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Germline Modification and Policymaking: The Relationship between Mitochondrial Replacement and Gene Editing

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'Mitochondrial replacement' and 'germline gene editing' are relatively new techniques that represent a significant moral, technological, and legal threshold, as they would introduce permanent and heritable changes to the human gene pool. This article examines the close relationship between these two technologies over time, considering what regulatory lessons can be learned from the former as attention turns to the latter. It argues that the UK's 'mitochondrial replacement' approval process should not be taken as a model for the wider regulation of germline gene editing, and that policymaking needs to contend with a comprehensive picture of the social and political meaning of these technologies in the world.

KEYWORDS human germline modification, germline gene editing, mitochondrial replacement, language, biopolicy, bioethics and biopolitics

The genetic modification of human sperm, eggs, or embryos for reproductive purposes represents a significant moral, technological, and legal threshold, as it would introduce permanent and heritable changes to the human gene pool. Every country that has considered legislation on this type of genetic modification has prohibited or restricted it due to the profound safety concerns and human rights implications involved in altering the genetic makeup of future generations. This includes 29 countries with an explicit ban and 10 additional countries with varying degrees of restrictions (Araki and Ishii 2014). International deliberations, as evidenced by the Council of Europe's Convention on Human Rights and Biomedicine and UNESCO's Universal Declaration on the Human Genome and Human Rights,

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have come to the same conclusion.[1] In a 2015 report intended to update its thinking in light of the new gene editing tool CRISPR, UNESCO called for a moratorium on germline modification, concluding that, 'Interventions on the human genome should be admitted only for preventive, diagnostic or therapeutic reasons and without enacting modifications for descendants. [The alternative would] jeopardize the inherent and therefore equal dignity of all human beings and renew eugenics' (UNESCO 2015).

The same year, however, the UK legalized a procedure that is technically a form of human germline modification, becoming the first country in the world to do so. Following a policy process that lasted several years, the UK Parliament voted to carve out an exception to its ongoing prohibition of human germline modification, to allow what it calls 'mitochondrial replacement' in cases where it is believed it could prevent the transmission of severe mitochondrial disease (Le Page 2016).[2] This controversial policy has served to create, for some, a convenient global precedent for other countries and related technologies, such as germline gene editing (Adashi and Cohen 2016).

Both 'mitochondrial replacement' and 'germline gene editing' are relatively new techniques that can be used to modify the human germline. It is essential to consider their close relationship over time, as well as what regulatory lessons can be learned from the former as attention turns to the latter.

The aim of this article is twofold. First, it provides a much needed, comprehensive overview of the history and current state of 'mitochondrial replacement' technology, and of the key policy processes, safety concerns, and widespread misconceptions related to it. Second, it examines the technique's connections with and divergences from 'germline gene editing', concluding that it would be a serious mistake to use the 'mitochondrial replacement' approval process in the UK as a model for the proper regulatory handling of CRISPR germline editing or any other form of germline genetic modification. Our hope is that adding historical, social, and political context will lead to a better understanding of the interconnections between these technologies and the motivations behind their proposed uses, and will help broaden the current narratives of technological advance that surround them. As these technologies develop further, we argue that updated policies ought to contend with a comprehensive picture of the social and political meaning of their use in the world.

What is 'mitochondrial replacement?'

Mitochondria are organelles located outside the nuclei of cells, typically in large numbers in each cell. Each contains DNA, known as mitochondrial DNA, in the form of 37 genes. Mitochondria are fundamental to proper cell function; dysfunction

[1] Also known as the Oviedo Convention, the Council of Europe's Convention on Human Rights and Biomedicine indicates in Article 13 that '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' (Council of Europe 1997). UNESCO's Universal Declaration on the Human Genome and Human Rights states that 'germ-line interventions' could be 'contrary to human dignity' (UNESCO 1997).

