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The Regulation of Mitochondrial Replacement Techniques Around the World

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Abstract

Mitochondrial replacement techniques (MRTs, also referred to as mitochondrial replacement therapies) have given hope to many women who wish to have genetically related children but have mitochondrial DNA mutations in their eggs. MRTs have also spurred deep ethical disagreements and led to different regulatory approaches worldwide. In this review, we discuss the current regulation of MRTs across several countries. After discussing the basics of the science, we describe the current law and policy directions in seven countries: the United Kingdom, the United States, Canada, Australia, Germany, Israel, and Singapore. We also discuss the emerging phenomenon of medical tourism (also called medical travel) for MRTs to places like Greece, Spain, Mexico, and Ukraine. We then pull out some key findings regarding similarities and differences in regulatory approaches around the world.

INTRODUCTION

Mitochondrial replacement techniques (MRTs) have given hope to many women who wish to have genetically related children but have mitochondrial DNA mutations in their eggs. (MRTs are also referred as mitochondrial replacement therapies; for a discussion of the debate about this terminology, see References 14 and 75.) However, they have also spurred deep ethical disagreements and led to a plethora of different regulatory approaches worldwide. In this review, we discuss the current regulation of MRTs across several countries. After discussing the basics of the science, we describe the current law and policy directions in seven countries: the United Kingdom, the United States, Canada, Australia, Germany, Israel, and Singapore. We also discuss the emerging phenomenon of medical tourism (also called medical travel) for MRTs to places like Greece, Spain, Mexico, and Ukraine. We then pull out some key findings regarding similarities and differences in regulatory approaches around the world.

THE BASIC SCIENCE OF MITOCHONDRIAL REPLACEMENT TECHNIQUES

High loads of mutant mitochondrial DNA (mtDNA) bring about heritable incapacitating (and often fatal) maladies (2, 36, 90, 92). A cure remains beyond reach at this time, and prenatal risk stratification remains equally elusive (62, 98). Nevertheless, prevention of mitochondrial disease may now be possible by transferring the nuclei of at-risk zygotes and oocytes to donated unaffected and enucleated eggs or zygotes (26, 108). In the United States, the prevention of up to 1,000 affected births per year is at stake (37). Two technologies presently lead the way: pronuclear transfer (PNT) and maternal spindle transfer (MST). A series of additional promising technologies remain in various stages of development.

PNT requires the isolation and transfer of the male and female pronuclei of at-risk human zygotes to an enucleated disease-free donor zygote (27, 47). Successfully reconstituted zygotes, in turn, give rise to potentially transferable embryos (27, 47). When optimized, the PNT paradigm enhances the development of blastocyst-stage embryos without affecting the incidence of aneuploidy or gene expression patterns. The carryover of mutant maternal mtDNA is less than 2% in most PNT-derived blastocysts (47).

MST, an embryo-sparing option, entails the isolation and transfer of the metaphase II spindle complex of an at-risk oocyte to an enucleated disease-free donor egg (63, 109, 110). Successfully reconstituted and fertilized oocytes give rise to potentially transferable embryos (63, 109, 110). When assessed in nonhuman primates, MST gave rise to viable offspring whose postnatal growth and development were comparable to those of unaffected counterparts (96, 101). Negligible amounts of maternal mtDNA were present in postnatal somatic tissues of the progeny (96, 101) and in fetal somatic and germline elements. Studies of human oocytes revealed that MST is associated with normal fertilization rates as well as with virtual donor homoplasmy and metabolic rescue in derived embryonic stem cell lines (100, 102). Moreover, euploid MST-derived human zygotes give rise to blastocysts and embryonic stem cells at rates comparable to those of controls (100).

Work in progress has focused on the possibility of refining PNT and MST by deploying polar bodies. Polar bodies are extruded haploid products that are generated by the two meiotic divisions that lead to oocyte and zygote formation, and they are cytoplasm poor, membrane bound, and readily accessible. The product of asymmetric cytokinesis, polar bodies could well prove well suited for nuclear transfer. Preliminary studies in mouse models are promising. The transfer of the first polar body (PB1) into an enucleated oocyte proved compatible with normal fertilization, embryo development, and the generation of live offspring (56, 63, 109, 110). In addition, first- and

second-generation progeny were deemed free of maternal mtDNA (56). Much of the same held for polar body 2 (PB2) transfer, which entails the transfer of a second polar body into a zygote from which only the maternal pronucleus had been extracted (56). Viewed globally, polar body transfer appeared to have outdone PNT and MST in reducing maternal mtDNA carryover into derived offspring (56). Comparable studies in the human context revealed that oocytes reconstituted via PB1 transfer supported fertilization, meiosis completion, and the formation of normal diploid zygotes (60, 106, 111). Zygotes reconstituted via PB2 transfer, by contrast, displayed a more limited development potential. Still, embryonic stem cell lines derived from control and from PB2-transfer-derived blastocysts featured comparable genetic, epigenetic, and transcriptional patterns (60, 106, 111). Carryover of maternal mtDNA into reconstituted oocytes or zygotes proved highly limited (60, 106, 111).

Genome editing technology has also been explored with an eye toward preventing mtDNA diseases (29, 85). Assessed in a heteroplasmic (NZB/BALB) mouse model, mitochondrial genome editing of zygotes and oocytes all but precluded the germline transmission of select mtDNA haplotypes (85). Through the use of mitochondria-targeted restriction endonucleases or transcription activator–like effector nucleases (TALENs), mitochondrial genome editing reduced the intraoocytic representation of mutant human mtDNAs of Leber's hereditary optic neuropathy and of neurogenic muscle weakness, ataxia, and retinitis pigmentosa (85). Potential off-target effects were ruled out (85). Mitochondrial genome editing will likely continue to evolve should use be made of CRISPR/Cas9 and its multiple analogs (51).

THE UNITED KINGDOM

So far, the United Kingdom (UK) is the only country that has changed its laws and regulations to allow MRTs. In 2008, the UK Human Fertilisation and Embryology (HFE) Act 1990 was amended, and one of the changes was that future regulations may provide for certain modified eggs and embryos to be permitted in treatment without requiring changes to the primary legislation (45). The amended legislation—the HFE Act 1990 (as amended by the HFE Act 2008)—defines permitted gametes and permitted embryos, and only these can be placed in a woman's body (45). The procedures specified in the HFE Act (as amended) that would create the modified eggs and embryos are those aimed at preventing a serious mitochondrial disease (45).

