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SPECIAL ISSUE PAPERS

HUMAN NUCLEAR GENOME TRANSFER (SO-CALLED MITOCHONDRIAL REPLACEMENT): CLEARING THE UNDERBRUSH

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Abstract
In this article, I argue that there is no compelling therapeutic 'need' for human nuclear genome transfer (so-called mitochondrial replacement) to prevent mitochondrial diseases caused by mtDNA mutations. At most there is a strong interest in (i.e. 'want' for) this technology on the part of some women and couples at risk of having children with mitochondrial disease, and perhaps also a 'want' on the part of some researchers who see the technology as a useful precedent – one that provides them with 'a quiet way station' in which to refine the micromanipulations techniques essential for other human germline interventions and human cloning. In advance of this argument, I review basic information about mitochondrial disease and novel genetic strategies to prevent the transmission of mutated mitochondria. Next, I address common features of contemporary debates and discussions about so-called mitochondrial replacement. First, I contest the cliché that science-and-(bio)technology is fast outpacing ethics. Second, I dispute the accuracy of the term 'mitochondrial replacement'. Third, I provide a sustained critique of the purported 'need' for genetically-related children. In closing, I call into question the mainly liberal defense of human nuclear genome transfer. I suggest an alternative frame of reference that pays particular attention to issues of social justice. I conclude that our limited resources (time, talent, human eggs, and money) should be carefully expended in pursuit of the common good, which does not include pandering to acquired desires (i.e., wants).

INTRODUCTION

I am of the opinion that good-quality reasoning is essential for ethical problem-solving and ethical policy-making. Those who share this perspective should be as vexed as I am with several problematic claims that pepper contemporary discussions and debates on the ethics of human nuclear genome transfer (so-called mitochondrial replacement). First, there is the oft-repeated comment that science-and-(bio)technology are fast outpacing ethics (or, ethics is lagging behind science-and-(bio)technology). Second, there is the widespread use of inaccurate terminology to describe the transfer of a nucleus from one cell to another. Third, there are the inchoate assertions about the compelling need for genetically-related children. A common feature of these problematic claims is that they camouflage or downplay key aspects of the ethics, science, and (bio)technology of human nuclear genome transfer – they do so by suggesting that 'current ethical analysis is a turtle chasing a hare,'[1] and that human nuclear genome transfer both addresses an important therapeutic goal and increases reproductive choice.

[1] M.H. Shapiro. Is Bioethics Broke? On the Idea of Ethics and Law 'Catching Up' with Technology. *Indiana. Law Rev* 1999; 33: 17–162: 30.

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This article is presented in three parts. In Part I, I provide some basic information about mitochondrial disease, novel genetic strategies to prevent the transmission of mutated (i.e. dysfunctional) mitochondria, and recent research suggesting that these strategies are not yet ready for clinical use. In Part II, I discuss in turn each of the problematic claims identified above, in an effort to sharpen the ethics discourse on human nuclear genome transfer. First, I comment on why the cliché about the relationship between ethics and science-and-(bio)technology is a myth. Next, I review efforts to finesse the ethics debate through use of the term 'mitochondrial replacement'. Finally, I provide a sustained critique of the purported need for genetically-related children. My hope is that in clearing away this distracting underbrush, we might see more clearly the bias that informs current ethics discussions and debates. In Part III, I call into question the mainly liberal defense of human nuclear genome transfer that invariably reduces the ethics to individual freedom and procreative liberty (or reproductive liberty, or reproductive autonomy).[2,3] An alternative frame of reference is proposed – one that is 'firmly grounded in our common interests in preventing illness, building physically and socially healthy communities and eliminating health inequities.'[4]

PART I: MITOCHONDRIAL DISEASE AND HUMAN NUCLEAR GENOME TRANSFER

Mitochondria are the energy sources inside our cells, and each cell contains hundreds to thousands of copies of mitochondria. All of our mitochondrial DNA (mtDNA) are inherited from our genetic mothers. In healthy tissues, all mtDNA molecules are identical (homoplasmy); there are no mtDNA mutations. When there are such mutations, they typically affect some, but not all of the mtDNA in the cell. In such cases, cells contain a mixture of normal and dysfunctional mtDNA (heteroplasmy). When the percentage of dysfunctional mtDNA exceeds a certain threshold (which varies depending upon the tissue and mutation type, but is usually between 60–90%),[5] there is mitochondrial disease.[6]

Mitochondrial diseases are variable both in severity and in the body systems that are affected. They range from mild to severely debilitating (depending upon the extent of the heteroplasmy), with onset during infancy, childhood, or adulthood. These diseases include poor growth, deafness, blindness, heart disease, liver disease, kidney disease, learning disabilities, loss of muscle coordination, muscle weakness, and neurological problems. Indeed, the varied manifestations of mitochondrial disease are the result of what has been described as a 'veritable Pandora's box of pathogenic mutations and rearrangements'.[7] Mitochondrial diseases can be caused by dysfunctional mtDNA, or by dysfunctional nuclear DNA (nDNA) involved in mitochondrial function.[8] Typically, nDNA-based mitochondrial diseases are earlier onset and more severe than mtDNA-based mitochondrial diseases. Also, in general, mitochondrial diseases are worse when the dysfunctional mitochondria are in the brain, heart, muscle, or nerve tissues.[9] This is because the cells in these tissues consume proportionately larger amounts of energy (as compared with other cells of the body).

At the present time, there is no effective treatment for mitochondrial diseases and available therapies are mostly limited to symptomatic relief.[10] Research suggests, however, that it may be possible to avoid some mitochondrial diseases by removing the nDNA from eggs provided by a woman with dysfunctional mtDNA, and placing this nDNA into eggs provided by a woman with normal (i.e. healthy/unaffected/nonpathogenic) mtDNA from which the nDNA has been removed.[11] In 2003[12] and then in 2016,[13] a team of

[2] National Academies of Sciences, Engineering, and Medicine. 2016. *Mitochondrial Replacement Techniques: Ethical, Social, and Policy Considerations*. Washington, DC: The National Academies Press. Available at: http://www.nap.edu/catalog/21871/mitochondrial-replacement-techniques-ethical-social-and-policy-considerations [Accessed 27 Jun 2016].

[3] Nuffield Council on Bioethics. 2012. *Novel Techniques for the Prevention of Mitochondrial DNA Disorders: An Ethical Review*. London, UK: Nuffield Council on Bioethics. Available at: http://www.nuffield-bioethics.org/sites/default/files/Novel_techniques_for_the_prevention_of_mitochondrial_DNA_diseases_compressed.pdf/ [Accessed 9 Sept 2016].

[4] F. Baylis, N. Kenny, & S. Sherwin. A Relational Account of Public Health Ethics. *Public Health Ethics* 2008; 1(3): 196–209: 196.

[5] P. Amato, M. Tachibana, M. Sparman, & S. Mitalipov. Three-Parent IVF: Gene Replacement for the Prevention of Inherited Mitochondrial Diseases. *Fertil Steril* 2014; 101(1): 31–35.

[6] R.W. Taylor & D. Turnbull. Mitochondrial DNA Mutations in Human Disease. *Nat Rev Genet* 2005; 6(5): 389–402; S. DiMauro. Mitochondrial DNA Mutation Load: Chance or Destiny? *JAMA Neurology* 2013; 70(12): 1484–1485.

[7] S. Dimauro & G. Davidzon. Mitochondrial DNA and Disease. *Annals of Medicine* 2005; 37(3): 222–232: 222.

[8] A majority of childhood manifestations of mitochondrial disease involve mutations of nDNA.

[9] Amato et al., *op. cit*. note 5.

[10] L. Craven, J.L. Elsom, L. Irving, S.J. Harbottle, J.L. Murphy, L.M. Cree et al. Turnbull. Mitochondrial DNA Disease: New Options for Prevention. *Hum Mol Genet* 2011; 20(R2): R168-R174.

[11] M. Tachibana, M. Sparman, H. Sritanaudomchai, H. Ma, L. Clepper, J. Woodward et al. Mitochondrial Gene Replacement in Primate Offspring and Embryonic Stem Cells. *Nature* 2009; 461: 367–372; L. Craven, H.A. Tuppen, G.D. Greggains, S.J. Harbottle, J.L. Murphy, L.M. Cree et al. Pronuclear Transfer in Human Embryos to Prevent Transmission of Mitochondrial DNA Disease. *Nature* 2010; 465: 82–85.