[2] The UK has considered itself a leader in innovative reproductive technologies since the 1978 birth of the world's first child created via in vitro fertilization (IVF), Louise Brown, and some have posited that a drive to secure other 'world firsts' is behind these new policy deliberations, see Dickenson and Darnovsky 2014.

can have system-wide implications including organ damage and even death. Mitochondrial DNA is known to determine certain disease inheritance, and play an important role in metabolism, obesity, and lifespan. The technique known as 'mitochondrial replacement' involves transferring the nucleus of one woman's egg to another, which results in a hybrid egg or embryo with nuclear DNA and mitochondrial DNA from different individuals. The most widely stated goal of the technique is to allow a small number of individuals with severe disease caused by dysfunctional mitochondrial DNA to have healthy and mostly genetically related children.[3]

There are several 'mitochondrial replacement' techniques. The two main techniques are very similar, differing only in the timing of fertilization. In maternal spindle transfer (MST), a donor egg's nucleus is removed and replaced by the nucleus of the intending mother, then fertilized. In pronuclear transfer (PNT), a donor egg and intending mother's egg are fertilized separately, and the donor egg's fertilized nucleus removed and replaced by the fertilized nucleus of the intending mother's egg. In both techniques, a small amount of the intending mother's mitochondria are transferred to the donor egg along with the nucleus (Yamada *et al.* 2016), with potential health consequences detailed later in this paper.

'Mitochondrial replacement' and germline gene editing are considerably different in technical terms. The first recombines intact sequences of mitochondrial DNA and nuclear DNA in novel biological constructs; the second makes changes to nuclear DNA sequences themselves. Both techniques represent major interventions in the genomes of future children that would not occur naturally. Thus, both are forms of human germline modification.[4] And while both are typically represented as ways to prevent the births of children with inherited disease, both could also be used for non-disease purposes.

The use of 'mitochondrial replacement' for non-disease related fertility treatments has been part of the rationale for pursuing the technology from the start. A precursor technique, known as ooplasmic transfer, was first developed in the 1990s to treat general infertility. For some, this aspiration has continued through the present day. Several of the main researchers working with 'mitochondrial replacement' techniques are transparent about their hopes to use it for this purpose in the fertility sector. We describe this connection in more detail below.

The importance of language

The language used to describe any technological development is powerful, and often shapes public perception. 'Mitochondrial replacement' is one of a number of terms used to refer to the set of techniques described above that combine genetic material

[3] As Baylis (2017) notes, the technique is often described in the largely unquestioned terms of satisfying a 'need' for genetically-related children. She argues that this constitutes an 'inappropriate overvaluing of genetic relatedness within families,' and that genetic-relatedness does not constitute a need, but only a 'desire'. Baylis further suggests that, as this technology responds to the wants of 'an infinitesimally small number of people,' it does not warrant the investment of public research funds that would be better spent ameliorating larger social and health inequities.

[4] However, unlike germline gene editing, changes made via 'mitochondrial replacement' techniques are only heritable through the female line. Newson and Wrigley (2017) therefore propose the term 'conditionally inheritable genomic modification' for these techniques.

from the gametes of three individuals for the purpose of creating a new embryo. For this particular technology, terminology has been a fascinating site of dispute. Here we explore its implications.

Two terms widely used by the media – 'three-parent IVF' and 'three-parent babies' – emphasize the biological novelty of enabling someone to have more than two genetic parents. These terms have been criticized for several reasons. Some point out that they can be seen as demeaning nontraditional families. Others claim that the relatively minor genetic contribution of the donor egg cytoplasm and mitochondria does not constitute a claim of genetic parenthood, an argument that draws upon a wider misconception that mitochondria can be understood simply as a cell's batteries. The idea that mitochondria are passive powerhouses has been disputed, however, and there is evidence that mitochondria in fact influence many of our traits (Hamilton 2014). We consider the variant term 'three-person IVF' preferable, as its use of 'person' instead of 'parent' simply describes the fact that there are three genetic contributors, while avoiding more loaded associations with parenthood.

The terms most commonly used in the scientific community include 'mitochondrial replacement' and 'mitochondrial transfer,' which many prefer because they are seen as less sensational. These terms also evoke a possible rationale for the techniques, which is to make use of a donor's healthy mitochondria. Variations on these terms, which gained prominence in the UK during the effort to legalize the technique, include 'mitochondrial donation' and 'mitochondrial replacement therapy,' both of which add affective words that make these technologies seem inherently beneficial.

However, some find these terms highly misleading. Stuart Newman, Professor of Cell Biology and Anatomy at New York Medical College, argues that they are scientifically spurious, since they emphasize an egg's mitochondria over its cytoplasmic and membrane composition, and intentionally obscure the fact that what is actually transferred from one egg or embryo to another is a nucleus, not mitochondria.[5] Newman and others use the term 'nuclear genome transfer' to reflect what they consider a significant biological point (Newman 2014).[6]

It is possible that some researchers avoid the more technical term 'nuclear genome transfer' because it acknowledges that the techniques in question are the same as that used for cloning, and they are wary of encouraging this association in popular opinion. We understand that the use of different terms can make sense in different contexts.[7] However, with the readership of this journal in mind, we henceforth use the term 'nuclear genome transfer' (NGT) with the aim of being as scientifically precise as possible.