The relevant regulations, the Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015, came into force on October 29, 2015 (46). The regulations passed only after a long process that involved several reports on the techniques, public dialogue across the UK, and public consultations (30). Here is a brief summary of the most important moments of that process: In 2005, the House of Commons Science and Technology Committee published a report in which it supported research on techniques that would help avoid the inheritance of mtDNA diseases. (For lists of key publications, see References 105 and 107.) The committee supported this research being carried out because the UK already allowed research on human embryos. In 2008, the HFE Act 2008 passed, allowing researchers to develop techniques to avoid the inheritance of mtDNA diseases. In 2011, the Human Fertilisation and Embryology Authority (HFEA)—the UK's independent regulator that superintends the use of embryos and gametes in infertility treatment and research—put together an expert panel to assess whether MRTs are safe and effective, and the panel produced a first report on such matters. In 2012, the Nuffield Council on Bioethics published its report *Novel Techniques for the Prevention of Mitochondrial DNA Disorders* (72), which concluded that if MRTs were safe and effective, then it would be ethical for families to use them. In July 2012, the HFEA organized a series of public engagement events across the UK, and in September of that same year it launched a public consultation on MRTs. In 2013, the HFEA

published both an updated scientific review of MRTs and a report on its public consultation. In June 2014, it published draft regulations for MRTs and initiated a three-month-long public consultation on the regulations. In 2014, the expert panel published an updated review of the safety and efficacy of MRTs, followed by an addendum that explored polar body transfer techniques. In July 2014, the Department of Health published its response to the public consultation on draft regulation pertaining to MRTs. In December of that same year, the House of Commons put forth the Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015. In 2016, the expert panel published a new report on the safety and efficacy of MRTs. While some have regarded this process as an exercise in deliberative democracy, others, such as Dimond & Stephens (30), have argued against this claim, suggesting instead that the MRT legalization process was driven mainly by scientists and patient groups.

The UK regulations allow only two MRT types: PNT and MST. Neither PB1 transfer nor PB2 transfer is authorized. The expert panel conveyed by the HFEA concluded that polar body transfer was at an early stage of development, and this seems to be one of the reasons for their exclusion from the regulations (43). The 2015 regulations also restrict the use of MRTs to avoiding the creation of children with serious mtDNA diseases, meaning that the use of PNT or MST to treat infertility is not allowed in the UK. According to the regulations, the circumstances in which MST and PNT are permitted are those in which there is a particular risk that any egg (or embryo created with such egg) may have mitochondrial abnormalities caused by mtDNA and that a person possessing such abnormalities will have or develop a serious mtDNA disease [46, para. 5(a)(i–ii) and para. 8(a)(i–ii)(4)].

Only fertility clinics with a specific license can perform MRTs in the UK. A clinic must request a license from the HFEA's Licence Committee, and the license is granted only when the HFEA has confirmed that it has the capacity to perform one or both techniques. It is important to stress that the fact that a clinic has a license to carry out PNT and/or MST does not mean that it can freely offer such procedures to women judged to have heritable mitochondrial abnormalities caused by mtDNA. At present, any woman who might benefit from an MRT procedure needs approval of her case by the HFEA's Statutory Approvals Committee. Only once these two requirements have been satisfied can the MRT procedure be lawfully carried out. In 2017, the Newcastle Fertility Centre at the International Centre for Life became the first center in the UK to be licensed to conduct PNT (70), and in February 2018, the first two women were granted approval to undergo an MRT procedure (88). No live birth following an MRT has yet been reported in the UK.

When considering how the UK's MRT experience compares with those of other countries, there are a few elements worth highlighting. First, two main themes drove the process of MRT legalization in the UK: the claim by proponents that there is an important distinction between nuclear DNA (which confers personal characteristics) and mtDNA (which does not) and the claim that, in MRTs, no DNA modification occurs, since the procedure only replaces naturally occurring DNA with naturally occurring DNA (94). Second, under the UK regulations, the mitochondrial egg donor is not a legal parent. When commenting on the term "three-parent families," the UK government asserted, "We regard this term as completely inappropriate. Gamete donors. . .are not treated as the legal parent of any resulting child and there is therefore no justification to regard mitochondrial donors, who would provide only 0.1 per cent of the child's genes, as such" (104, p. 29). Third, the regulations do not mandate that children born after an MRT should be enrolled in any type of long-term follow-up. Nevertheless, the UK's expert panel recommended that clinics offering MRTs should encourage patients and their offspring to take part in long-term follow-up, in order to collect information about safety and efficacy (44, p. 7). Fourth, the regulations do not require that only male embryos be transferred to a woman's womb, in contrast to the position of the US Institute of Medicine (IOM) (discussed below). The expert panel argued that

the additional manipulation of the MRT embryo to determine its sex, the reduction in available embryos for transfer, and the exclusion of female embryos were reasons to reject such a proposal. Furthermore, the HFE Act (as amended) allows sex selection only for sex-linked diseases, thus apparently foreclosing this regulatory option. Finally, unlike children born through regular egg donation, MRT-conceived children can obtain only nonidentifying information about the egg donor. Additionally, MRT-conceived children cannot obtain information as to whether they share an egg donor with other MRT-conceived children (46).

THE UNITED STATES

Both policy makers and scientists in the United States keenly watched the UK developments regarding MRTs. The US Food and Drug Administration (FDA) has claimed jurisdiction over the approval of MRTs. More specifically, MRTs fall under the mandate of the Office of Cellular, Tissue, and Gene Therapies of the Center for Biologics Evaluation and Research, which has been charged with overseeing "human cells used in therapy involving the transfer of genetic material by means other than the union of gamete nuclei" (22, p. 179). Under the usual FDA process, approval of the therapeutic use of MRTs would occur only after FDA evaluation following the conduct of phased clinical trials pursuant to an Investigational New Drug Application (22).

