

Implications of Law's Response to Mitochondrial Donation

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Abstract: Changes to Australian law in 2022 made Australia the second country to expressly permit the clinical use of mitochondrial donation (MD), a technology that makes heritable changes to the human genome. This paper considers these changes in the context of Australia's broader controls on human embryo use to provide insights into future regulatory responses to other emerging genetic technologies, which could be used in reproduction.

Keywords: legal regulation; mitochondrial donation; genome editing; genetic technology; embryo research

1. Introduction

The first substantive changes in nearly two decades to Australian regulation of human embryos were made by the passage of Maeve's Law in 2022.¹ That law, more correctly known as the *Mitochondrial Donation Law Reform (Maeve's Law) Act 2022 (Cth)*, made Australia the second nation to expressly legalise the clinical use of mitochondrial donation (MD).² MD is a genetic technology that, when used together with in vitro fertilisation (IVF), offers families the only realistic hope for minimising the risk of passing on certain debilitating genetic diseases while having a genetically related child. Prior to Maeve's Law, clinical use of the technology was prohibited in Australia, as was much of the related research.

Mitochondrial diseases are caused by mutations in nuclear or mitochondrial DNA and have a range of severity of symptoms and age of onset, including multiple organ dysfunction or failure and death (Nuffield Council on Bioethics 2012, pp. 19–20). There is no known cure for the more than 350 genetic diseases caused by faulty mitochondria, the small organelles responsible for producing cellular energy (on the role of mitochondria see Borchering and Brestoff 2023).

MD provides a scientifically feasible way to avoid these diseases in future children, where they are caused by mutations in mitochondrial DNA. MD transfers the intending mother's nuclear DNA to an egg from a second woman which has had its own nucleus removed. The donor egg provides biological material other than the nucleus, including mitochondria without disease-causing mutations. As explained below, the transfer occurs before fertilisation of the eggs in some forms of MD, such as maternal spindle transfer (MST), or after fertilisation of the eggs of both the intending mother and donor in other forms, such as pronuclear transfer (PNT). The nuclear DNA of the resulting child will in all cases, however, come from its intended parents.

This paper aims to consider justifications for and responses to MD, to identify the insights that can be drawn from the legislative changes to permit MD and the public inquiries and Parliamentary debates that preceded them. The paper concludes that Australia's regulation of MD demonstrates its willingness to use new regulatory approaches to provide more immediate access to new health technology. These techniques also enable debate on



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¹ The term 'embryo' is defined in various regulatory schemes including the Australian framework amended by Maeve's Law. This paper adopts the definition used by the International Society for Stem Cell Research as a generic term to describe all stages of development from the first cleavage of the fertilised egg to 9 weeks post-fertilisation (International Society for Stem Cell Research 2021, p. 63).

² Other terms are used to refer to this technology, including mitochondrial replacement therapy. MD is used in this paper because that is the term used in Australia's legislation.

the regulation of broader embryo research to be avoided. These conclusions may be useful for other jurisdictions considering implementing MD. Furthermore, a similar approach to that taken to permit MD could be adopted for other genomic technologies, such as heritable human genome editing (HHGE), should that occur in the future, adding further value to the discussion.

Section 2 puts Australia's legalisation of MD into a global context before moving to consider Australia's broader embryo research regulatory framework and the regulatory strategy used to rapidly permit MD for reproductive purposes in Australia in Section 3. The Australian public's attitudes to possible uses of MD are examined in Section 4. Section 5 then considers the regulatory controls on MD, including restrictions on access and use, and the legislative amendments made to achieve legalisation. Parliamentary concerns around MD are then explored in Section 6 through an analysis of responses to the two most developed forms of MD. The insights to be drawn from the legislative changes to permit MD and the public inquiries and Parliamentary debates that preceded them are discussed in Section 7 before conclusions are brought together in Section 8.

2. Global MD Use

This section places Australia's response to MD in a global context and explores the range of national responses to it.

The United Kingdom and Australia are the only countries to have expressly legalised the clinical use of MD.³ But that does not mean MD is prohibited everywhere else. There is no multilateral international agreement on MD, and the modern form of MD, which uses nuclear transfer, has already been used in reproduction outside of the United Kingdom and Australia. The first baby born after conception involving MD was born in the USA in 2016, following embryo transfer in Mexico (Zhang et al. 2017, pp. 361–62; Kolata 2016). That same year, existing legislation was applied by the Greek National Authority of Assisted Reproduction to allow an MD clinical trial to treat infertility (Johnson and Bowman 2022). The trial concluded in 2020, and at least six children are reported to have been born as a result of the trial (Costa-Borges et al. 2020). At least one more live birth has been reported by a Ukrainian clinic, which began offering MD through a clinical trial in 2017 to treat infertility (Mazur et al. 2019; Singapore Bioethics Advisory Committee 2018).

In contrast, other countries expressly prohibit MD. China, for example, moved to prohibit MD after the unsuccessful use of an earlier form of MD using cytoplasmic transfer in that country (Ishii 2023, p. 200). But most jurisdictions do not specifically regulate MD one way or the other. In some cases, existing ART or embryo research regulations apply, but in others, there is no such regulatory framework. The USA regulator, e.g., the USA Food and Drug Administration (FDA), considers that MD is prohibited in that country leading it to sanction the CEO of the clinic responsible for the birth of the first 'MD baby' (Malarkey 2017; Cohen et al. 2020).

