A disease, although there are many discrepancies. 5
the mutant mtDNA load, the higher the risk of severe
mtDNA. Substantial evidence suggests that the higher
well as the total amount and ratio of normal to mutant
depends on the cell's specific energy requirements as
energy-demanding tissues, such as brain and muscle,
amost commonly, but not exclusively, affected.
Mitochondrial disorders are caused by mutations in
either the mitochondria's own DNA (mtDNA; many
copies of a 16 569 base pair circular genome) or in
the 3.2 billion base pair nuclear DNA (nDNA; in 46
chromosomes) present in each cell. 2 Unlike nDNA,
which is inherited from both parents, mtDNA is
maternally inherited, and mtDNA variants cause
maternally inherited mitochondrial disease (Box 1).
The transmission of mutant mtDNA into individual
oocytes, and subsequent distribution to different
embryonic cells after fertilisation, is a complex
and largely unpredictable process that continues
throughout life. Most affected individuals have both
normal and mutant mtDNA in each cell (known as
heteroplasmy). Variable mutational loads in different
individuals and different cell types result from
unequal segregation of normal and mutant mtDNA as
cells divide. 2 Programmed reduction in mitochondrial
copy number in primordial germ cells can select
against particular mtDNA variants, causing a shift in
heteroplasmy from one generation to the next. 3,4 The
cellular dysfunction caused by mtDNA mutations
depends on the cell’s specific energy requirements as
well as the total amount and ratio of normal to mutant
mtDNA. Substantial evidence suggests that the higher
the mutant mtDNA load, the higher the risk of severe
disease, although there are many discrepancies. 5
Over 250 pathological mtDNA mutations have
been identified, 1 with each likely to have their
own threshold load for causing mitochondrial
dysfunction. 6,7 This complex and nuanced genetic
transmission puts mtDNA-mediated mitochondrial
disease in a separate category of inherited genetic
diseases to nDNA mutations, which are transmitted
by largely predictable Mendelian genetics. Patients with
mitochondrial disease require diagnosis and familial
risk evaluation by highly skilled clinicians who
understand this complexity.

In Australia, the incidence of mtDNA mutations is
predicted to be at least 1:250, with several hundred
families already diagnosed, although many carriers
remain unidentified. 4,8 Some families have multiple
generations of affected individuals, often with
devastating consequences. Their health care needs
present enormous emotional, physical, social, and
financial burdens on families, leading many couples
to seek options to prevent disease transmission
to their offspring. Their current choices include
voluntary childlessness, adoption, using eggs
donated by unaffected women, or prenatal and pre-
implantation genetic diagnosis. For couples wanting
to have genetically related children, prenatal and
pre-implantation genetic diagnosis are not reassuring
options because all of the woman's oocytes may
produce embryos with high levels of mutant mtDNA
in some cells. 9 Recent developments in mitochondrial
donation now present a promising path forward
to reduce disease transmission in these families by
replacing faulty mitochondria containing mutant
mtDNA with healthy mitochondria containing normal
mtDNA. 10 To ensure all cells of the offspring contain
healthy mitochondria, this replacement must be done
at the one-cell stage of conception, using procedures
to manipulate mature or newly fertilised oocytes that
are currently prohibited under Australian legislation.

After lengthy and extensive scientific review and
public consultation, the United Kingdom changed its
legislation in 2015 to allow mitochondrial donation
under specified regulation. 11 Following this lead,
the Australian Senate initiated an inquiry in 2018 to
consider the appropriateness of the technology in the
Australian context. A Citizens’ Jury and a National
Health and Medical Research Council (NHMRC)
Mitochondrial Expert Working Committee and
Citizens’ Panel facilitated wide-ranging community
consultation12,13 over 3 years that preceded drafting
of the Mitochondrial Donation Law Reform (Maeve’s
Law) Bill 2021, currently under Parliamentary
review. In this article, we outline the scientific and
ethical issues raised by mitochondrial donation
and the changes to legislation needed before its
implementation in Australia.