In 2014, the FDA convened the Cellular, Tissue, and Gene Therapies Advisory Committee to discuss "oocyte modification in assisted reproduction for the prevention of transmission of mitochondrial disease" (22, p. 179). The FDA did not vote on any way forward as a result of the discussion, and Reuters quoted the chairman of the committee as saying that several panelists felt "there was probably not enough data in animals. . .to move on to human trials without answering a few additional questions" (7). Rather than seeking to answer those questions itself, the FDA commissioned the IOM (now called the National Academy of Medicine) to author a report addressing how the United States should regulate MRTs (21). Commissioning the IOM to author a report was viewed as, in effect, an order that halted any FDA consideration of MRTs until the report was completed.

Without doing true justice to an excellent and comprehensive report, in sum, the IOM recommended that the FDA permit initial clinical investigations to go forward (i.e., culminating in the typical FDA review process) if the following conditions were met (67, pp. 10–13):

- The initial safety and minimization of risk of MRTs were established.
- The efficacy of MRTs was established through in vitro, animal, and other testing.
- Clinical investigation was limited to women with serious mtDNA diseases where the consequences for offspring are likely to be severe.
- Nonviable human embryos were used to develop MRTs.
- When it was not possible to use nonviable human embryos, as few embryos as possible and the least developed viable human embryos were used to develop MRTs.
- Intrauterine transfer during initial clinical trials was limited to male embryos.
- Research would be allowed on female embryos only if (*a*) clear evidence of safety from male cohorts using identical MRT procedures emerged, regardless of how long it took to collect this evidence; (*b*) animal testing showed evidence of intergenerational safety and efficacy; and (*c*) significant public and scientific deliberation concerning the ethical issues raised by heritable genetic modification occurred.

The IOM offered the male-only condition as an attempt to address concerns over germline transmission of alterations, as the IOM believed that male embryos were unable to transmit the modified mtDNA to their progeny (20, 67).

The IOM's recommendations, however, were preempted by legislative and executive branch action. Congress passed, and President Obama signed into law, an appropriations rider that effectively precludes any clinical trials on MRTs in the United States. The Consolidated Appropriation Act of 2016 directs the FDA to refrain from considering applications for "an exemption for investigational use. . .in research in which a human embryo is intentionally created or modified to include a heritable genetic modification" (24, sec. 749). The rider was introduced, without any debate, by Representative Robert Aderholt, a Republican from Alabama (65, 66).

Because there was no debate, it is hard to be sure, but all indications, including what was said in the law's most recent renewal (49), suggest that the prohibition was aimed at germline gene editing more generally, without the case of MRTs—which many think of as socially, ethically, and scientifically distinct (69)—in mind. It is not completely clear that the language of the rider applies to all forms of MRTs—that is, whether all forms of MRTs constitute "research in which a human embryo is intentionally created or modified to include a heritable genetic modification" (24, sec. 749). In particular, one might argue that the male-only MRTs recommended by the IOM do not fall within this language, but the FDA has thus far taken the position that all forms of MRTs are covered by the rider and thus has refused to consider applications. Indeed, the FDA has dispatched at least one letter to a US clinician–researcher, Dr. John Zhang, for "using MRT to form a genetically modified embryo" in the United States even though the embryo implantation took place in Mexico (19, p. 449; 112).

During the 2019 appropriations process, there was an attempt to alter the legislation. In a markup of the bill, some members of the US House of Representatives initially sought to omit the appropriations rider in that year's bill. The effect would have been to allow the FDA to consider the technology directly, as it would any other similarly situated technology. Ultimately, however, over one dissenting vote, the relevant subcommittee voted to reinsert the appropriations language. In what might seem like a hopeful sign for consideration of MRTs separate from gene editing, it was reported that Representative Sanford Bishop Jr., who chaired the subcommittee, said he wanted Congress to discuss allowing MRTs, "but today is not that time, and this appropriations committee markup is not that place" (49).

Separate from the congressional rider and FDA policy, which focus on actual use of MRTs, as the IOM recognized, "[f]ederal funding for MRT research would likely be unavailable because of current legislative restrictions against funding research on human embryos" (67, p. 59).

In sum, the United States has taken a fairly restrictive approach to MRTs, and one that seems unlikely to change in the near term.

CANADA

In 2004, Canada passed the Assisted Human Reproduction Act (AHRA), a federal law meant to regulate the use of assisted reproductive technologies (ARTs) throughout Canada. While the AHRA focuses on the clinical applications of ARTs, it also prohibits research involving in vitro or in vivo germline modifications, stating 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" [4, sec. 5(1)(f)]. Canadian law thus does not distinguish between MRTs and gene editing, but rather regards both as prohibited types of heritable genetic modifications. MRTs are forbidden regardless of whether they are intended to treat infertility or to prevent the transmission of mitochondrial disease to offspring.

Moreover, Canada bans not only the clinical use of these techniques but also basic research that involves such modifications, even in the absence of any plan for clinical translation and regardless of the source of funding (public or private) used to support the research. Canada does

distinguish between somatic and germline genetic modification. Therefore, while such research on somatic cells would fall under the Tri-Council Policy Statement on Ethical Conduct for Research Involving Humans (13) and could be approved, research involving germline cells is strictly forbidden. Since criminal law falls under the legislative jurisdiction of the federal government, the AHRA's prohibitions are criminal, with serious sanctions ranging from a fine of up to $500,000 to imprisonment of up to 10 years.

The AHRA was successfully challenged in 2010 by the government of Quebec (the largest Canadian province), which argued that certain sections violate the federal–provincial division of powers, since in Canada the provision of health services falls under provincial jurisdiction. Consequently, the AHRA was gutted of much of its content, and the Canadian Supreme Court returned the authority to regulate most aspects of ARTs to provinces and territories. However, certain sections survived the challenge, including the prohibition of germline modifications. While the AHRA was supposed to be reviewed 5 years after coming into force, this has still not occurred 15 years later (53).

The AHRA was enacted during a period of intense international debate following the 1996 birth of Dolly, the first cloned mammal. In Canada, this was accompanied by the scandal surrounding the Quebec-based Raëlian sect, which falsely announced in 2003 the birth of the first cloned human baby (15), a hoax that received much media attention. Canadian public opinion was thus shaped by concerns about dangerous applications of cloning and other reproductive technologies. This resulted in the AHRA banning not only cloning but also any inheritable genetic modification and led to a ban that extends to research with current technologies, including MRTs.