[12] J. Zhang, G. Zhuang, Y. Zeng, C. Acosta, Y. Shu, & J. Grifo. Pregnancy Derived From Human Pronuclear Transfer. *Fertil Steril* 2003; 80 (Suppl.3): S56 (Abstract # O-148).

[13] J. Zhang, G. Zhuang, Y. Zeng, J. Grifo, C. Acosta, Y. Shu, & H. Liu. Pregnancy Derived from Human Zygote Pronuclear Transfer in a Patient Who Had Arrested Embryos After IVF. *Reprod BioMed Online* 2016; 33(4):529–533.

Chinese scientists reported on an *in vitro* fertilization (IVF) pregnancy established in 2003 that involved the use of pronuclear transfer to treat unexplained infertility (i.e. the transfer of pronuclei from eggs with dysfunctional mtDNA into enucleated eggs with normal mtDNA). Five reconstructed embryos were transferred and a triplet pregnancy was achieved. This pregnancy was reduced to a twin pregnancy by foetal reduction, and later there was premature delivery and death of the other two foetuses – one at 24 weeks and the other at 29 weeks. In their conclusion, the authors note that their technique could be used to prevent the vertical transmission of mitochondrial disease. This hypothesis may soon be tested in a clinical setting in the UK (the only country to explicitly permit under law the creation of IVF babies using genetic material from three people). The Human Fertilisation & Embryology Authority (HFEA), in accordance with *The Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015*,[14] is poised to license and regulate the technology.

The genetic manipulations involved in the transfer of nDNA can be done in unfertilized or fertilized eggs. In unfertilized eggs, the technology is called maternal spindle transfer. This involves the transfer of nDNA in the form of the pronucleus from an unfertilized egg with dysfunctional mtDNA into an enucleated unfertilized egg with normal mtDNA. The reconstructed egg is then fertilized. In fertilized eggs, the technology is called pronuclear transfer. This involves the transfer of nDNA from a fertilized egg with dysfunctional mtDNA into an enucleated fertilized egg with normal mtDNA. A third option is polar body transfer. This can involve the transfer of the first polar body (which contains nDNA and a very little mtDNA) into an enucleated unfertilized egg with normal mtDNA after which the reconstructed egg is fertilized. Or, this can involve the transfer of the second polar body (which also contains nDNA and a very little mtDNA) into an enucleated fertilized egg with normal mtDNA.[15]

The potential benefit of this technology is that the woman with dysfunctional mtDNA, who would otherwise pass on her dysfunctional mtDNA to all of her children (as inheritance is through the maternal line), could have children that are genetically-related to her and under ideal circumstances they would be free of mitochondrial disease. Children born of this technology would be created using IVF technology with genetic material from three individuals – a male sperm provider and two female egg providers (one to provide nDNA and one to provide normal mtDNA);[16] hence, the reference to three-parent IVF.[17] While there would be three genetic parents, the usual expectation is that there would only be two social parents (sometimes called intended parents) – the male sperm provider and the female egg provider whose nDNA was used to create the child(ren).

In June 2016, Dieter Egli and colleagues in the US reported that while nuclear transfer between fertilized eggs was technically possible, there was the potential for genetic drift (where small amounts of dysfunctional mtDNA carryover).[18] Their research (using human mitochondrial replacement stem cell lines) showed low-level carryover of transferred mtDNA resulting in what Egli described as 'unstable mixtures of different mitochondrial genotypes [heteroplasmy].'[19] Shortly thereafter, this risk of heteroplasmy was independently confirmed by Mary Herbert and colleagues in the UK. Their preclinical studies of pronuclear transfer identified a 4% risk of mtDNA carryover.[20] While Herbert and colleagues do not appear to believe this 'low' level of carryover warrants a delay in clinical applications, Egli and others[21] insist that the risk of mtDNA carryover is reason enough to postpone clinical applications (perhaps for several years). It remains to be seen whether the HFEA will grant a license for clinical applications.

PART II: PROBLEMATIC CLAIMS

Science-and-(bio)technology are fast outpacing ethics

Statements about 'science outpacing ethics' and 'ethics lagging behind science' are commonplace, as are admonitions for ethics to catch-up.[22] The problem with these

[14] United Kingdom Government. 2015. *The Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015* No. 572. London, UK: The National Archives. Available at: http://www.legislation.gov.uk/ukdsi/2015/9780111125816/contents [Accessed 8 Sept 2016].

[15] Craven et al., *op. cit*. note 11; Nuffield Council on Bioethics, *op. cit*. note 3; National Academies of Sciences, Engineering, and Medicine, *op. cit*. note 2.

[16] F. Baylis. The Ethics of Creating Children with Three Genetic Parents. *Reprod Biomed Online* 2013; 26(6): 531–534.

[17] For example, Amato et al., *op. cit*. note 5; T. Rulli. What is the Value of Three-Parent IVF? *Hastings Cent Rep* 2016; 46(4): 38–47.

[18] M. Yamada, V. Emmanuele, M.J. Sanchez-Quintero, B. Sun, G. Lallos, D. Paull et al. Genetic Drift Can Compromise Mitochondrial Replacement by Nuclear Transfer in Human Oocytes. *Cell Stem Cell* 2016; 18(6): 749–754.

[19] D. Egli interviewed by P. Knoepfler. 9 Jun 2016. Mitochondrial Replacement Hype Goes Nuclear Including by Wellcome Trust. *The Niche: Knoepfler Lab Stem Cell Blog*. Available at: http://www.ipscell.com/2016/06/mitochondrial-replacement-hype-goes-nuclear-including-by-wellcome-trust/ [Accessed 8 Sept 2016].

[20] L.A. Hyslop, P. Blakeley, L. Craven, J. Richardson, N.M. Fogarty, E. Fragouli et al. Towards Clinical Application of Pronuclear Transfer to Prevent Mitochondrial DNA Disease. *Nature* 2016; 534(7607): 383–386.

[21] P. Knoepfler. 8 Jun 2016. New Herbert Lab Nature Paper Reinforces Mitochondrial Replacement Achilles Heel. *The Niche: Knoepfler Lab Stem Cell Blog*. Available at: https://www.ipscell.com/2016/06/new-nature-paper-reinforces-that-mitochondrial-replacement-has-achilles-heel/#more-19470 [Accessed 27 Jun 2016].

[22] Shapiro, *op. cit*. note 1.

statements is that for many they are simple truisms and as such they are never interrogated.[23]

And yet they need to be interrogated in the interest of good-quality reasoning. For example, are such statements intended to suggest that our ethics is crude and thus ill-equipped to address sophisticated science-and-(bio)technology? Or, is the underlying suggestion that our ethics is reactionary and unable to generate trustworthy answers to complex questions? Or, perhaps our ethics is unfocused as we have not yet settled on a common set of accepted norms. Alternatively, perhaps our accepted norms are not really ethical (owing to a lag in knowledge or an absence of willpower).[24] The point here is that there is no good reason to assume that ethics, science, and technology should be temporally aligned. Moreover, as Michael Shapiro explains, to assume this is to seriously misconceive the relationship between ethics and science. According to Shapiro, at most, catching-up on the part of bioethics might involve '(i) incremental improvements in our thinking about critical moral and legal concepts that (ii) may allow individuals to better discern morally and legally relevant considerations and (iii) heighten the prospects for consensus.'[25] Given this perspective, Mark Rothstein suggests that the exhortation for ethics to catch-up with science-and-(bio)technology is perhaps best understood as a call for a reconsideration of fundamental concepts, careful attention to new biological knowledge or techniques, increased caution, public and media education, and expert consultation.[26]

Another reason to interrogate statements about 'science outpacing ethics' and 'ethics lagging behind science' is that such statements are often untrue. As David Orentlicher reports, evidence suggests that 'bioethical thought anticipates developments in science and technology more than it lags behind those developments.'[27] One of many examples provided by Orentlicher in support of this claim concerns the ethics of cloning. It was only in 1997 that Scottish scientists announced the birth of Dolly the cloned sheep. Long before this, as Orentlicher points out, a major academic debate about cloning was initiated by Joshua Lederberg in 1966. Since then, before and after the birth of Dolly, a wide range of ethical concerns about human cloning for the purpose of creating children have been (and continue to be) identified and debated. Concerns include: potential physical and psychological harms to children born of cloning, children's rights to an open future, children's rights to a unique genetic identity, the commodification of children, implications for parenting, abuse by authoritarian regimes, respect for procreative autonomy, and the potential accrual of medical and other benefits.

