The Senate

Community Affairs References Committee

Science of mitochondrial donation and related matters

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45th Parliament

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ABBREVIATIONS

AMDF	Australian Mitochondrial Disease Foundation
ART	assisted reproductive technology
ART Guidelines	*Ethical Guidelines on the use of assisted reproductive technology in clinical practice and research*
Cloning Act	*Prohibition of Human Cloning for Reproduction Act 2002*
committee	Senate Community Affairs References Committee
DNA	deoxyribonucleic acid
Embryo Research Act	*Research Involving Human Embryos Act 2002*
Fertility Society	Fertility Society of Australia
Health Ethics Committee	Australian Health Ethics Committee
HFEA	Human Fertilisation and Embryology Authority, United Kingdom
Human Research Guidelines	*National Statement on Ethical Conduct in Human Research*
IVF	in vitro fertilisation
LHON	Leber's Hereditary Optic Neuropathy
mtDNA	mitochondrial DNA
Murdoch Children's Research Institute	Murdoch Children's Research Institute and Victorian Genetic Clinical Services
NDIS	National Disability Insurance Scheme
NHMRC	National Health and Medical Research Council
PGD	pre-implantation genetic diagnosis
PNT	pronuclear transfer technique

RTAC	Reproductive Technology Accreditation Committee of the Fertility Society of Australia
SCNT	Somatic cell nuclear transfer
SIRT	Scientists in Reproductive Technology of the Fertility Society of Australia
UK	United Kingdom
UK Regulations	The Human Fertilisation and Embryology (Mitochondrial Donation) Regulation 2015
USA	United States of America

LIST OF RECOMMENDATIONS

Recommendation 1

5.99 The committee notes the strong potential of mitochondrial donation to address the debilitating effects of inheriting mitochondrial disease. The committee recommends that public consultation be undertaken regarding the introduction of mitochondrial donation to Australian clinical practice. To facilitate this consultation, the committee further recommends the Australian Government prepare a consultation paper, including options for legislative change that would be required. The Minister for Health should seek advice from the National Health and Medical Research Council on the most appropriate timing and format for this consultation.

Recommendation 2

5.100 The committee recommends that the Australian Government task the National Health and Medical Research Council with advising on the following questions:

- **Whether mitochondrial donation is distinct from germline genetic modification.**
- **Is there any new information to indicate that research findings from the United Kingdom, that the science of mitochondrial donation is safe for introduction into controlled clinical practice, cannot be applied in an Australian context?**
- **Whether other approaches to inheriting mitochondrial disease should also be the focus of Australian research.**

5.101 The committee recommends the findings be used to inform future legislative process.

Recommendation 3

5.103 The committee recommends the Minster for Health take the findings of this report to the Council of Australian Governments (COAG) Health Council to progress the implementation of this report's recommendations with the states and territories.

Recommendation 4

5.104 The committee recommends, noting the need for community consultation and scientific review, the urgency of treatment for current patients and the small number of patients seeking this treatment, that the Australian Government initiate dialogue with the relevant authorities in the United Kingdom to facilitate

access for Australian patients to the United Kingdom treatment facility as an interim measure.

Chapter 1

Introduction

1.1 Mitochondrial donation is a reproductive technology procedure to reduce the chances of a woman passing on mitochondrial disease—a potentially life-threatening condition—to her children.

1.2 Mitochondrial donation was legalised for use on humans in the United Kingdom (UK) in 2015. The UK is the only jurisdiction in the world that has legalised mitochondrial donation for clinical application, and to date, no children have been born using this process in the UK. Since then, there have been discussions in the Australian scientific and medical communities about the possibility of this technique being made legal for clinical practice in Australia.

1.3 This report looks at the science of mitochondrial donation, the safety and efficacy on the technique as well as the ethical considerations of such technology, and evaluates whether the Australian Government should consider making mitochondrial donation available within Australia, and if so, under what kind of regulatory regime.

1.4 The report uses information provided in the course of this inquiry, and also relies on the significant body of evidence gathered during the 12 year process to evaluate and ultimately legalise mitochondrial donation in the UK.

What is mitochondrial disease?

1.5 Mitochondria are found in the fluid surrounding the nucleus of cells. They are responsible for making energy within the cell, without which the cells would not survive. In order to work, the mitochondria have their own mitochondrial DNA (mtDNA).[1] Mitochondrial disease can be caused by mutations in the mtDNA or in the nuclear DNA.

1.6 In some cases, mitochondrial disease is caused by genetic mutations in the nuclear DNA – most of our DNA (over 99 per cent) is found in the nucleus of the cell and we inherit this from our mother and our father. Mitochondrial disease can also arise as a spontaneous genetic mutation at conception.

1.7 Mitochondrial disease varies in presentation. It can be mild with little or no symptoms or can be severe enough to be life threatening. It tends to affect parts of the body that require a lot of energy, like the brain, muscles, kidney and heart. While some symptoms can be managed, there are no effective treatments available for serious mitochondrial disease and there is no cure.[2]

1.8 Common symptoms of mitochondrial disease include developmental delays, seizures, weakness and fatigue, muscle pain, vision loss, and heart problems, leading

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1 Deoxyribonucleic acid (DNA) is a chain of nucleotides carrying the genetic instructions for the growth, development, functioning and reproduction of living organisms.

2 House of Commons Library (UK), *Mitochondrial Donation*, Standard Note: SN/SC/6833, 29 January 2015, p. 5.

to morbidity and in some cases premature death.[3] Chapter two discusses mitochondrial disease and related illnesses in greater detail.

Causes of mitochondrial disease

1.9 In about half of all known cases, mitochondrial disease is caused by mutations in the mtDNA, which are inherited matrilineally, from mother to children through multiple generations.[4] This is because the mother's oocytes (eggs) contain significant amounts of mtDNA, while the mtDNA contained in a father's sperm is lost at fertilisation. The level of mutated mtDNA a child will inherit, or the severity of any subsequent mitochondrial disease, is unpredictable.[5]

Having children

1.10 For women with a known mtDNA mutation who want to have a child with a genetic link, there are currently two key options to reduce the chance of passing on mitochondrial disease.

1.11 The first is to use prenatal diagnosis, conducted on a pregnant woman at around 11–14 weeks gestation, usually by performing a genetic test on a placental tissue biopsy. If an mtDNA mutation is found, parents then face a choice of either continuing or terminating the pregnancy.

1.12 The other option is to use pre-implantation genetic diagnosis (PGD), where embryos are created using in vitro fertilisation (IVF) and then tested before implantation to look for embryos with the lowest proportion of mutated mtDNA.

1.13 There are limitations to this method because it cannot be used by all women with mtDNA mutations and it can only reduce, not eliminate, the risk of having a baby affected by mitochondrial disease. In some cases, there are no embryos with an acceptably low mtDNA mutation load and the IVF cycle must be abandoned.

1.14 Additionally, even if unaffected themselves, girls born after the use of PGD may themselves still be at risk of having affected children, as some abnormal mitochondria may be present in their oocytes.[6]

1.15 The full range of reproductive choices available to people with a mitochondrial mutation are discussed in greater detail in chapter two.

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3 Committee on the Ethical and Social Policy Considerations of Novel Techniques for Prevention of Maternal Transmission of Mitochondrial DNA Diseases, US Institute of Medicine, *Mitochondrial Replacement Techniques: Ethical, Social, and Policy Considerations*, February 2016, p. 1.

4 This subset of mitochondrial disease is often referred to as mtDNA disease.

5 Australian Mitochondrial Disease Foundation (AMDF), *Mitochondrial Disease: the need for mitochondrial donation*, p. 1.

6 House of Commons Library (UK), *Mitochondrial Donation*, Standard Note: SN/SC/6833, 29 January 2015, pp. 6–7.

Mitochondrial donation

1.16 Mitochondrial donation (or mitochondrial replacement techniques) is designed to prevent the transmission of mtDNA diseases from mother to child by creating an embryo with nuclear DNA from the intended mother and mtDNA from a donor with nonpathogenic mtDNA through modification of either an oocyte or zygote (fertilised egg).[7]

1.17 mtDNA does not contribute to a person's genetic identity because mtDNA only provides energy to the cells. Nuclear DNA is responsible for a person's physical, cognitive and behavioural characteristics. A recipient of donated mtDNA will not resemble the donor.[8]

1.18 Mitochondrial donation only assists women with mtDNA mutations—the cause of approximately half of mitochondrial disease—and assists in reducing the risk of mothers with this form of mitochondrial disease passing it on to their children.

1.19 The various methods of mitochondrial donation and the benefits, risks and ethical considerations of the differing techniques are discussed in greater detail in chapters three and four.

Regulation of mitochondrial donation and related research

1.20 Under current Australian legislation, some forms of mitochondrial research are prohibited entirely because it requires fertilising an egg with the genetic material of more than two people, while others can be researched under license but must be destroyed within 14 days.[9]

1.21 There are two key pieces of legislation which prohibit the research and clinical implementation of mitochondrial donation in Australia. Additionally, there are a range of other regulatory instruments and bodies which are relevant to mitochondrial donation.

1.22 The National Health and Medical Research Council (NHMRC) is Australia's peak body for supporting health and medical research, including providing advice on ethical behaviour in health care and in the conduct of health and medical research. The NHMRC is responsible for administering the two pieces of legislation relevant to mitochondrial donation – *Research Involving Human Embryos Act 2002* (Embryo Research Act) and the *Prohibition of Human Cloning for Reproduction Act 2002* (Cloning Act).[10]

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7 Committee on the Ethical and Social Policy Considerations of Novel Techniques for Prevention of Maternal Transmission of Mitochondrial DNA Diseases, US Institute of Medicine, *Mitochondrial Replacement Techniques: Ethical, Social, and Policy Considerations*, February 2016, p. 1.

8 Ainsley Newson, Stephen Wilkinson and Anthony Wrigley, 'Ethical and legal issues in mitochondrial transfer', *EMBO Molecular Medicine*, June 2016, p. 2.

9 National Health and Medical Research Council (NHMRC), *Submission 4*, p. 7.

10 NHMRC, *Submission 4*, p. 1.

1.23 Two relevant committees of the NHRMC include the Australian Health Ethics Committee (Health Ethics Committee) and the Embryo Research Licensing Committee.

Embryo Research Licensing Committee

1.24 The Embryo Research Licensing Committee of the NHMRC is responsible for administering the Cloning Act and the Embryo Research Act. Both Acts regulate activities that relate to mitochondrial donation and would have to be amended if mitochondrial donation was to be permitted in Australia.[11]

1.25 A detailed discussion of what is currently allowed under legislation and the amendments required to permit the implementation of mitochondrial donation in clinical practice is included in chapter five.

Health Ethics Committee

1.26 The Health Ethics Committee of the NHMRC provides advice on ethical issues relating to health, and develops human research guidelines. Guidelines relevant to mitochondrial donation include the *Ethical Guidelines on the use of assisted reproductive technology in clinical practice and research* (ART Guidelines)[12] and the *National Statement on Ethical Conduct in Human Research* (Human Research Guidelines).[13]

1.27 While the Health Ethics Committee is responsible for guidelines on how Assisted Reproductive Technologies (ART) such as IVF should be implemented, it is not responsible for the regulation and monitoring of ART use in clinical practice. The Embryo Act requires all ART clinics to be accredited by the Reproductive Technology Accreditation Committee (RTAC) of the Fertility Society of Australia (Fertility Society).[14]

Regulation of ART clinics

1.28 The Fertility Society is the peak body for those professionals involved in reproductive medicine in Australia, including gynaecologists, scientists, nurses and counsellors.[15] The reproductive medicine sector is self-regulating under the Fertility Society accreditation scheme managed by the RTAC, which regulates and licenses the 88 clinics across Australia which perform ART techniques for individuals.[16]

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11 NHMRC, *Submission 4*, p. 1.

12 NHMRC, *Ethical Guidelines on the use of assisted reproductive technology in clinical practice and research* (ART Guidelines), 2007, https://www.nhmrc.gov.au/guidelines-publications/e79 (accessed 22 May 2018).

13 NHMRC, *National Statement on Ethical Conduct in Human Research*, 2007, https://www.nhmrc.gov.au/guidelines-publications/e72 (accessed 22 May 2018).

14 NHMRC, *Submission 4*, p. 1.

15 Fertility Society of Australia (Fertility Society), *Submission 27*, p. 1.

16 Dr Petra Wale, Board Member, Fertility Society, *Committee Hansard*, 17 May 2018, p. 41.

1.29 As part of the RTAC assessment process, ART clinics are assessed for compliance with the RTAC Code of Practice, which in turn requires compliance with the NHMRC ART Guidelines.[17]

1.30 The Fertility Society includes the scientists' sub-group Scientists in Reproductive Technology (SIRT), with over 500 members in Australia, New Zealand and internationally. The goals of SIRT are to:

> [P]romote professional excellence through education, training, research and dissemination of scientific information; to increase the profile and professional status of scientists in assisted reproduction; and, finally, to act as a resource for formulating a consensus on scientific issues and guidelines for best scientific practice, predominately for the Fertility Society of Australia but also for other professional bodies.[18]

1.31 Dr Nadine Richings, Vice Chair of SIRT, told the committee that embryologists working in ART clinics are not currently required to be certified in Australia, although SIRT is currently developing a certification scheme for embryologists to be accredited by a third party.[19]

1.32 Suggestions from the Fertility Society and SIRT on an appropriate certification and regulation framework for mitochondrial donation in Australia is discussed in further detail in chapter five.

Overseas status of mitochondrial donation

United Kingdom

1.33 The UK undertook a 12 year process to allow for the research of mitochondrial donation from 2005, leading to the legalisation of this technique for clinical implementation in 2015, and a licence to administer this as a treatment being granted to a fertility clinic in 2017.

1.34 There were a significant number of scientific and ethical reviews, as well as community consultations to ensure that the technology could be safely and ethically undertaken and that there was public support for the measure.

1.35 The timeline below gives a brief outline of the process:

Date	**Consideration**
1990	The Human Fertilisation and Embryology Authority (HFEA) is created to review information relating to embryos and advise the Secretary of State.
2005	HFEA grants research licence for pronuclear transfer.

17 NHMRC, *Submission 4*, p. 1.

18 Dr Nadine Richings, Vice Chair, Scientists in Reproductive Technology (SIRT), *Committee Hansard*, 17 May 2018, p. 42.

19 Dr Richings, *Committee Hansard*, 17 May 2018, p. 42.

April 2011	HFEA releases first scientific review and recommends further research.
June 2011	HFEA's Ethics and Law Committee considers ethical issues.
January 2012 – March 2013	HFEA undertakes public dialogue work on the ethics and public attitudes towards mitochondrial replacement. Public were generally supportive of these techniques, although concerns around safety, the donor role and the regulation of the techniques were highlighted.
June 2012	Nuffield Council on Bioethics publishes its ethical review.
September 2012 – December 2012	Open consultation questionnaire, meetings and patient focus group takes place.
January 2013	HFEA releases second scientific review.
June 2013	The Government announces it will move forward with public consultation on draft regulations for the use of mitochondrial donation to prevent mothers passing on serious mitochondrial diseases to their children.
June 2014	HFEA releases third scientific review on safety and efficacy.
December 2014	Legislation to legalise mitochondrial legislation put before UK Parliament.
February 2015	The Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015 passes.
October 2015	The Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015 come into force. Requires both the clinic and the patient to be licenced by the HFEA.
December 2016	Final regulations governing mitochondrial donation are endorsed by the HFEA.
March 2017	HFEA grants licence to provide mitochondrial donation to the Newcastle Fertility Centre.
February 2018	HFEA grants licence to undergo mitochondrial donation to two UK women carrying mtDNA mutations.

As of 30 April 2018	HFEA's Statutory Approvals Committee has considered 6 applications to carry out mitochondrial transfer.[20]

Source: HFEA, *Third scientific review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception: 2014 update*, additional information received 30 May 2018, pp. 6–8; AMDF, *Submission 26*, pp. 6–7 and AMDF, *Mitochondrial donation*, https://www,amdf.org.au/mitochondrial-donation/ (accessed 15 June 2018).

United States of America

1.36 The consultation process for mitochondrial transfer in the United States of America (USA) to date has been less structured than in the UK, mostly due to the lack of a specialised agency for human reproduction and fertility.[21]

1.37 In 2014 the USA Food and Drug Administration requested the Institute of Medicine of the National Academies of Sciences, Engineering and Medicine to review the broader implications of mitochondrial transfer. The review was quite cautious, recommending that future clinical trials are restricted to women with serious risks of transmitting mitochondrial disease to their children, and for which the mitochondrial mutation is pathogenic and highly likely to be manifested in a severe clinical way; and that mitochondrial transfer only be made to male embryos to prevent any transfer of the donated mitochondria to future generations.[22]

1.38 However, federal restrictions on funding and research 'in which a human embryo is intentionally created or modified to include a heritable genetic modification' mean that clinics in the USA cannot currently conduct research in this area.[23]

Singapore

1.39 Singapore is currently carrying out public consultation on whether or not mitochondrial donation should be permitted to prevent heritable mitochondrial disorders.[24]

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20 Minutes for three decisions have been published: two applications were approved and for the other application, more information was requested regarding alternative options available to the patient. See *Reports archive* available at https://www.hfea.gov.uk/choose-a-clinic/clinic-search/results/17/.

21 R J Castro, 'Mitochondrial replacement therapy: the UK and US regulatory landscapes', *Journal of Law and the Biosciences*, vol. 3, no.3, 1 December 2016, pp. 726–735.

22 National Academies of Sciences, Engineering and Medicine (USA), *Mitochondrial Replacement Techniques: Ethical, Social, and Policy Considerations*, 3 February 2016, available at http://www.nationalacademies.org/hmd/Reports/2016/Mitochondrial-Replacement-Techniques.aspx.

23 *Consolidated Appropriations Act 2018*, Pub L No 115-141, §734.

24 Straits Times, 'Bioethics committee seeks views of emerging genetic modification technology to prevent disorders', 19 April 2018, https://www.straitstimes.com/singapore/health/bioethics-committee-seeks-views-on-emerging-genetic-modification-technology-to (accessed 8 May 2018).

Report structure

1.40 Following this introductory chapter, this report consists of four subsequent chapters:

- Chapter two outlines the impact of mitochondrial disease on individuals and their families, the rates of mitochondrial disease and mtDNA mutations and the cost to the health sector;
- Chapter three discusses the science of mitochondrial donation;
- Chapter four discusses the ethics and possible health risks; and
- Chapter five reviews the regime recently introduced in the UK to regulate the clinical implementation of mitochondrial donation, and compares that to the existing regulatory regime in Australia. Chapter five also provides the recommendations and conclusions of the Senate Community Affairs References Committee (committee).

Conduct of the inquiry

1.41 On 21 March 2018 the Senate referred the science of mitochondrial donation to the committee for inquiry and report by 19 June 2018 with the following terms of reference:

(a) the science of mitochondrial donation and its ability to prevent transmission of mitochondrial disease;

(b) the safety and efficacy of these techniques, as well as ethical considerations;

(c) the status of these techniques elsewhere in the world and their relevance to Australian families;

(d) the current impact of mitochondrial disease on Australian families and the healthcare sector;

(e) consideration of changes to legal and ethical frameworks that would be required if mitochondrial donation was to be introduced in Australia;

(f) the value and impact of introducing mitochondrial donation in Australia; and

(g) other related matters.[25]

1.42 On 19 June 2018 the Senate granted an extension of time for reporting to 27 June 2018.

Submissions

1.43 The inquiry was advertised on the committee's website and the committee wrote to stakeholders inviting them to make submissions.

25 *Journals of the Senate*, No. 90, 21 March 2018, p. 2864.

1.44 The committee also issued media releases to promote public awareness about ways individuals could engage with the inquiry. Media releases were published on the committee's website and were tweeted using the @AuSenate handle.

1.45 The committee invited submissions to be lodged by 11 May 2018. Submissions continued to be accepted after this date.

1.46 The committee published 53 submissions from government agencies, organisations and individuals. A further 7 submissions were accepted as confidential submissions. A list of submissions provided to the inquiry is available on the committee's website[26] and in Appendix 1.

Public hearings

1.47 The committee held a public hearing on 17 May 2018 in Sydney, NSW. A list of witnesses who provided evidence at the public hearing is available at Appendix 2.

Notes on references

1.48 In this report, some references to *Committee Hansard* are to proof transcripts. Page numbers may vary between proof and official transcripts.

26 See: www.aph.gov.au/Parliamentary_Business/Committees/Senate/Community_Affairs/MitochondrialDonation.

Chapter 2

Living with mitochondrial disease

> Mitochondrial disease is a horrible disease, and you wouldn't wish it upon your worst enemy.[1]

What is mitochondrial disease?

2.1 As outlined in chapter one, mitochondria are found in the fluid surrounding the nucleus of cells and are responsible for making energy within the cell. In order to work, the mitochondria have their own mitochondrial DNA[2] (mtDNA).

2.2 In about half of all known cases, mitochondrial disease is caused by mutations in the separate mtDNA that we inherit matrilineally (only from our mother). This form of mitochondrial disease is known as mitochondrial DNA disease. In other cases, mitochondrial disease is caused by genetic mutations in the nuclear DNA we inherit equally from our mother and our father. Mitochondrial disease can also arise as a spontaneous genetic mutation at conception.[3]

2.3 Mitochondrial disease is varied in presentation — it can be mild with little or no symptoms or can be severe enough to be life threatening. It tends to affect parts of the body that require a lot of energy, like the brain, muscles, kidney and heart.[4] Mr Sean Murray, Chief Executive Officer of the Australian Mitochondrial Disease Foundation (AMDF) told the committee 'there are hundreds of types of mitochondrial disease. Saying "mitochondrial disease" would be perhaps something like saying "cancer"'.[5]

2.4 AMDF summarised mitochondrial disease as:

> Mitochondrial disease is a debilitating genetic disorder that starves the body's cells of energy, causing multiple organ dysfunction or failure and potentially death. Mitochondrial disease occurs when a person's mitochondria are not functioning properly. It primarily affects the muscles and major organs, such as the brain, heart, liver, inner ears and eyes, but can cause any symptom in any organ at any age.
>
> …
>
> Depending on which parts of a person's body are affected and to what degree, people with mitochondrial disease may: have strokes or seizures; be

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1 Mr Sean Murray, Chief Executive Officer, Australian Mitochondrial Disease Foundation (AMDF), *Committee Hansard*, 17 May 2018, p. 1.

2 Deoxyribonucleic acid (DNA) is a chain of nucleotides carrying the genetic instructions for the growth, development, functioning and reproduction of living organisms.

3 AMDF, *Mitochondrial Disease: the need for mitochondrial donation*, p. 1.

4 House of Commons Library (UK), *Mitochondrial Donation*, Standard Note: SN/SC/6833, 29 January 2015, p. 5.

5 Mr Murray, *Committee Hansard*, 17 May 2018, p. 4.

> unable to walk, eat, swallow or talk normally; develop liver disease or diabetes; suffer heart, respiratory or digestive problems; lose their sight or hearing; suffer muscle weakness and pain; and experience developmental delays or intellectual disability.[6]

2.5 These diseases vary in presentation and severity, but common symptoms include developmental delays, seizures, weakness and fatigue, muscle pain, vision loss and heart problems, leading to morbidity and in some cases premature death.[7]

2.6 Professor John Christodoulou, Chair in Genomic Medicine at the Murdoch Children's Research Institute and the University of Melbourne Department of Paediatrics, told the committee that mitochondrial disease can be immediately present at birth, or can manifest itself later in childhood, or even as an adult:

> For instance, in some mitochondrial disorders, particularly those affecting children, children will appear to be normal for a period of time, maybe even for a few years, and then, when they have their very first major significant illness and their body needs additional energy to be made, they can't meet that need. That's when the disease may first manifest itself.[8]

2.7 Rhonda told the committee her families first experience of mitochondrial disease came without warning:

> Our first exposure to mitochondrial disease was when my brother was rushed to hospital with what we thought was a stroke. He was 34 years old. As part of determining what caused Peter's stroke, my whole family was tested and it was identified that my two brothers, two sisters, my mother and myself carried the defective gene.[9]

Lack of awareness

2.8 Submitters and witnesses told the committee there is a lack of awareness of mitochondrial disease even within the medical community, and this often leads to poor health treatment. AMDF told the committee that patients and parents of young children who have mitochondrial disease often 'feel like they're explaining what mitochondrial disease is to the medical community'.[10]

2.9 One submitter pointed to delayed emergency treatment due to this lack of awareness:

> I can be screaming in pain, and having my family tell them she has Mitochondrial Disease, just for them to question what the disease really is

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6 AMDF, *Submission 26*, p. 2.

7 Committee on the Ethical and Social Policy Considerations of Novel Techniques for Prevention of Maternal Transmission of Mitochondrial DNA Diseases: US Institute of Medicine, *Mitochondrial Replacement Techniques: Ethical, Social, and Policy Considerations*, February 2016, p. 1.

8 Professor John Christodoulou, Chair, Genomic Medicine, Department of Paediatrics, University of Melbourne, *Committee Hansard*, 17 May 2018, p. 13.

9 Rhonda, *Committee Hansard*, 17 May 2018, p. 33.

10 Mr Murray, *Committee Hansard*, 17 May 2018, p. 2.

> and how they should they treat me for the pain/reason I have presented to emergency.[11]

2.10 Another submitter outlined that after the birth of a family member, the Consultant Neonatologist at the neonatal intensive care unit at their hospital 'admitted that he needed a two-hour meeting with the [neonatal intensive care unit's] genetics/metabolics team to help him understand what this disease was all about and how it was affecting M because mitochondrial disease was such a rare, recently identified condition that he learnt nothing of it when he went through medical school'.[12]

2.11 Due to this lack of awareness, some people experienced a delayed diagnosis of mitochondrial disease:

> [Y]ou're underweight and you think it's just the case that you're genetically that way. Then you start losing your hearing and you think: 'Well, that's okay. We'll deal with that.' Then all of a sudden you have diabetes and you deal with that. You don't always put the picture together. For many people, it's a long, long time to come up with a diagnosis—many, many years.[13]

2.12 One witness, Rhonda, had a similar experience of delayed diagnosis in her family:

> With my brother's diagnosis, once he had his first stroke it was quite a quick diagnosis. But, as a teenager, he was diagnosed with having what was called a sleeping sickness. I mean, what is that? The doctors didn't know what it was. Before that, my grandmother had the same symptoms had the same symptoms [sic] as my mother, my brother and me. We just thought, 'Oh, well, she's hard of hearing and she's not quite right,' but there was no diagnosis. So I suppose, with mitochondrial disease in our family, the diagnosis hasn't exactly been quick. It's been hanging around for a long time.[14]

2.13 Others, particularly parents of children who died, did not receive a formal diagnosis until years later when other family members became symptomatic and underwent genetic testing.[15]

2.14 Professor Carolyn Sue, Director of the Mitochondrial Disease Research Centre at the Kolling Institute of Medical Research, leads a mitochondrial disease clinic at the Royal North Shore Hospital. Professor Sue told the committee that the referral patterns she sees in her patients, indicates that patients have 'hidden disease'

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11 Name Withheld, *Submission 32*, p. 2.

12 Name Withheld, *Submission 39*, p. 1.

13 Shelley, *Committee Hansard*, 17 May 2018, p. 38.

14 Rhonda, *Committee Hansard*, 17 May 2018, pp. 38–39.

15 Shelley, *Committee Hansard*, 17 May 2018, p. 38.

and she estimates on average, patients have seen eight to 10 doctors before coming to her clinic for a final diagnosis.[16]

2.15 AMDF echoed this view, telling the committee that:

> It's not uncommon for patients to have found their way to a mitochondrial disease diagnosis having spent 10 or so years bouncing around from one specialist to another… So the medical community is treating them and looking at their symptoms in silos, and it's not until somebody connects the dots of all of these symptoms that somebody suspects mitochondrial disease. In fact, it's not been uncommon for us to have patients report that they've ended up at a psychiatrist or a psychologist because the medical community says, 'There couldn't possibly be this many things wrong with you; it must be all in your head.'[17]

Rate of mtDNA mutation and mitochondrial disease

2.16 Because mitochondrial disease is poorly understood both in the general Australian community and within the medical professions, it is often thought of as a rare disease. However, AMDF told the committee it is more common than people think and 'it's estimated that one in 5000 people born will ultimately develop a life-threatening form of mitochondrial disease in their lifetime.'