In countries where MD may be permitted, only certain forms of MD may be allowed, and in some cases, questions remain about exactly what use of MD is permitted. For example, Japan's regulations mean some forms of MD are prohibited but other forms are allowed, and the permitted use of them includes the treatment of infertility (Ishii 2023). This is in stark contrast to the position in Australia before Maeve's Law, where no clinical use of MD was permitted, and research was limited to the form(s) of MD prohibited in Japan.

3. Australia's Embryo Research Regulatory Framework

A national regulatory framework to enable MD in Australia had two significant challenges. First, legislative responsibility around health and science is shared between the Australian federal and state governments. This means that uniform regulation needs the approval of all jurisdictions. Secondly, the national regulatory framework for human

³ Legalisation in the United Kingdom occurred pursuant to the Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015 (UK).

embryo research needed amendment. After first describing the current state of play for the legalisation of MD around Australia, this section examines the regulatory techniques used to address these challenges.

Maeve's Law, passed in 2022 after conscience votes in each house of Australia's Parliament, permits research into and the clinical use of MD.⁴ These changes are intended to operate in all Australian states and territories but because of differences in state legislation, MD remains prohibited in Western Australia even after Maeve's Law ([Ministerial Expert Panel on Assisted Reproductive Technology and Surrogacy 2023](#), pp. 18–19). The Western Australian Government has said this will be changed when that state replaces its current assisted reproductive technology (ART), surrogacy and embryo research legislation ([Government of Western Australia 2023](#), pp. 1, 3), but no bill to achieve this is publicly available.

Maeve's Law amends federal legislation at the centre of Australia's national regulatory framework for human embryo research, including the *Prohibition of Human Cloning for Reproduction Act 2002* (Cth) (PHCR Act) as it is now known and the *Research Involving Human Embryos Act 2002* (Cth) (RIHE Act). To address constitutional limits and create a nationally consistent scheme, all Australian federal, state and territory jurisdictions have previously agreed that each would have its own legislation based on the federal legislation.⁵ This agreement, updated in 2007 ([Council of Australian Governments' Meeting 2007](#), p. 8) after important amendments to the federal Acts in 2006 discussed below, means licences issued under the RIHE Act permit research into, and a clinical trial of, MD throughout Australia except in Western Australia.⁶

The PHCR Act creates a series of prohibitions. The most significant is its prohibition of the deliberate creation of embryos for research purposes, by fertilisation of an egg by sperm (s 12). Other prohibitions relevant to MD include those against combining more than two peoples' DNA in an embryo (ss 13 and 23) and prohibiting intentional heritable changes to the human genome (s 15). Placing prohibited embryos into a woman is also an offence (s 20). The RIHE Act creates a licensing regime for the creation and research use of human embryos, provided those embryos are excess ART embryos or created by means other than by fertilisation (such as by nuclear transfer).⁷ As considered below, both these Acts have now been amended to permit MD.

A two-stage model is used for MD's introduction. As Ludlow and Newson explain, this begins with a pilot clinical trial expected to last 10–12 years and then moves to broader clinical use, provided certain prerequisites are satisfied ([Ludlow and Newson 2022](#), p. 1143). Those prerequisites include the demonstration of the safety, efficacy and clinical utility of MD by the clinical trial permitted during stage 1. Two regulatory approaches new to Australian embryo research regulation are used in this model. First, rather than requiring Parliamentary approval to amend the legislation if and when those prerequisites are met, Maeve's Law amendments mean that the move to the second stage instead requires approval by the federal Health Minister based on expert recommendations. Enactment will then occur via regulations, which, although tabled in Parliament where they can be

⁴ Maeve's Law passed in the House of Representatives on 30 November 2021 and Senate on 30 March 2022.

⁵ Northern Territory does not have such legislation in place. Legislation in other jurisdictions is as follows: *Prohibition of Human Cloning for Reproduction Act 2002* (Cth), *Research Involving Human Embryos Act 2002* (Cth); *Human Cloning and Embryo Research Act 2004* (ACT); *Human Cloning for Reproduction and Other Prohibited Practices Act 2003* (NSW), *Research Involving Human Embryos (New South Wales) Act 2003* (NSW); *Research Involving Human Embryos and Prohibition of Human Cloning for Reproduction Act 2003* (Qld); *Prohibition of Human Cloning for Reproduction Act 2003* (SA), *Research Involving Human Embryos Act 2003* (SA); *Human Cloning for Reproduction and Other Prohibited Practices Act 2003* (Tas), *Human Embryonic Research Regulation Act 2003* (Tas); *Research Involving Human Embryos Act 2008* (Vic), *Prohibition of Human Cloning for Reproduction Act 2008* (Vic); *Human Reproductive Technology Act 1991* (WA).

⁶ Western Australia's legislation (*Human Reproductive Technology Act 1991* (WA)) was not updated following the 2006 amendments. This caused the WA legislation to lose its status as a corresponding state law and prevented all research on human embryos in WA involving new and emerging technologies ([Ministerial Expert Panel on Assisted Reproductive Technology and Surrogacy 2023](#), pp. 18–19).

⁷ Nuclear transfer involves the insertion of a nucleus of a cell into an ovum from which the nuclear material has been removed ([International Society for Stem Cell Research 2021](#), p. 64).

disallowed, do not require Parliamentary debate before coming into effect. This makes the move from stage 1 to stage 2 much quicker and possibly less divisive than if an amendment of the principal Acts was needed. While this approach was used in the United Kingdom for the introduction of clinical MD,⁸ this is the first use of delegated legislation to make significant changes to Australia's embryo research regulatory framework.