Prominent mischaracterizations

The variety and euphemistic nature of much of the terminology used to refer to nuclear genome transfer (NGT) has been a source of confusion surrounding the

[5] See also Baylis 2017; Gómez-Tatay *et al.* 2017; Jones 2015; Nisker 2015.
[6] See also Baylis 2017.
[7] González-Santos (2017) provided a recent compelling argument surrounding this controversy over terminology, https://doi.org/10.1093/jlb/lsx022.

technology. There have, however, been a number of other sources as well. In this section, we discuss six prominent mischaracterizations that serve to illustrate the ongoing difficulty of broad and open conversation about this technology.[8] These mischaracterizations also illuminate the limits of the UK legalization process of NGT as a policy model. They further point to other lessons that can be drawn from the UK policy process.

The first mischaracterization that distorts the conversation surrounding NGT is that it can 'save lives.' As a 2016 report by the National Academies of Sciences, Engineering and Medicine concluded, NGT 'does not address a medical need,' as it 'would not treat an existing person for a disease, illness, or condition.' The saving of a life requires an existing, living person to treat. NGT does not treat an existing person, but instead creates a new person. When speaking of human gametes or embryos, this type of language is usually used by those who consider embryos to have personhood. In this case, it is frequently invoked by others.

The second mischaracterization is that mitochondria simply provide a cell's energy. They are widely misportrayed as the 'powerhouses of the cell,' similar to a 'battery pack.' However, mitochondrial genes play an integral role in the outcome of processes involving nuclear DNA, are replicated thousands of times in most of our cells and affect numerous organs, and are known to impact the phenotype in numerous ways (Chatre and Ricchetti 2013). For example, there is evidence that suggests correlations between mitochondrial DNA (mtDNA) and cognition (Roubertoux *et al.* 2003), aging and cancer (Desler *et al.* 2011), and metabolic disorders that have been associated with familial deafness and some cases of Alzheimer's Disease and Parkinson's Disease (Wallace 1994). Further, it is not merely pathogenic mtDNA variations that affect physiology, although clearly these tend to be easier to trace. Mismatches between nuclear and mitochondrial DNA, as often happen in NGT, have been shown in mice to lead to an increase in oxidative stress, which can produce a variety of impactful physiological shifts (Latorre-Pellicer *et al.* 2016). At present, the interaction between nuclear and mitochondrial genomes is imperfectly understood, and language that implies simple cut-and-paste solutions hides more than it reveals.

A third mischaracterization is that NGT is the only, or at least the best, option for women at risk of passing on mitochondrial disease who want to have a genetically-related child. Yet, preimplantation genetic diagnosis (PGD), the genetic screening of IVF embryos, is an increasingly useful tool for preventing the transmission of mitochondrial diseases while maintaining genetic relatedness. PGD for mitochondrial diseases is more complicated than for monogenic inherited disease, but its use to select embryos below a certain threshold of mitochondrial mutation percentage appears promising (Sallevelt *et al.* 2013). Although PGD is not a complete guarantee, it is both safer and less ethically fraught than biological manipulation techniques like NGT. It is unclear how many cases exist where PGD would not produce a single viable embryo for transfer. However, other options are also available to couples that want an unaffected child, such as to obtain a donated egg or embryo, or to adopt.

[8] See also Knoepfler 2015.

A fourth, related mischaracterization of NGT is that there is an urgent medical need for it. This rhetoric was spurred by such statements as, 'Around one in 200 children are born each year with a form of mitochondrial disease,' which was formerly on the UK's Human Fertilisation and Embryology Authority's (HFEA) webpage introducing this technology. This statistic has been repeated in a number of news articles and commentaries over the years (Sample 2015).[9] Although around one in 200 people have mutations in their mitochondrial DNA, only around one in 5,000 people have mitochondrial disease (Mitalipov and Wolf 2014). Further, a large majority of these cases are caused by variants in nuclear genes that regulate and maintain mitochondrial function (Alston *et al.* 2017), where NGT would be irrelevant. The bottom line is that the number of candidates for NGT treatment is quite small, with estimates for the number in the UK ranging from several dozen to several score.