Despite significant changes in the science and the legal landscape due to the Supreme Court's intervention, the AHRA has not been revised. Now, considering emerging technologies such as CRISPR and MRTs, there is growing awareness that "criminal bans are not a suitable instrument to regulate scientific research" (53, p. 1) and that a thorough revision of the AHRA is overdue. Since in Canada the fundamental barrier to change does not seem to be pro-life political agendas that demand respect for in vitro human embryos, but rather an absence of political will, a group of Canadian experts was formed to explore the challenges of revising the AHRA. This resulted in the publication of a consensus statement, based on several academic publications (12, 53, 54, 73, 84), recommending that "basic and pre-clinical research on human germ cells and embryos in the earliest stages of development should be allowed" and that "mitochondrial replacement therapy to prevent the transmission of serious mitochondrial diseases should be permitted when demonstrated to be safe and effective" (55, p. 1). The group also stated that "MRT is a novel, promising intervention" and that "Canada should not curtail scientific exploration that might lead to its safe and effective clinical application" (54, p. 917).

The expert group called attention to the distinction between using MRTs to prevent the transmission of severe mitochondrial diseases and using them to improve fertility outcomes, arguing that these applications are ethically distinct. It argued that the prevention of disease justifies an immediate move away from a criminal ban, calling for a national consultation that would lead to the creation of proportional and appropriate oversight mechanisms.

Pending a possible revision of the AHRA, a potential way forward for Canada could be to consider male-only MRTs that would not transmit modified mtDNA to offspring, thus not violating the current prohibition. Alternatively, Health Canada (the Canadian ministry of health) could issue a clarification specifying that "altering the genome" refers to nuclear DNA and not mtDNA, a move similar to that of the UK.

Going forward, some Canadian provinces may choose to adopt more permissive approaches toward MRTs, and possibly toward research involving germline genetic modifications more broadly,

to remain scientifically competitive and allow their citizens access to cutting-edge therapies. Recently, the Quebec government convened a working group to explore the implications of such a move, which resulted in the publication of a report offering principles for future regulation (23). The report proposed that "mitochondrial transfer be applied initially to male embryos only, to avoid transmission of the modification to future generations" and argued that "if Health Canada decides to permit clinical applications of genetic modifications to germ cells and embryos," regulations should "limit this type of intervention to very serious, high penetrance diseases, where there are no other reproductive or therapeutic options available, in order to limit the target population and the scope of any impacts on the human gene pool" (23, p. 18).

AUSTRALIA

In June 2018, the Australian Senate's Community Affairs References Committee issued a comprehensive report entitled *Science of Mitochondrial Donation and Related Matters* (6), which documented the legal status of MRTs in Australia, provided an ethical analysis, and made recommendations for further steps. As a threshold matter, the Senate concluded that an existing piece of legislation aimed at regulating human cloning, the Prohibition of Human Cloning for Reproduction Act 2002 (82), had language that presented a potential legislative barrier to MRTs in Australia. In particular, it pointed to three relevant provisions of that act: section 13, which "prohibits the creation of a human embryo outside the body of a woman which contains genetic material from more than 2 persons"; section 20, which prohibits placing such an embryo into a woman for gestation; and section 15, which "prohibits the alteration of the genome of a human cell where that alteration is inheritable" (6, part 5.15). The committee heard expert testimony as well as submissions on the question of whether MRTs constitute "germline genetic modification" and recognized "the majority of the evidence presented that mitochondrial donation is not considered a form of germline genetic modification as envisioned by Australian laws which prohibit cloning and other similar forms of genetic modification," but concluded that "the committee. . .does not have the required expertise to make such a determination, and notes a formal determination must be taken by an appropriate body with the relevant expertise. If this view is confirmed, then appropriate amendments should be made to Australian law to keep it up-to-date with science and to allow for, and only allow for, mitochondrial donation" (6, parts 5.15, 5.25, and 5.26).

The committee also endorsed a "two-pronged approach" that would allow for a "limited clinical trial" of MRTs "before full introduction of mitochondrial donation" while "additional research could be simultaneously conducted" (6, parts 5.30 and 5.31). In terms of the circumstances under which MRTs would be appropriate, the committee characterized as the "universal view" of those that it heard from—quite similar to the IOM report in the United States—that "the unknown risks may be acceptable to take for reducing the generational transmission of severe mitochondrial disease to children" but were "not considered appropriate to take for other diseases or as an ART enhancement at this point in time" (6, part 5.43). At the same time, it recognized that there may be a need for some flexibility in assessments and implementation and believed that a licensing approach similar to the UK's was the best way of accomplishing this (6, part. 5.49). More generally, the committee made four major recommendations to the Australian government: that the government (*a*) undertake public consultation on the possible introduction of mitochondrial donation into Australian clinical practice, (*b*) obtain expert advice through the National Health and Medical Research Council about key scientific questions relating to mitochondrial donation, (*c*) engage with state and territory governments on the findings of the inquiry, and (*d*) seek access for Australian patients to mitochondrial donation procedures in the UK, by starting a dialogue between the Australian government and the relevant UK authorities (5; see also 6).

In January 2019, the Australian government issued its response to the Senate report (79). After recognizing the "testimonies from those who have suffered with, or lost a loved one to, mitochondrial disease" and the government's "established record of supporting cutting edge research and funding the safest, most clinically and cost effective medical services for the Australian population" (79, p. 3), the government characterized the Senate's recommendations as falling into two categories: "providing for informed consultation and decision making for the public and governments" and "seeking access to international services as a short term solution" (79, p. 4).

On the latter, the government was fairly circumspect, committing only to "reconsider the proposal based on consultation outcomes and relevant expert advice" (79, p. 6). It further noted that "only one child has been born through mitochondrial donation internationally" (now an outdated estimate, as discussed below) and that the technology was at an early stage without knowledge of long-term outcomes, such that only sometime in the future would sending Australians abroad for MRTs be considered for "discussions between governments about appropriate regulatory and funding" (79, p. 6).