A second novel regulatory technique involves using a clinical trial at stage 1 to ensure that regulatory responsibility for MD remains with the national medical research regulator, the National Health and Medical Research Council (NHMRC). Alternative possible regulators of MD were existing state authorities responsible for the regulation of ART in their own jurisdictions or a new federal body created particularly for the purpose. While MD is still in its experimental phase, giving responsibility for oversight to the NHMRC takes advantage of its experience and expertise in the regulation of embryo research and clinical trials. It also avoids creating a new federal regulatory body such as the Human Fertilisation and Embryology Authority (HFEA), the United Kingdom's central regulator of both ART and embryo research. Australia does not have an existing equivalent to HFEA. Instead, ART regulation in Australia comprises legislation in four states⁹ together with the NHMRC Ethical Guidelines on the use of assisted reproductive technology 2017 (updated 2023) (NHMRC ART Guidelines) and professional codes of conduct that apply in all Australian jurisdictions.

More importantly, classification as research for the purposes of the RIHE Act ensures that the national regime is the relevant regulatory framework. This avoids the need to amend state ART legislation before stage 1 could commence, giving Australians more timely access to MD. However, any move to stage 2 will likely require regulatory responsibility to shift from the embryo research regulatory framework to that around ART clinical practice. State ART legislation is not consistent throughout Australia, and although the NHMRC ART Guidelines have already been updated following Maeve's Law, legislative amendment by four state Parliaments could take considerable time ([Australian Government Department of Health 2021a](#), pp. 7, 8; [Commonwealth House of Representatives 2021](#)).

An Australia-wide consortium led by Monash University has been funded by the Federal Government and involved organisations to conduct the MD pilot program called the mitoHOPE (Healthy Outcomes Pilot and Evaluation) Program ([Butler 2023](#)). This team is now developing the required protocols, seeking necessary licences and taking expressions of interest from people considering participating in the pilot trial. As well as conducting a clinical trial, mitoHOPE includes a research program to refine and continue to improve available MD approaches. When can and should MD be used in Australia after Maeve's Law? The controls on access and the Australian public's attitudes to possible uses are considered in the next section.

4. Access to MD and Public Attitudes to Its Use

The regulatory frameworks for MD in Australia and the United Kingdom control access to MD, enabling its use only in particular circumstances. Laboratories and clinics undertaking MD must be licensed, and for clinical use, the intending parent must be approved. In Australia, licences and approvals are granted by a pre-existing expert committee within the NHMRC, the Embryo Research Licensing Committee, the powers and membership of which have been expanded for this purpose ([Australian Government Department of Health 2021a](#), Appendix 1). The regulatory tools used to enable access to MD include assessment of the risk of disease inheritance (a particular risk of inheritance of predisposition to mitochondrial diseases), the type of disease that may be inherited (a significant risk that the mitochondrial disease would result in serious disease or medical condition), and whether

⁸ Relevant legislation in the United Kingdom (*Human Fertilisation and Embryology Act 1990* c 37) was amended in 2008 to allow enactment of regulations at a later date to allow clinical MD. Such regulations were passed in October 2015.

⁹ *Assisted Reproductive Technology Act 2007* (NSW), *Assisted Reproductive Treatment Act 1988* (SA), *Assisted Reproductive Treatment Act 2008* (Vic), *Human Reproductive Technology Act 1991* (WA).

there are appropriate alternatives to MD (such as embryo selection) and counselling (RIHE Act s 28P(4)). Clinical and diagnostic information needed by the expert committee to assess these matters are being developed, as is a protocol for monitoring any children born after the use of MD.

These controls reflect that the technique's use in Australia is aimed at minimising the risk of passing on genetic diseases caused by mutations in the mitochondrial DNA (mtDNA) rather than treating intractable infertility or creating genetic kinship ties in non-heteronormative families (RIHE Act s 28P). This is also the case in the United Kingdom. Nevertheless, as noted above, MD has been used as an infertility treatment in other countries (Japan and Greece) despite the lack of scientific evidence of its effectiveness for that purpose ([International Society for Stem Cell Research 2021](#), p. 42).

Public consultations on MD undertaken around the world have largely excluded these broader possible uses. Public consultation on MD undertaken by the Nuffield Council on Bioethics in the United Kingdom excluded alternative uses from the consultation's scope ([Nuffield Council on Bioethics 2012](#), p. xv). Similarly, the 2018 public consultation undertaken by the Singapore Bioethics Advisory Committee was limited to the use of MD to prevent heritable mitochondrial disorders ([Singapore Bioethics Advisory Committee 2018](#): [1] and [51]).

In Australia, opportunities for public comment have also largely been limited to MD use for the prevention of heritable mitochondrial disease (e.g., [Australian Senate Community Affairs References Committee 2018](#)). Following calls by mitochondrial disease community groups to legalise MD in Australia after legalisation in the United Kingdom ([Dow and Cunningham 2017](#)), a 2018 Senate committee offered qualified support for the clinical use of MD. Focused on MD use to prevent mitochondrial disease, the committee called for further public and expert consultation ([Australian Senate Community Affairs References Committee 2018](#), recommendations 1 and 2). The consultation was undertaken through a series of activities managed by the NHMRC in 2019.

