpretation and Application). Definitions [online]: Available from laws-lois.justice.gc.ca/eng/acts/a-13.4/page-1.html#h-6012.

Go to Citation Google Scholar

Assisted Human Reproduction Act, S.C. 2004, c. 2. Section 5 (Prohibited Activities). Article (5)(1)(f) [online]: Available from laws-lois.justice.gc.ca/eng/acts/a-13.4/page-1.html#h-6052.
Go to Citation Google Scholar

Assisted Human Reproduction Act, S.C. 2004, c. 2. Section 60 (Offences). Article 60(a) [online]: Available from laws-lois.justice.gc.ca/eng/acts/a-13.4/page-4.html#h-6276.
Go to Citation Google Scholar

Australian Government. 2006. Prohibition of Human Cloning for Reproduction and the Regulation of Human Embryo Research Amendment Act 2006. No. 172. Part 2—Prohibited practices. Division 1—Practices that are completely prohibited (15 Offence)—heritable alterations to genome [online]: Available from legislation.gov.au/Details/C2006A00172.
Go to Citation Google Scholar

Australian Government. 2019. Australian Government response to the Senate Community Affairs References Committee Inquiry into: the science of mitochondrial donation and related matters [online]: Available from aph.gov.au/Parliamentary_Business/Committees/Senate/Community_Affairs/MitochondrialDonation/Government_Response/.
Go to Citation Google Scholar

Baylis F. 2013. The ethics of creating children with three genetic parents. Reproductive BioMedicine Online, 26(6): 531–534.
Go to Citation Crossref PubMed Google Scholar

Baylis F. 2017. Human nuclear genome transfer (so-called mitochondrial replacement): clearing the underbrush. Bioethics, 31(1): 7–19.
Go to Citation Crossref PubMed Google Scholar

Baylis F. 2018. 'No' to lesbian motherhood using human nuclear genome transfer. Journal of Medical Ethics, 44: 865–867.
Go to Citation Crossref PubMed Google Scholar

BioTexCom. 2021. Center for human reproduction [online]: Available from biotexcom.com/services/#mitochondrial-replacement-therapy.
Go to Citation Google Scholar

Castro RJ. 2016. Mitochondrial replacement therapy: the UK and US regulatory landscapes. Journal of Law and the Biosciences, 3(3): 726–735.
Go to Citation Crossref PubMed Google Scholar

Cavaliere G, and Palacios-González C. 2018. Lesbian motherhood and mitochondrial replacement techniques: reproductive freedom and genetic kinship. Journal of Medical Ethics, 44: 835–842.
Go to Citation Crossref PubMed Google Scholar

Cecchino GN, Seli E, Alves da Motta EL, and García-Velasco JA. 2018. The role of mitochondrial activity in female fertility and assisted reproductive technologies: overview and current insights. Reproductive BioMedicine Online, 36(6): 686–697.
Go to Citation Crossref PubMed Google Scholar

Community Affairs References Committee. 27 June 2018. Science of mitochondrial donation and related matters. Commonwealth of Australia [online]: Available from aph.gov.au/Parliamentary_Business/Committees/Senate/Community_Affairs/MitochondrialDonation.
Go to Citation Google Scholar

Craven L, Tuppen HA, Greggains GD, Harbottle SJ, Murphy JL, Cree LM, et al. 2010. Pronuclear transfer in human embryos to prevent transmission of mitochondrial DNA disease. Nature, 465(7294): 82–85.
Go to Citation Crossref PubMed Google Scholar

Creswell JW, and Creswell JD. 2017. Research design: Qualitative, quantitative, and mixed methods approaches. Sage Publications. [online]: Available from us.sagepub.com/en-us/nam/research-design/book255675.
Go to Citation Google Scholar

Darwin Life Nadiya. 2021 [online]: Available from nadiya.clinic/services/pro-transfer/.
Go to Citation Google Scholar

Gómez-Tatay L, Hernández-Andreu JM, and Aznar J. 2017. Mitochondrial modification techniques and ethical issues. Journal of Clinical Medicine, 6(3): 25.
Go to Citation Crossref PubMed Google Scholar

Gorman GS, Schaefer AM, Ng Y, Gomez N, Blakely EL, Alston CL, et al. 2015. Prevalence of nuclear and mitochondrial DNA mutations related to adult mitochondrial disease. Annals of Neurology, 77(5): 753–759.
Go to Citation Crossref PubMed Google Scholar

Hahn A, and Zuryn S. 2019. The cellular mitochondrial genome landscape in disease. Trends in Cell Biology, 29(3): 227–240.
Go to Citation Crossref PubMed Google Scholar

Human Fertilisation and Embryology Authority (HFEA). 1990. Human Fertilisation and Embryology Act 1990. Section 3ZA [online]: Available from legislation.gov.uk/ukpga/1990/37/section/3ZA.
Go to Citation Google Scholar

Human Fertilisation and Embryology Authority (HFEA). November 2016. Scientific review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception: 2016 update. Report to the Human Fertilisation and Embryology Authority (HFEA) [online]: Available from hfea.gov.uk/media/2611/fourth_scientific_review_mitochondria_2016.pdf.
Go to Citation Google Scholar

Institute of Life. 2021 [online]: Available from iolife.eu/treatments/innovative-treatments/maternal-spindle-transfer-technique-mst-treatment-infertility/.
Go to Citation Google Scholar

Ishii T, and Palacios-González C. 2017. Mitochondrial replacement techniques: genetic relatedness, gender implications, and justice. Gender and the Genome, 1: 129–134.
Go to Citation Crossref PubMed Google Scholar

Kang E, Wu J, Gutierrez NM, Koski A, Tippner-Hedges R, Agaronyan K, et al. 2016. Mitochondrial replacement in human oocytes carrying pathogenic mitochondrial DNA mutations. Nature, 540(7632): 270–275.
Go to Citation Crossref PubMed Google Scholar

Lee HS, Ma H, Juanes RC, Tachibana M, Sparman M, Woodward J, et al. 2012. Rapid mitochondrial DNA segregation in primate preimplantation embryos precedes somatic and germline bottleneck. Cell Reports, 1(5): 506–515.
Go to Citation Crossref PubMed Google Scholar

Ministry/Agency: Ministry of Health and Social Affairs. 2006. The Genetic Integrity Act (2006:351). Swedish Code of Statutes no 2006:351 [online]: Available from icj.org/wp-content/uploads/2013/05/Sweden-Genetic-Integrity-Act-2006-eng.pdf.
Go to Citation Google Scholar

Mito Foundation. 2021 [online]: Available from mito.org.au/mitochondrial-donation/.

Go to Citation Google Scholar

National Academies of Sciences, Engineering, and Medicine (NASEM). 2016. Mitochondrial replacement techniques: ethical, social, and policy considerations. The National Academies Press, Washington, D.C.
Go to Citation Crossref Google Scholar

Ng YS, and Turnbull DM. 2020. When to think about mitochondrial disease. Practical Neurology, 20: 260–261.
Go to Citation Crossref PubMed Google Scholar

Patton MQ. 2015. Qualitative research & evaluation methods: integrating theory and practice. 4th edition. Sage Publications, Thousand Oaks, California.
Go to Citation Google Scholar

QSR International. 2020 [online]: Available from qsrinternational.com/nvivo-qualitative-data-analysis-software/about/nvivo.
Go to Citation Google Scholar

Rhys-Evans S. 2020. Should mitochondrial replacement therapy be funded by the National Health Service? Journal of Medical Ethics. Published Online First: 23 June 2020.
Go to Citation Crossref PubMed Google Scholar

Ritchie J, Lewis J, Nicholls CM, and Ormston R (*Editors*). 2013. Qualitative research practice: A guide for social science students and researchers. Sage Publications, Thousand Oaks, California.
Go to Citation Google Scholar

Rulli T. 2016. What is the value of three-parent IVF? Hastings Center Report, 46(4): 38–47.
Go to Citation Crossref PubMed Google Scholar

Russell OM, Gorman GS, Lightowlers RN, and Turnbull DM. 2020. Mitochondrial diseases: hope for the future. Cell, 181(1): 168–188.
Go to Citation Crossref PubMed Google Scholar

Schaefer GO, and Labude MK. 2017. Genetic affinity and the right to 'three-parent IVF'. Journal of Assisted Reproduction and Genetics, 34(12): 1577–1580.
Go to Citation Crossref PubMed Google Scholar

Shoubridge EA, and Wai T. 2007. Mitochondrial DNA and the mammalian oocyte. Current Topics in Developmental Biology, 77: 87–111.
Go to Citation Crossref PubMed Google Scholar

Singapore Statutes Online. Revised Edition 2005. Human Cloning and other Prohibited Practices Act (CHAPTER 131B) (Original Enactment: Act 35 of 2004) [online]: Available from sso.agc.gov.sg/Act/HCOPPA2004/.
Go to Citation Google Scholar

The National Health and Medical Research Council (NHMRC). 2020a. Expert Statement Mitochondrial Donation Expert Working Committee. Australian Government, Medical Health and Research Council [online]: Available from nhmrc.gov.au/health-advice/all-topics/mitochondrial-donation#download.
Go to Citation Google Scholar

The National Health and Medical Research Council (NHMRC). 2020b. Mitochondrial Donation Community Consultation Report. Australian Government, Medical Health and Research Council [online]: Available from nhmrc.gov.au/health-advice/all-topics/mitochondrial-donation#download.
Go to Citation Google Scholar

Wai T, Teoli D, and Shoubridge EA. 2008. The mitochondrial DNA genetic bottleneck results from replication of a subpopulation of genomes. Nature Genetics, 40(12): 1484–1488.

Go to Citation Crossref PubMed Google Scholar

Wallace DC, and Chalkia D. 2013. Mitochondrial DNA genetics and the heteroplasmy conundrum in evolution and disease. Cold Spring Harbor Perspectives in Biology, 5(11): a021220.
Go to Citation Crossref PubMed Google Scholar

Wolf DP, Mitalipov N, and Mitalipov S. 2015. Mitochondrial replacement therapy in reproductive medicine. Trends in Molecular Medicine, 21(2): 68–76.
Go to Citation Crossref PubMed Google Scholar

CHAPTER 3: Mitochondrial Replacement Therapy: In Whose Interests?

Preface

In identifying the challenges of MRT's clinical implementation, a key question concerns the legitimacy of using this technology to fulfill the interest in having and raising healthy genetically related children. This manuscript addresses the strengths and weaknesses of those objections to MRT that assert MRT has limited social value as it is neither a "treatment" nor a "cure," and that prospective parents have egg and embryo donation as well as adoption as alternatives to MRT for having children.

Author contributions:

- Forough Noohi proposed the research study and its scope, wrote the manuscript, and managed its submission and contact with the editor.
- Vardit Ravitsky reviewed and revised the manuscript.
- Bartha Maria Knoppers reviewed and revised the manuscript.
- Yann Joly reviewed and revised the manuscript.
- All authors read and approved the final manuscript.

Mitochondrial Replacement Therapy: In Whose Interests?

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3.1 Abstract

Mitochondrial replacement therapy (MRT), also called nuclear genome transfer and mitochondrial donation, is a new technique that can be used to prevent the transmission of mitochondrial DNA diseases. Apart from the United Kingdom, the first country to approve MRT in 2015, Australia is the only other country with a clear regulatory path for the clinical applications of this technique. The rapidly evolving clinical landscape of MRT makes the elaboration and evaluation of the responsible use of this technology a pressing matter. As jurisdictions with less strict or non-existent reproductive laws are continuing to use MRT in the clinical context, the need to address the underlying ethical issues surrounding MRT's clinical translation is fundamental. Among

objections to researching and developing MRT are that: (1) prospective parents have other reproductive options, so their interest in having and raising genetically related children free of mitochondrial disease does not establish any rights to this technology, and (2) MRT does not "cure" or "treat" existing individuals, but rather it creates healthy people who would not otherwise exist. This paper offers a reflection on the strengths and weaknesses of these arguments with the aim of advancing and nuancing this important debate for researchers and clinicians in the field.

3.2 Introduction

In identifying the challenges of MRT's clinical implementation, a key question concerns the legitimacy of using this technology to fulfill the parental interest in having and raising genetically related children free of mitochondrial DNA disease. Debates on the ethics of introducing new reproductive technologies are centered on the requirement of balancing possible benefits and risks and protecting the reproductive freedom of prospective parents. In this article, we focus on and respond to two objections to MRT: (1) MRT has limited social value as the technique is neither a "treatment" nor a "cure," and (2) prospective parents have other reproductive alternatives such as egg and embryo donation, as well as adoption. We begin by presenting a brief review of the science of MRT. We then examine and respond to the objections to the parental "interest" in having genetically related children and the "therapeutic" nature of MRT. Finally, we highlight the tension between the applications of MRT: to prevent disease vs. to treat infertility, an area of societal interest regarding MRT requiring further exploration.

3.2.1 Mitochondria: "Power plants" of the cell

Mitochondria are membrane-bound microscopic organelles responsible for cellular respiration (the breakdown of carbohydrate substrates in the presence of oxygen) and energy production. Mitochondria have their own DNA (mtDNA), separate from the nuclear DNA (nDNA). Mitochondrial DNA is typically a small circular double-stranded molecule containing 37 genes which encode the core components of the mitochondrial respiratory complexes.[1] A given cell can house anywhere from zero (red blood cells) to thousands of mitochondria, depending on the cell type, structure, and function.[2]

Mitochondrial DNA mutations are associated with a broad phenotypic spectrum, ranging from mild myopathies to devastating multisystem syndromes.[3] It is estimated that 1 in 4300 people are affected by primary mitochondrial diseases.[4] Mitochondrial disorders can be present at birth or manifest later in life. They cause devastating physical, developmental, and cognitive impairments that are progressive. There is no cure for inherited mtDNA diseases, and for the vast majority of patients, therapy is limited to the early detection and alleviation of symptoms.[5]

3.2.2 Mitochondrial Replacement Therapy (MRT)

Methods used for potentially diagnosing and preventing the transmission of mitochondrial disorders include prenatal diagnosis (PND) and preimplantation genetic diagnosis (PGD). These techniques, though, cannot benefit a wide range of women who are at risk of transferring harmful mitochondrial mutations to their descendants. PND could be invasive and if it was confirmed that

the fetus had a mtDNA deficiency, parents would need to choose between continuing with the pregnancy or terminating it. PGD carries a certain degree of uncertainty in predicting the degree of mtDNA heteroplasmy transmitted to future children and the risk of disease manifestation.[6]

For families who wish to have children free of mtDNA disease, egg and embryo donation, as well as adoption, are considered alternatives.[7] For those who wish to have genetically related children free of mtDNA disease, MRT could be a possible option. The most notable methods of MRT include Pronuclear Transfer (PNT) and Maternal Spindle Transfer (MST).[8] PNT entails fertilizing a healthy donated egg and the prospective mother's oocyte with the father's sperms. Fertilized oocytes then develop until the early zygote stage. The pronuclei of the zygote formed by the donated oocyte is discarded and replaced by the intending mother and father's pronuclei. In MST, the parental nDNA transfer happens before fertilization. This technique requires discarding the metaphase II spindle from the donor oocyte. The mother's spindle complex will then be delivered to the enucleated donor oocyte, followed by fertilization.[9] It is important to recognize that clinics in countries where reproductive laws are less stringent or absent are already using MRT (e.g., Ukraine and Greece). To our knowledge, seventeen children have already been born using this technology.[10]

3.3 Policy developments

Thus far, the United Kingdom (UK) and Australia are the only countries that have adopted legislation regarding the clinical implementation of MRT. In 2015, following an ethical assessment conducted by the Nuffield Council on Bioethics (2012), a public dialogue and deliberation carried

out by the Human Fertilisation and Embryology Authority (HFEA) (2012-2013), a public consultation on draft regulations performed by the Department of Health (2014), and three separate reports on the safety and efficacy of MRT (2011, 2013, 2014) (HFEA 2021a), the UK passed the *Human Fertilisation and Embryology (Mitochondrial Donation) Regulations*. The law mandates a case-by-case assessment of applications proposing to use MRT. The technique may only be used to prevent *serious* mitochondrial diseases.[11] In 2018, two women affected by myoclonic epilepsy with ragged red fibers were permitted by the HFEA to use MRT.[12] News about the UK's first MRT babies has not yet been published.

In Australia, following the release of two reports (an expert statement on the science of MRT and a public consultation) by the National Health and Medical Research Council, the *Mitochondrial Donation Law Reform (Bill 2021)* was introduced into Parliament in March 2020. A vote on the Bill is expected in the next few months. On May 11, 2021, the Australian Government pledged $10.3M over 10 years to the implementation of MRT in research and clinical contexts in Australia.[13]

3.4 MRT and the interest in having genetically related children

In the context of MRT, several objections have been raised in the bioethics literature, such as the slippery slope toward genetic modification, potential non-therapeutic uses, potential harms to egg providers, to future generations, or to society.[14] The crux of the ethical argument in favor of MRT is the need to fulfill prospective parents' strong interest in having and raising genetically related children free of mtDNA disease. Over the last four decades, the interest in having genetically

related children has been perceived as strong enough to justify a wide array of assisted reproduction technologies, such as IVF. It has been argued that this interest is deep and broad and that MRT extends this recognition and the reproductive autonomy of prospective parents.[15]

According to certain critics, considering the *need* to access MRT as a "compelling" one, overvalues genetic relatedness and devalues non-genetic familial ties: "if there is a compelling argument to be made it is an argument against human nuclear genome transfer on the grounds that a desire for genetically related children, though often interpreted as a need, is at most a want."[16] MRT, it is thus argued, ought not be a priority for society since alternatives, such as egg and embryo donation, as well as adoption, do exist.[17]

The interest in genetically related children may be considered a preference, a powerful desire, or even a right. Regardless of one's view on this matter, to many, genetic relatedness matters and bears a strong, profound meaning. In the absence of a responsible MRT framework, women have to choose from a set of alternatives (i.e., egg and embryo donation, adoption, childlessness, or risk having an affected child). In the first qualitative interview study on the Canadian perspective toward MRT, Noohi et al. (2021) addressed the seemingly controversial objective of MRT: having children free of mtDNA disease while maintaining genetic relatedness between mother and child. Of eight individuals affected by primary mtDNA diseases who either had affected children or no children at all, seven maintained that they did not consider the said alternatives to MRT as viable options:[18]

> "I'm gonna be honest with you. I have a daughter. I don't want her to live through what I lived through. God forbid if she doesn't make it to her child-bearing years. If she does, she will be informed that if she wants a child of her own, there are countries that could help her. We have money aside for that. I know that it's a very very sad thing to talk

about, but I want her to have the opportunity to have and to carry a child of her own that will not land her in the hospital like I did. I think everybody is equally allowed to have that. […] and what's great in her case is that she was born in 2011, she has a lot of time in front of her for this to become legal, or for research to advance. I didn't, but that's okay, we will deal with what it is now. But for her, there is a promising future, and a way to prevent it from continuing, right?"

"[…] I think it's more psychological, and that you should have the right to have a family however way you want to. Whether you adopt, you have a surrogacy, you have a biological child… People who adopt are seen differently in society than people who have biological children. Not because it's right or wrong. You will meet people who will never be able to love a child if they adopt [as if they were their own biological child]. People will present themselves and say yes, I would not be able to… I had this discussion with my husband. My husband would be like: I have two biological children now and if you tell me that I am going to adopt now, I can tell you for sure that I will never be able to love that child like my own kids."

"[…] I would do anything to have a biological kid. I have always wanted my own kids, but I don't have that kind of lifestyle that I can just quit my job and go to another country to get the process of MRT and get pregnant. If MRT doesn't become legal [in Canada] by the time I am ready to have children, I am going to adopt or try other means of non-biological children by myself."

Mitochondrial disease patients' profound interest in having genetically related children free of mitochondrial disease is rooted in deep generational pain and grief. Many mothers, having gone through the excruciating pain of having passed on debilitating mutations to their progeny, see MRT as a promising future that could grant their children's children an equal opportunity at a chance of life without dreadful diseases.[19]

Indeed, in considering the clinical introduction of MRT, it is essential to consider the interests and the rights of all parties: children born of MRT, prospective parents, and egg donors. As recognized by the International Commission on the Clinical Use of Human Germline Genome Editing (2020),

the UK's MRT policy is an example of a stepwise clinical introduction that future preventive interventions need to follow: (1) support from patient groups advocating in favor of the technology; (2) public engagement regarding ethical aspects; (3) safety and efficacy reviews conducted by independent expert panels; and (4) regulatory approval on a case-by-case basis.[20]

Choices related to human reproduction are central to personal autonomy and deeply rooted within our most profound individual nature. Article 16 of the *Universal Declaration of Human Rights* proclaims that all adults have the *right* to "found a family."[21] An approach to reproductive autonomy that is broad in scope and attentive to context is crucial for preparing for a future in which ever-evolving technologies, such as MRT and CRISPR, continue to expand reproductive options.

Considering millions of children worldwide who could benefit from adoption, another argument against MRT states that parents seeking to use this technique should adopt, rather than create *new* life:

> "The reasons for wanting a genetic child do not defeat a *pro tanto* duty to adopt children instead, with a possible exception. These reasons are too trivial, presuppose the value of the genetic connection, are inappropriate in a normative parental context, or fail to make a relevant distinction between genetic and adopted children. A promising candidate for a one-time exception may be grounded in a woman's strong desire to experience pregnancy."[22]

Adoption is indeed an excellent family-building choice for many people. However, as forty years of IVF have shown, it is not an option that provides a suitable alternative for all. The journey to adoption can be long and complex, entail financial and emotional burdens, and might not be

completed successfully. A putative 'moral duty to adopt' ought to be considered a responsibility shared by *all persons* capable and willing to be parents, not solely those at-risk of transmitting serious genetic diseases to their progeny. Hence, prospective parents who suffer from mitochondrial diseases have the right to choose the route to parenthood that suits their values and preferences, as long as this does not necessarily create undue burdens or risks for others.[23] Certainly, conventional egg and embryo donation, like adoption, does not represent a devalued alternative of family building. Rather, the deep interest in procreation is about individual *choice* and interest in being genetically related with one's child.

3.5 MRT: Is it a "therapy"?

Another criticism is based on the notion that the rhetoric of parental autonomy in the context of MRT conceals an economic drive to promote a technology that does not provide a *cure*, because it allows the creation of *new* people, rather than treating *existing* ones: "MRT is not a standard cure or a therapy; rather it helps to create a healthy person who otherwise would not exist. A non-existing child has no interest in being created. We do not have a moral reason to create healthy people for their sake."[24]

It is true that MRT is not a therapeutic intervention for people who have mitochondrial diseases. "Therapy" may thus be a misleading description of the technology. MRT is a form of IVF that gives women affected by mitochondrial diseases the opportunity to have healthy children. Still, it is important to bear in mind that there are no proven therapies for mitochondrial diseases. With co-factor cocktails and stem cell transplants, one might be fortunate enough to manage symptoms

sufficiently well to maintain a reasonable quality of life for a reasonable length of time. However, there is no getting around the fact that patients with mitochondrial diseases will be hugely impacted by a disease that is, at the very least, life-limiting.[25]

Not everyone considers the alternatives to MRT as viable options.[26] As such, in the absence of a comprehensive regulatory framework, prospective parents may well seek MRT in jurisdictions with no established regulations. This further exposes them to the associated risks and shortcomings of unregulated practices around the world.[27] As Norman Daniels argued, the case for a moral right to health care relies on promoting equal opportunity by preventing and curing disease.[28] Thus, efforts must be made to consider what the clinical translation of this technology would look like from a scientific, ethical, and policy perspective.