On engaging the public, the government was more enthusiastic, and it tasked the National Health and Medical Research Council to engage in a public consultation. While acknowledging the view of the Senate committee that "Australians may not find mitochondrial donation controversial," it nonetheless believed it "essential to provide the Australian people, peak bodies and other stakeholder groups, and governments with information about the procedure and the opportunity to respond" (79, p. 4). It also explicitly acknowledged "the complexity of the discussions about the social and ethical implications of making such a change to the genomic makeup of an embryo, even for the purpose of avoiding a potentially fatal disease" and that "these issues remain, however small the amount of genetic material that is changed, especially where the change can be carried to following generations" (79, p. 5). On the legal side, it acknowledged the complex interplay of various nationwide and state laws but suggested that only after "the outcomes of the consultation phase are known" would "comprehensive and careful examination of all relevant legal and ethical frameworks. . .be required to manage any proposals for change and avoid unintended consequences," including "arrangements at the state and territory level, impacts on other legislation like the Gene Technology Act 2000, as well as other review activities such as the Third Review of the Gene Technology Scheme" (79, p. 6).

In September 2019, the National Health and Medical Research Council began its consultation process, which it characterized as "a public process to obtain views from the Australian community on the social and ethical issues associated with mitochondrial donation" (5). To date, the events it has undertaken or scheduled include an online submission portal, an issues-paper release, two citizen panels, a targeted roundtable for invited stakeholders, two webinars, and public forums.

GERMANY

In Germany, there seems to be a general public understanding that MRTs are prohibited. It is not unusual to find comments in the German media such as that "in Germany, the present legal situation clearly excludes an approval of this method" (41). As is so often true in law, however, it is in fact unclear and contestable whether MRTs are prohibited or permitted under German law. Germany does not have explicit provisions that regulate MRTs. The criminal liability of these techniques is to be judged according to the German Embryo Protection Act (EPA) (34). The EPA was promulgated on December 13, 1990, and was last amended by article 1 of the Preimplantation Genetic Diagnosis Act of November 21, 2011 (35). The EPA is a criminal law, and as such, under German law it may not be interpreted beyond its wording to the detriment of a possible offender [38, art. 103(2); 93; 103, sec. B, part III, para. 18]. This leads to several problems with interpreting the act in this context.

The first key question is whether MRTs are covered by the ban on germline intervention under section 5 of the EPA. Under section 5(1), "anyone who artificially alters the genetic information of a human germ line cell will be punished with imprisonment up to five years or a fine." Under section 5(2), "likewise anyone will be punished who uses a human germ cell with artificially altered genetic information for fertilization." And under section 8(3), "germline cells" are "all cells that lead in a cell line from the fertilized egg to the egg and sperm of the human being who has resulted from it and, further, the egg from injection or penetration of the sperm until the ending of fertilization by fusion of the nuclei." Germ cells are thus eggs and sperm.

It is a matter of controversy whether in MST the isolated nucleus of the prospective mother's egg to be transferred into an egg cell envelope with normal mitochondria is still a human germ cell under the EPA (91, 93). It is also contestable whether MRTs more generally involve an artificial alteration of genetic information within the meaning of the act (32, p. 5; 91, 93). The better reading, though not without doubt (28), is that MRTs do not involve an alteration under the EPA since an exchange of genetic information (not an alteration of that information) takes place (33, p. 15; 39, sec. 5, para. 14; 52; 64, sec. 5, para. 2; 113). Thus, even if the entity resulting from an MRT is a human germ cell under the EPA (93), under this reading MRTs would not violate the ban on germline intervention according to sections 5(1) and 5(2).

There are, however, other provisions in the act that could still forbid MRTs. Under section 1(1), clauses 1 and 2, "anyone will be punished with up to three years imprisonment or a fine" who "transfers into a woman a foreign unfertilized egg" or "attempts to fertilize artificially an egg for another purpose than bringing about a pregnancy of the woman from whom the egg originated." According to the prevailing view, the impregnated egg in the pronuclear stage (i.e., when the sperm has already penetrated or has been injected into the plasma of the egg, but the two pronuclei have not yet fused) is also considered unfertilized within the meaning of the act [39, sec. 1(2), para. 2; 50, sec. A, part II, para. 36; 93].

The term foreign is crucial here: An egg is considered foreign within the meaning of the act if the egg does not originate from the woman into whom it will be transferred [103, sec. 1(1), clause 1, para. 17]. It is a matter of controversy whether the reconstructed egg resulting from an MRT originates from the woman into whom it will be transferred. There is an ongoing debate on whether it is the nuclear DNA (and not the mtDNA, which accounts for only approximately 0.001% of the whole genome) (39, sec. 5, para. 14; 50, sec. A. part II, para. 16) that determines whether an egg is foreign (76). If one accepts the argument that the nuclear DNA determines whether an egg is foreign (93), then MRTs—regardless of whether the resulting reconstructed egg is an unfertilized egg under the EPA—would not violate section 1(1), clause 1, of the EPA since the nuclear DNA originates from the woman into whom the reconstructed egg will be transferred. The same logic applies to section 1(1), clause 2.

Section 1(2) of the EPA protects the "impregnated egg in the pronuclear stage" from improper use [39, sec. 1(2), para. 2]. Under this provision, anyone who "brings about artificially the penetration of a human egg by a human sperm" or "injects a human sperm into a human egg artificially, without intending to bring about a pregnancy of the woman from whom the egg originated," will be punished with up to three years of imprisonment or a fine. Thus, MST and PB1 transfer are not prohibited under section 1(2) of the EPA since the reconstructed egg will be impregnated with the father's sperm in order to bring about a pregnancy of the woman from whom the nuclear DNA, and therefore the reconstructed egg, originated. However, PNT and PB2 transfer are covered by the prohibition in section 1(2) of the EPA with regard to the impregnation of the donor's egg with the father's sperm because there is no intention to bring about a pregnancy from the donor from whom the egg originated.

In sum, the best arguments support the view that, under German law, MRTs are not covered by the ban of germline intervention under section 5 of the EPA. MST and PB1 transfer are not prohibited under the EPA, whereas PNT and PB2 transfer are prohibited under section 1(2) with regard to the impregnation of the donor's egg.

The language of the EPA was not passed with MRTs in mind. Like other jurisdictions discussed in this article, it would be useful for Germany to consider whether its existing law fits in legislative goals in this area and for the German legislature to consider enacting a new Reproductive Medicine Act (58) or at least clarifying the application of the EPA to MRTs.