The final report on community consultation notes that a citizens' panel supported the introduction of clinical MD ([Australian Government NHMRC 2020a](#), Appendix E). The most significant reasons for that support focus on the benefits of avoiding mitochondrial disease rather than other uses, including that MD offers people at risk of mitochondrial disease the opportunity to conceive healthy, genetically related children and secondly, MD assists in preventing children from being born with mitochondrial disease, preventing suffering and untimely death. For families, an option to use MD to help break the cycle of mitochondrial disease, with the consequential benefits of reducing emotional trauma and improving mental health and well-being, was another reason for support. A fourth significant reason for the panel's support of MD was the reduction in community costs of providing healthcare and disability support to people affected by mitochondrial disease and their families.

Public comments were later sought on the first public draft of Maeve's Law. These were summarised by the Government as showing that MD support was based on the right of a child to the highest attainable standard of health, prevention of disease and disability, promotion of choice and reproductive freedom and reduced burden of disease for the community ([Australian Government Department of Health 2021b](#), p. 2).

On the other hand, objections to MD's introduction were related to the newness of the science, ethical concerns about its use and public funding of it. However, and importantly for future technologies that avoid the destruction of embryos, the key ethical issue identified by opponents of MD was the creation and destruction of human embryos. These objections to MD were reflected in the Parliamentary debates on Maeve's Law, discussed below after considering how Maeve's Law reformed the law to permit MD.

5. Road to Legalisation

The many differences between Australia and the United Kingdom's roads to MD legalisation reflect differences in governance and culture between the two countries. Australia

has a long history of prohibiting embryo research. In contrast, the United Kingdom has a longstanding, liberal attitude to supporting licensed embryo research to enable scientific developments including the creation of embryos by fertilisation for research purposes (Dimond and Stephens 2023, pp. 88–89). Contrasting events during the creation of the embryo research regulation in both countries illustrates this. A 1998 expert report on the United Kingdom's law (*Human Fertilisation and Embryology Act 1990*) recommended permitting research (but not clinical) licenses for the use of new techniques to secure potential benefits including the development of therapy for mitochondrial diseases (United Kingdom Department of Health 2000). New regulations (*Human Fertilisation and Embryology (Research Purposes) Regulations 2001*) reflected those recommendations. Amendments to the legislation in 2008 (*Human Fertilisation and Embryology Act 2008*), allowed the clinical use of these new therapies, provided certain prerequisites were met. In contrast, a 2001 expert report in Australia, despite referring to the same techniques intended to address mitochondrial diseases as the earlier UK report, recommended the prohibition of such research (*Human Cloning: Scientific, Ethical and Regulatory Aspects of Human Cloning and Stem Cell Research 2001*: [10.86]). The Australian Parliament adopted that recommendation in its 2002 legislation. Even after reforms in 2006, research opportunities into MD in Australia remained very limited. Most significantly, even after the 2006 amendments Australia's embryo research legislation continues to prohibit the creation of embryos for research purposes by fertilisation of an egg by sperm. MD pursuant to licences permitted by Maeve's Law is the first exception to this. Additional existing legislative provisions, noted above, that create other offences relevant to MD also needed to be amended. But rather than repealing these provisions, Maeve's Law creates exceptions in limited circumstances (essentially where an MD licence is granted). This approach of using exceptions to avoid making wider changes to existing regulations could be adopted for future technologies.

The reforms made to the United Kingdom's legislation in 2008 also enabled the United Kingdom to respond more quickly to promising therapies developed by the fast-moving field of embryo research that had been missing in Australia until Maeve's Law. For Australia, there has been a long reluctance to permit even embryo research, and legislative review has only occurred after strong political pressure, even where review has been required by the legislation itself (Ludlow 2020). Before Maeve's Law, there had been only two legislative reviews of embryo research regulation since its introduction in 2002 (*Legislation Review: Prohibition of Human Cloning Act 2002 and the Research Involving Human Embryos Act 2002*. Australian Government 2005; *Legislation Review: Prohibition of Human Cloning Act 2002 and the Research Involving Human Embryos Act 2002*. Legislation Review Committee, Australian Government 2011) and one round of amendment. The earliest of these had recommended that MD research be licensable, but this recommendation was not adopted, and no explanation for this was provided by the Government.

Maeve's Law also introduces a new Part 2 Division 4A into the RIHE Act. Under this, licenses can be issued in the circumstances described in the legislation. This controls access as described above and limits the use of MD for approved purposes. Other regulatory amendments made by Maeve's Law include aligning a child's right to know donors' identity with usual state regulations on parentage and amending other related legislation, including removing children conceived with the assistance of MD from the scope of Australia's legislation on genetically modified organisms.

Importantly, using exceptions to the legislative prohibitions and introducing a new strict licensing regime to regulate MD avoided the need to open wider debates around Australia's arguably outdated legislation on embryo research. This is reflected in the legislative obligation to review the Maeve's Law amendments within seven years of enactment (PHCR Act s 25; RIHE Act s 47B), but lack of obligation to consult with the public or to review the rest of the legislation even though science in the field is rapidly developing. So, what is behind Australia's reluctance to permit embryo research? This is considered in the next section.

6. Reasons for Reluctance to Permit Embryo Research

Concerns of today's public and Parliamentarians around embryo research were demonstrated in their discussions of the two most developed forms of MD, pronuclear transfer (PNT) and maternal spindle transfer (MST). These are contrasted in Table 1. In both forms, eggs from two people are used and there is a transfer of the intended mother's nuclear DNA to an enucleated donor egg. But there is a difference in the timing of the transfer depending on which form of MD is used.

