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Our Ref: LS/10/RLR/Consultation/2018/BAC/GG/kl/yj
Your Ref: To be advised

29 June 2018

BY EMAIL
bioethics_singapore@moh.gov.sg

Bioethics Advisory Committee Secretariat
1 Maritime Square,
Harbourfront Centre, #11-23,
Singapore 099253

Dear Sir / Mdm,

CONSULTATION PAPER ON ETHICAL, LEGAL AND SOCIAL ISSUES ARISING FROM MITOCHONDRIAL GENOME REPLACEMENT TECHNOLOGY

1. We refer to the Bioethics Advisory Committee Secretariat's (**"BAC"**) email dated 25 April 2018 inviting the Law Society to provide its views on the potential issues related to the clinical application of this emerging technology in humans.

2. The consultation was referred to an Ad-hoc Committee which was set up to respond to two of BAC's previous Consultation Papers. The Committee's views are enclosed in **Annex A**.

3. Thank you for giving the Law Society the opportunity to present our views on this matter.

Yours faithfully,

Genie Sugene Gan (Ms)
Director, Representation and Law Reform Department

Annex A

COMMENTS ON THE BIOETHICS ADVISORY COMMITTEE'S CONSULTATION PAPER ON MITOCHONDRIAL GENOME REPLACEMENT THERAPY

1. We have been asked by the Law Society of Singapore to provide our comments on the Bioethics Advisory Committee's ("**BAC**") Consultation Paper entitled "Ethical, Legal & Social Mitochondrial Genome Replacement Technology: A Consultation Paper" (**"Consultation Paper"**). As in the Consultation Paper, we will refer to Mitochondrial Genome Replacement Therapy as "**MGRT**".

2. The members of this ad-hoc committee advise and represent individuals and organizations within the healthcare industry as part of their legal work. Some are also members of various ethics committees, including Institutional Review Boards, Clinical Ethics Committees and Transplant Ethics Committees. The members are:
    (i) Ms Kuah Boon Theng SC (Legal Clinic LLC)
    (ii) Ms Rebecca Chew (Rajah & Tann Singapore LLP)
    (iii) Mr Philip Fong (Eversheds Harry Elias LLP)
    (iv) Ms Audrey Chiang (Dentons Rodyk & Davidson LLP)
    (v) Ms Mak Wei Munn (Allen & Gledhill LLP)

3. Our comments on the BAC's Consultation Paper on MGRT are in relation to the following issues:
    a. Is there sufficient evidence supporting MGRT to ensure that "the clinical application of MGRT" will not run foul of Clause B6 of the Singapore Medical Council Ethical Code and Ethical Guidelines (**"ECEG"**) 2016 (i.e. that doctors should not be engaged in "untested practices" and must treat patients only according to generally accepted methods, based on a balance of available evidence and accepted best practices)?
    b. Should MGRT instead be regarded as "innovative therapy" and hence should only be offered in the context of formal and approved clinical trials, which would be subject to the ethics of research?
    c. Are there core ethical concerns regarding MGRT that remain unresolved, for example, whether this can be considered a form of eugenics or alteration of the human germline?

d. Are our current laws sufficiently robust to clarify the rights of the parties involved in MGRT, including whether egg donors could potentially have any rights in relation to the children born from MGRT?
e. Could MGRT give rise to significant risk of potential wrongful life and/or wrongful birth claims in the future?

Untested Practices and the ECEG

4. All medical procedures are associated with some degree of risk. The fact that there may be unknown risks (especially longer term risks) associated with a proposed treatment would not in itself prohibit the offering of such treatments to patients, so long as there is sufficient scientific evidence to support the clinical basis of the treatment, and it is offered only where there are sufficient clinical indications to do so. However, existing laws, regulations and guidelines can prohibit "untested practices". This may occur where there is lack of sufficient data justifying the efficacy and safety of the treatment and therefore insufficient basis to conclude that the risks or uncertainties involved in the treatment would be outweighed by its potential benefits. Treatments could also be prohibited due to the morally or ethically objectionable nature of the treatments themselves.

5. In the Consultation Paper, the BAC explains that international developments in medical science are such that today, some evidence exists to demonstrate that MGRT techniques (MST, PNT and PBT) can not only produce live births, but can successfully reduce the risk of transmission of serious mitochondrial disorders in the process. However, it appears that in spite of these developments, the evidence to date does not allow the scientific community to determine the reasonable criteria for implantation of such embryos that would safeguard the longer term health and mortality of the children born from possibly severe debilitating effects of abnormal mtDNA and symptoms of serious mitochondrial disorders. The complexity of the science involved, taking into account the fact that "[d]ifferent mtDNA mutations have different threshold levels of abnormal mtDNA load which are more likely to produce symptoms" (paragraph 11), the fact that "different individuals may tolerate the same abnormal load differently" (paragraph 11), as well as the phenomenon known as reversion, means that there is as yet no medical consensus on how to determine the criteria by which embryos would ultimately be chosen for implantation, irrespective of whether MST, PNT or PBT is the technique of choice.