2.17 AMDF further told the committee that at least one in 200 people carry one of the genetic changes in their mtDNA which can cause mitochondrial disease.[18] A groups of leading scientists in this field submitted that these carriers are likely to have 'symptoms that are common in the general population and unlikely to prompt suspicion of mitochondrial disease while these individuals are in the reproductive age group'.[19] The submission states that these carriers are likely to remain a 'hidden burden of mitochondrial disease, at least until community genetic screening becomes available that would detect people at risk of mitochondrial DNA disease'.[20]

2.18 Professor David Thorburn, Head of Mitochondrial Research and Diagnostic Laboratories at the Murdoch Children's Research Institute told the committee that:

> [W]e believe that about 60 children born in Australia each year will develop severe mitochondrial disease at some stage during their lifetime. I have helped to diagnose

16 Professor Carolyn Sue, Director, Kolling Institute of Medical Research, Mitochondrial Disease Research Centre, *Committee Hansard*, 17 May 2018, p. 26.

17 Mr Murray, *Committee Hansard*, 17 May 2018, p. 3.

18 Mr Murray, *Committee Hansard*, 17 May 2018, p. 2. It was later clarified that not all the 1 in 200 individuals will develop sever mitochondrial disease. See AMDF, *Submission 26.1*, p. 3.

19 Professors David Thorburn, John Christodoulou, Carolyn Sue, John Carroll, Mike Ryan and Aleksandra Filipovska, *Submission 59*, p. 3.

20 Professors Thorburn, Christodoulou, Sue, Carroll, Ryan and Filipovska, *Submission 59*, pp. 3–4.

> more than 600 children with mitochondrial disease, the vast majority of whom have died in childhood as our treatments do remain largely ineffective.[21]

2.19 Professor Sue provided evidence that the rates of mitochondrial disease in adults is largely unquantified:

> Our bottleneck is really how many patients we can fit in the clinic as to how many patients are out there, because I can tell you now that we won't be able to see a hundred thousand patients in our clinic in any one day or month. However, we know that patients are hidden in various different clinics—diabetic clinics, hearing loss clinics, cardiac clinics and probably infertility clinics as well—where patients have died without the cause being known.[22]

2.20 Professor Sue furthermore told the committee that the diagnosis rate of mitochondrial disease is likely to increase in coming years:

> We're looking at big data in trying to work out some of this, but the size of the problem is only going to grow, in my opinion. It has grown. The trajectory is going up. That's what I've seen from 20 years ago, and it's getting higher and higher. We're trying to work out ways to service those patients as much as trying to help them.[23]

Broader health impacts

> Many experts refer to Mitochondrial Disease as the 'Notorious Masquerader' because it wears the mask of many different illnesses.[24]

2.21 As outlined earlier in this chapter, mitochondrial disease often has a delayed diagnosis due to a lack of awareness in the medical community. It is increasingly the view of the medical and scientific community that mitochondrial disorders may be present in a larger range of illnesses than previously thought. AMDF contends that there is strong evidence that impaired mitochondrial function is important in Parkinson's disease, diabetes and diabetic complications. Disorders such as Alzheimer's, autism, cardiovascular disease and some forms of cancer have also been associated with mitochondrial dysfunction, as has the process of ageing.[25]

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21 Professor Thorburn, Head of Mitochondrial Research and Diagnostic Laboratories, Murdoch Children's Research Institute and Victorian Clinical Genetics Services, *Committee Hansard*, 17 May 2018, p. 11.

22 Professor Sue, *Committee Hansard*, 17 May 2018, p. 26.

23 Professor Sue, *Committee Hansard*, 17 May 2018, p. 26.

24 United Mitochondrial Disease Foundation, *Mitochondrial Disease in Adults*, http://www.umdf.org/mitochondrial-disease-in-adults/ (accessed 30 May 2018).

25 AMDF, *Mitochondrial Disease Information: Where does mitochondrial disease hide if it is NOT diagnosed*, https://www.amdf.org.au/mito-info/ (accessed 31 May 2018).

Diagram 2.1—Where does mitochondrial disease hide?

Source: AMDF, *Mitochondrial Disease Information: Where does mitochondrial disease hide if it is NOT diagnosed*, https://www.amdf.org.au/mito-info/ (accessed 31 May 2018).

Treatment

2.22 There are few effective treatments and no cures for mitochondrial disease. AMDF submits that this means the impacts on individuals and families of mitochondrial disease are devastating.[26]

2.23 Professor Christodoulou, a specialist in paediatric metabolic diseases and a clinical geneticist, told the committee that although the capacity to diagnose these diseases has been greatly enhanced in the past decade, 'where we've failed our patients has been in the identification and delivery of effective treatments for the vast majority of them'.[27]

Living with mitochondrial disease

2.24 As outlined earlier in this chapter, mitochondrial disease is a debilitating genetic disorder that can cause multiple organ dysfunction or failure and potentially death. It primarily affects the muscles and major organs, such as the brain, heart, liver, inner ears and eyes, but can cause any symptom in any organ at any age.

2.25 Professor Thorburn told the committee that of the approximately 600 children he has diagnosed with mitochondrial disease, the vast majority have died.

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26 AMDF, *Submission 26*, p. 2.

27 Professor Christodoulou, *Committee Hansard*, 17 May 2018, p. 12.

2.26 A mother whose child died of mitochondrial disease described her daughters condition:

> She had gone from the flourishing 8yr old, full of hope, dreams and motivation, to having dementia, deafness, partial blindness, tube feeds, incontinence, immobile, seizures, diabetes, multi-organ failure, dysphasia and extreme fatigue.[28]

2.27 The submitter went on to describe her work on a helpline:

> So many of the hundreds of patients and families I spoke to over those years, were like us, mortified, existing to survive now rather than live. Trying their utmost to create as many precious memorable moments, always looking for the smile in their child's or partner's face.[29]

2.28 A submitter described the symptoms of her mitochondrial disease, which in her case was categorised as mild:

> It currently causes extreme fatigue and pain in all my muscles. I have all my organs checked annually, visit my neurologist and an array of other health professionals regularly. I can't work full time anymore, can't exercise anymore and need a lot of sleep (10-12 hours a few times a week).[30]

2.29 A sibling of a man who died of mitochondrial disease submitted a list of his symptoms as 'loss of hearing, multiple stroke-like episodes, seizures, extreme fatigue, muscle wastage, cognitive impairment, poor balance and loss of motor skills. He also endured tonsil cancer and underwent radiotherapy which affected his voice, his saliva glands and the muscles in his neck which never recovered, leaving him with a permanently drooping head'.[31] This submitter listed the number of family members with mitochondrial disease, or mtDNA mutations, as being his mother, a sister who died at three days old, three other sisters and their children. This submitter likened mitochondrial donation as a 'chance to break this cycle of generation after generation of health catastrophes in families like mine'.[32]

2.30 Other submitters described the 'dashed hopes, heartbreak and utter despair' of being a parent to a child with mitochondrial disease:

> Our oldest son…presented in 1980 at the age of four with intermittent rhythmic convulsions of his right hand. These became progressively more frequent and more violent until he died three years later.
>
> When a precious seven-year-old son, his frail body wracked by convulsions, asks if he's going to die what does one say? [He] knew, and

28 Name Withheld, *Submission 18*, p. 1.

29 Name Withheld, *Submission 18*, p. 1.

30 Name Withheld, *Submission 9*, p. 1.

31 Name Withheld, *Submission 36*, p. 1.

32 Name Withheld, *Submission 36*, pp. 1–2.

> told us what he wanted to do before he died - another visit to the Snake Hut at Taronga Zoo, a special cake for afternoon tea and much more.[33]

2.31 A submitter described the impact of mitochondrial disease on her son, diagnosed at age 22:

> He is now age 40 years and the disease is slowly affecting his ability to cope with everyday living. At age 22 when he was first diagnosed with the disease he had a double chamber pace maker fitted to his heart. Since then the disease has been gradually affecting his health in areas such as hearing and eye sight. He now requires hearing aids and regular eye testing. He is at the stage where he has very poor vision in one eye and needs glasses to help with his sight. It is affecting his balance and he is reluctant to negotiate stairways etc. He has also been told he is on the verge of being affected with diabetes but is trying to avoid it with healthy diet and exercise. All brought about by mitochondrial disease. Although he tries to stay positive I can see at times that he has his down moments trying to cope with daily life. Unfortunately there is no known cure for this disease and no way of knowing what further health implications may arise for him in the future.[34]

2.32 Shelley told the committee of her brother's condition, which affected his energy:

> It was something that I didn't consider in terms of energy. Energy is also about swallowing. It's about having the energy to swallow. It's about having the energy to breathe, because all of those muscles are affected, and all of that energy is used. Your brain uses 20 per cent of your energy, so you're using so much of that energy every day to do things. So he struggled to eat. He struggled to put on weight. He struggled to keep that energy maintained. With the myoclonus seizures and the hearing loss, he then started experiencing vomiting. He would experience severe headaches. He was then investigated a bit further, and he was then given a diagnosis of stroke-like episodes, where he would suddenly lose strength in one side. But these sorts of strokes are more metabolic crises. It's that energy that you lose in your brain, which resulted in hallucinations. He started seeing little people on the floor. It also resulted in him not being able to communicate, because he had words in his head that he couldn't get out.[35]

2.33 Justin told the committee of the impact that losing his sight, as result of mitochondrial disease, had on his life: 'As you can imagine, when you lose your sight in the middle of your life it can have a devastating effect on your psychology, on your way forward and on your life generally. I am a single man and live alone, and so my independence has paid a price for that'.[36]

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33 Name Withheld, *Submission 14*, p. 1.

34 Name Withheld, *Submission 11*, p. 1.

35 Shelley, *Committee Hansard*, 17 May 2018, pp. 33–34.

36 Justin, *Committee Hansard*, 17 May 2018, p. 35.

Impact to families

2.34 Submitters and witnesses described the devastating effects of mitochondrial disease, both on the impacted individual and on their families. Ms Monica Ferrie, Chief Executive Officer of the Genetic Support Network of Victoria described the 'suffering' of Australian families:

> Children are being born with preventable disease and people are living with diseases that would be preventable through mitochondrial donation. Mothers pass this mitochondrial DNA onto their children and sometimes they can suffer as a result of knowing that their DNA has passed the disease on to their children.[37]

2.35 A submitter with three children affected by mitochondrial disease described the impact to her family:

> The personal, emotional, social and financial impact of the illness within our family, the loss of a daughter at age 18 after a 10yr battle, the decline in our 17yr old son who is potentially repeating the same battle again, and to look into the eyes of our 12yr old daughter who wonders if she is next and not wanting a child of her own dying the same way, is an impact I even find hard to imagine and repeatedly pinch myself, hoping to awake from this 'dream'.[38]

2.36 Another woman with mitochondrial disease submitted that her diagnosis directly impacted her decisions whether to have children:

> During my pregnancy I had no idea that my condition could be genetic and could affect my child, who is now 21yrs. Upon realising the then [sic] possibility of genetic implications, I made the sad decision that I would not risk passing mitochondrial disease onto any of my future children [and] that I would not have any more children. When he was younger, my son David would ask if he could have a sibling, unfortunately he grew up as an only child [and] we do not yet know if he will become affected by mitochondrial disease as I still have not yet received a genetic diagnosis.[39]

2.37 Mary told the committee of the significant impact that mitochondrial disease had in her family, which included 19 people with mitochondrial disease. 'I am in a position where I have the disease. I look after children who have the disease, and I'm also a carer for my mother who has mitochondrial disease. It really has devastated every generation of our family'.[40] Mary went on to state that in her family, mitochondrial disease was also characterised by stillbirth and late miscarriage, and

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37 Ms Monica Mary Ferrie, Chief Executive Officer, Genetic Support Network of Victoria, *Committee Hansard*, 17 May 2018, p. 2.

38 Name Withheld, *Submission 18*, p. 2.

39 Name Withheld, *Submission 33*, p. 2.

40 Mary, *Committee Hansard*, 17 May 2018, p. 34.

more broadly mitochondrial issues have a strong association with autism and other complications.[41]

Costs of mitochondrial disease

2.38 There are many costs for people living with mitochondrial disease, both to the healthcare and social services systems, as well as significant out of pockets costs to individuals. There are also related costs that are more difficult to quantify, such as carer costs of reduced economic participation.

Healthcare costs

2.39 AMDF provided an estimate of lifetime health care costs for a child born with a rare disease at around A$2.5 million in the UK and about A$5 million in the United States of America (USA).[42]

2.40 Other submitters also pointed to the very high costs of medical care for babies with severe mitochondrial disease. One submitter, the grandparent of a baby who lived only a few months, provided an estimation of medical costs:

> On top of the very sad personal and social costs of this trauma, the economic costs to the national healthcare budget of M's short life were significant and should be noted. Based on the 2013 schedule of fees for non-eligible (foreign visitor) patients for Eastern Health (BHH), it has been estimated that over M's life, true (not out-of-pocket) costs might have amounted to $300–350 thousand dollars. …
>
> If M had had a less severe version of mitochondrial disease and lived longer, the public costs via [the National Disability Insurance Scheme] and other schemes of assistance would have been much greater.[43]

2.41 One submitter outlined the varied medical costs as including 'constant visits to endocrinologists, cardiologists, neurologists, physiotherapists, psychologists and other professionals, as well as medication and transport costs etc'.[44] The submitter went on to cite the introduction of the National Disability Insurance Scheme (NDIS) as an opportunity to coordinate services for people, but stated that because mitochondrial disease often takes years to diagnose, there will still be a strain on the medical system for many more years than necessary.[45]

2.42 AMDF also noted the NDIS as an improvement to the lives of some families living with mitochondrial disease, citing information gathered from members of the mitochondrial disease community that prior to the NDIS, families were paying thousands of dollars out of pocket for medical and therapy costs. AMDF estimated

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41 Mary, *Committee Hansard*, 17 May 2018, pp. 34–35.

42 AMDF, *Submission 26*, p. 12.

43 Name Withheld, *Submission 39*, p. 2.

44 Name Withheld, *Submission 8*, p. 2.

45 Name Withheld, *Submission 8*, p. 2.

that the cost to taxpayers via the NDIS could range up to $120 000 per month for one individual child with mitochondrial disease.[46]

2.43 One submitter with mitochondrial disease outlined an estimate of costs for their case of adult mitochondrial disease:

> The amount I have used the Medicare system and gone beyond my threshold in the last 2 years is unbelievable. In 2016 alone Medicare had to pay for approximately $4000 worth of testing and Medical Professionals Fees. So for myself alone without adding up all of what other mitochondrial Disease patients use, it is taking a lot out of the system and if this can be prohibited for future generations, I believe this is our best option.[47]

2.44 Justin also pointed to the high health care costs of mitochondrial disease and told the committee that even with his diagnosis, which he described as relatively straightforward, his testing included 'two MRIs, lots of blood and urine tests, audiology testing, cardiology testing, gene testing and visual exams, all funded by the public purse'.[48] Justin went on to say his ongoing care included seeing 'many different specialists in Adelaide, where I live, and also here in Sydney. I see four different specialists here, including Professor Sue. It's also funded by Medicare, of course. I also have a heavy reliance on my GP, of course'.[49]

2.45 An economic analysis of the health system and administrative costs of introducing mitochondrial donation undertaken by the Health Department in the UK calculated a net benefit of GBP32 million per annum (approximately A$61 million) for mitochondrial donation if it enabled the births of just 20 healthy children per year.[50]

2.46 That estimate does not include savings from social services, income support or the increase in economic participation of affected individuals, parents and other carers. Other health cost information from submitters shows that in the USA, direct costs for hospitalisation of mitochondrial disease patients is approximately US$113 million per annum.[51]

2.47 Professor Thorburn provided an estimated health care savings of A$33 million to A$66 million per year from introducing mitochondrial donation in Australia, resulting in a conservative estimate of five to 10 children born without mitochondrial disease.[52]

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46 AMDF, *Submission 26*, p. 12.

47 Name Withheld, *Submission 32*, p. 2.

48 Justin, Committee Hansard, 17 May 2018, p. 36.

49 Justin, *Committee Hansard*, 17 May 2018, p. 36.

50 Professors Thorburn, Christodoulou, Sue, Carroll, Ryan and Filipovska, *Submission 59*, p. 4.

51 Associate Professors Catherine Mills and Karinne Ludlow, Professor Robert Sparrow, Dr Narelle Warren, *Submission 20*, p. [11].

52 Murdoch Children's Research Institute and Victorian Clinical Genetics Services, *Submission 23*, p. 16.

Other costs

2.48 Submitters described the cost of mitochondrial disease as being much broader than the medical costs, as people with the disease – and their carers – have significant loss of economic activity:

> She was unable to work, drive a car or socialize. Eventually she lost all independence and could not cook or care for herself. One of us, usually her mother, had to be with her constantly.[53]

2.49 A young woman with mitochondrial disease submitted that she often relied on family assistance for daily activities. She submitted 'I become reliant off their assistance for the things that I can no longer do myself. They help me cook, shower, drive, and constantly support me through my darkest of times'.[54]

2.50 The parents of a young boy with mitochondrial disease outlined the costs of mitochondrial disease as being threefold. Firstly there were medical and support costs of medical specialists, classroom supports, subsidised medicine, weekly therapy sessions and an assumed lifetime of welfare dependency. Secondly, the parents had an economic participation cost, as both had worked part-time since their child's diagnosis and it was expected at least one parent would have to quit working to become a full time carer. Thirdly, the parents pointed to the emotional cost, saying '[t]he emotional drain on our lives, the lives of our families and friends have been significant, this has impacted our sense of wellbeing and happiness in society'.[55]

2.51 Justin told the committee that due to his vision loss from mitochondrial disease, he received a blind pension, as did his sister: 'I also receive a mobility allowance and transport concessions that are very useful but are, of course, a drain on the public purse. Likewise, my return to work has been facilitated by very expensive technology that allows us to adapt our workplace through software and other modifications. I would estimate, from what I understand, $25 000 to $30 000 has been spent on that alone. That process has been assisted by the support of a disability support organisation, also funded by the public purse.' Justin also pointed to the impact to his economic activity, as he formally had a senior role in the South Australian Government and now had a part-time role in a less senior position.[56]

2.52 Professor Aleksandra Filipovska, an expert in mitochondrial disease with the Harry Perkins Institute of Medical Research, outlined the varied costs of mitochondrial disease and their impact to individuals and families:

> Because of the severe and drawn-out course of these diseases, the emotional, societal, and financial costs are devastating. As a researcher who has had experience in providing molecular diagnosis for patients and families affected by mitochondrial disease I have seen the devastation it

53 Name Withheld, *Submission 14*, p. 2.

54 Name Withheld, *Submission 32*, p. 2.

55 Name Withheld, *Submission 38*, p. 2.

56 Justin, *Committee Hansard*, 17 May 2018, p. 36.

> causes not just in terms of the difficult pathologies but the stress and emotional turmoil in caring for the affected loved ones as well as the concerns related to future family planning.[57]

Options for having children

2.53 A diagnosis of mtDNA mutations, whether or not it has manifested itself into mitochondrial disease, has strong implications for the ability to have healthy children because the mutations are inheritable. Professor Thorburn noted that, in some cases there is a 100 per cent chance of passing on the mtDNA mutation.

2.54 A submitter affected by mitochondrial disease considered its heritability to be one of the worst aspects of the disease:

> The trauma of watching both my mum and brother deteriorate so rapidly and so devastatingly, will stay with me forever…Knowing all this, and losing half my family in 16 months is difficult. What makes it even more life changing is finding out that I too have this disease and will possibly face the same devastating journey. But worse than this, I would almost certainly pass this disease on to my children.[58]

2.55 A submitter described the option of having children without intervention as a gamble:

> [I]f you have a defect in your mitochondrial DNA, you're essentially making a gamble. There's no way of knowing if you'll pass on a little bit of the defected mitochondria or all of your defected mitochondria. Meaning the child could have a mild to extreme form of the illness. Mild like me or extreme and be terminal. And we're just not the gambling types.
>
> However, the introduction mitochondrial donation IVF, literally removes the risk of throwing the dice and gambling with a future child's health.[59]

2.56 Another submitter described mitochondrial disease as a 'ticking time bomb' hanging over multiple generations of their family.[60]

2.57 One submitter, a parent of a young child with mitochondrial disease, described the situation faced by people with mitochondrial disease when considering having children:

> Families with Mitochondrial disease face a terrible choice. Do they run the risk of passing their mitochondrial donation onto the next generation or lose the opportunity to have children?[61]

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57 Professor Filipovska, *Submission 17*, p. 1.

58 Name Withheld, *Submission 8*, p. 1.

59 Name Withheld, *Submission 9*, p. 1.

60 Name Withheld, *Submission 39*, p. 2.

61 Name Withheld, *Submission 38*, p. 2.

2.58 Shelley told the committee about the increased importance of having a child with a genetic link to couples who faced the potential of one of them dying early from mitochondrial disease:

> We're not going to play god. We don't want to design a baby. We just want to have a healthy child as much as possible and be able to call them our own. If something were to happen to me, which I believe it will, my husband can look at that child and say: "You've got your mum's eyes. You've got her personality. You've got her smile. You're just as kind as she was." So, for us, that's a really important component that we believe this can offer us.[62]

2.59 The current options available to women with mtDNA mutations when considering having children are primarily to use donated eggs or to adopt.

2.60 For women who want to have a child with a genetic link, an option is in vitro fertilisation (IVF) using pre-implantation genetic diagnosis (PGD), where embryos are tested before implantation to look for those with the lowest proportion of mutated mtDNA. This option only works for some types of mitochondrial disease and has other limitations.

2.61 The various options for having children with a reduced risk of mitochondrial disease are outlined below.

IVF and Pre-implantation genetic diagnosis (PGD)

2.62 As discussed above, PGD is an IVF technique used to test the embryo prior to implantation. A key limitation to this method is it cannot be used by all women with mtDNA mutations. Some women have normal and mutated mtDNA in their cells (heteroplasmy) and others have all mutated mtDNA (homoplasmy). PGD can only benefit women who are heteroplasmic. Moreover, this technique can only reduce, not eliminate the risk of having an affected baby. Even if unaffected themselves, girls born after the use of this procedure may themselves still be at risk of having affected children, as some abnormal mitochondria may be present in their eggs.[63]

2.63 A group of leading scientists in the field of mitochondrial disease submitted that women with lower amounts of mtDNA mutations are at lower risk of having a child affected by mitochondrial disease and techniques such as PGD can be appropriate.[64] However, the submission goes on to state:

> [I]t remains impractical to predict the actual risk for most women, many of whom are thought to have a risk of between 50% to 100% of having a child with severe disease. Thus for probably most women from families with

62 Shelley, *Committee Hansard*, 17 May 2018, p. 34.

63 House of Commons Library (UK), *Mitochondrial Donation*, Standard Note: SN/SC/6833, 29 January 2015, pp. 6–7.

64 Professors Thorburn, Christodoulou, Sue, Carroll, Ryan and Filipovska, *Submission 59*, p. 1.

> mtDNA disease, mitochondrial donation offers the best prospect of having a healthy child related to both parents.[65]

Prenatal diagnosis

2.64 Prenatal diagnosis can be conducted on a pregnant woman at around 11–14 weeks gestation, usually by performing a genetic test on a placental tissue biopsy. If an mtDNA mutation is found, parents then face a choice of either continuing or terminating the pregnancy.[66]

2.65 Professor Christodoulou explained the improvements in prenatal testing in determining potential genetic mutations in a foetus:

> [D]epending on which specific mitochondrial DNA change you're looking at, you can actually be very accurate in your prediction about what the likely outcome of that will be to subsequent babies…for instance, for a particular mitochondrial DNA mutation, pre-implantation genetic diagnosis is a very viable alternative to mitochondrial donation. However, for many other mitochondrial DNA mutations, mitochondrial donation is really the only option.[67]

2.66 Professor Thorburn further told the committee that for some women, a low mtDNA mutation load means they have a low risk of passing on mtDNA mutations to children and prenatal diagnosis and PGD are good options, however 'for the majority of women, there is going to be a substantial amount of the mutant mitochondrial DNA in many or all of their eggs and so it's very unlikely that those techniques will work. It's quite complicated genetics'.[68]

2.67 A submitter affected by mitochondrial disease explained the PGD process she had undertaken. She had undertaken five IVF cycles – at a cost of $7000 per cycle – which retrieved around 50 eggs, from which only two embryos had a relatively low mutation loading of 32 per cent, not meeting the generally accepted benchmark of a maximum 15 per cent mutation load:

> Emotionally, the rollercoaster of having to desperately rely on success at each stage – retrieving as many eggs as possible, having them fertilise, seeing how many survive and grow to day 5, then biopsy the surviving embryos to establish their mutation loading. Going through each stage of a cycle generally means going from 14 eggs down to 3 biopsied embryos only to find out that they do not meet the loading threshold. It is a difficult and draining process that seems unfair and frustrating. With any couple

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65 Professors Thorburn, Christodoulou, Sue, Carroll, Ryan and Filipovska, *Submission 59*, pp. 1–2.

66 Mitochondrial Disease News, *Prenatal Diagnostic Testing for Mitochondrial Diseases May Help Future Parents, UK Study Shows*, 10 March 2015, https://mitochondrialdiseasenews.com/2015/03/10/prenatal-diagnostic-testing-for-mitochondrial-diseases-may-help-future-parents-a-study-in-uk-shows/ (accessed 15 June 2018).

67 Professor Christodoulou, *Committee Hansard*, 17 May 2018, p. 16.

68 Professor Thorburn, *Committee Hansard*, 17 May 2018, pp. 15–16.

> trying to have a child, time is a factor, as well as health. For us, PGD seems to show little success.[69]

2.68 Another submitter described the PGD process that her daughter had undertaken, after losing a baby to mitochondrial disease. The daughter had undergone a year of IVF with PGD and had embryos implanted, but had no success through IVF. The submitter argued that they considered the best option for their family was one that was not open to them because mitochondrial donation is prohibited by legislation.[70]

2.69 Mary described her experiences with IVF and genetic counselling as a 'process of discussing the value of our unborn children's lives'. Mary further told the committee that:

> Mitochondrial donation gives my children a chance to not go through that, to not have to consider the value of their own lives and those of their unborn children, and to raise healthy children who, in turn, will then have healthy children. If we choose not to do this there is no choice for our family. There will just be generation after generation of this terrible disease.[71]

Non-genetic options: adoption, fostering or donated eggs

2.70 Submitters who were not in favour of mitochondrial donation, generally for ethical reasons, argued that other options could be used for people with mtDNA mutations who wished to have children. These were primarily adoption or fostering, or the use of donor eggs for IVF.

Donor eggs

2.71 Another option that was suggested as a possible alternative to mitochondrial donation was using IVF in conjunction with an egg donated from an unaffected woman.

2.72 As outlined by Professor Sheryl de Lacey from Flinders University, most egg donation in Australia relies on local donors who are often family members. Egg donation from family members is obviously not suitable for mitochondrial disease which is a genetic condition. An estimated 25 per cent of Australian patients who cannot get a local donor acquire one from overseas. This raises its own ethical challenges due to differing regulation of the donor process and information in those jurisdictions.[72]

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69 Name Withheld, *Submission 8*, pp. 1–2.