Table 1. Comparison of PNT with MST.

Technique	PNT Reconstructs embryo, requiring the destruction of a second fertilised egg	MST Reconstructs egg, which is then fertilised
Legal status prior to Maeve's Law	Limited research permitted	Prohibited
Legal status in Australia after Maeve's Law	Yes	Yes
Australian Parliamentary attitude	More controversial	
Clinical use in the UK	Yes	Yes
First 'MD baby' (USA)	No	Yes
Legal status in the USA	No	No
Legal status in Japan	No	Yes
Clinical use in Greek trial	No	Yes
Clinical use in Ukraine	Yes	No

In MST, transfer of the intended mother's nucleus occurs before the eggs are fertilised, creating a reconstructed egg, which is then fertilised. In PNT, the transfer of nuclear DNA occurs after the fertilisation of both eggs, creating a reconstructed embryo. However, despite MST being less controversial to some because changes are to an unfertilised egg, research using MST was not licensable in Australia before Maeve's Law. This is because the timing of the transfer of nuclear DNA means that MST involves the creation of a research embryo through the fertilisation of an egg (albeit a reconstructed egg). Unlike in the United Kingdom, where licensed creation of embryos for research purposes by fertilisation was permitted even before amendments to permit clinical MD use, this was and remains strictly prohibited in Australia except where the MD exception applies.

In contrast, research using PNT (where the second fertilised egg is destroyed and the remaining embryo contains DNA of more than two people) was licensable in Australia before Maeve's Law, because PNT is considered close enough to techniques used in cloning to fall within the 2006 legislative amendments, which allowed the licensed creation of embryos for research purposes, provided that fertilisation was not used in that creation. During the passage of Maeve's Law, an important flashpoint for opponents was an objection to the deliberate creation of fertilised eggs (embryos) intending that they be destroyed. For example, members of the lower house objected to MD because it involves the creation of embryos solely for the intended purpose of destruction ([Commonwealth Parliamentary Debates, House of Representatives, Bills. 'Mitochondrial Donation Law Reform \(Maeve's Law\) Bill 2021' 30 November 2021a](#), Joyce, Barnaby (Member for New England) p. 11164).

There was also a stronger objection to PNT rather than MST despite the reality that PNT research was already permitted in Australia. For example, during Parliamentary debates in the lower house, one Parliamentarian explained that although she supported MST, she did not support PNT, which requires the intentional creation of an embryo to destroy it ([Commonwealth Parliamentary Debates, House of Representatives, Bills. 'Mitochondrial](#)

[Donation Law Reform \(Maeve's Law\) Bill 2021' 30 November 2021a](#), Wicks, Lucy (Member for Robertson) p. 11173).

As part of opposition to Maeve's Law, amendments to the bill were introduced by Kevin Andrews, a member of the lower house ([Commonwealth Parliamentary Debates, House of Representatives, Bills. 'Mitochondrial Donation Law Reform \(Maeve's Law\) Bill 2021' 30 November 2021a](#), Andrews, Kevin (Member for Menzies) p. 11189). These amendments proposed that forms of MD involving deliberate destruction of embryos, such as PNT, be removed from the bill. Ultimately the Andrews amendments were rejected by a large majority (92 v 29). Interestingly, Andrews had led the 2001 expert committee that constructed Australia's original embryo research regulatory framework prohibiting all forms of MD. This raises the question of whether the proposed amendments show that his attitudes (and perhaps those of the people he represents) have changed. Alternatively, the proposed amendments may have been a tactic to slow down the clinical use of MD given that PNT is the most advanced form of MD. Although MST has been used in Greek and Japanese clinics as well as the conception of the first MD baby in the USA, it is PNT that is used in the Ukraine clinic and the licensed clinic in the United Kingdom, which has been the subject of most scientific development.

Setting the explanation aside, Maeve's Law expands a regime where limited PNT research was already permitted in Australia. Because PNT does not create embryos using traditional fertilisation, research into that technique was already licensable following the 2006 amendments. Those amendments permit the licensed creation of embryos for research through ways other than fertilisation. But Maeve's Law amendments mean that Australian researchers are no longer limited to excess ART embryos donated to research or non-traditional embryos (that is, those created other than by fertilisation of an egg by sperm). Restrictions to such embryos have effectively prevented research in Australia because excess ART embryos are too developed for meaningful use. However, the amendment to permit the creation of embryos by fertilisation for research purposes applies only to MD.

Both MST and PNT can now be licensed for use in reproduction during the pilot trial, although a clinical trial licence is needed before embryos can be transferred to a trial participant. Both pre-clinical research and training and clinical trial research and training licences are needed before a clinical trial licence can be granted. Three other forms of MD can be the subject of licenses permitting pre-clinical research and training (first polar body transfer, which, like PNT, is undertaken on fertilised eggs; second polar body transfer and germinal vesicle, which, like MST, involve unfertilised eggs), but new regulations will be needed before they are also licensable for reproductive use. As with the transition from stage 1 to stage 2 after the pilot trial, the change to introduce other forms of MD for reproductive use requires only the enactment of regulations rather than a legislative amendment. Newer but currently unknown techniques can also be added when proven safe and effective using the same process. These steps assist in future-proofing the amendments by responding more quickly to scientific advances and, once again, minimise Parliamentary debate around changes to embryo research regulation.

