NUFFIELD COUNCIL ON BIOETHICS

BACKGROUND PAPER

Germline therapies

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American Association for the Advancement of Science (AAAS)
Washington, DC, USA

Forward Look
19-20 May 2011

Note
The authors were commissioned by the Nuffield Council on Bioethics to write this paper in order to inform the Council's discussions about possible future work on this topic. The paper is intended to provide an overview of key clinical, ethical, social, legal and policy issues, but is not intended to offer any conclusions or recommendations regarding future policy and practice. Any views expressed in the paper are the views of the authors and not those of the Nuffield Council on Bioethics.

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Summary

1 This paper reviews the issues precipitated by scientific advances in proposed treatment of mitochondrial disease by genetic modification. It discusses those advances and the accompanying ethical and policy issues as research on such therapy moves forward.

Introduction: germline therapy

2 The term "germline" refers to genetic material that is hereditable from parent to child. Historically, the discovery of DNA, elucidation of its structure, and refinement of recombinant DNA methods raised significant concern about the potential for intentional or inadvertent genetic modification of human germline DNA, as these changes would be passed down to all subsequent generations. After extensive discussion and some degree of consensus on the topic a decade ago, recent years have seen comparatively little consideration of the ethics of germline modification. Initial concern was theoretical, however. Recent developments in techniques intended to prevent mitochondrial disease, particularly by the Newcastle group under Human Fertilisation and Embryology Authority (HFEA) license, and possible legislative changes in the UK prompt a timely revisiting of the topic.

Mitochondrial disease

3 Mitochondrial diseases are caused by disorder of oxidative phosphorylation, a process by which cellular energy is produced, and may result from either nuclear DNA (nDNA) or mitochondrial DNA (mtDNA) mutation. The proportion of individuals affected, though difficult to determine, is estimated[1] to be 1 in

[1] Schaefer, A.M. et al. (2004). The epidemiology of mitochondrial disorders – past, present and future. *Biochimica et Biophysica Acta 1659,* 115-120.

5000. Furthermore, research suggests as many as 1 in 200 people[2] may at birth carry one of a number of identified pathogenic mtDNA mutations. Mitochondrial diseases, which preferentially affect postmitotic tissues such as brain and muscle, are progressive, severely debilitating, and often fatal. Treatment for mitochondrial disease is merely palliative, not curative. Due to the expense of treatment and loss of function in affected individuals, mitochondrial diseases collectively present a large burden to society. Prevention of the onset of disease is the ultimate treatment goal for families that carry mtDNA mutations.

4 Prevention of mtDNA disease is complicated by the fact that its non-Mendelian pattern of heredity is different from that of most genetic disorders. MtDNA is typically passed on from mother to child through the cytoplasm of the egg gamete (ooplasm). Only in very rare instances does the father contribute to any portion of the child's mtDNA.[3] Unlike nDNA in the embryo, which is passed on from parents to child as a single, diploid set of chromosomes, mtDNA exists in multiple cytoplasmic mitochondria which may be genetically different – a condition termed heteroplasmy. A mitochondrial disease phenotype is very commonly heteroplasmic. Furthermore, in oocyte genesis mitochondria pass through a genetic bottleneck such that comparatively few mitochondria from the mother hereditably become the mitochondria of the child. Since mothers with a mitochondrial genetic mutation are often heteroplasmic, and the mitochondrial genetic bottleneck dictates that only a few mitochondria contribute to the genotype of offspring, the chance that a given child of an affected mother will be susceptible to mtDNA disease can be difficult to predict.

5 Ethical questions that arise from mtDNA disease treatment depend significantly on the state of the science. Thus, an understanding of different techniques of mitochondrial donation and alternative preventive treatment options is necessary.

State of the science of mitochondrial disease prevention

Nuclear Transfer

6 A hypothetical use of nuclear transfer (NT) in the prevention of mtDNA disease was proposed in 1995.[4] In recent years, technical advances have made remarkably similar procedures imminently feasible. NT, a technique shared by forms of reproductive cloning, involves the transfer of an intact nucleus and its nuclear DNA from one cell to another with its nucleus previously removed.[5] In

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2 Elliott, H.R. et al. (2008). Pathogenic mitochondrial DNA mutations are common in the general population. *The American Journal of Human Genetics 83,* 254-260.

3 Schwartz, M. and Vissing, J. (2002). Paternal inheritance of mitochondrial DNA. *The New England Journal of Medicine 347*(8), 576-580.

4 Rubenstein, D. S. et al. (1995). Germ-line therapy to cure mitochondrial disease: protocol and ethics of *in vitro* ovum nuclear transplantation. *Cambridge Quarterly of Healthcare Ethics 4,* 316-339.

5 St John, J.C. and Campbell, K.H.S. (2010). The battle to prevent the transmission of mitochondrial DNA disease: is karyoplast transfer the answer? *Gene Therapy 17,* 147-149.

2003 in China, an otherwise-infertile woman became pregnant through use of NT, though the fetus did not survive to term.[6]

7 To ensure prevention of mtDNA disease, NT must achieve complete or near-complete substitution of donor mtDNA for parental mtDNA.[7] In 2010 a UK-based mitochondrial disease research group, referred to in this paper as the Newcastle group, announced the successful transfer of donor pronuclei from an abnormally fertilized embryo to a recipient egg. Their version of NT, pronuclear transfer, resulted in minimal carryover of donor mtDNA, and a number of experimental embryos survived to the blastocyst developmental stage *in vitro*, at which point researchers ended the experiment as per the terms of their research license.[8] Similarly, in 2009 researchers in the United States produced healthy nonhuman primate offspring using a technique termed spindle transfer, which transfers the meiotic metaphase II spindle from one egg to another for eventual fertilization and implantation. This technique also exhibited minimal carryover of donor mtDNA.[9] However, NT experiments done in nonhuman primates and human embryos have not yet modeled mtDNA disease.