70 Name Withheld, *Submission 39*, p. 2.

71 Mary, *Committee Hansard*, 17 May 2018, p. 35.

72 Professor Sheryl de Lacey, *Submission 55*, p. 3.

Adoption and fostering

2.73 Critics of mitochondrial donation argued that adoption or fostering 'would offer a simpler path'[73] to parenthood. However, adoption and fostering programs in Australia have strict eligibility criteria, including health screening. AMDF has sought information on eligibility for people with mitochondrial disease (or asymptomatic mtDNA mutations) and in a submission indicates a lack of definitive advice on eligibility. AMDF notes that this is generally due to a lack of specific preclusions.[74]

2.74 AMDF further notes in a submission that given the level of trauma that children involved in adoption have faced, states and territories 'have a preference towards prospective parents who have the highest possibility of seeing children into adulthood'.[75]

2.75 Anglicare is an Anglican diocese-run charitable organisation that offers foster care and adoption services. On its website, Anglicare lists its eligibility criteria for families looking to adopt. One of the criterion relates to health which relevantly provides:

> Health – Applicants must be non-smokers, in good general health with normal life expectancy.[76]

2.76 Even if people living with mitochondrial disease were eligible to adopt, Professor de Lacey explained that adoption is not a simple substitute for biological reproduction. In Australia, there are few children in need of adoption and most children are adopted by people who already care for them.[77]

2.77 Professor de Lacey provided the committee with the statistics on local Australian adoptions in 2016–17:

> Of the total number of adoptions only 42 (13%) were 'local' adoptions, ie. Adoptions of an Australian child to parents not previously known to them.

2.78 While it might entail less scientific risk than mitochondrial donation, it is not clear that adoption is necessarily an option for women living with a mitochondrial disease.

2.79 For some submitters, adoption or fostering was not considered a suitable option, as they had a strong desire to have a genetically linked child:

> We have considered all the other avenues of egg donor, adoption or not having children. We have a strong desire to have our own child who

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73 Australian Catholic Bishops Conference, *Submission 28*, p. 2. See also Australian Christian Lobby, *Submission 51*, p. 8; Social Issues Committee of the Anglican Church Diocese of Sydney, *Submission 56*, p. 3.

74 AMDF, *Submission 26.1*, [p. 13].

75 AMDF, *Submission 26.1*, [p. 13].

76 Anglicare, *Looking to Adopt*, https://www.anglicare.org.au/what-we-offer/foster-care-adoption/adoption/looking-to-adopt/ (accessed 30 May 2018).

77 Professor de Lacey, *Submission 55*, p. 3.

> inherits our genes, our personalities, ourselves. If something were to happen to either of us, we would still have a part of each other. When we heard about mitochondrial donation, we felt that this would provide us with the opportunity to have a child who would be genetically (99%) ours, but most importantly healthy.[78]

Remaining childless

2.80 Critics of mitochondrial donation have also proposed the option for remaining childless should be considered by people with a risk of passing on mitochondrial disease. Archbishop Anthony Fisher, Archbishop of Sydney and Vice Chair of the Australian Catholic Bishops Commission, told the committee that 'obviously the more serious the risk [of passing on mitochondrial disease] the more you are going to have to think very carefully and act responsibly'.[79]

2.81 The submission from the Anglican Church Diocese of Sydney states:

> [W]e do not believe that a 'right' to a biological child exists, and can see no grounds by which such a right would be established.
>
> We therefore do not accept the premise that any means available to obtain offspring should be made available to individuals suffering from the inability to ensure that their offspring is healthy.[80]

Committee view

2.82 The committee notes that for many people there is a desire to have a genetically linked child.

2.83 The committee also notes that reproductive technology is widely used by the Australian community, including the use of donor gametes. Donor gametes are commonly used to overcome medical infertility, social infertility or transferable genetic conditions. As a result many families are successfully created where the resulting offspring is not genetically linked to one or both parents.

2.84 The committee notes that reproductive technology is expensive for both taxpayers and prospective parents. The committee considers that it is desirable for governments to support fertility treatment as a social good. However, it does not support the notion that the state has an unlimited responsibility to support people to become parents, and considers that any such treatments should be provided on an equitable basis.

Mitochondrial donation

2.85 As outlined in chapter one, mitochondrial donation is a technique to replace the mutated mtDNA in an egg, or a pre-embryonic fertilised egg. Chapter three discusses the science in greater detail.

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78 Name Withheld, *Submission 8*, p. 2.

79 Archbishop Anthony Fisher, Vice President, Australian Catholic Bishops Conference, *Committee Hansard*, 17 May 2018, p. 68.

80 Social Issues Committee of the Anglican Church Diocese of Sydney, *Submission 56*, p. 1.

2.86 A number of witnesses and submitters impacted by mitochondrial disease made strong requests for this technology to be made available to Australian families. A submitter who had two children die from mitochondrial disease described mitochondrial donation as an opportunity for future children to 'experience the joys and sorrows of a full life that [their children] couldn't'.[81] The submitter went on to state:

> Our remaining children have had their DNA sequenced and they know they won't develop mitochondrial disease so in that sense the uncertainty for our family is over. But for other families with mito around Australia who want to have children, their nightmare is only beginning. The constant anxiety and sense of hopeless foreboding at knowing that their precious child could be affected is overwhelming.[82]

2.87 Another submitter argued that as there is no cure for mitochondrial disease, mitochondrial donation is the only hope for some families:

> A big black cloud that has been hanging over my family for years is slowly starting to dissipate. If this technology was available when I was having my children, I most certainly would have used it and I will be strongly encouraging my daughters… to consider Mitochondrial Donation if ever they decide to start a family.[83]

2.88 Professor Sue, a clinician working in mitochondrial disease, told the committee of that she sees patients on a weekly basis who are asking for access to this technology 'because the patients are traumatised by family members being lost, they live day to day with the burden of illness of this disorder and they are keen to have children without this disorder.'[84]

2.89 Another submitter put their request very simply:

> Please approve [mitochondrial donation]…no Mother should have to sit by a bed watching their children die of something that you have in your power to help prevent.[85]

Committee view

2.90 The committee agrees that mitochondrial disease is a devastating and often life-threatening condition. The traumatic impact to parents who have watched their child die, in some cases more than one child, cannot be overstated.

2.91 The committee further agrees that there is a desire in most people to have a genetically linked child.

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81 Name Withheld, Submission 14, [p. 2].

82 Name Withheld, *Submission 14*, [p. 2].

83 Name Withheld, *Submission 15*, p. 2.

84 Professor Sue, *Committee Hansard*, 17 May 2018, p. 24.

85 Name Withheld, *Submission 6*, p. 1.

2.92 There are a range of options for people impacted by this genetic condition to have children. However, many of those options do not result in a genetically linked child and others are not suitable for women with certain mtDNA mutations. For those women, and indeed the children they wish to bring safely into this world, mitochondrial donation may provide a new option.

2.93 The committee is cognisant that this technology, like all new medical therapies, comes with risk and ethical concerns that must be taken into consideration prior to any possible change in legislation.

Chapter 3

Science of mitochondrial donation

3.1 Chapters one and two of this report briefly covered what mitochondria are and how mutations in mitochondrial DNA[1] (mtDNA) can cause mitochondrial disease.

3.2 Mitochondrial donation techniques allow the mother's mutated mtDNA, which will lead to the potential formation of a mitochondrial disease, to be substituted for a donor's healthy mtDNA.

3.3 This chapter will cover the mitochondrial donation techniques that could be used to prevent the transmission of this mutated mtDNA to the children of women living with a mitochondrial disease and will consider some of the scientific risks associated with these techniques.

Mitochondrial donation techniques

3.4 Throughout the course of this inquiry, the committee was advised there were four possible methods of mitochondrial donation: maternal spindle transfer, pronuclear transfer, polar body transfer and germinal vesicle transfer. These techniques are outlined below.

Maternal spindle transfer

3.5 Maternal spindle transfer is a technique in which the spindle shaped group of chromosomes containing the mother's nuclear DNA, known as the 'maternal spindle', is extracted from one of the mother's eggs (oocytes) and transferred to an unfertilised donor egg from which the maternal spindle has been removed and that contains healthy mtDNA.[2]

3.6 Once the maternal spindle has been transferred to the donated egg with the healthy mtDNA, the egg is fertilised with the father's sperm and then implanted into the uterus in a manner similar to other in vitro fertilisation (IVF) techniques.[3]

3.7 By removing the maternal spindle and inserting it into an egg with healthy mtDNA, the resulting offspring will receive the 22 000 base pairs of nuclear DNA from the parents, but will have the 37 base pairs of healthy mtDNA from the oocyte donor.[4]

3.8 A visual diagram of a maternal spindle transfer is included below.

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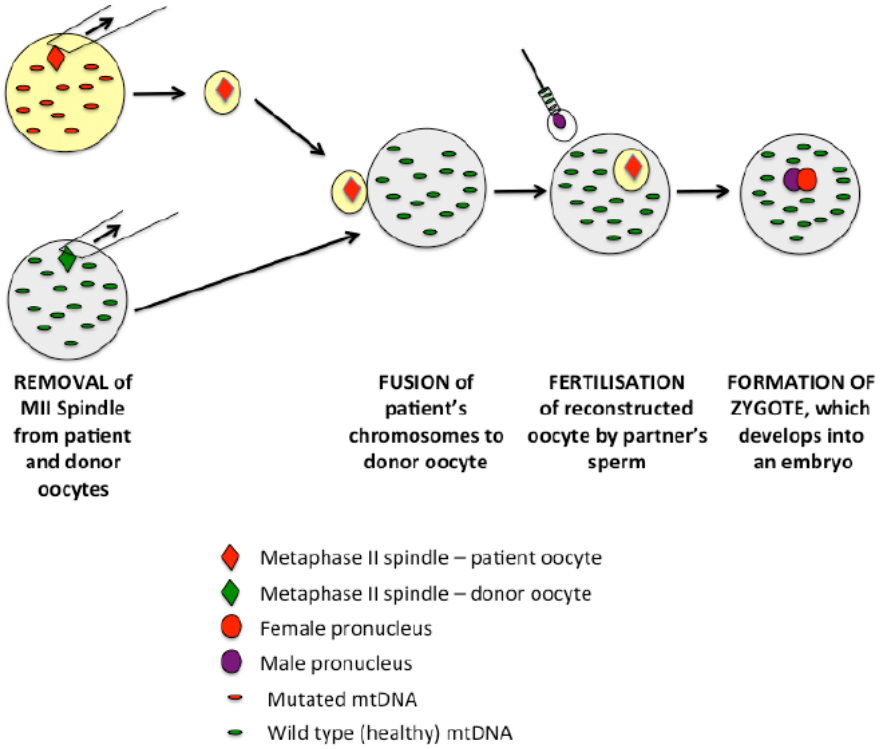
1 Deoxyribonucleic acid.

2 Wellcome Trust, *Submission 1—Attachment 3*, [p. 3]; National Health and Medical Research Council (NHMRC), *Submission 4*, p. 3; Dr Peter McCullagh, *Submission 46*, [p. 6].

3 Wellcome Trust, *Submission 1—Attachment 3*, [p. 3].

4 Mr Sean Murray, Chief Executive Officer, Australian Mitochondrial Disease Foundation (AMDF), *Committee Hansard*, 17 May 2018, pp. 3–4.

Figure 3.1—Maternal spindle transfer



Source: Professor Justin St John, *Submission 31*, [p. 7].

Current status

3.9 In the United Kingdom (UK), maternal spindle transfer is one of two methods that have been legalised by The Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015 (UK).[5]

3.10 As it is not the method that is preferred by the clinic that is currently licensed to conduct mitochondrial donation, less research has been conducted using this method. Professors David Thorburn, John Christodoulou, Carolyn Sue, John Carroll, Mike Ryan and Aleksandra Filipovska advised the committee that this technique has been used successfully in Macque monkeys by a research group in Oregon in the United States of America (USA) and has led to one live birth.[6] However, at this stage, maternal spindle transfer has not yet 'been fully optimised for human eggs'.[7]

5 The Human Fertilisation and Embryology (Mitochondrial Donation) Regulation 2015 (UK), reg. 4 (UK Regulations).

6 Professors David Thorburn, John Christodoulou, Carolyn Sue, John Carroll, Mike Ryan, Aleksandra Filipovska, *Submission 59*, p. 5. See also J Zhang, H Liu, S Luo, Z Lu, A Chavez-Badiola, Z Liu, M Yang, Z Merhi, SJ Silber, S Munne, M Konstantinidis, D Wells, JJ Tang, T Huang, 'Live birth derived from oocyte spindle transfer to prevent mitochondrial disease', *Reproductive Biomedicine Online*, vol. 34, no. 4, pp. 361–368.

7 Professors David Thorburn, John Christodoulou, Carolyn Sue, John Carroll, Mike Ryan, Aleksandra Filipovska, *Submission 59*, p. 5.

3.11 In Australia, the National Health and Medical Research Council (NHMRC) has advised the committee that research on maternal spindle transfer is currently prohibited by section 13 of the *Prohibition of Human Cloning for Reproduction Act 2002* (Cloning Act) which provides:

> A person commits an offence if:
>
> (a) the person intentionally creates or develops a human embryo by a process of the fertilisation of a human egg by a human sperm outside the body of a woman; and
>
> (b) the human embryo contains genetic material provided by more than 2 persons.
>
> Penalty: Imprisonment for 15 years.

3.12 The maternal spindle transfer method is prohibited because the process requires fertilising a human egg, creating an embryo with genetic material from more than two persons.

Pronuclear transfer

3.13 The same difficulty is not experienced with the pronuclear transfer technique because the egg is fertilised, prior to the nuclear DNA transfer occurring.[8] When an egg is fertilised and becomes a zygote, two pronuclei are formed (one from the mother and one from the father) containing the parents' nuclear DNA. For pronuclear transfer, a second zygote must be created from a donor egg and the father's sperm. The two pronuclei from the first zygote are removed and transferred to the donor zygote with healthy mtDNA.[9] The donor zygote, which needs to be at the same stage of development, has had its pronuclei removed to facilitate the transfer.[10]

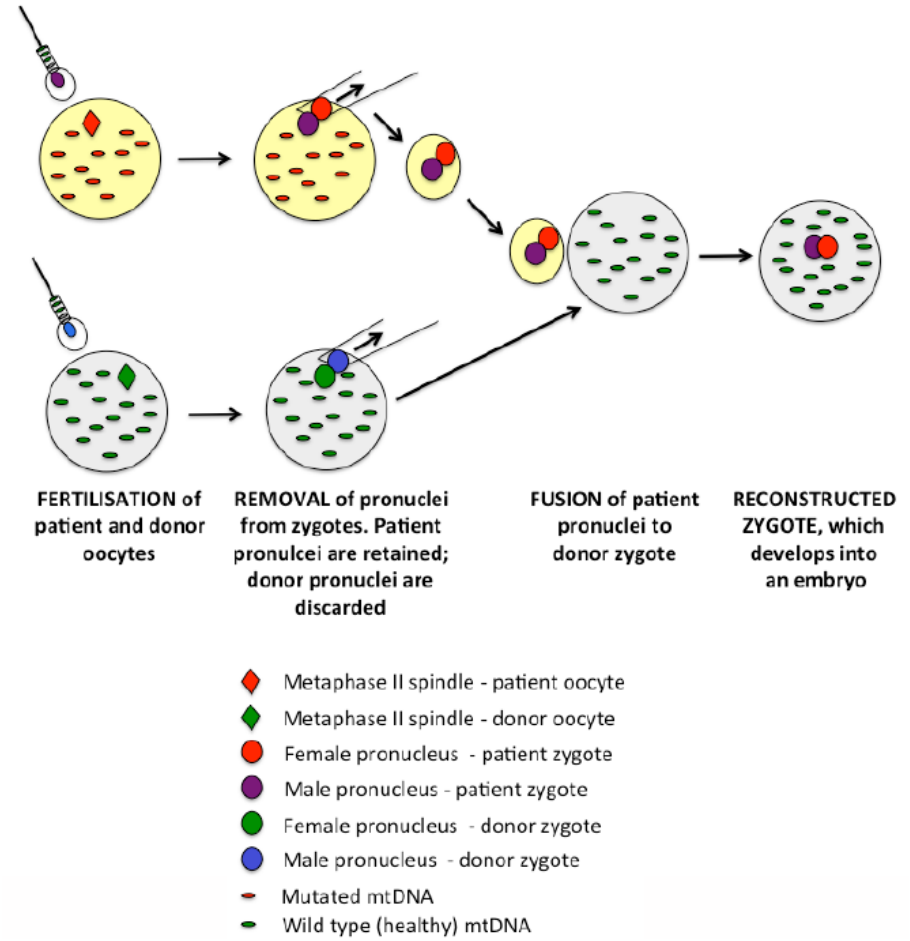
3.14 A visual diagram of pronuclear transfer is included below.

8 A zygote is a fertilised egg which may then develop into an embryo.

9 Professors Thorburn, Christodoulou, Sue, Carroll, Ryan, Filipovska, *Submission 59*, p. 4.

10 Professor Justin St John, Professor and Head, Mitochondrial Genetics Group, Hudson Institute of Medical Research, *Committee Hansard*, 17 May 2018, p. 44.

Figure 3.2—Pronuclear transfer



Source: Professor Justin St John, *Submission 31*, [p. 7].

Current status

3.15 Pronuclear transfer is the second method that has been legalised in the UK.[11]

3.16 Pronuclear transfer is the technique that has been investigated in greater depth by the clinic at the University of Newcastle-upon-Thyne in the UK which holds the licence from the Human Fertilisation Embryology Authority (HFEA) to perform mitochondrial donation.[12]

3.17 In Australia, the NHMRC has advised the committee that a licence to research the pronuclear transfer technique can be granted under current legislation because the egg has already been fertilised prior to its transfer to the donor egg.

11 UK Regulations, reg. 7.

12 Mr Murray, *Committee Hansard*, 17 May 2018, p. 4; Professor John Carroll, Director, Monash Biomedicine Discovery Institute, Monash University, *Committee Hansard*, 17 May 2018, p. 25.

3.18 It is, however, subject to two other restrictions: first, the Cloning Act restricts the development of any embryo outside the body of a woman to a period of 14 days.[13] The NHMRC explained that it was possible for some research to be conducted:

> The creation of the reconstructed embryo could also be licensed under paragraph 20(1)(c) and it could be maintained in culture to assess the success of the procedure provided it was discarded before 14 days had elapsed.[14]

3.19 The second restriction precludes pronuclear transfer, or any other form of mitochondrial donation technique, from being used for reproduction. This restriction arises because any embryo containing the genetic material of more than two persons is considered to be a prohibited embryo for the purposes of the Cloning Act and cannot be implanted into a uterus for development into a foetus.[15]

Polar body transfer

3.20 A third possible method for mitochondrial donation is known as polar body transfer. There are two different techniques for polar body transfer.

3.21 During each menstrual cycle, some eggs are 'selected' for maturation and growth. As part of this process, the cell divides and leads to the formation of a secondary egg that contains mostly nuclear DNA and very little cytoplasm, which is the surrounding material in which the mitochondria are found. This is known as the first polar body.

3.22 The first polar body transfer technique extracts the first polar body, which sits outside of the main egg, and fuses it to an unfertilised egg that has had its maternal spindle removed. The reconstituted egg is then fertilised by the patient's partner's sperm.

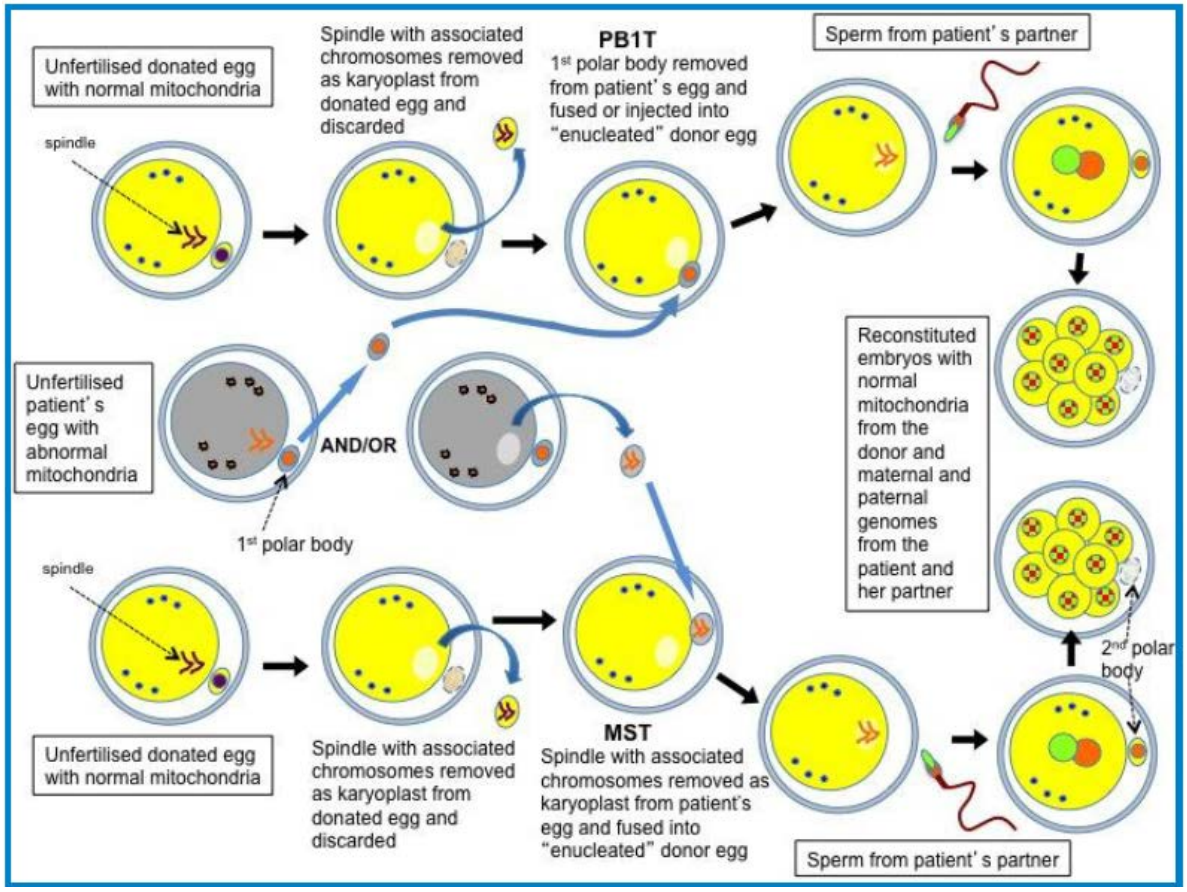
3.23 A visual representation of the first polar body technique in comparison to the maternal spindle transfer technique is included below.

13 *Prohibition of Human Cloning for Reproduction Act 2002* (Cloning Act), s. 14; NHMRC, *Submission 4*, p. 7.

14 NHMRC, *Submission 4*, p. 7.

15 Cloning Act, s. 20; NHMRC, *Submission 4*, p. 7.

Figure 3.3—First polar body transfer



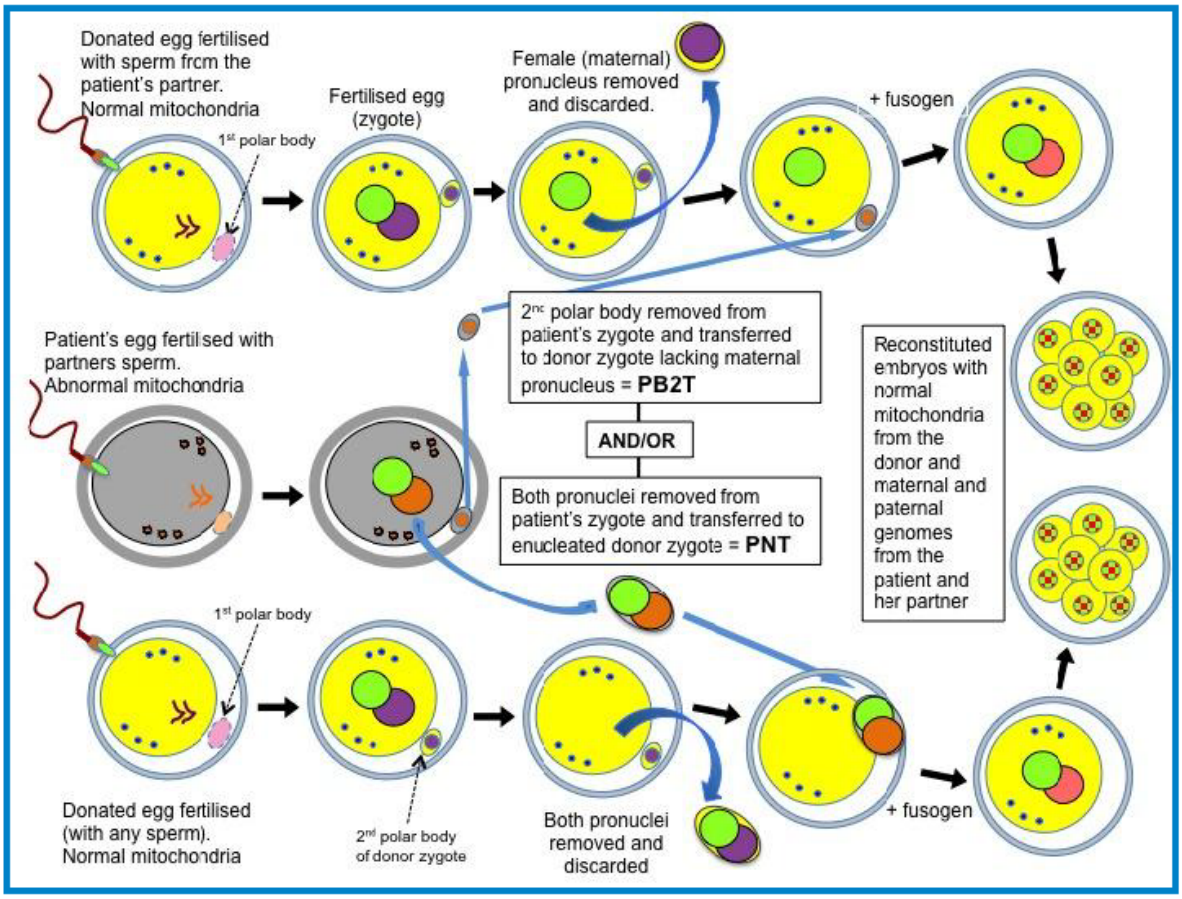
Source: HFEA, *Review of the safety and efficacy of polar body transfer to avoid mitochondrial disease*, October 2014, additional information received 30 May 2018, p. 17.

3.24 The second polar body is formed during fertilisation when the egg splits again. The second polar body transfer technique involves extracting the second polar body after fertilisation and transferring it to a newly fertilised egg that has had its maternal nuclear DNA removed.[16] The second polar body is then fused into the reconstituted egg.

3.25 A visual representation of second polar body transfer and how it compares to pronuclear transfer is included below.

16 Human Fertilisation and Embryology Authority (HFEA), *Review of the safety and efficacy of polar body transfer to avoid mitochondrial disease*, October 2014, additional information received 30 May 2018, p. 4.

Figure 3.4—Second polar body transfer



Source: HFEA, *Review of the safety and efficacy of polar body transfer to avoid mitochondrial disease*, October 2014, additional information received 30 May 2018, p. 18.

3.26 There may be advantages to using polar body transfer over maternal spindle transfer or pronuclear transfer because it may:

- reduce mtDNA carryover;
- reduce the risk of leaving chromosomes behind in maternal spindle transfer; and
- be possible to carry out both polar body transfer and either maternal spindle transfer or pronuclear transfer.[17]

3.27 However, at this stage it does not appear that polar body transfer techniques have been as advanced as some of the other methods.

Current status

3.28 In the UK, polar body transfer cannot legally be used in clinical practice. A safety and efficacy review of polar body transfer conducted by the HFEA found that

17 HFEA, *Review of the safety and efficacy of polar body transfer to avoid mitochondrial disease*, October 2014, additional information received 30 May 2018, p. 6.

while polar body transfer techniques were developing quickly, they were still at an early stage.[18]

3.29 Professors Thorburn, Christodoulou, Sue, Carroll, Ryan and Filipovska advised the committee that they understand that the technique is still at the preclinical study stage and further work is still required to understand and optimise the procedure.[19]

3.30 The committee is not aware of polar body transfer research being conducted in Australia.

Germinal vesicle transfer

3.31 Another possible technique pioneered by Professor Justin St John is called germinal vesicle transfer. This method, which was not well-known by many of the submitters, is similar to maternal spindle transfer except that it uses an egg that is at an earlier stage of development.

