Australian Genomics Health Alliance

Submission on the Mitochondrial Donation Issues Paper – Ethical and Social Issues for Community Consultation

1. Is it important to expand the options available to parents at risk of conceiving a child with mitochondrial disease by introducing mitochondrial donation into clinical practice in Australia?

Women who carry a pathogenic mitochondrial DNA (mtDNA) variant have the potential to pass the variant on to a child, in an unpredictable manner and with unpredictable consequences. This means that conceiving a child through mitochondrial donation may be the only way some parents can have a child biologically related to the mother and with a low chance of developing a mitochondrial disorder. Given that mitochondrial disorders are a prevalent rare disease, with no cure or effective treatments, mitochondrial donation would therefore be an important reproductive option for some families affected by mitochondrial disorders. This technology has the potential to stop mitochondrial disease in its tracks in families who have a diagnosed mitochondrial disorder with a mtDNA cause. Importantly though, it will not eradicate the disease, due to the complexity in disease aetiology, presentation and current diagnostic utility.

Since the legislation was passed in the UK (in 2015) and the first licences issued in 2018, already up to 14 applications for license to access the technology (anecdotally) have been approved. This indicates precedent for providing access to this technology in Australia. Given the cost of the treatment is estimated to be not much more than current IVF treatments, health economic modelling predicts significant health cost savings compared to lifetime treatment costs for an individual with a mitochondrial disorder. The UK Department of Health economic assessment reported that 20 healthy births per year would result in a cost saving of GBP33.5 million per year[1].

Given the presumed complexity of the licensing process, and the still remaining unknowns for the health of children born from the technology that families need to consider, the number of applications in the UK indicates strong support from the families at risk of passing on mitochondrial disorders. Alleviation of the psychological, psychosocial, financial and other impacts on families affected by mitochondrial disorder is another strong argument for legislating the technology.

In determining whether the Australian government will allow access to this technology, it will be important to accurately assess what the demand in Australia would be, and it was also deemed important during the UK debate to determine how many women could benefit. The UK data suggested that there are 152 births per year among women at risk of passing on mtDNA disorders[2], and so simple population based extrapolation estimates that there are 60 births per year in Australia among women at risk of transmitting mtDNA disorders. Whether all of those women would pursue mitochondrial donation is unknown, as there are other reproductive options available depending on individual circumstances (eg adoption, IVF with PGD, egg donation). Longer term studies will be required to measure what proportion of at-risk women take up the reproductive option if it

[1] http://www.legislation.gov.uk/ukia/2015/138/pdfs/ukia_20150138_en.pdf
[2] Gorman et al., N Engl J Med (2015) DOI: 10.1056/NEJMc1500960

becomes available. Of note, the UK study also found that mtDNA disorders do not affect female fertility (including for severely symptomatic carriers).

The Australian Genomics Mitochondrial Disease Flagship may reveal more about the potential application of the technology in relation to the current ability to diagnose mtDNA disorders. The Flagship has recruited 126 male and female participants with mitochondrial disease for genomic testing to diagnose the genetic cause of the condition, comparing two approaches: whole exome sequencing (WES)+mtDNA sequencing, or whole genome sequencing (WGS). Both approaches capture mtDNA sequences. Combining the two approaches, a genetic diagnosis was achieved in approximately 40% of cases and approximately one quarter of those diagnoses were a mtDNA rather than nuclear DNA variant. Considering that the mitochondrial donation technology is only available to females carrying a diagnosed mtDNA variant, this suggest that around 7-8 of those 126 participants in the study may have been or would be able to benefit from mitochondrial donation technology during their reproductive years. However, it should be noted that the group enrolled in the study may not fully reflect the broader population affected by mitochondrial disorders, for example because of the study eligibility criteria.

If mitochondrial donation is introduced, but not supported by an MBS item number, less families will be able to access it which will affect a proper assessment of demand and also raise inequity issues. It will also be important to accurately assess the demand from a service provision point of view, and for planning adequate health follow up through health services as well as research.