As for human nuclear genome transfer, while no child has yet been born of this technology, a number of ethical issues have been identified and debated since the mid-1990s when the micromanipulation technique now referred to as maternal spindle transfer was but a theoretical proposal. Initially, in the ethics literature, the proposed technique was called '*in vitro* ovum nuclear transfer'[28] and later called 'egg cell nuclear transfer'[29] and 'oocyte cytoplasm transfer'.[30] Ethical concerns noted at the time focused on potential physical harms to children, issues of informed consent, and possible links to intentional human germline genetic modification and human cloning.

Then, in 1997, Jacques Cohen and colleagues announced the first birth of a child following human cytoplasmic transfer.[31] In an effort to treat infertile patients with recurrent implantation failure, normal ooplasm from donated human eggs was injected into the eggs of infertile patients. By 2001, there were an estimated 30 live births worldwide from this procedure.[32] Thereafter, research involving human cytoplasmic transplantation came to an abrupt halt.[33] Ethical concerns noted at this time focused on potential harms to future offspring, issues related to kinship and family law, and the risk of inadvertent germline genetic

[23] Science Outpacing Ethical Studies in Genetics. *Can Med Assoc J* 1978; 119(1): 78–80; N. Wosnick. 10 May 2012. As our DNA Defines Us, Science Outpaces Ethics. *Globe & Mail*. Available at: http://www.theglobeandmail.com/opinion/as-our-dna-defines-us-science-outpaces-ethics/article4105699/ [Accessed 27 Jun 2016].

[24] Thanks are owed to Tim Krahn for encouraging me to think about this issue in these terms.

[25] Shapiro, *op. cit*. note 1.

[26] M.A. Rothstein. Science and Society: Applications of Behavioural Genetics: Outpacing the Science? *Nat Rev Genet* 2005; 6(10): 793–798.

[27] D. Orentlicher. The Misperception that Bioethics and the Law Lag Behind Advances in Biotechnology: A Response to Michael H. Shapiro. *Indiana Law Rev* 1999; 33(1): 163–172: 164.

[28] D.S. Rubenstein, D.C. Thomasma, E.A. Schon, & M.J. Zinaman. Germ-line Therapy to Cure Mitochondrial Disease: Protocol and Ethics of In Vitro Ovum Nuclear Transplantation. *Camb Q Healthc Ethics* 1995; 4(3): 316–339; M.D. Bacchetta & G. Richter. Response to 'Germline Therapy to Cure Mitochondrial Disease: Protocol and Ethics of In Vitro Ovum Nuclear Transplantation' by D.S. Rubenstein, D.C. Thomasma, E.A. Schon, & M.J. Zinaman (*CQ* Vol.4, No.3). *Camb Q Healthc Ethics* 1996; 5(3): 450–457.

[29] A.L. Bonnicksen. Transplanting Nuclei Between Human Eggs: Implications for Germ-Line Genetics. *Politics the Life Sci* 1998; 17(1): 3–10

[30] J.A. Robertson. Oocyte Cytoplasm Transfer and the Ethics of Germline Interventions. *J Law Med Ethics* 1998; 26(3): 211–220.

[31] J. Cohen, R. Scott, T. Schimmel, J. Levron, & S. Willadsen. Birth of Infant After Transfer of Anucleate Donor Oocyte Cytoplasm Into Recipient Eggs. *Lancet* 1997; 350(9072): 186–187.

[32] J.A. Barritt, C.A. Brenner, H.E. Malter, & J. Cohen. Mitochondria in Human Offspring Derived From Ooplasmic Transplantation. *Hum Reprod* 2001; 16(3): 513–516.

[33] Fertility specialists in the US were informed by the Food and Drug Administration that an investigational new drug exemption was required for them to pursue this research. Later, a public meeting was held after which the Food and Drug Administration concluded that clinical trials could not proceed without further preclinical research. See F. Baylis. 'Babies with Some Animal DNA in Them': A Woman's Choice? *Int J Fem Approaches Bioeth* 2009; 2(2): 75–96.

modification.[34] Years later, in 2005, a licence for mitochondrial research involving human cytoplasmic transplantation was granted by the HFEA.[35] Ethical discussion and debate continued with particular attention to potential medical and psychological harms to children born of human nuclear genome transfer, questions of identity, children's rights to an open future, the ethics of germline genetic modification, the ethics of sex selection, legal and genetic parentage, harms to egg providers, harms to specific interest groups, harms to society, and slippery slope concerns.[36] Against this backdrop, what does it mean to suggest that 'science is outpacing ethics?'

Most recently, in 2015, the UK Parliament approved regulations permitting the clinical use of maternal spindle transfer or pronuclear transfer.[37] The following year, in 2016, the US National Academies of Sciences, Engineering and Medicine issued a report on 'Mitochondrial Replacement Techniques' concluding that it was ethically premature to endorse germline modification given the limited available evidence of safety and efficacy. To avoid the possibility of introducing heritable genetic modifications, the US report only approved clinical research involving the transfer of reconstructed male embryos for gestation.[38] The law in the UK and the recommendations generated in the US differ in important respects. Does it follow that ethics is keeping pace with science-and-(bio)technology in one country and is lagging behind in the other? I think not.

In my view, at all times we ought to contest claims about science-and-(bio)technology fast outpacing ethics and instead insist on a clear description of the perceived ethical problem the aphorism is meant to allude to.

So-called mitochondrial replacement

There is good reason to question the relatively recent and almost imperceptible shift (in policy debates and documents, as well as media reports) away from such terms as 'germline gene replacement therapy',[39] 'nuclear transfer techniques',[40] and 'nuclear genome transplantation,'[41] to popular euphemisms such as 'mitochondria replacement therapy',[42] 'mitochondrial manipulation',[43] and 'mitochondrial donation'.[44] This shift in language is 'scientifically inaccurate and ethically misleading'[45] – it masks the fact that the micromanipulation techniques involved are the same techniques used for nDNA germline modification and human somatic cell nuclear transfer (i.e. cloning). Terms like 'mitochondrial replacement', and 'mitochondrial donation' allude to the replacement of dysfunctional mtDNA with normal mtDNA. In sharp contrast, the terms 'germline gene replacement', 'nuclear transfer techniques', and 'nuclear genome transplantation' draw attention to the fact that nDNA is being transferred from one cell to another.

To be clear, the terms 'mitochondrial replacement' and 'nuclear genome transfer' describe one and the same *techne*. The difference is one of implied directionality. On this point, Erica Haimes and Ken Taylor argue (and I agree) that terms like 'mitochondrial replacement' and 'mitochondrial donation' 'are misleading as they imply a direction of travel for the mitochondria that is in fact the opposite of what will actually occur…. The egg provider's mitochondria … are not moved anywhere.'[46] Rather, it is the prospective social parent's nDNA that is transplanted into the enucleated egg. As such, the actual transfer of material is in the opposite direction to that which is implied with the term 'mitochondrial replacement'. Jeff Nisker makes the same point:

[34] R.K. Naviaux & K.K. Singh. Need for Public Debate About Fertility Treatments. *Nature* 2001; 413(6854): 347; E. Parens & E. Juengst. Inadvertently Crossing the Germ Line. *Science* 2001; 292(5516): 397; A. Templeton. Ooplasmic Transfer—Proceed with Care. *N Engl J Med* 2002; 346: 773–775.

[35] HFEA Grants Licence to Newcastle Centre at LIFE for Mitochondrial Research. 8 Sept 2015. London, UK: Human Fertilisation & Embryology Authority. Available at: http://www.hfea.gov.uk/671.html [Accessed 27 Jun 2016].

[36] A. Bredenoord & P. Braude. Ethics of Mitochondrial Gene Replacement: From Bench to Bedside. *Br Med J* 2011; 342: 87–89; A. Bredenoord, W. Dondorp, G. Pennings, G. de Wert. Ethics of Modifying the Mitochondrial Genome. *J Med Ethics* 2011; 37: 97–100; Nuffield Council on Bioethics, *op. cit*. note 3; Baylis, *op. cit*. note 16; J.B. Appleby. The Ethical Challenges of the Clinical Introduction of Mitochondrial Replacement Techniques. *Med Health Care Philos* 2015; 189(4): 501–514.

