SUPPLEMENTARY SUBMISSION TO THE SENATE COMMUNITY AFFAIRS LEGISLATION COMMITTEE

Re: Mitochondrial Donation Law Reform (Maeve's Law) Bill 2021

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INTRODUCTION

The Mito Foundation acknowledges the right for groups and individuals to oppose Maeve's Law and to provide reasons, including moral, ethical and religious, for doing so.

The foundation is, however, extremely disappointed and saddened by some of the comments made by those opposing Maeve's Law including some of the selected quoting of documents that has occurred to date that, when take in isolation, may appear to support their arguments while ignoring the clear and different conclusions of the quoted documents.

This supplementary submission addresses these matters and reinforces some of the facts relating to mitochondrial donation.

MITOCHONDRIAL DONATION WILL **NOT** RESULT IN DESIGNER BABIES

Any suggestion that mitochondrial donation will result in designer babies fundamentally misunderstands the science involved and the nature of mitochondrial DNA.

The principal purpose of mitochondria is to help translate the energy consumed by an individual to help the body operate effectively. Mitochondrial DNA does not influence personal characteristics such as height, eye colour, intelligence and so forth – these personal characteristics are determined by nuclear DNA which is not affected by mitochondrial donation.

As such, mitochondrial donation will not enable people to choose the characteristics of their children but rather enable them to have the opportunity to have a child with healthy mitochondria and without a life-threatening form of mitochondrial disease.

MITOCHONDRIAL DONATION IS **NOT** GENE EDITING

Numerous comments in relation to mitochondrial donation appear to conflate mitochondrial donation with a range of terms such as germline genetic modification/changes and germline gene editing in a way that may mislead recipients.

The Mito Foundation supports the international moratorium on germline gene editing. Gene editing technology involves cutting nuclear DNA or mitochondrial DNA and, when applied to non-germline tissues, shows promise in treating some genetic conditions. However, it is currently too immature and inefficient to be regarded as likely to be safe and effective as a germline therapy.

The Mito Foundation's position statement[1] describes how mitochondrial donation is clearly different to gene editing and other forms of germline genetic modification since it does not cut or modify DNA but replaces the entire mitochondria without modifying the mitochondrial DNA they contain.

[1] Mito Foundation position statement on whether mitochondrial donation is distinct from germline genetic modification - https://www.mito.org.au/wp-content/uploads/2021/07/Mito-Foundation-Position-Statement-re-Mitochondrial-Donation-and-Germline-Genetic-Modification.pdf accessed 10 August 2021

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In the UK, these distinctions were considered in a series of four scientific reviews by the Human Fertilisation and Embryology Authority plus a review by the Nuffield Council on Bioethics. The UK Parliament concluded that mitochondrial donation was not germline genetic modification and changed its legislation in 2015 to enable mitochondrial donation to be offered to parents at high risk of mitochondrial DNA disease in a carefully regulated manner.

In the USA, mitochondrial donation is called mitochondrial replacement therapy (MRT) and the National Institute of Health (NIH) commissioned a review by the Institute of Medicine entitled *Mitochondrial Replacement Techniques: Ethical, Social, and Policy Considerations*. The panel specifically considered whether mitochondrial donation should be considered as germline genetic modification and noted an important distinction between modification of mitochondrial DNA versus nuclear DNA (nDNA) in terms of technology, traits and potential for enhancement. Their 2016 report concluded that "*These distinctions could allow justification of MRT independent of decisions about heritable genetic modification of nDNA*".

More recently, in 2021, the **International Society for Stem Cell Research (ISSCR)** released new guidelines for Stem Cell Research and Clinical Translation. Whilst the ISSCR Guidelines do not recommend heritable genome editing – where individual nuclear or mitochondrial DNA genes are cut and repaired – representatives of the Society appearing at the Senate Inquiry were clear that they support the use of mitochondrial donation in appropriate circumstances and that the oversight and uses envisaged and outlined in Maeve's Law are consistent with their guidelines.

For example, the ISSCR Guidelines include:

1) explicitly stating that research involving transferring human embryos to a human uterus following mitochondrial replacement is permissible following relevant specialised scientific and ethical review processes, and
2) Mitochondrial Replacement Techniques should be offered only in the context of clinical investigation that is subject to strict regulatory oversight, limited to patients at high risk of transmitting serious mitochondrial DNA-based diseases to their offspring, when no other treatments are acceptable, and where long-term follow-up is feasible.