The technology and the law
Mitochondrial donation refers to assisted reproductive
technologies used to uncouple the inheritance of an
affected woman’s nDNA (normal) from her mtDNA
(mutant). Two techniques approved for clinical use
in the UK are maternal spindle transfer (MST) and
pronuclear transfer (PNT) (Box 2). Preclinical studies
indicate that in both methods there may be some
carry-over of mutant mtDNA during the transfer of
nDNA, but at a level unlikely to cause severe disease in
the offspring. 14 In the single live birth so far reported,
using MST, the low levels of mtDNA found in newborn
tissues were well below the threshold for risk of the
particular mitochondrial disease. 15
1 Common clinical syndromes caused by maternally inherited mutations in mitochondrial DNA (mtDNA) *

| Clinical syndrome | Clinical phenotype | Age of onset | Common causative mtDNA mutations |
|-------------------|--------------------|--------------|----------------------------------|
| Maternally inherited Leigh syndrome (MILS) | Motor and intellectual developmental delay and neurological disability, early death (by 3 years) | 3–12 months | MT ATP6 point mutation (m.8993T>G/C) in > 90% of mtDNA |
| Neurogenic weakness with ataxia and retinitis pigmentosa (NARP) | Ataxia, pigmented retinopathy, weakness, seizures, neuropathy | Childhood or early adult life | MT ATP6 point mutation (m.8993T>G/C) in 70–80% of mtDNA |
| Mitochondrial encephalopathy, lactic acidosis, stroke-like episodes (MELAS) | A broad spectrum of clinical phenotypes including stroke-like episodes with encephalopathy, recurrent headaches, and seizures manifesting in severe cases. Variable presence of myopathy, deafness, endocrinopathy (eg, diabetes and short stature), ataxia, and early death (10–35 years) | Originally described in childhood but can present across the lifespan | MT TL1 point mutations (m.3243A>G in 80%, m.3252A>G, m.3271T>C); MT TQ and NADH dehydrogenase subunit and ND5 point mutations (m.432G>A, m.13513G>A) |
| Myoclonus, epilepsy, and ragged-red fibres (MERRF) | Stimulus-sensitive myoclonus, generalised focal seizures, ataxia, cardiomyopathy, and/or lipomas. A minority of patients have progressive external ophthalmoplegia | Adolescent or early adult life | MT TK point mutations (m.8344A>G most common, m.8356T>C, m.8363G>A) and MT TH point mutation (m.12147G>A) |
| Chronic progressive external ophthalmoplegia (CPEO) | Ptosis and ophthalmoparesis, frequent proximal myopathy and variable other clinical features such as ataxia and cardiac arrhythmias or cardiomyopathy | Any age but more severe phenotype with younger onset | Single deletions and MT TL1 and MT TK point mutations (including m.3243A>G, m.8344A>G) |
| Leber hereditary optic neuropathy (LHON) | Subacute painless unilateral progressing to bilateral visual failure. May also have dystonia, cardiac pre-excitation syndromes and, in rare cases, (usually females) demyelination (Harding disease) | Typically in early adulthood, more common in males | MT ND1, ND4 and ND6 point mutations (m.3460C>G, m.11778G>A, m.14484T>C) |

*Some related clinical syndromes are caused by mutations in nuclear DNA (nDNA) but are not included in this table. ☞