Animal models

8 Animal models of mtDNA disease do exist in certain breeds of mice, termed "mito-mice."[10] In 2005, a research group in Japan successfully eliminated mtDNA disease in a particular type of mito-mice through NT.[11] Many obstacles to extending the success of these mouse model experiments exist. Foremost is the development of similar models in higher animals, needed because of the much longer lifespan of humans as compared to mice.

Alternatives to NT

9 Preimplantation Genetic Diagnosis (PGD) and Prenatal Diagnosis (PND) have been proposed to detect mtDNA mutation and reduce the risk of giving birth to a child affected by mitochondrial disease.[12] PGD is a genetic analysis performed on a cell sample taken from an *in vitro* embryo after its fertilization, but prior to transfer to the prospective mother's womb. In clinical practice, PGD involves sampling of a number of candidate embryos and selecting a subset for transfer.[13] In contrast, PND is performed during pregnancy by analyzing DNA

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6 Zhang, J. et al. (2003). Pregnancy derived from human nuclear transfer. *Fertility and Sterility 80*(3), 56.

7 Spikings, E.C. et al. (2006). Transmission of mitochondrial DNA following assisted reproduction and nuclear transfer. *Human Reproduction Update 12*(4), 401-415.

8 Craven, L. et al. (2010). Pronuclear transfer in human embryos to prevent transmission of mitochondrial DNA disease. *Nature*, *465*(7294), 82-85.

9 Tachibana, M., et al. (2009). Mitochondrial Gene Replacement in Primate Offspring and Embryonic Stem Cells. *Nature, 461*(7262), 367-372.

10 Wallace, D.C. (2002). Animal models for mitochondrial disease. In W. C. Copeland (ed.), *Methods in Molecular Biology, vol. 197: Mitochondrial DNA: Methods and Protocols* (pp. 3-54). Totowa, NJ: Human Press, Inc.

11 Sato, A. et al. (2005). Gene therapy for progeny of mito-mice carrying pathogenic mtDNA by nuclear transplantation. *Proceedings of the National Academy of Sciences, 102*(46), 16765-16770.

12 Dean, N.L. et al. (2003). Prospect of preimplantation genetic diagnosis for heritable mitochondrial DNA diseases. *Molecular Human Reproduction, 9*(10), 631-638.

13 Sermon, K. et al. (2004). Preimplantation genetic diagnosis. *The Lancet, 363,* 1633-1641.

from the fetus.[14] Traditional PND techniques, such as amniocentesis and chronic villus sampling, may soon be joined by a non-invasive method, maternal serum cell-free fetal DNA testing. Although not yet ready for wide use as a diagnostic, its non-invasive feature of requiring only a blood sample from the pregnant woman will likely make it an attractive option relative to current methods.[15] For certain mtDNA mutations, the proportion of mutant heteroplasmy, and, therefore, likelihood of disease in the child, can be detected by either PGD or PND. Ethical concerns about PGD and PND are discussed below.

10 Ooplasm transfer (OT), the supplementation of recipient egg ooplasm with injected donor ooplasm, has been shown in animal models to pass on donor mtDNA.16 OT has been previously proposed as a possible method to prevent mtDNA disease. Critics of the method contend that it results in a high degree of mitochondrial heteroplasmy that is itself a health risk, and also OT may not effectively treat mtDNA disorder due to high levels of remaining mother's mtDNA. As such, OT is not a favored approach.[17] Indeed, use of the technique a decade ago18 led to widespread alarm and its de facto prohibition by the US Food and Drug Administration (FDA).[19]

Ethical issues: mtDNA and the germline

11 Much of the extensive past debate on the ethics of germline genetic modification need not be revisited in this paper.[20] However, the emergence of new or refined techniques and the possibility of mitochondrial donation as a germline modification test case raise issues surrounding the germline that may be informed by and also challenge previous discussions.

Definition of "germline"

12 Previously, this paper defined "germline" as hereditable genetic material. Originally, the germline was considered to refer to gametes, the sperm or eggs

[14] Prenatal Diagnosis. Available at: http://ghr.nlm.nih.gov/glossary=prenataldiagnosis

[15] Greely, H.T. and King, J.S. (2010). The coming revolution in prenatal genetic testing. *Professional Ethics Report 23*(2), 1-3.

[16] Ferreira, C.R. et al. (2010). Pronounced segregation of donor mitochondria introduced by bovine ooplasmic transfer to the female germ-line. *Biology of Reproduction 82,* 563-571.

[17] Fulka, J. et al. (2007). Transmission of mitochondrial DNA disorders: possibilities for the elimination of mutated mitochondria. *Cloning and Stem Cells 9*(1), 47-50.

[18] Barritt, J.A. et al. (2001). Mitochondria in human offspring derived from ooplasmic transplantation: Brief communication. *Human Reproduction 16,* 513-516.

[19] Zoon, K.C. (2001). Human cells used in therapy involving the transfer of genetic material by means other than the union of gamete nuclei [letter]. U.S. Food and Drug Administration. Available at: http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ucm105852.htm

[20] For a look at this past debate, see: Chapman, A.R. and Frankel, M.S. (Eds.). (2003). *Designing our descendants: The promises and perils of genetic modifications.* Baltimore and London: The Johns Hopkins University Press.

in the human body passed on to the next generation in the course of reproduction.[21] In the context of mitochondrial donation, which is done in either the egg or the embryo, the gamete-specific germline definition seems less relevant, as the embryo eventually differentiates into all tissues, including gametes. In place of germline, some prefer the term "inheritable genetic modification" (IGM). IGM more clearly captures the variety of ways in which information may be passed to the next generation – through nuclear and extra-nuclear genomes such as the mitochondrial genome, as well as the epigenome.[22] Regardless of the term or definition used, types of genetic heredity and possible distinctions between them should be noted.