The relevant sections of the ISSCR Guidelines can be accessed at this link: https://www.isscr.org/policy/guidelines-for-stem-cell-research-and-clinical-translation/key-topics/mitochondrial-replacement-techniques-mrt[2]

In Australia, discussion about the distinction between mitochondrial donation and germline genetic modification underwent much discussion in (i) the 2018 Senate Community Affairs References Committee Inquiry and Report on *Science of mitochondrial donation and related matters,* and (ii) the discussions and consultations that were part of the NHMRC Mitochondrial Donation Expert Working Committee Report. That report concluded that "*The term 'germline genetic modification' has conceptual drawbacks and therefore would not be appropriate for classifying mitochondrial donation*". These discussions underpinned the Government's decision to draft the *Mitochondrial Donation Law Reform (Maeve's Law) Bill*.

[2] ISSCR Guidelines – Mitochondrial Replacement Techniques - https://www.isscr.org/policy/guidelines-for-stem-cell-research-and-clinical-translation/key-topics/mitochondrial-replacement-techniques-mrt accessed 10 August 2021

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MITOCHONDRIAL DONATION IS **NOT** CLONING OR CRISPR TECHNOLOGY

Various statements appear to conflate mitochondrial donation with a range of terms such as cloning or CRISPR technology. This is simply not the case as highlighted by the NHMRC at the Senate Inquiry hearings on 6 August 2021.

In addition, the Dean of Harvard Medical School, Dr George Daley, emphatically stated at that same Inquiry hearings, that mitochondrial donation is not cloning. Whilst some of the methods and science involved may be similar, both Dr Daley and Prof Kelso, CEO of Australia's NHMRC, were clear that mitochondrial donation and cloning are not the same. The term cloning describes the creation of genetically identical individuals by copying DNA from a single individual. Any child born following mitochondrial donation will have the same genetic diversity as other children, as they will inherit a random combination of their parents' genes.

Further, Dr Daley commented that no reasonable scientist would suggest cloning as a means of bringing a child into the world. However, as he also commented, the consensus of the International Society for Stem Cell Research (ISSCR), as reflected in their guidelines, is that the introduction of mitochondrial donation is now timely following relevant specialised scientific and ethics review process although it should be offered only in the context of clinical investigation that is subject to strict regulatory oversight and to patients at high risk of transmitting serious mitochondrial DNA-based diseases to their offspring.

Dr Daley and the ISSCR have indicated their support for the regulatory safeguards and systems outlined in Maeve's Law.

Nor is mitochondrial donation CRISPR technology. CRISPR is one of several types of gene editing technology that can potentially be used to try to cut and repair genes. CRISPR technologies show promise for treatment of some inherited conditions and cancer, but the scientific consensus is they should only be used for targeting non-germline tissues. Mitochondrial DNA cannot currently be targeted by CRISPR gene editing due to being located inside the mitochondria. Mitochondrial donation does not involve any cutting, editing or genetic engineering of mitochondrial DNA, nor does it involve removal of mitochondrial DNA from inside mitochondria. Mitochondrial donation involves placing the parent's nuclear genes inside a donor egg or zygote containing healthy mitochondria.

MITOCHONDRIAL DONATION IS **NOT** A PROCESS SUPPORTED ONLY BY SCIENTISTS AND OPPOSED BY ETHICISTS

At the Senate Inquiry hearings on 6 August 2021, Mrs Francis for the Australian Christian Lobby suggested that submissions from ethicists opposed Maeve's Law while scientists largely supported it. We note that there were submissions to this Inquiry from three of the leading academic biomedical ethics groups in Australia – Sydney Health Ethics, Monash Bioethics Centre and the Biomedical Ethics Research Group from Murdoch Children's Research Institute and the University of Melbourne. As with the Nuffield Bioethics Council Review in the UK, these groups all provide support for mitochondrial donation to be offered in a targeted, carefully regulated manner as is occurring in the UK and is being proposed for Australia. Dr Gyngell also noted in his testimony to the hearings that "This bill is compatible with the human rights frameworks that have been outlined in the International Covenant on Economic, Social and Cultural Rights and the Convention on the Rights of the Child."