In Australia, the Prohibition of Human Cloning for Reproduction Act 2002 (the Act) prohibits the creation of a human embryo containing genetic material from more than two persons and bars the alteration of a genome of a human cell where that alteration is heritable through the germline. Since mtDNA is heritable through female gametes, the utilisation of a donor oocyte in mitochondrial donation means that genetic material from three persons is used to create the embryo (Box 2). However, mtDNA makes no contribution to the characteristics of an individual other than cellular bioenergetics. Moreover, unlike nDNA, mtDNA sequences are not unique to an individual but are shared by mothers and all their offspring, making mtDNA an identifier of families rather than individuals. There is a scientific view that a woman donating oocytes for mitochondrial donation does not contribute genetic material to the child’s unique genomic identity. Moreover, scientists consider that transfer of nDNA between oocytes does not constitute alteration of the genome, even though this replacement is heritable, since neither nDNA nor mtDNA are modified in any way. UK legislation refers specifically to nuclear DNA from the contributing eggs in the processes that are permitted under the regulation.10 The extensive consultation undertaken in Australia indicates mixed views on these matters. Maeve’s Law has been drafted to permit mitochondrial donation by exemption to the provisions of the Act, with strict regulation under a licensing framework to be administered by the NHMRC Embryo Research Licensing Committee.

The ethical and regulatory framework

While the potential benefits of mitochondrial donation for many families are well recognised, concerns remain about ethical risks. Apart from religious and moral views regarding interventions using assisted reproductive technologies in the formation of human life, the primary ethical concerns are about the rights of the children and oocyte donors and long term safety of the procedure for offspring born.13 Australia recognises the rights of children born from assisted reproductive technologies to know their genetic origins, and this right would extend to information about individuals donating oocytes for mitochondrial donation. Such access would need to be strictly controlled to protect the privacy of donors. While substantial pre-clinical studies indicate the procedures are feasible and safe enough for clinical implementation, evidence of true efficacy is limited since only one live birth has so far been reported in the public domain. It is, however, recognised by scientists and clinicians that further technical refinements are needed to minimise the carry-over of mutant mtDNA, as even very low levels of certain mtDNA mutations carry risks of severe or late onset disease in the individual or selective
Perspectives

Mitochondrial donation can significantly reduce the risk of maternally inherited mitochondrial disease transmission to offspring and, for some families, provides their only option to have unaffected, genetically related children. Australia has the clinical and scientific expertise to introduce mitochondrial donation in a highly regulated environment, but requires changes in legislation to adopt this innovative technology, as proposed in the Maeve’s Law currently under parliamentary review. A cautionary, staged approach is being considered for implementation in Australia. Establishment of a coordinated network of clinics forming a national service would allow equitable access to the procedure and the clinical expertise necessary to evaluate patient outcomes, provide expert follow-up, and support research and training in this important area.

Conclusions

transmission to their offspring. As with any new medical technology, further testing and refinement can be achieved most effectively in a clinical setting. The UK Parliament took a cautionary approach in allowing the procedure in licensed centres for stringently selected high risk cases with a requirement for follow-up and reporting of outcomes. A similar but even more cautious approach is being proposed for Australia. If passed by Parliament, Maeve’s Law will enable a staged implementation of mitochondrial donation, with licensing for research and training and a clinical trial over 10 years to provide evidence of safety and efficacy before approval is given for clinical use.

Australia has a long history in, and an excellent regulatory environment for, procedures involving assisted reproductive technologies, through both federal and state legislation. Clinics require accreditation through the Reproductive Technology Accreditation Committee and must comply with the NHMRC Ethical guidelines on the use of assisted reproductive technology in clinical practice and research. Applications to develop new procedures need approval by the NHMRC Embryo Research Licensing Committee, which would regulate licenses for mitochondrial donation, guided by clinical experts. Australia has the clinical expertise in mitochondrial disease to evaluate and select eligible families, and provide clinical oversight of mitochondrial donation. Eligible couples and oocyte donors will require expert counselling to ensure they do not have unrealistic expectations about the outcomes, understand the rights of any offspring to know their genetic history, and can make informed decisions regarding their reproductive options.

Acknowledgements: Carolyn Sue is a Medical Research Future Fund National Health and Medical Research Council Practitioner Fellow (APP1136800).

Competing interests: No relevant disclosures.

Provenance: Not commissioned; externally peer reviewed.

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