Obviously, "a non-existing child has no interest in being created." The philosophically challenging Non-Identity Problem aside, society does have a moral duty to those children who are born due to their parents' choices. If children cannot be harmed by being born into impaired states, they may nonetheless be harmed if those states fail to adhere to a minimal standard of "sufficiency" to which all children are supposedly entitled.[30] Every child has the right to "the enjoyment of the highest attainable standard of health."[31] *Health* is one desirable outcome of socially *just* decision-making that reflects a moral concern with reproductive autonomy, which is central to women and couples' welfare. *Just* institutions must prioritize the health and overall well-being and interests of children. This would follow the pragmatic reasoning that securing children's health is a prerequisite to their enjoyment of self-respect, attachment, and autonomy later in life.[32]

3.6 MRT: A "treatment" for infertility?

A key area regarding requiring further exploration is the tension surrounding the possible applications of the technology. While the primary aim of MRT is to prevent mitochondrial diseases, the technology could also be used to "treat" infertility. The claim that MRT maybe a new means of solving issues of infertility is based on the notion that oocyte mitochondria are the cause of some cases of infertility.[33] As such, in Ukraine, the Darwin Life-Nadiya clinic advertises MRT as an "alternative to egg donation treatment" and a potential solution to female-related infertility.[34] Also, Greece's Institute of Life has been conducting a clinical trial led by Greek and Spanish doctors since 2019. This pilot study is "researching multiple IVF failures caused by cytoplasmic dysfunctions of oocytes, and the potential of addressing serious mitochondrial diseases."[35]

According to critics, encouraging alternative uses of MRT "concerns the common strategy of arguing for the introduction of an ethically controversial technology by insisting on its potential therapeutic benefits and only later defending its potential non-therapeutic uses once it has been successfully introduced."[36] Some have argued that the criteria for accessing MRT are grounded mainly in the reproductive autonomy of future parents; thus, "the therapeutic/non-therapeutic moral boundary does not exist" in this context.[37] However, there is a lack of solid evidence demonstrating that MRT provides higher live birth rates than standard IVF. The application of MRT as a "treatment" for infertility; thus, remains uncertain.[38]

In a robust regulatory framework, MRT should only be allowed in clearly defined situations of otherwise "serious" mitochondrial disorders. Although important socio-ethical issues revolve around MRT's clinical translation, the most pertinent of them can be addressed by limiting the use

of the technology (i.e., defining a distinct boundary between using MRT to prevent debilitating diseases and "treating" infertility).[39]

3.7 Conclusion

Against the backdrop of the ongoing policy and bioethical debates surrounding MRT, its research and clinical landscapes are rapidly evolving. In identifying the challenges to the clinical implementation of MRT, we should address the legitimacy of using this technology to fulfill the deep interest of many in having and raising genetically related children free of mtDNA disease. Risk/benefit issues remain one of the prominent arguments in resisting this interest; yet, the importance of addressing the legitimacy of genetic kinship remains underexplored. As a fundamental bioethical principle, respect for one's autonomy guides reproductive rights, and should be carefully considered in assessing the risks and benefits of MRT.

MRT could be considered a viable option for women with mitochondrial diseases for whom predictive tests (i.e., preimplantation genetic diagnosis and prenatal diagnosis) are inappropriate or likely to be inappropriate, who qualify to use the technology, and want genetically related children free of mtDNA disease. Still, since MRT is an invasive procedure that requires great skill, it is essential to have the highest level of guidance to ensure all the technical conditions are optimized. As stated in the UK's scientific reports on the safety and efficacy of MRT (2011-2016),[40] there will always be some risks and uncertainties associated with the use of MRT in humans until it is widely implemented in the clinical context and evidence accumulates. Thus, MRT needs to be initially used as a risk reduction treatment for carefully selected patients.

Mitochondrial diseases shorten lives, cause severe disability, and leave anguish in their wake. MRT has already moved from theory and research into clinical practice, and its responsible use could make a real difference for thousands of families with mitochondrial diseases.

3.8 References

1. Russell, O.M., Gorman. G.S., Lightowlers R.N., Turnbull, D.M. (2020). Mitochondrial Diseases: Hope for the Future. *Cell*, 181(1): 168-188.

2. Wolf, D.P., Mitalipov, N., Mitalipov, S. (2015). Mitochondrial replacement therapy in reproductive medicine. *Trends Mol Med*, 21(2): 68-76.

3. Frazier, A.E., Thorburn, D.R., Compton, A.G. (2019). Mitochondrial energy generation disorders: genes, mechanisms, and clues to pathology. *J Biol Chem*, 294(14), 5386-5395; Thompson, K., Collier, J.J., Glasgow, R.I.C., Robertson, F.M., et al. (2020). Recent advances in understanding the molecular genetic basis of mitochondrial disease. *J Inherit Metab Dis*, 43(1): 36-50.

4. Gorman, G.S., Schaefer, A.M., Ng, Y., et al. (2015). Prevalence of nuclear and mitochondrial DNA mutations related to adult mitochondrial disease. *Ann. Neurol*, (77): 753–759.

5. Ng, Y.S. and Turnbull, D.M. (2020). When to think about mitochondrial disease. *Practical Neurology*, 20: 260-261.

6. Wai, T., Teoli, D., Shoubridge, E.A. (2008). The mitochondrial DNA genetic bottleneck results from replication of a subpopulation of genomes. *Nat Genet*, 40(12), 1484-8; Shoubridge, E.A. and Wai, T. (2007). Mitochondrial DNA and the Mammalian Oocyte, *Current Topics in Developmental Biology*, Academic Press, 77: 87-111.

7. Baylis, F. (2013). The ethics of creating children with three genetic parents. *Reprod Biomed Online*, 26(6), 531-4; Rulli, T. (2017). Mitochondrial Replacement 'Therapy' Myth. *Bioethics*, 31(5): 368-374, at 373.

8. The National Health and Medical Research Council (NHMRC). (2020a). Australian Government, Medical Health and Research Council. Expert Statement Mitochondrial Donation Expert Working Committee. https://www.nhmrc.gov.au/health-advice/all-topics/mitochondrial-donation#download

9. Craven, L., Tuppen, H., Greggains, G., et al. (2010). Pronuclear transfer in human embryos to prevent transmission of mitochondrial DNA disease. *Nature*, 456(7294): 82-85; Kang, E., Wu, J., Gutierrez, N.M., Koski, A., et al. (2016). Mitochondrial replacement in human oocytes carrying pathogenic mitochondrial DNA mutations. *Nature*, 540(7632): 270-275.

10. Darwin Life Nadiya. (2021). http://dl-nadiya.com/nuclear-transfers; BioTexCom. Center for human reproduction. (2021). https://biotexcom.com/services/#mitochondrial-replacement-therapy; Institute of life. (2021). https://www.iolife.eu/en/us/mst-research/; Palacios-González C, Medina-Arellano M. 2017. Mitochondrial replacement techniques and Mexico's rule of law: on the legality of the first maternal spindle transfer case, *Journal of Law and the Biosciences*, 4 (1):50-69, https://doi.org/10.1093/jlb/lsw065

11. Castro R. J. (2016). Mitochondrial replacement therapy: the UK and US regulatory landscapes. *Journal of law and the biosciences*, *3*(3), 726–735. https://doi.org/10.1093/jlb/lsw051; The Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015 No. 5 https://www.legislation.gov.uk/ukdsi/2015/9780111125816/contents

12. Sherratt, S. 2018. Women selected for mitochondrial donation in UK. BioNews 1000. https://www.bionews.org.uk/page_96351

13. Mito Foundation. 2021. https://www.mito.org.au/mitochondrial-donation/; Australian Government. 2021. Legalisation of Mitochondrial Donation in Australia. https://ris.pmc.gov.au/2021/04/06/legalisation-mitochondrial-donation-australia

14. Baylis, *supra* note 7

15. Schaefer, G.O., Labude, M.K. (2017). Genetic affinity and the right to 'three-parent IVF'. *J Assist Reprod Genet*, 34(12), 1577-1580; Ishii, T. and Palacios-González, C. (2017). Mitochondrial Replacement Techniques: Genetic Relatedness, Gender Implications, and Justice. *Gender and the Genome*, 1(4), 129-134; Cavaliere G, Palacios-González C. 2018. Lesbian motherhood and mitochondrial replacement techniques: reproductive freedom and genetic kinship *Journal of Medical Ethics* 2018;44:835-842.

16. Baylis, F. (2017). Human Nuclear Genome Transfer (So-Called Mitochondrial Replacement): Clearing the Underbrush. *Bioethics*, 31(1): 7–19, at 12-13.

17. Baylis, supra note 16; Rulli, T. (2014). Preferring a Genetically-Related Child. *Journal of Moral Philosophy*. 13(6): 1-30.

18. Noohi, Li, Joly. (2021). Clinical translation of mitochondrial replacement therapy in Canada: A qualitative study of stakeholders' attitudes. *FACETS*, 6(1): 449-464.

19. The National Health and Medical Research Council (NHMRC). (2020b). Mitochondrial Donation Community Consultation Report. Australian Government, Medical Health and Research Council. https://www.nhmrc.gov.au/health-advice/all-topics/mitochondrial-donation#download

20. National Academy of Sciences. (2020). Heritable Human Genome Editing. Washington, DC: The National Academies Press. https://doi.org/10.17226/25665

21. Universal Declaration of Human Rights (UDHR). Article 16.

22. Rulli, *supra* note 17

23. Cavaliere and Palacios-González, *supra* note 15

24. Rulli, *supra* note 7

25. Craven, L., Murphy, J., Turnbull, D.M., Taylor, R.W., Gorman, G.S., McFarland, R. (2018). Scientific and Ethical Issues in Mitochondrial Donation. *New Bioeth*. 24(1): 57-73.
26. Noohi, *supra* note 18

27. Ishii and Palacios-González, *supra* note 15

28. Daniels, N. (1985). Just Health Care (Studies in Philosophy and Health Policy). Cambridge: Cambridge University Press.

29. Stanford Encyclopedia of Philosophy. The Nonidentity Problem. First published Tue Jul 21, 2009; substantive revision Tue Apr 2, 2019. https://plato.stanford.edu/entries/nonidentity-problem/

30. Wrigley, A., Wilkinson, S., Appleby, J.B. (2015). Mitochondrial Replacement: Ethics and Identity. *Bioethics*, 29(9), 631-638; Magnusson, E. (2019). Children's rights and the non-identity problem. *Canadian Journal of Philosophy*, 49(5), 580-605; Powers, M. and Faden, R. (2006). Social Justice: The Moral Foundations of Public Health and Health Policy. Oxford University Press.

31. Convention on the Rights of the Child. Adopted and opened for signature, ratification and accession by General Assembly resolution 44/25 of 20 November 1989 entry into force 2 September 1990, in accordance with article 49. Article 24.

32. Powers and Faden, *supra* note 31

33. Cecchino, G.N., Seli, E., Alves da Motta, E.L., García-Velasco, J.A. (2018). The role of mitochondrial activity in female fertility and assisted reproductive technologies: overview and current insights. *Reprod Biomed Online*, 36(6): 686-697.

34. Darwin Life Nadiya and Institute of Life, *supra* note 10

35. Institute of life, *supra* note 10

36. Baylis, F. (2018). 'No' to lesbian motherhood using human nuclear genome transfer. *Journal of Medical Ethics,* 44, at 1.

37. Palacios-González, C. and Cavaliere, G. (2018). 'Yes' to mitochondrial replacement techniques and lesbian motherhood: a reply to Françoise Baylis. *Journal of Medical Ethics*, 45: 280-281.

38. Cecchino et al., *supra* note 33; European Society of Human Reproduction and Embryology (ESHRE) position statement. (2019). Spindle transfer in the treatment of infertility. https://www.eshre.eu/Press-Room/ESHRE-News/2019

39. Knoppers BM, Leader A, Hume S, et al. (2017). Mitochondrial Replacement Therapy: The Road to the Clinic in Canada. Journal of Obstetrics and Gynaecology Canada. 39(10):916-918.

40. Scientific Review of the Safety and Efficacy of Methods to Avoid Mitochondrial Disease through Assisted Conception: 2016 Update. Report to the Human Fertilisation and Embryology Authority (HFEA). November 2016.

CHAPTER 4: Mitochondrial Replacement Therapy in Canada: Points to Consider in the Path to the Clinic

Preface

Clinics in jurisdictions where the regulation of health technologies and products are less strict or absent are moving forward with the clinical applications of MRT. Reproductive autonomy warrants the consideration of MRT, once proven safe and effective, as a viable option for women with mitochondrial diseases (for whom predictive tests are inappropriate or likely to be unsuccessful). As such, there should be attempts to consider what the clinical translation of this technology would look like from a scientific, ethical, and policy perspective. By reviewing MRT's policy literature in combination with CHAPTER 2, this manuscript proposes evidence-based policy points to consider in the clinical introduction of MRT in Canada.

Author contributions:

- This manuscript utilizes the qualitative interview study results presented in Chapter 2 in combination with a scoping literature review. Forough Noohi conducted the literature review, designed the study and the interview guide, conducted and transcribed half of the interviews verbatim, initially organized and coded all transcripts into manageable text segments, and systematically coded them using NVivo12. She obtained the ethics approval from McGill, wrote the manuscript, and managed its submission.

- Yann Joly reviewed and revised the manuscript.

- Both authors read and approved the final manuscript.

Mitochondrial Replacement Therapy in Canada: Points to Consider in the Path to the Clinic

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4.1 Abstract

In Canada, Mitochondrial Replacement Therapy (MRT) is a criminal offense according to article 5(1)(f) of the 2004 *Assisted Human Reproduction Act*. MRT is a form of in vitro fertilization designed to prevent mitochondrial diseases caused by mitochondrial DNA deficiencies. In order to examine the possibility of drafting a robust approach to the clinical translation of MRT in Canada, it is essential to identify and address challenges that arise from this technique. Through the review of MRT's policy literature in combination with a qualitative study that examines key stakeholders' attitudes toward the use of MRT, this manuscript proposes evidence-based points for policymakers to consider in the clinical introduction of MRT in Canada.

Keywords: Mitochondrial replacement therapy, Canada, Assisted Human Reproduction Act, Health policy

4.2 Introduction

In Canada, the 2004 *Assisted Human Reproduction Act* (AHRA) 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" [1]. Thus, Mitochondrial Replacement Therapy (MRT), a technique that could prevent mitochondrial DNA (mtDNA) related diseases, is prohibited in both research and clinical contexts. Clinics in jurisdictions where the regulation of health technologies and products are less strict or absent are moving forward with the clinical application of MRT [2, 3, 4]. As such, there should be attempts to consider what the clinical translation of this technique would look like from a scientific, ethical, and policy perspective. By reviewing MRT laws and policies and building on the results of a qualitative study about Canadian stakeholders' attitudes, this report provides policymakers with evidence-based data to guide the potential introduction of MRT in Canada. After discussing the basics of mitochondrial diseases and available diagnostic tests, we present the science of MRT, describe its pending status, and different uses (to prevent disease vs. to treat infertility). Next, we review cases of babies born through MRT and laws and policy directions in global and Canadian contexts. We conclude with key policy points to consider in MRT's path to the clinic in Canada.

4.2.1 Mitochondrial diseases

Mitochondrial diseases are among rare inherited disorders that can be present at birth or manifest later in life. They cause severe physical, developmental, and cognitive impairments that are progressive and have no available cure. It is believed that 1 in 4300 people are affected by primary mitochondrial diseases [5, 6]. There is no known cure for inherited mitochondrial diseases, and for most patients, therapy is restricted to symptomatic relief and timely identification of symptoms [7].

4.2.2 Diagnostic testing

Prenatal Diagnosis (PND) and Preimplantation Genetic Diagnosis (PGD) are among diagnostic tests that can be used to prevent the transmission of some mitochondrial diseases. PND is carried out by testing the placenta or the amniotic fluid between eleven and fifteen weeks into a pregnancy. This technique could be invasive, and if it was confirmed that the fetus had a mitochondrial deficiency, parents would need to choose between continuing with the pregnancy or terminating it [8]. PGD may be a compelling choice for women carrying heteroplasmic mitochondrial DNA (mtDNA) mutations (where mutant and normal mtDNA co-exist in an affected individual). However, in women with homoplasmic mtDNA mutations (where 100% of the mtDNA is pathogenic) or high degrees of heteroplasmy, PGD based on the ratio of mutant and normal mtDNA is not helpful. Due to uncertainties in predicting the degree of heteroplasmy transmission, the risk of disease manifestation can be challenging to assess even in low heteroplasmic mtDNA mutations [9].

4.2.3 Mitochondrial Replacement Therapy (MRT)

Because of the lack of effective therapies and the remarkably damaging phenotypes in various patients, preventing the transmission of mitochondrial disease is essential for many families [10]. For those who wish to have genetically related children free of mtDNA disease, egg and embryo donation, as well as adoption, are among the available options [11]. MRT is a potential alternative for families with mitochondrial diseases who want to have healthy, genetically related children. This technique aims to prevent the transmission of mtDNA diseases [12]. The two most investigated methods of MRT are Pronuclear Transfer (PNT) and Maternal Spindle Transfer (MST). PNT involves fertilizing the healthy egg(s) from a donor with the father's sperm(s). Concurrently, the mother's oocytes are fertilized. Both sets of fertilized oocytes are permitted to mature until the initial zygote stage, at which point the pronuclei are visible. The pronuclei of zygotes built by donated oocytes are extracted and replaced by the prospective parents' pronuclei [13]. In MST, the transfer of parental nuclear DNA (nDNA) happens before fertilization. This method consists of removing and discarding the metaphase II spindle from the donor oocyte. The chromosome-spindle complex will then be removed from the intending mother's oocyte and transferred to the enucleated donor oocyte, followed by fertilization with the intending father's sperm [14].

4.2.4 MRT and a pending status

Whether MRT should be considered germline genetic modification has been the center of controversy in debating the legitimacy of MRT among relevant stakeholders [15, 16, 17]. Germline

modification could be misused to create dystopic scenarios involving eugenics, human enhancement, and genetic discrimination. As such, germline altering techniques are considered risky and morally dubious, hence, prohibited in most developed countries [18].

Since discussions about genetic technologies began, the moral line separating non-reproductive somatic cell modification and germline modification has been a comforting principle for bioethics [19]. The rising interest in preventing the transfer of harmful, inherited diseases to future children calls this moral line into question. There is no general agreement in the research community on the status of MRT so far; though, there have been attempts at separating the technique from the field of germline genetic modification. Some tend to believe that MRT is not genetic modification mainly because (1) MRT does not modify or edit the nDNA or the mtDNA sequence; (2) mitochondrial DNA contribution to the overall genome is quantitatively negligible (less than 0.1%); and (3) the mtDNA is exclusively transferred through the maternal line so any supposed modification stops in the first generation if only male embryos are selected for implantation [20].

4.2.5 The use of MRT: Preventing disease vs. treating infertility

MRT could also be used for treating infertility and maintaining genetic ties to both mothers in lesbian motherhood [2, 21]. Although there is no reliable evidence connecting mitochondria with infertility in the general population, several clinics in jurisdictions, such as Greece and Ukraine are using MRT to “treat infertility” [3, 15, 22].

On July 9, 2019, The European Society of Human Reproduction and Embryology (ESHRE), in a position statement, “strongly discouraged” using MRT to treat fertility problems. The ESHRE affirmed that as a treatment for infertility, MRT’s application is uncertain and questionable as there is a lack of concrete evidence demonstrating the technique has a higher success rate compared with the standard in vitro fertilization (IVF). On the safety and efficacy of MRT, the ESHRE stated that “the recent report in Science on the untested interplay between mitochondria and nucleus remains unclear in the possible generation of short- and long-term side effects (Science 364, eaau6520, 2019). The current lack of solid scientific evidence providing safety reassurance requires more study and continued vigilance” [23].

4.2.6 Clinical applications

It is imperative to acknowledge that clinics in jurisdictions where reproductive laws are less strict or non-existent have been moving forward with clinical applications of MRT, notably in Mexico, Ukraine, and Greece. The first-ever MRT baby (a boy) was born in Mexico in 2016 to a Jordanian couple who had lost two previous children to Leigh Syndrome and had suffered four miscarriages [24]. Dr. John Zhang of New York City’s New Hope Fertility Center performed MST to create five embryos; only one developed normally. MRT was not approved in the United States (US), so Dr. Zhang conducted the procedure in Mexico, a country he infamously claimed had “no rules” [25]. Zhang had created the embryo in the US and later implanted it into the woman’s uterus in Mexico [21].

In Ukraine, Nadiya clinic, with Dr. Zhang as the CEO, currently advertises MRT as an "alternative to egg donation treatment" and a potential solution to female-related infertility. Nadiya clinic created the first MRT baby using PNT in January 2017 [26].

On April 15, 2019, Greece's Institute of Life announced a baby boy's birth as a part of a clinical trial led by Greek and Spanish doctors. The mother, a 32-year-old woman from Greece, had previously experienced four unsuccessful IVF cycles. The Greek team worked with the Spanish center, Embryotools, which announced that 24 other women were enrolled in the trial. So far, five "healthy" babies have been born in the context of this pilot study [3].

One clinic that epitomizes well-established concerns about medical tourism is BioTexCom in Ukraine. The company's offers of all-inclusive packages include a "Guaranteed Success" package with a money-back guarantee after a total of five unsuccessful IVF cycles. The company's definition of success is a pregnancy that passes twelve weeks. As of early 2019, BioTexCom has been marketing MRT as a standard IVF "add-on" [4, 27]. Still, there are no published reports of babies born using MRT at BioTexCom.

Finally, in the UK, several individuals have been permitted by the HFEA to use MRT [28]. However, news about the UK's first MRT babies has not been published yet.

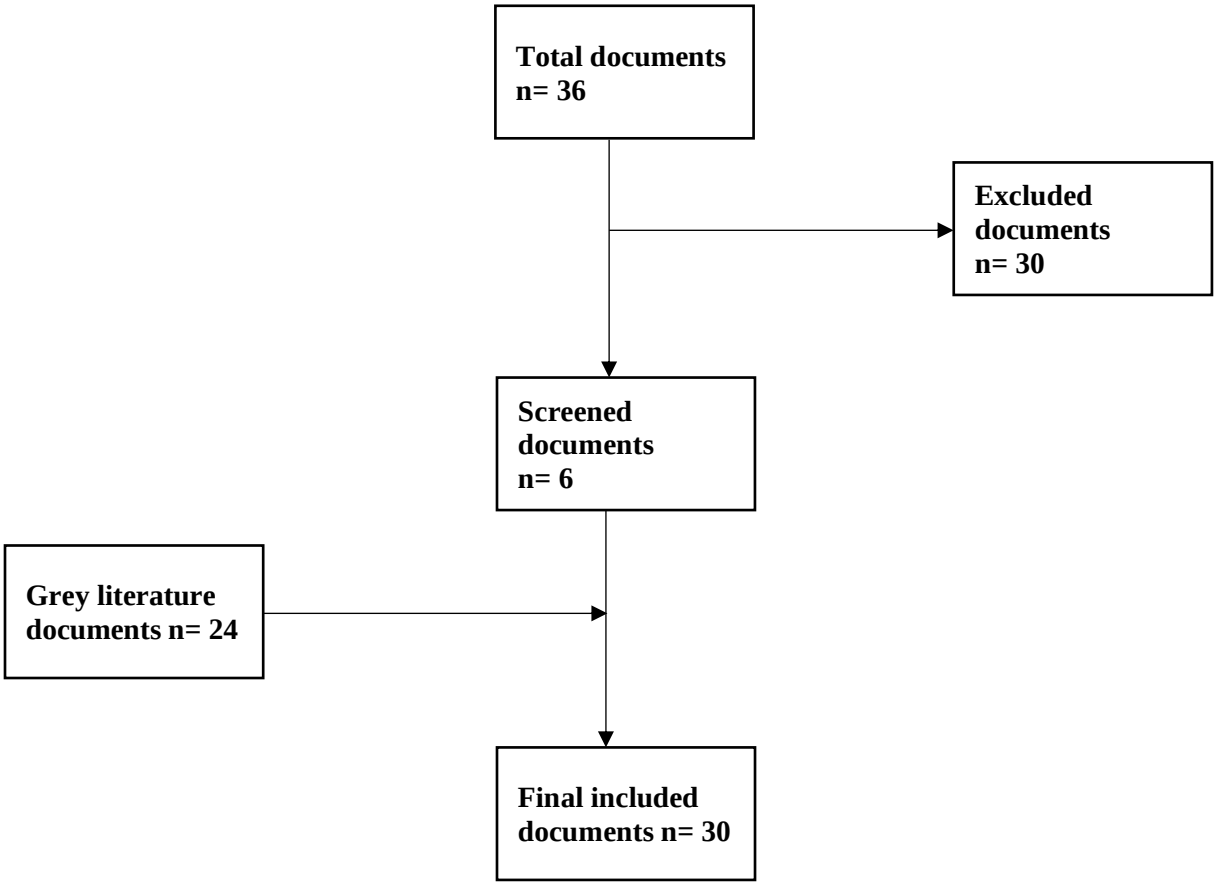
4.3 Materials and Methods

Results of an international scoping review of MRT's laws, policies, and professional recommendations findings were synthesized and contrasted with semi-structured interviews with Canadian stakeholders that covered reasoning and attitudes related to the implementation of MRT in Canada.