Distinction between nDNA and mtDNA

13 Past discussion of germline genetic modification has had primary, though not exclusive, focus on nDNA. For ethical purposes, clarification of any meaningful conceptual distinction between mtDNA and nDNA is necessary. Several differences exist, not least of which is size. In humans, the nuclear genome contains around 20,000-25,000 genes, whereas the mitochondrial genome consists of a mere 37 genes, of which only 13 code for proteins.[23] These mtDNA gene products are used exclusively in mitochondrial function. nDNA, on the other hand, codes for the remainder of human tissues, including a range of physical and personal characteristics. Furthermore, some believe that the "endosymbiont hypothesis" – the theory that the mitochondrion organelle evolved from a symbiotic relationship between eukaryotes and a type of foreign bacterium specializing in energy production – indicates a fundamental difference between nDNA and mtDNA based on origin.[24] A distinction between the practice of nDNA and mtDNA genetic modification is the level of cellular intervention required for each.[25] Mitochondrial donation, the mechanism of genetic modification in question in this paper, entails donation of whole, intact mitochondria. Neither the nuclear envelope nor mitochondrial membranes need be disturbed to achieve the desired result, nor are recombinant DNA techniques required. In contrast, nDNA germline modification would, at least, require penetration into the nucleus and probably DNA recombination to effect gene transfer, both of which are of greater technical complexity and imply greater safety concerns.

14 Because of the differences noted above, some researchers and clinicians restrict the definition of germline modification to modification of nDNA alone.[26]

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21 Cited in Juengst, E. and Parens, E. (2003). Germ-line dancing: Definitional considerations for policy makers. In Chapman, A.R. and Frankel, M.S. (Eds.), *Designing our descendants: The promises and perils of genetic modifications* (pp. 20-36). Baltimore and London: The Johns Hopkins University Press.

22 Juengst and Parens, supra, (2003)

23 Mitochondrial DNA. Available at: http://ghr.nlm.nih.gov/chromosome/MT

24 Cited in Bonnicksen, A.L. (1998). Transplanting nuclei between human eggs: implications for germ-line genetics. *Politics and the Life Sciences 17*(1), 3-10.

25 Rubenstein, supra, (1995)

26 North East England Stem Cell Institute (NESCI). (2008). Briefing paper on the need to protect the future possibility of treating mitochondrial disease and other conditions by a procedure that involves mitochondrial transplantation. Available at:

However, many argue that mtDNA modification does indeed amount to germline modification.[27,28,29] Since mtDNA and nDNA both contribute gene products to cellular energy processes and engage in regulatory crosstalk,[30] mutation and disorder in either the mtDNA or the nDNA genes affecting energy production can be severely debilitating to the affected person. Based on this functional similarity, classifying nDNA as part of the germline and mtDNA as not may seem arbitrary. However, even if altering mtDNA modifies the germline, there may still be ethical distinctions between types of germline modification.

Principle, or degree of germline change

15 The possibility of different types of germline changes suggests the question: Is germline modification ethically indefensible in principle, or is there a degree of germline modification that may be acceptable? The differences between mtDNA and nDNA modifications explained above could be used as justification for ethical distinction between types of germline modification. It has already been proposed that, in light of the prospect of mitochondrial donation through both OT and NT, a more nuanced germline debate is due.[31] MtDNA and nDNA germline modification will entail different purposes, methods, and safety concerns, or a larger or smaller extent of change. Any of these factors could serve as conditions for the acceptability of a particular germline modification.

MtDNA and identity

16 The mitochondrial donation test case in particular raises the issue of identity, which warrants special attention because the prospect of altering the identity of the future child has been cited as support for the position that germline modification is ethically unacceptable.[32] Furthermore, as discussed in the policy section below, a number of governments and international organizations have adopted statements protecting the right of an individual to an "unaltered genetic identity."[33]

17 Different constituencies have conflicting perspectives on the effect of mtDNA on identity. The HFEA in 2005 narrowly defined mtDNA as not part of the “genetic structure“of the cell and “not associated with identity.”[34] In contrast, some

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http://www.nesci.ac.uk/assets/docs/NESCIbriefon2008HFEbill-MitochondrialTransplants-Vers01-6.pdf

27 Bredenoord, A.L., et al. (2008). Ooplasmic and nuclear transfer to prevent mitochondrial DNA disorders: conceptual and normative issues. *Human Reproduction Update, 14*(6), 669-678.

28 Bonnicksen, supra, (1998)

29 Robertson, J.A. (1998). Oocyte cytoplasm transfers and the ethics of germ-line intervention. *Journal of Law, Medicine, and Ethics 26,* 211-220.

30 Lloyd, R.E. et al. (2006). Aberrant nucleo-cytoplasmic cross-talk results in donor cell mtDNA persistence in cloned embryos. *Genetics 172,* 2515-2527.

31 Robertson, supra, (1998)

32 Cited in Bredenoord, A.L., et al. (2011). Ethics of modifying the mitochondrial genome. *Journal of Medical Ethics, 37*(2), 97-100.

33 Holtug, N. (1998). Identity, integrity, and nuclei transplantation. *Politics and the Life Sciences 17*(1), 20-21.

34 HFEA. (2005). Mitochondrial DNA disorders – is there a way to prevent transmission? Summary of how the HFEA made its decision to license this project of research. Available at:

ethicists have argued that mtDNA has significant effect on identity.[35] Differences over whose identity is at stake complicate analysis of the issue. Clearly, in some respect, the resulting child is the individual to whom identity concerns apply. Many ethicists claim, however, that when genes, even mitochondrial genes, are modified, the identity of the resulting child changes to such an extent that a *different* child is produced.[36] Whose right to an unaltered genetic identity do we protect in the case of mitochondrial donation, if a different child results?

The nuclear germline slippery slope

18 Position on the impact of mtDNA on identity could lead down an ethical slippery slope. A very recently published paper argues, "As we concluded earlier that modification of the mtDNA is not substantively different from modification of the nuclear DNA in terms of its effects on the identity of the future person, any conclusion regarding the moral acceptability of modifying the mtDNA applies mutatis mutandis[37] to modification of the nuclear genome."[38] Thus, discussion of distinction between nDNA and mtDNA is critical to the slippery slope from mtDNA germline modification to nDNA germline modification. To be sure, safety and efficacy concerns are amplified in the prospect of nDNA modification. However, if it can be concluded that mtDNA contributes to one's identity, and that mtDNA modification is acceptable, one might ask whether a significant step has been made on the path to nDNA germline modification.