[37] United Kingdom Government, *op. cit*. note 14.

[38] National Academies of Sciences, Engineering, and Medicine, *op. cit*. note 2.

[39] Amato et al., *op. cit*. note 5.

[40] Craven et al., *op. cit*. note 11; Nuffield Council on Bioethics, *op. cit*. note 3.

[41] Newcastle Fertility Centre. 2016. *Mitochondrial Transmission*. Newcastle, UK: Newcastle upon Tyne Hospitals, NHS Foundation Trust. Available at: http://www.newcastle-hospitals.org.uk/services/fertility-centre_research-and-technology_mitochondrial-transmission.aspx [Accessed 27 Jun 2016].

[42] D.P., Wolf, N. Mitalipov, & S. Mitalipov. Mitochondrial Replacement Therapy in Reproductive Medicine. *Trends Mol Med* 2015; 21(2): 68–76: 75.

[43] Food and Drug Administration. 25–26 Feb 2014. Briefing document, Cellular, Tissue, and Gene Therapies Advisory Committee. Meeting #59 *Oocyte Modification in Assisted Reproduction for the Prevention of Transmission of Mitochondrial Disease or Treatment of Infertility*. Available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/CellularTissueandGeneTherapiesAdvisoryCommittee/UCM385461.pdf [Accessed 27 Jun 2016].

[44] Human Fertilisation & Embryology Authority. *Code of Practice*, 8th Edition. Oct 2015. London, UK: Human Fertilisation & Embryology Authority. Available at: http://www.hfea.gov.uk/docs/HFEA_Code_of_Practice_8th_Edtion_(Oct_2015).pdf [Accessed 27 Jun 2016].

[45] D. Jones. The Other Woman: Evaluating the Language of 'Three Parent' Embryos. *Clin Ethics* 2015; 10(4): 97–106.

[46] E. Haimes & K. Taylor. Rendered Invisible? The Absent Presence of Egg Providers in U.K. Debates on the Acceptability of Research and Therapy for Mitochondrial Disease. *Monash Bioeth Rev* 2015; 33(4): 360–378: 364–365.

> What is actually happening in 'mitochondrial replacement' is not mitochondrial replacement; instead, it is the transfer of the *nucleus* from the oocyte of an IVF patient seeking to be a genetic parent to the enucleated oocyte of a woman who is being paid to undergo IVF to provide an ooplasmic vessel containing supposedly healthy mitochondria.[47]

Nisker offers two reasons why the 'camouflage term 'mitochondrial replacement''[48] is used instead of 'germ-line nuclear transfer' – namely, to side-step legal prohibitions on germline nuclear transfer, and to garner public support for this and future germline modifications.[49] To explain, the term 'mitochondrial replacement' keeps the focus on the proposed therapeutic objective of helping to prevent the transmission of mitochondrial disease. The technology is thus amenable to being perceived as a relatively benign therapeutic intervention that can be effectively regulated. The term "germ-line nuclear transfer" (or 'nuclear genome transfer'), on the other hand, more readily evokes concerns about potential germline genetic modification, human cloning, and myriad other possible future reproductive and enhancement technologies.

In my earlier writings on the ethics of this science, as the language was settling, I used terms in general use at the time including 'cytoplasmic transplantation',[50] '*in vitro* ovum nuclear transfer'[51] and, more recently, 'mitochondrial replacement'.[52] As the language now appears to have settled and the term 'mitochondrial replacement' has entered the general lexicon, I find myself wanting to insist on the use of the descriptively more accurate term 'nuclear genome transfer'. As noted above, this term makes it clear that the technology involves the transfer of nDNA from one cell to another – in this case from the egg of a woman with mitochondrial disease caused by dysfunctional mtDNA into the enucleated egg of a woman without mitochondrial disease. Use of this term also makes it possible for people to more readily appreciate how promoting this technology to prevent the inheritance of mitochondrial disease caused by dysfunctional mtDNA is also about securing a 'relatively uncontentious setting for the refinement of cloning [and other] procedures.'[53]

As Andrea Bonnicksen remarked nearly 20 years ago, so-called mitochondrial replacement (which she labelled 'egg cell nuclear transfer') 'presents a backdoor approach to germ-line therapy by presenting a relatively nonthreatening technique designed to address a specific medical purpose.'[54] It provides scientists with 'a quiet way station' in which to refine the micromanipulations techniques essential for other human germline interventions (including nDNA germline modification) and human cloning.[55]

Intellectual honesty requires us to use descriptively accurate terms that elucidate rather than obfuscate relevant ethical issues, so that these may be addressed head-on.

The desire for genetically-related children

Recently, Neal Mahutte, then president of the Canadian Fertility and Andrology Society, is reported to have said that '… the families who suffer from these [mitochondrial] diseases make a very compelling case that it's worth trying under an appropriately supervised system'.[56] This claim is not original. Indeed, a version of this claim has ricocheted around the world for the past several years, essentially unchecked, and has now become entrenched in policy documents, academic articles, and media reports. The supposed compelling case for human nuclear genome transfer is anchored in the presumed need of prospective parents to have genetically-related children hopefully free of mitochondrial disease caused by mtDNA mutations.

There are many reasons, however, to think that this case is anything but compelling. For example, one might reasonably counter that the perception of a compelling need for human nuclear genome transfer suggests an inappropriate overvaluing of genetic relatedness within families (which in turn wrongly undermines and thereby threatens valuable and meaningful non-genetic family relations). From my perspective, if there is a compelling argument to be made it is an argument against human nuclear genome transfer on the grounds that a desire for

[47] J. Nisker. The Latest Thorn by Any Other Name: Germ-Line Nuclear Transfer in the Name of 'Mitochondrial Replacement'. *J Obstet Gynaecol Can* 2015; 37(9): 829–831: 829.
[48] Ibid: 830.
[49] Haimes and Taylor also suggest that the term 'mitochondrial replacement' is used to camouflage the role and importance of the women who provide the eggs with healthy mtDNA. They describe this as a 'deliberate strategy of persuasion'. See Haimes & Taylor, *op. cit.* note 53, p.361.
[50] Baylis, *op. cit.* note 34.
[51] F. Baylis & J.S. Robert. 2005. Radical Rupture: Exploring Biological Sequelae of Volitional Inheritable Genetic Modification. In J.E.J. Rasko, G.M. O'Sullivan, & R.A. Ankeny, eds. *The Ethics of Inheritable Genetic Modification*. Cambridge: Cambridge University Press: 131–148.
[52] Baylis, *op. cit.* note 16; F. Baylis. 23 Feb 2015. The Truth about Mitochondrial Replacement. *Impact Ethics.* Available at: http://impactethics.ca/2015/02/23/the-truth-about-mitochondrial-replacement/ [Accessed 27 Jun 2016]; F. Baylis. 2 Jul 2013. Ethical Objections to Mitochondrial Replacement. *Impact Ethics.* Available at: http://impactethics.ca/2013/07/02/ethical-objections-to-mitochondrial-replacement/ [Accessed 27 Jun 2016].
[53] Bonnicksen, *op. cit.* note 30, p.3.
[54] Ibid: 9.
[55] Ibid.
[56] S. Kirkey. 23 Dec 2015. Three-parent Babies: How the Future of Fertility Will Challenge Ideas of Parenthood. *National Post*. Available at: http://news.nationalpost.com/news/canada/three-parent-babies [Accessed 27 Jun 2016].

genetically-related children, though often interpreted as a need, is at most a want (an interest, a preference).

According to Aristotle, there are two kinds of desires – natural desires (i.e. needs) and acquired desires (i.e. wants). As paraphrased by Mortimer Adler, '[n]eeds are inborn or innate desires – desires inherent in our human nature because we have certain natural capacities or tendencies, capacities or tendencies common to us all because we all have the same human nature.'[57] Our natural needs (needs that all humans share in common) include such things as food and drink, as well as clothing, shelter, and sleep as these are essential for staying alive. While a person does not acquire a desire for natural needs, she may acquire wants in relation to her natural needs. For example, a person's natural desire (i.e. need) for food and drink may be accompanied by an acquired desire (i.e. want) for a particular kind of food or drink. Importantly, a person's natural desire (i.e. need) for food and drink can be satisfied even if the food or drink for which they have acquired a desire (i.e. want) is not available.[58]

As it happens, we often want things that we do not need, and moreover we often make the mistake of describing the things that we want as needs (particularly in contexts where we have been socialized or conditioned to think of our wants as needs). Further, sometimes we want things that are not good for us, as when we have acquired a desire for something that is injurious to our health and well-being (which is another kind of mistake). Aristotle makes the point that whereas our natural needs are *always* good for us, our acquired wants may not be good for us.