3.32 In germinal vesicle transfer, the germinal vesicle (which will develop into the maternal spindle) is extracted from an egg that is at an earlier stage of development and the germinal vesicle is allowed to develop in vitro.[20]

3.33 Professor St John explained that there may be benefits to using this technique because it would not require the woman to undergo superovulation protocols and may give the chromosomes 'a bit longer to readjust to the new environment they are in'.[21]

3.34 Currently, there is little data of germinal vesicle transfer. [22]

3.35 Professors Thorburn, Christodoulou, Sue, Carroll, Ryan and Filipovska advised the committee that success rates using this technique are currently low that 'the need to retain the egg's supporting cells will create technical challenges'.[23]

3.36 A visual diagram of the germinal vesicle transfer technique is included below.

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18 HFEA, *Review of the safety and efficacy of polar body transfer to avoid mitochondrial disease*, October 2014, additional information received 30 May 2018, pp. 5–6.

19 Professors Thorburn, Christodoulou, Sue, Carroll, Ryan, Filipovska, *Submission 59*, p. 7.

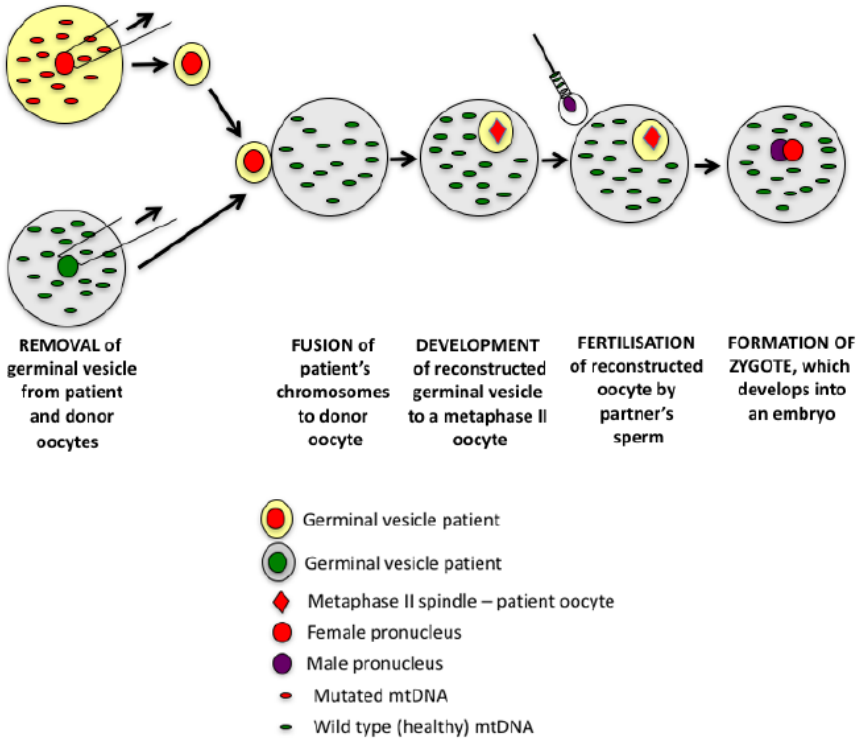
20 Professor Justin St John, *Submission 31*, [p. 2].

21 Professor St John, *Committee Hansard*, 17 May 2018, p. 43.

22 Professor St John, *Committee Hansard*, 17 May 2018, p. 43.

23 Professors Thorburn, Christodoulou, Sue, Carroll, Ryan, Filipovska, *Submission 59*, p. 5.

Figure 3.5—Germinal vesicle transfer



Source: Professor St John, *Submission 31*, [p. 9].

Current status

3.37 Germinal vesicle transfer has not been legalised in the UK for clinical implementation. In Australia, the same restrictions are likely to apply as currently apply to maternal spindle transfer.

Potential risks

3.38 Any emerging reproductive technology includes a degree of risk.[24] Witnesses and submitters to the inquiry explained the risks that may exist with mitochondrial donation techniques.

3.39 The threshold question for the committee's consideration of the matter was whether mitochondrial donation techniques are considered to be safe to perform on human embryos that will develop into live babies.

3.40 Submitters to the inquiry were largely of the opinion that mitochondrial donation is now safe to perform.[25]

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24 Professor David Thorburn, Head of Mitochondrial Research and Diagnostic Laboratories, Murdoch Children's Research Institute and Victorian Clincial Genetics Services, *Committee Hansard*, 17 May 2018, p. 12; Associate Professors Catherine Mills and Karinne Ludlow, Professor Robert Sparrow, Dr Narelle Warren, *Submission 20*, p. 3; Murdoch Children's Research Institute and Victorian Clinical Genetics Services (Murdoch Children's Research Institute), *Submission 23*, p. 4; AMDF, *Submission 26*, [p. 10]; Biomedical Ethics Group, Murdoch Children's Research Institute, *Submission 34*, [p. 2].

3.41 Before mitochondrial donation was legalised in the UK, these techniques were subject to four scientific reviews. The Wellcome Trust, a UK based charitable foundation that funds mitochondrial disease research, told the committee that scientific reviews conducted prior to legalisation concluded that the techniques were safe:

> Safety of the techniques is, and will always be, of paramount importance and has received unprecedented scrutiny. On three separate occasions the HFEA's specially convened independent Expert Scientific Review panel examined the safety and efficacy of mitochondrial donation. The panel reported that they found no evidence to suggest that the techniques are unsafe for clinical use, and concluded that both techniques have the potential to be used in patients with mitochondrial disease.[26]

Box 3.1—UK Scientific Reviews

Before mitochondrial donation was legalised in the UK three scientific reviews were undertaken by an expert panel convened by the regulator, the HFEA, to assess the safety and efficacy of the techniques.

The third scientific review was completed in 2014. The 2014 review recommended that:

a) additional experiments needed to be conducted to corroborate and improve the efficiency of the maternal spindle transfer technique;

b) additional experiments needed to be conducted to compare pronuclear transfer ooyctes with intracytoplasmic sperm injection oocytes; and

c) consideration should be given to mtDNA haplogroup matching.[27]

The fourth scientific review was completed in 2016. The 2016 review was conducted to update the 2014 scientific review and to consider whether the recommendations made in that report had been met. The review considered that good progress had been made on each recommendation. In addition, it recommended that clinicians carefully select patients, conduct prenatal testing and follow up and maintained the recommendation to use haplogroup matching as a precautionary step.[28]

25 Wellcome Trust, *Submission 1—Attachment 1*, p. 2; The Human Genetics Society of Australia, *Submission 2*, [p. 1]; Monash Biomedicine Discovery Institute, *Submission 19*, [p. 2]; Murdoch Children's Research Institute, *Submission 23*, p. 2; AMDF, *Submission 26*, [p. 10]; Fertility Society of Australia, *Submission 27*, p. 2 (Fertility Society); Dr Nigel Turner, *Submission 37*, [p. 1]; Nuffield Council on Bioethics, *Submission 43*, [p. 1]; Wellcome Centre for Mitochondrial Research, *Submission 45*, [p. 3]; Dr Shanti Balasubramaniam, *Submission 52*, [p. 3].

26 Wellcome Trust, *Submission 1—Attachment 1*, p. 2.

27 HFEA, *Review of the safety and efficacy of methods to avoid mitochondrial disease*, June 2014, additional information received 30 May 2018, p. 5.

28 HFEA, *Review of the safety and efficacy of methods to avoid mitochondrial disease*, November 2016, additional information received 30 May 2018, p. 5.

3.42 A similar conclusion has been reached by Australian experts. Professor John Carroll, Director of the Monash Biomedicine Discovery Institute at Monash University told the committee that the evidence did not indicate that there were any serious safety concerns:

> …a good deal of research has been done, and to date there's really very little evidence for serious safety concerns and certainly nothing that comes anywhere near close to the impact that genetic disease has. Being able to assess the risks associated with the procedure with the alternative outcome, I think there's very little doubt in my mind, at least, that they're very well balanced, and we should be able to proceed with investigating the treatment.[29]

3.43 Professor John Christodoulou, Chair of Genomic Medicine in the Department of Paediatrics at the University of Melbourne told the committee that he was unaware of any evidence that pointed to there being significant risks to a child born of a mitochondrial donation:

> There has been some theorizing that mitochondrial donation through proposed epigenetic mechanisms, or as a consequence of not using mtDNA haplogroup matched donor egg cells for the procedure, could lead to untoward effects on the health of the embryo or the child after birth. However, I am aware of no such evidence supporting the notion that there would be any significant risks to children born following mitochondrial donation.[30]

3.44 Some submitters though were more cautious about declaring the techniques as being safe to use. The submission from the NHMRC noted that although one child is known to have been born in Mexico using the maternal spindle transfer technique, his mutation load is currently unknown because:

> …his parents have requested no more testing for mtDNA unless there is a clinical benefit. Consequently, it may be difficult to assess the long-term success of the procedure.[31]

3.45 Professor St John considered that additional studies were required on large animal models to test the consequences of mtDNA carryover and test the effects of using eggs with different haplotypes.[32] These issues are considered in turn below.

Carryover of mutated mtDNA

3.46 Some submitters and witnesses to the inquiry expressed concerns about the potential effect of carrying over mutated mtDNA to the reconstituted donor egg during the transfer process.[33]

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29 Professor Carroll, *Committee Hansard*, 17 May 2018, p. 22.

30 Professor Christodoulou, *Submission 12*, p. 2.

31 NHMRC, *Submission 4*, p. 4.

32 Professor St John, *Submission 31*, [p. 4].

3.47 Professor Christodoulou explained that when the nucleus of the cell is transferred from one egg to another, a certain amount of the mutated mtDNA may be carried over:

> The process involves removing a nucleus and then implanting that nucleus into the egg cell that's had the nucleus removed and has the mitochondria. In the early days, the process of removing the nucleus, as part of it, took a number, or a proportion, of mitochondria—and therefore mitochondrial DNA—along with it in that process. That's that sort of carryover phenomenon.[34]

3.48 Some submitters expressed concern that if mutated mtDNA is transferred to the donor egg, the child may still end up with a mitochondrial disease.

3.49 According to Professor Christodoulou, the expert committee for the HFEA recommended that mtDNA carryover rates should not exceed two per cent and should be no greater than 10 per cent per embryo.[35] A number of witnesses who provided evidence to the committee, including Professor Christodoulou, endorsed the two per cent figure as representing a safe level below which a child was unlikely to develop a mitochondrial disease.[36]

3.50 This figure is considered to be a safe level because, as Associate Professor Damian Dowling from the School of Biological Sciences at Monash University explained in his submission, mutations in mtDNA do not generally cause mitochondrial disease until the mutated mtDNA comprises 70–80 per cent of the pool of mtDNA.[37] However, Associate Professor Dowling suggested that even a small amount of carryover may present a risk to the child. The risk may exist because mtDNA cell numbers are not static across a person's life and experimental studies have shown that the unhealthy mtDNA cells can 'outcompete' the healthy mtDNA cells:

> Experimental studies in flies, yeast, worms, and human cell lines have shown that defective mtDNA molecules often proliferate more rapidly than healthy molecules, and can thus, somewhat ironically, outcompete their healthy mtDNA counterparts…This means that mitochondrial disease could plausibly reemerge in children born to the technique, or in the children of daughters born to this technique. [38]

3.51 Professor St John and Dr Ian Trounce both noted that there have been some studies in which the original mtDNA outcompeted the donor's mtDNA to become the

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33 Associate Professor Damian Dowling, School of Biological Sciences, Monash University, *Committee Hansard*, 17 May 2018, p. 52; Associate Professor Dowling, *Submission 25*, p. 2.

34 Professor John Christodoulou, Chair, Genomic Medicine, Department of Paediatrics, University of Melbourne, *Committee Hansard*, 17 May 2018, p. 17.

35 Professor Christodoulou, *Submission 12*, p. 3.

36 Professor Christodoulou, *Submission 12*, p. 3.

37 Associate Professor Dowling, *Submission 25*, p. 2.

38 Associate Professor Dowling, *Submission 25*, p. 2.

dominant mtDNA in the population.[39] Murdoch Children's Research Institute and Victorian Clinical Genetic Services and Professor Mary Herbert also noted that in 15–20 per cent of cases, stem cells tested after mitochondrial donation showed that the mtDNA had reverted to the maternal mtDNA.[40]

3.52 Professors Thorburn, Christodoulou, Sue, Carroll, Ryan and Filipovska doubted whether reversion to the maternal mtDNA would be seen in live babies, noting significant differences between the long-term culture of stem cells and live births:

> …embryonic stems cells are considered a poor proxy for normal development in the womb…The state of pluripotency, which allows stem cells to proliferate indefinitely in cell culture, lasts for only a few days during normal development.[41]

3.53 Furthermore, international evidence suggests that there is not significant drift overtime and the amount of mutated mtDNA present at the eight-cell stage and the prenatal diagnosis stage is consistent with the 'level found in multiple tissues at birth'.[42]

3.54 Many submitters were of the opinion that mtDNA carryover could be managed and minimised. In its submission, the Wellcome Centre for Mitochondrial Research, the clinic that currently holds the licence to conduct trials from the UK's HFEA, told the committee that in its initial studies the level of carryover was minimal:

> The study revealed that human PNT embryos had the potential for onward development and importantly, that the level of mtDNA co-transferred with the nuclear DNA during the procedure was minimal (<2% on average). This is well below the level of mutant mtDNA associated with clinical symptoms and led us to conclude that PNT had the potential to prevent transmission of mitochondrial disease.[43]

3.55 Since then, additional studies have been done to examine whether there was the potential for the mutated mtDNA to increase to substantial levels. In a joint submission, the Murdoch Children's Research Institute and Victorian Clinical Genetic Services advised the committee that additional research had been conducted in the UK which found that the levels of mtDNA did not increase provided the original transfer was kept to below two per cent of the mutated mtDNA:

> Additional safety experiments were performed to determine whether there was any potential for mitochondrial DNA carry-over to result in the original mitochondrial DNA from the mother's egg increasing back up to substantial

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39 Professor St John, *Committee Hansard*, 17 May 2018, p. 41; Professor St John, *Submission 31*, [p. 2]; Dr Ian Trounce, *Submission 47*, [p. 1].

40 Murdoch Children's Research Institute, *Submission 23*, p. 5; Professor Mary Herbert, *Submission 49*, p. 3.

41 Professors Thorburn, Christodoulou, Sue, Carroll, Ryan, Filipovska, *Submission 59*, p. 6.

42 Professors Thorburn, Christodoulou, Sue, Carroll, Ryan, Filipovska, *Submission 59*, p. 6.

43 Wellcome Centre for Mitochondrial Research, *Submission 45*, [p. 2].

> levels. Their data showed that this did not happen so long as the procedure ensured no more than 2% of the mother's mitochondrial DNA was present in the embryo after mitochondrial transfer.[44]

3.56 Professor Carroll advised the committee that he considered that, if good techniques are used, the risks of the baby acquiring a genetic disease were low:

> My view is that, once you're doing the mitochondrial procedure, the risks of carryover that are sufficient to contribute to the baby having any genetic disease is so low that I don't think it's a necessary part of the procedure... I think that the mitochondrial donation procedure leads to so few mitochondria, using good techniques, being donated to the new embryo that it's unlikely to be propagated.[45]

3.57 The Fertility Society of Australia (Fertility Society) also acknowledged that, whilst a small risk exists, it is worth taking if it means that a child will not be born with a fatal disease:

> Based on the scientific advice of our membership, we believe that the balance of safety versus risk has been addressed. There is no question that new technology does occasionally bring negative results, but given the fatal nature of Mitochondrial disease we believe that miniscule risk is worth taking.[46]

The potential of sex-selection

3.58 As noted above, some researchers have raised a risk of mitochondrial disease re-emerging in the children or the children of daughters born to mitochondrial donation techniques because of mtDNA carryover.[47]

3.59 Dr Peter McCullagh, a British medical practitioner who followed the developments in the UK, noted that there had been a proposal to restrict clinics to selecting males embryos for clinical implantation to mitigate this risk:

> To ensure that the mutated mtDNA is not transmitted to any children leading to a risk of transgenerational impacts, it has been proposed that licences to undertake mitochondrial transplantation should be restricted to British clinics which commit to gender selection for males. There have been warnings that, even if the first generation of females is not clinically affected, mitochondrial coded disease may nevertheless emerge in later

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44 Murdoch Children's Research Institute, *Submission 23*, p. 4. See also Louise A Hyslop, Paul Blakeley, Lyndsey Craven, Jessica Richardson, Norah M E Fogarty, Elpida Fragouli, Mahdi Lamb, Sissy E Wamaitha, Nilendran Prathalingam, Qi Zhang, Hannah O'Keefe, Yuko Takeda, Lucia Arizzi, Samer Alfarawati, Helen A Tuppen, Laura Irving, Dimitrios Kalleas, Meenakshi Choudhary, Dagan Wells, Alison P Murdoch, Douglass M Turnbull, Kathy K Niakan, Mary Herbert, *Nature*, vol. 534, pp. 383–386.

45 Professor Carroll, *Committee Hansard*, 17 May 2018, p. 25.

46 Fertility Society, *Submission 27*, p. 2.

47 Associate Professor Dowling, *Committee Hansard*, 17 May 2018, p. 52; Dr McCullagh, *Submission 46*, [p. 6].

> ones. Birth of a clinically normal infant may not necessarily guarantee similar normality in the following generation.[48]

3.60 That argument found favour with the National Academies of Sciences, Engineering and Medicine (NASEM) in the United States of America. A report by the NASEM for the USA Food and Drug Administration recommended that initially only male embryos should be transferred because there was a 'need to proceed slowly and to prevent potential adverse and uncertain consequences of MRT [mitochondrial replacement techniques] from being passed on to future generations'.[49]

3.61 Under the American proposal, female children would only be able to be born after adequate follow-up and satisfactory findings in male children.[50] This is because mtDNA cannot be inherited through the male line.

3.62 Mr Sean Murray from the Australian Mitochondrial Disease Foundation (AMDF) told the committee that only selecting male embryos could be considered in Australia as an interim safeguard measure:

> I think the recommendation was made as a risk mitigation there, because, as I explained before, in my situation I can't pass on my mitochondrial DNA to my children, and I think that that's the rationale behind that. So that could definitely be viewed as a safeguard measure while we figure this out in more detail.[51]

3.63 Some submitters noted that a prohibition on implanting female embryos would halve the efficiency of the techniques and would potentially require women to undergo additional ovarian hyperstimulation to produce additional eggs.[52]

3.64 Many of the scientists the committee spoke to considered that it was not a necessary prohibition. Professor Thorburn noted that, even though it was considered, the UK ultimately decided not to impose such a prohibition because it was not considered to be necessary.[53]

3.65 Professors Thorburn, Christodoulou, Sue, Carroll, Ryan and Filipovska advised the committee that, in their opinion, the same risks existed for male and female embryos, meaning that there was no clear reason to prohibit the implantation of female embryos.[54]

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48 Dr McCullagh, *Submission 46*, [p. 6].

49 National Academies of Sciences, Engineering and Medicine (USA), *Mitochondrial Replacement Techniques: Ethical, Social and Policy Consideration*, February 2016, quoted in NHMRC, *Submission 4*, p. 5.

50 NHMRC, *Submission 4*, p. 5.

51 Mr Murray, *Committee Hansard*, 17 May 2018, p. 6.

52 Professor Thorburn, *Committee Hansard*, 17 May 2018, p. 15; Dr Balasubramaniam, *Submission 52*, [p. 4].

53 Professor Thorburn, *Committee Hansard*, 17 May 2018, p. 15.

54 Professors Thorburn, Christodoulou, Sue, Carroll, Ryan, Filipovska, *Submission 59*, pp. 6–7.

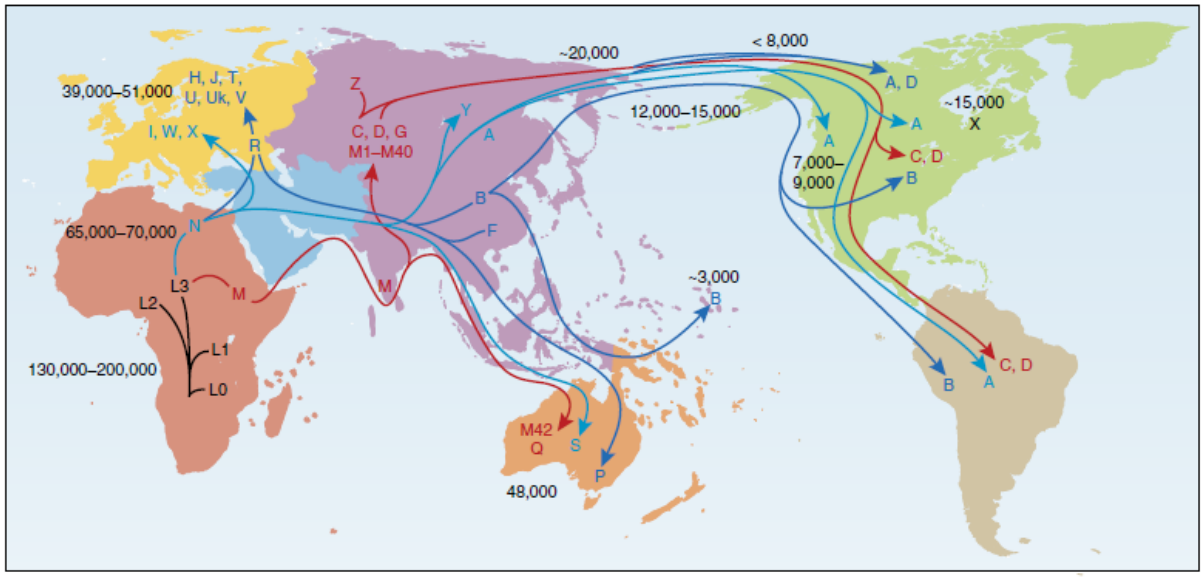
3.66 Some submitters considered that while a degree of risk exists, the question whether to implant female embryos should be considered by the prospective parents after counselling.[55]

mtDNA matching

3.67 As noted in chapter one, mtDNA is maternally inherited. Different people have different mtDNA if they come from a different haplogroup (also sometimes called a haplotype). A haplogroup corresponds to the common maternal origins of the species. In humans, there are about 25 different major variations of the mtDNA sequence and they largely correspond to continental population groups.[56]

3.68 A visual representation of the distribution of those haplogroups is included below.

Figure 3.6—Haplogroup distribution



Source: Professor Robin Lovell-Badge, *Submission 58—Attachment 1*, p. 1061.

3.69 Submitters to the inquiry noted that a person's haplogroup can influence a number of factors related to a person's health, including 'sperm motility, infection resistance, susceptibility to neurodegenerative disease and ageing'.[57]

3.70 Some submitters have expressed concern that a failure to match the haplogroup of the egg donor to the haplogroup of the mother's nuclear chromosomes may lead to potential negative health effects on the child born of the technique. Professor St John explained to the committee the nature of his concern:

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55 Professor Carolyn Sue, Director, Kolling Institute of Medical Research, Mitochondrial Disease Research Centre, *Committee Hansard*, 17 May 2018, p. 26; Professors Thorburn, Christodoulou, Sue, Carroll, Ryan, Filipovska, *Submission 59*, p. 7.

56 Professor St John, *Submission 31*, [p. 3]; Associate Professor Dowling, *Submission 25*, p. 3.

57 Murdoch Children's Research Institute, *Submission 23*, p. 6. See also Associate Professor Dowling, *Submission 25*, p. 4.

> We know from certain studies in both human and mouse models that, if you increase the genetic distance between the source of the eggs from which the chromosomes are coming and the donor egg itself, that can influence the outcome and the phenotype of the offspring and the cells you're trying to make.[58]

Incompatibility between different haplogroups

3.71 There were two areas of concern where it was suggested there could be negative consequences of unmatched haplogroups. The first of these was that mtDNA from a different haplogroup may be inconsistent or incompatible with the mother's chromosomes and this may in turn affect potential gene expression.

3.72 The first mechanism was raised by Professor St John, Associate Professor Damian Dowling and Dr Ian Trounce who drew the committee's attention to studies that primarily used mice and fruit flies and indicated that a failure to match the mother's mtDNA haplogroup with the egg donor's mtDNA haplotype had the potential to lead to changes in gene expression.[59]

3.73 Professor St John advised the committee that studies on mouse stem cells had demonstrated using mtDNA from distantly related haplogroups could have an effect on the health of the mouse.[60]

3.74 Associate Professor Dowling similarly observed that different variations may alter the efficiency of the gene expression and 'in theory could therefore affect individual performance'.[61] He noted though that some mtDNA mutations could be beneficial in some environments, for example the same mutation that causes the debilitating Leber's Hereditary Optic Neuropathy (LHON) is the same mutation that can help humans to survive at high altitudes in oxygen deficient environments.[62]

3.75 Other submitters were less certain that mtDNA matching was necessary. Professor David Thorburn, Head of Mitochondrial Research and Diagnostic Laboratories at the Murdoch Children's Research Institute and Victorian Clinical Genetic Services questioned that the studies on mice and fruit fly would necessarily translate to humans:

> There are experiments in animals, particularly in inbred mice, flies and worms, which suggest that there could be some degree of incompatibility between distantly related haplogroups...They tend to be more distantly related than humans are, and they tend to be inbred rather than outbred, so

58 Professor St John, *Committee Hansard*, 17 May 2018, p. 41.

59 Professor St John, *Committee Hansard*, 17 May 2018, pp. 41–42; Professor St John, *Submission 31*, [p. 3]; Associate Professor Dowling, *Submission 25*, p. 3; Dr Trounce, *Submission 47*, [p. 1].

60 Professor St John, *Committee Hansard*, 17 May 2018, pp. 41–42; Professor St John, *Submission 31*, [p. 3].

61 Associate Professor Dowling, *Submission 25*, p. 3.

62 Associate Professor Dowling, *Submission 25*, p. 3.

> you can measure outcomes very accurately. My personal view is that this is unlikely to be an issue…[63]

3.76 Professor Thorburn also pointed to studies conducted with Macque monkeys and the limited human evidence that is available to indicate that unmatched mtDNA haplogroups have not led to health problems:

> It's very reassuring that when this has been done in the macaque monkeys, there hasn't been any evidence seen for this drift of maternal versus donor haplogroups happening. Those monkeys have been healthy when studied—at least the males have been shown to be fertile; the female has just reached reproductive age I think—and the limited information of the one child born from this technique in Mexico, which was a terrible regulatory process, has had about the same amount of the mutation in cord blood and cheek wash and all those sorts of non-invasive tests of tissues and placenta. So the available evidence suggests that it hasn't been seen in primate models—monkeys or humans.[64]

3.77 Professors Thorburn, Christodoulou, Sue, Carroll, Ryan and Filipovska note that while there is still some uncertainty, they consider that the 'likely risks are relatively low'.[65]

Nuclear-mitochondrial interaction

3.78 The second area of concern where there may be negative consequences of not matching haplogroups, is that there may be an evolutionary link or interaction between the mtDNA and the nuclear DNA and breaking the link between the two may lead to potential negative consequences.