The enhancement slippery slope

19 The limited, but nevertheless emerging successes of gene therapies as well as ongoing animal research have led to increasing interest in the applications of the techniques of gene therapy to competitive sport.[39] Scientists have reported using oral drugs to activate a "genetic switch" that turned laboratory mice into long-distance runners and conferred many other benefits of exercise.[40] Likewise, since "[g]ood mitochondrial DNA could facilitate athleticism, and reduce risk for obesity or diabetes," refinement of mitochondrial donation presents the possibility of a slippery slope from treatment of mtDNA disease to enhancement of normal energy production capabilities.[41] This interaction between mtDNA and enhancement raises important ethical and social issues that merit broader discussion.

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http://www.hfea.gov.uk/docs/R0153_How_the_decision_was_made_to_licence_this_research_project__2_.pdf

35 Ossorio, P.N. (2003). Inheritable genetic modifications: Do we owe them to our children? In Chapman, A.R. and Frankel, M.S. (Eds.), *Designing our descendants: The promises and perils of genetic modifications* (pp. 252-271). Baltimore and London: The Johns Hopkins University Press; Bredenoord, supra, (2011)

36 Holtug, supra, (1998); Ossorio, supra, (2003); Bredenoord, supra, (2011)

37 analogously

38 Bredenoord, supra, (2011)

39 Friedmann, T. et al. (2010). Gene doping and sport. *Science 327*(5966), 647-648.

40 Narkar, V.A. et al. (2008). AMPK and PPARδ agonists are exercise mimetics. *Cell 134*(3), 405-415.

41 Waters, R. (2009, August 26). Gene mix in monkeys fixes defects, opens new ethics debate. *Bloomberg.* Available at: http://www.bloomberg.com/apps/news?pid=21070001&sid=aMTU6ucOhbnw

Ethics of intergenerational clinical practice: subjects, patients, informed consent, and safety

20 Aside from broad ethical issues surrounding germline therapies, there are specific issues with regard to mitochondrial donation and clinical practice. Presumably, current practice of mitochondrial donation would be a therapy targeting serious disease, rather than an enhancement of normal human capability. Medical administration of a therapy implies a subject/patient, who may give informed consent and subsequently be treated. Who, then, is the subject of the mitochondrial donation therapy? If mitochondrial donation is successful, the resulting child will not have mtDNA disease, and never will have had such disease. Is it accurate to say this child was "treated"? Is, instead, the parent the subject of therapy?[42] The parent(s) will provide consent and undergo some form of treatment, e.g., standard IVF cycles. However, the substantive, novel component of mitochondrial donation treatment, nuclear transfer and swap of genetic material, will occur *in vitro* and develop into a distinct person.

21 Informed consent is a common concern in investigational biomedical treatments with uncertain risks and benefits. mtDNA donation procedures evoke further concern with respect to informed consent because they involve not only the patient or subject at hand, but also future generations.[43] The idea of "proxy consent" has developed to address the issue of the need for parental consent to a treatment in a child's best interests. However, it may be a stretch, ethically speaking, to extend proxy consent across multiple generations, indefinitely into the future.[44]

22 Similarly, the intergenerational nature of heritable genetic modification suggests a higher threshold of safety because treatment may impact all succeeding generations. Animal studies cited above, which demonstrate the effective treatment of disease in mice and the feasibility of mitochondrial donation in non-human primates, have reported results from only one generation of offspring. To inform first-in-human use, safety and efficacy data will need to be collected from experiments in mice and in higher animals extending across multiple generations. Additionally, a recent HFEA report,[45] "Scientific review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception," recommends more research on early human embryos before human application of mitochondrial donation, and, following human use, tracking of data on health effects for an "extensive period."

Mitochondrial donation: an embryonic transplant?

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[42] Graumann, S. and Haker, H. (1998). Some conceptual and ethical comments of egg cell nuclear transfer. *Politics and the Life Sciences 17*(1), 17-19.

[43] Bonnicksen, supra, (1998)

[44] Frankel, M.S. and Chapman, A.R. (2000). Human inheritable genetic modifications: assessing scientific, ethical, religious, and policy issues, p. 34. Washington, DC: American Association for the Advancement of Science.

[45] HFEA. (2011). Scientific review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception, paragraphs 6.2 and 6.9. Available at: http://www.hfea.gov.uk/docs/2011-04-18_Mitochondria_review_-_final_report.PDF

23 Researchers in the Newcastle group have used the term “mitochondrial transplantation” to refer to their developed technique of swapping pronuclei into a donor egg.[46] Typically, a transplant refers to the exchange of a tissue or organ from a donor to a recipient in response to a recipient’s medical need. Mitochondrial donation, in contrast, is exchange of cellular organelles. Organelles serve an analogous function in cells to that of organs in the body, but are much different in other ways. In terms of size, organelles are subcellular structures present in all cells, whereas organs are specialized, particularly configured collections of differentiated cells. A comparison has been made to the relatively small amount of genetic material exchanged in both organ transplant and mitochondrial donation, but in the case of mitochondrial donation, the genetic material is passed on to subsequent generations. Organ transplants do not typically affect the genetic germline of the recipient.[47]

The expressivist argument

24 There is a tension between policies that favor reproductive choice and respect for persons with genetic disabilities. The "expressivist argument" contends that seeking to eliminate certain disabilities through genetic intervention is discriminatory against those who currently suffer from such conditions and those diagnosed with them in the womb.[48] Part of the expressivist argument relies upon classifying the disability in question as an element of the identity of the disabled person,[49] a position explained in a statement by the UK Human Genetics Commission that “the aim of ‘eradicating rare hereditary diseases’ from a population may imply lack of respect for the dignity of people living with genetic conditions and, in particular, express the morally unacceptable proposition that it is undesirable to have people with such conditions as members of society.”[50] Of relevance in this paper is whether nuclear transfer and mitochondrial donation are viewed as treatment that would prevent having to abort a fetus or select an unaffected embryo using PGD, and, as such, would be more acceptable to those endorsing the expressivist argument. Some have argued, however, that the expressivist argument fails to make the distinction, seemingly equating “eliminating the dysfunction [through treatment] and eliminating the dysfunctional individual [via abortion],”[51] a position that others have criticized as leading to “absurd consequences.”[52]