In 1978, the first IVF baby was born. Since then an impressive number of adjunct assisted reproductive technologies have been introduced, nominally to respond to reproductive needs. In a 30-year retrospective of assisted reproductive technologies, Søren Holm writes:

> Since the invention of In Vitro Fertilisation (IVF) there has been an explosion in different kinds of ART each presumably responding to the *reproductive needs and desires* of a particular subset of would be reproducers. Intracytoplasmatic Sperm Injection allows men with very few, or only immature sperm to reproduce; the use of surrogate gestational mothers responds to the *need* of women who cannot gestate or of male homosexual couples; Preimplantation Genetic Diagnosis (PGD) for genetic disorders helps families with known genetic problems to avoid prenatal diagnosis and abortion etc. etc. If we further add the possibilities of using donor sperm and eggs, of freezing embryos and eggs, and possibly in the future of creating gametes from stem cells or performing reproductive cloning or germ line genetic modification we have a situation where there is a possible ART solution to the *reproductive needs and desires* of almost any combination of would be reproducers.[59] (emphasis added)

In this spirit, there have been a number of enthusiastic endorsements of human nuclear genome transfer as a solution to so-called reproductive needs. For example, in writing on the ethics and regulation of 'mitochondrial replacement therapy' Don Wolf and colleagues insist that:

> The *need* for MRT [mitochondrial replacement therapy] is apparent for families carrying mtDNA based disease and for older infertility patients without cryostored young oocytes and refractile to conventional IVF. So if the *need* exists, and the risk to benefit ratio is favorable, then the question becomes how we move towards implementation.[60] (emphasis added)

The point I want to make here concerns the failure to meaningfully interrogate the conditional clause 'if the need exists'. All too often, claims about a 'need' for human nuclear genome transfer to satisfy a 'need' for genetically-related children are asserted as though uncontroversial, when they should be interrogated. For example, Bonnicksen writes: 'The decision to use egg cell nuclear transfer depends upon a couple's felt *need* to have a child genetically related to the female partner. . . it is the felt *need* to preserve and pass on genes that is at issue in egg cell nuclear transfer.'[61] (emphasis added)

At this time, there is a wide array of assisted human reproductive technologies available to single persons, infertile couples, couples in same sex-relationships, and individuals and couples at risk of having children with serious genetic disease(s). Some of these reproductive options facilitate biological and genetic relatedness, others do not. When there is a choice to be made between such options, typically the option that will create a child(ren) who is genetically-related to one or both prospective social parents is the preferred option. But is it rational, Michael Bayles asks, to want and value a genetic tie to the child(ren) one is raising?[62] There are those who would have us believe that 'the desire for a family rises unbidden from our genetic souls,'[63] that having

[57] M.J. Adler. 1978. *Aristotle for Everybody*. New York: Macmillan Publishing: 85.

[58] This example is taken from Adler, ibid.

[59] S. Holm. The Medicalization of Reproduction – A 30 Year Retrospective. In F. Simonstein, ed. 2009. *Reprogen-Ethics and the Future of Gender*. Published online by Springer as *International Library of Ethics, Law, and the New Medicine* 2009; 43: 29–36. Available at: http://link.springer.com/book/10.1007%2F978-90-481-2475-6 [Accessed 9 Sept 2016].

[60] Wolf et al., *op. cit*. note 49: 75.

[61] Bonnicksen, *op. cit*. note 30, p.5.

[62] M.D. Bayles. 1984. *Reproductive Ethics*. Englewood Cliffs, NJ: Prentice Hall: 13.

[63] S. Franklin. 1990. Deconstructing 'Desperateness': The Social Construction of Infertility in Popular Representations of New Reproductive Technologies. In M. McNeil, I. Varco, & S. Yearley, eds. *The New Reproductive Technologies*. London, UK: Palgrave Macmillan UK: 200–229: 207.

one's own 'children must be among the most basic human instincts.'[64] As Dorothy Roberts effectively counters, however, '[t]he desire to have genetically related children is not entirely natural, but is determined by our political and cultural context.'[65] From this perspective, it is important to interrogate the claim that there is an innate (as contrasted with culturally prescribed and reinforced) genetic imperative to reproduce oneself.

From another perspective, there are those who argue that biological family relations between parents and children are critically important for the healthy psychological development of children.[66] Others,[67] argue that adoptive parents, foster parents, and biological parents can have equally rewarding experiences raising children, and that children raised in such families can be equally well-adjusted.[68] In addition, there are those, such as Tina Rulli, who argue that 'there is a duty to adopt a child rather than create one.'[69] In developing her argument in favour of adoption over genetic procreation, Rulli critically examines the common reasons given for preferring genetically-related children and finds that all but the last of these reasons fail to defeat the duty to adopt (meaning they lack moral heft). The reasons examined include a preference

> 'for parent-child physical resemblance, for family resemblance, for psychological similarity, for the sake of love, to achieve a kind of immortality, for the genetic connection itself, to be a procreator, and to experience pregnancy.'[70]

According to Rulli,

> 'these reasons are too trivial, presuppose the value of the genetic connection, are inappropriate in a normative parental context, or fail to make a relevant distinction between genetic and adopted children.'[71]

As for the last of these reasons, experiencing pregnancy need not involve a preference for a genetic connection as when the gametes are provided by another.

Currently, women with dysfunctional mtDNA who are at risk of having children with mitochondrial disease can choose to remain childless or, if they already have an affected child, they can choose to avoid having more genetically-related children. If they want to have (more) children and if they believe that the priority in family-making is social and not biological (which is to say that the priority is to establish loving, caring, and nurturing relationships with one's child(ren) independent of biological relationships or genetic ties), they can choose adoption or they can choose to foster children. For some women with dysfunctional mtDNA, however, these alternatives may not be attractive options. For example, the bureaucratic aspects of adoption can be very onerous.[72] Also, some women with dysfunctional mtDNA may want to experience pregnancy and among those who want to experience pregnancy some may want to have a genetic link to their child(ren).

Women with a low proportion of dysfunctional mtDNA can choose sexual or assisted reproduction followed by genetic testing, knowing that they will pass on their dysfunctional mtDNA to all of their children (as inheritance is through the maternal line). Those who choose sexual reproduction can have prenatal testing (amniocentesis or chorionic villus biopsy) possibly followed by elective termination of pregnancy.[73] Those who choose assisted human reproduction can have pre-implantation genetic diagnosis (PGD)[74] followed by the selective transfer of embryos with mutation levels below the disease threshold. IVF followed by PGD and selective embryo transfer is not a suitable option, however, for an estimated 20% of women who are at risk of having children with mitochondrial disease because of their high mutation load.[75]

In summary, there are different kinds of wants with respect to the acquired desire to have a family that includes children, many of which can be met by existing, safe alternatives to human nuclear genome transfer. There

[64] R.G. Edwards & D.J. Sharpe. Social Values and Research in Human Embryology. *Nature* 1971; 231(5298): 87–91: 87.

[65] D.E. Roberts. The Genetic Tie. *Univ Chic Law Rev* 1995; 62(1): 209–273: 215.

[66] See, for example, J.D. Velleman. Family History. *Philosophical Papers* 2005; 34(3): 357–378; J.D. Velleman. Persons in Prospect. *Philos Public Aff* 2008; 36(3): 221–288.

[67] See, for example, C. Witt. 2014. A Critique of the Bionormative Concept of the Family. In F. Baylis & C. McLeod, eds. *Family-Making: Contemporary Ethical Challenges*. Oxford: Oxford University Press: 49–63.

[68] Baylis & McLeod, eds., ibid.

[69] T. Rulli. Preferring a Genetically-Related Child. *J Moral Philos* Nov 2014; DOI: 10.1163/17455243-4681062: 1–30. Available at: http://trulli.faculty.ucdavis.edu/wp-content/uploads/sites/86/2014/07/17455243_4681062_text.pdf [Accessed 9 Sept 2016].

