

OVERVIEW

Mitochondrial donation is a relatively new scientific advance in the sphere of assisted reproductive technologies. It allows for the replacement of mitochondrial DNA affected by mutations in an egg or zygote by transferring the nuclear DNA into a healthy donated egg that is not affected. The aim of this is to stop the transmission of mitochondrial disease, which is inherited from the maternal line.

In 2015, the British Parliament legalised the clinical use of mitochondrial replacement therapy (MRT). Significantly, these techniques allow for interventions that may be inherited by all subsequent generations of offspring of the person that the modified embryo may grow to be. Further, the embryo created using MRT contains the genetic material of three people.

These international developments raise significant questions about the moral and legal permissibility of MRT, which Western Australia and other Australian jurisdictions must address now in order to moderate undesirable effects and capitalise on positive ones. Clinical use of this technique is currently prohibited under Western Australian legislation, as are some forms of basic research. However, the breadth of that prohibition and the legal consequences of amendment to legalise some or all uses of these techniques is unclear. Further, the normative justification for continuing prohibition or amending the law must be examined in light of the new realities of human genetic modification.

Given the uniquely interdisciplinary nature of our research team, we are able to provide insight across many of the Review's terms of reference. In the following submission, we particularly address points 1, 2, 9 and 11 with respect to the *HRT Act*, as well as point 1 with respect to the *Surrogacy Act*.

Our study also comprises qualitative interviews with scientists, policy makers, disability representatives, and people living with mitochondrial disease. Interviewees are asked to speak to how viable heritable genetic modification techniques are, what ethical issues might be associated with them, what the arguments in favour and against are, and how effective the Australian ethics and policy landscape is in this context. Data collection and analysis is currently underway. However, we present select preliminary findings for the Review's consideration in this submission.

1. B: ETHICAL CONSIDERATIONS, INCLUDING SAFETY AND EFFICACY CONCERNS

1.1 Genetic interventions in assisted reproduction have traditionally been seen as characterised by a moral ‘bright line’ that separates **somatic (non-heritable) from germline (heritable) modifications**. Many see heritable modification as objectionable on grounds of safety and ethics. Mitochondrial replacement therapy sits in an ambiguous position to this distinction, due to the uncertain status of mitochondrial DNA.

There are **notable differences in how the UK, US, and Australia respond to fundamental questions** related to mitochondrial donation. For example, both Australia and the UK treat mitochondrial donation as a kind of germline modification, unlike in the US. Somewhat in contradiction, UK regulation does not treat mitochondrial donation as a form of inheritable *genetic* modification, which they limit to heritable changes to nuclear DNA. We think there is little justification for this limitation to nuclear DNA.

The US have sidestepped the issue of heritability by recommending that only male embryos are selected following mitochondrial donation, to ensure that no modified mitochondrial DNA is later passed on. This effectively nullifies the most widely acknowledged issue with germline modification, that it has roll-on effects for future generations. However, this option requires the sex selection of embryos for non-medical reasons, which is currently not permissible in Western Australia.

We consider mitochondrial donation under the umbrella of ‘heritable genetic modifications’, which we define as genetic changes that can be passed on to subsequent generations.

- However, our interviews suggest mitochondrial donation is not seen as posing the same ‘slippery slope’ risks as, for example, gene editing (eg. using CRISPR-Cas9), which risks being misused to enhance personal characteristics. Our respondents considered mitochondrial donation as more difficult to misuse than gene editing.

1.2 Much of the public debate of mitochondrial donation focuses on the issue of safety; however, these concerns are unlikely to rule out the use of the technology in the longer term.¹ **It is never possible to know in advance whether new reproductive technologies will risk the health of the children born as a result, or their descendants.** The first use of any new reproductive technology will be essentially experimental and risk unanticipated consequences for those children born of it, no matter how carefully it has been tested *in vitro* or in animal models. Presuming that it is implausible to argue that it would *never* be ethical to trial a new reproductive technology, **the real question about risk, then, is: when it is ethical to impose unknown risks on future children?**

- Interviewees for our project agree that ensuring the **safety of mitochondrial donation** is paramount, and also point out that some degree of uncertainty at the time that this technology enters clinical use will be unavoidable. One interviewee suggested that a licensing model similar to that used in the UK would help to ensure a sound and well regulated environment for mitochondrial replacement therapy in practice.