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46 NESCI, supra, (2008)

47 But consider the transplant of ovaries. See Wong ,T.T. et al. (2011). Zebrafish germline chimeras produced by transplantation of ovarian germ cells into sterile host larvae. *Biology of Reproduction,* published online January 19, 2011. Available at: http://www.biolreprod.org/content/early/2011/01/17/biolreprod.110.088427.full.pdf

48 Parens, E. and Asch, A. (2000). The disability rights critique of prenatal genetic testing: reflections and recommendations. In Parens, E. and Asch, A. (Eds.), *Prenatal testing and disability rights* (pp. 3-43). Georgetown: Georgetown University Press.

49 Edwards, S.D. (2004). Disability, identity and the “expressivist objection.” *Journal of Medical Ethics 30,* 418-420.

50 Human Genetics Commission. (2009). Re: “Proposal for a Council recommendation on a European action in the field of rare diseases.” Available at: http://www.hgc.gov.uk/Client/document.asp?DocId=197&CAtegoryId=8

51 Nelson, J.L. (2000). Prenatal diagnosis, personal identity, and disability. *Kennedy Institute of Ethics Journal 10*(3), 213-228.

52 Edwards, supra, (2004)

A child with three parents?

25 Use of a donor egg cytoplasm in mitochondrial donation implies possible concerns about genetic parenthood similar to those already presented by the use of donor gametes in assisted reproductive technologies. Whether the mitochondrial donor is thought to be a like a transplant donor or a genetic parent is pertinent to discussion surrounding parenthood (see paragraph 23 above). However, the mitochondrial donor is unlike a transplant donor because she contributes genes to the resulting child, and is also unlike a genetic parent because she contributes only a very small proportion of the typical genetic complement passed on by a genetic mother. Should the donor of mitochondrial genes be treated as a third parent, and if so, with what social or legal significance?[53] This issue will likely have special import for matrilineal cultures, where matrilineal primogeniture has implications for inheritance and "blood-line" successions.

Reproductive alternatives

26 Since reproductive options available impact the use of mitochondrial donation, the ethics of these options should be explored. PGD and PND, particularly non-invasive PND, mentioned above as a possible method of screening for embryos or fetuses, bring with them a number of serious ethical and legal issues. The benefits of non-invasive PND are substantial. It poses virtually no risk to mother or the fetus. Diagnosis would be earlier in pregnancy than is now possible, result in lower medical costs, and, when chosen as an option, would lead to safer terminations of a pregnancy. The ethical issues raised by this emerging technology are very similar to those raised by current PND techniques. However, in this case, the potential users/market for a non-invasive diagnostic method will likely increase considerably beyond the numbers now availing themselves of existing techniques, making it imperative that the individual and social consequences accompanying such an expansion be carefully thought through.[54] Complicating analysis is the fact that for both PGD and PND, diagnosis of eventual emergence of mtDNA disease is fundamentally uncertain; PGD and PND may measure the percentage of mtDNA mutant heteroplasmy, but uncertainty and variability in development of mtDNA disease in a given individual can lead to false positive and false negative diagnoses.[55] There are other ethical issues. For PND, selective abortion of the fetus is morally contentious, while for PGD, selection of favorable transfer or disposal of embryos with unfavorable traits is likewise controversial.

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[53] Robertson, J.A. (1999). Reconstituting eggs: The ethics of cytoplasm donation. *Fertility and Sterility 71*(2), 219-221.

[54] Benn, P.A. and Chapman, A.R. (2009). Practical and ethical considerations of noninvasive prenatal diagnosis. *Journal of the American Medical Association 301*, 2154-2156.

[55] Bredenoord, A.L. et al. (2008). Dealing with uncertainties: ethics of prenatal diagnosis and preimplantation genetic diagnosis to prevent mitochondrial disorders. *Human Reproduction Update 14*(1), 83-94.

27 Most approach mitochondrial donation with the assumption that the essence and right of parenting is to replicate the DNA of the parents.[56] To what extent should society facilitate what some term a "felt need"? After all, the options of traditional egg donation and adoption already exist. In the case of egg donation, the resulting child would still be the genetic child of one of the two parents, if the father's sperm is used to fertilize the donated egg. Study of child development outcomes in cases of gamete donation is ongoing, but evidence suggests that such children do well, overall.[57] Others contend that genetic parenthood is a "real human good" that benefits societies and individuals, but should be tempered with concerns about the equitability of what is likely to be an expensive treatment.[58] If genetic parenthood is considered a positive right to be assisted by society, then the limits of that right should be clearly delineated.

Sex selection

28 Sex selection could be used in combination with either PGD or NT as a way to eliminate the risk of transmission of any potential remaining mtDNA mutations to subsequent generations.[59] Since mtDNA is maternally transmitted, selecting for males would exclude an undesirable mtDNA mutation from the blood line. However, whether male or female, the as-of-yet unborn child would bear equal risk of developing mtDNA disease. According to the HFEA, "In the UK sex selection is only allowed for medical reasons," to prevent sex-linked genetic disorder.[60] When applied to the intergenerational prevention of mtDNA disease, though, is sex selection done for appropriate "medical reasons?" Concern has been raised that sex selection for the purpose of eliminating disease in future generations[61] may confuse "doing something for a medical reason" with "having a good medical reason to do it."[62]

Moral status of the embryo

29 Discussion of the moral status of the human embryo is beyond the scope of this paper. However, it should be noted that the two nuclear transfer methods proposed to prevent mtDNA disease differ in a significant respect: pronuclear transfer involves transfer of the nuclei of a human embryo into a donor egg,

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56 McGee, G. and McGee, D.B. (1998). Nuclear meltdown: ethics of the need to transfer genes. *Politics and the Life Sciences 17*(1), 26-29.