[70] Ibid: 1.

[71] Ibid: 29.

[72] C. McLeod & A. Botterell. 'Not for the Faint of Heart': Assessing the Status Quo on Adoption and Parental Licensing. In Baylis & McLeod, eds., *op. cit*. note 74.

[73] As the proportion of dysfunctional mtDNA can vary between cells, care must be taken with prenatal testing.

[74] While some insist that PGD is a safe and practical alternative to nuclear genome transfer (likely to be effective for a majority of patients), others insist that the technology is of limited efficacy. See: A. Greenfield—Review panel chair. Jun 2014. Third Scientific Review of the Safety and Efficacy of Methods to Avoid Mitochondrial Disease through Assisted Conception: 2014 Update. London, UK: Human Fertilisation & Embryology Authority. Available at: http://www.hfea.gov.uk/docs/Third_Mitochondrial_replacement_scientific_review.pdf [Accessed 27 Jun 2016]; Amato et al., *op. cit*. note 5; and J. Richardson, L. Irving, L.A. Hyslop, M. Choudhary, A. Murdoch, D. Turnbull, & M. Herbert. Concise Reviews: Assisted Reproductive Technologies to Prevent Transmission of Mitochondrial DNA Disease. *Stem Cells* 2015; 33(3): 639–645.

[75] Human Fertilisation & Embryology Authority, *op. cit*. note 81.

is, however, one very small group of women with dysfunctional mtDNA who are at risk of having children with mitochondrial disease, for whom the specific want for a healthy, genetically-related child(ren) (who under ideal circumstances will be free of mitochondrial disease), cannot be met using existing technologies (excepting human nuclear genome transfer). In response, there are many things people want that they cannot (or should not) have.

PART III: CHANGING LENSES

If a woman with mitochondrial disease caused by dysfunctional mtDNA is of reproductive age, wants to have a child(ren), is sufficiently healthy to become pregnant, and specifically wants a genetically-related child(ren), then, according to some, human nuclear genome transfer is a legitimate option. This perspective, however, presumes that the only relevant considerations are patient autonomy and reproductive liberty and, moreover, that it is reasonable to endorse (and respond to) the acquired desire for a genetically-related child(ren). On this view, if a research ethics committee confirms that certain safety and efficacy thresholds have been met, then there is no ethical reason not to proceed with research to develop and perfect human nuclear genome transfer for the specific benefit of women with dysfunctional mtDNA who want genetically-related children.

But are patient autonomy and reproductive liberty, taken together, a sufficiently rich ethical frame for appreciating what 'all' is at stake in researching, developing, and eventually distributing (including selling) this technology? Is it reasonable to expend considerable human and financial resources to respond to individual wants for genetically-related children? My answer to both of these questions is 'no'. In my view, there is good reason to approach this issue from a public health perspective, and to think carefully about the obligation to expend limited human and financial resources to prevent and treat illness in existing persons, to build physically and socially healthy communities, and to eliminate health inequities – thereby privileging shared needs over individual wants.

In this final section of the article, I look at human nuclear genome transfer from a broader societal perspective. I show that this technology, as a therapeutic intervention, will at most respond to the wants of an infinitesimally small number of people and I suggest that this does not warrant the investment of public research funds. I then briefly hint at the fact that there may be other scientific reasons for pursuing this research.

Addressing the wants of the few

Recent calculations by Gráinne Gorman and colleagues – using estimates about the prevalence of potentially inheritable mtDNA mutations in women 15 to 44 years of age, and available data about fertility rates in the UK (1.85 in 2013) and in the US (1.88 in 2012) – suggest that the maximum potential direct benefit of this technology is 152 healthy births per year in the UK (a country of close to 65 million) and 778 healthy births per year in the US (a country of close to 320 million).[76] As given, these numbers are very small and should raise questions about the value of investing in the science of manipulating human embryos to avoid mitochondrial disease caused by dysfunctional mtDNA. Having said this, these very small numbers are probably a significant overestimate.[77] These numbers assume that all women with dysfunctional mtDNA who are at risk of having children with mitochondrial disease will choose to reproduce using egg providers, IVF, and human nuclear genome transfer. For a number of reasons, this assumption is very likely incorrect.

First, some women with dysfunctional mtDNA who are at risk of having children with mitochondrial disease may not want a family that includes children. Second, among those who do want children, some may reasonably choose an option that does not involve pregnancy because of the potential harms to themselves and future offspring that are associated with pregnancy and mitochondrial disease.[78] Third, while some women with dysfunctional mtDNA may choose to take on the risks associated with pregnancy, they may not want the additional risks associated with IVF followed by human nuclear genome transfer. Fourth, among those who want IVF using an egg provider followed by human nuclear genome transfer, there will be some for whom this will not be an option. There are socio-cultural, emotional, infrastructural, geographic, and economic barriers to

[76] G.S. Gorman, J.P. Grady, Y. Ng, A.M. Schaefer, R.J. McNally, P.F. Chinnery et al. Mitochondrial Donation – How Many Women Could Benefit? *N Engl J Med* 2015; 372(9): 885–887.

[77] The estimated number of healthy births per year could also be an underestimate. This would be the case if the original data set (the Mitochondrial Disease U.K. Cohort) which is used to establish the claim that the fertility rate for women with mitochondrial disease is the same as for women without mitochondrial disease, is not representative of the population of persons with mitochondrial disease. How, for example, were the people in the Mitochondrial Disease U.K. Cohort identified? More specifically, were adult women identified through follow-up of an affected child, in which case women without children (by choice or by miscarriage) might be underrepresented? What about women with mitochondrial disease who have had normal children, who are unaware of their status as persons with mitochondrial disease, and who would not be included in the U.K. Cohort?

[78] H. Turnbull, R. Say, M. Smith, V. Nesbitt, R. McFarland, D. Turnbull, & M. Schaefer—The Guideline Development Group. Jun 2011. *Newcastle Mitochondrial Disease Guidelines: Pregnancy in Mitochondrial Disease*. Available at: http://www.mitochondrialncg.nhs.uk/documents/Pregnancy_Guidelines_%202011.pdf [Accessed 27 Jun 2016].

infertility and assisted human reproduction services,[79] and (some of) these barriers will apply to IVF using an egg provider followed by human nuclear genome transfer. Finally, among those women with dysfunctional mtDNA who are able to avail themselves of the technology, some will not succeed in establishing a pregnancy. For these (and other) reasons, the estimated maximum potential direct benefit of 152 healthy births per year in the UK, and 778 healthy births per year in the US is probably a significant overestimate.

Below, I briefly expand on all but the first of these five reasons. All that need be said about the first reason is that not all women yearn to become mothers.

i) Risks associated with pregnancy for women with mitochondrial disease

Little is known about the pregnancy risks for women with mitochondrial disease. These are difficult to document and assess because of differences in the presentation and penetrance of mitochondrial diseases. A systematic review of the literature on mitochondrial disease in pregnancy confirms that preterm labour and preeclampsia are the most common complications.[80] Other negative side-effects include myopathy (negligible exercise intolerance or muscle weakness to the development of severe fatigue), gestational diabetes, symptomatic Wolff-Parkinson-White Syndrome, persistent paraesthesia, and focal segmental glomerulosclerosis.[81] Ongoing research aims to assess whether the increased respiratory demand during pregnancy (and with the onset of labour) is especially problematic for women with mitochondrial disease.[82]

Women with mitochondrial disease might reasonably prefer to avoid the risks of pregnancy and for this reason may choose a family-making strategy that does not involve pregnancy.

ii) Risks associated with IVF followed by human nuclear genome transfer

Women with dysfunctional mtDNA who are at risk of having children with mitochondrial disease who want to consent to (research on) human nuclear genome transfer, must also consent to the use of third party gametes and IVF. IVF is both onerous and risky because of the potential harms associated with egg collection. For a start, the daily hormone injections required to induce egg production can be uncomfortable and painful. In addition, there are the many and varied potential side-effects of hormonal stimulation. Minor side-effects include cramping, abdominal pain, nausea, vomiting, bloating, mood changes and irritability. More serious side-effects include rapid weight gain and respiratory difficulty, damage to other organs such as the bladder, bowel, and uterus, decreased fertility, infertility, and life-threatening hemorrhage, thromboembolism, and ovarian, breast, or colon cancer. In addition to the potential physical harms, there are the potential psychological harms including significant stress and sequelae.[83]

In addition, there are potentially significant short- and long-term health consequences with human nuclear genome transfer for any resulting children and their descendants. In very general terms, the genetic manipulations may not be successful and, worse, new mutations that result in serious harms may be introduced.[84] Bredenoord and Braude put the matter succinctly: 'we do not know … whether a mixture of mtDNA from two different origins is safe'.[85] Safety issues pertaining to offspring that have been identified to date include: (i) damage to the manipulated egg; (ii) carryover of dysfunctional mtDNA and long-term risks associated with heteroplasmy in the resulting children; (iii) nuclear-mitochondrial 'mismatch' and possible epigenetic modification of nDNA; and (iv) abnormal embryo/foetal development.[86] As a result of one or more of these safety issues, children conceived using an egg provider, IVF, and human nuclear genome transfer may be born with serious disorders. In the alternative, these children may be born healthy. In later years, however, they may experience serious health problems attributable to the genetic manipulations. If there are harmful health consequences, and if they only become evident in later life and after these individuals have reproduced, there could be serious 'trickle-down' harms to future generations.