The German Ethics Council has only recently, in May 2019, published an opinion titled *Intervening in the Human Germline*, which focused on intervention in the genome of the nucleus (and not MRTs) (33). The council especially highlighted that "the ethical analysis does not lead to any categorical inviolability of the human germline" (33, p. 36). However, it also pointed out that a sufficient degree of safety and efficacy of such interventions is the prerequisite for permissibility and recommended an international moratorium on the clinical application of human germline interventions (33, p. 36). Whether the council's opinion on germline gene editing prompts legislative actions that also implicate MRTs remains to be seen.

ISRAEL

In 1999, Israel passed the Prohibition of Genetic Intervention (Human Cloning and Genetic Manipulation of Reproductive Cells) law (81). This law was subsequently amended in 2004, 2009, and 2016, with its current version set to expire in May 2020 (83). Discussions leading to this legislation were inspired by the 1996 birth of the first cloned mammal, Dolly, in Scotland, which led to laws banning reproductive cloning in numerous other countries as well.

The law prohibits two activities: human reproductive cloning (sec. 3.1) and the use of "reproductive cells that have undergone a permanent intentional genetic modification. . .to cause the creation of a person" (sec. 3.2). The criminal sanction for violation is up to four years of imprisonment or a fine amounting to approximately US$400,000.

The prohibition of cloning is irrelevant to the discussion of MRTs because the law specifically bans "the creation of a human embryo genetically identical to another, person or embryo, alive or dead" (81, sec. 2.b). The second prohibition, however, is indeed relevant to the question of MRTs, since the prohibition of the use of "reproductive cells that have undergone a permanent intentional genetic modification" can be interpreted to apply not only to modifications in nuclear DNA but also to those related to mtDNA.

While MRTs were not considered at the time the law was discussed and enacted, its wording clearly permits such an interpretation. The intention of the legislature was to ban germline genetic modifications that are "permanent" and "intentional," which would apply to MRTs as well. While contrary interpretations might be possible, erring on the side of caution, one would be justified in interpreting the prohibition widely to include MRTs, unless or until the legislature clarifies the Israeli position regarding a technology that was not envisioned at the time.

This prohibition would apply to reproductive use and not to basic research. Unlike in many other jurisdictions, the Prohibition of Genetic Intervention law does not include a prohibition on creating human embryos for research, which would be permitted as long as they are not used for reproductive purposes (after having been genetically modified). One explanation for this distinction between reproduction and research involves the Israeli cultural context: According to Jewish tradition, an embryo acquires the status of a "living being" only 40 days after fertilization and until then is considered "merely water" (95). Research using MRT technologies would thus be permitted if approved both by a hospital institutional review board and subsequently by the

National Committee for Human Medical Research, which must grant special approval for all medical research involving genetics or ARTs in humans.

What makes the Israeli case interesting is that the law targets interventions in "reproductive cells," and these are defined very specifically as "human sperm or oocyte" (81, sec. 2.2). However, it does not define the term embryo and does not explicitly ban genetic modification of embryos. This is understandable when one remembers that the impetus behind the law was the specific concern regarding cloning, which involved genetic intervention prior to conception. Now, however, this distinction between intervention in a reproductive cell versus an embryo (or a fertilized oocyte) has critical implications for MRTs. A reasonable interpretation of the law implies that MST would be prohibited, since it is an intervention in the oocyte, while PNT would be permitted, since the fertilized oocyte is no longer a reproductive cell but rather is a biological entity that the law does not refer to.

Although this suggested interpretation of the Prohibition of Genetic Intervention law means MST would be prohibited, the law left an opening to allow safe and effective ways of preventing genetic diseases to be used in the future. It thus includes a section that allows the minister of health to permit, through regulations and as an exception to the overall prohibition, specific genetic interventions in reproductive cells (81, sec. 5.a). This built-in option that allows exceptions to the rule was deemed more efficient than having to modify the law in the future. To date, the minister of health has not resorted to this mechanism, but it remains a viable approach if the minister deems MST therapeutically valuable, safe, effective, and in line with considerations of human dignity.

Finally, the stated purpose of the law is "to prevent reproductive cloning in humans by establishing that certain kinds of genetic interventions shall not be performed on human beings in view of the moral, legal, social and scientific aspects of the prohibited forms of intervention and their implications on human dignity, and in order to asses public policy regarding those kinds of intervention in view of those aspects, considering freedom of scientific research for the advancement of medicine" (81, sec. 1). This rationale would definitely apply to MRTs, since this technology has raised controversy worldwide. If Israel decides to clarify its legal or regulatory position regarding MRTs more specifically, such a move would probably be preceded by public debate and discussion in the Knesset (the Israeli Parliament).

SINGAPORE

In March 2017, in *ACB v. Thomas Medical*, the Supreme Court of Singapore acknowledged the interest in genetic affinity (1). Based on the court's decision, Schaefer & Labude (89) have argued for a right to "three-parent IVF" as a negative right (i.e., the right against blanket legal prohibitions on MRTs). Perhaps based on this case law, or separately by legislation, Singapore could become, after the UK, the second country that explicitly permits MRTs (74).

In April 2018, Singapore's Bioethics Advisory Committee (BAC) published a consultation paper that examined the ethical, legal, and social issues arising from MRTs (9). The BAC, established in December 2000, is an independent advisory committee that studies evolving areas in human biomedical research and recommends policies to the Singapore government as appropriate (9, 11). Such recommendations are based on "the aim of protecting the rights and welfare of individuals, while allowing the biomedical sciences to develop and realize their full potential for the benefit of humankind" (9, 11). The BAC has had these issues on its radar for a long time, and indeed, in November 2005 it released a report on genetic testing and research in which it recommended that "the clinical practice of germline genetic modification should not be allowed at this time" (8, pp. 10 and 38). In this report, the BAC defined "germline genetic modification" as "a type of gene technology that involves the alteration of a person's genetic makeup in a manner that is

permanent and can be transmitted to his or her offspring" (8, p. 37). However, due to new technological advances and international discussions, it has since reconsidered its position on germline modification, focusing on MRTs for the prevention of mitochondrial disorders, and thus issued a consultation paper in April 2018 as a first step toward the development of recommendations to the Singapore government (9, p. 1).