(1) **Scoping review:** we performed a scoping review of MRT's public policy texts (laws, professional recommendations, and government-issued reports) in both global and Canadian Contexts. The search included academic publications in peer-reviewed journals and reports in English and French. Scopus, LexisNexis, and grey literature (National Academies of Sciences, Medicine, and Engineering, National Institutes of Health, Human Fertilisation and Embryology Authority, the UK's Department of Health, World Health Organization, and websites of key organizations interested in mitochondrial disease, IVF, MRT, and assisted procreation) were searched to identify the publications. We searched for the chosen keywords (see Supplementary Material, Table 1) in the title and abstracts of articles and reports. Documents that were not in English or French, did not discuss MRT laws or policies, or were not peer-reviewed articles we removed (see Figure 4.1). Lastly, documents that were not government-issued or professional guidance were removed to obtain a final list of documents (see Supplementary Material, Table 2). We used a thematic analysis to identify and report themes from the reviewed documents. Identified themes fell under five categories: risks and benefits, the slippery slope toward genetic modification, the use of MRT as a preventive tool versus in the context of infertility, genetic

kinship, and MRT's status as a germline modifying technique. We reported the identified themes under *legislation and policy* and *professional recommendations* in global and Canadian contexts.

Figure 4.1: The process of elimination of the articles



(2) **Qualitative study:** We sought out Canadian stakeholders' perceptions, expectations, and concerns toward clinical applications of MRT in a study published in *FACETS* entitled "Clinical translation of mitochondrial replacement therapy in Canada: a qualitative study of stakeholders' attitudes." In this study, we reported on the attitudes of thirty-two Canadian stakeholders: experts (researchers and clinicians), patients, egg donors, and members of the general public [10]. Our study was approved by McGill's Faculty of Medicine Institutional Review Board (IRB Study Number: A06-B43-19B). We used a thematic analysis to identify, analyze, and report themes from the data. Identified themes fell under five categories: motives for using MRT, terminology, an outdated criminal ban, practical and theoretical risks and benefits, and the feasibility of MRT's clinical translation.

(3) **Contrasting the results of the scoping review and the qualitative study to determine key policy points**: We organized and coded our data (30 final documents included in the literature review and the 32 interview transcripts (see Figures 4.1 and 4.2 and Supplementary Material, Table 2)) into manageable text segments, and systematically coded them using NVivo12. We then contrasted the policy rationale identified in our scoping review with stakeholders' opinions synthesized in our qualitative study to identify policy points to consider in MRT's path to the clinic.

4.4 Results

4.4.1 Scoping review

4.4.1.1 The Global Context: Legislation and policy

4.4.1.1.1 The United Kingdom: Mitochondrial Donation Regulations (2015)

The UK is the first and only country to date to authorize and regulate the clinical applications of PNT and MST. In the UK, IVF and embryo research are regulated by the Human Fertilisation and Embryology Authority (HFEA), which 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" [29]. In recognizing the progress being made in research, the Act was amended in 2008. Parliament introduced provisions to permit MRT to prevent "serious" mitochondrial diseases [30]. As a result, the Act expanded the definitions of permitted eggs and embryos to include those that have had applied to them "in prescribed circumstances a prescribed process designed to prevent the transmission of serious mitochondrial disease" [31]. This expansion of definition was introduced to encompass MST and PNT research.

In 2010, the Department of Health took forward steps to develop MRT regulations. Over the next five years, there was an ethical assessment conducted by the Nuffield Council on Bioethics (2012), public dialogue and deliberation carried out by the HFEA (2012-2013), and a public consultation on draft regulations performed by the Department of Health (2014). There were also four separate reports on the safety and efficacy of MRT by an Expert Panel assembled by the HFEA [28]. In

2011, the Panel reported that both MST and PNT had the potential to prevent mitochondrial diseases; although, there was no evidence to recommend one method over the other. The Panel also recommended that while there was no evidence that either method was "unsafe," a minimum set of further experiments should be undertaken [32]. Subsequent reviews were carried out to consider the progress made since the first scientific report was published and to review the safety and efficacy of polar body transfer methods. The Panel again expressed the view that there remained insufficient research to recommend one particular method over the other. It also recommended that there should be long-term follow-up monitoring of any children born as a result of MRT [33-35]. In the 2016 report, the Scientific Panel deemed PNT and MST as "sufficiently safe," in restricted circumstances, citing tremendous progress made since both MST and PNT were deemed to be "not unsafe" [35].

In 2015, the UK passed the *Human Fertilisation and Embryology (Mitochondrial Donation) Regulations*. As a result of the 2015 reforms, it was made clear that the legal status of parenthood cannot be granted to egg donors in the context of MRT and that children can only have access to limited nonidentifying information about the egg donors. Under the new regulations, a case-by-case assessment of applications proposing to use MRT is conducted, and the technique may only be used to prevent *serious* mitochondrial diseases [36].

The Nuffield Report (2012) concluded that in case MRT were proven to be safe and effective and subject to the appropriate oversight, it would be ethical for families to use the technique. This conclusion accounted for the health and social benefits to prospective children and families where parents choose to have genetically related children. The Nuffield Report did not consider either

PNT or MST to be ethically preferable to the other. The Report also stated that in the absence of MRT, a specific group of patients would have no way of having healthy genetically related children. This would restrain the prospective parents' reproductive autonomy, cause emotional distress, and create health risks of pregnancy termination. The Report asserted that "reproductive autonomy is a principle concerning the non-interference in reproductive decision-making. This could mean allowing potential parents to exercise freedoms in deciding if, when, how many, and to a limited extent 'what kind of' children they have" [17; p. 79].

In order to distinguish between modifying the nuclear genome and the mitochondrial genome, during discussions about MRT, the UK's Department of Health used the following working definition of genetic modification: "genetic modification involves the germline modification of nuclear DNA (in the chromosomes) that can be passed on to future generations" [37; p, 15]. While the UK's position accepted that MRT has germline implications (i.e., the result of mitochondrial donation will be passed down to future generations), it rejected the view of MRT as a form of "genetic modification" on the grounds that it does not involve the heritable modification of the nDNA. Accordingly, MRT would not alter personal characteristics and traits, as only unaltered nDNA is transferred to an egg or embryo, while unhealthy mitochondria are replaced by healthy ones [37, 30].

The UK's theoretical approach in using a "working definition" of genetic modification places MRT outside of sanctioned germline genetic interventions. This approach demarcates the boundaries between MRT and nuclear modification. On this account, MRT becomes an inheritable

germline modification technique that, unlike other genetic manipulations, has a unique pattern of inheritance (i.e., matrilineal transmission).

4.4.1.1.2 The Swedish National Council on Medical Ethics: Mitochondria replacement in cases of serious diseases–ethical aspects (2013)

Sweden's *Genetic Integrity Act (2006)* prohibits any treatment that brings about heritable genetic changes in both research and clinical practice [38]. In 2013, the Swedish National Council on Medical Ethics published a report entitled "Mitochondrial replacement in cases of serious diseases–ethical aspects." Citing safety uncertainties and available alternatives for having children free of mitochondrial diseases, the Council did not consider MRT ethically acceptable. However, the Council declared that MRT might eventually be considered ethically admissible, provided it is proven safe and both short- and long-term effects are deemed acceptable [39].

4.4.1.1.3 The US National Academies of Sciences, Medicine, and Engineering: Mitochondrial Replacement techniques: Ethical, social and policy considerations (2016)

The US has no federal legislation explicitly addressing human genetic modification (including germline and/or somatic cells). However, there are restrictions that apply to MRT and other germline modification techniques [16]. In the US, MRT research is restricted by the Dickey-Wicker amendment, a rider on the US Department of Health and Human Services (HHS) appropriation bill that bans the HHS funding to be used to create embryos for research [40]. Also, MRT is subject to the Food and Drug Administration (FDA) oversight in the clinical context. In

2014, the FDA assembled experts to discuss MRT's medical and scientific reasoning [41]. Following this meeting, the FDA requested that the National Academies of Sciences, Engineering, and Medicine (hereafter NASEM) assemble a committee to examine and analyze MRT's socio-ethical concerns and address policy issues in developing its initial clinical investigations. The report was of the opinion that it is ethically acceptable to use MRT in the clinical context given the safety and efficacy of the technique are established, trials are limited to women at risk of transmitting serious mitochondrial diseases, implantation is limited to male embryos, and mtDNA haplogroups matching are reviewed in order to reduce the potential risk of mtDNA and nDNA incompatibilities [16].

The NASEM report concluded that MRT involves genetic modification but only constitutes heritable genetic modification if used to produce female offspring. This approach contrasts with the UK model, which does not consider MRT genetic modification. The NASEM report emphasizes the importance of limiting MRT use to male offspring to prevent any potential genetic modifications from being passed on to future generations [16].

4.4.1.1.4 Singapore's Bioethics Advisory Committee: Ethical, legal and social issues arising from mitochondrial gnome replacement technology: A consultation paper (2018)

Singapore's *Human Cloning and Other Prohibited Practices Act (2004)* does not allow the clinical practice of human germline modification [42]. On April 19, 2018, Singapore's Bioethics Advisory Committee (BAC) reviewed its 2005 position, which had recommended against MRT given insufficient scientific evidence [43]. BAC published its consultation paper on April 19, 2018, in

which public comments were invited on whether the clinical applications of MRT should be permitted for the prevention of heritable mitochondrial disorders [44]. Among questions in the consultation document were the potential benefits of MRT, the welfare of future generations, the slippery slope argument, and ethical differences between MST, PNT, and polar body transfer methods. The consultation took place for eight weeks, beginning on April 20, 2018 [44]. The Committee has yet to publish its recommendations to the Government about whether MRT should be permitted in Singapore.

4.4.1.1.5 Australia: On a similar path as the UK? (2021) updates

Australia's 2006 Prohibition of Human Cloning for Reproduction and Regulation of Human Embryo Research Amendment Act bans the introduction of heritable changes into the germline [45]. In June 2018, the Senate Community Affairs Reference Committee drafted recommendations supporting MRT [46]. In a Position Statement, Mito Foundation strongly encouraged the government to address recommendations from the Senate Report "as a matter of urgency" [47]. In January 2019, the government indicated that MRT is of great interest to the Australian community while acknowledging that "the technology involves changing the genetic make-up of the embryo, the safety and efficacy of this technology is unclear, and evidence from clinical practice is unavailable" [48; p, 3]. The Response from the government asserted that decisions about regulatory or legislative changes should be thorough and will only be considered once the results from public consultations and expert advisory groups are finalized [48].

In September 2019, the Mito Foundation announced the start of an online public consultation period and a series of public forums across Australia, which ended on November 29, 2019 [49]. On June 5, 2020, the National Health and Medical Research Council (NHMRC) released three reports about MRT (mitochondrial donation). These reports included an expert working committee statement on the science of MRT (Expert Statement), a public consultation on the technique's social and ethical issues (Consultation Report), and a Position Statement [15, 50, 51]. Australia's Expert Working Committee concluded that additional developments had been made on some aspects of MRT's science since the HFEA's 2016 scientific review. However, there was no significant new evidence reported on the safety and efficacy of the technique. The Committee advised that further in vitro, animal, and clinical research into the safety and efficacy of MRT would enable the technique to be better understood and refined. The Expert Committee also concluded that it is essential to recognize the potential inheritability of changes to the genome introduced by MRT indifferent of whether it is considered germline genetic modification. Still, the Committee recognized that the term germline genetic modification has "conceptual drawbacks and would not be appropriate for classifying mitochondrial donation" [15; p. 4-5].

On March 24, 2021, the Mitochondrial Donation Law Reform (Bill 2021) was introduced into Parliament. A vote on the Bill is expected soon. On May 11, 2021, the Australian government pledged $10.3M over ten years to implement MRT in research and clinical contexts in Australia [49].

4.4.1.2 The Global Context: International professional recommendations concerning MRT

4.4.1.2.1 The European Neuromuscular Centre workshop: Developing guidelines for management of reproductive options for families with maternally inherited mtDNA disease (2019)

Between March 22-24, 2019, the 243rd European Neuromuscular Centre (ENMC) workshop met in the Netherlands to examine viewpoints and new information about reproductive options available to patients with mitochondrial diseases. Citing the HFEA regulations, the workshop concluded that "MST or PNT (should be offered) to patients for whom PGD is inappropriate or likely to be unsuccessful and who exhibit or are predicted to exhibit high levels of germline heteroplasmy or homoplasmy." More importantly, the consensus opinion of experts at the meeting was that patients should be informed that MRT does not eliminate the risk of mitochondrial disease [52].

4.4.1.2.2 Heritable Human Genome Editing: International Commission on the Clinical Use of Human Germline Genome Editing. A Consensus Study Report of the National Academy of Medicine and the National Academy of Sciences and the Royal Society (2020)

The International Commission's assignment on the scientific and technological questions arising from human germline genome editing transpired after the birth of "CRISPR babies" in China. The Commission aimed to elaborate on what would be required in establishing a safe and reliable clinical translation of heritable human genome editing. The final report was released on September 3, 2020, which used the UK's implementation of MRT as an example of stepwise clinical

introduction of human genome editing techniques. These measures included: "(1) a legal regulatory foundation; (2) an initial demonstration of potential feasibility; (3) support from patient communities seeking MRT to prevent disease; (4) public engagement and ethical dialogues; (5) legislative approvals; (6) independent expert reviews of safety and efficacy; and (7) regulatory review and approval for clinical use on a case-by-case basis" [53; p. 25-26]. Highlighting MRT, the Report echoed the sentiment that progress toward the clinical implementation of heritable human genome editing requires an extensive public debate [53].

4.4.1.2.3 International Society for Stem Cell Research (ISSCR) Guidelines for Stem Cell Research and Clinical Translation (2021)

The ISSCR report on stem cell research and clinical translation was published in May 2021. On MRT, the report emphasized the need for further research to assess the safety and efficacy of the technique to minimize the risk of mitochondrial carryover, investigate disruptions to the nDNA and mtDNA interactions, explore PBT methods, and use genome editing to reduce or eliminate pathogenic mtDNA [54].

4.4.1.3 The Canadian Context: Legislation and policy

4.4.1.3.1 Assisted Human Reproduction Act (AHRA)

It has been thirty-two years since Canada took the first step toward regulating new reproductive and genetic technologies. With a mandate to examine the ethical, legal, social, health and economic

implications of Assisted Reproductive Technologies (ARTs), the Royal Commission on New Reproductive Technologies was formed in 1989. After four years and consulting thousands of Canadians, the Commission drafted 293 recommendations in a final report, published on November 15, 1993, entitled Proceed with Care [55]. The Commission advised on three broad topics: (1) using the criminal code to ban certain activities and technologies; (2) regulating permissible activities; and (3) establishing a federal regulatory and licensing body that would oversee ARTs. The Commission urged criminalizing the commercialization of reproductive cells, zygotes, fetal tissue, embryos, and surrogacy. The Commission also endorsed forbidding non-medical sex selection, germline genetic modification, and cloning [56]. After the Commission published its 1993 report, there were a series of federal attempts at regulating ARTs, including a voluntary moratorium announced in June 1996 on nine of the practices for which the Commission had advised criminal bans. There was also five tabled legislation that died on the Order Paper until Bill C-6 received Royal assent on March 29, 2004, and the AHRA came into force [57].

The AHRA contained criminal prohibitions to prevent harmful technologies and behaviors and a framework for permitted activities. Assisted Human Reproduction Canada was the national agency established to oversee the AHRA. In June 2008, following a constitutional inquiry by Quebec's attorney general, the Quebec Court of Appeal determined that notable parts of the AHRA were unconstitutional for violating provincial jurisdiction over health. In December 2010, the Supreme Court of Canada confirmed that most of the challenged sections were unconstitutional; thus, the legislation was substantially amended, and the national agency overseeing it was shut down. Next, Health Canada took over the responsibility related to the remainder of the Act [58].

4.4.1.3.2 AHRA's Prohibited Activities and MRT

Section 5 of the AHRA bans scientific research and clinical activities that involve human cloning, creating an embryo for non-reproductive purposes, keeping an embryo outside the human body exceeding the fourteenth day, sex selection for non-medical reasons, creating a chimera or a hybrid, and *introducing heritable changes in the genome* [1]. More specifically, Article 5(1)(f) of the AHRA 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." This, in both research and clinical practice [1]. A person who violates this prohibition will be punished with a fine of up to $500,000 and/or imprisonment for up to ten years [59].

4.4.1.4 The Canadian Context: Professional recommendations

4.4.1.4.1 Mitochondrial Replacement Therapy: The Road to the Clinic in Canada (2017)

On March 24, 2017, the Stem Cell Network (SCN), in collaboration with the Centre of Genomics and Policy (CGP) (McGill University), held a workshop regarding the AHRA research prohibition on MRT with various stakeholders present. The workshop was part two in a series of five workshops about the review of the AHRA [60-64]. Knoppers et al. (2017b) concluded that criminal bans are not a suitable instrument to regulate MRT and that Canada should not "curtail scientific exploration that might lead to MRT's safe and effective clinical application" [61; p. 917]. The

authors also asserted that existing legislation should be subject to periodic review to be more responsive to advances in science [61].

4.4.1.4.2 CIHR Best Brains Exchange: A Path Forward for the Assisted Human Reproduction Act (2018)

On March 13, 2018, Health Canada and the Knowledge Translation Strategy Unit of the Canadian Institutes of Health Research (CIHR) convened a one-day Best Brain Exchange meeting with experts in ARTs. Among the addressed topics were the regulatory administration of the AHRA, the need to address identified gaps in previous ART discussions, and different ways of involving Canadians on the subject of assisted reproduction [65]. On MRT, Dr. Bartha Maria Knoppers (Canada Research Chair in Law and Medicine and Director of the CGP) presented the results of her previous work (the CGP and the SCN MRT workshop, as well as a consensus achieved as a result of the workshop series held on the review of the AHRA). This Consensus Statement had asserted that the use of MRT to prevent severe mitochondrial diseases should be permitted once proved to be safe and effective [62]. At the CIHR meeting, Dr. Francoise Baylis (Canada Research Chair in Bioethics and Philosophy at Dalhousie University) stated that she supported the AHRA's prohibitions of human genome editing and MRT. She declared her support for using the legal prohibition to protect the public's health and safety from unethical procedures. She also noted that as the AHRA had never been entirely operational, it was yet to be truly tested [65].

4.4.1.4.3 Bébés génétiquement modifiés: enjeux éthiques soulevés par la modification génétique des cellules germinales et des embryons (Genetically modified babies: Ethical issues raised by the genetic modification of germ cells and embryos) (2019)

On March 21, 2019, Quebec's Commission on Ethics in Science and Technology released the results of its deliberation on assessing and addressing the ethical issues raised by human genome editing and MRT. Considering the uncertainty revolving around the safety and efficacy of germline modification techniques, potential transmissibility of germline alterations, and the severity and irreversibility of such interventions' health risks, the Commission recommended to (1) foster high scientific standards for investigating the safety and effectiveness of genetic modification procedures; (2) restrict germline intervention to severe, high penetrance diseases; (3) at first, limit the use of MRT to male embryos; and (4) have the Ministère de la Santé et des Services sociaux conduct longitudinal follow-up of children born using genetic modification technologies until they reach the consent age [66].

Furthermore, the Commission stated that the desire for genetically related children, while "understandable, is not a medical need or a right" [66; p. 13]. Thus, this desire does not constitute a duty for society to promote genetic modification interventions. However, considering the importance of genetic relationship for some individuals and predictive tests' inability to help a wide range of individuals, the Commission declared using germline genetic modification to prevent severe disease as medically justifiable. This conclusion was limited to cases where no other reproductive or therapeutic options are available to prospective parents [66].

4.4.1.4.4 MitoCanada Foundation Position Statement (2019)

The MitoCanada Foundation is the only registered national charity focused on mitochondrial diseases in Canada. To inform the public of the safety and efficacy and the scientific and ethical indications of MRT, the Foundation released a Position Statement in 2019. Reflecting on the research and clinical advancements of the technique and the Canadian debates concerning MRT, the Statement encouraged additional research to adequately judge the safety and efficacy of MRT in preventing mitochondrial disease [67].

4.4.2 Qualitative study

4.4.2.1 Clinical translation of mitochondrial replacement therapy in Canada: A qualitative study of stakeholders' attitudes (2021)

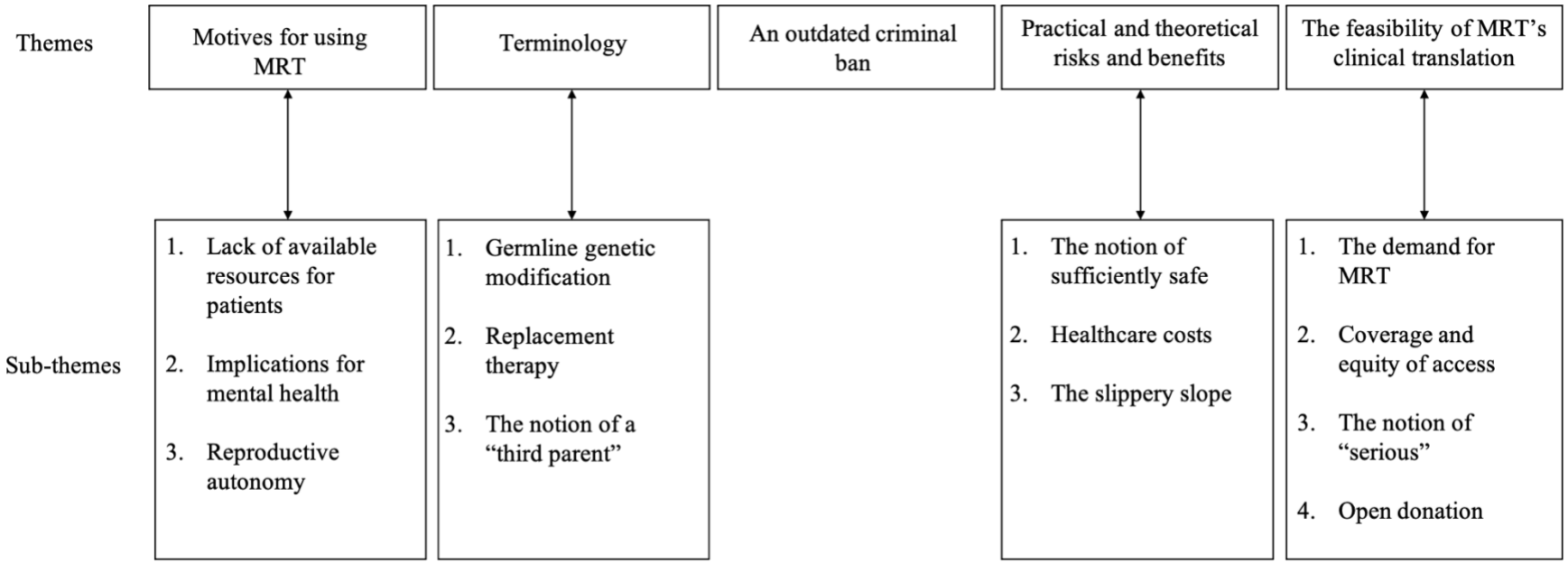
Between 2019-2020, we conducted a qualitative interview study of key stakeholders' attitudes toward the clinical translation of MRT in Canada (CHAPTER 2). This study synthesized the attitudes of key stakeholders (researchers, clinicians, patients, and egg donors) and members of the general public and opened the discussion on revisiting the AHRA's prohibition of MRT [10].