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MITOCHONDRIAL DONATION IS **NOT** AT ODDS WITH ANY INTERNATIONAL SCIENTIFIC CONSENSUS

It is simply incorrect to suggest this Bill will put Australia at odds with any global consensus as outlined above. A more accurate description would be that Australia is only the second country to have completed the process of detailed scientific, ethical and legal discussions together with the significant and considerable community engagement that are appropriate prior to legalising mitochondrial donation.

AUSTRALIA WOULD **NOT** BE AN INTERNATIONAL OUTLIER

It has been suggested that Australia would be entering the "Wild West" by legalising mitochondrial donation as outlined in Maeve's Law. This appears to be based on the notion that mitochondrial donation is not legalised in the United States or various other countries.

As highlighted above, international scientific consensus is that the science of mitochondrial donation is at a stage where undertaking clinical research is an appropriate next step.

In addition, while it is true that the United States has not legalised mitochondrial donation, it needs to be recognised that there are a number of religious and other elements at work in the United States that impact access to women's health, including IVF, birth control and abortion. As such, it is not an appropriate comparator.

Mitochondrial donation is legal in the United Kingdom where health and medical ethics are similar to Australia as is the structure of health systems and medical training.

Further, Australia's long history in relation to IVF and assisted fertility treatment should be recognised. Australia led the world in IVF and has strong regulatory and health systems supporting assisted fertility treatment in both clinical research and practice.

The introduction of a carefully designed regulatory and licensing system in Australia will ensure that Australia's expertise in this area continues at the same time that Australian families have access to mitochondrial donation, and their children to appropriate health monitoring, which might otherwise not be available.

As highlighted in its original submission, the Mito Foundation is aware of instances where mitochondrial donation has been utilised in unregulated health systems or for conditions not related to the avoidance of mitochondrial disease. The foundation has been approached on occasion by overseas organisations seeking to offer access to mitochondrial donation to Australian families and has long been concerned that, without an appropriate domestic regulatory framework, the risk exists that vulnerable families might be tempted to access these techniques in these unregulated jurisdictions. This should not be encouraged.

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MITOCHONDRIAL DONATION IS **NOT** A SLIPPERY SLOPE TO OTHER TECHNIQUES

Humans have a total of approximately 20,000 genes, nearly all of which are located in the cell's nucleus and inherited equally from both parents. Mitochondria are specific structures within the cell that contain a separate small mitochondrial DNA genome that encodes 37 genes required for energy generation.

We currently know of more than 6000 genes in which mutations cause inherited rare diseases. Mitochondrial DNA disease is caused when one of its 37 genes is mutated. Mitochondrial DNA disease is transmitted from mother to child since all the mitochondria in the fertilised egg have come from the egg itself, not from the sperm.

The process of mitochondrial donation involves replacing the mother's mitochondria with mitochondria from a donor egg. Mitochondrial donation has clear potential for prevention of diseases caused by mitochondrial DNA mutations. Mitochondrial donation cannot be used to prevent diseases caused by mutations in any of the nuclear genes associated with the vast majority of inherited rare diseases.

Hence, there is no prospect that mitochondrial donation could be used to prevent any other form of inherited disease.

Further, despite the fact that from a scientific perspective mitochondrial donation is not relevant to any other inheritable disease, Maeve's Law clearly limits these techniques to those at serious risk of passing on mitochondrial DNA-related disease to their children.

Detailed reviews by government-appointed bodies in the UK, USA and Australia have also concluded that mitochondrial donation should be regarded as distinct from any other forms of germline therapy, such as CRISPR gene editing.

The Mito Foundation has consistently advocated for legislation to restrict the use of mitochondrial donation to women at increased risk of transmitting severe mitochondrial DNA disease. The legislation takes this approach and thus clearly prohibits using it for any other purpose. Hence, the legislation does not set a precedent for expansion to germline therapies for diseases caused by mutations in nuclear genes.

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DEBATE ABOUT DEFINITIONS

The Mito Foundation notes the ongoing debate about definitions of terms such as 'embryo' and at what time and stage an 'embryo' is considered an embryo under law.

While noting the importance of having a clear legal definition of all terminology in Maeve's Law, the Mito Foundation would like to point to comments regarding this from the Lockhart Review which, in 2005, undertook a review of the Commonwealth legislation regulating human embryo research.