7. Discussion

This section considers the insights to be drawn from Australia's regulatory changes to permit MD and the debates that accompanied them. Ethical concerns raised by MD have been well studied in the literature and are not the focus of this paper (see, e.g., [Bredenoord et al. 2011](#); [Nuffield Council on Bioethics 2012](#); [Baylis 2013](#); [National Academies of Sciences, Engineering, and Medicine \(NASEM\) 2016](#); [Palacios-González 2016, 2017](#); [Appleby et al. 2017](#); [Singapore Bioethics Advisory Committee 2018](#); [Scott and Wilkinson 2017](#); [Sparrow et al. 2023](#)). Instead, the focus of this section is the regulatory techniques used to permit MD in the face of objections, particularly concerns around embryo destruction, use of three genetic sources in the creation of an embryo, changes to the human germline, genetic modification and selection of embryos. Each of these is now considered.

As noted in Section 6, a key objection to MD for Australians was the creation and destruction of embryos (as to the moral distinction between forms of MD on this basis, see [Palacios-González 2017](#); [Singapore Bioethics Advisory Committee 2018](#)). Despite this, MD has been legalised, largely justified on the basis that MD offers intending parents the opportunity to have a healthy, genetically related child ([Australian Senate Community Affairs References Committee 2018](#), Recommendation 1). The regulatory tools discussed in Section 4 confine MD use to enabling the birth of healthy, genetically related children but nevertheless also permit a technology that for the first time allows the creation of embryos in Australia with the intention that they will be destroyed. The strict licensing regime introduced by Maevé's Law may provide some comfort to opponents that there is sufficient oversight over that creation but does not remove all such concerns.

Similarly, when we focus on concerns around MD's use of a third person's biological material in the creation of a child, the legalisation of MD means that such concerns are not sufficient to prevent its use. Nevertheless, the use of a third person's material makes modern forms of MD unacceptable for some cultural groups in Australia. Ishii has suggested that the absence of a third person's biological material was significant in the use of the older form of MD—cytoplasmic transfer or autologous MD rather than nuclear transfer—in Taiwan, China and Japan to enable genetically related offspring without using donor eggs ([Ishii 2023](#)). However, these older forms of MD or other technologies such as HHGE that do not need a third person's material currently lack scientific support for their effectiveness and safety. Furthermore, and more relevantly here, they cannot be used in Australia because of the regulations' careful delineation of the MD techniques that are available for licensing.

While having noted the lack of current scientific support, however, some emerging technologies offer other advantages compared with MD. The development of genome editing techniques such as CRISPR to make targeted changes to DNA to repair genetic mutations is an example here. Genome editing is significant for mitochondrial disease because it may enable a broader group of diseases to be addressed without the destruction of embryos. CRISPR genome editing has already been used on human embryos, resulting in the controversial birth of at least two children in China ([Cyranoski 2020](#)). Next-generation techniques, such as base editing to change single bases in the genome, are improving outcomes ([Thomas et al. 2019](#); [Yi et al. 2023](#)) with other next-generation genome editing techniques, such as prime editing, offering the opportunity to introduce new DNA without double-stranded breaks of the recipient DNA, which are known to increase the risk of unnecessary mutation ([Anzalone et al. 2019](#)).

Genome editing offers the opportunity to address mutations in the *nuclear* DNA that cause approximately 80% of mitochondrial disorders, severely affecting babies and children, which cannot be addressed by MD (National Academy of Sciences, p. 26). However, it is unlikely that genome editing would replace MD in addressing diseases caused by *mtDNA* mutations, given that an egg may have up to 500,000 copies of mtDNA, the majority of which would need to be edited to avoid diseases ([Australian Government NHMRC 2020b](#)). Nevertheless, genome editing could be used together with MD to shift the percentage of mutated mtDNA in an egg or zygote (known as heteroplasmy) to prevent the transmission of mitochondrial diseases caused by mtDNA mutations by, for example, selectively inhibiting replication of mutant mtDNA or selectively cleaving mutant mtDNA ([Hashimoto et al. 2015](#); [Bacman et al. 2018](#)). Alternatively, the cells of specific tissues of those with mtDNA disease, which contain significantly fewer copies of mtDNA than an egg, are a likely subject of genome editing if such cells can be targeted ([Australian Government NHMRC 2020b](#)).

Regarding mitochondrial diseases caused by nuclear DNA mutations, no country has yet decided that it would be appropriate to move forward with clinical applications of genome editing to germ cells (that is, eggs, sperm and embryonic cells) ([National Academy of Sciences 2020](#), p. 1), but that may change, at least for some countries. As an expert at the March 2023 international proceedings on human genome editing convened by the UK Royal Society, UK Academy of Medical Sciences, US National Academies of Sciences

and Medicine and The World Academy of Sciences, explained '[c]ountries that place a premium on the ability to create a family by bearing children could see applications that overcome infertility or enable biological parenthood as promoting human well-being. In those circumstances, countries could have compelling reasons for adapting or changing their laws on heritable human genome editing' (Levy-Lahad 2023, p. 10). International bodies such as the International Society for Stem Cell Research (ISSCR) and the WHO Expert Committee on Human Genome Editing have already begun making recommendations for regulation if unintended deleterious consequences that cause expert bodies to currently counsel against HHGE are overcome.¹⁰ The International Commission on the Clinical Use of Human Germline Genome Editing convened by the US National Academy of Medicine, the US National Academy of Sciences and the UK's Royal Society is focused on creating a framework for scientists, clinicians and regulatory authorities to consider when assessing potential clinical applications of HHGE, rather than the issue of whether clinical use of HHGE should occur (National Academy of Sciences 2020, p. 23). These regulatory proposals may look to regulatory responses to MD to inform their approach.