A fifth mischaracterization is that NGT doesn't really constitute human genetic modification. Prior to changing its law to allow for the technique, the UK government began comparing NGT to a blood transfusion or transplant, arguing that although it resulted in germline modification, it wasn't genetic modification. In order to make this claim, it redefined genetic modification to solely refer to changes in nuclear DNA, rather than changes to the overall genetic composition of an individual's cells. In response, numerous scientists and members of the public accused the government of dishonesty in the service of swaying public opinion. Ted Morrow, an evolutionary biologist at the University of Sussex, said at the time: 'My impression is the Government is doing all it can to contain and define these kinds of terms in ways that favour mitochondrial replacement being introduced as an uncontroversial therapy' (Connor 2014). David King, of the UK advocacy group Human Genetics Alert, stressed: 'Their restriction of the term to nuclear inheritable changes is clearly political. They don't want people like me saying that they are legalising GM babies' (ibid). Many others acknowledge that NGT is in fact inheritable genetic modification, and that the UK became the first country in the world to allow this in any form (Cussins 2015). Despite this biased portrayal, the approval of NGT in the UK is being used post hoc to assert the possible legitimacy of other forms of human germline modification (Stephens and Dimond 2016).

The final mischaracterization we will discuss here is the notion that there is broad public support in the UK for NGT. The HFEA carried out a public consultation on the topic, and at its conclusion in 2013 announced in a press statement that it had found 'broad support for permitting mitochondria replacement' (HFEA 2013b). This was repeated by nearly all of the numerous media reports on the consultation, but is a spurious portrayal of the HFEA's own published data. In the only public portion of the consultation, the majority of its 1,800 participants wrote that they disagreed with the introduction of what was being called mitochondrial replacement due to a range of technical, ethical, and social concerns (HFEA 2013a). Subsequent independent polls found similar reservations, particularly among women (ComRes 2015).

[9] The United Mitochondrial Disease Foundation's 2015 Position Statement on Mitochondrial Replacement Therapy cites these misleading statistics as well, http://www.umdf.org/mitochondrial-replacement-therapy/.

How then could the HFEA claim broad public support for the legalization of NGT? The organization defended its assertion by appealing to the fact that the public consultation was only one of the 'many strands' throughout its broader consultative process (HFEA 3013c). Notably, the HFEA seems to have devalued the results of this portion precisely because it was open. The final report on the findings states, 'As anyone who wanted to could participate, the views expressed cannot be considered representative of the wider population' (HFEA 2013a).

It is not hard to understand how these mischaracterizations would have skewed understanding of the debate about this new technology. If you believe that you can help save 1 in 200 children a year while offering women the best option to have a child of their own, criticism seems out of place. It is only when you understand the biological experimentation involved, the small number of women actually eligible for the procedure, the reality of much safer alternatives, and the intrinsic ethical dilemmas involved, that the strong push to change national legislation to enable NGT appears misguided.

What might be the consequences of this debate and policy process, marked by numerous mischaracterizations, for deliberations about other developments in the life sciences? The UK legislation that prohibited human germline modification was not, after all, passed because there were insufficient or inadequate techniques with which to modify embryos at the time,[10] but because of the profound social, ethical, and political consequences that could emerge as a result. The widespread use of euphemistic and medicalised language for NGT as a fertility treatment provides a glimpse of what we can expect with subsequent technologies that would also genetically alter human gametes or embryos.

Is it safe?

In the late 1990's, a technique called cytoplasmic or ooplasmic transfer was used by a small number of US fertility clinics ostensibly to treat general infertility. This technique, conceptually related to NGT but procedurally distinct, was supposed to help infertile women by injecting mitochondria-rich cytoplasm or ooplasm from one individual into the intending mother's egg. It was thought that the addition of 'youthful mitochondria' might 'rejuvenate' a woman's eggs.

At least 13 pregnancies were established before the FDA intervened in 2001 (Krimsky 2015). The FDA reported that two of the fetuses were karyotypically 45, XO (Turner's syndrome) and that one of these fetuses aborted spontaneously and the other pregnancy was terminated. The FDA determined the procedure to be 'de facto germline gene transfer' that was being conducted despite safety concerns and meager evidence of efficacy (USFDA 2002).