4.4.2.2 Research purpose

In March 2018, the CBC Radio reported on a family from Hudson, Quebec. The mother and her two kids (a boy and a girl) were affected by mitochondrial complex III deficiency. The family expressed that they hoped the government would legalize MRT, so their daughter could have a healthy child of her own one day. When approached by CBC to comment on the story, Health Canada stated that it "recognized the importance for the AHRA to reflect advances in science and the views of Canadians." This included revisiting the prohibition of MRT in Canada. The key point of Health Canada's statement appeared to be the need to ensure whether changes to the AHRA prohibitions would "continue to reflect the values of Canadians" [68].

In light of the fast-evolving advancements in the field of new assisted reproductive technologies and considering the mounting concerns about reproductive tourism and the alternative uses of MRT, we sought to explore various stakeholders and members of the public's attitudes toward the clinical translation of the technique in Canada. We used a thematic analysis to identify, analyze, and report themes from the data. Identified themes fell under five categories: motives for using MRT, terminology, an outdated criminal ban, practical and theoretical risks and benefits, and the feasibility of MRT's clinical translation [10] (see Figure 4.2).

Figure 4.2: Attitudes toward the clinical translation of MRT



For the purpose of synthesizing policy points to consider in MRT's path to the clinic in Canada, expert opinions on the feasibility of the technique's clinical implementation to prevent 'serious' mitochondrial diseases (see illustrative quotes below) were contrasted with policy rationale identified in the scoping review.

4.4.2.3 Experts' illustrative quotes:

On the AHRA, most experts believed that it was time to revisit the criminal prohibitions of MRT in light of the UK ruling:

> "I think we need to lift the ban totally because there are aspects of the research that need further investigations, but those are not fundamentally changing to a large extent, the safety is just looking at some epigenetic changes and a few other things that may be more interesting to the basic scientists. But they need to be allowed to do this [MRT]. I think there is enough evidence specially with the UK ruling and the UK experience. I think we are ready to go ahead clinically using this [MRT] at this point, in specific cases. And that is for a mom who is proven to have mitochondrial DNA mutation that is pathogenic."

> "Well, first you have to change the law, step one, and then, I mean, who knows how long that would take. I mean, they were supposed to revisit this thing, right? Every five years, I think, and nothing's been done. But I don't think there's, you know, I don't think that's on the top of the government's list of things to do. I think you need to try to build a pipeline before they do because they've got other things on their mind, so it would have to come from, the pressure would have to come from some kind of groundswell in the community, the community being the patients. People involved, saying we need to revisit this, we need to go and change the Act since it [MRT] is not a criminal act, and we could actually start to investigate how to implement this and come with a plan. Here's the number, these are the number of patients that would be eligible each year. Here's how we would envision setting it up, here's how many clinics. I mean you need a plan, right? and my sense is that now, given what's happened in England, that the government would be open to revisit some of these things."

Others agreed with having laws that did not hinder scientific advancements and differentiated between MRT and other genetic modification techniques:

> "So, zero regulation, It's frightening. If somebody wanted to open up some IVF clinic and decided they were going to do some kind of designer thing. I think that will be harder because you know, it's dealing with reproduction […], desperate people with resources will sometimes do desperate, you know, desperate things. The mainstream healthcare system is never going to do designer babies. Not gonna happen. But I completely agree with the parts that you should regulate it; have oversight."

> "[…] there shouldn't be any kind of criminality associated with it, so I suppose that changing the law, or being more specific that MRT is different than genetic modification; that would be a good first step."

Several experts focused on the lack of proper funding for mitochondrial disease in both research and healthcare as well as the absence of organized care offered to complex disease patients:

> "I think it's gonna be very difficult to do much research in this area [mitochondrial disease]. We just put in for the Centre of Excellence in Canada, that did not get funded. So, they are not funding the top people to do research in this area, I don't think there is a strong appetite for mitochondrial disease research in Canada. I think because of the limitations in funding, overall, the funding groups are generally going for the more common things: cancer, Parkinson's, Alzheimer's, some of the big diseases, so, it's very difficult for rare diseases to get funded in Canada, so that's gonna limit our ability to do much research in the area. But that does not limit our ability to start doing this clinically because, I think, the road's already been paved by the UK group."

> "I don't think the healthcare system knows what to do with complex patients. Meaning, the rare complex patients we have, I find that we're underfunded in terms of caring for these patients. They're not very many, each individual disease, they're not very many, but they do account for a large number of patient visits, and I don't necessarily think we do the best job in organizing care for complex patients like this. We do have high technology dependent patients that I think we do much better with. So, if the patients have G-tubes and traches, I think we do okay with that, but the patients that don't have those technologies but still have multiorgan involvement, I don't think we're very good at treating those patients. We need to be more cohesive in our follow-up. We need to have patient advocators meaning we need to have somebody that's organizing the care so we're

not bringing them back to respirology one day, cardiology, two days later, nephrology next week. We tend to do that. And I don't think it's ideal for the families and I don't think it's ideal for the patients and also the communication between the doctors. What are you doing and how are you doing it? So, I think that needs to change as well."

In terms of available options open to mitochondrial disease patients for having genetically related children, the experts also discussed the credibility of preventive testing (i.e., PGD and PND):

"[…] PGD is possible. The only concern there is that you still are picking an embryo that has maybe a lower heteroplasmy, but we don't know at this point quite enough about the bottleneck theory and mitochondrial DNA segregation to be absolutely sure that as the embryo grows, they are not going to have a higher heteroplasmy that just randomly starts to accumulate in the brain. So, it is certainly an option, but I don't think we have enough knowledge at this point to be as confident that we are going to definitely tell the mom: look, because we have picked an egg that has got very low heteroplasmy, that definitely means you are not going to have higher heteroplasmy in the brain as the child continues to grow and we get replicative segregation. […] We have had a number of folks [mitochondrial patients] and because it's [MRT] not available in Canada, we have done prenatal diagnosis. The problem there, of course, is you do your CVS, or your amniotic sampling and you say okay, the heteroplasmy is fairly low. That is a risky procedure because you are putting a needle in and there is a small risk of inducing spontaneous abortion when you do this number one, and number two, if the child was found to have a very high heteroplasmy for mitochondrial disease, where there is a good relationship between high heteroplasmy and a bad outcome, it's a very difficult decision for the mom to make because then they have to go through full abortion procedure, which places the mom at risk. So, that's another reason why I would like MRT moving forward because certainly talking to the moms who have actually done that, it's a very emotionally and potentially physically risky thing for these people to go through."

On MRT's safety and efficacy, most experts emphasized the importance of addressing the notion of "sufficiently safe" in the context of new technologies and believed that the UK experience showed the technique's readiness for its clinical implementation:

[…] "what's that mean? Really? How safe do you have to be? Everything is a risk. Amniocentesis is a risk. Everything, every medical procedure has some risk associated

with it. And the question is, what's the risk/benefit, I guess, and so, if it could be shown that there's X percent of risk, I don't see why we couldn't offer it. It's not so complex because, it's not like we have to develop a whole new technology. I mean the technology is out there, you know, in centers that are experts at it [in the UK]. So, it's a lot trickier than just doing in vitro. But you know, the laparoscopes, the whole, the hardware, is already there, essentially in assisted reproduction clinics."

"Well, people always want the raw answer: 'is it safe?' But what does that mean? Do you mean that it's a hundred percent of the time you're not going to have a problem? or is it something that most people would accept the risk for? If you get IVF, would people consider that safe? They would, but it's got risks and problems too. Safe is used in language to indicate absolute certainty, and it's misused in many ways. The question is really, is it a risk that's commonly acceptable to people who are users of that technology? And the answer to that is yes, most people who use IVF technologies understand that there's a risk, and they wouldn't be engaging in it if it wasn't acceptable."

"I think the risks are pretty low for its proper intended use and I am in favor of its use for women who have severe mitochondrial disease or have children with severe disease and have ovum that likely result in more kids with severe disease. I think at this point in time, the evidence would support, and the experience would support that this [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, with copy number variation and these sorts of things. Life is risk/benefit and when you have a kid who is going to die, I think a small risk from this whole procedure is well worth taking."

Others believed that more research was needed in the field of MRT before it could be offered in Canadian clinics:

"So, what is left is still the fact that we do not completely understand a few processes around the mitochondrial genome. In general, we understand it's replication, we understand transcription and translation, more or less. Do we understand mitochondrial DNA repair? No, we don't, right? To the point that we still have no proteins that we know of that can be said directly to be involved in mitochondrial DNA repair. The other thing is diagnostics with respect to mitochondrial DNA. And everybody's going to NextGen sequencing, but I have yet to see a really good, really deep comparison of how accurate that NextGen sequencing is for mitochondrial DNA mutations."

> "[…] the other thing that I think probably needs a lot more investigation is early developmental studies. And that's of course also not allowed under the current laws. I can't remember how many cell stage embryos, but you're basically not allowed to go past a certain amount. And yet, I think it proves that when you have the results of an MRT procedure, I think it's really important to go as far in development as you can to understand the consequences at each of the known stages of development. I mean, really what you are doing right now, you're using a procedure and it's basically a black box, right?"

Many believed labeling a disease "serious" was mostly open to interpretation and that a committee consisting of at least two clinicians would suffice to deem a disease "severe":

> "What we know about mitochondrial disease in general is that they are progressive, right? So, you first have one mild symptom and then there's another mild symptom and so you don't know what that's gonna look like in 5 years, in 10 years. If you have the molecular data that says, for instance, you're carrying the 4243 MELAS mutation, then you have a mitochondrial disease. And maybe you don't feel hugely impacted, but you are playing the dice; you're playing Russian roulette if you go ahead and have a child, because you have no idea. That child could have 0 mutant load or that child could have 80% mutant load and be really severely impacted, right? You just don't know. So, maybe clinicians can see the distinction between a mild mitochondrial disease and a severe […], but I don't. Once you've got the mitochondrial disease mutation, you've got a mutation and it's potentially a problem."

> "Well, it's so open to interpretation. I think, clearly, someone would have to come up with a law or something to the extent that they do with the MAiD program: two clinicians who are experts in mitochondrial medicine would have to conclude that the mother had a child or would be expected, based on their mitochondrial DNA mutation, to have a child who would have a disease which would likely shorten their life span or have a serious impact on their functional capacity, and then if two clinicians agree under circumstances you can't […] I think, that would be sufficient enough to move forward."

> "I think it is difficult to precisely quantify that. So, I think in general what physicians mean by severe conditions are mitochondrial mutations or conditions that can lead to significant functional impairment and to a quality of life for individuals. Rather than mitochondrial disorders that may cause early deafness that can be corrected, or diabetes at a later age in life. However, in mitochondrial disorders, it's not necessarily the genetic

> variants that cause the severity; it's the mutant load in a particular tissue. So, you know, 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. So, there are some variants that cause, you know, issues at an older age group that are potentially treatable. Whether these variants are appropriately categorized […] for example, there's a variant that people think causes deafness with the additional exposure to certain antibiotics or to toxic medications. So, you know the approval for MRT shouldn't be for that variant. I wouldn't advocate approval for that variant. But for example, variants that can potentially cause MELAS, which is a disease that can cause really early neurological and cardiac abnormalities, yes."

Finally, some experts believed that MRT does not entail germline modification:

> "I see the germline as being the chromosomes and the sex chromosomes and the autosomes. That's to me the germline. So, how I see the mitochondrial genome is if there's no nuclear genome, the mitochondrial genome is dead in the water. So, for me, I don't see it [MRT] as changing the germline when you suddenly have mitochondria or mitochondrial DNA depending on how you do it [...]

> "[…] That's not, in my opinion, it's not altering the germline. The mitochondrial DNA is in some ways subservient to the nuclear genome. That's the way I look at it. Because the mitochondria, without the nucleus, are nothing."

While others believed MRT to be technically modifying the germline, they asserted that the implications of the technique differed from those manipulations of the nuclear DNA:

> "You're adding a handful of genes. So, it is germline genetic modification. There's no question about it in my mind. You're adding, you're swapping genetic material and you're altering what would have been in that woman's germline, genetically, but it's a handful of genes. So, it's not like we're going and creating designer babies or something like that. I don't think it's anything wicked like that."

> "Well, genetic by definition involves some genetic material, mitochondrial DNA is genetic material, so by definition it [MRT] is a genetic manipulation. Generally, we think of the germline as nucleus. Modifying the nucleus is a different scenario. So, this is a genetic modification in my mind. […] it does change the germline, but I think manipulating the nuclear genes is different."

4.4.3 Policy Points to Consider

Contrasting the results of the scoping review and the experts' opinions were concluded in the following points, which policymakers should consider in the clinical translation of MRT in Canada.

(i) The need for engaging the broader community and seeking further Canadian expertise

(1) Additional work is needed to engage the greater public in exploring the need for a revised AHRA. Future consultations should involve engaging and informing stakeholders about the complex interplay of scientific and socio-ethical issues through public forums and advisory groups, which include the Canadian Fertility and Andrology Society, the Canadian Academy of Health Sciences, the Canadian College of Medical Geneticists, and the Canadian Association of Genetic Counsellors, among others.

(2) Considering the number of unknowns within the field (e.g., the nuclear-mitochondrial interactions, mtDNA carryover and reversion, and patterns of mtDNA transmission and inheritance), it would be essential to convene Canadian experts to assess the evidence on MRT in order to inform decision-making in Canada. An independent panel of qualified experts convened by the Council of Canadian Academies could carry out an assessment of the scientific advancements within the field of MRT.

(ii) Establishing consensus on the status of MRT

Existing prohibitions on MRT in countries like Canada that regulate research and clinical applications of assisted reproductive technology are primarily in place to prevent so-called "designer babies" [18]. When the AHRA came into force in 2004, the notion of germline genetic modification under the subject of MRT was not yet under consideration. The AHRA describes the *genome* as "the totality of the deoxyribonucleic acid sequence of a particular cell" [69]. The Act bans any practice that "alter(s) the genome of a cell of a human being or in vitro embryo such that the alteration is capable of being transmitted to descendants" [1]. Because this explanation of *genome* covers all the genetic information in a cell, this prohibition also applies to MRT. In this sense, reaching expert consensus on the status of MRT could have immense implications for MRT's research and clinical practice.

(iii) The importance of a measured introduction of MRT in Canada

Canada should initially invest in developing expertise in the field of MRT. Australia's model is a well-calculated approach for Health Canada to consider in advancing towards the clinical implementation of MRT. The rights of children born using MRT, prospective parents, and egg donors should be central preoccupations in creating a robust policy framework.

(IV) The need to address issues of inequality between provinces and territories in accessing innovative treatments

Future community engagements must also take into account ensuring the equity of access to MRT across Canada. The principal aim of Canadian health care policy is "to protect, promote and restore the physical and mental well-being of residents of Canada and to facilitate reasonable access to health services without financial or other barriers" [70]. Still, health care services are not equally provided to all Canadians [71, 72]. A prime example in this regard is the evident inequality in accessibility and availability of health services between Indigenous communities and the rest of Canada. Indigenous peoples continue to encounter hurdles to health services due to socioeconomic status and geographical location and discrimination and stereotyping. These result in substantial health disparities experienced by Indigenous peoples compared to other Canadians [73, 74]. Besides considering the perspectives of Canada's indigenous communities regarding emerging new reproductive technologies, a fair and more innovative financial scheme needs to be established to fund the use of these technologies by Indigenous persons.

4.5 References

1. Assisted Human Reproduction Act, S.C. 2004, c. 2. Section 5 (Prohibited Activities). Article (5)(1)(f). https://laws-lois.justice.gc.ca/eng/acts/a-13.4/page-1.html#h-6052
2. Darwin Life Nadiya. 2021. http://dl-nadiya.com/nuclear-transfers
3. Institute of life. 2021. https://www.iolife.eu/en/us/mst-research/
4. BioTexCom. Center for human reproduction. 2021. https://biotexcom.com/services/#mitochondrial-replacement-therapy
5. Thompson K, Collier JJ, Glasgow RIC, Robertson FM, et al. 2020. Recent advances in understanding the molecular genetic basis of mitochondrial disease. *J Inherit Metab Dis* 43(1):36-50. doi: 10.1002/jimd.12104
6. Gorman GS, Schaefer AM, Ng Y, et al. Prevalence of nuclear and mitochondrial DNA mutations related to adult mitochondrial disease. *Ann. Neurol* 2015; (77): 753–759. doi:10.1002/ana.24362.
7. Ng YS and Turnbull DM. 2020. When to think about mitochondrial disease. *Practical Neurology*; 20:260-261. http://dx.doi.org/10.1136/practneurol-2020-002501
8. Craven L, Alston CL, Taylor RW, Turnbull DM. 2017. Recent Advances in Mitochondrial Disease. Annu Rev Genomics Hum Genet. 2017 Aug 31;18:257-275. doi: 10.1146/annurev-genom-091416-035426.
9. Marlow FL. Mitochondrial matters: Mitochondrial bottlenecks, self-assembling structures, and entrapment in the female germline. Stem Cell Res. 2017 May; 21:178-186. doi: 10.1016/j.scr.2017.03.004.

10. Noohi, Li, Joly. 2021. Clinical translation of mitochondrial replacement therapy in Canada: A qualitative study of stakeholders' attitudes. FACETS. DOI: 10.1139/facets-2020-0062
11. Baylis F. 2017. Human Nuclear Genome Transfer (So-Called Mitochondrial Replacement): Clearing the Underbrush. Bioethics, 31(1), pp. 7-19. https://doi.org/10.1111/bioe.12309
12. Craven L, Murphy JL, Turnbull DM. Mitochondrial donation-hope for families with mitochondrial DNA disease. *Emerg Top Life Sci* 2020;4(2):151-154. doi: 10.1042/ETLS20190196
13. Craven L, Tuppen H, Greggains G, et al. Pronuclear transfer in human embryos to prevent transmission of mitochondrial DNA disease. *Nature* 2010; 456(7294): 82-85 doi: 10.1038/nature08958
14. Kang E, Wu J, Gutierrez NM, Koski A, et al. 2016. Mitochondrial replacement in human oocytes carrying pathogenic mitochondrial DNA mutations. Nature. 540, 7632, 270-275. DOI: 10.1038/nature20592
15. The National Health and Medical Research Council (NHMRC). 2020a. Australian Government, Medical Health and Research Council. Expert Statement Mitochondrial Donation Expert Working Committee https://www.nhmrc.gov.au/health-advice/all-topics/mitochondrial-donation#download
16. National Academies of Sciences, Engineering, and Medicine (NASEM). 2016. Mitochondrial replacement techniques: Ethical, social, and policy considerations. Washington, DC: The National Academies Press. DOI: 10.17226/21871

17. Nuffield Council on Bioethics. 2012. Novel techniques for the prevention of mitochondrial DNA disorders: an ethical review. https://www.nuffieldbioethics.org/wp-content/uploads/2014/06/Novel_techniques_for_the_prevention_of_mitochondrial_DNA_disorders_compressed.pdf
18. Isasi R, Kleiderman E, Knoppers BM. 2016. Editing policy to fit the genome. *Science*. 351(6271). 337-339. https://science.sciencemag.org/content/351/6271/337/tab-article-info
19. Collins F. Director, National Institutes of Health (NIH) (2015). Statement on NIH funding of research using gene-editing technologies in human embryos. https://www.nih.gov/about-nih/who-we-are/nih-director/statements/statement-nihfunding research-using-gene-editing-technologies-human-embryos/
20. Gómez-Tatay L, Hernández-Andreu JM, Aznar J. 2017. Mitochondrial Modification Techniques and Ethical Issues. Journal of clinical medicine, 6(3), 25. https://doi.org/10.3390/jcm6030025
21. Palacios-González C and Medina-Arellano M. 2017. Mitochondrial replacement techniques and Mexico's rule of law: on the legality of the first maternal spindle transfer case, *Journal of Law and the Biosciences*. 4 (1)50–69, https://doi.org/10.1093/jlb/lsw065
22. Cecchino GN, Seli E, Alves da Motta EL, García-Velasco JA. 2018. The role of mitochondrial activity in female fertility and assisted reproductive technologies: overview and current insights. *Reprod Biomed Online*. 36(6):686-697. DOI: 10.1016/j.rbmo.2018.02.007

23. Spindle transfer in the treatment of infertility: an ESHRE position statement. European Society of Human Reproduction and Embryology. 2019. https://www.eshre.eu/Press-Room/ESHRE-News/2019
24. Zhang J, Liu H, Luo S, et al. 2017. Live birth derived from oocyte spindle transfer to prevent mitochondrial disease, *Reproductive BioMedicine Online*;34 (4): 361- 368
25. Hamzelou J. World's First Baby Born With New '3 Parent' Technique. 2016. *New Scientist.* https://www.newscientist.com/article/2107219-exclusive-worlds-firstbaby-born- with-new-3-parent-technique/
26. Coghlan A. 2017. First baby born using 3-parent technique to treat infertility. NewScientist. https://www.newscientist.com/article/2118334-first-baby-born-using-3-parent-technique-to-treat-infertility/
27. Hasson. 2020. The Scandal-Plagued Company behind Stranded Surrogacy Babies is Also Promoting a Controversial IVF Technique. Center for Genetics and Society. https://www.geneticsandsociety.org/biopolitical-times/risky-business-company-behind-stranded-surrogacy-babies-also-promoting
28. Human Fertilisation and Embryology Authority (HEFA). 2021. https://www.hfea.gov.uk/treatments/embryo-testing-and-treatments-for-disease/mitochondrial-donation-treatment/
29. Human Fertilisation and Embryology Act (HFE Act), 1990. Section 3ZA. https://www.legislation.gov.uk/ukpga/1990/37/section/3ZA
30. Castro RJ. Mitochondrial replacement therapy: the UK and US regulatory landscapes. 2016. *J Law Biosci*;3(3):726-735. doi:10.1093/jlb/lsw051

31. Human Fertilisation and Embryology Act, 2008, Part 1, Amendments of the Human Fertilisation and Embryology Act 1990. https://www.legislation.gov.uk/ukpga/2008/22/contents
32. Human Fertilisation and Embryology Authority (HFEA). April 2011. Scientific review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception.
33. Human Fertilisation and Embryology Authority (HFEA). update March 2013. Scientific review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception.
34. Human Fertilisation and Embryology Authority (HFEA). 2014 update. Third scientific review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception. file:///Users/mitochondria/Downloads/HFEA%201%2030%20May%20(1).pdf
35. Human Fertilisation and Embryology Authority (HFEA). November 2016. Scientific Review of the Safety and Efficacy of Methods to Avoid Mitochondrial Disease through Assisted Conception: 2016 Update. https://www.hfea.gov.uk/media/2611/fourth_scientific_review_mitochondria_2016.pdf
36. The Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015 No. 572 https://www.legislation.gov.uk/ukdsi/2015/9780111125816/contents
37. Department of Health. Government response to the consultation on draft regulations to permit the use of new treatment techniques to prevent the transmission of a serious mitochondrial disease from mother to child. 2014. Health Science and Bioethics Division. Mitochondrial Donation.

https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/332881/Consultation_response.pdf

38. Genetic Integrity Act (2006:351). Ministry/Agency: Ministry of Health and Social Affairs. Swedish Code of Statutes no 2006:351. https://www.icj.org/wp-content/uploads/2013/05/Sweden-Genetic-Integrity-Act-2006-eng.pdf
39. The Swedish National Council on Medical Ethics Summary of the original Report. Mitochondria replacement in cases of serious diseases– ethical aspects 2013:2. Summary of a report. Mitokondriebyte vid allvarlig sjukdom – etiska aspekter, 2013:2. https://www.smer.se/wp-content/uploads/2013/11/Mitochondria-replacement-sammanfattning-eng2.pdf
40. Consolidated Appropriations Act, 2019, Sec. 733. https://www.congress.gov/bill/116thcongress/house-bill/648/text
41. Food and Drug Administration (FDA) Cellular Tissue and Gene Therapies Advisory Committee. 2014. Oocyte modification in assisted reproduction for the prevention of transmission of mitochondrial disease or treatment of infertility.
42. Human Cloning and Other Prohibited Practices Act. (CHAPTER 131B) (Original Enactment: Act 35 of 2004). https://sso.agc.gov.sg/Act/HCOPPA2004
43. Bioethics Advisory Committee (BAC). Genetic Testing and Genetic Research. 2005. A Report by the Bioethics Advisory Committee. Singapore. https://www.bioethics-singapore.gov.sg/files/publications/reports/genetic-testing-and-genetic-research-full-report.pdf
44. Bioethics Advisory Committee (BAC). Ethical, Legal and Social Issues Arising from Mitochondrial Genome Replacement Technology. A Consultation Paper. 2018.