Making significant changes to legislation to allow this technology to be introduced based on low demand may attract criticism from some community groups, or conversely inspire other interest groups to pursue medical and scientific advances where the investment is significant but the benefits are applicable to small numbers of community members. Such circumstances can be offset by reference to the social benefits of reducing mitochondrial disease and the UK health economic modelling which reported on the significant health cost savings associated with the prevention of disease.

While legislative and service provision changes are being actioned in Australia, people should be able to travel to the UK for treatment, supported by Australian government. Alternatively, if evidence on the demand in Australia is produced, it may suggest that for the time being offering treatment in the UK is the most cost-effective strategy, assuming there is sufficient accredited providers and capacity in the UK to meet the UK demand as well as requests from families from other countries of which Australia may be just one.

Australian government should consider seeking a formal partnership with the UK Human Fertility and Embryology Authority (HFEA), for advice on progress to date, assistance and knowledge transfer.

In summary, Australian Genomics supports the expansion of reproductive options for parents likely to pass on mitochondrial disease, but highlights the need for the government to make evidence based decisions.

2. What risks and benefits are the most important to consider when thinking about the possible introduction of mitochondrial donation in Australia?

The anticipated benefits of mitochondrial donation were well articulated by the families who contributed submissions to the senate inquiry, and supported by Sean Murray of the Mito Foundation as part of the mitochondrial donation public consultation activities. The benefits of accessing the technology include the reduction of stress and uncertainty for couples who would otherwise "roll the dice" by conceiving naturally despite mtDNA variants being diagnosed in the family. Further, utilising mitochondrial donation technology would reduce the uncertainty which families live with regarding onset and progression of mitochondrial disease, and the financial, practical and psychosocial burden of caring for a child with significant health challenges. As mentioned above, significant financial benefits to the healthcare system would result from fewer cases of mitochondrial disorders. This would also result in increased availability of existing healthcare personnel and resources.

While discussion of the scientific and technical risks of the technology theoretically lies outside the scope of this consultation on the ethical and social implications of mitochondrial donation, many of those risks are linked. For example, there is uncertainty of long term outcomes for children born from the technology. Some predict that donated mtDNA may be incompatible with or alter gene expression of maternal nuclear genome, that carryover of mutant mitochondria may cause a problem, or that mismatched haplotypes may have unexpected consequences. The restrictions on this technology mean there is a limited international body of evidence regarding its longer-term outcomes. This uncertainty can only be overcome through measured access to the technology, and well-designed research conducted in parallel with clinical delivery. The introduction of IVF several decades ago was rapid and widespread, and even now the health of IVF babies into adulthood is a polarising topic. A Google search links IVF babies with increased birth defects, intellectual disability, autism and cancer (among other health concerns), yet recent evidence from a high profile study by leading Melbourne based researchers showed that on a number of measures, IVF babies are no different from their naturally conceived peers[3]. It is possible that without a measured and evidence-based approach, similar divergent research outputs and opinion will follow for decades after the introduction of mitochondrial donation. However, Australian scientific and medical experts in this field predict that children will be healthy, and this was also the finding of the extensive UK scientific review of the technology.

Not participating in the implementation of this technology increases the risk of medical tourism, as there has been publicly documented unregulated use of this technique[4]. Medical tourism in other instances has had serious consequences, and should be avoided.

[3] Halliday et al., Fertility and Sterility (2019) doi.org/10.1016/j.fertnstert.2019.03.001
[4] https://www.newscientist.com/article/2107219-exclusive-worlds-first-baby-born-with-new-3-parent-technique/

Another identified risk has been the perception that changing the legislation will create a "slippery slope" in terms of introducing gene editing techniques. While the legislation will be carefully amended to ensure this does not happen, at the same time the public need to become more familiar with gene based therapies (not necessarily gene editing) because they will be increasingly developed, for example as a priority area of the MRFF's Genomics Health Futures Mission.

If Australia does not introduce the technology, it risks falling behind on the world stage of internationally competitive health technology research. Having a long history in ARTs and playing a significant role in the development of IVF, and with internationally recognised mitochondrial disease research, Australia is in a position to become a world leader in mitochondrial donation technology. Australian scientific and medical research strategy consistently highlights the importance of innovation, and this is an opportunity for Australia to demonstrate commitment to leadership in innovation.