In determining the appropriate balance of risks and benefits, mitochondrial donation has to be assessed in the **context of existing (medical) options for potential users**, ie couples affected by mitochondrial disease who are wish to reproduce and seek to ensure that their child is not affected by mitochondrial disease. Existing reproductive options, such as Preimplantation Genetic Diagnosis (PGD), may be objectionable to some prospective parents on religious grounds, since it entails the destruction of embryos. Moreover, PGD is not reliable for the detection of mitochondrial disease, since PGD tests one cell of a very early embryo, and mitochondrial diseases may not appear in all cells. Nevertheless, there are safe reproductive options available, such as the use of donor gametes (eggs), or in some circumstances, adoption. The promotion of mitochondrial donation as the only option for prospective parents affected by these conditions is premised on the unquestioned value of genetic parenthood (see further on this below).

We believe it is important to maintain transparency about the **therapeutic efficacy** of mitochondrial donation, as well as in discussions of **access** to the technology. Mitochondrial diseases can be caused by mutations in nuclear DNA that control mitochondria, as well as mitochondrial DNA. While the latter of these is inherited maternally, the former follows Mendelian patterns of inheritance. Further, in some cases, mitochondrial disease results from new (de novo) mutations in genes and occurs in people without any family history of the disease. It is important in

discussions of mitochondrial donation that its capacity to ‘cure’ mitochondrial disease is not overstated. In fact, this technology only addresses mitochondrial disease that arises from mitochondrial DNA. There are also efficacy and safety issues to consider here, such as the current incomplete understanding of the interaction of donor DNA with nuclear DNA.

For mitochondrial donation to be performed as safely and ethically as possible, the whole of a patient’s medical team (including specialists, general practitioners, genetic counsellors, etc) will need regularly updated **training and education about the technology**. As mitochondrial donation would enter the clinical sphere as a novel medical technology, it should not be assumed that this expertise would be currently available. Potential introduction of the technology also requires developing expertise in the clinical setting in advance.

1. 3 Other ethical considerations beyond safety and efficacy also arise with mitochondrial donation. One concern is the relatively unquestioned moral value of its therapeutic purpose. The perceived benefits and moral permissibility of mitochondrial donation and other genetic modification technologies typically rest on their utility in correcting genetic disorders in human embryos. Indeed, it has been argued that it would be morally negligent not to use genetic technologies for this reason where possible.²

However, the identification of a condition as a disability or disease, and thus as eligible for treatment, is informed by cultural and medical conceptions of normality. While these may have a profound impact on the experience of living with a condition, they do not necessarily determine that experience.³ The perspectives of persons living with disabilities may challenge the “therapeutic imperative” that drives much discussion of inheritable genetic modification.⁴ In fact, inheritable genetic modification raises questions not only about the first-person valuation of life with disability, but wider societal valuations as well.

Disability scholars have argued that using genetic selection technologies constitutes a form of **discrimination against people with disabilities** insofar as it ‘sends a message’ to persons with disability that their lives are not worth living.⁵ This expressive characteristic may also be born out by inheritable genetic modifications, including mitochondrial donation. Further, inheritable genetic modification also raises the possibility of a world in which some genetic conditions no longer exist. For most commentators, this seems an unmitigated good. But from another perspective, it raises questions about the social value of disability and the loss entailed in its elimination, and the correlative reduction in genetic diversity. Garland Thomson has recently made a case for the importance of conserving disability, while Sparrow has criticized this idea.⁶

The “therapeutic imperative” is underpinned by a **conception of disability and disease** that sees it as necessarily a harm that ought to be prevented or avoided.⁷ It is often taken for granted in contemporary debates that procreators should be at liberty to make decisions about reproduction – including when, how, with whom – based on their own values. But typically this autonomy is limited to actions that do not cause significant harm to others, prompting questions about what constitutes harm, and what is significant enough as to place limits on liberty. These questions are especially complicated in regards to reproduction, where harm may be considered either ‘person affecting’ or ‘non-person-affecting’. This distinction emerges from the so-called ‘non-identity problem’, which indicates that, so long as a congenital condition is not so bad as to make life not worth living, then no harm is done to the person born with that condition (since otherwise they would not be born at all). In relation to mitochondrial donation, this raises a question about the extent to which couples affected by mitochondrial disease who are seeking to reproduce would be obliged to or feel pressured to use the technology of mitochondrial donation if it were available.