In this paper, the BAC explored three techniques for preventing mitochondrial disorders: MST, PNT, and polar body transfer. In contrast to the UK, which allows only MST and PNT in clinical applications, and only under certain conditions (see above), the BAC has also entertained the possible legalization of polar body transfer in Singapore (9, p. 7). It also gave arguments for and against the clinical application of MRTs and discussed issues such as possible benefits, reproductive autonomy, fairness, and welfare of future generations (9, pp. 18–27). In particular, the paper acknowledged concerns about a slippery slope from MRTs to germline gene modification. This worry is grounded in the fact that Singapore currently has no explicit legal ban on nuclear germline modification except for the BAC's recommendation for an ethical moratorium on germline genetic modification in clinical practice (8, pp. 10 and 38; 9, pp. 14 and 26). At the same time, as the BAC recognized, there are some safeguards in places—notches along the slippery slope—since any new assisted reproductive service and/or human biomedical research involving the use of human embryos or human eggs requires approval from the director of medical services (9, p. 26; 42, sec. 31 and Fourth Schedule; 97, p. 20). The BAC recommended that current regulations could be enhanced by limiting the use of MRTs—similar to the regulations in the UK (46)—to the prevention of serious mitochondrial disease (9, p. 26). It also proposed a clear regulatory line that could be drawn based on the material distinction between the nuclear genome and the mitochondrial genome (9, p. 26).

As a second step toward the development of recommendations to the Singapore government, the BAC asked the public for opinions on whether the clinical application of MRTs should be permitted (9, pp. 1 and 27). It asked for feedback on the consultation paper by June 15, 2018, including comments on any other relevant aspects that are not discussed in the paper (9, pp. 1 and 27). It also held two public dialogue sessions, in which one of the most common concerns expressed among the Singaporean public was the issue of self-identity—that a child born from an MRT would have parts of the genomes of three people (10, para. 10; 74). The National Council of Churches of Singapore, for example, responded to the BAC's consultation paper in a 24-page document that concluded that "while the National Council of Churches recognizes the plight of women with mitochondrial disease, it cannot endorse or support the legislation and application of Mitochondrial Replacement Technology because of the serious theological, ethical and social issues and concerns associated with this technology" (68, p. 24).

Based on its findings, the BAC had planned to make formal recommendations to the Singapore government in 2018 on whether the clinical application of MRTs should be permitted in Singapore (9, p. 27; 74). Neither the Singapore government nor the BAC has issued a public statement as of December 2019, but it is likely only a matter of time. It thus remains to be seen whether and (if so) to what extent Singapore will permit the clinical application of MRTs.

MEDICAL TRAVEL FOR MITOCHONDRIAL REPLACEMENT: MEXICO, UKRAINE, GREECE, AND SPAIN

The seven countries discussed above do not exhaust the sites of interest for MRTs. As is true with other reproductive technologies where the regulatory playing field is uneven, such as surrogacy (18), the citizens of one country may flock to another in order to obtain a health care intervention that is otherwise banned or unavailable. This has proved true for MRTs in Mexico, Ukraine,

Greece, and Spain, each of which has been involved in processes that led to the birth of MRT-conceived children. Mexico was part of the first live birth of a child conceived through MST in order to avoid an mtDNA disease. Ukraine became prominent because the first live birth of a child conceived through PNT as part of infertility treatment happened there. And Spain and Greece are important to consider because the first live birth of a child conceived through MST as part of infertility treatment happened in Greece, after a joint venture between Spanish and Greek scientists and physicians.

On April 6, 2016, a Jordanian couple in the United States had the first live birth of an MST-conceived boy (87). In addition to the actual scientific feat, one of the reasons the news attracted global attention was the report that the parents of the child "were treated by a US-based team in Mexico" (40). Later it came to light that the MRT procedure itself took place in the United States and the embryo transfer occurred in Mexico (61, 112). At the federal level, Mexico does not have specific laws or regulations regarding assisted reproduction, and no federal agency or organization exists that regulates, evaluates, or compiles information pertaining to ARTs (78). In fact, there is nothing in Mexico's federal health law, the General Health Law, that in principle prohibits carrying out MRT clinical research in the country to avoid an mtDNA disease or treat infertility.

Nevertheless, some federal regulations do apply to all MRT clinical research, namely the Regulations of the General Health Law on Health Research (86). According to article 56 of these regulations, research on what is called "assisted fertilization," which includes MRTs, is permissible only when it is aimed at solving infertility problems that cannot be solved otherwise. This means that, at the federal level, clinical research on MRTs can be carried out only when aimed at solving this type of problem, and all instances of MRTs are classified as research in Mexico due to their novel nature (48, 77). At the state level, 9 of the 32 Mexican states prohibit PNT because their local constitutions protect human life from the moment of fertilization (78). At present, a series of amendments to the General Health Law pertaining to assisted reproduction are being discussed in the Mexican Senate; however, they do not mention or prohibit MRTs. This means that if these amendments are enacted into law, MRT clinical research would, in principle, still be allowed in Mexico at the federal level when it conforms with article 56 of the Regulations of the General Health Law on Health Research.

On January 5, 2017, the first live birth of a PNT-conceived girl happened in Kiev, Ukraine. In this case, PNT was employed to treat infertility and not to prevent an mtDNA disease (17). Emily Mullin recently reported that at least seven more PNT-conceived children have been born following treatment in Ukraine (65). So far, there have been no academic publications following such births, so all that is known from these cases comes from a poster presentation at a conference, media reports, and the information given on the website of the fertility clinic, which offers PNT (65). The intention behind using PNT in the first instance was to avoid embryo arrest. Even though Ukraine has no explicit legal restrictions on MRTs, the director of the clinic where the procedure took place has been quoted as stating, "We received special permission for clinical trials" (80), apparently referring to approval being granted by the Ukrainian Association of Reproductive Medicine (16). If a clinical trial is in fact going on, then according to media reports, it charges US$8,000 per cycle to Ukrainian couples and US$15,000 per cycle to couples from abroad. So far, there have been no reports regarding whether long-term follow-up is planned or about whether and (if so) in what way the health and development of such children are being monitored. It is also important to note, just as in the US/Mexico case, that in Ukraine MRTs have been provided to foreign couples, including one from Sweden that underwent PNT (99). This, of course, raises more general ethical questions regarding medical tourism for accessing novel reproductive biotechnologies.