The technique was novel both because it was a form of germline genetic modification, and because it inserted a third person's DNA into the process of creating a

[10] This is reminiscent of a comment made by Richard Hynes, co-author of a 2017 National Academies of Sciences, Engineering, and Medicine report on human genome editing, at the report's press release in February 2017, suggesting that the only reason for previous opposition to germline editing in the past was because it was not safe or feasible. See Lowthorp 2017.

child. Ooplasmic transfer is a much less invasive technique than NGT, as it keeps a woman's egg nearly intact, though modifying it by adding another individual's mitochondria to her own. NGT, on the other hand, involves removing the nucleus from the intending mother's egg and putting it into a donor's enucleated egg or embryo. As a result, the primary mitochondrial function must come from the donor egg, and the resulting mismatched mitochondria and nucleus, as well as both sets of mitochondria (majority donor and minority intended mother), must be able to seamlessly integrate. However, as we've seen in animal studies, this isn't always successful (Ma *et al.* 2016).

Limited follow-up of the children born in the early 2000s following ooplasmic transfer was conducted in 2016 (Chen *et al.* 2016). In a small survey-based study, researchers found that among 17 children born from 13 couples, parents reported several adverse conditions, including chronic migraines and borderline pervasive developmental disorder, but that their kids generally had good health. The study's authors acknowledged that it had major limitations, as all information was based on limited email surveys completed by parents with no follow-up testing of the children themselves. In addition, the parents of quadruplets who represented 25% of the study declined to participate.[11] This study was largely misrepresented in the media, which falsely equated NGT and ooplasmic transfer, thereby claiming that the study provided evidence that NGT must be safe. Martin Johnson, editor of *Reproductive BioMedicine Online* and former HFEA member, characterized this misleading media coverage as 'shoddy scientific journalism' because the two techniques 'differ markedly in intent, methods and outcomes … (and) the method used, ooplasmic injection as per ICSI, was far less invasive.' In fact, the small study about ooplasmic transfer says nothing about the safety of NGT.[12]

Several safety concerns remain for NGT. The first is that of epigenetic harm, which could produce unpredictable health consequences. Many scientists consider experimental nuclear genome transfer techniques to be unsafe, as they have unknown and unforeseeable health consequences for resulting children as well as future generations. NGT is a biologically extreme procedure that is unprecedented in human evolution, and we have no idea what the ultimate consequences may be for people created as a result. As UC Davis stem-cell biologist Paul Knoepfler has written,

> moving one oocyte nucleus into the enucleated oocyte of another person could trigger all kinds of devastating problems (most likely through epigenetic changes) that might not manifest until you try to make a human being out of it. Then it's too late. (Knoepfler 2012)

This procedure could easily exploit vulnerable families to put their future children at serious risk (Cussins 2014b).

There are significant risks involved when mitochondrial DNA and nuclear DNA are mismatched within a cell. Mitochondrial DNA and nuclear DNA have co-evolved within cells for millennia, and a number of studies have concluded that mitochondria play a vital role in nuclear gene expression. Mismatched

[11] See Lowthorp 2016b.
[12] See Johnson 2016 for more details.

mitochondrial and nuclear DNA could therefore have serious implications for disease susceptibility, gene expression, and cell function.[13] One study has determined that reversion, the phenomenon whereby carried-over 'faulty' mtDNA multiply faster than donor mtDNA and eventually take over the donor egg, is a serious problem caused by mitochondrial and nuclear DNA mismatch (Yamada *et al.* 2016). As *Scientific American* reporter Karen Weintraub has explained, this means that mitochondrial diseases 'can come back to sicken a child, even when 99 percent of the mother's own mitochondria are eliminated' (Weintraub 2016).[14]

In addition, mitochondria *do* impact inherited traits, so NGT could lead to unexpected phenotypic outcomes.[15] As journalist Garry Hamilton (2014) has reported in *New Scientist*, 'mitochondria influence some of the most important aspects of human life — from memory and aging to combating stress and disease.' These findings led *New Scientist* to publish an editorial called, 'Three-parent babies: It's more messy than we thought' (Editors 2014). If a child produced through NGT actually inherits traits from three people rather than its cells simply getting new 'batteries,' there is much more at stake both ethically and procedurally (Cussins 2014c).

Finally, there is another kind of harm, one which has been often overlooked in discussions of the technology: a resulting increased demand for eggs would put at risk the health of greater numbers of women. Egg extraction poses a number of serious risks, including memory loss; depression; joint, muscle, and bone pain; formation of blood clots; seizures; ovarian hyperstimulation syndrome (OHSS); and even death.[16] Many have expressed alarm that the need for larger numbers of eggs for NGT, and offers of money for them, will lead to increased pressure on women to undergo egg extraction (Baylis 2013).