While there is currently no data about **attitudes toward mitochondrial donation** from persons with mitochondrial disease themselves in Australia [such data will be compiled as part of this project], there is some data from the UK. This suggests that attitudes toward mitochondrial donation of women affected by mitochondrial disease is varied. For instance, while some women were not opposed to making mitochondrial donation available, they expressed reluctance about using the technology themselves. This was because of concerns about safety and not wanting to undertake what is essentially an experimental procedure, or a more general sense that mitochondrial donation overly technologized pregnancy. For these reasons, women sometimes expressed a preference for safer alternative options such as donated gametes and/or adoption.⁸

1. 4. The prospect of the clinical use of mitochondrial donation has generated significant concern about the genetic parenthood of children created using the technique. There has been much media and bioethics discussion of ‘3-parent babies’, and the implications this might have for the resulting children and for ideas of parenthood. Some commentators worry that, if used widely, such techniques would precipitate a rupture in familial and personal narratives, possibly in ways that do damage to personal identity, especially to the children born of the technology.⁹

However, this line of thinking remains underdeveloped, and the normative implications of such a rupture in narratives of identity are unclear.

Further, it remains unclear whether mitochondrial donors should be considered parents, at least in a minimal genetic sense. UK legislation treats mitochondrial donors as equivalent to organ, rather than gamete (egg or sperm), donors. This means that they have no rights to a parental relationship with the recipient of their mitochondrial DNA (or parental obligations to them). However, the reasoning behind this decision is inconsistent (see Ludlow, 2018 for a full discussion): it hinges on the supposedly inconsequential status of mitochondrial DNA, at the same time as mitochondrial donation is seen as necessary because of the significant consequences of mitochondrial DNA.¹⁰ Other analysts, including the US National Academies and the Nuffield Council of Bioethics, acknowledge that mitochondrial DNA might also contribute to personal characteristics in ways that are not yet well understood.

Concerns about the capacity of assisted reproductive technologies to **“confuse and disrupt” our understanding of kinship, parenting and familial identity** have been central to bioethical discussion of genetics for some time. This capacity is further increased with mitochondrial donation, since it not only raises questions about the value of genetic relatedness, but also fundamentally disrupts our understanding of what it entails (ie. two genetic progenitors rather than three). While it has long been recognised that being a genetic progenitor is not necessary to establish parenthood (as in adoption), it is something else again to suggest that being a genetic progenitor is not sufficient to establish genetic parenthood.

Establishing parenthood has significant implications, both ethical and legal. For instance, recent interventions consider the obligations parents acquire in bringing children into the world.¹¹ It may be that inheritable genetic modification technologies extend the obligations that parents have to their own children in various ways. For instance, if a genetic modification affects not only the resultant child, but also that child's offspring, what, if any, obligations do the parents have to the 'more than next' generation? Legally, the status of parenthood may potentially allow children born of mitochondrial donation to find out information about their donor. This is discussed further in the following section of this submission.

Consideration of these moral topics has direct bearing on the justification of legal frameworks that regulate research and clinical application of technologies using human embryos and assisted reproductive technologies in Western Australia. However, the relevant legislation and NHMRC Guidelines were developed in a context where inheritable genetic modification technologies such as CRISPR-Cas9 and mitochondrial replacement therapies were not yet a scientific or clinical reality. In light of recent technological and legal developments, a question arises as to whether, and if so how, Australian and State legislation ought to be reformed in order to meet this new reality. Our ongoing research will address this question through consideration of the moral issues at stake in the inheritable genetic modification of humans, and the consequences of these for potential legal reform.

E: LEGAL FRAMEWORKS AND CHANGES THAT WOULD BE REQUIRED IF MITOCHONDRIAL DONATION WAS TO BE INTRODUCED IN WESTERN AUSTRALIA

If legalised, regulation of **mitochondrial donation will span federal (and corresponding state) regulation of embryo use and state regulation of clinical assisted reproductive technologies** in a novel fashion. **Multiple governance bodies will be implicated in any attempt to legalise clinical use of mitochondrial donation.**

Western Australia's current regulatory frameworks for dealing with embryo use and assisted reproductive technologies was developed in a context where mitochondrial donation was not yet clinically feasible. Consequently, a question arises about whether this framework is adequate to meet this new reality.