3.79 Associate Professor Dowling explained in his submission that evolutionary theory indicates that the mtDNA and the nuclear DNA have evolved together. He suggested that in this way the nuclear DNA and the mtDNA were like pieces of a jigsaw that would not necessarily be compatible with other mtDNA and may cause negative health consequences in the offspring.[66]

3.80 Associate Professor Dowling expressed concern about this and pointed to a number of studies that indicated there may be effects on humans as a result of mitochondrial donation. However, he noted that it was uncertain whether creating novel mitochondrial and gene combinations would lead to health benefits or detriments:

> The evidence to date suggests that it's more likely there will be effects than no effects by creating novel combinations of mitochondrial and nuclear genotype as mitochondrial donation will do. However, it's not clear. We have, at this stage, no way to predict whether or not the effects will actually be advantageous to the child and improve the performance of what the child

63 Professor Thorburn, *Committee Hansard*, 17 May 2018, p. 15.

64 Professor Thorburn, *Committee Hansard*, 17 May 2018, p. 18.

65 Professors Thorburn, Christodoulou, Sue, Carroll, Ryan, Filipovska, *Submission 59*, p. 5.

66 Associate Professor Dowling, *Submission 25*, p. 4.

> would have been in the event that it hadn't originally carried the pathogenic mtDNA mutation, or whether it will result in a decrease in performance in the child. The majority of evidence suggests the negative effects are more common than the positive effects, but it can go either way.[67]

3.81 In particular, Associate Professor Dowling pointed to a 2018 meta-analysis study that suggested that 'humans showed stronger effects' than other animals to mitochondrial donation.[68] The meta-analysis referred to by Associate Professor Dowling estimated 'negative effects in at least one in every 130 resulting offspring born to the therapy'.[69] Professors Thorburn, Christodoulou, Sue, Carroll, Ryan and Filipovska submitted that if that estimate is correct, the resulting risks are 'lower that the approximately 3% risk for any couple of having a child with some kind of genetic anomaly'.[70]

3.82 Other submitters disagreed that this would be a problem. The Progress Educational Trust dismissed the suggestion that disrupting co-evolution could lead to adverse consequences:

> Some have argued that mitochondrial donation could disrupt relationships that have developed between mitochondrial and nuclear DNA via co-evolution, and that this could have adverse consequences. There is little evidence for this view.
>
> There have been experiments on animals where co-evolved relationships between mitochondrial and nuclear DNA were deliberately disrupted. However, this has only been shown to have a mildly adverse effect in two situations, and neither of these situations is applicable to mitochondrial donation in humans.[71]

3.83 The Progress Educational Trust was clear that while the nuclear genes have an effect on the mtDNA, the effect only operates in one direction:

> It is known that nuclear gene products can and do leave the nucleus and have an effect on mitochondrial DNA. However, the reverse is not true – there is no evidence of mitochondrial gene products leaving the mitochondria and having an effect on nuclear DNA.

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67 Associate Professor Dowling, *Committee Hansard*, 17 May 2018, p. 53.

68 Associate Professor Dowling, *Submission 25*, p. 4; Ralph Dobler, Damian K Dowling, Edward Morrow, Klaus Reinhardt, 'A systematic review and meta-analysis reveals pervasive effects of germline mitochondrial replacement on components of health', *Human Reproduction Update*, 2018, pp. 1–16.

69 Ralph Dobler, Damian K Dowling, Edward Morrow, Klaus Reinhardt, 'A systematic review and meta-analysis reveals pervasive effects of germline mitochondrial replacement on components of health', *Human Reproduction Update*, 2018, p. 2.

70 Professors Thorburn, Christodoulou, Sue, Carroll, Ryan, Filipovska, *Submission 59*, p. 5.

71 Progress Educational Trust, *Submission 48—Attachment 1*, p. 3 (footnotes removed).

> The relationship between the nucleus and the mitochondria is therefore one-sided. This makes it highly unlikely that donated mitochondria could relate to the nucleus in a dysfunctional way.[72]

3.84 This view was supported by Professor Carolyn Sue, Director of the Mitochondrial Research Centre at the Kolling Institute of Medical Research, who pointed to other clinical situations where no haplogroup matching exists and continues without consequence:

> My feelings are that with any tissue donation—such as liver transplants, heart transplants and bone marrow transplants—there is no haplogroup matching, so these are models that existed in patients that I see in hospital every day. Patients get better from their transplants. They go around with different parts of DNA—both nuclear and, in this case, mitochondrial DNA. But everybody forgets about that. We know that there are patients who have mixed components of mitochondrial DNA accepting therapies, benefiting from therapies and having their lives improved by these techniques. I see mitochondrial donation as something like this.[73]

3.85 This view has been supported by the experimental data from the Wellcome Centre for Mitochondrial Research in the UK that found no difference in gene expression between the control group and the pronuclear transfer embryos.[74]

3.86 As noted above, the scientific reviews conducted in the UK recommended that haplogroup matching be used as a precautionary step. Submitters to the inquiry generally agreed that, in the interests of caution, mtDNA matching should be considered.[75]

3.87 However, Professor Thorburn explained that the regulator in the UK did not mandate that haplogroup matching must be undertaken and instead left the decision to the families involved:

> What they concluded—and I agree with it—was this should be mentioned in discussions with the families, that there may be advantages in matching the haplogroup but that it shouldn't be a barrier to families choosing an unmatched donor, because it greatly restricts the number of donors that would be potentially available.[76]

3.88 Leaving the decision to about whether to use haplogroup matching, after counselling, to the prospective parents was endorsed by the Australian Academy of Sciences, Murdoch Children's Research Institute and Victorian Genetic Clinical

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72 Progress Educational Trust, *Submission 48—Attachment 1*, p. 3.

73 Professor Sue, *Committee Hansard*, 17 May 2018, p. 23.

74 Wellcome Centre for Mitochondrial Research, *Submission 45*, [p. 3].

75 Professors Thorburn, Christodoulou, Sue, Carroll, Ryan, Filipovska, *Submission 59*, p. 6.

76 Professor Thorburn, *Committee Hansard*, 17 May 2018, p. 14. See also HFEA, *Scientific review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception: 2016 update*, November 2016, additional information received 30 May 2018, p. 8.

Services and Professors Thorburn, Christodoulou, Sue, Carroll, Ryan and Filipovska.[77]

Is an additional scientific review required?

3.89 Four safety and efficacy reviews have been conducted in the UK, the last of which was published in 2016.[78] The safety and efficacy reviews were carried out by an expert panel of members who had 'no direct interests in the outcome of the review'.[79] The scientific reviews took evidence from a range of domestic and international experts including from the USA and the Netherlands. Based on those factors, questions were raised at the committee's public hearing about whether there was a need for an Australian scientific review to be conducted.

3.90 The AMDF did not consider that an Australian scientific review was necessary:

> …in terms of a suggestion of a review of the science, gauging the public reaction and public opinion on this and looking at the ethics, that is something that we are partly doing right now. I think the AMDF, certainly, would draw upon the exhaustive and lengthy experience and process that was undertaken in the UK, where three independent scientific reviews were undertaken in relation to the science of mitochondrial donation… From the foundation's point of view, from a science perspective, we can certainly rely on the science that has been undertaken around the world. I don't know that there is any Australian nuance to the science of mitochondrial disease; I don't think anything changes around the science because we're here in Australia [80]

3.91 The Murdoch Children's Research Institute and Victorian Clinical Genetic Services noted that Australia could adopt most of the outcomes from the process undertaken in the UK rather than attempting to recreate the process from scratch.[81]

Australian clinical capacity

3.92 Discussions of the safety of the science, must also take into consideration the safety of implementing the science in the Australian clinical context.

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77 Murdoch Children's Research Institute, *Submission 23*, p. 14; Australian Academy of Sciences, *Submission 35*, p. 5; Professors Thorburn, Christodoulou, Sue, Carroll, Ryan, Filipovska, *Submission 59*, p. 7.

78 HFEA, *Scientific review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception: 2016 update*, November 2016, additional information received 30 May 2018. The reviews were carried out in 2011, 2012–13, 2014 and 2016.

79 HFEA, *Scientific review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception: 2016 update*, November 2016, additional information received 30 May 2018, p. 55.

80 Mr Murray, *Committee Hansard*, 17 May 2018, p. 8.

81 Murdoch Children's Research Institute, *Submission 23*, p. 2.

3.93 A number of witnesses and submitters to the inquiry indicated that the Australian Assisted Reproductive Technology (ART) industry currently has relevant clinical skills necessary to deliver mitochondrial donation.[82]

3.94 The Fertility Society submitted that 'Australia has been on the leading edge of development in ART for the last 4 decades' and that in Australia 'we are fortunate in having embryologists who have the skills and expertise to undertake the necessary techniques to allow Mitochondrial transfer'.[83]

3.95 Professor Christodoulou submitted that the UK facility licenced to undertake mitochondrial donation has offered to work with Australian centres which may wish to offer these techniques, to provide any necessary instruction or guidance.[84]

3.96 In addition to the expertise of embryologists who would undertake the donation techniques, another ART function is the necessary counselling procedures to ensure that potential users of this technology understand the risks and ethics, and are therefore able to provide informed consent. The Fertility Society submitted that the Australian ART industry 'has demonstrated rigorous counselling and consenting processes for standard IVF treatment as well as the more complex issues around PGD [pre-implantation genetic diagnosis]'.[85]

Committee view

3.97 The committee understands that there are a number of possible mitochondrial donation techniques that may be used to ensure that women living with a mitochondrial disease do not pass it on to their children.

3.98 The committee acknowledges that these techniques – like any new reproductive technique – involves uncertainty and a degree of risk. However, the committee heard evidence that suggests the risks are manageable and proportionate relative to the serious risks posed to the wellbeing of a child if it inherits mitochondrial disease.

3.99 The committee considers that the scientific studies that have been conducted in the UK indicate that mitochondrial donation is a procedure that can be safely performed, and that these studies included contribution from international experts in this field.

3.100 However, it is not the role of a Senate committee to make definitive scientific findings. The committee therefore believes that formal endorsement of the UK scientific findings should be made by a panel of Australian experts with relevant

82 Monash Biomedicine Discovery Institute, *Submission 19*, [p. 3]; Monash Children's Research Institute, *Submission 23*, p. 14; Fertility Society, *Submission 27*, p. 1. See also Professor Sue, *Committee Hansard*, 17 May 2018, p. 24; Professor Carroll, *Committee Hansard*, 17 May 2018, p. 24.

83 Fertility Society, *Submission 27*, p. 1.

84 Professor Christodoulou, *Submission 12*, pp. 2–3.

85 Fertility Society, *Submission 27*, p. 2.

scientific knowledge. This panel would be appropriately constituted and overseen by the NHMRC.

3.101 Evidence provided to this committee indicates there are some areas for continued scientific consideration of emerging issues such as mtDNA carrying over during mitochondrial donation and haplogroup matching.

3.102 Whilst the committee recognises that there is still some dispute about the potential effects of mtDNA carryover, the committee considers that it is reasonable to consider the introduction of mitochondrial donation in Australia, subject to further consultation.

3.103 The committee agrees that haplogroup matching requires further scientific assessment, noting that such a step could reduce the pool of available donors.

3.104 The committee understands that the Australian ART industry performs at world-leading standards, and has the capacity to adapt existing skills to undertake these techniques for safe treatment in a clinical setting. The committee also understands that such clinics have indicated strong support for mitochondrial donation, and are ready to support the implementation should it be made lawful. It should be noted that these clinics could receive a financial benefit from any legislative change that would permit mitochondrial donation in Australia. The committee heard in evidence that local clinics could serve as a 'southern hemisphere' hub for mitochondrial donation if this technique was legalised:

> So if Australia were to follow, there would probably be two choices—a north and a south. It would probably attract people.[86]

3.105 The committee is aware that a preferred method for mitochondrial donation does not appear to have yet been identified. Because additional research is being performed in this field around the world, the committee considers that serious consideration needs to be given to the way any possible regulation is framed to permit the safest and most up-to-date scientific techniques to be used in Australia. The committee's views on regulatory issues are considered in greater detail in chapter five.

3.106 The committee acknowledges that, separate to the scientific safety of mitochondrial donation, there are significant ethical issues to consider prior to any decision on whether to allow mitochondrial donation in Australia. These will be discussed in the following chapter.

86 Dr Petra Wale, Board Member, Fertility Society, *Committee Hansard*, 17 May 2018, p. 46.

Chapter 4

Ethics of mitochondrial donation

4.1 A number of submitters to this inquiry expressed ethical concerns about the techniques used in mitochondrial donation. Noting that different people have different ethical frames of reference, this chapter examines the ethical issues that have been raised during the inquiry.

4.2 The ethical issues can be broadly categorised under three themes:

- Moral issues: including questions about the moral status of embryos and who should be considered to be a parent;
- Medical and health ethics: including questions about whether a child has a right to know the genetic contributors; how donors are treated; whether consent can be anticipated and the degree to which medical science intervenes in the life of a child born to the technique; and
- Scientific ethics: including questions about when a technology should be considered to be safe for use; whether the technology will affect future generations and the degree of risk to them and whether the technology could inadvertently be used for other things.

4.3 All witnesses and submitters to this inquiry agree that mitochondrial disease is a terrible disease, with devastating impacts to individuals and their families. Submitters with an ethical objection to mitochondrial donation expressed great compassion for families impacted by mitochondrial disease:

> Our hearts go out to families dealing with these diseases and who have the understandable desire that their children should not also be born with these burdens. It is a natural human longing to spare children of illness and suffering.[1]

Moral issues

Moral status of human embryos

4.4 As discussed in chapter three, the pronuclear transfer technique requires two fertilised eggs, one from the mother with the mutated mitochondrial deoxyribonucleic acid (mtDNA) and one from a donor with healthy mtDNA. The pronuclear transfer technique results in a reconstituted egg with the parents' nuclear DNA, but it requires the disposal of the fertilised pronuclei that were contained in the donor egg.[2]

4.5 Submitters such as the Social Issues Committee of the Anglican Church Diocese of Sydney, the Plunkett Centre for Ethics, the Australian Catholic Bishops

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1 Australian Catholic Bishops Conference, *Submission 28*, p. 2.

2 Dr Petra Wale, Board Member, Fertility Society of Australia, *Committee Hansard*, 17 May 2018, p. 44; Professor Justin St John, Professor and Head, Mitochondrial Genetics Group, Hudson Institute of Medical Research, *Committee Hansard*, 17 May 2018, p. 44.

Conference and Catholic Health Australia raised an ethical concern that the creation of an embryo for the purpose of destroying it violates the dignity that is owed to the embryo.[3] The legislative changes required to permit the pronuclear transfer technique of mitochondrial donation in Australia would represent the only permissible creation of an embryo with no potential to develop into a viable pregnancy, outside of somatic cell nuclear transfer (SCNT) research conducted under license.

4.6 The Australian Catholic Bishops Conference explained that its objection about the ethical use of embryos was not limited to mitochondrial donation, but was a common concern about all forms of assisted reproductive technology (ART):

> Human beings have inherent dignity and their rights as people must be respected including their right to life from the moment the first cell of the human zygote is formed by whatever means it comes to be.
>
> A logical ethical sequence of this dignity is that the life of each human embryo is to be considered inviolable. [ART] may involve the discarding of human embryos and may involve the formation of an embryo of a laboratory procedure replacing…marital intercourse…with a technical procedure.[4]

4.7 The Plunkett Centre for Ethics raised a similar concern about the creation of an embryo to obtain the donor egg and mitochondria:

> Treating an embryo merely as a *means* and not also as an *end in itself* violates the respect owed to embryonic human life.[5]

4.8 For these submitters, the end to which the procedure is directed is irrelevant.[6] Their belief in the dignity of the embryo means that their opposition is not specific to mitochondrial donation, but to any interference with human embryos that leads to their destruction:

> I think, of course, that we should never have legalised research on human embryos that involves their destruction, and I have no doubt there will be plenty more destructive research on human embryos to develop any of these techniques. There's no doubt about that.[7]

4.9 Other submitters recognised that questions about the moral status of embryos were neither new nor particular to mitochondrial donation.[8]

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3 Social Issues Committee, Anglican Church Diocese of Sydney, *Submission 56*, p. 2; Plunkett Centre for Ethics, *Submission 30*, p. 2; Australian Catholic Bishops Conference, *Submission 28*, p. 3; Catholic Health Australia, *Submission 60*, pp. 1–2.

4 Australian Catholic Bishops Conference, *Submission 28*, p. 3.

5 Plunkett Centre for Ethics, *Submission 30*, p. 2 (emphasis in original).

6 Plunkett Centre for Ethics, *Submission 30*, p. 1.

7 Dr Bernadette Tobin, Director, Plunkett Centre for Ethics, *Committee Hansard*, 17 May 2018, p. 65. The Plunkett Centre for Ethics is a collaboration between the Australian National University, St Vincent's Health Network Sydney and Calvary Health Care.

8 Mr Ash Howlett and Dr Steve Mercer, *Submission 40*, [p. 4]; Associate Professor Ainsley Newson, *Submission 29*, p. 5.

4.10 As noted in earlier chapters, one current option that is available to women who live with a mitochondrial disease who are considering having children is to have the embryos tested through a process known as pre-implantation genetic diagnosis. In their submission to the committee, Mr Ash Howlett and Dr Steve Mercer explained that they could see little ethical difference between the mitochondrial donation techniques and other procedures that had already been legalised, such as pre-implantation genetic diagnosis:

> Perhaps the most similar technique on ethical terms currently employed in Australia is Preimplantation Genetic Diagnosis (PGD). With PGD, many embryos are created for the purpose of removing cells for genetic testing. Embryos that are deemed unfit are destroyed, likely many more than are destroyed during a single mtDNA donation process depending on the number of embryos tested during PGD. This leads us to an ethical area that is contested by people who believe that life begins at the embryonic stage of development, and those that believe that it is more ethically justifiable to suggest that life begins later on during pregnancy, around when neural structures are forming. A government that allows PGD as well as other embryo or foetal destroying procedures such as abortion, should not be swayed by appeals to the moral status of an embryo.[9]

4.11 Bioethicist Dr Ainsley Newson also noted that current ART already requires the destruction of a number of embryos and the introduction of mitochondrial donation would not add substantially to the number of embryos that are destroyed each year:

> We also have quite small numbers here. This is a background of a technology where fewer than 100 people a year are likely to use it, compared to the 13,000 cycles of assisted reproductive techniques. Embryo discard in that context would be significantly higher. If your position is one where that is problematic too then that is not going to be information that is convincing or of comfort.[10]

4.12 In summary, while there are a range of views about the moral status of embryos, there is little about mitochondrial donation that is different to other forms of ART. As Dr Newson submitted to the committee:

> There are a range of views on embryo moral status in Australia. Mitochondrial donation does not add anything new to existing issues regarding the ethics of the use of embryos in research and clinical treatment, from the perspective of the moral status of the embryo.[11]

Committee view

4.13 The committee understands that some people will have ethical concerns about the destruction of human embryos. That is an understandable concern; however, the question is whether those concerns should preclude the progression of mitochondrial

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9 Mr Howlett and Dr Mercer, *Submission 40,* [p. 4].

10 Associate Professor Ainsley Newson, *Committee Hansard*, 17 May 2018, p. 58.

11 Associate Professor Newson, *Submission 29,* p. 5.

donation techniques. The committee has reached a view that the ethical concerns should not prohibit further scientific review and community consultation on the use of mitochondrial donation in Australia.

4.14 The committee has received evidence that all forms of ART result in some destruction of embryos and pregnancy screening techniques present parents with a choice of continuing a pregnancy or undergoing a termination. As concerning as that may be, ART has been available in Australia for a number of decades and is well accepted. The committee accepts that arguments against mitochondrial donation based solely on the absolute moral status of the embryo are a continuation of an older debate over reproductive rights.

4.15 However, mitochondrial donation does potentially raise new and different ethical concerns regarding embryos that must be considered. The legislative changes required to permit the pronuclear transfer technique of mitochondrial donation in Australia would represent the only permissible creation of unique and potentially viable embryos with no potential to develop into a viable pregnancy outside of SCNT research conducted under license. This is a new moral question that would require community consultation as well as a change to the legal prohibition of such activity under current law.

4.16 The committee considers that mitochondrial donation techniques do not present new ethical concerns, but they do present a scientifically supported source of hope that future generations of Australians may be able to live free of the diseases that have plagued generations of their families.

mtDNA parent or mtDNA donor?

4.17 One of the ethical concerns about mitochondrial donation is the inclusion of genetic material from a third person in the creation of the embryo. The phrase that has sometimes been used in the media is that mitochondrial donation creates 'three-parent babies'.[12]

4.18 The ethical concern about the use of a third person's genetic material was expressed by Dr Bernadette Tobin, Director of the Plunkett Centre for Ethics as a violation of 'the child's right to a natural biological heritage'.[13]

4.19 This argument can be separated into two parts: the first part is an argument that the introduction of a third genetic donor violates the dignity of the unborn child and the second is that the child will be confused or will experience distress because

12 Dr John A Duley, *Submission 7*, [p. 2]; Associate Professor Catherine Mills, Associate Professor Karinne Ludlow, Professor Robert Sparrow and Dr Narelle Warren, *Submission 20*, [p. 9]. See for example: Tracy Bowden, 'Three-parent babies: calls to allow controversial mitochondrial donation procedure in Australia', *ABC News*, 19 November 2017, http://www.abc.net.au/news/2017-11-20/three-parent-babies-and-mitochondrial-donation/9100228 (accessed 29 May 2018).

13 Dr Tobin, *Committee Hansard*, 17 May 2018, p. 65.

they are uncertain about their parentage.[14] Central to both arguments is a question about whether an mtDNA donor is or should be considered to be a parent.

4.20 Dr Newson notes that there is a difference between genetic and social parenting:

> …the term 'three parent baby' has numerous problems. It conflates genetic and social parenting. It overlooks that the genetic contribution from the 'third parent' is vastly smaller than the commissioning couple's and that an epigenetic contribution from a woman pregnant with a foetus conceived via oocyte donation could also be said to be a 'genetic contribution'.[15]

4.21 From a genetic perspective, some submitters suggested that the phrase is misleading. The Wellcome Trust, in an attachment to its submission, explained that children who are born using these techniques will only have nuclear DNA from the mother and the father:

> In mitochondrial donation, almost all of the child's genes will come from its parents; the mitochondrial donor will only contribute 37 genes (0.1% of total DNA), which enable the mitochondria to produce energy. The donor mitochondrial DNA will not affect the child's appearance, personality or any other features that make a person unique – it will simply allow the mitochondria to function normally and the child to be free of mitochondrial DNA disease. Mitochondrial donation involves two-parent fertilisation in the same way that IVF does, and any child would be genetically unique, with a natural combination of nuclear genes from both parents…
>
> The term "three-parent children" is misleading. These children will only have two biological parents…[16]

4.22 Professor John Christodoulou, Chair of Genomic Medicine at the Department of Paediatrics at the University of Melbourne suggested that the fact that mtDNA does not contribute to physical, cognitive or behavioural characteristics was relevant to considering whether the mtDNA donor should be considered to be a parent:

> Certainly, it's DNA that is different from the parent's, but it is 0.1 per cent of the total amount of genetic material in terms of what makes us us. As I said, the mitochondrial DNA really is only involved in making energy; it's not about other physical, cognitive or behavioural characteristics.[17]

4.23 Associate Professor Damian Dowling from the School of Biological Sciences at Monash University also thought that the genetic contribution of the mtDNA donor was so small that the donor should not be considered to be a third parent:

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14 Dr Tobin, *Committee Hansard*, 17 May 2018, p. 65; Australian Christian Lobby, *Submission 51*, p. 5.

15 Associate Professor Ainsley Newson, *Submission 29*, p. 4.

16 Wellcome Trust, *Submission 1—Attachment 3*, [p. 4].

17 Professor John Christodoulou, Chair of Genomic Medicine, Department of Paediatrics, University of Melbourne, *Committee Hansard*, 17 May 2018, p. 16.

> From a technical genetic point of view, if we just consider the nuclear chromosomes and ignore the mtDNA, the children produced will clearly be two-parent babies. But, as others have pointed out, if we consider all of the unique protein-coding genes dispersed across the nuclear and mitochondrial genome—of which there are 37 mitochondrial and close to 20,000 nuclear genes—the children produced would be 2.002-parent babies.[18]

4.24 If the three-parent issue is considered from a social perspective, in the United Kingdom (UK) the mtDNA donor is not considered to be a parent, but the equivalent of an organ donor.[19]

4.25 Some submitters observed that organ donation and tissue donation includes a complement of DNA being placed into the body of the recipient.[20] Professor Christodoulou noted that the additional genetic complement does not change the way society views that person:

> Bone marrow transplantation can be considered to have DNA from three individuals. That's very acceptable; we don't call that person a three-person bone marrow recipient.[21]

4.26 Similarly, according to Professor Carolyn Sue, Director of the Mitochondrial Research Centre at the Kolling Institute of Medical Research based at the Royal North Shore Hospital in Sydney, surveys of patients who live with mitochondrial disease indicates that they conceive of the procedure as being similar to organ or tissue donation:

> When you hear the 'three parent' terminology, I guess they want you to hear that it's like a bone marrow transplant or a heart transplant. Those patients also have three components of DNA within their body, but really that doesn't impact on their day-to-day lives, apart from the fact that it's improved their health outcomes.[22]

4.27 Fears that transplantation or an infusion might change a person are also not new. Dr John Duley, a scientist who has worked in the area of mitochondrial disease, recalled that similar fears were raised when heart transplants were first conducted:

> In people's minds this organ was endowed with almost mystical qualities—it was the seat of love and other emotions… Its transfer from one person to

18 Associate Professor Damian Dowling, School of Biological Sciences, Monash University, *Committee Hansard*, 17 May 2018, p. 53.

19 Wellcome Trust, *Submission 1—Attachment 3*, [p. 4].

20 Professor Carolyn Sue, Director, Kolling Institute of Medical Research, Mitochondrial Research Centre, *Committee Hansard*, 17 May 2018, p. 23; Professor Christodoulou, *Committee Hansard*, 17 May 2018, p. 16.

21 Professor Christodoulou, *Committee Hansard*, 17 May 2018, p. 16.

22 Professor Sue, *Committee Hansard*, 17 May 2018, p. 21.

> another was regarded as an unnatural act, meddling with 'personhood' and trespassing into territory that had a spiritual quality.[23]

4.28 Science and the ethical debates about transplantation have evolved since that time and transplants are now a standard part of medical practice. The broader Australian community accepts that organ donation is ethical and it is something that the medical community actively promotes:

> In Australia, we already support organ donation; it is legal, it is common practice and we actively promote it. Somebody who has an organ donated has more DNA from somebody else than we are talking about in mitochondrial donation.[24]

4.29 Concepts around the genetic contribution of mtDNA versus nuclear DNA have broader application than simply a question of contribution to the parentage of a particular child. It also reflects on whether mtDNA donation is considered to be a germline genetic modification in the same way that some nuclear DNA modifications can be. This is an issue that will be considered in greater detail below.

Committee view

4.30 The committee understands that there are people who have concerns that mitochondrial donation techniques may lead to children having three genetic parents. This is not the case. The benefit of mitochondrial donation is that it affords people living with mitochondrial disease the opportunity to have a genetically related child whilst dramatically reducing the child's chance of developing a serious mitochondrial disease.

4.31 The committee considers that an mtDNA donor should be conceptualised as being similar to an organ donor. The committee notes that there are already procedures being performed, such as bone marrow or organ transplants, that results in genetic material being transferred to a person who needs it for a medical reason. These do not appear to have led to adverse consequences for the individuals involved in the transplant procedures. There may be reasons to hold concerns about mitochondrial donation, but the committee does not have any reservation that the children born of this technique will have only two parents. The question of whether mtDNA donation should be anonymous, similar to organ donation, is discussed below.

Medical and health ethics

4.32 Four main ethical questions were raised by submitters that can be broadly categorised as concerning medical and health ethics:

- should mtDNA donation be anonymous?
- will the mtDNA donors be exploited?

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23 Raymond Hoffenberg, 'Christian Barnard: his first transplants and their impact on concepts of death', *British Medical Journal*, vol. 324, 2001, pp. 1478–1480 quoted in Dr Duley, *Submission 7*, [p. 2].

24 Ms Monica Ferrie, Chief Executive Officer, Genetic Support Network of Victoria, *Committee Hansard*, 17 May 2018, p. 2.

- would a child consent to be conceived by mitochondrial donation?
- should a child be required to participate in ongoing follow up?

4.33 Each of these questions is considered below.

Should mtDNA donation be anonymous?