57 See: Golombok, S. et al. (2006). Non-genetic and non-gestational parenthood: consequences for parent-child relationships and the psychological well-being of mothers, fathers and children at age 3. *Human Reproduction 21*(7), 1918–24; Golombok, S. et al. (2004). Parenting infants conceived by gamete donation. *Journal of Family Psychology 18*(3), 443–52; Owen, L. and Golombok, S. (2009). Families created by assisted reproduction: parent-child relationships in late adolescence. *Journal of Adolescence 32*, 835–48.

58 Cahill, L.S. (1998). Genetics in context: beyond autonomy and the market. *Politics and the Life Sciences 17*(1), 14-16.

59 Bredenoord, A.L. et al. (2010). Avoiding transgenerational risks of mitochondrial DNA disorders: a morally acceptable reason for sex selection? *Human Reproduction 25*(6), 1354-1360.

60 HFEA. Sex selection. Available at: http://www.hfea.gov.uk/pgd-sex-selection.html

61 For example, in order to eliminate the X-linked disorder hemophilia from the descendants of affected men in Spain, clinicians have already used a strategy of selecting for unaffected male embryos in order to avoid hemophilia-carrier female embryos.

62 HFEA. Sex selection: choice and responsibility in human reproduction, p. 22. Available at: http://www.hfea.gov.uk/docs/Sex_Selection_choice_and_responsibility.pdf

while spindle transfer is done in the developing egg, prefertilization. Thus, those who morally object to research on or manipulation of human embryos may have a distinct preference for the spindle transfer technique of mitochondrial donation. Neither technique is permitted for treatment under current UK law.

Social justice: access to treatment

30 Assisted reproductive technology (ART) is expensive, and different countries provide or require varying amounts of reimbursement for it.[63] ART poses both economic burden and benefit that may be more or less equitably distributed. Some argue that medical practitioners have an obligation to reduce costs of ART as much as is practical,[64] and the prospect of public funding of ART demands "equitable allocation of resources, since many mothers and children lack even basic perinatal care."[65] Furthermore, any government regulation of or reimbursement for assisted reproduction technologies suggest the possibility of discrimination against non-traditional family structures and individuals who may not comport to socially-approved parenting practices.[66]

31 Critical to the social justice issues raised by mitochondrial donation is to what degree carrying a mtDNA mutation can be considered a medical condition for which treatment is necessary. Infertility is recognized as a medical condition in many developed countries, but will carrying a deleterious mtDNA mutation be recognized as such, and, if so, what treatments should be authorized in light of reproductive options? How many IVF/mitochondrial donation procedures should be covered? It has been suggested that funding a discrete number of treatments per patient is equitable.[67]

Positions taken

32 Much of this paper concerns the relation of mtDNA modification to perspectives on germline modification. Specific positions have been taken on both the mitochondrial donation issue and germline therapies more generally. On mtDNA, the HFEA has judged that it is not identity determining, does not exist as the "genetic structure" of the cell, and is over-ridden by nDNA when nuclei are swapped.[68]

33 On the issue of germline modification generally, some organizations hold a position that germline modification is not ethically permissible now or in the future.[69] Other international organizations such as UNESCO have adopted

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63 Connolly, M.P. et al. (2010). The costs and consequences of assisted reproductive technology: an economic perspective. *Human Reproduction Update 16*(6), 603-613.

64 Pennings, G. et al. (2008). ESHRE Task Force on Ethics and Law 14: Equity of access to assisted reproductive technology. *Human Reproduction 23*(4), 772-774.

65 Cahill, supra, (1998)

66 Peterson, M.M. (2005). Assisted reproductive technologies and equity of access issues. *Journal of Medical Ethics 31,* 280-285.

67 Pennings, supra, (2008)

68 HFEA, supra, (2005). Mitochondrial DNA disorders – is there a way to prevent transmission?

69 Council for Responsible Genetics. (2001). Position paper on human germline manipulation. Available at: http://www.councilforresponsiblegenetics.org/ViewPage.aspx?pageId=101

statements expressing serious concern about germline modification (see below).

34 Intermediate positions that consider mtDNA modification to be significant germline modification yet still ethically permissible are possible. An example is the argument that nuclear transfer for mtDNA disorder protects a child's right to an open future, and as such should be allowed pending appropriate safety and efficacy considerations.[70] Other possible arguments for mtDNA donation that could be used as justification are:[71] (1) genetic diseases may morally require doctors to use the best available treatments, (2) parental rights may dictate their access to any technology that could be used to have a healthy child, and (3) scientific freedom, a perspective that argues against unduly restricting scientists from pursuing sensitive research topics.

Policy and regulation

35 With respect to reproductive and genetic technologies, methods of oversight should be evaluated with an eye toward maximizing benefit and minimizing risk. Policies and regulations can significantly influence research on the technique of mitochondrial donation and eventual practices. A variety of regulatory approaches exist nationally and internationally, which may vary in type from proscriptive or pre-emptive to gradual and incremental.[72]

Regulation in the UK

36 Regulation of reproductive technology is most complete and consistent in the UK, where it is overseen by the HFEA. The HFEA, created by the HFE Act of 1990, oversees the licensing of human embryo research and of ART clinical procedures, among its other duties. Regulation employs a mixture of proscriptive and incremental policies that are dictated in part by HFE Act language. Licensable subject matter is subject to approval based on safety, efficacy, and other concerns.

37 The HFE Act was amended in 2008 with an eye toward the developments in mitochondrial disease research discussed in this paper. The 2008 amendment allows for further Parliamentary action specific to permitting licensing of techniques of nuclear transfer and mitochondrial donation for treatment of mitochondrial disease. In February of this year, the HFEA publicly called for scientific evidence in support of the safety and efficacy of methods to prevent mitochondrial disease.[73] A report[74] of the HFEA review was submitted to the

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70 Bredenoord, supra, (2011)

71 Wivel, N.A. and Walters, L. (1993). Germ-line gene modification and disease prevention: some medical and ethical perspectives. *Science 262,* 533-538.