On April 9, 2019, a Greek woman gave birth to the first MST-conceived child where the procedure was specifically aimed at treating infertility (31). This was achieved by Spanish and Greek scientists and physicians working in Greece. They were working in Greece because Spanish law allows only artificial insemination, in vitro fertilization, intracytoplasmic sperm injection, and gamete intrafallopian transfer. Using any other ARTs in Spain requires overcoming two hurdles: First, the National Commission on Human Assisted Reproduction must grant a favorable report, and second, the relevant health authority must authorize the technique(s) for provisional experimental use (59). One of the senior members of the Spanish team asserted that they would seek approval from Spanish authorities after their MST trial ends in Greece (3). The trial, which was approved by the Greek National Authority of Assisted Reproduction and the institutional review board of IASO Maternity Hospital, aims to study whether MST can be used for the treatment of infertility problems associated with poor oocyte quality. Oddly, its lay summary misrepresents how MST is carried out, describing it as "a new IVF technique. . ., named spindle transfer, that allows the replacement of the entire cytoplasm of poor quality eggs" (57). Information from this "pilot trial," as they have called it, comes from three sources: one conference paper, an International Standard Randomised Controlled Trial Number (ISRCTN) registry, and media reports (25, 57, 65). From these sources, we know that the trial has three inclusion criteria: Women must be under age 40, must have been diagnosed with infertility problems due to poor oocyte quality, and must have had at least two previous failed in vitro fertilization attempts. We also know that it is not a randomized trial and that they aim at enrolling 25 women (57).

DISCUSSION

Even when countries adopt seemingly similar approaches to a problem, we should always be careful in comparative legal exercises because surface similarities may mask deeper differences in legal or political traditions. With those cautions in mind, though, our comparative study does suggest a few commonalities among the countries we have reviewed, which we summarize below.

In most of these countries, the specific legislation relating to reproductive technologies is somewhat dated in terms of its interface with MRTs. In attempting to understand what the actual text of the legislations or regulations means for MRTs, one encounters considerable interpretive uncertainty. In particular, legislators in multiple countries have struggled with questions of whether MRTs involve gene alteration or editing within the meaning of their laws and whether the alterations are heritable, especially in the case of male-only MRTs. On the other hand, there have been a few instances (medical travel to Mexico, for example) of attempts to take advantage of lack of clarity to offer services. Some of the countries (such as Canada) have interpreted their law to treat all forms of MRTs in the same way, while others (the UK, and perhaps Germany and Israel) have laws that may be read to permit some forms and prohibit others.

Of the seven main countries we have reviewed, Canada and the United States on the one hand and the UK on the other have taken the most diametrically opposed positions. The United States enacted an appropriations law that appears to prohibit MRTs, and attempts to remove it from the annual 2019 funding bill failed; in Canada, both reproductive and research use are banned by existing laws. On the other end, the UK has recently introduced a robust regulatory scheme to allow MRTs. Australia and Singapore are following in the footsteps of the UK and have already begun a public consultation process before potentially taking steps to legalize MRTs. In Canada, by contrast, the possible reconsideration of policy is more at the governmental and academic levels. From what we can tell—and some of the attempts to engage the public are ongoing—there are significant differences in how much the public consultations attempt to use formal methods of deliberative democracy (such as citizen juries) as opposed to more general attempts to engage the public's view (71).

One recurring issue, as a matter of both legislative interpretation and political rhetoric, is whether to view MRTs in the same way as germline gene editing. The United States and Canada have grouped the two together, the UK has very distinctly treated them as different, and the other countries seem to be moving in the direction of separate regulatory treatments of the two.

Most of the countries we have reviewed are at what we would characterize as the first stage of regulatory design questions regarding MRTs: whether to permit or forbid them, full stop. Unsurprisingly, as the country that has gone the furthest in permitting MRTs, the UK has done more to consider what we think of as successive questions: Will mitochondrial egg donors be treated as legal parents? Will donor-conceived children have access to their identities? How, if at all, should MRTs be financed? If more countries explicitly regulate MRTs, we expect they too will face these questions and perhaps come to different answers.

While there has been some medical tourism for MRTs, for the most part this phenomenon has not been a major part of the policy discourse in the seven countries we have discussed. The United States has acted against a doctor for carrying out an MRT procedure and for exporting the embryo, and the Australian Senate report did highlight the question of sending Australians abroad for treatment, but overall the medical tourism angle has not been very prominent in the policy discourse. Of particular interest is that, unlike instances of commercial surrogacy (18), we have not yet seen questions about recognizing parentage or citizenship of children born abroad through MRTs when that technique is prohibited at home. It may be that there just have been too few births to raise this issue to prominence but that it will be faced in short order.

Finally, we highlight two more general legal system design questions that have intersected with the MRT question. The first is whether to regulate reproductive technologies primarily at a civil or administrative regulatory level or at a criminal law level (as in Germany and Canada), which, among other things, raises different approaches to legislative interpretation. The second is the role of federalism and open questions as to whether in some places MRTs will be permitted in some states or provinces but not others.

CONCLUSION

For some families, MRTs represent their only chance to have genetically related children and avoid transmitting terrible, and currently incurable, diseases to their offspring. As our review reveals, multiple MRT-related policy experiments are going on across the world. In many of the countries we have reviewed, MRT policies were formed by happenstance or design fused with policy decisions regarding germline gene editing. In other countries, legislators and regulators are adopting what we view as the better course: considering the best approach to MRTs on their own, correctly recognizing that they raise quite different issues, benefits, and risks than gene editing.

While some countries, like the UK, through its HFEA, are well set up to make quite specific and fine-grained regulatory licensure decisions, in other countries the existing regulations of reproductive technologies force a blunter all-or-nothing approach. We are excited that several countries are taking seriously the need to engage the public regarding MRT policy, but also conscious that in many of these countries such public consultations have not been the norm, such that there are no established playbooks regarding how to best engage in deliberative democracy. At the same time, the hope is that what is learned here may be transferable to other reproductive and nonreproductive policy conundrums of the future.

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