These numbers would be exponentially larger if NGT comes to be used in fertility clinics to treat age-related infertility. That situation could lead to an exploitive global market in eggs, used only for their mitochondrial parts. It would differ from the existing global demand in the fertility sector for eggs from women with socially valued traits, particularly that of white skin, because children born as a result of NGT would not necessarily exhibit the physical traits of their egg providers. Significant numbers of women around the world, whose eggs would not be highly valued for others' reproductive purposes if used whole, would be at risk as egg providers for NGT.

'Everything we do is a step toward designer babies'

In the end, the UK was not the first country with an NGT birth. In fact, no child has yet been born as a result of these techniques in the UK, although the HFEA recently approved the first NGT pregnancies.[17] Instead, several children have been born via

[13] See Gómez-Tatay *et al.* 2017; Muir *et al.* 2016; Dunham-Snary and Ballinger 2015.
[14] Dieter Egli, a noted scientist from the Yamada *et al.* (2016) study, viewed this mtDNA carryover and reversion as serious enough to postpone any clinical applications of NGT (Knoepfler 2016b). Despite this, the HFEA's Fourth Review of NGT concluded that it was not a serious concern (Lowthorp 2016a), and, less than six months after the study was published, the HFEA approved the clinical application of the technology.
[15] See Gómez-Tatay *et al.* 2017.
[16] See Norsigian 2006; see also Ikemoto 2009; Schenker and Ezra 1994.
[17] See Lowthorp 2018; Sample 2018.

NGT in countries without explicit regulations. In September 2016, reports surfaced that a baby had been born as a result of NGT the previous April to a Jordanian couple affected by mitochondrial disease. The procedure was conducted by Dr. John Zhang, a New York City-based fertility doctor who openly admitted that he did the work in Mexico in order to evade the US regulatory process.[18] A report of the process was published in April 2017, a full year after the birth (Zhang *et al.* 2017).

The case went largely uncriticized by the scientific community, although the media reported that it raised serious concerns among some scientists. These include misgivings about Zhang's flouting of regulations and the subpar nature of the work itself (Reardon 2016), his conducting what was essentially an unethical human experiment (Knoepfler 2016a), the unknown long-term effects of the technique on the child born (Poulton 2016), and Zhang's promotion of medical tourism (ibid). Despite this, much of the media coverage celebrated Zhang as an altruistic doctor simply seeking to prevent the transmission of mitochondrial disease, while downplaying the serious risks involved for the baby and future generations. Zhang's widely quoted justification, 'To save lives is the ethical thing to do,' was never questioned, despite the conclusion of a 2016 National Academies of Science, Engineering and Medicine report, discussed above, that this technique has nothing to do with saving lives, as it 'would not treat an existing person for a disease, illness, or condition.'

Just the year before, Zhang gave a talk at the 2015 Assisted Reproductive Technologies World Congress in New York, entitled 'Rejuvenation of human oocyte through cell reconstruction by nuclear transfer: is it science fiction or a reality?' Set to the music of *Chariots of Fire*, the iconic soundtrack of inspirational events, Zhang extolled the promise of NGT techniques for treating age-related infertility with no mention of mitochondrial disease.[19] Only a few months before the child's birth, Zhang similarly released a video lauding the technique as a treatment for infertility, only briefly mentioning its potential use for the prevention of mitochondrial disease.[20]

It was therefore not surprising that less than two weeks after the story of the Mexico birth was reported, another emerged about NGT techniques used in the Ukraine to ostensibly treat general infertility.[21] Valery Zukin, a fertility doctor in Kiev, reportedly used the technique to overcome the early stage embryo arrest that affected some of his IVF patients. Two women reportedly delivered children in early 2017.[22] Unlike the Zhang birth, the first of these children was female, meaning that changes made to her DNA are heritable (Hamzelou 2016).