2.1 Legality of Technique's Use - We draw the Review's attention to a publication by Ludlow (2018), which analyses possible governance responses to mitochondrial donation, noting in particular the following:

- The most straightforward legal route would be to treat mitochondrial DNA as separate from the human genome. This approach parallels the UK process and resonates with existing legislation of embryos and cloning, as well as current legal definitions of genetic material and the genome, which are highly opaque. There are alternative approaches but these raise their own, not necessarily insurmountable, challenges:

- Repeal the prohibition on heritable genetic changes or include an exception allowing the technique, which may contravene UNESCO's Universal Declaration on the Human Genome and Human Rights, to which Australia is a signatory; or
 - Revise regulation around embryo sex selection to enable the technique's use only in male embryos, which could attract opposition given the recent public rejection of sex selection in family planning contexts.
- Key definitional issues which must be resolved before legislation can be developed around mitochondrial donation include:
 - whether this technology constitutes genetic modification / gene technology according to current definitions;
 - whether it can be considered either germline or somatic modification, and whether this distinction remains useful; and
 - how mitochondrial and nuclear DNA should be defined and regulated.
 - A regulatory framework for clinical use will need development, addressing governance issues such as access to the technique for reasons other than to address mitochondrial disease.

2.2 Parentage and Kinship - We draw the Review's attention to a publication by Ludlow (2015), which summarises current legislation in Western Australia and across Australian federal and other state jurisdictions regulating genetic and legal parentage through the lens of mitochondrial donation, noting in particular the following:

- **Parentage and kinship in Australia is regulated at the state level.** By current definitions in the *HRT Act*, *Surrogacy Act 2008* and *Artificial Conception Act 1985*, a mitochondrial DNA donor would likely be considered to be the resulting child's biological and genetic, though not legal, parent. In such an arrangement, the child would have access to information on the donor's identity.
- Mitochondrial donation may be used in the conception of a child, who is then to be gestated by a surrogate. The *Surrogacy Act* requires that donors whose gamete (egg) is to be used for conception sign a written agreement before pre-approval of the surrogacy arrangement. Consideration is needed of the appropriateness of the consequential extension of this requirement to mitochondrial donors because of the mitochondrial donor's classification as a gamete donor.
- Western Australian law (namely, pursuant to the *HRT Act*) requires that the genetic origins of the resulting child not be deliberately confused. This does not prevent mitochondrial donation but constrains the implantation of more than one embryo into one woman where mitochondrial donation has been used.

There are lessons to be taken from the development of legislation around mitochondrial donation in other countries. For example, the UK, US, and Australia differ in many critical respects: the UK treats mitochondrial donation as germline modification, yet UK regulation does not consider it to be *genetic* modification. UK legislation also positions mitochondrial DNA donors as more analogous with organ rather than gamete (egg or sperm) donors, redacting any rights to a parental relationship with the resulting child. However, the reasoning behind these decisions is inconsistent (see Ludlow 2018 for a full discussion), and does not align with the views of some international bodies, for example the US National Academies and the Nuffield Council of Bioethics.

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- ² Harris, J. 2007. *Enhancing Evolution: The Ethical Case for Making Better People*. Princeton: Princeton UP.
- ³ Warren, N. and L. Manderson. eds. 2013. *Reframing Disability and Quality of Life: A Global Perspective*. Springer: Dordrecht.
- ⁴ Scully, J.L. 2006. IGM and Disability: Normality and Identity. In *The Ethics of Inheritable Genetic Modification: A Dividing Line?*. J.E.J. Rasko, G.M. O'Sullivan, and R.A. Ankeny (eds). Cambridge: Cambridge UP: 175-192.
- ⁵ Parens, E. and A. Asch. 2000. *Prenatal Testing and Disability Rights*. Washington D.C: Georgetown UP.
- ⁶ Garland Thomson, R. 2012. The Case for Conserving Disability. *J Bioeth Inq.* 9(3): 339-55. Sparrow, R. 2015. Imposing Genetic Diversity. *Am J Bioeth.* 15(6): 2-10.
- ⁷ Mills, C., 2011. *Futures of Reproduction: Bioethics and Biopolitics*. Dordrecht: Springer.
- ⁸ Herbrand, C. 2017. Mitochondrial replacement techniques: who are the potential users and will they benefit? *Bioethics*. 31(1): 46-54.
- ⁹ Baylis, F. and J.S. Robert, 2006. Radical Rupture: Exploring Biological Sequelae of Volitional Inheritable Genetic Modification. In *The Ethics of Inheritable Genetic Modification: A Dividing Line?*, J.E. Rasko. et.al, eds. Cambridge: Cambridge UP: 131-148.
- ¹⁰ For a fuller discussion, see Ludlow, K. 2018. The policy and regulatory context of US, UK and Australian responses to mitochondrial donation governance. *Jurimetrics*. 58: 247-265.
- ¹¹ DeGrazia, D. 2012. *Creation Ethics: Reproduction, Genetics and Quality of Life*. New York: Oxford UP. Prusack, B.G. 2013. *Parental Obligations and Bioethics: The Duties of a Creator*. New York: Routledge.