At that point, the Committee noted that different people and groups hold differing views about the meaning and use of the term 'embryo', both in medical science and as a more general term. Further:

> "The Committee considers that it is essential that the terminology used in the legislation is biologically accurate, clearly understandable by all stakeholders, and unambiguous to regulators, scientists and the public. However, **while it is critical to be clear about the terminology used, definitional clarity does not, in itself, resolve moral concerns and it is likely that, whatever language is used, different moral interpretations will be made regarding the status of such entities and the obligations owed to them**."[3]

The foundation notes that many of the debates regarding definitions actually do appear to point to moral differences and notes the above as relevant in discussions about definitions.

THERE ARE UNKNOWN ASPECTS OF MITOCHONDRIAL DONATION

Like any new medical technology, there are uncertainties in relation to mitochondrial donation.

Maeve's Law acknowledges these uncertainties but also recognises that there are known risks of having a baby born with mitochondrial disease, principally that the child will subsequently die of mitochondrial disease.

Maeve's Law seeks to address the uncertainties related with mitochondrial donation and acknowledges the long history of research and work into mitochondrial donation. As a result, Maeve's Law has been drafted so that a clinical trial will be undertaken prior to being introduced into general clinical practice.

Clinical trials are designed to generate evidence both about the benefits and risks of any medical intervention – that is the specific purpose of clinical trials – and one of the reasons that Maeve's Law is well-designed and appropriate in its proposed two-stage approach.

This approach is supported by the outcomes of the public consultation which indicate that Australians support the introduction of mitochondrial donation despite the awareness of the uncertainties related to it.

[3] Legislation Review Committee, "*Legislation Review: Prohibition of Human Cloning Act 2002 and Research Involving Human Embryos Act 2002*", December 2005, xiv-xv. https://www.nhmrc.gov.au/file/14449/download?token=iGY6wE7b accessed August 2021

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POTENTIAL RISKS TO AN EGG DONOR

The potential risk to an egg donor of donating eggs for the purposes of mitochondrial donation has been raised. The Mito Foundation acknowledges that risk does exist in choosing to become an egg donor but is deeply concerned by the implication that women choosing to become egg donors are not capable of assessing these risks and making their own informed decision, as currently occurs.

The foundation notes that women seeking to donate eggs are provided with appropriate medical information regarding the risks and benefits of doing so and considers this both essential and appropriate. The foundation also respects the rights of those women to then make their own decisions regarding egg donation.

LACK OF CONSENT FROM THE UNBORN BABY

Some arguments against mitochondrial donation include the suggestion that it should not be approved because the baby born from mitochondrial donation cannot give consent.

This argument is fatuous. No child has ever given consent to being born regardless of involving any assisted reproductive technique or not, and this has not prevented the legalisation of IVF or other assisted reproductive techniques.

At the same time, it has been recognised during the extensive public consultation and scientific review undertaken to date that it would be unlikely that any child would choose to be born with mitochondrial disease should a choice be possible.

PUBLIC CONSULTATION & SCIENTIFIC REVIEW HAS BEEN EXTENSIVE

Engagement of the Australian community around issues related to mitochondrial donation has been via a wide range of mechanisms as listed below.

These have included two citizen's jury or panel approaches involving members of the public with little prior knowledge of mitochondrial donation. They were exposed to information from proponents and critics of the process and had time to deliberate on issues such as international approaches, uncertainties, ethics and potential health risks. In both cases, a substantial majority of the participants determined that the potential benefits outweighed potential risks.

Community engagement has included:

1) 2017 Citizens' Jury on mitochondrial donation organised by Prof Ainsley Newson and described in a peer reviewed publication available at https://academic.oup.com/humrep/article/34/4/751/5377828. The Citizens' Jury process involves a group of lay citizens coming together to deliberate on evidence about a challenging policy issue, with each juror contributing to a 'verdict' in response to the 'charge'. The jury watched four pre-recorded presentations, including two about mitochondrial disease and its treatment and prevention plus one from a proponent of

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legalising mitochondrial donation and one from an evolutionary biologist who had published concerns regarding health risks that might arise in children born via mitochondrial donation.