For prospective parents, the potential benefit is the birth of a healthy, genetically-related child(ren). The potential harms are spontaneous abortion, elective abortion following prenatal testing, the birth of a child who dies within a few hours or days after birth, the birth of a child with serious defects, the birth of child with mitochondrial disease (despite the decision to pursue human nuclear genome transfer), the birth of a child with some

[79] E.Y. Adashi & L.A. Dean. Access to and Use of Infertility Services in the United States: Framing the Challenges. *Fertil Steril* 2016; 105(5): 1113–1118.

[80] R.E. Say, R.G. Whittaker, H.E. Turnbull, R. McFarland, R.W. Taylor, & D.M. Turnbull. Mitochondrial Disease in Pregnancy: A Systematic Review. *Obstet Med* 2011; 4(3): 90–94.

[81] Ibid; Turnbull et al., *op. cit*. note 78.

[82] University College London. 2016. *Incidence of Complications of Pregnancy in Patients Diagnosed with Mitochondrial Disease or Carrying a Mitochondrial DNA Mutation*. London, UK: Queen Square for Neuromuscular Diseases. Available at: http://www.cnmd.ac.uk/research/clinical_trial/incidence-of-complications-of-pregnancy-in-patients-diagnosed-with-mitochondrial-disease-or-carrying-a-mitochondrial-dna-mutation [Accessed 9 Sept 2016].

[83] American Society for Reproductive Medicine. Fact Sheet: Side Effects of Injectable Fertility Drugs (Gonadotropins). Available at: http://www.reproductivefacts.org/uploadedFiles/ASRM_Content/Resources/Patient_Resources/Fact_Sheets_and_Info_Booklets/Gonadatrophins-Fact.pdf [Accessed 16 Nov 2016].

[84] Nuffield Council on Bioethics, *op. cit*. note 3.

[85] Bredenoord & Braude, *op. cit*. note 39.

[86] Food and Drug Administration, *op. cit*. note 50: pp.3, 15, 23.

other serious disease or disorder (because of the decision to pursue human nuclear genome transfer), and the birth of a seemingly healthy child who later has children who suffer from some relevantly caused disease or disorder.

For the resulting children, the potential benefit is 'life', as they might not otherwise have come into existence. The potential harms are life with mitochondrial disease, or with some other (potentially more serious) disease or disorder resulting from the genetic manipulations. It is unclear how prospective parents, researchers, research ethics review committees, and society can properly weigh the potential harms and benefits to prospective parents and possible future children, and then affirm that there is a favourable harm-benefit ratio that justifies proceeding with the research.

In any case, some women with dysfunctional mtDNA might reasonably prefer to avoid these health risks to themselves and any resulting children they may have. For this reason they may choose a family-making strategy that does not involve IVF using an egg provider followed by human nuclear genome transfer.

iii) Limited access to IVF

I am not aware of data specifically on access to IVF and so the illustration below relies on data about access to infertility services. This includes, but clearly is not limited to, data on assisted human reproduction and more specifically IVF. Access to IVF and assisted human reproduction services is limited by a number of factors including socio-cultural, emotional, infrastructural, geographic, and economic factors.

As reported in 2001 by the European Society of Human Reproduction and Embryology (ESHRE), approximately 50% of infertile couples seek medical care.[87] As reported by Jacqueline Boivin and colleagues in 2007, an average of 56.1% of infertile couples seek medical care.[88] More recent US specific data published by Anjani Chandra and colleagues in the *US National Health Statistics Reports* suggest that the use of fertility services is much lower: 'When limited to nulliparous women aged 25–44 with current fertility problems, 38% of such women in 2006–2010 had ever used fertility services compared with 56% in 1982.'[89] Notably, during this same time period (2006–2010), there were no significant increases in adoption or voluntary childlessness in the US, suggesting that barriers to access are not inconsequential.

If these data about access to fertility services by infertile women and couples are relevant to women with dysfunctional mtDNA then, contrary to Gorman and colleagues, still fewer than the predicted 152 births per year in the UK and 778 births per year in the US might benefit from IVF using an egg provider followed by human nuclear genome transfer.[90] Quite simply, this is because only a subgroup of the population that might benefit from the technology will be able, or will choose if able, to access it. If, as with access to infertility services, only between 38%-56% of those who could benefit from IVF using an egg provider followed by human nuclear genome transfer are able, and would choose, to access the technology,[91] then the maximum potential direct benefit of the technology is reduced to between 58–85 births per year in the UK (152 x 38% and 152 x 56%) and 296–436 births per year in the US (778 x 38% and 778 x 56%).

As noted above, however, the starting numbers (viz, 152 healthy births per year in the US and 778 healthy births per year in the UK) are probably a significant overestimate. Some women with dysfunctional mtDNA will choose not to have children, some will have children without pregnancy and some will choose pregnancy but without using IVF and human nuclear genome transfer. If the starting numbers are an overestimate, then so too are the reduced numbers. This fact applies to the further analysis below.

iv) Limited success rates with IVF

If we add to the above analysis about access to IVF, the fact that the live birth rate per IVF cycle is not 100%, the maximum potential benefit of IVF using an egg provider followed by human nuclear genome transfer is further reduced. In the UK, the live birth rate per IVF cycle for women of all ages is currently around 26%.[92] This suggests that the maximum potential direct benefit of the technology is reduced from 58–85 births per year in the UK to 15–22 births per year. In the US, the data on live birth rates is provided by age group. For women aged 35–37 the live birth rate is nearly 32%, and for women aged 38–40 it is around 21%.[93] If we take the average of 26% (which coincidentally mirrors the percentage in the UK), then the maximum potential direct benefit of the

[87] The ESHRE Capri Workshop Group. Social Determinants of Human Reproduction. *Hum Reprod* 2001; 16(7): 1518–1526.

[88] J. Boivin, L. Bunting, J.A. Collins, & K. Nygren. International Estimates of Infertility Prevalence and Treatment-Seeking: Potential Need and Demand for Infertility Medical Care. *Hum Reprod* 2007; 22(6): 1506–1512.

[89] A. Chandra, C.E. Copen, & E.H. Stephen. Infertility Service Use in the United States: Data from the National Survey of Family Growth, 1982–2010. *National Health Statistics Report* 22 Jan 2014; 73: 1–21.

[90] Gorman et al., *op. cit*. note 84.

[91] For the record, it is important to note that only a fraction of the 38%-56% who access fertility services access IVF. It follows that suggested numbers for IVF using an egg provider followed by human nuclear genome transfer are an overestimate.

[92] Human Fertilisation & Embryology Authority. 2013. Fertility Treatment in 2013: Trends and Figures. London, UK: Human Fertilisation & Embryology Authority: 17. Available at: http://www.hfea.gov.uk/docs/HFEA_Fertility_Trends_and_Figures_2013.pdf [Accessed 9 Sept 2016].