3. How can the interests and wellbeing of the child (and future adult) who may be born as a result of mitochondrial donation best be promoted and protected when considering the introduction of this new technology?

The best interest of the child is to have a healthy start to life, which is something that mitochondrial donation can offer families. A child born from this technology should, at minimum and consistent with the approach to mitochondrial donation in the UK, have the right to know *non-identifying* information about their genetic background. Or, more preferably and consistent with current NHMRC ART ethical guidelines[5], the child should be able to access *identifying* information about the mitochondrial donor. Access to this information will be important from a social and ethical point of view, but also from medical and research follow up perspectives. The child should also be able to expect that their privacy will be protected and they will not be identified as having been born as a result of the technology. However, privacy concerns will need to be balanced with the need for clinical and research access to information to inform ongoing evaluation of the technology.

Females born from the technique would in turn need to be supported in their reproductive choices. Females may need to make informed choices about having their mtDNA assessed in the context of passing donated mtDNA to the next generation, or to learn of an expanded mutational load of their original maternal mtDNA (if mtDNA carryover had occurred during the procedure).

4. What implications of mitochondrial donation for future generations are the most important to consider?

[5] https://www.nhmrc.gov.au/sites/default/files/documents/reports/use-assisted-reproductive-technology.pdf

Future generations of children born with a history of mtDNA donation should also have the right to know their genetic background, and to be involved in choices about participation in medical and research follow up.

On the broader society level, future generations should be able to expect that births resulting from the technology were adequately followed up from a health and research perspective, to ensure ongoing safety, quality and improvement.

5. Are there ethical issues for the status of embryos in mitochondrial donation that are distinct from those for existing reproductive technologies such as IVF?

One ethical issue distinct from other ARTs that may concern donors, recipients, religious groups and others within the community is that the pronuclear transfer technique necessitates the creation of a zygote/embryo with the intention of being discarded. This is different to IVF or PGD, where embryos are created on the basis they will hopefully progress through development. Though in truth, ART techniques result in a proportion of embryos that do not progress for various reasons. Despite the concerns about the status of embryos generated for the technique, it will be of upmost importance that the methodology used for mitochondrial donation is the best available and by weight of evidence the safest for the child who is born from the technology.

Additionally, Australia should seek expert training from the UK licensed provider to minimise the use of embryos for training in mitochondrial donation techniques.

6. Are there ethical issues for women who donate eggs for mitochondrial donation that differ from other current assisted reproductive technologies?

Women who donate their eggs must provide informed consent if there is potential for their eggs being used for mitochondrial donation. This means the woman understanding that her nuclear DNA will be removed from the egg but the rest of the egg will be used. As discussed during the stakeholder roundtable event, this could be efficiently incorporated into the consent process for all egg donors. However, UK researchers have reported greater success with pronuclear transfer when the donor egg is fresh rather than frozen[6]. While a technical issue, this may present challenges for consent processes and donor egg availability as it means it would unlikely be feasible to tap into unused, leftover eggs from other ART instances as a source for mitochondrial donation.

Questions raised at the stakeholder roundtable event included “will women still be willing to donate eggs if their nuclear DNA is not used?” and “why would a woman want her egg dissected for parts?”. The opposing view is that some women would prefer their eggs be used to assist with mitochondrial donation rather than to produce a child with their nuclear DNA and thus their characteristics. There will always be a range of views, and the only way to manage the differences in perspectives is to

[6] Hyslop, L., et al. Nature (2016) doi:10.1038/nature18303

provide all of the necessary information to support individual, informed decision-making and consent, and to allow withdrawal of consent.

Women who donate eggs for the purpose of mitochondrial donation should have their mtDNA tested and have the option to be told if they carry mtDNA variants of concern.

The UK model of "recommending the child has access to non-identifying information such as screening tests, family health and personal information provided by the donor" should be followed in Australia, at a minimum. However, if the current NHMRC ethical guidelines on ART in clinical and research contexts are followed, the child will be able to access identifying information about the donor, and the donor should be made aware of this.