Singapore. https://www.bioethics-singapore.gov.sg/files/publications/consultation-papers/mitochondrial-genome-replacement-tech.pdf

45. Prohibition of Human Cloning for Reproduction and the Regulation of Human Embryo Research Amendment Act (2006). No. 172. Part 2—Prohibited practices. Division 1—Practices that are completely prohibited. (15 Offence)—heritable alterations to genome. https://www.legislation.gov.au/Details/C2006A00172
46. Australian Government response to the Senate Community Affairs References Committee Inquiry into: The Science of Mitochondrial Donation and Related Matters 2019. https://www.aph.gov.au/Parliamentary_Business/Committees/Senate/Community_Affairs/MitochondrialDonation/Government_Response/
47. Mito Foundation Position Statement. 2019. Mitochondrial donation: providing reproductive choice to women carrying maternally inheritable mitochondrial disease. Mito foundation. June 2019 Update. file:///Users/mitochondria/Downloads/Mito-Foundation-position-statement_Mitochondrial-donation-March-2019%20(2).pdf
48. Australian Government response to the Senate Community Affairs References Committee Inquiry into: The Science of Mitochondrial Donation and Related Matters 2019. https://www.aph.gov.au/Parliamentary_Business/Committees/Senate/Community_Affairs/MitochondrialDonation/Government_Response/
49. Mito Foundation. 2021. https://www.mito.org.au/mitochondrial-donation/
50. The National Health and Medical Research Council (NHMRC). 2020b. Mitochondrial Donation Community Consultation Report. Australian Government, Medical Health and

Research Council. https://www.nhmrc.gov.au/health-advice/all-topics/mitochondrial-donation#download

51. The National Health and Medical Research Council (NHMRC). 2020c. Mitochondrial Donation Community Consultation Citizens' Panel Position Statement. https://www.nhmrc.gov.au/health-advice/all-topics/mitochondrial-donation#download
52. Poulton J, Steffann J, Burgstaller J, et al. 2019. 243rd ENMC international workshop: Developing guidelines for management of reproductive options for families with maternally inherited mtDNA disease, Amsterdam, the Netherlands, 22-24 March 2019. Neuromuscul Disord. 29(9):725-733. doi: 10.1016/j.nmd.2019.08.004
53. National Academy of Sciences. 2020. Heritable Human Genome Editing. Washington, DC: The National Academies Press. https://doi.org/10.17226/25665
54. International Society for Stem Cell Research (ISSCR) Guidelines for Stem Cell Research and Clinical Translation. 2021. https://www.isscr.org/policy/guidelines-for-stem-cell-research-and-clinical-translation
55. Proceed with care - final report of the Royal Commission on New Reproductive Technologies / Patricia Baird, chairperson. 1993. https://publications.gc.ca/site/eng/9.699855/publication.html
56. Royal Commission on New Reproductive Technologies. 1993. http://publications.gc.ca/site/eng/9.699855/publication.html
57. Snow D. 2014. Failure to Reproduce: Assisted Reproductive Technology Policy in Canada (doctoral thesis). University of Calgary, Calgary, AB. doi:10.11575/PRISM/26158. http://hdl.handle.net/11023/1418

58. Toward a Strengthened Assisted Human Reproduction Act: A Consultation with Canadians on Key Policy Proposals. 2018. Health Canada. https://www.canada.ca/en/health-canada/programs/consultation-assisted-human-reproduction/document.html

59. Assisted Human Reproduction Act, S.C. 2004, c. 2. Section 60 (Offences). Article 60(a). https://laws-lois.justice.gc.ca/eng/acts/a-13.4/page-4.html#h-6276

60. Knoppers BM, Isasi R, Caulfield T et al. 2017a. Human gene editing: revisiting Canadian policy. NPJ Regen Med. 5;2:3. doi: 10.1038/s41536-017-0007-2

61. Knoppers BM, Leader A, Hume S, et al. 2017b. Mitochondrial Replacement Therapy: The Road to the Clinic in Canada. Journal of Obstetrics and Gynaecology Canada. 39(10):916-918. doi: 10.1016/j.jogc.2017.05.007

62. Knoppers B.M., Ogbogu, U., Ravitsky, V, et al. 2018. Consensus Statement: Gene Editing, Genetic Testing and Reproductive Medicine in Canada. https://stemcellnetwork.ca/wp-content/uploads/2018/02/Consensus-Statement_.pdf

63. Ogbogu U, Zarzeczny A, Baltz J, et al. 2018. Research on Human Embryos and Reproductive Materials: Revisiting Canadian Law and Policy. *Healthc Policy*.13(3):10-19. doi:10.12927/hcpol.2018.25401

64. Ravitsky V, Nguyen MT, Birko S, et al. 2019. Pre-implantation Genetic Diagnosis: The Road Forward in Canada. J Obstet Gynaecol Can. 2019 Jan;41(1):68-71. doi: 10.1016/j.jogc.2018.08.001.

65. CIHR Best Brains Exchange: A Path Forward for the Assisted Human Reproduction Act. 2018. Canadian Institutes of Health Research. https://cihr-irsc.gc.ca/e/51215.html

66. Bébés génétiquement modifiés: enjeux éthiques soulevés par la modification génétique des cellules germinales et des embryons. 2019. Commission de l'éthique en science et en technologie. https://www.ethique.gouv.qc.ca/fr/publications/modification-genetique-lignee-germinale/

67. Mitochondrial Replacement Therapy (MRT). MitoCanada Foundation Position Statement. 2019. https://mitocanada.org/wpcontent/uploads/2019/11/MitoCanada_Position-Statement_MRT_25Nov2019.pdf

68. Scientists say it's time to make '3-parent baby' technology legal in Canada. 2018. CBC Radio. https://www.cbc.ca/radio/quirks/march-24-2018-an-alien-looking-skeleton-three-parent-families-in-canada-and-more-1.4588650/scientists-say-it-s-time-to-make-3-parent-baby-technology-legal-in-canada-1.4588671

69. Assisted Human Reproduction Act, S.C. 2004, c. 2. Section 2 (Interpretation and Application). Definitions. https://laws-lois.justice.gc.ca/eng/acts/a-13.4/page-1.html#h-6012

70. Canada Health Act. R.S.C., 1985, c. C-6. https://laws-lois.justice.gc.ca/eng/acts/c-6/fulltext.html/

71. Horrill T, McMillan DE, Schultz ASH, Thompson G. 2018. Understanding access to healthcare among Indigenous peoples: A comparative analysis of biomedical and postcolonial perspectives. *Nurs Inq*. 25(3): e12237. doi:10.1111/nin.12237

72. Greenwood M, de Leeuw S and Lindsay N. 2018. "Challenges in health equity for Indigenous peoples in Canada." The Lancet, 391, 1645-47. DOI: https://doi.org/10.1016/S0140-6736(18)30177-6

73. Browne AJ. 2017. Moving beyond description: Closing the health equity gap by redressing racism impacting Indigenous populations. Soc Sci Med.184: 23-26. doi: 10.1016/j.socscimed.2017.04.045.

74. Cameron BL, Carmargo Plazas Mdel P, Salas AS et al. 2014. Understanding inequalities in access to health care services for aboriginal people: a call for nursing action. ANS Adv Nurs Sci. 37(3): E1-E16. doi: 10.1097/ANS.0000000000000039

CHAPTER 5: CONTRIBUTIONS TO THE FIELD AND DISCUSSION

5.1 Contributions to the field

By analyzing perceptions and expectations of Canadian stakeholders (Chapter 2) in combination with a review of MRT's ethics and policy literature (Chapter 1 and Chapter 4), this thesis project provides policymakers with evidence-based data and key policy points. Chapter 3 addresses the main objection to promoting MRT in the bioethics literature, which questions the very need for the existence of MRT children. This manuscript offers a reflection on the strengths and weaknesses of this objection. It also offers strong arguments to set aside this objection and consider the clinical translation of MRT in a well-regulated environment.

5.2 Discussion

5.2.1 Lessons from Australia

In Australia, *Mitochondrial Donation Law Reform (Maeve's Law) Bill 2021* amends the *Prohibition of Human Cloning for Reproduction Act 2002* (Prohibition of Human Cloning for Reproduction Act 2002) and the *Research Involving Human Embryos Act 2002* (Research Involving Human Embryos Act 2002) to allow MRT. The Bill introduces five types of MRT licenses: 1) a pre-clinical research and training license; 2) a clinical trial research and training license; 3) a clinical trial license; 4) a clinical practice research and training license; and 5) a clinical practice license. What is authorized under each of the MRT licenses, including the criteria for applications, are detailed provisions included in the Bill. The administration and regulation of

the licenses will be managed by the Embryo Research Licensing Committee of the NHMRC (Mitochondrial Donation Law Reform (Maeve's Law) Bill 2021). The legislation proposes a two-stage path towards the clinical introduction of MRT in Australia. During stage 1, only licenses pertaining to pre-clinical and clinical trial research and training and clinical trial activities will be available from the NHMRC. This proposed stage is meant to build scientific evidence and help determine the safety, efficacy, and feasibility of MRT as a preventive measure for mitochondrial disease. Stage 2 would then allow the use of MRT in the clinical context. Advancing to stage 2 will be subject to further amendments to the legislation which will be informed by the clinical trials results, expert opinion, and additional consultations (Mitochondrial Donation Law Reform (Maeve's Law) Bill 2021).

Much like Canada, Australia does not have extensive experience in the field of MRT (NHMRC 2020a). As Australia has envisioned under a well-defined licensing framework, the gradual introduction of MRT furthers research and develops expertise. This strategy would be a good approach for Health Canada to consider in advancing towards the clinical introduction of MRT. Investing in research and training the next generation of experts in the field must, indeed, be a priority in considering the clinical introduction of MRT in Canada. In this sense, the path Australia has taken towards adopting MRT is a well-thought-out model to pursue.

5.2.2 Main contrasts of the two frameworks: The UK vs. Australia

The Australian approach to regulating MRT resembles the two-fold licensing scheme in the UK with the same requirements to be met by those patients hoping to use the technique. For now, only

one clinic in Newcastle is authorized to offer MRT in the UK (HFEA 2021a). Likewise, in Australia, one clinic will be licensed to offer MRT during the first stage of the proposed policy (Mitochondrial Donation Law Reform (Maeve's Law) Bill 2021). Sex selection and donor identity policies in the Australian plan differ from the UK design (Koplin 2021).

5.2.2.1 MRT and sex selection

As discussed in Chapter 4, NASEM argued that only male embryos should be implanted to achieve a pregnancy in practicing MRT. This was concluded in order to prevent the transmission of so-called changes to the germline and their afterward implications for future generations. The UK, instead, deemed PNT and MST "sufficiently safe" for clinical use, hence, did not consider sex selection appropriate (Mitochondrial Donation Regulations 2015). Australia's 2021 Bill proposes to allow parents to decide whether to select a male embryo or proceed without sex selection: "After attending the counselling […] the woman and her spouse (if any) so request; and (ii) it is practicable and safe to do so; only male embryos are selected for implantation in the woman" (Mitochondrial Donation Law Reform (Maeve's Law) Bill 2021; Sec 28Q (ii)). This stance, though, falls short of settling down issues revolving around sex selection. Allowing only male embryos to be selected in the context of MRT does not quite fit within the realm of justifiable medical reasons for which sex selection has been deemed ethically acceptable (Ethics Committee of the American Society for Reproductive Medicine 2015). If MRT were proven safe and efficacious, sex selection would not be inherently justifiable against the background of this emerging technique.

5.2.2.2 Mitochondrial donor's identity: To disclose or not to disclose?

Children born through IVF have a right to acquire identifying information about their gamete donors as they enter adulthood in the UK and Australia (HEFA 2021b; Assisted Reproductive Treatment Amendment Act 2016). According to the proposed Australian model, MRT children would have the same right concerning their mitochondrial donors (Mitochondrial Donation Law Reform (Maeve's Law) Bill 2021). In the UK, on the contrary, children born using MRT can only have access to non-identifying information about their donors (Mitochondrial Donation Regulations 2015). The basis for the UK approach is mainly rooted in the claim that mitochondrial donors contribute a small percentage to the resulting children's genetic makeup (less than 0.1%) (Taylor et al. 2001). As such, the identity of mitochondrial donors should be less of a concern compared to the identity of conventional egg donors. This quantity argument does not recognize the crucial role healthy mitochondria play in the future of prospective children. As such, the approach to disclosing donor identity is a strong feature of the Australian framework (Koplin 2021). Once the safety and efficacy of the technique are established and MRT is deemed ethically sound, there is no ground for pushing mitochondrial donors aside and take the emphasis off the crucial role they play.

5.2.3 The cost of MRT

5.2.3.1 IVF coverage and the estimated cost of MRT in Canada

In Canada, IVF can cost up to $20,000 per round, including medication (Lee 2018). While there is no comprehensive coverage for IVF, varying treatment coverage exists in four provinces. Ontario, Quebec, Manitoba, and New Brunswick offer funding for one treatment cycle or tax credit/assistance fund for fertility treatment fees and related prescription drugs. The other nine provinces and territories have no coverage (Fertility Matters Canada 2020). There needs to be an understanding of the economics of MRT to guide clinical practice and inform policy.

5.2.3.2 Estimated cost of MRT according to the UK reports

In 2014, the UK's economic assessment was made by studying fertility treatment costs and deliberation with the Wellcome Trust Centre for Mitochondrial Research in Newcastle (Impact Assessment, Department of Health 2014). As the Newcastle Mitochondrial Clinic was predicted to be the only provider of MRT initially, they were declared the best cost estimate reference at the time of the report. The Wellcome Trust Centre considered the costs of performing one round of PNT to be £13,000 (around 23,000 CAD)[1]. In contrast, a round of MST, a somewhat more complicated procedure, was assessed to cost £14,000 (around 25,000 CAD). Assuming both PNT

[1] Bank of Canada Daily Exchange Rates Lookup

and MST would be used equally, it was estimated that one round of MRT should cost £13,500 (around 24,000 CAD). The overall MRT cost was considered to consist of three rounds of IVF (two rounds for prospective mothers and one round for the mitochondria donor), a round of PNT or MST, and facilities costs (supposing 20 procedures per year). Taking into account that treatment costs were going to differ around the UK, the Department of Health used an estimate of "unavoidable cost differences between healthcare providers" (Market Forces Factor (MFF)) (Consultation on 2021/22 National Tariff Payment System 2021). As a result, the national MRT treatment (average of PNT and MST) was estimated to cost £14,500 (around 26,000 CAD).

Like IVF, MRT's success rate will vary from patient to patient. IVF typically results in a live birth 25% of the time (i.e., following the fourth round of treatment) (HFEA 2020). The Department of Health predicted that four rounds of MRT should be sufficient to achieve a live birth. This brought the total estimated cost of MRT to £58,000 (around 100,000 CAD) per person (Impact Assessment, Department of Health 2014).

5.2.4 MRT, Canadian values, and a justice-oriented approach

In 2018, when approached to comment on the possibility of MRT's clinical translation, Health Canada stated that it "recognized the importance for the AHRA to reflect advances in science and the views of Canadians" as long as any potential considerations to change the prohibitions of the AHRA "continue to reflect the values of Canadians" (CBC 2018). The University of Waterloo Canadian Index of Wellbeing has reported on a list of Canadian values resulting from consultation research between 2004-2007. Core consensus values are "fairness, inclusion, economic security,

diversity, *health*, democracy, equity, safety, and sustainability" (Canadian Index of Wellbeing 2008). Health is a Canadian value and indeed one desirable outcome of *just* institutions. The human right to health creates a responsibility to ensure that the social conditions necessary to achieve a sufficient level of health are in place (Powers and Faden 2006). Surely, the values and priorities of society are expressed through its institutions, laws, and funding arrangements. As research moves astonishingly fast, though, ethics and policy need to progress to keep up the pace. The criminalization of MRT under the AHRA concerns most stakeholders, from the medical and research communities to patients and egg donors (Noohi et al. 2021). Criminal law is intended to be a power of last resort. A criminal ban on MRT research limits scientific inquiry and criminalizes the safe practice of women's reproductive autonomy.

Once delving into societal priorities and values in the context of MRT, seeking a fuller, justice-oriented approach to reproductive autonomy seems intimidating. In Madison Powers and Ruth Faden's global health policy theory, social justice is concerned with human "well-being;" a multidimensional facet that includes health, security, reasoning, respect, attachment, and self-determination. Any loss of capacity that threatens the individuals' prospects for "sufficiency" in these dimensions comprises an important functional impairment. "Sufficiency," in this regard, represents "a moral minimum of justice," and inequalities in which individuals fail to meet this moral minimum are among those that need to be addressed with moral urgency (Powers and Faden, 2006). In this respect, *health* is a product of socially *just* decision-making that reflects a moral concern with reproductive autonomy, which is central to the welfare of women.

On the other hand, concerning children, there is a stricter *duty* to ensure they experience a sufficient level of health. As such, just institutions must prioritize the health and overall well-being of

children. Securing children's health is necessary to their enjoyment of self-respect, attachment, and autonomy later in life (Powers and Faden, 2006).

Aristotle identifies *justice* in terms of what is *lawful* and *fair* in correct establishments. This justice is "the whole, not a part, of virtue and the injustice contrary to it is the whole, not a part, of vice" (Nicomachean Ethics; 1130a10). Aristotle asserts that *justice* as the "complete virtue to the highest degree" (though not without qualification) is "another person's good" and that the difficult task of ensuring another's gain is the quality of "the best person" (Nicomachean Ethics; 1130a7). Aristotle stresses the fact that it is no easy task to be just: "knowing how actions must be done, and how distributions must be made, if they are to be just, takes more work than it takes to know about healthy things" (Nicomachean Ethics; 1137a12-14). In declaring that no individual shall be abandoned because the prevention and/or treatment of their genetic disorder is not a "cost-effective" use of societal resources, we reflect on a counter-utilitarian code of ethics. In a purely utilitarian approach, society is left to determine whether to leave out people in support of maximum utility or relinquish efficiency in favor of equity. Among all rare diseases identified (6000-8000), most are genetically inherited and have a childhood-onset (McMillan and Campbell 2017). As such, investment in the prevention of rare diseases does seem to carry a societal benefit.

After all, harmful mutations in the mtDNA result in rare, disabling, progressive, and, at times, deadly disorders with no known cure. These disorders burden the quality of life significantly and impose a tremendous amount of pain on affected individuals and their families (Noohi et al. 2021). With the lack of treatments available for patients, while acknowledging the profound interest in having genetically related children, there is a need for approaches that prevent the transmission of

inherited mitochondrial diseases in Canada. Canada's legal barriers deny Canadians access to MRT, pushing them to use alternatives, which many individuals might consider less than ideal (Noohi et al. 2021). Today, the world's attention is focused on the catastrophic Covid-19 pandemic. While the outlook of heritable germline modification is very different from this urgent issue, it is critical to acknowledge that a small number of Canadian families with serious heritable genetic diseases are likely to seek out MRT. Society has a responsibility to safeguard the reproductive decisions of the intended parents. Such safeguards should extend to the safe and responsible use of MRT to prevent disease while setting boundaries to prevent unintended uses of the technique (i.e., to treat infertility) that most scientists consider questionable.

CHAPTER 6: CONCLUSIONS AND FUTURE DIRECTIONS

Today, at the center of the controversy surrounding the regulation of new reproductive technologies is human genome editing—more specifically—the manipulation of human embryos and the human germline. In recognizing the hurdles to clinical implementation of MRT, there is a clear need to discuss the legitimacy of using this technology and recognize the profound interest in having and raising healthy genetically related children. Inherited mitochondrial diseases are severe and progressive disorders that have no cure (Ng and Turnbull 2020). Predictive tests are unable to help many women at risk of transmitting serious mitochondrial diseases to their children (Lee et al. 2012; Wai et al. 2008; Shoubridge and Wai 2007).

As already presented in this thesis, there are several prominent facets to debating the legitimacy of using MRT. The novelty of the technique's science makes demonstrating the safety and efficacy of MRT an absolute priority. The long-term effects of the technique and the potential epigenetic changes are the underexplored realms that will need to be thoroughly investigated over the coming years. Indeed, all eyes will be on the initial outcomes of the UK's clinical experience with MRT. Nations like Canada with less practical knowledge of the technique will need to invest substantially in research and training the next generation of experts.

Another unresolved aspect of MRT debates is determining the "eligible" candidates at risk of transmitting "serious" mtDNA-related diseases to their progeny. International professional guidance has consistently recommended using MRT only in the context of preventing "serious" disease when no other option seems to be appropriate (e.g., preimplantation testing)—

contemplating the idea of "serious," though, will remain open to interpretation. In global discussions, diseases that cause high mortality and severe morbidity are regarded as "serious" (ISSCR 2021). However, what will be considered a "severe" mitochondrial condition will ultimately be up to individual jurisdictions.

As already discussed, MRT's status has been a hot topic in developing MRT policies in the US, the UK, and Australia. The portrayal of MRT and children born as a result of it in the media as "three-parent babies," "three-parent IVF", and "Frankenstein babies" added fuel to the burning controversy surrounding MRT since the beginning of its discussions (Picard 2016). Indeed, MRT crosses the germline barrier by introducing a third source of genetic material into prospective children's genetic makeup. The implications of this type of "modification," though, differ immensely from those of modifying the nuclear genome via new germline altering techniques, like CRISPR. Although the significance of MRT concerning identity remains to be understood, identity shaping features have been solely related to those functions of the nDNA in the UK model (Department of Health 2014). What is missing in determining identity-forming characteristics is narrowing down the contributions of the mtDNA to such attributes.

Due to lack of scientific evidence, using MRT to "treat infertility," as most international reports have suggested, must not be attempted presently (ESHRE 2019; ISSCR 2021). In discussing alternative uses of MRT, Chapter 2 explores the perspectives of Canadian stakeholders. Although 17/32 participants were willing to see the use of this technique extended to other potential users (i.e., those affected by infertility), it is essential to bear in mind that this group of participants was predominantly comprised of non-specialists (i.e., egg donors, patients, and the general public). As

such, it is crucial to engage the public in conversations regarding the scientific evidence and ethical implications of the alternative uses of MRT.