4.34 Another ethical concern raised by submitters was whether mtDNA donors should be anonymous or whether the child has a right to know the identity of the donor. This question needs to be considered from the perspective of the donor and from the perspective of the child who may be born of the technique. In the UK, the regulations allow a child born of the technique to discover only non-identifying information about the donor from the age of 16, making mtDNA donation anonymous.[25] A donor is entitled to know how many children have been born from their donated material, the sex of those children, and what years the children were born.[26]

4.35 Dr Newson explained that the rationale for making mtDNA anonymous in the UK was that mitochondrial donation is more akin to organ or tissue donation than reproductive donation and the preference for anonymity reflects that fact.[27]

4.36 However, opinions on whether mtDNA donors should be anonymous vary. Professor John Christodoulou supported anonymous mtDNA donation because he considered it to be important to the donor.[28] Professor Sue informed the committee that some people living with mitochondrial disease have indicated that they would prefer mitochondrial donation to be anonymous because they considered that the techniques were akin to organ or tissue donation and because they were concerned about the risk of stigma.[29]

4.37 Other submitters to the inquiry argued that, if Australia allowed mtDNA donation, the child should be entitled to know the identity of the mtDNA donor. Dr Petra Wale, a board member of the Fertility Society of Australia told the committee that most donor-conceived people want to know their genetic heritage:

> People want to know where they come from. As a society and as a practice we don't have anonymous donation anymore. Anybody donating in the current climate, and this has been for many years—whether it be a sperm donor, an egg donor or an embryo donor—is made aware that that resulting offspring will know who you are and have the opportunity to have identifying information about you. I struggle to think that there will be a lot circumstances where this would be anonymous. There would probably be a

25 Professors David Thorburn, John Christodoulou, Carolyn Sue, John Carroll, Mike Ryan and Aleksandra Filipovska, *Submission 59—Attachment 1*, [33.28].

26 Professors Thorburn, Christodoulou, Sue, Carroll, Ryan, Filipovska, *Submission 59—Attachment 1*, p. 191.

27 Associate Professor Newson, *Submission 29*, p. 4.

28 Professor Christodoulou, *Committee Hansard*, 17 May 2018, p. 13.

29 Professor Sue, *Submission 24*, p. 4.

> lot of people who have people helping them out. That's what happens now with egg donation. It's usually altruistic from other family members and from best friends. There are always stories. Their best friends and other people help them out. Making it anonymous will come back to bite us.[30]

4.38 Some submitters, such as the Australian Christian Lobby and the Australian Catholic Bishops Conference, considered that the child's right 'to know and be cared for by his or her parents' includes a moral right to know the circumstances of a person's conception.[31]

4.39 Archbishop Fisher drawing on the experiences of adopted children, pointed to the psychological distress that can result from a lack of knowledge about their genetic history:

> When we think of what confusion that might create in a child regarding their lineage, their genetic heritage, the families they belong to, we know already the problem of genealogical bewilderment or children that go searching for donor parents or searching for their natural parents when they been adopted. We would risk creating another group of children in search of their genealogy.[32]

4.40 Dr Tobin from the Plunkett Centre agreed the move away from anonymous donation was to be commended and that it should not be considered for mtDNA donation:

> To add to what you said, that we have gotten rid of anonymous donation is a great Australian ethical development that has been picked up in some parts of the world. This was a wonderful achievement of the NHMRC 10 or 15 years ago. I do hope that nothing that the legislators consider will have us back-sliding on that one.[33]

4.41 In her submission, Dr Newson explained that she conducted a citizen's jury to understand community attitudes to mitochondrial donation. According to Dr Newson, one of the issues that many of the jurors were concerned about was ensuring that children had a right to know their donor if they wished to do so.[34]

4.42 Dr Newson noted that allowing the mtDNA donor to be known also validates the contribution that the mtDNA donor made to the child's life:

> Women who choose to donate oocytes for mitochondrial donation are making a small but very fundamental contribution to this process and also to the genetic complement of any children who are born as a result. The

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30 Dr Wale, *Committee Hansard*, 17 May 2018, p. 46.

31 Australian Catholic Bishops Conference, *Submission 28*, p. 3; Australian Christian Lobby, *Submission 51*, p. 5.

32 Archbishop Anthony Fisher, Vice President, Catholic Bishops Conference and Chairman, Bishops Commission for Family, Youth and Life, *Committee Hansard*, 17 May 2018, p. 64.

33 Dr Tobin, *Committee Hansard*, 17 May 2018, p. 68.

34 Associate Professor Newson, *Submission 29*, p. 8. Additional information about the citizen's jury process can be found in Associate Professor Newson's submission.

> presumption that this complement is too small to warrant recognition of the donor, to me, overlooks the significance of the physical process of donation and also that the donated material makes a significant difference between someone having mitochondrial disease and not in the future.[35]

4.43 Professor John Christodoulou told the committee that, like other ethical issues involving mitochondrial donation, the committee needs to consider carefully about community morals and expectations regarding the process:

> [T]his is an area where we need to understand what the community by and large wants or finds acceptable. Certainly, everyone is entitled to their own individual want and desire, but I guess if we are talking about changing legislation for the whole community we have to take into account what the whole community's desire is.[36]

Committee view

4.44 The committee understands that people have different views about whether mtDNA donation should be anonymous. The committee considers that a child's right to know their biological heritage should be paramount. The committee acknowledges that there has been a shift in Australian attitudes towards making information about a person's biological heritage known in both the adoption space and in other forms of ART. The committee considers that children who are born from a mitochondrial donation technique should be entitled to know their donor if they want to.

4.45 The committee notes that it proposes treating mtDNA donation differently from either gamete or organ donation. The committee considers that an mtDNA donor should be conceptualised as being similar to an organ donor because they are donating non-nuclear genetic material. However, recognising that biological or heritage questions may arise for children born of this process, the committee considers that mtDNA donors should not be anonymous.

4.46 Women who donate their mtDNA should be made aware that if a child is born from their donated mtDNA then the child may be given identifying information about the donor at an appropriate time.

Will mtDNA donors be exploited?

4.47 Mitochondrial donation requires human eggs that contain healthy mitochondria. Some submitters expressed concerns about where the eggs would come from and whether the egg donor would be exploited.[37]

4.48 The Social Issues Committee of the Anglican Church Diocese of Sydney raised concerns that women may be financially coerced into donating their eggs for this purpose:

> …there are also ethical issues pertaining to the egg donor herself. It is known that egg donation is potentially dangerous due to the risks of

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35 Associate Professor Newson, *Committee Hansard*, 17 May 2018, p. 50.

36 Professor Christodoulou, *Committee Hansard*, 17 May 2018, p. 14.

37 Social Issues Committee of the Anglican Church Diocese of Sydney, *Submission 56*, p. 2.

> associated hormonal stimulation. As a result, egg donors can be difficult to find. This leads to pressure from lobby groups to introduce payment for gamete donation, which leads to vulnerable women being financially coerced into undergoing a potentially life-threatening harvesting procedure. This is unethical.[38]

4.49 This concern was shared by the Catholic Church. Archbishop Anthony Fisher, the Catholic Archbishop of Sydney and Chairman of the Bishops Commission for Family, Youth and Life told that committee that he was concerned that eggs needed to be obtained from women through invasive procedures:

> The availability of human ova is often assumed when people talk about reproductive technology as if they were somehow there in a cupboard to be used. In fact, it means women have to be used to obtain these eggs. They are extracted by invasive procedures that do carry some risk.[39]

4.50 Professor David Thorburn, Head of Mitochondrial Research and Diagnostic Laboratories at the Murdoch Children's Research Institute and Victorian Clinical Genetic Services told the committee that the eggs required for these procedures would most likely come from excess eggs that were donated after in vitro fertilisation procedures or from women who were close to the family.[40]

4.51 Professor Sue told the committee that her research indicated that most women would be happy to be able to donate their excess eggs after in vitro fertilisation:

> In this case it is going to be donor women, who are presumably and most commonly donating their eggs because they've had an IVF procedure themselves. When we asked those patients, we found a huge level of altruism about this. The women who were having IVF procedures for infertility reasons, for example, would most commonly be the donors, and the excess eggs would probably be the donor material. There was this altruistic feeling. They were delighted, happy, that their excess eggs had, first of all, a purpose or could have a legal purpose and also that they would be helping other people who faced a similar but slightly different dilemma from theirs.[41]

4.52 The *Ethical guidelines on the use of assisted reproductive technology in clinical practice and research, 2017* (ART Guidelines) made by the National Health and Medical Research Council (NHMRC) relevantly provides that both commercial trading and direct and indirect inducements are prohibited by legislation to prevent this type of exploitation:

> The current situation in Australia is that gamete donation must be altruistic, and that commercial trading in human gametes or the use of direct or

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38 Social Issues Committee of the Anglican Church Diocese of Sydney, *Submission 56*, p. 2.

39 Archbishop Fisher, *Committee Hansard*, 17 May 2018, p. 64.

40 Professor David Thorburn, Head of Mitochondrial Research and Diagnostic Laboratories, Murdoch Children's Research Institute and Victorian Clinical Genetic Services, *Committee Hansard*, 17 May 2018, p. 19.

41 Professor Sue, *Committee Hansard*, 17 May 2018, p. 31.

> indirect inducements is prohibited by legislation. This position reflects concerns about the potential exploitation of donors (particularly egg donors) and the potential risks to all parties.[42]

4.53 However, the ART Guidelines permit the reimbursement of some out-of-pocket expenses that are directly incurred by the donor.[43]

4.54 Another potentially concerning form of exploitation could stem from overuse of the same donor's genetic material. Currently, the ART Guidelines specify that only a limited number of families can be created from a single egg or sperm donor and that consideration must be given to the number of persons already born from the donor's donated genetic material in deciding whether to use that donor's material.[44] The same standards may be applied to egg donors who donate eggs for mtDNA donation.

Committee view

4.55 The committee understands the concerns about the potential exploitation of mtDNA donors. However, the committee has confidence that the existing ethical standards for egg donation are consistent with community expectations. The committee expects that the same ethical safeguards that protect egg donors would be applied to egg donors who donate their eggs for mtDNA donation if it was introduced in Australia. The regulatory aspects of mitochondrial donation are discussed in greater detail in chapter five.

Would a child consent to mitochondrial donation?

4.56 Consent is an important ethical principle that is derived from the rights of autonomy and dignity. Some submitters raised concerns that a child that is yet to be born cannot, and, if they had the requisite capacity, may not consent to such a procedure.

4.57 The Australian Christian Lobby noted that anticipated consent is an important principle in considering whether mitochondrial donation should be permitted:

> …children with three biological parents are a brave experiment which will have a significant effect on a person not-yet-born who is unable to consent to the procedure. Ethicist Margaret Sommerville speaks of the principle of 'anticipated consent' where a person is affected by a decision to which they cannot give consent. Such a decision, made by the parents on behalf of the child, may have serious consequence for the child and their sense of self.[45]

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42 National Health and Medical Research Council (NHMRC), *Ethical guidelines on the use of assisted reproductive technology in clinical practice and research, 2017* (ART Guidelines), p. 43, https://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/ethics/16506_nhmrc_-_ethical_guidelines_on_the_use_of_assisted_reproductive_technology-web.pdf (accessed 7 June 2018).

43 NHMRC, ART Guidelines, pp. 43–44.

44 NHMRC, ART Guidelines, p. 43.

45 Australian Christian Lobby, *Submission 51*, p. 5.

4.58 This is a principle that can have practical implications and can be an important ethical guide for people who are making decisions about the care of people who are unable to provide consent. However, Dr Tobin questioned whether the principle would apply in the case of a person born because of a mitochondrial donation technique:

> We came up with a formula which said: … if you could anticipate that they would consent—then it would be legitimate... it's obviously very relevant here. All we can really do is do thought experiments, because, if you ask me what I think a child so manufactured will think when he or she grows up, I don't know.[46]

4.59 People who live with a mitochondrial disease and their children had little difficulty imagining whether a person who was born from a mitochondrial donation technique would consent. Mary, a person living with a mitochondrial disease, asked her children whether they thought they would have consented to the procedure:

> In the process of preparing my submission, I talked to my children about this and I said to them: 'What do you think?' They said, 'If we had a child with mitochondrial disease, we would love that child we would understand what the child was going through.' But their view was that everyone who has mitochondrial disease, their families that are affected by it, should have this choice.[47]

4.60 Justin, who also lives with a mitochondrial disease, told the committee that he believes that a child who was born of the technique would understand the choice that had been made for them:

> What I have learned over the last 2½ years is that having a disability or a sickness like we've got is about compromise. You are compromising the whole time about what you used to have in your life that you don't have anymore. Being part of a family where the other members of the family are disabled or are sick and is also about compromise—you can't do the things you need to do. So I'm confident that any child, if this technology was to go forward, born through mitochondrial donation would understand that life is about compromises when you are in this situation. If that means that I can't participate in recreational genetics, if that means that a second woman gave me the slightest part of my DNA, I think that would be a compromise I would be able to live with.[48]

Committee view

4.61 The committee acknowledges that some submitters have ethical concerns about whether a child would consent to a medical procedure that had the potential to prevent it from having a debilitating illness. The committee considers that the child's consent could be anticipated. Whilst we cannot know for certain, the evidence from

46 Dr Tobin, *Committee Hansard*, 17 May 2018, p. 67.

47 Mary, *Committee Hansard*, 17 May 2018, p. 38.

48 Justin, *Committee Hansard*, 17 May 2018, p. 37.

submitters living with the disease is that they and their children would like to have the choice to determine whether or not the technique is right for them and their child.

Ongoing follow up

4.62 Scientific and medical research depends on data. Submitters told the committee that they considered that follow up should be conducted with the children who are born to these techniques. A number of submitters told the committee that there should be a rigorous follow-up study conducted by the fertility clinics to inform the scientific evidence base.[49]

4.63 The NHMRC told the committee that obtaining the best data about people born to this technique will requires significant long-term follow up, potentially over multiple generations:

> Ideally, this monitoring would be multi-generational, that is, children born following mitochondrial donation would be monitored into adulthood and their children, if any, would also be monitored.[50]

4.64 In the UK, the team at the Wellcome Centre for Mitochondrial Research developed an innovative clinical method through the National Health Service's routine check-ups:

> Feedback from [patient focus] groups states that patients wanted to be involved in long term follow up but at the same time, did not want to 'medicalise' an otherwise healthy child. Taking this into consideration, the follow up pathway takes advantage of the routine NHS health checks offered to all children born in the UK, with only a small amount of extra information collected during these appointments.[51]

4.65 In Australia, the NHMRC acknowledged that obtaining data may be difficult to obtain if a child does not wish to be monitored into the future:

> However, while the parents may have consented to ongoing monitoring on behalf of the child, the child has not been involved in this decision and may not consent to long-term follow-up. Therefore, while the importance of follow-up for the safety and well-being of the child can be emphasised, there are significant ethical issues associated with ongoing monitoring that would need to be explored further.[52]

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49 Professor John Carroll, Director, Monash Biomedicine Discovery Centre, *Committee Hansard*, 17 May 2018, p. 30; Dr Nadine Richings, Vice-Chair, Scientists in Reproductive Technology (SIRT), *Committee Hansard*, 17 May 2018, p. 42; Professor Aleksandra Filipovska, *Submission 17*, p. 2; Biomedical Ethics Research Group, Murdoch Children's Research Institute, *Submission 34*, [p. 2]; Australian Academy of Sciences, *Submission 35*, p. 5; Nuffield Council on Bioethics, *Submission 43*, [p. 2].

50 NHMRC, *Submission 4*, p. 4.

51 Wellcome Centre for Mitochondrial Research, *Submission 45*, [p. 5].

52 NHMRC, *Submission 4*, p. 4.

4.66 Dr Newson raised concerns regarding the child's right to privacy, noting that 'the balance between monitoring and invasiveness should be carefully considered'.[53]

4.67 Professor Sheryl de Lacey, a Professor of Nursing at Flinders University, noted that it may be possible to ask the parents to participate in a study about the health and wellbeing of their children:

> Taking part in a clinical trial necessitates an agreement to participate in follow-up studies. This is a view that a child should not be created so as to be identifies as 'different' and subjected to mandatory procedures in the interests of science. However my experience in social research suggests that it is possible to track the progress and development of children through enrolment of the parents in the trial.[54]

4.68 Professor de Lacey noted that the failure to conduct a long-term study can make it challenging to understand the effects of a particular technology for a substantial period of time:

> Follow up of children was never successfully achieves when IVF was introduced and we are now reliant on retrospective epidemiological studies to indicate the health outcomes for children.[55]

4.69 The NHMRC's ART Guidelines currently require clinics to record and retain certain information for the purposes of follow up.[56] Clinics are required to make this data available in a non-identifiable format to ensure accountability and for research purposes.[57] Similar and additional requirements may be imposed if mitochondrial donation is legalised for clinical use in Australia.

Committee view

4.70 The committee considers that clinical follow-up is important to monitor the health of children born to the technique and for epidemiological health reasons it is important to know about the risks that may be presented by the technology. The committee acknowledges the concerns that unnecessary or intrusive follow up risks 'medicalising' an otherwise healthy child. The committee considers that this is a matter that needs to be considered in the regulatory design if the government decides to legalise mitochondrial donation.

Scientific ethical considerations

4.71 The most important stakeholder in any discussion about mitochondrial donation is the child whose life will be affected by the use of the technique. In this section, the following questions will be discussed:

- should the technology be used if there is a potential for harm?

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53 Associate Professor Newson, *Submission 29*, p. 5.

54 Professor Sheryl de Lacey, *Submission 55*, p. 2.

55 Professor Sheryl de Lacey, *Submission 55*, p. 2.

56 NHMRC, ART Guidelines, pp. 83–85.

57 NHMRC, ART Guidelines, p. 85.

- is mitochondrial donation germline genetic modification?
- is it ethically relevant that mitochondrial donation is not a cure?
- could allowing mitochondrial donation lead to a 'slippery slope'?

Should the technology be used if there is a potential for harm?

4.72 In chapter three, it was noted that there are still some aspects of the science of mitochondrial donation that are not completely known and that there could potentially be some harm to the children born to the technique if some of the concerns are realised.

4.73 The question that needs to be considered is whether the technology should be authorised for use if there is some risk of harm. The Murdoch Children's Research Institute and Victorian Clinical Genetic Services consider that the potential risks and the potential benefits need to be weighed up in considering whether to authorise any technique:

> It is unlikely that any IVF technique or most other medical advances could ever have been introduced if absolute certainty was a pre-condition of their application to human subjects. It is thus necessary to consider the balance of potential benefits and potential harms to decide whether application to human subjects is appropriate and what types and duration of monitoring should be in place to assess safety and efficacy if the benefits outweigh the harms.[58]

4.74 The Biomedical Ethics Research Group at the Murdoch Children's Research Institute noted that the potential to avoid passing on a devastating and life-threatening illness to an unborn child was a clear ethical imperative that weighed in favour of allowing mtDNA donation.[59]

4.75 The countervailing factor that the Biomedical Ethics Group at the Murdoch Children's Research Institute pointed out was that there were factors that suggested that the science was not yet certain and potentially unsafe:

> [Mitochondrial Replacement Therapy] is a new technology. It could have unexpected and harmful consequences, which should be fully investigated before MRT is used clinically. Concerns have been raised about the potentially harmful effects that could arise as a result of a genetic misalignment between mitochondrial and nuclear DNA.[60]

4.76 Distinguished Professors Jenni Millbank and Isabel Karpin and Professor Anita Stuhmcke argued that a harm minimisation approach balanced the rights of parents against the potential safety risks:

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58 Murdoch Children's Research Institute and Victorian Clinical Genetic Services, *Submission 23*, p. 4.

59 Biomedical Ethics Research Group, Murdoch Children's Research Institute, *Submission 34*, [p. 2].

60 Biomedical Ethics Research Group, Murdoch Children's Research Institute, *Submission 34*, [p. 2].

> In the interests of protecting and supporting Australians we believe that a harm minimisation approach is urgently needed that ensures the health and well-being of both the family and their future offspring. Such an approach accords with human rights principles and the well accepted right to form a family. In the case of those seeking treatment for mitochondrial disease a legal prohibition is both onerous and discriminatory towards people who carry the gene for this disabling condition.[61]

Committee view

4.77 The committee considers that a harm minimisation approach is appropriate in the circumstances. The committee accepts that the potential to alleviate significant suffering is a morally compelling reason to permit mitochondrial donation, though it notes that the hope for the technology needs to be balanced against the potential risks. At this point, the risks appear to be sufficiently manageable to allow the use of the technology. However, it is not the role of a Senate committee to make definitive scientific or medical findings. The committee considers that formal review and potential endorsement of the UK scientific findings should be made by a panel of Australian experts with relevant scientific and medical knowledge. The committee considers that an independent panel of Australian scientists and medical practitioners should be asked to consider whether the science is sufficiently certain for clinical use.

Germline alteration

4.78 Some submitters raised ethical concerns about whether mitochondrial donation would alter the human germline and whether that should be permitted. In gene therapy, a distinction can be drawn between somatic gene therapy, an alteration of a cell that only affects the current generation, and germline gene therapy which alters a gene that is passed on to future generations.[62] In most jurisdictions, heritable gene alteration, or germline gene therapy, is not permissible.[63] It is thought of as a 'bright line' in terms of both safety and ethics.[64]

4.79 Different jurisdictions have come to different positions on whether mitochondrial donation should be considered to be an inheritable gene alteration or replacement. In chapter three it was noted that the National Academies of Sciences, Engineering and Medicine in the United States of America proposed the implantation of only male embryos for a period of time to monitor the effects of mitochondrial donation while effectively removing the potential for the mitochondria to passed on to future generations.[65] In the UK, mitochondrial donation was considered to be a

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61 Distinguished Professor Jenni Millbank, Distinguished Professor Isabel Karpin and Professor Anita Stuhmcke, *Submission 57*, [p. 5].

62 Associate Professor Catherine Mills, *Committee Hansard*, 17 May 2018, p. 50.

63 Associate Professor Newson, *Committee Hansard*, 17 May 2018, p. 55; Murdoch Children's Research Institute and Victorian Clinical Genetic Services, *Submission 23*, p. 8; Dr Newson, *Submission 29*, p. 3.

64 Associate Professors Mills and Ludlow, Professor Sparrow and Dr Warren, *Submission 20*, p. 3.

65 NHMRC, *Submission 4*, p. 5.

germline therapy because the mitochondria will be inherited by future generations from a female born to the technique if she has children, but it was not considered to be a form of human genetic modification.[66] However, these terms generally relate to nuclear genes rather than organelles, like mitochondria.

4.80 Submitters to the inquiry who supported mitochondrial donation considered that the question about whether mitochondrial donation was a germline alteration did not arise because it was separate from the nuclear genes. Dr Newson suggested that mitochondrial replacement should be considered neither germline or somatic gene therapy but as 'conditionally inheritable genomic modifications'.[67] Mitochondria is conditionally inheritable because it can only by passed through the female line; in a male embryo the mitochondrial donation is similar to somatic gene therapy. In a female embryo, the mitochondria is inheritable and forms part of the genetic information that is passed on to future generations.

4.81 Professors Thorburn, Christodoulou, Sue, Carroll, Ryan and Filipovska noted that mitochondrial donation should be thought of ethically as being distinct from germline genetic modification because mtDNA is distinct from the nuclear genes.[68]

4.82 These submitters also noted that mtDNA was not unique to individuals, but was shared with the other members of the maternal haplogroup.

4.83 Submitters who were concerned about germline alteration were most concerned about the effects of mtDNA donation on future generations.[69] For these submitters, the scientific uncertainty raised a moral concern about whether the lives of people who are not yet born may be affected by the carrying out of the mitochondrial donation procedure.[70] These concerns were prompted by some of the scientific questions that were raised in chapter three, such as questions about possible mito-nuclear interactions.

4.84 Dr Tobin from the Plunkett Centre told the committee that she had no principled objection to altering a person's genes to correct a genetic defect even if there was a risk that the modification could be inherited, if it could be shown it could be done safely:

> It may be that with some of the new genetic techniques, so-called CRISPR, where, at least theoretically, it may be possible to correct a genetic defect in

66 Associate Professors Mills and Ludlow, Professor Sparrow and Dr Warren, *Submission 20*, [pp. 16–17]. See Karinne Ludlow, 'The policy and regulatory context of U.S., U.K., and Australian responses to mitochondrial donation governance', *Jurimetrics*, vol. 58, p. 256.

67 Associate Professor Newson, *Submission 29*, p. 3. See Ainsley Newson and Anthony Wrigley, 'Is mitochondrial donation germ line gene therapy? Classifications and ethical implications', *Bioethics*, vol. 31, pp. 55–67.

68 Professors Thorburn, Christodoulou, Sue, Carroll, Ryan and Filipovska, *Submission 59*, pp. 8–9.

69 Australian Christian Lobby, *Submission 51*, p. 7.

70 Australian Christian Lobby, *Submission 51*, p. 8; Catholic Health Australia, *Submission 60*, [p. 2].

> a young human being or adult human being such that that person no longer has that disease or susceptibility to disease, and that affects that person's germ line, a time comes when that is safe. If so, I don't see an in-principle objection to that. I don't think we're there now.[71]

4.85 Dr Newson told the committee that mitochondrial donation was the first process that would be permitted to deliberately alter heritable characteristics, but it was up to the committee to determine whether that was ethically important:

> Senator Brockman's question was around if this is the first thing that we know of that will lead to these kind of changes in a deliberately intervening way; my answer to that is yes. The questions from an ethical perspective are, 'What does that matter? What do we make [of] this from a moral perspective?'[72]

4.86 Whether Australia determines that mtDNA amounts to germline modification or not will have implications for how mitochondrial donation can be legalised in Australia. This will be discussed in greater detail in chapter five.

Committee view

4.87 The committee recognises that there are many ethical views regarding mitochondrial donation. In particular, the committee understands that some submitters have concerns about whether mitochondrial donation constitutes a form of germline gene therapy. The committee understands mtDNA is inherited from the mother and that changes to mtDNA of an egg or embryo will affect future generations. However, the committee accepts that there is an ethical difference between the manipulation of nuclear DNA and the manipulation of mtDNA, primarily because mtDNA does not contribute to the characteristics of inheritable genetics in the manner traditionally thought of, at the time such manipulations were prohibited through anti-cloning laws.

4.88 The committee acknowledges that there is a degree of scientific uncertainty as to how to characterise the modification of mtDNA, and that these definitions might have unanticipated impacts, such as legalising other techniques of gene manipulation. As with other areas of science discussed in this report, the committee acknowledges it does not have the expertise to make a formal finding, but recognises that further exploration is required.

4.89 Therefore, the committee considers that the questions of whether mtDNA should be considered a germline genetic modification, and does that preclude it use, should be considered by a panel of expert Australian scientists and bioethicists as a foundational question to be answered prior to any legalisation of mitochondrial donation.

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71 Dr Tobin, *Committee Hansard*, 17 May 2018, p. 66.

72 Associate Professor Newson, Committee Hansard, 17 May 2018, p. 55.

Does it matter if it is not a cure for mitochondrial disease?

4.90 There is currently no cure for mitochondrial disease.[73] Mitochondrial donation is also not a cure for mitochondrial disease; it prevents the transmission of the mitochondrial disease to the next generation.[74]

4.91 Some submitters considered that it was morally relevant that mitochondrial donation was not a 'cure' for mitochondrial disease. For these submitters, a distinction could be drawn between alleviating the suffering of a living person and intervening to prevent a person from acquiring a mitochondrial disease.

4.92 The Australian Christian Lobby clearly told the committee that interference at a genetic level was of concern:

> Mitochondrial donation does not cure mitochondrial disease. It is not 'treatment'. It is genetic manipulation to ensure that mutant mtDNA is not transmitted to future generations. This has serious ethical implications.[75]

4.93 Dr Tobin from the Plunkett Centre elaborated on this concern:

> I think it is important to note that, were you to recommend the legalisation of this procedure, it is a procedure that doesn't cure anyone of this disease, even in its mild forms let alone in its severe forms. The risks that it involves are, strictly speaking, unnecessary. I think there are alternative ways in which people with this disease, which can be so debilitating, can have children.[76]

4.94 For these submitters, the fact that mitochondrial donation was not a cure militated against its legalisation, but the Australian Mitochondrial Disease Foundation (AMDF) argued that the lack of any cure for mitochondrial diseases gave ethical weight to the argument in favour of legalising mitochondrial donation:

> Unfortunately at this time there is no cure and few treatments for mitochondrial disease which is one of the reasons its impacts on patients and families are so devastating and why the community is seeking the

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73 Wellcome Trust, *Submission 1—Attachment 3*, [p. 2]; Professor Filipovska, *Submission 17*, p. 1; Associate Professors Mills ans Ludlow, Professor Sparrow and Dr Warren, *Submission 20*, p. 249; Professor Sue, *Submission 24*, p. 2; Associate Professor Dowling, *Submission 25 — Attachment 1*, [p. 1]; Australian Mitochondrial Disease Foundation (AMDF), *Submission 26*, [p. 2]; Australian Academy of Sciences, *Submission 35*, p. 2; Lily Foundation, *Submission 44*, [p. 2]; Wellcome Centre for Mitochondrial Research, *Submission 45*, [p. 5]; Dr Shanti Balasubramaniam, *Submission 52*, [p. 6]; Professor Sheryl de Lacey, *Submission 55*, p. 1; Dr Robin Lovell-Badge, *Submission 58—Attachment 1*, p. 1060.