7. If mitochondrial donation is introduced into clinical practice, who should be allowed to access mitochondrial donation? Who should decide who has access in specific cases? What conditions, if any, should be imposed on patients and clinicians?

Any woman with a diagnosed mtDNA pathogenic variant should be considered for access to mitochondrial donation, particularly those with above threshold mutational load and in circumstances where preimplantation genetic testing of embryos is not likely to increase reproductive confidence. ART conditions should also be applied - in Victoria, those conditions include having been counselled, not deemed infertile due to age, or have a record of violent or sexual crime or a child protection order removing a child[7] .

A committee with the appropriate scientific and medical expertise should be established to review individual cases. A clear framework for assessing who should be able to access the technique should be in place which follows a standardised PICO evidence based medicine approach. Risks to the mother should also be assessed, particularly on whether she can safely (for herself and the child) carry a pregnancy. An assessment on whether the mother and father/guardians are able to reasonably care for the child may be a more controversial issue but nevertheless part of the discussion.

Government should consider whether participation in research and health follow-up for a defined number of years should be a condition of accessing the technique. It may be reasonable to request this follow up until the child is old enough to consider whether they wish to continue to participate. In human research ethics terms, this would usually be considered to be around 12-14 years of age.

8. Having considered the issues outlined in this paper and your answers to the previous seven questions, would you support the introduction of mitochondrial donation to prevent the transmission of severe mitochondrial DNA disease at this time?

[7] *Assisted Reproductive Treatment Act 2008*

We support the introduction of mitochondrial donation technology in Australia <u>at this time</u>. In summary this is based upon:

1) The widespread and unwavering support from Australian families, experts in mitochondrial disease medicine and scientific research, and patient advocacy groups, namely the Mito Foundation.
2) The rigorous scientific review and regulatory processes undertaken in the UK, which ultimately resulted in approval of the technology, combined with the thorough scientific and ethical review undertaken in Australia.

We recommend the following issues be considered and resolved in parallel:

1) Public messaging and education, including aiming to avoid the term three parent babies, which detracts from the importance of social parents and risks medicalising the child.
2) Development of a rigorous and transparent PICO model to determine eligibility to access the technology.
3) An MSAC application for an item number to ensure equity of access.
4) Adjusting the legislation to enhance research capability - to resolve the best technique, study long term health implications, and to contribute to international evidence.
5) Follow up research and evaluation of children born from the technique – including scientific and medical research, as well as qualitative research on patient experience.
6) Establishing formal knowledge transfer agreements with the UK HFEA, for quality monitoring and improvement purposes.
7) Decisions are reached on whether males and females will be allowed to be born from the technology, whether haplotype matching is done, and which are the best technique(s) for the procedure.

9. If Australia did decide to change the law to allow mitochondrial donation, how important would it be to limit its use initially to research studies? Would it be appropriate to introduce it directly into clinical practice?

Our preferred model for the introduction of mitochondrial donation would be directly into clinical practice, with research participation and follow up either strongly encouraged or as a condition of access. Children should not be born as the result of a research study.

Laws should be amended where necessary to allow research *in vitro* using human tissues and to support research in appropriate animal models to refine the technology and learn more about the long term consequences of mitochondrial donation.

10. Does this paper explore the relevant ethical and social considerations associated with the introduction of mitochondrial donation? Are there any additional ethical or social issues that need to be considered?

The Mitochondrial Donation Issues Paper is an excellent communication which clearly and impartially explains the main ethical and social issues associated with legislating mitochondrial

donation. In relation to the description of the different mitochondrial donation techniques, there was no reference to the differences in the success of the outcomes or pros and cons of each technique. This was more clearly addressed in the senate inquiry report and we believe has relevance to aspects of the discussion on ethical and social issues.

Another potential issue gleaned from the senate inquiry report and worth consideration is that many of the choices about having mitochondrial donation were suggested to fall back onto the parents. These choices included whether the couple would select for male children only (limiting the mtDNA transfer to another generation) and whether haplotype matching should be pursued. Highly technical issues like these should be decided upon by scientific and medical experts prior to the introduction of the technology, looking to the UK experience for guidance.