A third concern explored in the literature is whether MD is a heritable and/or germline change (see, e.g., UK Department of Health 2014; National Academies of Sciences, Engineering, and Medicine (NASEM) 2016; Newson and Wrigley 2017; Australian Senate Community Affairs References Committee 2018, pp. 79–81; Singapore Bioethics Advisory Committee 2018). Heritable or germline changes are changes to DNA that can be passed on to the next generations. For example, genome editing of germ cells, that is eggs, sperm, or early embryonic cells used in reproduction, will change not only that individual's DNA but that of their descendants, changing what is called 'the human genome'. Genome editing of somatic cells (all other cells besides germ cells), on the other hand, results in changes only to that individual's DNA. Concerns arising whether MD constitutes a germline or heritable change are addressed in the literature (see, e.g., Nuffield Council on Bioethics 2012) but include, for example, concerns related to the potential failure of that change as well as concerns related to their success (Ormond et al. 2017).

In any case, most agree that clinical MD is a heritable change to the human genome. For example, the ISSCR Guidelines address MD in its section on clinical research involving heritable changes to the human genome (International Society for Stem Cell Research 2021, sec. 3.4.8). Similarly, the International Commission on the Clinical Use of Human Germline Genome Editing referred to above describes MD as 'the only technology currently approved anywhere in the world that results in genetic changes that can be inherited' (National Academy of Sciences 2020, p. 24). The UK's Nuffield Council also concluded that MD is a germline change (Nuffield Council on Bioethics) as did the UK Department of Health during its consideration of the regulatory changes in that country (2014).

Relevantly here is the fact that mitochondria are passed down the female line. Mitochondria in the sperm are lost after fertilisation, and the new embryonic cells are populated only by the egg's mitochondria. This has led some, such as an ethics body in the USA, to suggest limiting MD to male embryos because only females pass their mtDNA on to offspring (National Academies of Sciences, Engineering, and Medicine (NASEM) 2016, p. 34). NASEM concluded that limiting MD to male embryos ensured that any significant adverse consequences would not be transmitted irreversibly to future generations via any female offspring. This in effect limited the change to a single embryo in the interest of avoiding a life-threatening disease and addressed objections that heritable modifications are unacceptable, where they may have adverse effects and are unbounded in duration in terms of the number of future individuals affected (National Academies of Sciences, Engineering, and Medicine (NASEM) 2016, p. 94). Similarly, the Singapore Bioethics Advisory Committee considered MD to be germline modification although it and others have noted that a distinction could be made on the basis of whether nuclear or mitochondrial DNA is

¹⁰ For a review of the most significant international reports on HHGE, see (National Academy of Sciences 2020, pp. 20–21).

the subject of change (see also [Australian Government NHMRC 2020b](#); [UK Department of Health 2014](#)). It also considered that selecting male embryos could avoid inter-generational impacts ([Singapore Bioethics Advisory Committee 2018](#)). Importantly, during the passage of Maeve's Law, Australian Parliamentarians used such terminology to indicate they opposed the legalisation of MD, one objecting that permitting MD 'would allow deliberate heritable human germline gene manipulation and transfer' ([Commonwealth Parliamentary Debates, House of Representatives, Bills. 'Mitochondrial Donation Law Reform \(Maeve's Law\) Bill 2021' 30 November 2021a](#), Keogh, Matthew (Member for Burt), p. 11165) and another raising concern about MD creating a blended germline ([Commonwealth Parliamentary Debates, House of Representatives, Bills. 'Mitochondrial Donation Law Reform \(Maeve's Law\) Bill 2021' 1 December 2021b](#), Gillespie, David (Member for Lyne) p. 11301).

The original draft of Maeve's Law included the option for prospective parents to use only male embryos to prevent the re-emergence of mitochondrial disease in future generations. This option was removed in a last-minute amendment in the lower house to ensure the bill's passage. The legislation now instead expressly provides that human embryos created using MD are not to be selected on the basis of sex (RIHE Act s 28Q(1)(d)).

The term 'germline' is not used in Australia's legislation, but the section intended to prevent such changes (PHCR Act s 15) does use the words 'heritable' and 'genome', which are not defined. Scholars have considered the meaning of these terms in the context of the legislation ([Newson and Wrigley 2017](#); [Taylor-Sands and Gyngell 2018](#); [Ludlow 2018](#)), but the approach taken in Maeve's Law avoids answering questions around the boundaries of these terms for the purposes of Australian law. Instead, as discussed above, exceptions to all statutory provisions that may arguably be relevant to MD were inserted by the reforms. The new definition of 'MtD technique' introduced by Maeve's Law uses a term new to Australian embryo research regulation, namely 'modify', when making it clear that intentionally changing nuclear or mt DNA remains prohibited (RIHE Act s 8(c)(i)).