74 NHMRC, *Submission 4*, p. 9; Plunkett Centre for Ethics, *Submission 30*, p. 1; Australian Christian Lobby, *Submission 51*, p. 3; Dr Cathy Herbrand, *Submission 54*, p. 3; Professors Thorburn, Christodoulou, Sue, Carroll, Ryan and Filipovska, *Submission 59*, p. 1; Catholic Health Australia, *Submission 60*, [p. 1].

75 Australian Christian Lobby, *Submission 51*, p. 4.

76 Dr Tobin, *Committee Hansard*, 17 May 2018, p. 65.

> opportunity for Australia to adopt mitochondrial donation as an option for affected families.[77]

4.95 AMDF's argument was supported by a number of leading scientists in the field who told the committee:

> The fact that there is no cure for mitochondrial disease emphasizes the need and the urgency for allowing women from affected families to have the best chance of having biologically related children who are unaffected by mitochondrial disease...Like almost all assisted reproduction approaches, it should be regarded as mitigating risk, rather than eliminating it. It is worth noting that about 3% of all births are affected by a serious genetic anomaly or disorder.[78]

Committee view

4.96 The committee understands that mitochondrial donation is not a cure, but it presents an opportunity to prevent a child from developing a specific disease. Whilst there are ethical questions about whether this should be permitted for nuclear cells, the committee considers that correcting the mtDNA may be ethically permissible.

The start of the slippery slope?

4.97 Some submitters raised concerns that the same reasoning that is used to allow the replacement of mtDNA to avoid a disease could be used to justify the alteration of nuclear genes of unborn children to alleviate disease. These submitters were concerned that this would be a step towards genetic engineering and a lack of human diversity.

Committee view

4.98 While the committee understands this argument, it is not the proposition before the committee. The committee is satisfied that mitochondrial donation can be legalised in a manner that does not permit the alteration of nuclear germline genes.

Concluding committee view

4.99 The report, so far, has considered the evidence presented to the committee by submitters, including prominent members of the scientific and medical community who work in fields relevant to mitochondrial disease, and concluded that mitochondrial donation is a safe and effective treatment to prevent transmission of mitochondrial disease to the next generation in cases where the disease develops because of mutated mtDNA.

4.100 Chapter one outlined that this treatment has been legalised in the UK, after an extensive 12 year path of scientific and ethical review, combined with community education and consultation.

4.101 Chapter two discussed mitochondrial disease and its impact to individuals and families, as well as provided some estimates of the health costs associated with this

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77 AMDF, *Submission 26.1*, [p. 4].

78 Professors Thorburn, Christodoulou, Sue, Carroll, Ryan and Filipovska, *Submission 59*, p. 1.

disease. Compelling evidence was presented to this committee on the devastating impacts of this disease on families, particularly as its genetic nature means it tends to impact multiple members of the same family, with high child mortality.

4.102 Chapter three discussed the evidence provided on the science and safety of mitochondrial donation. Evidence to the committee noted that while there are still some unknown risks associated with mitochondrial donation, they are far outweighed by the known risks of mitochondrial disease.

4.103 The committee recognises the clinicians' argument that most new medical therapies involve a degree of risk and the last stage of the development of medical treatments usually involve controlled clinical trials. The committee considers that mitochondrial donation has reached this stage. As discussed in chapter three, the committee believes that a formal determination that the science of mitochondrial donation is ready for clinical trial in Australia should be made by independent experts with relevant scientific and medical expertise.

4.104 This chapter discussed the ethics of mitochondrial donation. Many of the ethical concerns considered the mechanics of mitochondrial donation because it necessitates the destruction of embryos and interferes with dignity of natural conception. The committee recognises that these concerns are not specific to mitochondrial donation, and can be applied to any form of ART. However, the committee acknowledges that the creation of viable, distinct embryos with no potential to develop into a viable pregnancy is a new moral question that would require community consultation as well as a change to the legal prohibition of such activity under current law.

4.105 One key ethical concern specific to mitochondrial donation remains unresolved: whether or not mitochondrial donation is genetic engineering of the human genome similar to germline modification, and if so, whether that in itself is enough to reject mitochondrial donation as a medical therapy to prevent children being born with a high risk of developing mitochondrial disease.

4.106 The committee heard evidence that mitochondrial donation is not a form of germline modification as that term was understood at the time genetic modification was prohibited under Australian law. However, the committee recognises that an independent determination that mitochondrial donation is not a form of germline modification would most appropriately be made by a panel of scientists and bio-ethicists.

4.107 These foundational questions remain to be answered before the committee can make a finding that mitochondrial donation is a medical therapy that is safe to be introduced into Australia in the form of a clinical trial, which could lead to clinical practice.

4.108 To achieve this, legislative change must occur at commonwealth and state level to make mitochondrial donation lawful, and a regulatory regime must be created to oversee research, clinical trial and later public rollout. The next chapter discusses the evidence presented to the committee on the most effective ways to regulate for Australia.

Chapter 5
Regulation

Introduction

5.1 The previous chapters of this report have examined evidence on the safety, efficacy and ethical considerations of using mitochondrial donation to reduce the chance of a mother passing on mutated mitochondrial DNA[1] (mtDNA) to a child, potentially leading to mitochondrial disease.

5.2 The issue that remains to be examined is what legislative amendments would need to be made if mitochondrial donation was to go ahead. The most evident place to start, is to look to the example set in the United Kingdom (UK).

UK path to regulation

5.3 As outlined in previous chapters, in 2015 the UK Parliament passed regulations to legalise mitochondrial donation for women with a high chance of passing on mitochondrial disease to their children. The change to law authorised the regulation of mitochondrial donation to be undertaken by the Human Fertilisation and Embryology Authority (HFEA), as the UK's independent regulator of fertility treatment and research using human embryos.[2] Some research has suggested that having an agency dedicated to fertility and embryology has assisted the UK to make advances in this field.

5.4 The new UK regulations require that a licence from the HFEA for mitochondrial donation is needed for the clinic administering the treatment, as well as for individual women seeking treatment.[3] As of 30 April 2018, the HFEA Statutory Approvals Committee[4] has considered six applications from individual women to access mitochondrial donation treatment. Minutes for three applications have been published: two were approved and the third was rejected pending more information showing that alternative options available to the patient were not suitable.[5]

5.5 As shown by the above HFEA approvals process, access to the treatment is highly restricted and it is not anticipated that access requirements will be relaxed in the foreseeable future.

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1 Deoxyribonucleic acid.

2 Human Fertilisation and Embryology Authority (HFEA), *Submission 53*, p. 1.

3 National Health and Medical Council (NHMRC), *Submission 4*, p. 5.

4 The HFEA Statutory Approvals Committee is supported by an international panel of experts in mitochondrial disease, including Professor David Thorburn. This panel conducts peer review of applications.

5 HFEA, *Reports archive*, https://www.hfea.gov.uk/choose-a-clinic/clinic-search/results/17/ (accessed 12 May 2018).

5.6 As a first stage prior to clinical use, the HFEA reconvened its expert advisory panel to advise on whether science suggested mitochondrial donation was sufficiently safe to be offered in treatment. It was ultimately decided that the science was safe enough for carefully limited application. Secondly, the HFEA established a regulatory regime to oversee how and when those licences would be issued.

5.7 The HFEA established a detailed Code of Practice for the use of mitochondrial donation and its Statutory Approvals Committee was authorised to approve access to treatment on a case-by-case basis as 'a clinical risk reduction treatment for carefully selected patients'.[6]

5.8 The HFEA Code of Practice covers issues such as:

- the consent process;
- the information required to be provided to the participants;
- selection criteria for gamete (egg and sperm) providers;
- the requirement for a clinic to hold a licence authorising it to offer mitochondrial donation at a designated site;
- the requirement for HFEA to approve individual patients' access to mitochondrial donation and for those patients to be at high risk of transmitting mutations that will lead to serious mitochondrial disease;
- the requirement that only named embryologists are permitted to undertake the procedure;
- the expertise available in the clinic including mitochondrial disease specialists, reproductive specialists, embryologists, clinical geneticists, genetic counsellors and molecular geneticists;
- the requirement for a documented process for long-term medical follow-up of children born following mitochondrial donation, provided patients have consented to that follow-up, and
- the requirement to report to the HFEA if the clinic becomes aware of any adverse outcomes following treatment involving mitochondrial donation.[7]

5.9 The UK regulations allow for mitochondrial donation to be undertaken for a couple at serious risk of passing on severe mitochondrial disease. While no specific definitions have been outlined in the regulations, the determination of what is considered 'serious risk' of 'severe mitochondrial disease' is ultimately determined by the licensing panel at the HFEA. In practice, the Australian Mitochondrial Disease Foundation (AMDF) submitted that 'severe' is generally considered to be a condition which would have an early onset in a child's life and significantly impact their day-to-day functioning and quality of life. It may, but would not necessarily, be life-limiting.[8]

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6 NHMRC, *Submission 4*, p. 4.

7 NHMRC, *Submission 4*, pp. 4–5.

8 Australian Mitochondrial Disease Foundation (AMDF), *Submission 26.1*, p. 4.

5.10 To support an application for a licence for an individual to undergo mitochondrial donation, a clinic must provide patient-specific information, including:

- the patient's medical history;
- the patient's mutant mtDNA load;
- the patient's family medical history of the mtDNA mutation or disease;
- scientific literature relevant to the mtDNA mutation or disease, and
- any additional information which the clinician may consider is relevant to the application.[9]

5.11 The Murdoch Children's Research Institute submitted that in creating a flexible regulatory regime overseen by an expert government body 'the UK Parliament recognized that developing detailed legislation to regulate all aspects of the mitochondrial donation process was impractical and they devolved much of this responsibility to the HFEA to determine exactly when and how mitochondrial donation would be delivered in the UK'.[10]

5.12 The majority of submitters and witnesses to this inquiry recommended a cautiously staged introduction of mitochondrial donation in Australian clinical practice, based on the findings of the HFEA in the UK that mitochondrial donation is sufficiently safe to be introduced into clinical practice in specific circumstances. The AMDF submitted:

> The rigour and depth of the reviews and process undertaken in the UK should provide the Senators with the confidence that mitochondrial donation could be introduced into the Australian context. Whilst some of the regulations adopted in the UK may need to be adapted to align with Australia's specific expectations or current laws regarding IVF [or ART], they provide a strong basis from which to work towards offering Australian parents the capacity to access these techniques.[11]

5.13 However, prior to examining whether the UK regulatory regime provides good examples for any Australian regulation, a definitional barrier remains, in that Australian anti-cloning legislation as it is currently drafted prohibits this technique. This issue is discussed below.

Australian legislative prohibitions on germline modification

5.14 The main legislative barrier to mitochondrial donation is the blanket prohibition on any form of germline genetic modification contained in the *Prohibition of Human Cloning for Reproduction Act 2002* (Cloning Act).

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9 HFEA, *Submission 53—Attachment 1*, pp. 4–5.

10 Murdoch Children's Research Institute and Victorian Genetic Clinical Services (Murdoch Children's Research Institute), *Submission 23*, p. 8.

11 AMDF, *Submission 26*, p. 9.

5.15 There are three relevant provisions within the Cloning Act: section 13 prohibits the creation of a human embryo outside the body of a woman which contains genetic material from more than 2 persons and section 20 prohibits placing such an embryo into a woman. Section 15 prohibits the alteration of the genome of a human cell where that alteration is inheritable.

5.16 However, as discussed in chapter four, evidence to the committee is that many submitters and witnesses do not consider mitochondrial donation as a traditional germline (inheritable) genetic modification. While there was some distinction between how different witnesses characterised it, most agreed that mitochondrial donation was a new form of genomic modification and should be treated as such. Associate Professor Catherine Mills, a philosopher and bioethicist at Monash University, told the committee that because current legislative prohibitions were 'formulated prior to the possibility of mitochondrial donation, it's now time for it to be reconsidered.'[12]

5.17 This approach accords with the UK regulations allowing for mitochondrial donation, which classified the treatment as germline modification, but not genetic modification.[13]

5.18 The Human Genetics Society of Australasia submitted that 'ethical reviews in the UK and USA have also recognised that…mitochondrial donation is distinct from germline genetic modification and should not be prevented based on false equivalency arguments.'[14]

5.19 Bioethicist Dr Ainsley Newson characterised mitochondrial donation as a novel class of 'conditionally inheritable genomic modifications' and advised:

> The conditional inheritance of mitochondrial donation makes it conceptually distinct from other inheritable (or germ-line) genetic modifications. This means its automatic prohibition on this ground is not warranted.[15]

5.20 A simple approach to eliminating the legislative restrictions was suggested by the National Health and Medical Research Council (NHMRC) as amending legislation:

> …so that mtDNA was not included when determining how many people had contributed genetic material to an embryo (PHCR [Cloning] Act section 13, section 20). However, it would require careful drafting to ensure that this did not inadvertently allow other activities that may be unacceptable to the community.[16]

5.21 Academics from Monash University put forward a similar suggestion, that:

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12 Associate Professor Catherine Mills, *Committee Hansard*, 17 May 2018, p. 50.

13 Associate Professors Mills and Karinne Ludlow, Professor Robert Sparrow and Dr Narelle Warren, *Submission 20*, p. 6.

14 Human Genetics Society of Australasia, *Submission 2*, p. 2.

15 Associate Professor Ainsley Newson, *Submission 29*, p. 3.

16 NHMRC, *Submission 4*, p. 7.

> 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.[17]

5.22 However, the submission goes on to state that key definitional issues must be resolved before legislation can be developed around mitochondrial donation, including:

- 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.[18]

5.23 Dr Newson submitted that mitochondrial donation is a good example of how 'black letter law' can be an imperfect instrument for regulating emerging reproductive technologies and that regulatory instruments such as the genetic privacy regulations under the *Privacy Act* (Cth) have more flexibility for change than primary legislation.[19]

5.24 The Human Genetics Society of Australasia concurred with this view, and submitted:

> We would strongly advocate for a flexible and adaptive system of governance, to help avoid the problems that have come from the existing regulatory regime; in particular there being no further reviews required to the cloning/embryo laws. This and similar areas of reproductive science are fast-moving; and regulation needs to be similarly flexible and adaptive.[20]

Committee view

5.25 As outlined in chapter four, the committee recognises 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.

5.26 However, the committee remains of the belief that it 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.

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17 Associate Professors Mills and Ludlow, Professor Sparrow and Dr Warren, *Submission 20*, p. 5.

18 Associate Professors Mills and Ludlow, Professor Sparrow and Dr Warren, *Submission 20*, p. 5.

19 Associate Professor Newson, *Submission 29*, p. 5.

20 Human Genetics Society of Australasia, *Submission 2*, p. 3.

Australian approach to introduction

5.27 As outlined earlier in this chapter, the UK process is similar to an Australian clinical trial process,[21] which is overseen by the NHMRC,[22] or the regulation of medical therapies with restricted access such as the Life Saving Drugs Program, where a clinician must submit medical evidence on a patient's health condition which is evaluated by a panel of experts prior to any approval to access the medication.[23]

5.28 The NHMRC submitted that there are two paths by which mitochondrial donation could be introduced into Australia. The first would be to follow the process undertaken in the UK, by allowing a small number of centres in Australia to conduct research, validation and training activities, which include the creation and destruction of human embryos, prior to any clinical use. A second option, allowing immediate clinical use but prohibiting the creation of embryos for research, training and validation, would mean that children 'born following the first use of mitochondrial donation in Australia would bear the increased risk associated with establishing expertise in the new technique'.[24]

5.29 The NHMRC recommended that if mitochondrial donation is to be allowed in Australia, it should first be conducted within a research context—or clinical trial—to increase the evidence base for the safety and efficacy of this technique.[25]

5.30 An Australian introduction was generally seen by submitters as a two-pronged approach of allowing almost immediate access to the treatment for a limited number of women (potentially as a clinical trial) as soon as a clinic demonstrated the required expertise in administering the treatment, and at the same time allowing for additional research to be undertaken.[26] Any clinical use of mitochondrial donation would of course require legislative amendments as described above.

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21 A clinical trial usually involves a double-blind study of the efficacy of a treatment or medication, which would not be appropriate in the context of mitochondrial donation. Notwithstanding this, the term clinical trial is useful for a layperson to conceptualise the limitations that would be placed on accessing mitochondrial donation if introduced in a controlled manner to Australian clinical practice. An appropriate description would be an observational clinical trial.

22 Department of Industry, Innovation and Science and NHMRC, *What is a clinical trial?* https://www.australianclinicaltrials.gov.au/what-clinical-trial (accessed 13 May 2018).

23 Department of Health, *Life Saving Drugs Program*, http://www.health.gov.au/LSDP (accessed 13 May 2018).

24 NHMRC, *Submission 4*, p. 6.

25 NHMRC, *Submission 4*, p. 6.

26 An approach to allow immediate limited clinical application of mitochondrial donation was recommended by the following key organisations: Australian Academy of Science, *Submission 35*, p. 2; AMDF, *Submission 26*, [p. 12]; Fertility Society of Australia (Fertility Society), *Submission 27*, p. 3; Monash Biomedicine Discovery Institute, *Submission 19*, [p. 3]; Murdoch Children's Research Institute, *Submission 23*, p. 2 as well as a number of individual clinicians and researchers with specialities in mitochondrial disease.

Committee view

5.31 The committee considers that a limited clinical trial should be considered before full introduction of mitochondrial donation and that additional research could be simultaneously conducted. The committee notes that medical trials would require a change of legislation before they could proceed.

Australian regulatory regime

5.32 Most submitters and witnesses in favour of mitochondrial donation put forward the UK system as a good basis for a regulatory system in Australia, with some modification.[27]

5.33 The Genetic Support Network of Victoria stressed the importance of well-planned implementation managed by experts:

> Implementation is very important. It will require responsible and very clear messaging that will be based on a very clear decision. We need a clear and effective regulatory environment to support mitochondrial donation and we need to allow our clinical experts to do the job.[28]

5.34 AMDF submitted that '[t]he UK regulatory process reflects significant work and effort over many years in its development and, whilst some tweaking may need to occur, Australia already has a framework in existence that could be adapted to address and regulate mitochondrial donation'.[29]

5.35 A common recommendation was to use the current Australian system for regulating both human embryo research and Assisted Reproductive Technology (ART) clinics. This would entail the Embryo Research Licensing Committee (Licensing Committee) of the NHMRC to be responsible for the licensing of centres and individuals seeking treatment, and the Reproductive Technology Accreditation Committee (RTAC) of the Fertility Society of Australia (Fertility Society)[30] to have a role in providing advice on the clinical capacity of ART clinics to provide this service,

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27 See for example AMDF, *Submission 26*, [p. 9]; Australian Academy of Science, *Submission 35*, p. 7; Biomedical Ethics Research Group, Murdoch Children's Research Institute, *Submission 34*, [p. 4]; Fertility Society, *Submission 27*, p. 2; Human Genetics Society of Australasia, *Submission 2*, p. 4; Monash Biomedicine Discovery Institute, *Submission 19*, [p. 2]; Murdoch Children's Research Institute, *Submission 23*, p. 2; Progress Educational Trust, *Submission 48*, p. 2; Wellcome Centre for Mitochondrial Research, *Submission 45*, [p. 6].

28 Ms Monica Mary Ferrie, Chief Executive Officer, Genetic Support Network of Victoria, *Committee Hansard*, 17 May 2018, p. 2.

29 AMDF, *Submission 26.1*, [p. 10].

30 The Embryo Research Act requires all Assisted Reproductive Technology (ART) clinics to be accredited by the Reproductive Technology Accreditation Committee of the Fertility Society, which regulates and licences the 88 ART clinics across Australia.

as well as an ongoing compliance monitoring role of clinics in collaboration with the Licensing Committee.[31]

5.36 The Licensing Committee of the NHMRC was seen to be the most suitable body to regulate licences, as it is has been responsible for the oversight of research involving the use of human embryos for 15 years, and is well placed to regulate research of mitochondrial donation on a case-by-case basis. The Murdoch Children's Research Institute submitted that there may be greater public confidence in the regulation of mitochondrial donation if the licences were granted by a body that is independent of the ART industry, such as the NHMRC, but suggested that '[i]f this was unsuitable then it may require an independent body to be set up, perhaps with input from the Australian Academy of Health and Medical Sciences.'[32]

5.37 The Australian Academy of Science further recommended the NHMRC 'oversee a publicly available database containing information about licences issued and outcomes, as well as regularly report to the Parliament of Australia'.[33]

5.38 A submission from a coalition of professors with expertise in mitochondrial disease noted that the current NHMRC Licensing Committee did not include a member with substantive clinical or scientific expertise in mitochondrial disorders and suggested 'a person with that expertise may be needed to supplement the committee's existing skills in embryology, ART technologies, ethics and community representation'.[34]

5.39 The RTAC of the Fertility Society submitted they would be able to include the regulation of mitochondrial donation in their current regulatory framework:

> RTAC is the accrediting body for ART in Australia, and would therefore take on clinic accreditation of this technique. If further legislative oversight was deemed necessary, the NHMRC embryo research licensing committee could require ART clinics to seek accreditation. These levels of controls would see that Mitochondrial transfer was conducted in the most stringent manner to ensure optimal outcomes for the families at risk and society in general.[35]

5.40 The majority of submitters were supportive of replicating the double-licensing system used in the UK, where both the clinic and the patient must have a licence prior to the use of mitochondrial donation. Professor Christodoulou outlined how this could work in practice:

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31 This model was supported by Australian Academy of Science, *Submission 35*, p. 7; Fertility Society, *Submission 27*, p. 2; Murdoch Children's Research Institute, *Submission 23*, p. 13, among others.

32 Murdoch Children's Research Institute, *Submission 23*, p. 14.

33 Australian Academy of Science, *Submission 35*, p. 7.

34 Professors David Thorburn, John Christodoulou, Carolyn Sue, John Carroll, Mike Ryan, Aleksandra Filipovska, *Submission 59*, p. 2.

35 Fertility Society, *Submission 27*, p. 2.

> Firstly, one wants to be confident that the organisation that's going to be offering the IVF technology has the skill set and expertise to be able to do that. That would require expert panels to review the scientific and clinical credentials of whatever the organisation was…
>
> And then the second aspect of the licensing—and this is very much following the UK model—is that one needs to be really careful about identifying for which families this technology will truly be of benefit. That would require the evaluation by an expert panel—which I would suggest should include both paediatric and adult mitochondrial specialists, IVF specialists, geneticists and, importantly, community representation as well—to identify on a case-by-case basis those individuals who would truly benefit by having mitochondrial donation versus others who might be better potentially directed towards traditional prenatal testing or preimplantation genetic diagnosis or where none of these technologies may be relevant.

5.41 There were a number of additional regulatory issues that were recommended by submitters and witnesses as important components to a regulatory regime that protected the safety and well-being of parents using mitochondrial donation, children born of this technique and potential donors. These are examined below.

Restrict purpose to mitochondrial disease

5.42 The clinical purpose of mitochondrial donation was discussed by multiple submitters and witnesses. Beyond preventing mitochondrial disease, mitochondrial donation has been tested as a treatment for certain infertility issues[36], and recent medical research has indicated that mtDNA mutations are implicated in many further health problems, such as diabetes, autism and some inheritable cancers.[37] Mitochondrial donation may well prove, at some unknown point in the future, to be a viable prevention treatment for health conditions beyond mitochondrial disease.

5.43 However, there was a universal view that while mitochondrial donation was still in its early years and is somewhat experimental, the unknown risks may be acceptable to take for reducing the generational transmission of severe mitochondrial disease to children, but was not considered appropriate to take for other diseases or as an ART enhancement at this point in time.[38]

5.44 Professor David Thorburn of the Murdoch Children's Research Institute recommended that limiting mitochondrial donation to preventing mitochondrial

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36 Murdoch Children's Research Institute, *Submission 23*, p. 10.

37 AMDF, *Mitochondrial Disease Information: Where does mitochondrial disease hide if it is NOT diagnosed*, https://www.amdf.org.au/mito-info/ (accessed 13 June 2018).

38 This view was put by many submitters and witnesses, for example: AMDF, *Submission* 26, [p. 9]; Murdoch Children's Research Institute, *Submission 23*, pp. 13–14; ProfessorDavid Thorburn, Head of Mitochondrial Research and Diagnostic Laboratories, Murdoch Children's Research Institute, *Committee Hansard*, 17 May 2018, p. 12; Professor John Christodoulou, Chair, Genomic Medicine, Department of Paediatrics, University of Melbourne, *Committee Hansard*, 17 May 2018, p. 13; Associate Professor Mills, *Committee Hansard*, 17 May 2018, p. 54; Associate Professor Newson, *Committee Hansard*, 17 May 2018, p. 54.

disease should be done in primary legislation.[39] However, Professor Thorburn further noted that while mitochondrial donation should be 'ring-fenced' to the purpose of mitochondrial disease, there is still a degree of flexibility required in the assessment of how to implement that in practice:

> I think it's impossible to put all the detail into the legislation. It's going to be quite complicated and it will be necessary to hand off—there's not exactly an equivalent of the Human Fertilisation and Embryology Authority in Australia, but it needs to be, to a degree, handed off to an expert independent committee to narrow down the details of how that can proceed in practice but be restricted to using it for mitochondrial DNA donation to prevent severe mitochondrial disease.[40]

5.45 Dr Newson also argued for some flexibility on the grounds that women most likely to pass on the more serious forms of mitochondrial disease are often too sick to be able to use mitochondrial donation.[41]

5.46 Associate Professor Catherine Mills agreed that it would be prudent to start with limiting access to those women most in need of this technology as 'women whose children would most clearly suffer from serious mitochondrial disease in the circumstance of not using the technology' and noted that the risks of this technology 'would still probably have lesser health impacts than the risks of mitochondrial disease'.[42]

5.47 Further to this, the UK restricts mitochondrial donation to couples for whom pre-implantation genetic diagnosis (PGD) or other methods would be inappropriate or unlikely to succeed. As stated earlier in this chapter, a person seeking a licence in the UK must demonstrate that other methods for having children are not an option.

5.48 Professor Thorburn supported this position and told the committee that '[p]re-treatment assessment must take into account a range of factors and I also believe this should be overseen by a body independent of the ART industry, which could presumably be the same body overseeing licensing of centres, with input from experts in multiple disciplines'.[43]

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39 Professor Thorburn, *Committee Hansard*, 17 May 2018, p. 12.

40 Professor Thorburn, *Committee Hansard*, 17 May 2018, p. 17.

41 Associate Professor Newson, *Submission 29*, p. 5.

42 Associate Professor Mills, *Committee Hansard*, 17 May 2018, p. 54.

43 Murdoch Children's Research Institute, *Submission 23*, pp. 6, 14.

5.49 In practice, many submitters and witnesses pointed to the UK regulation regime as a good way to restrict access to mitochondrial donation through the dual licensing system.[44]

Multiple donation techniques

5.50 As outlined in chapter three, evidence suggests a preferred method of mitochondrial donation does not appear to have yet been identified. Consideration needs to be given to the way any possible regulation is framed to permit the safest and most up-to-date scientific techniques to be used in Australia.