[93] Centers for Disease Control and Prevention. 2013 Assisted Reproductive Technology Fertility Clinic Success Rates Report. 2015. Available at: ftp://ftp.cdc.gov/pub/Publications/art/ART-2013-Clinic-Report-Full.pdf [Accessed 27 Jun 2016].

technology in the US is reduced from 296–436 births per year to 77–113 births per year. And, as noted above repeatedly, these numbers are probably a significant overestimate.

v) Opportunity costs

While it is possible to argue that the numbers do not matter, and more specifically that the exceedingly low number of potential beneficiaries should not deter us from pursuing human nuclear genome transfer, it seems reasonable to assert that a maximum potential direct benefit of less than 15–22 births per year in the UK and less than 77–113 births per year in the US is inconsequential against the backdrop of a combined total current population in these two countries of close to 400 million.[94] Indeed, these small numbers raise serious questions about the opportunity costs associated with investing limited resources (time, talent, human eggs, and money) into developing a technology that panders to desires acquired through socialization and conditioning (i.e. wants), as contrasted with responding to natural desires (i.e. needs).

Some of these resources could be better spent responding to the needs of those living with mitochondrial disease. In the alternative, some of these resources could perhaps be directed to other health priorities (e.g. providing resources for children in child protective services to improve the speed with which adoptions can be processed so that children spend less time in transient suboptimal conditions). Another alternative would be to direct some of these resources to health priorities that do not rely on medical interventions (e.g. education, or access to clean water).

One who shares my concerns about the ethics of resource allocation and the opportunity costs associated with investing public resources in research to develop (and presumably perfect) IVF using an egg provider followed by human nuclear genome transfer is Rulli. In her estimation, the very small population of affected persons and the non-urgent nature of the situation (notwithstanding inaccurate and exaggerated descriptions of this technology as a life-saving treatment) does not justify the allocation of public research funds.[95] For such spending to be justified, the technology would have to either 'uniquely be able to eradicate mitochondrial disease or be more economical or efficient at doing so.'[96]

Attempts at turning the few into the many

In an effort to shore up the number of potential beneficiaries of human nuclear genome transfer, James Grifo, back in 1997, suggested this technology could also be used to treat age-related infertility.[97] This idea was endorsed in the 2012 Nuffield Council on Bioethics Report[98] and has recently been championed by Shoukhart Mitalipov (the first scientist to clone human embryonic stem cells).[99] Numerically, age-related infertility is a much bigger problem than mitochondrial disease caused by dysfunctional mtDNA (at least in Western countries where increasingly women are delaying childbearing). Another possible use of human nuclear genome transfer, also endorsed in the 2012 Nuffield Council on Bioethics Report,[100] is the use of this technology to increase reproductive options for same-sex couples so that each partner could have a genetic link to their child(ren). Of note, however, these additional optional uses are still about catering to individuals' acquired desires (i.e. wants).

Addressing the needs of the many

From another perspective, there is one context in which it might be possible to consider research on human nuclear genome transfer a genuine need worthy of public investment. Aristotle identifies the need for knowledge as a natural need. From this perspective, one could argue that while there is only limited therapeutic value associated with the development of human nuclear genome transfer technology, there is considerable scientific value that should not be discounted insofar as it responds to the need for knowledge. This may well be the case, but then it becomes important to question the basis on which the technology has thus far been promoted and sanctioned.

My point here is that it may well be that the development of this technology is justified in terms of potential contribution to the need for knowledge, but this is not how the technology is being promoted or how the ethics surrounding it is being debated. The ethics debate has focused on the wants of the few for genetically-related children, not the natural need for knowledge that could potentially benefit the many. This implies that ideology, not proper reasoning, is being used to convince people of the so-called need for this technology – people who might otherwise object to the use of resources required for developing and distributing this technology.

[94] Note, the description "maximum potential direct benefit" assumes that nuclear genome transfer is 100% safe and effective and has no negative effect on the birth rate.
[95] Rulli, *op. cit*. note 17: 39.
[96] Ibid: 45.
[97] See, G. Kolata. 19 Aug 1997. Scientists Face New Ethics Quandaries in Baby-Making. *New York Times*. Available at: http://www.nytimes.com/1997/08/19/science/scientists-face-new-ethical-quandaries-in-baby-making.html?pagewanted=all [Accessed 27 Jun 2016].
[98] Nuffield Council on Bioethics, *op. cit*. note 3, p.82.
[99] S. Connor. 7 Feb 2015. Scientist Who Pioneered 'Three-parent' IVF Embryo Technique Now Wants to Offer it to Older Women Trying for a Baby. *Independent*. Available at: http://www.independent.co.uk/news/science/three-parent-embryos-an-ivf-revolution-or-a-slippery-slope-to-designer-babies-10031477.html [Accessed 9 Sept 2016].
[100] Nuffield Council on Bioethics, *op. cit*. note 3, p.82.

CONCLUSION

The suggestion that ethics lags behind science-and-(bio)-technology should be summarily dismissed. The term 'mitochondrial replacement' should be retired and replaced with the more accurate term 'human nuclear genome transfer'. The claim that people not only need children, but need genetically-related children should be set aside. The fact that some women with dysfunctional mtDNA who are at risk of having children with mitochondrial disease want genetically-related children should not take priority over the natural needs of the many. Our limited resources (time, talent, human eggs, and money) should be carefully expended in pursuit of the common good.[101]

In brief, there are serious opportunity costs associated with the research required to develop (and perfect) human nuclear genome transfer for the purpose of promoting the birth of genetically-related children free of mitochondrial disease. And, for what? To affirm the false belief that genetic relatedness matters, to legitimate the claim that 'rightly or wrongly, people do care about *biological* parenthood'?[102]

To my way of thinking, too much of the discussion and debate about the ethics of human nuclear genome transfer has been distorted by those who would have us focus on the potential benefits of this technology to early adopters, namely women with dysfunctional mtDNA who are at risk of having children with mitochondrial disease. Our focus should be much broader, with particular attention paid to issues of social justice. As I have argued elsewhere:

> While it is the norm to review and fund research on the basis of scientific excellence, we also need to consider social significance. Research resources should be directed to science that is not only excellent, but also socially valuable. At issue here is the ethical acceptability of allocating limited resources to research (and possibly future therapeutic interventions) to meet the needs of a very small minority for whom there are other reproductive options.[103]

Instead of investing limited research resources into avoiding the vertical transmission of mtDNA disease caused by dysfunctional mtDNA, we might usefully address broader (and diverse) reproductive health needs experienced by women in low, middle and high-income countries. In the alternative, we might direct some of these resources to other non-reproductive health priorities or even to other non-health priorities, especially those that could relieve our natural needs. As noted above, natural needs are needs that all humans share in common, including the need for food and drink, clothing, shelter, and sleep, as these are essential for staying alive.

This brings me to a final very brief comment about our failure to critically examine our ongoing efforts to develop reproductive technologies. We are on the verge of a global crisis as regards planetary sustainability owing to climate change, environmental destruction, and population growth.[104] There are billions and billions of us on this planet and our numbers are growing at a staggering rate. As our population grows, so too does the demand for resources including food, air and water quality and energy. And yet, we continue to invest in the development of increasingly esoteric reproductive technologies largely for the benefit of a very small number of persons in high-income countries.[105]

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[101] Baylis et al., *op. cit*. note 4.

[102] S. Wilkinson. 2 Feb 2014. *Mitochondrial Replacement Therapy: Ethics and Identity*. Presentation: Ottawa, ON.

[103] Baylis, *op. cit*. note 16.

[104] Among those who identify the climate crisis as a reproductive crisis is Travis N. Reider. In response to the threat of climate change he advocates a 'small family ethic' and pursuing 'fertility reduction efforts'. See, T.N. Reider. 12 Sept 2016. Why we should have fewer children: to save the planet. *The Guardian*. Available at: https://www.theguardian.com/commentisfree/2016/sep/12/why-we-should-have-fewer-children-save-the-planet-climate-change [Accessed 14 Sept 2016]. See also, T.N. Redier. 2016. *Toward a Small Family Ethic: How Overpopulation and Climate Change Are Affecting the Morality of Procreation*. Springer.

[105] Thanks are owed to Andrew Fenton for encouraging me to comment on this fact. As crowding is a problem for human and environmental sustainability on planet Earth, why are we investing in how to develop new technologies to create more beings? Without human genome nuclear transfer, some at-risk women and couples might use other technologies, but others might choose childlessness, or adoption, or fostering (options that do not involve the creation of new beings). Further, one could reasonably argue that the availability of children in need of families calls into question the use of other available assisted reproductive technologies solely motivated by a 'want' for a genetically-related child(ren).