72 Knoppers, B.M. (1998). Geneticism and the germ line: between courage and caution. *Politics and the Life Sciences 17*(1), 22-24.

73 HFEA. (2011). Call for evidence: Scientific review of the methods to avoid mitochondrial disease. Available at: http://www.hfea.gov.uk/docs/2011-02-17_Mitochondrial_review_-_priming_document_-_call_for_evidence.pdf

74 HFEA. (2011). Scientific review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception. Available at: http://www.hfea.gov.uk/docs/2011-04-18_Mitochondria_review_-_final_report.PDF

Department of Health on April 18, 2011. The HFEA has closely monitored developments related to mitochondrial disease prevention techniques in the past, conducting reviews of germline gene transfer in February 2008, genetic modification of embryos in January 2009, and mtDNA donation in May 2010.[75]

Regulation in other countries

38 Canada has a similar system to that of the UK, though thought to be less "permissive."[76] Its agency, Assisted Human Reproduction Canada (AHRC), established by the Assisted Human Reproduction (AHR) Act of 2004, regulates human embryo research and fertility clinics. The AHR Act prohibits "alter[ing] the genome of a cell of a human being or *in vitro* embryo such that the alteration is capable of being transmitted to descendants."[77] Worldwide, fertility clinics operate within at least 162 countries. Of the 103 nations with reliable information on oversight of ART, "42 operated with legislative oversight, 26 with voluntary guidelines, and 35 operated with neither," though distinction between those categories may be unclear in practice.[78] The US, for example, oversees reproductive and genetic technologies through a patchwork of professional guidelines and public regulation by state and federal levels of government.[79] The US Congress has not enacted ART legislation, nor does the US federal government regulate the practice of reproductive medicine. With respect to genetic modification, the Recombinant DNA Advisory Committee (RAC) of the National Institutes of Health (NIH) and the Food and Drug Administration (FDA) exercise some degree of regulatory oversight. The FDA, in particular, sees germline modification as unacceptable due to concerns about "safety, efficacy, and the protection of human subjects in clinical trials."[80] Many other countries have passed legislation that governs germline modification;[81] in a survey of human germline modification policy in 48 countries, 44 have policies prohibiting the practice; the remaining 4 have no policy on modification of the germline.[82]

Intergovernmental and transnational policy on germline modification

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75 Darby, H. (2008). Gene transfer into male germ lines and embryos. Available at: http://www.hfea.gov.uk/docs/SCAG_Gene_TransferFeb08.pdf ; Darby, H. (2009). Genetic modification of embryos: information for Research License Committee. Available at: http://www.hfea.gov.uk/docs/SCAAC_Genetic_ModificationJan09.pdf.pdf ; HFEA. (2010). Minutes of the Scientific and Clinical Advances Advisory Committee meeting. Available at: http://www.hfea.gov.uk/docs/1952_001.pdf

76 Center for Genetics and Society. Canada: The Assisted Human Reproduction Act. Available at: http://www.geneticsandsociety.org/article.php?id=335

77 AHR Act, 5(1)(f). Available at: http://laws-lois.justice.gc.ca/eng/acts/A-13.4/page-3.html#h-4

78 International Federation of Fertility Societies Surveillance 2010. Available at: http://www.iffs-reproduction.org/documents/IFFS_Surveillance_2010.pdf

79 Bonnicksen, A.L. (2007). Oversight of assisted reproductive technologies: the last twenty years. In Knowles, L.P. and Kaebnick, G.E. (Eds.), *Reprogenetics: law, policy, and ethical issues* (pp. 64-88). Baltimore: The Johns Hopkins University Press.

80 Reproduction and responsibility: the regulation of new biotechnologies. A report of the President's Council on Bioethics. (2004) p. 113.

81 Isasi, R.M. (2006). National regulatory frameworks regarding human genetic modification technologies (somatic and germline modification): a report for the Genetics and Public Policy Center. Available at: http://www.dnapolicy.org/pdf/geneticModification.pdf

82 BioPolicyWiki. Inheritable genetic modification. Available at: http://biopolicywiki.org/index.php?title=Inheritable_genetic_modification

39 Numerous intergovernmental organizations have positions placing constraints on human germline modification. Two positions are most frequently cited. First, in 1997 the United Nations Educational, Scientific and Cultural Organization (UNESCO) unanimously adopted the Universal Declaration on the Human Genome and Human Rights,[83] which contains provisions with implications for mitochondrial donation. Provisions in Section B, Article 5 dictate that human genome research must be done with (a) clear assessment of risks and benefits, and (b) informed consent, or (e) direct health benefit, if the subject does not have capacity to consent. Article 8 stipulates the right to reparation for damage resulting from a genome-affecting intervention. Under Section C, Article 12, the benefits of human genome research must be made available to all. Most importantly, Article 24 declares germline modification "could be contrary to human dignity." In 2003, the International Bioethics Committee (IBC) of UNESCO issued a report that noted widespread legislation against germline modification and reiterated their concerns about the practice.[84] Second, in 1997 the Council of Europe introduced its Convention on Human Rights and Biomedicine.[85] Article 13 of the Convention states, "An intervention seeking to modify the human genome may only be undertaken for preventive, diagnostic or therapeutic purposes and only if its aim is not to introduce any modification in the genome of any descendants." A 2002 bulletin published by the World Health Organization (WHO) declared an emerging international consensus on the unacceptability of germline modification, citing the above UNESCO Declaration and Council of Europe Convention.[86]

40 Several other international bodies have made statements on germline modification.[87] Of recent note, the European Parliament and Council of the European Union have stipulated in their Seventh Framework Programme that "research activity intended to modify the genetic heritage of human beings which could make such changes heritable" will not be funded.[88]

Cloning policies and other laws affecting the use of nuclear transfer techniques

41 Positions on somatic cell nuclear transfer (SCNT) and other methods of reproductive cloning are generally not intended to forbid the methods of nuclear transfer used in mitochondrial donation. However, the language in certain

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83 UNESCO. (1997).Universal Declaration on the Human Genome and Human Rights. Available at: http://portal.unesco.org/en/ev.php-URL_ID=13177&URL_DO=DO_TOPIC&URL_SECTION=201.html

84 UNESCO. (2003). Report of the IBC on Pre-implantation Genetic Diagnosis and Germ-Line Intervention. Available at: http://unesdoc.unesco.org/images/0013/001302/130248e.pdf

85 Council of Europe. (1997). Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine. Available at: http://conventions.coe.int/Treaty/en/Treaties/html/164.htm

86 Andorno, R. (2002). Biomedicine and international human rights law: in search of a global consensus. *Bulletin of the World Health Organization 80*(12), 959-963.