6. As for “what rigour and standard of evidence is required to establish safety”, one approach referred to in paragraph 75 of the Consultation Paper is to “define a maximum threshold of abnormal mitochondrial DNA (mtDNA) that an embryo can carry, below which any embryo would be deemed safe enough for implantation”. At the same time, the Consultation Paper also suggest that due to the “poor correlation between abnormal mtDNA load and manifestation of symptoms”, we should accept a “higher-than-threshold” level of risk. The “higher-than-threshold” level is suggested to be anything lower than the “otherwise high level that would be present by natural reproduction” (“**natural risk**”).

7. By natural risk, we assume that the BAC is referring to the natural risk *for such parents,* since it is only for these parents where the mothers are carriers that the risk of having a child born with severe mitochondrial disorders can be said to be at an “otherwise high level”. However, if “lower than natural risk” is adopted as the criteria for implantation, this would mean that in circumstances where the risk is only slightly lower, the embryo could potentially be selected for implantation, even if it still contains a significant level of abnormal mtDNA. This raises a concern as to whether such a criteria would be considered robust enough to safeguard the children born through these artificial reproduction techniques. Also, such a threshold is far from clear and would encounter challenges when being applied. After all, as the BAC acknowledges, there are other options for such parents [namely (1) adoption; (2) in-vitro fertilisation using healthy donor eggs; (3) pre-implantation genetic diagnosis; and (4) prenatal diagnosis (see paragraph 6)]. If the threshold risk criteria is set too high, it would be difficult for clinicians to offer any reasonable expectation of benefit for the parents who are considering MGRT in favour of other options.

8. Another issue relating to the risks of MGRT is the fact that there are risks posed to future generations. Since mtDNA only passes down through a maternal lineage, it is proposed that these risks be minimised by only allowing the implantation of only male embryos until the “safety and efficacy in the male cohorts [have] been established" (paragraph 48). Limiting implantation to male embryos could be considered a form of sex selection. In general, non-medical sex selection would be regarded as being ethically unacceptable because it is discriminatory. However, it is possible to argue that

there is a clear medical basis to limit implantation to male embryos, to avoid the potentially harmful transgenerational impact of MGRT.

Exception to the Prevailing Prohibition on Altering the Human Germline

9. In February 2015, the UK parliament voted in favour of regulations that would enable mitochondrial replacement techniques to be used in clinical practice in the UK. At the time, there was no universally agreed definition of 'genetic modification' (paragraph 45). It is unclear if the position has since changed. Whilst the issue of whether MGRT results in genetic modification remains open to discussion, it appears non-controversial that MGRT results in human germline alteration, which in the case of female children, will be passed down to future generations.

10. The BAC had in its 2005 Report on *Genetic Testing and Genetic Research,* recommended "a moratorium on germline genetic modification in clinical practice due to a serious concern that germline modification could have 'potentially great impact on future generations'" (paragraph 40), pending substantial research on its feasibility and safety. Whilst the Consultation Paper reports some progress on feasibility, again the research on safety appears to be lacking. Serious consideration ought to be given to whether the NMEC's ethical concerns in 2001 (paragraph 41) as to the 'uncertainty over its long-term safety and risks, the inadvertent selection against the elimination of alleles from the human gene pool that may benefit humans in potentially unknown ways, and the tenuous line between germline gene therapy and eugenics' have been addressed by good research data.

11. We acknowledge that the BAC has distinguished MGRT from the germline therapies previously discussed on the basis that: (1) in MGRT, only the mitochondrial genome is replaced (leaving the nuclear genome unchanged); (2) the resulting modification is transmissible through the maternal line only. Notwithstanding the distinction, MGRT results in altering the human germline throughout future generations, with the attendant ethical concerns associated with eugenics. The core of the ethical concern has therefore not been addressed. Sex selection as a means of mitigating against this concern would be unacceptable for the reason identified above.

Reproductive Autonomy

12. We note the arguments for reproductive autonomy and the desire to have genetically identical off-spring, which forms the premise underlying the desire for MGRT

(paragraph 54). However, until the scientific and medical communities can be assured that the rights and well-being of the unborn children (through future generations) are not jeopardised in favour of parental reproductive autonomy, we should be cautious about embracing MGRT as the solution. Well-established and accepted alternatives for the exercise of reproductive autonomy (some which provide partial genetic affinity) do exist.