This thesis project took the first step in focusing on the Canadian perspective on MRT. Canada needs to undertake an extensive societal dialogue before making decisions about emerging human germline modification technologies. Canada has a history of extensive public engagement around reproductive technologies (Royal Commission on New Reproductive Technologies 1993). The need for such dialogue is well justified in the wake of fast-developing new reproductive technologies, such as MRT and CRISPR. It is, however, difficult to cost-effectively engage a large number of Canadians on this issue. Producing Proceed with Care (1993) took four years and cost Canada 28 million dollars at the end (Snow 2014). Targeted engagement with specific stakeholders and deliberation with a small but representative sample of the public would be reasonable to move forward with a compelling MRT debate in Canada.

Indeed, future MRT community engagements must also consider ensuring the evaluation of equity of access. However, Canada's universal health care system does not cover assisted reproductive technologies, such as IVF. In this sense, MRT should not be treated any differently. Indeed, in an ideal world, all must have opportunities to build a family free from discrimination based on socio-economic status, geography, and reproductive health needs. There is no denying the fact that MRT, like IVF, will be costly. Singling out MRT on the premise of social inequities of access that may arise from financial barriers is not good enough of a basis on which to resist the inclination for MRT.

In discussing preventive measures for rare diseases in the Canadian context, the lack of a national framework needs to be acknowledged. Canada is one of the only developed countries without a rare disease strategy (Innovative Medicines Canada Submission to Health Canada Consultation on Drugs for Rare Diseases 2021). As mitochondrial research and understanding of MRT continues to gain momentum, the lack of resources for research, innovative clinical trials, and coordinated data-sharing, keep denying affected Canadians the benefits of standardized care. A robust plan is urgently needed which adequately addresses the needs of rare disease patients in Canada.

Lastly, while a periodic review of the AHRA was legally mandated in 2004 (Knoppers et al. 2017b), no such attempt has been made thus far. There is an absence of therapies open to mitochondrial patients, some of whom have a deep-felt yearning for having genetically related children. The review of the AHRA is long overdue. Investing in a public dialogue about a regulatory oversight broad in scope and mindful of context is essential for preparing for a future in which biotechnologies advance rapidly to expand prospective parents' reproductive options.

REFERENCES

Assisted Human Reproduction Act, S.C. 2004, c. 2. Section 5 (Prohibited Activities). Article (5)(1)(f). https://laws-lois.justice.gc.ca/eng/acts/a-13.4/page-1.html#h-6052

Alston CL, Rocha MC, Lax NZ, Turnbull DM, Taylor RW. 2017. The genetics and pathology of mitochondrial disease. *J Pathol.* 241(2):236-250. doi: 10.1002/path.4809.

Adashi EY, Cohen IG. 2017. Ideology v. Beneficence. *Journal of Law and the Biosciences*, Volume 4, Issue 2, 365–370. https://doi.org/10.1093/jlb/lsx023

Assisted Reproductive Treatment Amendment Act 2016 (NO. 6 OF 2016). http://classic.austlii.edu.au/au/legis/vic/num_act/artaa20166o2016486/

Consultation on 2021/22 National Tariff Payment System. 2021. A guide to the market forces factor. National Health Service (NHS). https://www.england.nhs.uk/wp-content/uploads/2021/03/21-22NT_Guide-to-the-market-forces-factor.pdf

Bredenoord AL, Dondorp W, Pennings G, De Wert G. 2011. Ethics of modifying the mitochondrial genome. *J Med Ethics.* 37(2):97-100. doi: 10.1136/jme.2010.037481.

Baylis F. 2013. The ethics of creating children with three genetic parents. *Reprod Biomed Online.* 26(6):531-4. https://doi.org/10.1016/j.rbmo.2013.03.006

Craven L, Tuppen H, Greggains G, et al. 2010. Pronuclear transfer in human embryos to prevent transmission of mitochondrial DNA disease. *Nature,* 456(7294): 82-85 doi: 10.1038/nature08958

Craven L, Alston CL, Taylor RW, Turnbull DM. 2017. Recent Advances in Mitochondrial Disease. Annu Rev Genomics Hum Genet. 18:257-275. doi: 10.1146/annurev-genom-091416-035426.

Craven L, Murphy J, Turnbull DM, Taylor RW, Gorman GS, McFarland R. 2018. Scientific and Ethical Issues in Mitochondrial Donation. *New Bioeth*. 24(1):57-73. doi:10.1080/20502877.2018.1440725

Cecchino GN, Seli E, Alves da Motta EL, García-Velasco JA. 2018. The role of mitochondrial activity in female fertility and assisted reproductive technologies: overview and current insights. *Reprod Biomed Online*. 36(6):686-697. DOI: 10.1016/j.rbmo.2018.02.007

Official Journal of the European Communities. 2001. Council Regulation. No 539/2001 of 15 March 2001. Official Journal of the European Communities. https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2001:081:0001:0007:EN:PDF

Convention for the protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine. 1997. Treaty No.164. https://www.coe.int/en/web/conventions/full-list/-/conventions/treaty/164

Cavaliere G, Palacios-González C. 2018. Lesbian motherhood and mitochondrial replacement techniques: reproductive freedom and genetic kinship. *Journal of Medical Ethics.* 44:835-842. https://jme.bmj.com/content/44/12/835

Cohen IG, Adashi EY, Ravitsky V. 2019. How bans on germline editing deprive patients with mitochondrial disease. *Nat Biotechnol.* 37(6):589-592. doi: 10.1038/s41587-019-0145-8.

Convention on the Rights of the Child. Adopted and opened for signature, ratification and accession by General Assembly resolution 44/25 of 20 November 1989
entry into force 2 September 1990, in accordance with article 49. Article 24. https://www.ohchr.org/EN/ProfessionalInterest/Pages/CRC.aspx

Canadian Index of Wellbeing. 2008. https://uwaterloo.ca/canadian-index-wellbeing/

CBC Radio. 2018. Scientists say it's time to make '3-parent baby' technology legal in Canada. https://www.cbc.ca/radio/quirks/march-24-2018-an-alien-looking-skeleton-three-parent-families-in-canada-and-more-1.4588650/scientists-say-it-s-time-to-make-3-parent-baby-technology-legal-in-canada-1.4588671

Dupras-Leduc R, Birko S, Ravitsky V. 2018. Mitochondrial/Nuclear Transfer: A Literature Review of the Ethical, Legal and Social Issues. *Can J Bioeth/Rev Can Bioeth.* 1(2):1-17. https://doi.org/10.7202/1058264ar

Darwin Life Nadiya. 2021. http://dl-nadiya.com/nuclear-transfers

Department of Health. Government response to the consultation on draft regulations to permit the use of new treatment techniques to prevent the transmission of a serious mitochondrial disease from mother to child. 2014. Health Science and Bioethics Division. Mitochondrial Donation. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/332881/Consultation_response.pdf

Eyre-Walker A. 2017. Mitochondrial Replacement Therapy: Are Mito-nuclear Interactions likely to be a problem? *Genetics.* 205(4):1365-1372. doi: https://doi.org/10.1101/078329

Ethics Committee of the American Society for Reproductive Medicine. 2015. Use of reproductive technology for sex selection for nonmedical reasons. Fertil Steril. 103(6):1418-22. doi: 10.1016/j.fertnstert.2015.03.035.

Fertility Matters Canada. 2020. https://fertilitymatters.ca/funding-by-province/

Fogleman S, Santana C, Bishop C, Miller A, Capco DG. 2016. CRISPR/Cas9 and mitochondrial gene replacement therapy: promising techniques and ethical considerations. *Am J Stem Cells*. 5(2):39-52. Published 2016 Aug 20. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5043096/

Gorman GS, Schaefer AM, Ng Y, et al. 2015. Prevalence of nuclear and mitochondrial DNA mutations related to adult mitochondrial disease. *Ann. Neurol.* (77): 753–759. doi:10.1002/ana.24362.

Gorman GS, Chinnery PF, DiMauro S, Hirano M, et al. 2016. Mitochondrial diseases. *Nat Rev Dis Primers*. 2:16080. doi: 10.1038/nrdp.2016.80.

Gómez-Tatay L, Hernández-Andreu JM, Aznar J. 2017. Mitochondrial Modification Techniques and Ethical Issues. Journal of clinical medicine, 6(3), 25. https://doi.org/10.3390/jcm6030025

Haimes E, Taylor K. 2015. Rendered invisible? The absent presence of egg providers in U.K. debates on the acceptability of research and therapy for mitochondrial disease. *Monash Bioeth Rev*. 33(4):360-78. doi: 10.1007/s40592-015-0046-7.

Harris J. 2016. Germline Modification and the Burden of Human Existence. *Cambridge Quarterly of Healthcare Ethics*. 25(1), 6-18. doi:10.1017/S0963180115000237

Harris J. 2015. Germline Manipulation and Our Future Worlds. *Am J Bioeth.*15(12):30-4. doi: 10.1080/15265161.2015.1104163.

Human Fertilisation and Embryology Authority (HEFA). 2021a. https://www.hfea.gov.uk/treatments/embryo-testing-and-treatments-for-disease/mitochondrial-donation-treatment/

Human Fertilisation and Embryology Authority (HEFA). 2021b. https://www.hfea.gov.uk/donation/donors/rules-around-releasing-donor-information/

Hyslop LA, Blakeley P, Craven L, Richardson J, et al. 2016. Towards clinical application of pronuclear transfer to prevent mitochondrial DNA disease. *Nature.* 534(7607):383-6. doi: 10.1038/nature18303.

Human Fertilisation and Embryology Authority (HFEA). April 2011. Scientific review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception.

Human Fertilisation and Embryology Authority (HFEA). update March 2013. Scientific review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception.

Human Fertilisation and Embryology Authority (HFEA). 2014 update. Third scientific review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception. file:///Users/mitochondria/Downloads/HFEA%201%2030%20May%20(1).pdf

Human Fertilisation and Embryology Authority (HFEA). November 2016. Scientific Review of the Safety and Efficacy of Methods to Avoid Mitochondrial Disease through Assisted Conception: 2016 Update. https://www.hfea.gov.uk/media/2611/fourth_scientific_review_mitochondria_2016.pdf

Human Fertilisation and Embryology Authority (HFEA). 2020. UK statistics for IVF and DI treatment, storage, and donation. https://www.hfea.gov.uk/about-us/publications/research-and-data/fertility-treatment-2018-trends-and-figures/

Institute of life. 2021. https://www.iolife.eu/en/us/mst-research/

Impact Assessment. Department of Health. 2014. https://www.legislation.gov.uk/ukdsi/2015/9780111125816/impacts

International Society for Stem Cell Research (ISSCR) Guidelines for Stem Cell Research and Clinical Translation. 2021. https://www.isscr.org/policy/guidelines-for-stem-cell-research-and-clinical-translation

Knoppers BM, Leader A, Hume S, et al. 2017b. Mitochondrial Replacement Therapy: The Road to the Clinic in Canada. Journal of Obstetrics and Gynaecology Canada. 39(10):916-918. doi: 10.1016/j.jogc.2017.05.007

Kang E, Wu J, Gutierrez NM, Koski A, et al. 2016. Mitochondrial replacement in human oocytes carrying pathogenic mitochondrial DNA mutations. Nature. 540, 7632, 270-275. DOI: 10.1038/nature20592

Koplin J. 2021. How should mitochondrial donation operate in Australia? BioNews. https://www.bionews.org.uk/page_155799

Luo S, Valencia CA, Zhang J, et al. 2018. Biparental Inheritance of Mitochondrial DNA in Humans. *Proceedings of the National Academy of Sciences of the United States of America*. 115(51):13039-13044. DOI: 10.1073/pnas.1810946115.

Lee HS, Ma H, Juanes RC, et al. 2012. Rapid mitochondrial DNA segregation in primate preimplantation embryos precedes somatic and germline bottleneck. *Cell Rep*.1(5):506-515. doi:10.1016/j.celrep.2012.03.011

Liao SM. 2017. Do Mitochondrial Replacement Techniques Affect Qualitative or Numerical Identity? *Bioethics.* 31(1):20-26. doi: 10.1111/bioe.12308.

Lee J. 2018. At up to $20K per round, IVF is out of reach for a growing number of Alberta couples, fertility doctor says. CBC. https://www.cbc.ca/news/canada/calgary/alberta-ivf-cost-1.4647224

MacKellar C. 2017. Kinship Identities in the Context of UK Maternal Spindle Transfer and Pronuclear Transfer Legislation. *The New Bioethics*, 23:2, 121-137, DOI: 10.1080/20502877.2017.1345090.

Maverick Philosopher. 2017. https://maverickphilosopher.typepad.com/maverick_philosopher/2017/01/numerical-andqualitative-identity.html

McGrath J, Solter D. 1984. Completion of mouse embryogenesis requires both the maternal and paternal genomes. *Cell.* 37(1):179-83. doi: 10.1016/0092-8674(84)90313-1.

Mito Foundation. 2021. https://www.mito.org.au/mitochondrial-donation/

McMillan HJ and Campbell C. 2017. We need a "made in Canada" orphan drug framework *CMAJ*. 189 (41) E1274-E1275; DOI: https://doi.org/10.1503/cmaj.170195

Mitochondrial Donation Law Reform (Maeve's Law) Bill 2021. https://www.legislation.gov.au/Details/C2021B00040

Morrison J. 2021. Descartes on Numerical Identity and Time Australasian Journal of Philosophy. https://doi.org/10.1080/00048402.2021.1907759

Newson AJ, Wrigley A. 2017. Is Mitochondrial Donation Germ-Line Gene Therapy? Classifications and Ethical Implications. Bioethics. 31(1):55-67. doi: 10.1111/bioe.12312.

Ng YS and Turnbull DM. 2020. When to think about mitochondrial disease. *Practical Neurology*; 20:260-261. http://dx.doi.org/10.1136/practneurol-2020-002501

Noohi, Li, Joly. 2021. Clinical translation of mitochondrial replacement therapy in Canada: A qualitative study of stakeholders' attitudes. FACETS. DOI: 10.1139/facets-2020-0062

National Academies of Sciences, Engineering, and Medicine (NASEM). 2016. Mitochondrial replacement techniques: Ethical, social, and policy considerations. Washington, DC: The National Academies Press. DOI: 10.17226/21871

Nuffield Council on Bioethics. 2012. Novel techniques for the prevention of mitochondrial DNA disorders: an ethical review. https://www.nuffieldbioethics.org/wp-content/uploads/2014/06/Novel_techniques_for_the_prevention_of_mitochondrial_DNA_disorders_compressed.pdf

Nicomachean Ethics. Aristotle. Third Edition. Translated by Terence Irwin. Hackett Publishing Company, 2019.

Palacios-González C. and Cavaliere G. 2018. 'Yes' to mitochondrial replacement techniques and lesbian motherhood: a reply to Françoise Baylis. *Journal of Medical Ethics*; 45:280-281

Powers M. and Faden R. Social Justice: The Moral Foundations of Public Health and Health Policy. Oxford University Press 2006

Paull D, Emmanuele V, Weiss KA, Treff N, et al. 2013. Nuclear genome transfer in human oocytes eliminates mitochondrial DNA variants. Nature, 493, 632–637. DOI:10.1038/nature11800

Picard C. "Three-Parent Babies" Could Soon Exist.

https://www.goodhousekeeping.com/health/news/a36731/three-parent-babies/

Prohibition of Human Cloning for Reproduction Act. No. 144, 2002.

https://www.legislation.gov.au/Details/C2017C00306

Research Involving Human Embryos Act 2002. No. 145, 2002.

https://www.legislation.gov.au/Details/C2016C00968

Rulli T. 2016. What Is the Value of Three-Parent IVF? *Hastings Center Report* 46, no. 4. 38-47. DOI: 10.1002/hast.594

Rius R, Cowley MJ, Riley L. et al. 2019. Biparental inheritance of mitochondrial DNA in humans is not a common phenomenon. *Genet Med.* 21, 2823–2826.

https://doi.org/10.1038/s41436-019-0568-0

Royal Commission on New Reproductive Technologies. 1993. Proceed with Care.

http://publications.gc.ca/site/eng/9.699855/publication.html

Schon EA, DiMauro S, Hirano M. 2012. Human mitochondrial DNA: roles of inherited and somatic mutations. *Nat Rev Genet.* 13(12):878-90. doi: 10.1038/nrg3275.

Scott R, Wilkinson S. 2017. Germline Genetic Modification and Identity: the Mitochondrial and Nuclear Genomes. *Oxf J Leg Stud.* 37(4):886-915. doi: 10.1093/ojls/gqx012.

Scully JL. 2016. A Mitochondrial Story: Mitochondrial Replacement, Identity and Narrative. https://doi.org/10.1111/bioe.12310

Shoubridge EA and Wai T. 2007. Mitochondrial DNA and the Mammalian Oocyte, Current Topics in Developmental Biology, Academic Press, Volume 77, Pages 87-111. https://doi.org/10.1016/S0070-2153(06)77004-1

Snow D. 2014. Failure to Reproduce: Assisted Reproductive Technology Policy in Canada (doctoral thesis). University of Calgary, Calgary, AB. doi:10.11575/PRISM/26158 http://hdl.handle.net/11023/1418

Taylor RW, Turnbull DM. 2005. Mitochondrial DNA mutations in human disease. *Nat Rev Genet.* 6(5):389-402. doi: 10.1038/nrg1606.

Tachibana M, Sparman M, Sritanaudomchai H, Ma H, Clepper L, et al. 2009. Mitochondrial gene replacement in primate offspring and embryonic stem cells. *Nature.* 461(7262):367-72. doi: 10.1038/nature08368.

Tang M, Guggilla RR, Gansemans Y et al. 2019. Comparative analysis of different nuclear transfer techniques to prevent the transmission of mitochondrial DNA variants. *Mol Hum Reprod.* 25(12):797-810. doi: 10.1093/molehr/gaz062

Tachibana M, Amato P, Sparman M, Woodward J, et al. 2013. Towards germline gene therapy of inherited mitochondrial diseases. *Nature.* 493(7434):627-31. doi: 10.1038/nature11647.

Thompson K, Collier JJ, Glasgow RIC, Robertson FM, et al. 2020. Recent advances in understanding the molecular genetic basis of mitochondrial disease. *J Inherit Metab Dis* 43(1):36-50. doi: 10.1002/jimd.12104

Towards a Value-based and Pan-Canadian Rare Disease Strategy. Innovative Medicines Canada Submission to Health Canada Consultation on Drugs for Rare Diseases. March 26, 2021. http://innovativemedicines.ca/wp-content/uploads/2021/03/20210326_IMC_Drug_Rare_Disease_Consultation_FINAL.pdf

Taylor RW, Taylor GA, Durham SE, Turnbull DM. 2001. The determination of complete human mitochondrial DNA sequences in single cells: implications for the study of somatic mitochondrial DNA point mutations. Nucleic Acids Res. 29(15):E74-e74. doi:10.1093/nar/29.15.e74

The National Health and Medical Research Council (NHMRC). 2020a. Australian Government, Medical Health and Research Council. Expert Statement Mitochondrial Donation Expert

Working Committee. https://www.nhmrc.gov.au/health-advice/all-topics/mitochondrial-donation#download

United Nations Educational, Scientific and Cultural Organization (UNESCO). Universal Declaration on the Human Genome and Human Rights. 1997. http://portal.unesco.org/en/ev.php-URL_ID=13177&URL_DO=DO_TOPIC&URL_SECTION=201.html

Wolf DP, Mitalipov N, Mitalipov S. 2015. Mitochondrial replacement therapy in reproductive medicine. *Trends Mol Med*. 21(2):68-76. doi:10.1016/j.molmed.2014.12.001

Wallace DC, Chalkia D. 2013. Mitochondrial DNA genetics and the heteroplasmy conundrum in evolution and disease. *Cold Spring Harb Perspect Biol*. 5(11):a021220. doi:10.1101/cshperspect.a021220

Woodruff E. 2017. We simply don't know: Egg donors face uncertain long-term risks. https://www.statnews.com/2017/01/28/egg-donors-risks/

Walton, D. 2017. The Slippery Slope Argument in the Ethical Debate on Genetic Engineering of Humans. *Science and Engineering Ethics.* 23(6),1507-1528. Available at SSRN: https://ssrn.com/abstract=3107283

Wrigley A, Wilkinson S, Appleby JB. 2015. Mitochondrial Replacement: Ethics and Identity. *Bioethics*. 29(9):631-638. doi:10.1111/bioe.12187

Wai T, Teoli D, Shoubridge EA. 2008. The mitochondrial DNA genetic bottleneck results from replication of a subpopulation of genomes. *Nat Genet*. 40(12):1484-8. doi: 10.1038/ng.258.

Wang T, Sha H, Ji D, Zhang HL, et al. 2014. Polar body genome transfer for preventing the transmission of inherited mitochondrial diseases. *Cell*. 157(7):1591-604. doi: 10.1016/j.cell.2014.04.042.

APPENDICES

Appendix A: Other publications

1. Granados Moreno, P. **Noohi, F.,** Joly, Y. (2018). Ethics and Genetics. Online Reference Module in Biomedical Sciences. (Book Chapter).

2. Knoppers, B.M., Nguyen, M., **Noohi, F.,** Kleiderman, E. (2018). Human Genome Editing: Ethical and Policy Considerations. Policy Position Paper for Genome Quebec Report. McGill University. (Report). https://www.genomequebec.com/DATA/PUBLICATION/34_en~v~Human_Genome_Editing_-_Policy_Brief.pdf

3. Knoppers, B.M., Nguyen, M., **Noohi, F.,** Kleiderman, E. (2018). L'ingénierie ciblée du génome humain: CONSIDÉRATIONS ÉTHIQUES ET POLITIQUES. DOCUMENT D'ORIENTATION POLITIQUE, Génome Québec. Université McGill. (Rapport). https://www.genomequebec.com/DATA/PUBLICATION/34_fr~v~Lingenierie_ciblee_du_genome_humain_-_document_d_orientation_politique.pdf

4. Knoppers, B.M., Leader, A., Hume, S., Shoubridge, E.A., Isasi, R., **Noohi, F.,** Ogbogu, U., Ravitsky, V., Kleiderman, E. (2017). Mitochondrial Replacement Therapy: The Road to the Clinic in Canada. *J Obstet Gynaecol Can*, 39(10):916-918. https://doi.org/10.1016/j.jogc.2017.05.007

5. Ogbogu, U., Zarzeczny, A., Baltz, J., Bedford, P., Du, J., Hyun, I., Jaafar, Y., Jurisicova, A., Kleiderman, E., Koukio, Y., Knoppers, B. M., Leader, A., Master, Z., Nguyen, M. T., **Noohi, F.,** Ravitsky, V., & Toews, M. (2018). Research on Human Embryos and Reproductive Materials: Revisiting Canadian Law and Policy. *Healthcare policy=Politiques de sante*, *13*(3), 10–19. https://doi.org/10.12927/hcpol.2018.25401

6. Choquet, K., Yang, S., Moir, R. D., Forget, D., Larivière, R., Bouchard, A., Poitras, C., Sgarioto, N., Dicaire, M. J., **Noohi, F.,** Kennedy, T. E., Rochford, J., Bernard, G., Teichmann, M., Coulombe, B., Willis, I. M., Kleinman, C. L., & Brais, B. (2017). Absence of neurological abnormalities in mice homozygous for the Polr3a G672E hypomyelinating leukodystrophy mutation. *Molecular brain*, *10*(1), 13. https://doi.org/10.1186/s13041-017-0294-y

Appendix B: Supplementary material for Chapter 2

Interview guide

Subsample 1: Parents with affected children

Preliminary questions:

1. Would you please tell me a bit about yourself, like how many children you have?
2. Would you please tell me about your experience with mitochondrial disease in your family?
3. Are you, your mother, sister, or a close relative other than your child, diagnosed with mitochondrial diseases?
4. Please tell me about the type of condition affecting your child.
5. Please tell me when and how you got the diagnosis for the mitochondrial disease.
6. Please tell me about the type of care your child is receiving (e.g., drugs, therapy)?
7. Would you please tell me if you plan to have another child in the future?