The literature is now using 'germline' to refer to modifications of embryos not intended for reproduction and the term 'heritable' when embryos intended for use in reproduction are modified ([WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing 2021a](#); see contra [Beriain et al. 2019](#)). Furthermore, and more importantly for emerging techniques, the Australian debates around MD show that the distinction between germline (not for reproduction) and heritable (for reproduction) is arguably less significant to the Australian public than the impact of the change caused by the technology on the resulting child. Both Australia's 2018 Senate inquiry and the later NHMRC consultation found that Australians consider it important whether a technology causes 'genetic modification' ([Australian Senate Community Affairs References Committee 2018](#); [Australian Government NHMRC 2020a](#)). These objections were also raised during Parliamentary debates with, for example, MD being described as a form of 'genetic modification' ([Commonwealth Parliamentary Debates, House of Representatives, Bills. 'Mitochondrial Donation Law Reform \(Maeve's Law\) Bill 2021' 30 November 2021a](#), Keogh, Matthew (Member for Burt), p. 11165) and as modifying the genome ([Commonwealth Parliamentary Debates, House of Representatives, Bills. 'Mitochondrial Donation Law Reform \(Maeve's Law\) Bill 2021' 1 December 2021b](#), Zappia, Antonio (Member for Makin) p. 11301).

Related to discussions about whether MD is genetic modification, distinctions are drawn on the basis of how the change is made. International expert bodies and scholars have pointed out that the change in MD is achieved by replacement rather than direct alteration of DNA ([Newson and Wrigley 2017](#); [Singapore Bioethics Advisory Committee 2018](#)). The International Commission on the Clinical Use of Human Germline Genome Editing (National Academy of Sciences, p. 26) has also noted that in MD 'no DNA sequences are directly altered; rather, entire chromosomes are transferred from one egg to another'.

These discussions around how changes are made and what is changed during MD reflect concerns within claims of genetic modification around the control and selection of attributes of the resulting child. Any suggestion that MD enables the future child's

attributes to be selected was largely avoided during Australian public consultation and in Parliamentary materials ([Commonwealth House of Representatives 2021](#), p. 77). This contrasts with the approach in the United Kingdom, which instead emphasised that mtDNA has little to no role in personal characteristics or identity ([UK Department of Health 2014](#); [Savulescu 2015](#); [Harris 2016](#)). This approach was used partly to support the United Kingdom's decision to adopt anonymous mtDNA donation and ensure that egg donors did not have parental status, as well as to address other concerns, such as suggestions that the 'identity' of the resulting child is changed or even selected when MD is used ([Scott and Wilkinson 2017](#) and the sources discussed therein). The absence of these concerns from much of the debates in Australia perhaps illustrates the care by legislators and advocacy groups to distance MD from suggestions of selection. Nevertheless, as Sparrow et al. observed, MD is performed precisely because mtDNA can have such a significant impact on phenotype and life ([Sparrow 2021](#)). MD's legalisation and the justifications given for it indicate that the majority of Australians and their Parliamentarians are willing to dismiss the significance of changing mtDNA in order to have healthy and genetically related children and minimise the risk of serious disease.

Arguably, changes made using other technologies to minimise or remove the risk of a genetic disease could also be acceptable to the Australian public, provided the risk of unintended harm is sufficiently low. But, as the WHO Committee has identified, use for the purposes of enhancement is likely to be the real concern (2021a [53]). If that is the case (as it is likely to be), regulatory tools for accessing the technology, like those used in MD regulation in both Australia and the United Kingdom, provide a useful way to address this. While acknowledging the challenge of drafting such tools, they provide a regulatory solution to the concern that new technology will be used beyond addressing the risks of serious genetic diseases. However, as has also been performed with the legalisation of MD, care must be taken not to suggest that there is a selection or choice regarding the outcomes. The WHO Expert Committee's recommendations around confining the results of HHGE are valuable and could be developed for these purposes. This committee has advised the WHO Director-General on appropriate oversight and governance mechanisms for human genome editing, both at the national and global levels ([WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing 2021a](#); [WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing 2021b](#)). Both the WHO Expert Committee and the ISSCR recommend that to minimise the potential for unintended deleterious consequences, editing should recreate common sequences known to have normal function. The WHO Expert Committee, for example, recommends that alterations made using HHGE 'should recreate a DNA sequence that is common in the relevant population or family, and is associated with normal function of the gene' (2021a [45]; see also [International Society for Stem Cell Research 2021](#), Recommendation 3.4.8.3.2).

8. Conclusions

This paper has considered the regulatory approach to Australia's legalisation of clinical MD. The approach demonstrates a willingness to update long-standing legislation to enable the use of a genetic technology that offers an opportunity for a genetically related child. Importantly, these regulatory changes occurred after the controversial births in China following the use of CRISPR genome editing, unlike the regulatory changes in the UK. Regulations around MD in the United Kingdom have already been considered as a potential model for governance and oversight of HHGE ([National Academy of Sciences 2020](#)). Maeve's Law provides a second useful example of what can be achieved in response to emerging genetic technologies.

Unfortunately, the regulatory approach taken in Maeve's Law means the Australian Parliament avoided definitively answering questions about the scope and meaning of concepts important to other emerging technologies. It also avoided committing to further review of the entire legislative regime, making it more difficult to predict whether and

when other technologies will be similarly treated. It is hoped that future regulatory changes address this, rather than creating additional exceptions. Nevertheless, regulatory controls such as those described above and those in the UK regulations (Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015), around assessment of the risk and seriousness of diseases to ensure that heritable changes to the genome occur only to minimise the risk of serious mitochondrial diseases, provide a useful model for confining the use of other technologies. These, together with the regulatory strategies adopted to speed up the introduction of MD and to future-proof the regulation, will be useful if Australia, or other nations, act to legalise other emerging technologies.

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