87 Frankel, M.S. and Chapman, A.R. (2001). Facing Inheritable Genetic Modifications, Supplementary Material. Available at: http://www.sciencemag.org/content/suppl/2001/05/18/292.5520.1303.DC1

88 Decision No 1982/2006/EC of the European Parliament and of the Council of 18 December 2006, Article 6, paragraph 2. Available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2006:412:0001:01:en:HTML

legislation can be interpreted in a manner that discourages certain techniques. In the UK, prior to amendment in 2008, language in the HFE Act prohibited the transfer of *nuclei* between embryos[89] as well as the alteration of the "genetic structure of any cell" while part of an embryo.[90] Thus, in order to obtain HFEA license, the Newcastle group was required to develop its *pronuclear* transfer method of mitochondrial donation. In Australia, law related to cloning and embryo research[91] has been under legislative review since 2010.[92] The law does not permit embryo research involving "three genomes," which has been interpreted to prohibit research on techniques of mitochondrial donation. The Australian Academy of Science has recommended the law "be corrected to allow research with several genomes when the research studies mitochondrial rather than nuclear genomes."[93] In the US, California human cloning state law prohibits "transferring the nucleus from a human cell from whatever source into a human or nonhuman egg cell,"[94] effectively banning the mitochondrial donation technique of spindle transfer if performed in humans.

Other gene therapy issues

42 Increased understanding of epigenetics also raises questions about germline modification other than that precipitated by nuclear or mitochondrial DNA, questions that have been virtually absent from bioethical analyses. We now know that genetic information passes from generation to generation through a process called epigenetic inheritance,[95] which may lead to changes later in life such as cancer or diabetes. Recent research has noted that "epigenetic modifiers have key roles in germ-cell development itself -- for example, epigenetics contributes to the gene-expression programme that is required for germ-cell development, regulation of meiosis and genomic integrity. Understanding epigenetic regulation in germ cells has implications for reproductive technologies and human health."[96] As such, the HFEA has recommended a "[d]etailed analysis of epigenetic modifications" that result from mitochondrial donation techniques.[97] While there is much more to learn about the relationship between germline biological processes and epigenetic

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89 Section 3(3)(d) of the HFE Act of 1990 as enacted, prior to 2008 amendment.

90 Schedule 2 Paragraph 3(4) of the HFE Act of 1990 as enacted, prior to 2008 amendment.

91 Prohibition of Human Cloning for Reproduction Act 2002, and Research Involving Human Embryos Act 2002.

92 See: https://legislationreview.nhmrc.gov.au/2010-legislation-review

93 The Australian Academy of Science. (2011). For consideration by the 2010 reviews of *Prohibition of Human Cloning for Reproduction Act 2002* and *Research Involving Human Embryos Act 2002.* Available at: http://www.science.org.au/reports/documents/ReviewHumanCloningandStemCellResearch.pdf

94 California Health and Safety Code Section 24185-24187. Available at: http://www.leginfo.ca.gov/cgi-bin/waisgate?WAISdocID=7118767542+0+0+0&WAISaction=retrieve; Other state cloning laws available at: http://www.ncsl.org/default.aspx?tabid=14284

95 Epigenetics and Inheritance. Available at: http://learn.genetics.utah.edu/content/epigenetics/inheritance/

96 Sasaki, H., & Matsui, Y. (2008). Epigenetic events in mammalian germ-cell development: reprogramming and beyond. *Nature Review Genetics, 9*(2), 129-140.

97 HFEA. (2011). Scientific review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception, paragraph 5.5. Available at: http://www.hfea.gov.uk/docs/2011-04-18_Mitochondria_review_-_final_report.PDF

alterations, enough is now known to warrant broader public discussion and ethical analysis of the implications.

43 The discovery several years ago that the technique of RNA interference (RNAi) can silence gene expression in mammals has led researchers to explore it as an approach to gene therapy,[98] and it has in the past decade quickly advanced from basic research to human application, with several clinical trials underway. RNAi is a treatment that targets and inactivates disease-linked mRNA transcripts, which then in turn inactivate the corresponding gene that produced them, effectively turning "off" the unwanted gene. Moreover, recent reports have shown proof of principle that RNAi-induced changes can be successfully transmitted through the germline of mice.[99] While much research remains to be done, RNAi is yet another technique that should be monitored for its capacity to modify the human genome.

Questions to consider

In the context of recent developments in the germline gene therapy of mitochondrial disease, there are a number of ethical and policy questions to consider:

- Is mitochondrial DNA part of the germline? How does germline modification by nuclear DNA or mitochondrial DNA differ, and are those differences of ethical significance?

- Is mitochondrial DNA associated with identity? If so, what is the nature of the connection and how might it affect ethical assessment of mitochondrial DNA alteration?

- Which is at issue when considering key ethical distinctions: the *principle* of germline modification, or the *degree* of germline modification? How should we characterize a degree of germline change?

- Should mitochondrial donation be thought of as a type of "transplant," or as a "systemic therapy"?

- What ethical concerns are raised by the possible use of mitochondrial donation for non-medical purposes?

- If mitochondrial donation is approved for medical purposes, what government policies or professional guidelines should be in place to promote ethically sound practices?

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98 Caplen, N.J. (2003). RNAi as a Gene Therapy Approach. *Expert Opinion on Biological Therapy*, *3*(4), 575-586.

99 Gao, X., & Zhang, P. (2007). Transgenic RNA Interference in Mice. *Physiology*, *22*(3), 161-166.