MRT: Issues and concerns

1. I would like to know your opinion about Mitochondrial Replacement Therapy (MRT); Please tell me if you have heard about the use of MRT and issues surrounding this new technology.
2. I would like to provide you with a brief background on the technique and its socio-ethical implications: MRT is a new type of *in vitro* fertilization (IVF) that aims to prevent the transmission of mitochondrial diseases, transferred from mothers to their children, by replacing mutated mitochondrial DNA with normal mitochondria from a healthy egg donor. Since as a result of MRT, permanent changes are made to the egg or the resulting embryo that would be transmitted through generations, MRT or "three-parent IVF" is considered germline genetic modification. Modifications within the germline are capable of being transmitted to all future descendants. Besides the UK, which became the first country to approve MRT in 2015, only a few countries have addressed MRT through public policy. Safety and efficacy, risks to future generation, issues of identity, risks to egg donors and concerns over the slippery slope of genetic modification that could lead to eugenics practices are among issues raised with regard to MRT.
3. Is this technique something you might consider as a potential way for having children? Please tell me why?
4. If you had access to the technique in the past, do you think you would have used it?
5. Less than one percent of the genetic composition of a child born as a result of MRT will come from an egg donor. Would you please tell me what you think about your child having three genetic contributors (yours, your partner's, and the egg donor's)?
6. MRT clinical trials have only recently started in the UK. Besides The UK, there are several clinics around the world that offer MRT. MRT is neither permitted nor prohibited in these countries. Is traveling abroad to use the technique something you would consider?

7. Under the *Assisted Human Reproduction Act, 2004*, MRT, in both research and practice, is currently prohibited in Canada. Would you please tell me what you think about this approach?

Subsample 2: Diagnosed and at-risk women who wish to have biological children

Preliminary questions:

1. Please tell me a bit about yourself. Do you have any children?
2. Would you please tell me about your experience with mitochondrial disease in your family?
3. Are you, your mother, sister, or close relative diagnosed with mitochondrial diseases?
4. Please tell me when and how you got the diagnosis for the mitochondrial disease.
5. Could you please tell me how many people are affected or considered carriers or at-risk for transmitting a mitochondrial disease in your family?
6. Would you please tell me if it is important for you to have biological children?
7. Could you tell me if embryo or egg donation is something you have considered or may consider in the future?
8. Would you please tell me if you have had a miscarriage or have had to terminate a pregnancy?
9. May I ask if the miscarriage or termination of the pregnancy was related to mitochondrial diseases?
10. Would you please tell me if you have considered or will consider adoption?

MRT: Issues and concerns

1. I would like to know your opinion about Mitochondrial Replacement Therapy (MRT); Please tell me if you have heard about the use of MRT and issues surrounding this new technology.
2. I would like to provide you with a brief background on the technique and its socio-ethical implications: MRT is a new type of *in vitro* fertilization (IVF) that aims to prevent the transmission of mitochondrial diseases, transferred from mothers to their children, by replacing mutated mitochondrial DNA with normal mitochondria from a healthy egg donor. Since as a result of MRT, permanent changes are made to the egg or the resulting embryo that would be transmitted through generations, MRT or "three-parent IVF" is considered germline genetic modification. Modifications within the germline are capable of being transmitted to all future descendants. Besides the UK, which became the first country to approve MRT in 2015, only a few countries have addressed MRT through public policy. Safety and efficacy, risks to future generation, issues of identity, risks to egg donors and concerns over the slippery slope of genetic modification that could lead to eugenics practices are among issues raised with regard to MRT.
3. Is this technique something you might consider as a potential way for having children? Please tell me why?

4. Less than one percent of the genetic composition of a child born as a result of MRT will come from an egg donor. Would you please tell me what you think about your child having three genetic contributors (yours, your partner's, and the egg donor's)?
5. MRT clinical trials have only recently started in the UK. Besides The UK, there are several clinics around the world that offer MRT. MRT is neither permitted nor prohibited in these countries. Is traveling abroad to use the technique something you would consider?
6. Under the *Assisted Human Reproduction Act, 2004*, MRT, in both research and practice, is currently prohibited in Canada. Would you please tell me what you think about this approach?

Subsample 3: The general public

MRT: Issues and concerns

1. I would like to know your opinion about Mitochondrial Replacement Therapy (MRT); Please tell me if you have heard about the use of MRT and the issues surrounding this new technology.
2. I would like to provide you with a brief background on the technique and its socio-ethical implications: MRT is a new type of *in vitro* fertilization (IVF) that aims to prevent the transmission of mitochondrial diseases, transferred from mothers to their children, by replacing mutated mitochondrial DNA with normal mitochondria from a healthy egg donor. Since as a result of MRT, permanent changes are made to the egg or the resulting embryo that would be transmitted through generations, MRT or "three-parent IVF" is considered germline genetic modification. Modifications within the germline are capable of being transmitted to all future descendants. Besides the UK, which became the first country to approve MRT in 2015, only a few countries have addressed MRT through public policy. Safety and efficacy, risks to future generation, issues of identity, risks to egg donors and concerns over the slippery slope of genetic modification that could lead to eugenics practices are among issues raised with regard to MRT.
3. MRT clinical trials have only recently started in the UK. Besides The UK, there are several clinics around the world that offer MRT. MRT is neither permitted nor prohibited in these countries. Do you agree with the idea of traveling abroad to use such technologies?
4. Under *the Assisted Human Reproduction Act, 2004* conducting MRT research and the clinical use of this technique is currently prohibited in Canada. Would you please tell me what you think about this approach?
5. Do you think such preventive measures (in the context of genetic diseases) should be available in Canadian clinics?
6. Would you please tell me how you feel about investing societal resources on rare diseases in either research or the clinical context?
7. Do you think MRT research should be funded in Canada?
8. Do you think MRT should be available in Canada if only offered through private practice?
9. Would you consider using MRT to have biological children, if you were in the position?

Subsample 4: Clinicians and/or researchers

MRT: Issues and concerns

1. I would like to know your opinion about Mitochondrial Replacement Therapy (MRT); Please tell me what you know about the use of MRT and the issues surrounding this new technology.
2. I would like to know your opinion about MRT's implementation in Canadian clinics.
3. Under the *Assisted Human Reproduction Act, 2004*, MRT, in both research and practice, is currently prohibited in Canada. Would you please tell me what you think about this approach?
4. Would you please tell me if you consider MRT germline genetic modification?
5. Do you think investing in MRT research would benefit the Canadian society at large?
6. Do you think such preventive measures should be available in Canadian clinics?
7. If yes, how do you think the clinical translation of MRT should look like in Canada?
8. Given the UK's scientific reviews found MRT to be *sufficiently safe*, if Canada were to permit MRT, should research be undertaken prior to the clinical applications of MRT?
9. Would you please tell me what you think about the slippery slope argument of germline modification techniques? What do you think could be possible safeguards in the context of MRT?
10. What do you think the potential risks and benefits of implementing MRT in the clinical contexts are?
11. Would you suggest MRT to your patients if they were willing to seek it abroad?
12. What do you think the first step in addressing the issues revolving MRT should be?
13. At this time, do you believe MRT to be safe?
14. Would you please tell me how you feel about investing on rare diseases in either research or the clinical context?
15. How do you think we should prioritize in investing in rare diseases?

Subsample 5: Egg donors

Preliminary questions:

1. Please tell me a bit about yourself. Do you have any children?
2. Why did you decide to donate your eggs?
3. How many times have you donated your eggs?
4. Do you plan on donating your eggs in the future?
5. Would you please tell me about any issues or difficulties you have experienced with donating your eggs (Physically, emotionally, or financially)?
6. Have you donated your eggs in any place other than Canada?
7. What do you think about the regulatory approach of Canada regarding egg donation and surrogacy?

MRT: Issues and concerns

1. I would like to know your opinion about Mitochondrial Replacement Therapy (MRT); Please tell me if you have heard about the use of MRT and the issues surrounding this new technology.
2. I would like to provide you with a brief background on the technique and its socio-ethical implications: MRT is a new type of *in vitro* fertilization (IVF) that aims to prevent the transmission of mitochondrial diseases, transferred from mothers to their children, by replacing mutated mitochondrial DNA with normal mitochondria from a healthy egg donor. Since as a result of MRT, permanent changes are made to the egg or the resulting embryo that would be transmitted through generations, MRT or "three-parent IVF" is considered germline genetic modification. Modifications within the germline are capable of being transmitted to all future descendants.
   Besides the UK, which became the first country to approve MRT in 2015, only a few countries have addressed MRT through public policy. Safety and efficacy, risks to future generation, issues of identity, risks to egg donors and concerns over the slippery slope towards genetic modification techniques that could lead to eugenics practices are among issues raised with regards to MRT.
3. Would you please tell me if you differentiate between donating your egg to be used as a whole and donating your egg to be used for MRT purposes?
4. Mitochondrial DNA from an egg donor counts for less than one percent of the resulting embryo's genes, but MRT is widely known as the "three-parent baby" technique. Would you please tell me what you think about this terminology?
5. Under the *Assisted Human Reproduction Act, 2004*, MRT, in both research and practice, is currently prohibited in Canada. Would you please tell me what you think about this approach?

Information and Consent Forms

Consent form 1: The general public

Study Title: Assessing the public and key Canadian stakeholders' perceptions toward Mitochondrial Replacement Therapy (MRT)

Project Leaders: Dr. Yann Joly and Forough Noohi, Department of Human Genetics, Centre of Genomics and Policy, McGill University

Research coordinator: Forough Noohi, Department of Human Genetics, Centre of Genomics and Policy, McGill University

Funders: Canadian Institute of Health Research

Introduction

You are invited to participate in a research project entitled: **Assessing the public and key Canadian stakeholders' perceptions toward Mitochondrial Replacement Therapy (MRT).** We will also interview parents of children affected by mitochondrial diseases, diagnosed and at-risk couples who wish to have biological children, egg donors, clinicians, and researchers.
Please read this form carefully, and feel free to ask any questions you may have.

Why is this research being done?

Mitochondrial diseases are serious genetic disorders that are estimated to affect 1 in 5000 newborns. There is no cure for these diseases and genetic testing technologies cannot be helpful for all women. Mitochondrial Replacement Therapy techniques (MRTs) are new types of *in vitro* fertilization (IVF) that aim to prevent the transmission of mitochondrial diseases, transferred through the maternal line, by replacing mutated mitochondrial DNA with normal mitochondria from a healthy egg donor. Currently, MRT in Canada is considered a criminal offence according to article 5(1)(f) of the *Assisted Human Reproduction Act (2004)* which 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." This prohibition inadvertently encourages medical tourism practices, and its relevance has been questioned by several Canadian experts. Critics of clinical

applications of MRT in Canada believe MRT might not be necessary since alternatives, such as egg and embryo donation, as well as adoption are available. Moreover, whether MRT should be considered genetic modification has been the center of the MRT debate among relevant stakeholders.

Hopefully, this project will ultimately lead to adopting approaches, which result in a shared understanding of what the evidence reveals to be best for Canada.

If I take part in this study, what do I need to do?

If you decide to participate in this study, we will invite you to take part in an interview. The interview will last an average of 45 minutes to an hour and will be held in an easily accessible place (e.g., a community center, university, hospital). If you prefer, we can arrange for the interview to take place over the phone or via Skype.
During the interview, we will ask you questions about:

- Your opinion about implementing MRT in Canadian clinics
- Your knowledge and view regarding MRT therapies and germline modification research and clinical practice
- Your opinion regarding investing in rare diseases research
- Your views and opinions on the use of MRT as a preventive tool
- Your views and opinions on Canada's approach in regulating MRT and related research and practice

With your consent, the interview will be audio recorded and transcribed.

Your Participation is Voluntary

Your participation in this study is completely voluntary. You are free to choose not to participate at all or decline to answer any question during the interview.

Will information be kept confidential/private?

All recordings or data collected from the interviews will be kept confidential. All information that may identify you will be removed from the transcriptions and coded with a number. Only members of the research team will be able to link your code with your personal information. Participants will not be personally identified in published papers or reports. All data will be kept until the completion of the study (scheduled for Fall 2021) and securely stored in a password-protected folder on McGill University servers. Any paper documents, such as consent forms, will be kept in a locked drawer at the Centre of Genomics and Policy, McGill University (Montreal), and only the researchers involved in this study will have access to the data and study documents.

For surveillance and monitoring purposes, collected data may be consulted by a person appointed by an ethics research committee, by an authorized public organization or by representatives of the funding agencies. All these people and organizations must comply with the privacy policies of their respective institutions, agencies, and departments.

What are the Possible Risks?

There are no physical risks involved in participating in this study. We expect that the personal or emotional risks involved in participating in this study are equivalent to the possible stress faced by participants who discuss their health experiences with friends, family or workplace colleagues. Should you feel uncomfortable sharing your opinion or experience at any time during the interview, you can refuse to answer any question that is asked.

What are the Possible Benefits?

By participating in this study, you will be providing information that will be shared with the research community, health care professionals, policymakers and the public. Results from this study will help in the elaboration of policies that may inform the application of MRT into a clinical setting. Through this study we hope to understand the manner and the circumstances in which MRT may be used.

If you agree to participate in this study, there may not be direct benefits for you. We hope the discussion will interest you, and that it will also help improve the delivery of health services.

Can I Withdraw from the Study?

You are free to withdraw from the study at any time and for any reason. Verbal notice to any member of the research team is sufficient. If you decide to withdraw before the interview, you will be removed from the study. If you withdraw during or after the interview, you may ask that your data be destroyed. However, if you decide to withdraw after the final results are in press or published, we will be unable to remove your supplied data from the study.

Will I be paid to participate?

Participants who are taking part in the interview will not be paid.

What happens to the information collected?

At the end of the project, a discussion paper and report will be prepared and submitted to a scientific journal for publication. If you ask us, we will send you copies of any final report or publications. The information collected will be destroyed after the completion of the project (scheduled for the Fall 2021).

Who do I contact if I have questions?

If you have any questions about this research project, you can contact the study coordinator, Forough Noohi, at forough.noohi@mail.mcgill.ca (514-398-8957). For questions about your rights as a research participant, please contact Ms. Ilde Lepore, Ethics Officer, at 514-398-8302 or by email at ilde.lepore@mcgill.ca

Consent Statement (Interview Participants):

I have read and reviewed the Information and Consent Form. The study was explained to me. My questions were answered to my satisfaction. I was given the time to think about whether I want to take part in this study. I have been told that I will receive a dated and signed copy of this form. By signing this consent form, I do not waive any legal rights. Furthermore, I do not relieve the investigator nor the sponsor from their legal and professional liabilities.

I agree to take part in this study according to the conditions set in this Information and Consent Form.

_____
(Printed Name of Research Participant)

_____ _____
(Participant Signature) (Date)

- ❑ Yes, I am interested in being contacted about future research related to MRT

Email Address: _____

Investigator:

_____
(Printed Name)

_____ _____
(Signature) (Date)

Consent form 2: Diagnosed or at-risk Canadian parents who wish to have biological children

Study Title: Assessing the public and key Canadian stakeholders' perceptions toward Mitochondrial Replacement Therapy (MRT)

Project Leader: Dr. Yann Joly and Forough Noohi, Department of Human Genetics, Centre of Genomics and Policy, McGill University

Research coordinator: Forough Noohi, Department of Human Genetics, Centre of Genomics and Policy, McGill University

Funders: Canadian Institute of Health Research

Introduction

As a prospective parent who is either diagnosed or considered to be a carrier of a serious mitochondrial disease, you are invited to participate in a research project entitled: **Assessing the public and key Canadian stakeholders' perceptions toward Mitochondrial Replacement Therapy (MRT).** We will also interview parents of children affected by mitochondrial diseases, members of the general public, egg donors, clinicians, and researchers.
Please read this form carefully, and feel free to ask any questions you may have.

Purpose of this research

Mitochondrial diseases are serious genetic disorders that are estimated to affect 1 in 5000 newborns. There is no cure for these diseases and genetic testing technologies cannot be helpful for all patients. Mitochondrial Replacement Therapy techniques (MRTs) are new types of *in vitro* fertilization (IVF) that aim to prevent the transmission of mitochondrial diseases, transferred through the maternal line, by replacing mutated mitochondrial DNA with normal mitochondria from a healthy egg donor. Currently, MRT in Canada is considered a criminal offence according to article 5(1)(f) of the *Assisted Human Reproduction Act (2004)* which 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." This prohibition inadvertently encourages medical tourism practices, and its relevance has been questioned by several Canadian experts. Critics of clinical

applications of MRT in Canada believe MRT might not be necessary since alternatives, such as egg and embryo donation, as well as adoption are available. Moreover, whether MRT should be considered genetic modification has been the center of the MRT debate among relevant stakeholders.

Hopefully, this project will ultimately lead to adopting approaches which result in a shared understanding of what the evidence reveals to be best for Canada.

If I take part in this study, what do I need to do?

If you decide to participate in this study, we will invite you to take part in an interview. The interview will last an average of 45 minutes to an hour and will be held in an easily accessible place (e.g. a community center, university, hospital). If you prefer, we can arrange for the interview to take place over the phone or via Skype.
During the interview, we will ask you questions about:

- Your experiences with the history of mitochondrial diseases in your family.
- Your knowledge and view regarding MRT therapies and germline modification research and clinical practice
- Your views and opinions on the use of MRT as a preventive tool
- Your views and opinions on Canada's approach in regulating MRT and related research and practice

With your consent, the interview will be audio recorded and transcribed.

Your Participation is Voluntary

Your participation in this study is completely voluntary. You are free to choose not to participate at all or decline to answer any question during the interview.

Will information be kept confidential/private?

All recordings or data collected from the interviews will be kept confidential. All information that may identify you will be removed from the transcriptions and coded with a number. Only members of the research team will be able to link your code with your personal information. Participants

will not be personally identified in published papers or reports. All data will be kept until the completion of the project (scheduled for Fall 2021) and securely stored in a password-protected folder on McGill University servers. Any paper documents, such as consent forms, will be kept in a locked drawer at the Centre of Genomics and Policy, McGill University (Montreal), and only the researchers involved in this study will have access to the data.

For surveillance and monitoring purposes, collected data may be consulted by a person appointed by an ethics research committee, by an authorized public organization or by representatives of the funding agencies. All these people and organizations must comply with the privacy policies of their respective institutions, agencies, and departments.

What are the Possible Risks?

There are no physical risks involved in participating in this study. We expect that the personal or emotional risks involved in participating in this study are equivalent to the possible stress faced by participants who discuss their health experiences with friends, family or workplace colleagues. Should you feel uncomfortable sharing your opinion or experience at any time during the interview, you can refuse to answer any question that is asked.

What are the Possible Benefits?

By participating in this study, you will be providing information that will be shared with the research community, health care professionals, policymakers and the public. Results from this study will help in the elaboration of policies that may inform the application of MRT into a clinical setting.

Through this study we hope to understand the manner and the circumstances in which MRT may be used.

If you agree to participate in this study, there may not be direct benefits for you. We hope the discussion will interest you, and that it will also help improve the delivery of health services.

Can I Withdraw from the Study?

You are free to withdraw from the study at any time and for any reason. Verbal notice to any member of the research team is sufficient. If you decide to withdraw before the interview, you will

be removed from the study. If you withdraw during or after the interview, you may ask that your data be destroyed. However, if you decide to withdraw after the final results are in press or published, we will be unable to remove your supplied data from the study.

Will I be paid to participate?

Participants who are taking part in the interview will not be paid.

What happens to the information collected?

At the end of the project, a discussion paper and report will be prepared and submitted to a scientific journal for publication. If you ask us, we will send you copies of any final report or publications. The information collected will be destroyed after the completion of the project (scheduled for Fall 2021).

Who do I contact if I have questions?

If you have any questions about this research project, you can contact the study coordinator, Forough Noohi, at forough.noohi@mail.mcgill.ca (514-398-8957). For questions about your rights as a research participant, please contact Ms. Ilde Lepore, Ethics Officer, at 514-398-8302 or by email at ilde.lepore@mcgill.ca.

Consent Statement (Interview Participants):

I have read and reviewed the Information and Consent Form. The study was explained to me. My questions were answered to my satisfaction. I was given the time to think about whether I want to take part in this study. I have been told that I will receive a dated and signed copy of this form.

By signing this consent form, I do not waive any legal rights. Furthermore, I do not relieve the investigator nor the sponsor from their legal and professional liabilities.

I agree to take part in this study according to the conditions set in this Information and Consent Form.

_____
(Printed Name of Research Participant)

_____ _____
(Participant Signature) (Date)

☐ Yes, I am interested in being contacted about future research related to MRT

Email Address: _____

Investigator:

_____
(Printed Name)

_____ _____
(Signature) (Date)

Consent form 3: Canadian clinicians and/or researchers

Study Title: Assessing the public and key Canadian stakeholders' perceptions toward Mitochondrial Replacement Therapy (MRT)

Project Leaders: Dr. Yann Joly and Forough Noohi, Department of Human Genetics and Centre of Genomics and Policy, McGill University

Research coordinator: Forough Noohi, Department of Human Genetics and Centre of Genomics and Policy, McGill University

Funders: Canadian Institute of Health Research

Introduction

As a Canadian clinician and/or researcher, you are invited to participate in a research project entitled: **Assessing the public and key Canadian stakeholders' perceptions toward Mitochondrial Replacement Therapy (MRT).** We will also interview parents of children affected by mitochondrial diseases, diagnosed and at-risk couples who wish to have biological children, members of the general public, and egg donors.

Please read this form carefully, and feel free to ask any questions you may have.

Purpose of this research

Mitochondrial diseases are serious genetic disorders that are estimated to affect 1 in 5000 newborns. There is no cure for these diseases and genetic testing technologies cannot be helpful to all patients. Mitochondrial Replacement Therapy techniques (MRTs) are new types of *in vitro* fertilization (IVF) that aim to prevent the transmission of mitochondrial diseases, transferred through the maternal line, by replacing mutated mitochondrial DNA with normal mitochondria from a healthy donor. MRT in Canada is considered a criminal offence according to article 5(1)(f) of the *Assisted Human Reproduction Act (2004)* which 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." This prohibition inadvertently encourages medical tourism practices and its relevance has been questioned by several Canadian experts. Critics of clinical applications of MRT in Canada believe MRT might not be necessary since alternatives, such as egg and embryo

donation, as well as adoption are available. Moreover, whether MRT should be considered genetic modification has been the center of the MRT debate among relevant stakeholders.
Hopefully, this project will ultimately lead to adopting approaches, which result in a shared understanding of what the evidence reveals to be best for Canada.

Format of the interview

If you decide to participate in this study, we will invite you to take part in an interview. The interview will last an average of 45 minutes to an hour and will be held in an easily accessible place (e.g., a community center, university, hospital). If you prefer, we can arrange for the interview to take place over the phone or via Skype.

During the interview, we will ask you questions about:

- Your views and opinions on the potential use of MRT in Canadian clinics
- Risks and benefits you see in implementing MRT in Canadian clinics
- Your views and opinions on Canada's approach in regulating MRT and related research and practice

With your consent, the interview will be audio recorded and transcribed.

Your Participation is Voluntary

Your participation in this study is completely voluntary. You are free to choose not to participate at all or decline to answer any question during the interview.