13. Overall, we are of the view that while MGRT is intended to reduce the risk of mitochondrial disease for high-risk patients, ultimately there remains uncertainty regarding MGRT's safety and efficacy and the feasibility of devising a robust clinical treatment protocol, to justify offering this as a clinical treatment option to high risk couples. Specifically, the lack of a clear standard for what would constitute an acceptable threshold risk for implantation, remains a troubling area. In addition, there are also core ethical concerns that have yet to be clearly resolved. For these reasons, we are of the view that in spite of the early evidence supporting the feasibility of MGRT, such treatments should at best be performed only as part of clinical research, where no positive claims regarding the benefits of the treatment should be made, and robust research protocols can be drawn up and consistently applied. The treatment outcomes can then be comprehensively followed up over time. Furthermore, if MGRT is allowed to be performed as part of clinical research, no doubt the respective Institutional Review Boards will have the opportunity to consider if there is a need to ensure that the specific consent of egg donors whose eggs are to be "disassembled" (i.e. have their nuclear DNA/pronuclei removed) has been sought, before the eggs are used for MGRT. It is our view that perhaps with more robust research on MGRT relating to the efficacy and safety of MGRT as a treatment option, one could gather a broader pool of research data covering outcomes under different clinical trials that may provide greater clarity on how to set an acceptable threshold risk for implantation.

Rights and Obligations of Egg Donors

14. It is relevant to consider if the introduction of new assisted reproductive techniques such as MGRT could inadvertently impact the legal rights and obligations of egg donors, as well as the parenthood status of the children born as a result of MGRT. The Consultation Paper (paragraph 72) correctly points out that the Status of Children (Assisted Reproduction Technology) Act (Cap. 317A) (Rev Ed. 2015) provides that the gestational mother would be regarded as the legal mother. Nevertheless, under section

10(2)(d) of the Act, “any other person, with the leave of the court" may apply to the court "for an order to determine the parenthood of a child". The applicants must demonstrate that they have "a sufficient interest in the parenthood of the child notwithstanding that he is not claiming to be treated as the parent of a child or seeking a court order declaring that he be treated as the parent of a child".

15. In our view, an egg donor is unlikely to be said to have “sufficient interest” because there is little genetic affiliation between the child and the donor. Although the egg donor does play a big part in ensuring that the child has a chance of avoiding mitochondrial disease, the donation is arguably more akin to a life-saving blood transfusion or bone marrow or organ donation – while it may save the child’s life, it has no significant impact on the child’s genetic makeup since the donor’s nuclear DNA is not used. Consequently, we believe that the risk of MGRT inadvertently affecting the legal rights and obligations of those involved in the process, such as egg donors, should be regarded as low.

Wrongful Life and Wrongful Birth Claims

16. There is still a lot that is unknown regarding the longer term effects of MGRT. A poor outcome could potentially give rise to wrongful birth or wrongful life claims.

17. Wrongful birth claims are typically brought by parents who claim that the healthcare professional has either failed to inform them of the pregnancy or the fact that the unborn child is likely to be disabled. The claim arises because the mother claims that she would have terminated the pregnancy had she been informed in a timely manner that her child would be disabled. Whether such claims are feasible in the case of MGRT pregnancies would depend on whether there are diagnostic tools that could allow the healthcare professional to screen the fetus-in-utero for mitochondrial disorders and how accurate these tools are.

18. Wrongful life claims are brought for the benefit of children with disabling conditions who claim that they were born as a result of negligence on the part of the healthcare professional. It is not inconceivable that children living with debilitating mitochondrial disease who believe that they are worse off than not having lived at all could have legal actions commenced on their behalf seeking compensation for the injury of being born. Even if their parents had made an informed choice in opting for MGRT, the child may

argue that he never consented to be conceived and to be born to a life of disability. He could even claim that the decision made by his parents to resort to MGRT rather than to conceive a child naturally only served to prolong his own suffering, when a child born without such techniques would have simply passed on naturally from severe mitochondrial disease.

19. There is a dearth of cases in Singapore dealing with wrongful life claims. However, we take reference from *JU and another v See Tho Kai Yin* [2005] 4 SLR(R) 96 (HC), where such a claim was dismissed by the High Court. In doing so, Lai J made reference to the common law position, which is that such wrongful life claims are regarded as being "contrary to public policy as a violation of the sanctity of human life".

20. It would thus appear that where a child born as a result of MGRT has failed to escape the fate of mitochondrial disease, he may have an uphill task in successfully establishing such a claim, and consequently may have no legal remedy in damages. This underscores the need for caution before allowing MGRT to be offered as a clinical treatment option in medical practice, at a time when the safety and long term health of children born through such techniques is still uncertain.

Thank you for giving us an opportunity to provide our inputs on the BAC guidelines.