5.51 Professor John Carroll from the Monash Biomedicine Discovery Institute noted that pronuclear transfer is the preferred method being investigated by the UK clinic licensed to undertake mitochondrial donation 'which gives me more confidence in being able to understand any technical details about making that as good as it possibly can be'. That being said, Professor Carroll recommended that both pronuclear transfer and maternal spindle transfer should be allowed for under any Australian regulatory regime, to 'give us the best flexibility and adaptability as we move forward through the process of learning how successful the technique is and how we can adapt it and improve it as will always happen in new techniques like this'.[45]

5.52 Professor Carolyn Sue, Director of the Mitochondrial Disease Research Centre at the Kolling Institute of Medical Research, agreed and noted that if both techniques for mitochondrial donation were available, patients with an ethical objection to the destruction of embryos would be able to access the treatment.[46]

5.53 Professor Justin St John, Head of the Mitochondrial Genetics Group at the Hudson Institute of Medical Research, presented evidence to the committee on new techniques for mitochondrial donation which uses eggs at an earlier development stage that currently used in maternal spindle transfer. This was discussed in detail in chapter three. Professor St John recommended that changes to law should be inclusive, to allow for scientific changes.[47]

Clinical capacity and numbers

5.54 The regulation of ART clinics offering mitochondrial donation in the UK is done by the HFEA. Professor Thorburn supported any Australian regulation to follow

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44 See for example: AMDF, *Submission 26*, [p. 9]; Australian Academy of Science, *Submission 35*, p. 7; Biomedical Ethics Research Group, Murdoch Children's Research Institute, *Submission 34*, [p. 4]; Fertility Society, *Submission 27*, p. 2; Human Genetics Society of Australasia, *Submission 2*, p. 4; Monash Biomedicine Discovery Institute, *Submission 19*, [p. 2]; Murdoch Children's Research Institute, *Submission 23*, p. 2; Progress Educational Trust, *Submission 48*, p. 2; Wellcome Centre for Mitochondrial Research, *Submission 45*, [p. 6].

45 Professor John Carroll, Director, Monash Biomedicine Discovery Institute, Monash University, *Committee Hansard*, 17 May 2018, p. 25.

46 Professor Carolyn Sue, Director, Kolling Institute of Medical Research, Mitochondrial Disease Research Centre, *Committee Hansard*, 17 May 2018, p. 27.

47 Professor Justin St John, Professor and Head, Mitochondrial Genetics Group, Hudson Institute of Medical Research, *Committee Hansard*, 17 May 2018, p. 45.

the approach of the HFEA, which imposes 'a requirement for appropriate levels of skill being demonstrated by named practitioners within a named clinic, and relevant key performance indicators being met, parameters that will be assessed by the HFEA'.[48]

5.55 Professor Thorburn recognised that regulation in Australia would be more complex than the UK method, as the clinical application of new ART techniques would need to be accredited by the RTAC of the Fertility Society.[49]

5.56 Most people and organisations in favour of mitochondrial donation recommended that clinic numbers be limited in the initial stage, to allow for one or two centres of excellence to be established. The Human Genetics Society of Australasia also submitted this would 'aggregate relevant clinical experience, provide training, patient follow-up and clinical audit so as to support the greatest possible benefits to patients and healthy outcomes for children'.[50]

5.57 Professor Sue told the committee that the capacity exists within Australian clinics to provide this treatment:

> When I speak to IVF centres, there is an appetite for this technology transferral. There's no real concern about not being able to do it. It's more about changing the legislation to make it legal and also determining the demand for this procedure. I think the capability is there, the appetite is there, but the legislation doesn't allow us to do it at this stage.[51]

5.58 Dr Petra Wale from the Fertility Society noted that mitochondrial donation would not be 'a routine offering on an IVF platform' and that limiting the numbers of clinics providing this treatment would create centres of excellence.[52]

5.59 Professor Sue also discussed the number of clinics which should be initially licensed, and noted that while the UK had licensed only one clinic at this stage, the geographical spread of Australia meant that a 'tyranny of distance' could create equity and fairness issues for patients should only a single clinic be licensed in Australia.[53]

Follow-up

5.60 AMDF pointed to the UK model for follow-up, where clinics offering mitochondrial donation must have a documented process for monitoring children born following mitochondrial donation, including medical follow-up, with mandatory reporting of any adverse events, such as birth defects, genetic abnormality or another

48 Murdoch Children's Research Institute, *Submission 23*, p. 13.

49 Murdoch Children's Research Institute, *Submission 23*, p. 13.

50 Human Genetics Society of Australasia, *Submission 2*, p. 4.

51 Professor Sue, *Committee Hansard*, 17 May 2018, p. 24.

52 Dr Petra Wale, Board Member, Fertility Society, *Committee Hansard*, 17 May 2018, p. 27.

53 Professor Sue, *Committee Hansard*, 17 May 2018, p. 27.

adverse outcome such as a miscarriage.[54] The Australian Academy of Science further recommended that haplotype information should also be collected.[55]

5.61 Dr Nadine Richings, Vice Chair of Scientists in Reproductive Technology (SIRT)[56] recommended rigorous follow-up similar to the procedures followed with the introduction of the ART process intracytoplasmic sperm injection, ICSI. Dr Richings informed the committee that:

> If mitochondrial donation was permitted Australia, SIRT would support and recommended rigorous evaluations of laboratory outcomes and also follow-ups of any children born through these procedures. The Australia and New Zealand Assisted Reproduction Database, ANZARD, could report this information. The purpose of ANZARD is to collect, monitor and monitor the perinatal outcomes of assisted reproduction and to assess the effectiveness of ART treatments. It would be an appropriate organisation or scheme to review this information.[57]

Haplogroup matching

5.62 Chapter three discussed the ongoing scientific debates around the need for haplogroup matching. This chapter highlighted that while there was still disagreement in the scientific community regarding the potential level of risk involved in 'mixing' haplogroups, there was consensus that any risk was far lower than the known risks of passing on mitochondrial disease.

5.63 Professor Thorburn submitted he is concerned that requiring haplogroup matching would reduce the pool of possible donor eggs and that:

> Until there is more experience with mitochondrial donation, it seems reasonable to recommend haplogroup matching if practicable but to enable couples to choose to use an unmatched haplogroup donor.[58]

5.64 Leaving the decision to about whether to use haplogroup matching, after counselling, to the prospective parents was endorsed by the Australian Academy of Sciences, Murdoch Children's Research Institute and Victorian Genetic Clinical Services and Professors David Thorburn, John Christodoulou, Carolyn Sue, John Carroll, Mike Ryan and Aleksandra Filipovska.[59]

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54 Mandatory reporting of any adverse events is required, such as birth defects, genetic abnormality or another adverse outcome such as a miscarriage.

55 Australian Academy of Science, *Submission 35*, p. 7.

56 Scientists in Reproductive Technology (SIRT) is a sub-committee of the Fertility Society, consisting of embryologists and other scientists involved in ART.

57 Dr Nadine Richings, Vice Chair, SIRT, *Committee Hansard*, 17 May 2018, p. 42.

58 Murdoch Children's Research Institute, *Submission 23*, p. 6.

59 Murdoch Children's Research Institute, *Submission 23*, p. 14; Australian Academy of Sciences, *Submission 35*, p. 5; Professors Thorburn, Christodoulou, Sue, Carroll, Ryan, Filipovska, *Submission 59*, p. 7.

Embryo sex selection

5.65 Many submitters and witnesses discussed the proposal in the United States that mitochondrial donation would be limited to only use male embryos, so that any negative germline modifications would not be passed on to subsequent generations. The Australian Academy of Science submitted that this was considered by the HFEA for mitochondrial donation in the UK, but was ultimately rejected due to concerns this would require another intervention, in this case PGD, in an embryo that had already been subject to heavy manipulation, and would also halve the number of suitable embryos and reduce the chance of achieving a pregnancy.[60]

5.66 The NHMRC ethical guidelines for ART allows for sex selection of embryos to reduce the risk of transmission of a genetic condition, disease or abnormality, but not for family balancing or other reasons.[61] Whether or not the selection of male embryos to reduce the chance of passing on inheritable changes brought about by mitochondrial donation would be considered under these guidelines as an acceptable option, would have to be explored by the NHMRC. The choice for undertaking sex selection would then lie with the parents.

5.67 Professor Sue noted that this would also require careful pre-treatment counselling from a qualified geneticist:

> [F]or patients who are dealing with a choice of having a male child with a maternity-transmitted disorder that may be something of importance and something that you or I are not able to inflict or control from any individual's choice. If the procedure is such that mitochondrial donation does or does not enable the choice of a male child, that is something I would have to guide the patient on: 'These are the risks. If you have the mitochondrial donation the risk is low. However, if they are a female they have a likelihood of passing it on if there is still some carryover'…That's something that a reproductive options clinic would offer and something that we would intend to do and evaluate after the procedure would be legalised.[62]

Pre-treatment counselling

5.68 The need for pre-treatment counselling was raised by multiple submitters, to ensure that couples considering using mitochondrial donation were fully informed of the known and unknown risks, the efficacy of the treatment, as well as other options for having genetically or non-genetically related children.[63]

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60 Australian Academy of Science, *Submission 35*, p. 5.

61 NHMRC, *Ethical Guidelines on the use of assisted reproductive technology in clinical practice and research*, para 8.1.

62 Professor Sue, *Committee Hansard*, 17 May 2018, pp. 25–26.

63 See for example: AMDF, *Submission 26.1*, [p. 6]; Australian Academy of Science, *Submission 35*, p. 5; Fertility Society, *Submission 27*, p. 2; Human Genetics Society of Australasia, *Submission 2*, p. 2; Murdoch Children's Research Institute, *Submission 23*, p. 2; Dr Shanti Balasubramaniam, *Submission 52*, [p. 5];Associate Professor Newson, *Submission 29*, p. 3.

5.69 The AMDF submitted that the UK model offers a good basis for pre-treatment counselling and closely aligns with Australian pre-treatment counselling for ART procedures. AMDF further submitted that:

> In terms of counselling, it seems appropriate that advice should be provided to prospective parents about the alternative options available to them in terms of their reproductive options and about the scientific concepts involved, such as pronuclear transfer, maternal spindle transfer, and potential haplogroup matching. In addition, in line with current medical practice regarding IVF, the risks and benefits of the procedures should be outlined.[64]

5.70 Professor Thorburn also stressed the range of information that should be provided to parents in order to facilitate informed consent.

> Parents need to know what the full range of options is, including adoption, egg donation, prenatal diagnosis, preimplantation genetic diagnosis and mitochondrial donation. Some of those options either will not be suitable for the families or will not be acceptable to the families, but it's important that they be provided with all the information about potential safety and efficacy.[65]

Committee view

5.71 The committee concurs with the views of the majority of submitters and witnesses, that the UK model of regulation provides a sound basis for adaptation to the Australian ART clinical context. The evidence shows that Australian clinics have the capacity to refine the skills necessary to undertake mitochondrial donation. Evidence also shows that the Australian research and clinical practice frameworks are sound and robust enough to be adapted to ensure that mitochondrial donation is regulated and appropriately monitored.

5.72 The committee notes that evidence presented to this inquiry on the areas of oversight for an appropriate regulatory regime will be useful to establishing an appropriate Australian system for mitochondrial donation.

5.73 The committee stresses the importance of detailed pre-treatment counselling for anyone who seeks mitochondrial donation as a treatment, to ensure they are fully aware of the risks, efficacy and other options that may be available to them.

Accessing overseas clinics

5.74 Professor Sue explained to the committee that her mitochondrial disease clinic has been in discussions with the fertility clinic in the UK which holds the licence to provide mitochondrial donation:

> Through our planned Reproductive Options Clinic, Australian women with MD will be provided with a pathway by which they can undergo mitochondrial donation under safe and regulated conditions at the

64 AMDF, *Submission 26.1*, [p. 9].

65 Professor Thorburn, *Committee Hansard*, 17 May 2018, p. 15.

> Mitochondrial Donation Centre in Newcastle, UK. However, this avenue, while helpful for some women, will be prohibitively expensive for others.[66]

5.75 However, Professor Sue also outlined that other countries such as Mexico and Vietnam are offering this technology as 'medical tourism', without adequate regulations or academic oversight. Professor Sue argues that allowing mitochondrial donation in Australia will 'provide Australians with the opportunity to undergo procedures that are quality controlled, approved and regulated'.[67] A number of other submissions also raised this as a significant concern and that Australian mitochondrial disease support groups have already been contacted by a clinic in Vietnam offering these services to Australians.[68]

5.76 Whether Australian legislative prohibitions on mitochondrial donation would make such actions an offence for an Australian couple has not yet been tested.[69]

5.77 To address the issue of Australians accessing treatment overseas, submitters recommended consideration of modifying Australian law to allow for this. Dr Newson further recommended there should be post-birth arrangement in place in Australia for any couples who successfully sought treatment overseas.[70]

Committee view

5.78 The committee understands that although the UK clinic offering mitochondrial donation is not yet accepting Australian patients, this may occur before this treatment is available in Australia. The committee also notes that mitochondrial donation may become available in less well-regulated countries. Any consideration of changes to legislation should take these issues into account.

State law

5.79 Many submitters pointed out that Victoria, New South Wales, South Australia and Western Australia have state-based legislation around reproductive technology, which would also have to be amended to allow for mitochondrial donation.[71]

5.80 For example, under state reproductive health laws, all Australian jurisdictions require the genetic origins of the resulting child be certain. In some states, this would constrain the implantation of more than one embryo where mitochondrial donation has

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66 Professor Sue, *Submission 24*, p.5.

67 Professor Sue, *Submission 24*, p.5.

68 Murdoch Children's Research Institute, *Submission 23*, pp. 10, 16. See also: AMDF, *Submission 26*, [pp. 9–10]; Professor Filipovska, *Submission 17*, p. 2; Human Genetics Society of Australasia, *Submission 2*, p. 3.

69 Distinguished Professors Jenni Millbank and Isabel Karpin and Professor Anita Stuhmcke, *Submission 57*, p. 5.

70 Associate Professor Newson, *Submission 29*, p. 6. This was also recommended by the Human Genetics Society of Australasia.

71 NHMRC, *Submission 4*, p. 1. See also Associate Professor Newson, *Submission 29*, p. 7; Australian Academy of Science, *Submission 35*, p. 7.

been used, and may also preclude anonymous mtDNA donation.[72] In other states, such as NSW, Commonwealth anti-cloning laws have been replicated and would require amendment to allow for mitochondrial donation to be undertaken in that jurisdiction.[73]

5.81 State-based laws do provide some regulatory opportunities, in that some states have regulatory bodies which could incorporate a role in overseeing mitochondrial donation, such as the Victorian Assisted Reproductive Treatment Authority. The Murdoch Children's Research Institute, however, argued that a national approach to regulation would be preferred.[74]

Committee view

5.82 The committee understands that reproductive technology is regulated at both a Commonwealth and state level. In some cases, states have replicated Commonwealth anti-cloning laws. In order for mitochondrial donation to be used in clinical practice, this will require some amendment to the state or territory laws of the jurisdiction where the initial clinic(s) are established. This will best be addressed by the relevant Health Ministers working collaboratively, potentially through a Council of Australian Governments process.

Public consultation

5.83 Given the ethical considerations of mitochondrial donation, many submitters and witnesses acknowledged that public consultation should occur prior to changes in the legislation and any rollout of the clinical use of mitochondrial donation. Professor Christodoulou noted that this is an area where the views of the whole community should be taken into account, not just those with a specific interest in this treatment.[75]

5.84 AMDF noted that this inquiry itself was part of the process to review the science and the ethics and gauge public opinion.[76]

> I believe that most Australians provided with the relevant information would support the use of mitochondrial donation to prevent the devastating outcomes of mitochondrial disease.[77]

5.85 Many submitters stressed the importance of accurate information being provided to the public during any consultation, and avoiding emotive and incorrect terms such as 'three-parent babies'.[78]

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72 Associate Professors Mills and Ludlow, Professor Sparrow and Dr Warren, *Submission 20,* p. 6.

73 *Human Cloning for Reproduction and Other Prohibited Practices Act 2003* (NSW), s. 8.

74 Murdoch Children's Research Institute, *Submission 23*, p. 13.

75 Professor Christodoulou, *Committee Hansard,* 17 May 2018, p. 14.

76 Mr Sean Murray, Chief Executive Officer, AMDF, *Committee Hansard,* 17 May 2018, p. 9.

77 Murdoch Children's Research Institute, *Submission 23*, p. 13.

78 Human Genetics Society of Australasia, *Submission 2*, p. 4. See also: Australian Academy of Science, *Submission 35*, pp. 4, 8; Biomedical Ethics Research Group, Murdoch Children's Research Institute, *Submission 34*, [p. 5]; Associate Professor Newson, *Submission 29*, p. 4.

5.86 Associate Professor Mills also stressed the importance of maintaining 'transparency and accuracy in discussions about the therapeutic efficacy of mitochondrial donation'. Associate Professor Mills told the committee:

> Mitochondrial diseases can be caused by mutations in nuclear DNA that control mitochondria as well as mitochondrial DNA. This technology only addresses mitochondrial disease that arises from mitochondrial DNA, which is inherited maternally. Given this, it's important in discussions of mitochondrial donation that its capacity to cure or treat mitochondrial disease is not overstated. It's not a cure for existing people but a means of preventing the birth of some people who are likely to be born with mitochondrial disease—or, to put the point more positively, enabling the birth of people without such diseases.[79]

5.87 Dr Newson discussed a citizens' jury she recently conducted into community attitudes on mitochondrial donation. Dr Newson submitted that '[i]f citizens are provided with good quality evidence and have the opportunity to reason and think on the question at hand, they will be able to come to a well-informed and soundly reasoned decision that reflects their values'. Dr Newson outlined the process where participants 'hear balanced evidence, [from expert witnesses] have the opportunity to ask the experts questions, deliberate (with and without a neutral facilitator present) and come to a decision – the "verdict", which can include dissenting opinions'. The jury ran over one and a half days and comprised 14 members from a range of ages and cultures, who had no experience of mitochondrial disease.[80]

5.88 Dr Newson submitted that while the report of the citizen's jury has not yet been published, she did note that a 11 of 14 jurors answered either 'yes' or 'yes with conditions' (such as an appropriate licensing regime) to the question of whether Australia should allow children to be born following mitochondrial donation.[81]

5.89 Associate Professor Mills summed up the need for public consultation to take place in Australia around mitochondrial donation:

> Furthermore, while we can learn from the UK process that took place in the lead-up to legislative reform, that process of public discussion can't simply replace a similar process in Australia. The issues involved in mitochondrial donation are sufficiently complex, and the potential regulatory reform sufficiently far-reaching, that a robust process of public and expert consultation and debate is required prior to its introduction into clinical practice.[82]

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79 Associate Professor Mills, *Committee Hansard*, 17 May 2018, p. 51.

80 Associate Professor Newson, *Submission 29*, p. 7.

81 Associate Professor Newson, *Submission 29*, p. 8. Citizen's jury outcomes quoted from 'Using deliberative engagement to assess public attitudes towards novel reproductive technologies: a citizens' jury on mitochondrial donation': Confidential attachment to *Submission 29*; cited with permission.

82 Associate Professor Mills, *Committee Hansard*, 17 May 2018, p. 52.

Committee view

5.90 The committee agrees that mitochondrial donation should not be introduced without allowing for public consultation.

5.91 The committee notes that this inquiry plays a part in public consultation, and considers that from the evidence presented so far, mitochondrial donation may not be seen as a controversial medical treatment.

5.92 The committee further notes that any legislative change will, most likely, involve a Senate legislation inquiry, which will give further opportunity for the Australian public to put their views to the parliament on whether this treatment should be legalised.

5.93 The committee agrees that public consultation is necessary before any full rollout of mitochondrial donation and that parliamentary inquiries alone will not be sufficient public consultation.

5.94 Evidence suggests that mitochondrial donation is a form of genetic modification that was not envisioned at the time that anti-cloning laws were enacted in Australia. As such, these laws prevent mitochondrial donation from being researched and used in clinical practice. Science has moved significantly faster than legislation.

5.95 Therefore, as outlined in chapter four, a foundational question must be answered before any possible introduction of mitochondrial donation into Australian clinical practice: does this treatment constitute germline gene modification in the manner known at the time that such practices were prohibited under Australian anti-cloning laws, and is it appropriate to modify laws to incorporate mitochondrial donation?

5.96 Defining what kind of gene modification this treatment is, is fundamental to developing the most appropriate legislative amendments to legalise mitochondrial donation if that is supported by the community. The committee does not envision this process as requiring an extensive or lengthy review.

5.97 The committee concurs with the views of many submitters and witnesses, that, should mitochondrial donation be introduced to Australia, enacting a regulatory and oversight regime for mitochondrial donation would be most appropriately done through regulations which empower the NHMRC, supported by the RTAC of the Fertility Society to manage the oversight and restricted access to mitochondrial donation as a clinical treatment.

5.98 In this way, regulations can be amended and adapted to keep up to date with changing scientific knowledge, with the review and approval of the Parliament of Australia.

Recommendations

Recommendation 1

5.99 The committee notes the strong potential of mitochondrial donation to address the debilitating effects of inheriting mitochondrial disease. The committee recommends that public consultation be undertaken regarding the introduction of mitochondrial donation to Australian clinical practice. To facilitate this consultation, the committee further recommends the Australian Government prepare a consultation paper, including options for legislative change that would be required. The Minister for Health should seek advice from the National Health and Medical Research Council on the most appropriate timing and format for this consultation.

Recommendation 2

5.100 The committee recommends that the Australian Government task the National Health and Medical Research Council with advising on the following questions:

- **Whether mitochondrial donation is distinct from germline genetic modification.**
- **Is there any new information to indicate that research findings from the United Kingdom, that the science of mitochondrial donation is safe for introduction into controlled clinical practice, cannot be applied in an Australian context?**
- **Whether other approaches to inheriting mitochondrial disease should also be the focus of Australian research.**

5.101 The committee recommends the findings be used to inform future legislative process.

5.102 The committee notes that the *Prohibition of Human Cloning for Reproduction Act 2002* and the *Research Involving Human Embryos Act 2002* would require amendment to insert a power to make regulations allowing for mitochondrial donation, with an appropriate regulatory regime overseen by the National Health and Medical Research Council.

Recommendation 3

5.103 The committee recommends the Minster for Health take the findings of this report to the Council of Australian Governments (COAG) Health Council to progress the implementation of this report's recommendations with the states and territories.

Recommendation 4

5.104 The committee recommends, noting the need for community consultation and scientific review, the urgency of treatment for current patients and the small number of patients seeking this treatment, that the Australian Government initiate dialogue with the relevant authorities in the United Kingdom to facilitate access for Australian patients to the United Kingdom treatment facility as an interim measure.

Senator Rachel Siewert

Chair

APPENDIX 1

Submissions and additional information received by the Committee

Submissions

1 Wellcome Trust (plus three attachments)

2 Human Genetics Society of Australasia

3 United Mitochondrial Disease Foundation

4 National Health and Medical Research Council

5 Name Withheld

6 Name Withheld

7 Dr John Duley

8 Name Withheld

9 Name Withheld

10 Confidential

11 Name Withheld

12 Professor John Christodoulou

13 Confidential

14 Name Withheld

15 Name Withheld

16 Confidential

17 Professor Aleksandra Filipovska

18 Name Withheld

19 Monash Biomedicine Discovery Institute, Monash University

20 Associate Professor Catherine Mills, Associate Professor Karinne Ludlow, Professor Robert Sparrow, Dr Narelle Warren

21 Scientists In Reproductive Technology

22 Confidential

23 Murdoch Children's Research Institute and Victorian Clinical Genetics Services

24 Professor Carolyn Sue

25 Associate Professor Damian Dowling (plus an attachment)

26 Australian Mitochondrial Disease Foundation (plus two attachments and a supplementary submission)

27 Fertility Society of Australia

28 Australian Catholic Bishops Conference

29 Dr Ainsley Newson

30 Plunkett Centre for Ethics

31 Professor Jus St. John

32 Name Withheld

33 Name Withheld

34 Biomedical Ethics Research Group, Murdoch Children's Research Institute

35 Australian Academy of Science

36 Name Withheld

37 Dr Nigel Turner

38 Name Withheld

39 Name Withheld

40 Mr Ash Howlett and Dr Steve Mercer

41 Ms Mary Price

42 NSW Stem Cell Network

43 Nuffield Council on Bioethics

44 Lily Foundation

45 Wellcome Centre for Mitochondrial Research

46 Dr Peter McCullagh

47 Dr Ian Trounce

48 Progress Educational Trust (plus two attachments)

49 Dr Mary Herbert

50 Confidential

51 Australian Christian Lobby

52 Dr Shanti Balasubramaniam

53 Human Fertilisation and Embryology Authority (plus an attachment)

54 Dr Cathy Herbrand

55 Professor Sheryl de Lacey

56 Social Issues Committee, Anglican Church Diocese of Sydney

57 Distinguished Professor Jenni Millbank, Distinguished Professor Isabel Karpin and Professor Anita Stuhmcke

58 Professor Robin Lovell-Badge (plus an attachment)

59 Professors David Thorburn, John Christodoulou, Carolyn Sue, John Carroll, Mike Ryan and Aleksandra Filipovska (plus an attachment)

60 Catholic Health Australia

Additional Information

1 Mitochondrial Disease: The Need for Mitochondrial Donation, from Australian Mitochondrial Disease Foundation, received 17 April 2018

2 Q&A: Mitochondrial donation, Wellcome Trust, from Australian Mitochondrial Disease Foundation, received 17 April 2018

3 Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015, from Australian Mitochondrial Disease Foundation, received 17 April 2018

4 House of Commons Mitochondrial Donation briefing, 29 January 2015, from Australian Mitochondrial Disease Foundation, received 17 April 2018

5 Third scientific review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception: 2014 update, June 2014, from UK Human Fertilisation and Embryology Authority, received 30 May 2018

6 Review of the safety and efficacy of polar body transfer to avoid mitochondrial disease, October 2014, from UK Human Fertilisation and Embryology Authority, received 30 May 2018

7 Scientific review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception: 2016 update, November 2016, from UK Human Fertilisation and Embryology Authority, received 30 May 2018

Answers to Questions on Notice

1 Answers to Questions taken on Notice during 17 May public hearing, received from Associate Professor Damian Dowling, 30 May 2018

2 Answers to Questions taken on Notice during 17 May public hearing, received from National Health and Medical Research Council, 31 May 2018

Tabled Documents

1 Mitochondrial donation / mitochondrial replacement / nuclear transfer, tabled by Professor Jus St. John, at Sydney public hearing, 17 May 2018

Correspondence

1 Correspondence clarifying evidence given at Sydney public hearing on 17 May 2018, received from Dr Ainsley Newson, 6 June 2018

APPENDIX 2

Public hearings

Thursday, 17 May 2018

Portside Centre, Sydney

Witnesses

Australian Mitochondrial Disease Foundation
MURRAY, Mr Sean, Chief Executive Officer

Genetic Support Network of Victoria
FERRIE, Ms Monica Mary, Chief Executive Officer

Murdoch Children's Research Institute and Victorian Clinical Genetics Services
THORBURN, Professor David, Head of Mitochondrial Research and Diagnostic Laboratories

Department of Paediatrics, University of Melbourne
CHRISTODOULOU, Professor John, Chair, Genomic Medicine

Kolling Institute of Medical Research, Mitochondrial Disease Research Centre
SUE, Professor Carolyn, Director

Monash Biomedicine Discovery Institute, Monash University
CARROLL, Professor John, Director
RYAN, Professor Mike, Professor and Associate Dean of Research

MARY, Private capacity

SHELLEY, Private capacity

RHONDA, Private capacity

JUSTIN, Private capacity

Fertility Society of Australia
WALE, Dr Petra, Board Member

Mitochondrial Genetics Group, Hudson Institute of Medical Research
St JOHN, Professor Justin (Jus), Professor and Head

Scientists In Reproductive Technology
RICHINGS, Dr Nadine, Vice Chair

NEWSON, Dr Ainsley, Private capacity

MILLS, Associate Professor Catherine, Private capacity

School of Biological Sciences, Monash University
DOWLING, Associate Professor Damian, Associate Professor

National Health and Medical Research Council
KELSO, Professor Anne, Chief Executive Officer
MACKERRAS, Dr Alison, Assistant Director
BARR, Ms Jillian, Acting Executive Director

Plunkett Centre for Ethics, Australian Catholic University; St Vincent's Health Network Sydney; Calvary Health Care
TOBIN, Dr Bernadette, Director

Australian Catholic Bishops Conference
FISHER, Archbishop Anthony, Vice President; Chairman, Bishops Commission for Family, Youth and Life