Your information will be kept confidential

All recordings or data collected from the interviews will be kept confidential. All information that may identify you will be removed from the transcriptions and coded with a number. Only members of the research team will be able to link your code with your personal information. Participants will not be personally identified in published papers or reports. All data will be kept until the completion of the project (scheduled for Fall 2021) and securely stored in a password-protected folder on McGill University servers. Any paper documents, such as consent forms, will be kept in

a locked drawer at the Centre of Genomics and Policy, McGill University (Montreal), and only the researchers involved in this study will have access to the data.
For surveillance and monitoring purposes, collected data may be consulted by a person appointed by an ethics research committee, by an authorized public organization or by representatives of the funding agencies. All these people and organizations must comply with the privacy policies of their respective institutions, agencies, and departments.

Possible Risks:

There are no physical risks involved in participating in this study. Should you feel uncomfortable sharing your opinion or experience at any time during the interview, you can refuse to answer any question that is asked.

Possible Benefits:

By participating in this study, you will be providing important information that will be shared with the research community, health care professionals, policymakers and the public. Results from this study will help in the elaboration of policies that may inform the application of MRT into a clinical setting. Through this study we hope to understand the manner and the circumstances in which MRT may be used.

Withdrawing from the Study:

You are free to withdraw from the study at any time and for any reason. Verbal notice to any member of the research team is sufficient. If you decide to withdraw before the interview, you will be removed from the study. If you withdraw during or after the interview, you may ask that your data be destroyed. However, if you decide to withdraw after the final results are in press or published, we will be unable to remove your supplied data from the study.

Compensation

Participants who are taking part in the interview will not be paid.

Information collected:

At the end of the project, a discussion paper and report will be prepared and submitted to a scientific journal for publication. If you ask us, we will send you copies of any final report or publications. The information collected will be destroyed after the completion of the project (scheduled for Fall 2021).

For more information:

If you have any questions about this research project, you can contact the study coordinator, Forough Noohi, at forough.noohi@mail.mcgill.ca (514-398-8957). For questions about your rights as a research participant, please contact Ms. Ilde Lepore, Ethics Officer, at 514-398-8302 or by email at ilde.lepore@mcgill.ca.

Consent Statement (Interview Participants):

I have read and reviewed the Information and Consent Form. The study was explained to me. My questions were answered to my satisfaction. I was given the time to think about whether I want to take part in this study. I have been told that I will receive a dated and signed copy of this form.
By signing this consent form, I do not waive any legal rights. Furthermore, I do not relieve the investigator nor the sponsor from their legal and professional liabilities.

I agree to take part in this study according to the conditions set in this Information and Consent Form.

_____
(Printed Name of Research Participant)

_____ _____
(Participant Signature) (Date)

☐ Yes, I am interested in being contacted about future research related to MRT

Email Address: _____

Investigator:

_____
(Printed Name)

_____ _____
(Signature) (Date)

Consent form 4: Canadian egg donors

Study Title: Assessing the public and key Canadian stakeholders' perceptions toward Mitochondrial Replacement Therapy (MRT)

Project Leader: Dr. Yann Joly and Forough Noohi, Department of Human Genetics and Centre of Genomics and Policy, McGill University

Research coordinator: Forough Noohi, Department of Human Genetics and Centre of Genomics and Policy, McGill University

Funders: Canadian Institute of Health Research

Introduction

As a previous, current, or future egg donor, you are invited to participate in a research project entitled: **Assessing the public and key Canadian stakeholders' perceptions toward Mitochondrial Replacement Therapy (MRT).** We will also interview parents of children affected by mitochondrial diseases, diagnosed and at-risk couples who wish to have biological children, members of the general public, clinicians, and researchers.
Please read this form carefully, and feel free to ask any questions you may have.

Why is this research being done?

Mitochondrial diseases are serious genetic disorders that are estimated to affect 1 in 5000 newborns. There is no cure for these diseases and genetic testing technologies cannot be helpful to all patients. Mitochondrial Replacement Therapy techniques (MRTs) are new types of *in vitro* fertilization (IVF) that aim to prevent the transmission of mitochondrial diseases, transferred through the maternal line, by replacing mutated mitochondrial DNA with normal mitochondria from a healthy donor. MRT in Canada is considered a criminal offence according to article 5(1)(f) of the *Assisted Human Reproduction Act (2004)* which 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." This prohibition inadvertently encourages medical tourism practices, and its relevance has been questioned by several Canadian experts. Critics of clinical applications of MRT in Canada believe MRT might not be necessary since alternatives, such as egg and embryo

donation, as well as adoption are available. Moreover, whether MRT should be considered genetic modification has been the center of the MRT debate among relevant stakeholders.
Hopefully, this project will ultimately lead to adopting approaches, which result in a shared understanding of what the evidence reveals to be best for Canada.

If I take part in this study, what do I need to do?

If you decide to participate in this study, we will invite you to take part in an interview. The interview will last an average of 45 minutes to an hour and will be held in an easily accessible place (e.g., a community center, university, hospital). If you prefer, we can arrange for the interview to take place over the phone or via Skype.

During the interview, we will ask you questions about:

- Your experiences with egg donation and your how you regard donating your egg to be used for reproductive purposes as a whole vs. donating your egg for MRT purposes
- Your knowledge and view regarding mitochondrial diseases, MRT, genetic research and human germline modification
- Your views and opinions on the use of MRT as a preventive tool

With your consent, the interview will be audio recorded and transcribed.

Your Participation is Voluntary

Your participation in this study is completely voluntary. You are free to choose not to participate at all or decline to answer any question during the interview.

Will information be kept confidential/private?

All recordings or data collected from the interviews will be kept confidential. All information that may identify you will be removed from the transcriptions and coded with a number. Only members of the research team will be able to link your code with your personal information. Participants will not be personally identified in published papers or reports. All data will be kept until the completion of the project (scheduled for Fall 2021) and securely stored in a password-protected folder on McGill University servers. Any paper documents, such as consent forms, will be kept in

a locked drawer at the Centre of Genomics and Policy, McGill University (Montreal), and only the researchers involved in this study will have access to the data.

For surveillance and monitoring purposes, collected data may be consulted by a person appointed by an ethics research committee, by an authorized public organization or by representatives of the funding agencies. All these people and organizations must comply with the privacy policies of their respective institutions, agencies, and departments.

What are the Possible Risks?

There are no physical risks involved in participating in this study. We expect that the personal or emotional risks involved in participating in this study are equivalent to the possible stress faced by participants who discuss their egg donation experiences with friends, family or workplace colleagues. Should you feel uncomfortable sharing your opinion or experience at any time during the interview, you can refuse to answer any question that is asked.

What are the Possible Benefits?

By participating in this study, you will be providing information that will be shared with the research community, health care professionals, policymakers and the public. Results from this study will help in the elaboration of policies that may inform the application of MRT into a clinical setting. Through this study we hope to understand the manner and the circumstances in which MRT may be used. In doing so, we will also interview mitochondrial diseases patient groups, common diseases patient groups, and clinicians.

If you agree to participate in this study, may not be direct benefits for you. We hope the discussion will interest you, and that it will also help improve the delivery of health services.

Can I Withdraw from the Study?

You are free to withdraw from the study at any time and for any reason. Verbal notice to any member of the research team is sufficient. If you decide to withdraw before the interview, you will be removed from the study. If you withdraw during or after the interview, you may ask that your data be destroyed. However, if you decide to withdraw after the final results are in press or published, we will be unable to remove your supplied data from the study.

Will I be paid to participate?

Participants who are taking part in the interview will not be paid.

What happens to the information collected?

At the end of the project, a discussion paper and report will be prepared and submitted to a scientific journal for publication. If you ask us, we will send you copies of any final report or publications. The information collected will be destroyed after the completion of the project (Fall 2021).

Who do I contact if I have questions?

If you have any questions about this research project, you can contact the study coordinator, Forough Noohi, at forough.noohi@mail.mcgill.ca (514-398-8957). For questions about your rights as a research participant, please contact Ms. Ilde Lepore, Ethics Officer, at 514-398-8302 or by email at ilde.lepore@mcgill.ca

Consent Statement (Interview Participants):

I have read and reviewed the Information and Consent Form. The study was explained to me. My questions were answered to my satisfaction. I was given the time to think about whether I want to take part in this study. I have been told that I will receive a dated and signed copy of this form.

By signing this consent form, I do not waive any legal rights. Furthermore, I do not relieve the investigator nor the Sponsor from their legal and professional liabilities.
I agree to take part in this study according to the conditions set in this Information and Consent Form.

_____
(Printed Name of Research Participant)

_____ _____
(Participant Signature) (Date)

☐ Yes, I am interested in being contacted about future research related to MRT

Email Address: _____

Investigator:

_____
(Printed Name)

_____ _____
(Signature) (Date)

Consent form 5: Parents of children affected by mitochondrial diseases

Study Title: Assessing the public and key Canadian stakeholders' perceptions toward Mitochondrial Replacement Therapy (MRT)

Project Leaders: Dr. Yann Joly, and Forough Noohi, Department of Human Genetics and Centre of Genomics and Policy, McGill University

Project coordinator: Forough Noohi, Department of Human Genetics and Centre of Genomics and Policy, McGill University

Funders: Canadian Institute of Health Research

Introduction

As a parent or caregiver of child affected by a mitochondrial disease, you are invited to participate in a research project entitled: **Assessing the public and key Canadian stakeholders' perceptions toward Mitochondrial Replacement Therapy (MRT).** We will also interview diagnosed and at-risk couples who wish to have biological children, members of the general public, egg donors, clinicians, and researchers.

Please read this form carefully, and feel free to ask any questions you may have.

Why is this research being done?

Mitochondrial diseases are serious genetic disorders that are estimated to affect 1 in 5000 newborns. There is no cure for these diseases and genetic testing technologies cannot be helpful to all patients. Mitochondrial Replacement Therapy techniques (MRTs) are new types of *in vitro* fertilization (IVF) that aim to prevent the transmission of mitochondrial diseases, transferred through the maternal line, by replacing mutated mitochondrial DNA with normal mitochondria from a healthy donor. MRT in Canada is considered a criminal offence according to article 5(1)(f) of the *Assisted Human Reproduction Act (2004)* which 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." This prohibition inadvertently encourages medical tourism practices, and its relevance has been questioned by several Canadian experts. Critics of clinical applications

of MRT in Canada believe MRT might not be necessary since alternatives, such as egg and embryo donation, as well as adoption are available. Moreover, whether MRT should be considered genetic modification has been the center of the MRT debate among relevant stakeholders.
Hopefully, this will ultimately lead to adopting approaches which result in a shared understanding of what the evidence reveals to be best practice for the Canadian healthcare context.

If I take part in this study, what do I need to do?

If you decide to participate in this study, we will invite you to take part in an interview. The interview will last an average of 45 minutes to an hour and will be held in an easily accessible place (e.g., a community center, university, hospital). If you prefer, we can arrange for the interview to take place over the phone or via Skype.

During the interview, we will ask you questions about:

- Your knowledge and view regarding MRT therapies and germline modification research and clinical practice
- Your views and opinions on the use of MRT as a preventive tool
- Your views and opinions on Canada's approach in regulating MRT and related research and practice

With your consent, the interview will be audio recorded and transcribed.

Your Participation is Voluntary

Your participation in this study is completely voluntary. You are free to choose not to participate at all or decline to answer any question during the interview.

Will information be kept confidential/private?

All recordings or data collected from the interviews will be kept confidential. All information that may identify you will be removed from the transcriptions and coded with a number. Only members of the research team will be able to link your code with your personal information. Participants will not be personally identified in published papers or reports. All data will be kept until the

completion of the project (Fall 2021) and securely stored in a password-protected folder. Any paper documents, such as consent forms, will be kept in a locked drawer at the Centre of Genomics and Policy, McGill University (Montreal), and only the researchers involved in this study will have access to the data.

For surveillance and monitoring purposes, collected data may be consulted by a person appointed by an ethics research committee, by an authorized public organization or by representatives of the funding agencies. All these people and organizations must comply with the privacy policies of their respective institutions, agencies, and departments.

What are the Possible Risks?

There are no physical risks involved in participating in this study. We expect that the personal or emotional risks involved in participating in this study are small – that is, they are equivalent to the possible stress faced by participants who discuss their health experiences with friends, family or workplace colleagues. Should you feel uncomfortable sharing your opinion or experience at any time during the interview, you can refuse to answer any question that is asked by remaining silent.

What are the Possible Benefits?

By participating in this study, you will be providing important information that will be shared with the research community, health care professionals, policymakers and the public. Results from this study will help in the elaboration of policies that may inform the application of MRT into a clinical setting. Through this study we hope to understand the manner and the circumstances in which MRT may be used.

If you agree to participate in this study, there may not be direct benefits for you. We hope the discussion will interest you, and that it will also help improve the delivery of health services.

Can I Withdraw from the Study?

You are free to withdraw from the study at any time and for any reason. Verbal notice to any member of the research team is sufficient. If you decide to withdraw before the interview, you will be removed from the study. If you withdraw during or after the interview, you may ask that your

data be destroyed. However, if you decide to withdraw after the final results are in press or published, we will be unable to remove your supplied data from the study.

Will I be paid to participate?

Participants who are taking part in the interview will not be paid.

What happens to the information collected?

At the end of the project, a discussion paper and report will be prepared and submitted to a scientific journal for publication. If you ask us, we will send you copies of any final report or publications. The information collected will be destroyed after the completion of the project (scheduled for Fall 2021).

Who do I contact if I have questions?

If you have any questions about this research project, you can contact the study coordinator, Forough Noohi, at forough.noohi@mail.mcgill.ca (514-398-8957). For questions about your rights as a research participant, please contact Ms. Ilde Lepore, Ethics Officer, at 514-398-8302 or by email at ilde.lepore@mcgill.ca.

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I have read and reviewed the Information and Consent Form. The study was explained to me. My questions were answered to my satisfaction. I was given the time to think about whether I want to take part in this study. I have been told that I will receive a dated and signed copy of this form.

By signing this consent form, I do not waive any legal rights. Furthermore, I do not relieve the investigator nor the Sponsor from their legal and professional liabilities.

I agree to take part in this study according to the conditions set in this Information and Consent Form.

_____

(Printed Name of Research Participant)

_____ _____
(Participant Signature) (Date)

☐ Yes, I am interested in being contacted about future research related to MRT

Email Address: _____

Investigator:

_____
(Printed Name)

_____ _____
(Signature) (Date)

Table 3 (S.1): Standards for Reporting Qualitative Research (SRQR)

O'Brien B.C., Harris, I.B., Beckman, T.J., Reed, D.A., & Cook, D.A. (2014). Standards for reporting qualitative research: a synthesis of recommendations. *Academic Medicine, 89(9),* 1245-1251.

No. Topic	Item	Page #
Title and abstract		
Title	Concise description of the nature and topic of the study identifying the study as qualitative or indicating the approach (e.g., ethnography, grounded theory) or data collection methods (e.g., interview, focus group) is recommended	1
Abstract	Summary of key elements of the study using the abstract format of the intended publication; typically includes objective, methods, results, and conclusions	1
Introduction		
Problem formulation	Description and significance of the problem/phenomenon studied; review of relevant theory and empirical work; problem statement	2
Purpose or research question	Purpose of the study and specific objectives or questions	2
Methods		
Qualitative approach and research paradigm	Qualitative approach (e.g., ethnography, grounded theory, case study, phenomenology, narrative research) and guiding theory if appropriate; identifying the research paradigm (e.g., positivist, constructivist/interpretivist) is also recommended	2-3

Researcher characteristics and reflexivity	Researchers' characteristics that may influence the research, including personal attributes, qualifications/experience, relationship with participants, assumptions, or presuppositions; potential or actual interaction between researchers' characteristics and the research questions, approach, methods, results, or transferability	10
Context	Setting/site and salient contextual factors; rationale	2-3
Sampling strategy	How and why research participants, documents, or events were selected; criteria for deciding when no further sampling was necessary (e.g., sampling saturation); rationale	2-3, Appendix 2
Ethical issues pertaining to human subjects	Documentation of approval by an appropriate ethics review board and participant consent, or explanation for lack thereof; other confidentiality and data security issues	3
Data collection methods	Types of data collected; details of data collection procedures including (as appropriate) start and stop dates of data collection and analysis, iterative process, triangulation of sources/methods, and modification of procedures in response to evolving study findings; rationale	2
Data collection instruments and technologies	Description of instruments (e.g., interview guides, questionnaires) and devices (e.g., audio recorders) used for data collection; if/how the instrument(s) changed over the course of the study	2-3, Appendix 1
Units of study	Number and relevant characteristics of participants, documents, or events included in the study; level of participation (could be reported in results)	3, Table 1
Data processing	Methods for processing data prior to and during analysis, including transcription, data entry, data management and security, verification of data integrity, data coding, and anonymization/deidentification of excerpts	3
Data analysis	Process by which inferences, themes, etc., were identified and developed, including researchers involved in data analysis; usually references a specific paradigm or approach; rationale	3
Techniques to enhance trustworthiness	Techniques to enhance trustworthiness and credibility of data analysis (e.g., member checking, audit trail, triangulation); rationale	3
Results/Findings		
Synthesis and interpretation	Main findings (e.g., interpretations, inferences, and themes); might include development of a theory or model, or integration with prior research or theory	3-8
Links to empirical data	Evidence (e.g., quotes, field notes, text excerpts, photographs) to substantiate	Table 2

	analytic findings	
Discussion		
Integration with prior work, implications, transferability, and contribution(s) to the field	Short summary of main findings; explanation of how findings and conclusions connect to, support, elaborate on, or challenge conclusions of earlier scholarship; discussion of scope of application/generalizability; identification of unique contribution(s) to scholarship in a discipline or field	9-10
Limitations	Trustworthiness and limitations of findings	9-10
Other		
Conflicts of interest	Potential sources of influence or perceived influence on study conduct and conclusions; how these were managed	10
Funding	Sources of funding and other support; role of funders in data collection, interpretation, and reporting	10

Appendix C: Supplementary material for Chapter 4

Table 4 (S.4.1): The Complete set of keywords

Keywords
((manipulation OR therapy OR replacement OR donation OR transfer OR modification) AND mitochondria) OR (("three parent" OR "three person") AND baby) AND (ethics OR policy OR recommendation) and controlled vocabulary terms.

Table 5 (S.4.2): Reviewed documents

Title	Type	Year	Publisher
Ethical, legal and social issues arising from mitochondrial genome replacement technology	Consultation paper	2018	Singapore Bioethics Advisory Committee
Mitochondrial Replacement Techniques: Ethical, Social, and Policy Considerations	Consensus Study Report	2016	The National Academy Press
Heritable Human Genome Editing	A Consensus Study Report	2020	The National Academies Press
BÉBÉS GÉNÉTIQUEMENT MODIFIÉS Enjeux éthiques soulevés par la modification génétique des cellules germinales et des embryons Résumé et recommandations	Consensus Study Report	2019	Commission de l'éthique en science et en technologie
Mitochondria replacement in cases of serious diseases – ethical aspects	Report	2013	The Swedish National Council on Medical Ethics

Developing guidelines for management of reproductive options for families with maternally inherited mtDNA disease	Workshop Report	2019	Neuromuscular Disorders
Novel techniques for the prevention of mitochondrial DNA disorders: an ethical review	Ethical Review	2012	Nuffield Council on Bioethics
Science of mitochondrial donation and related matters	Recommendations	2018	The Senate Community Affairs References Committee (Australia)
Australian Government response to the Senate Community Affairs References Committee Inquiry into: The Science of Mitochondrial Donation and Related Matters	Government Response	2019	Australian Government
Expert Statement Mitochondrial Donation Expert Working Committee	Statement Report	2020	National Health and Medical research Council
Mitochondrial Donation Community Consultation Report	Consultation Report	2020	National Health and Medical research Council
Mitochondrial Donation Community Consultation Citizens' Panel Position Statement	Position Statement	2020	National Health and Medical research Council
Mitochondrial donation: providing reproductive choice to women carrying maternally inheritable mitochondrial disease	Position Statement	2019	Mito Foundation
CIHR Best Brains Exchange A Path Forward for the Assisted Human Reproduction Act	Workshop Report	2018	Canadian Institute of Health Research, Government of Canada
Toward a Strengthened Assisted Human Reproduction Act: A Consultation with Canadians on Key Policy Proposals	Consultation Report	2017	Health Canada, Government of Canada

ISSCR Guidelines for Stem Cell Research and Clinical Translation	Guideline	2021	International Society for Stem Cell Research (ISSCR)
Scientific review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception: 2016 update	Review	2016	Human Fertilisation and Embryology Authority
Scientific review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception: 2014 update. Report provided to the Human Fertilisation and Embryology Authority (HFEA), June 2014.	Review	2014	Human Fertilisation and Embryology Authority
Scientific review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception. Human Fertilisation and Embryology Authority: update March 2013	Review	2013	Human Fertilisation and Embryology Authority
Scientific review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception	Review	2011	Human Fertilisation and Embryology Authority
Mitochondrial Donation A consultation on draft regulations to permit the use of new treatment techniques to prevent the transmission of a serious mitochondrial disease from mother to child	Stakeholders Consultation	2014	Health Sciences and Bioethics division, UK's Department of Health
Mitochondrial Donation Government response to the consultation on draft regulations to permit the use of new treatment techniques to prevent the transmission of a serious mitochondrial disease from mother to child	Government response	2014	Health Sciences and Bioethics division, UK's Department of Health
Mitochondria replacement consultation: Advice to Government	Advice to Government	2013	Human Fertilisation and Embryology Authority
House of Commons Science and Technology Committee Mitochondrial donation Correspondence received relating to the evidence hearing on 22 October	Evidence Hearing	2014	UK's House of Commons

2014			
Mitochondrial Replacement Therapy: The Road to the Clinic in Canada	Workshop Report/Commentary	2017	Journal of Obstetrics and Gynecology Canada
Consensus Statement: Gene Editing, Genetic Testing and Reproductive Medicine in Canada	Consensus Statement	2018	Stem Cell Network
Spindle transfer in the treatment of infertility: an ESHRE position statement	Position Statement	2019	European Society of Human Reproduction and Embryology
Position Statement Mitochondrial Replacement Therapy (MRT)	Position Statement	2019	MitoCanada Foundation
Responsible innovation in human germline gene editing: Background document to the recommendations of ESHG and ESHRE	Background document	2018	European Journal of Human Genetics
The responsible use of treatment add-ons in fertility services: a consensus statement	Consensus Statement	2019	Human Fertilisation and Embryology Authority

IRB approval

McGill

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CERTIFICATION OF ETHICAL ACCEPTABILITY FOR RESEARCH INVOLVING HUMAN SUBJECTS

The Faculty of Medicine Institutional Review Board (IRB) is a registered University IRB working under the published guidelines of the Tri-Council Policy Statement, in compliance with the Plan d'action ministériel en éthique de la recherche et en intégrité scientifique (MSSS, 1998), and the Food and Drugs Act (17 June 2001); and acts in accordance with the U.S. Code of Federal Regulations that govern research on human subjects. The IRB working procedures are consistent with internationally accepted principles of Good Clinical Practices.

At a full Board meeting on August 26, 2019, the Faculty of Medicine Institutional Review Board, consisting of:

Frances Aboud, PhD	Joséane Chrétien, MJur
Patricia Dobkin, PhD	Sally Mann, M.S.
Kathleen Montpetit, M. Sc.	Roberta Palmour, PhD
Maida Sewitch, PhD	Margaret Swaine, BA

Examined the research project **A06-B43-19B** titled: *Assessing key Canadian stakeholders' perceptions toward mitochondrial replacement therapy (MRT) – Qualitative interviews with patient groups, egg donors and clinicians*

As proposed by: Dr. Yann Joly (Applicant) to _____ (Granting Agency, if any)

And consider the experimental procedures to be acceptable on ethical grounds for research involving human subjects.

August 26, 2019
Date

Roberta Palmour
Chair, IRB

Dean/Associate Dean

Institutional Review Board Assurance Number: FWA 00004545