2) 2018 Senate Community Affairs References Committee Inquiry - Request for submissions on the terms of reference and public hearing

3) 2019 NHMRC multi-modal consultation strategy performed in conjunction with the Expert Working Committee process, as summarised below:

Time	Activity	The main purpose was to...
September 2019	Mitochondrial Donation Issues Paper released Postcards developed for distribution Twitter account and mailing list established NHMRC Online Services submission portal opened to public	Inform Inform Inform Capture views
October 2019	First meeting of Citizens' Panel Mitochondrial Donation information video released First public engagement webinar Targeted roundtable for professional stakeholders	Inform Inform Inform/support discussion Capture views
November 2019	Final meeting of Citizens' Panel Public forum held in Sydney Public forum held in Melbourne Second public engagement webinar NHMRC Online Services submission portal closed	Capture views/support discussion Inform/support discussion Inform/support discussion Inform/support discussion Capture views
December 2019 – March 2020	Analysis of community views obtained during consultation Preparation of Consultation Report	N/A

Table: Outline of key activities for the NHMRC community consultation on the social and ethical issues raised by mitochondrial donation. Extracted from NHMRC Mitochondrial Donation Community Consultation Report (p11)

The Citizens' Panel approach differed from the previous Citizens' Jury but both processes ensured that public opinion was drawn not only from the views of individuals with strong preconceived beliefs for or against a proposal. The Citizens' Panel was presented with information over the course of 4 days, providing time for them to digest and debate the risks and benefits. Maeve's Law has addressed their recommendations https://www.nhmrc.gov.au/mitochondrial-donation-0#download

4) March 2021. Department of Health Public Consultation Paper inviting submissions on the proposed process to introduce mitochondrial donation in Australia in a staged and closely monitored way.

5) July 2021. Senate Standing Committee on Community Affairs Legislation Committee Inquiry into the Mitochondrial Donation Law Reform (Maeve's Law) Bill 2021.

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PUBLIC CONSULTATION IS SUPPORTIVE OF MITOCHONDRIAL DONATION

The Citizens' Panel undertaken as part of the NHMRC's public consultation concluded that "We are aware of the unknowns related to mitochondrial donation, but the majority have the view that mitochondrial donation should be permitted"[4].

In addition to the Panel, hundreds of people contributed to the NHMRC's consultation through public forums, webinars, online submissions, and other activities.[5] Themes raised included outcomes from introducing mitochondrial donation; the wellbeing and rights of children; factors relating to egg donation and the donor; factors relating to the embryo in mitochondrial donation; and implementation considerations.[6]

A number of responses suggested that mitochondrial donation should initially be introduced as part of a clinical research study and mitochondrial donation should only be used in certain circumstances, such as when a significant risk of mitochondrial disease existed. Other respondents also indicated that appropriate oversight mechanisms would need to be introduced, including limiting mitochondrial donation only to clinics that had appropriate expertise.

A number of responses that were supportive of mitochondrial donation indicated that one of the reasons for this support was the option for families to have healthy children free from mitochondrial disease thus avoiding the impact of the disease on the child and their family.

Finally, a number of respondents acknowledged that risks exist with mitochondrial donation, but the benefits of mitochondrial donation outweigh these risks.

CONCLUSION

In closing, it is noted that reviews of the science and ethics of mitochondrial donation in the UK, USA and Australia have concluded that mitochondrial donation could be an appropriate and acceptable approach to prevention of mitochondrial DNA disease if offered in a cautious, regulated manner.

In the UK, after an approximately 9-year process of investigations and review, mitochondrial donation legislation was approved overwhelmingly by the House of Commons and the House of Lords. At that time, Sir Jeremy Farrar, the Director of the Wellcome Trust said "I don't think there's been any more rigorous look at any scientific endeavour coming into humans". The UK process involved extensive public engagement efforts.

This public engagement process was even more extensive in Australia and included a citizen's jury and a citizen panel review to ensure that feedback was not drawn only from the views of individuals with strong preconceived beliefs for or against a proposal. The support for mitochondrial donation from these panels adds further weight to the Mito Foundation's belief that most informed citizens would support mitochondrial donation and the hope it brings to families affected by mitochondrial DNA disease.

[4] Mitochondrial Donation Community Consultation Citizens' Panel Statement, https://www.nhmrc.gov.au/mitochondrial-donation-0#download accessed July 2021
[5] NHMRC, 'CEO Statement: should Australia introduce mitochondrial donation?", 5 June 2020. https://www.nhmrc.gov.au/mitochondrial-donation-0#download accessed 5 June 2020.
[6] NHMRC, *Report on NHMRC's public consultation on the social and ethical issues raised by mitochondrial donation*, June 2020. https://www.nhmrc.gov.au/mitochondrial-donation-0#download accessed 5 June 2020.

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