In June 2017, *MIT Technology Review* reported that John Zhang had founded a company in 2016, Darwin Life, to commercialize mitochondrial spindle transfer for use in treating both mitochondrial disease and age-related infertility. The article

[18] John Zhang was widely quoted in the press as claiming that 'there are no rules' in Mexico concerning this technology. As Palacios-González and De Jesús Medina Arellano (2017) have noted, however, Zhang may well have violated both Mexican federal and Jalisco state law. As Chan *et al.* (2017) have recently pointed out as well, Zhang's unauthorized cross-border procedure is a type of scientific tourism that can have harmful effects on science in developing countries.
[19] See Medscape 2016, https://www.pscp.tv/Medscape/1BRJjANLwVgGw.
[20] See New Hope Fertility Center 2016 video at 3:05, https://www.youtube.com/watch?v=h9AK-76_1AE&feature=youtu.be.
[21] See Gallagher 2016.
[22] See Scutti 2017.

quoted Zhang as saying, 'A future step will be to combine the technique with editing genes, so that parents can select hair or eye color, or maybe improve their children's IQ.' In his words, 'Everything we do is a step toward designer babies,' and a child created in such a way would be 'very much like an iPhone that's designed in California and assembled in China' (Mullin 2017a). The United States FDA sent a letter to Dr. Zhang shortly thereafter, ordering Darwin Life to cease both advertising unproven techniques and the illegal export of human embryos (USFDA 2017).

These examples clearly show that at least some of those who are developing and advocating NGT techniques both intend their widespread commercialization for age-related infertility, and acknowledge their clear connection to germline gene editing, with any number of editorial goals in mind.

A model for germline gene editing?

The UK has carried out the most extensive policy process surrounding the use of NGT to date. The HFEA held calls for evidence, published three safety reports, and led a public consultation. In the summer of 2014, the UK Department of Health created draft regulations on NGT with a three-month public consultation period. This was followed by an evidence hearing led by the UK House of Commons Science and Technology Committee, after which both the House of Commons and House of Lords approved the regulations in February 2015. In December 2016, the HFEA approved the clinical use of NGT in cases with 'no acceptable alternatives' for the purpose of avoiding serious mitochondrial disease (HFEA 2016).[23] As mentioned, no baby has yet been born in the UK, although a license for the purpose was granted to Newcastle University in 2016, and in early 2018, researchers there were given the green light to initiate the UK's first NGT pregnancies (Newcastle University 2017).

On the surface, these policy measures appear both comprehensive and inclusive of public opinion. Looking deeper, however, a number of concerns voiced during the consultation process appear to have been discounted. Among those raising issues were scientists who cited experiments that suggested negative outcomes from this degree of manipulation in early embryology.[24] At the evidence hearings, however, much of this concern was sidelined as irrational, theoretical, or religious (Cussins 2014d).

Some supporters of legalization compared the 'fear' around emerging reproductive technologies like NGT or germline gene editing to initial uncertainty about in vitro fertilization, suggesting that they will become accepted and normalized in the same way that IVF did.[25] This argument has been used before, for example in the early 2000s in relation to human cloning (Shanks 2003), but it is a misleading comparison.[26] IVF

[23] Eligible patients are described as 'patients in whose germ line there are likely to be high levels of heteroplasmy or homoplasmy for the abnormal (pathogenic) mtDNA, and who are thus unlikely to have any suitable embryos for transfer. Pre-treatment assessment would need to take into account the particular mutation involved, the inheritance pattern in the family, the likely clinical manifestations of disease, the efficacy of any previous treatments such as PGD, and the patient's understanding of the risks and limitations of what is being offered.'

[24] http://www.biopoliticaltimes.org/downloads/DKeefeMRconsiderations.pdf.

[25] For an example of this discourse in relation to gene editing, see Eschner 2017, and for a critique, see Shanks 2018.

[26] For an example of this discourse in relation to human cloning, see Shermer 2003.

was actually fairly widely accepted at the time of Louise Brown's birth in 1978, and a Harris poll that year found 85% of American women reporting that infertile couples should have the chance to try IVF (ibid). Many may similarly be drawing the wrong conclusions about the UK's legalization of NGT, holding it up in hindsight as a model for others, when in fact the policy process leading up to the technology's legalization was both fraught and problematic.

Several US-based researchers who had been closely involved in the UK debate hoped to initiate work in their own country. In February 2014, the FDA convened an expert committee to explore the techniques' safety and efficacy in a meeting that was open to the public (Cussins 2014a). After two days of testimony and deliberation, the committee concluded that significantly more evidence would be needed before safety or efficacy could be determined, and recognized that the related ethical and social policy issues were outside of their purview.

The FDA subsequently commissioned the National Academy of Medicine (called the Institute of Medicine at the time) to explore this. The NAM committee's final report was released in early 2016, and concluded that although it 'does not address a medical need,' the clinical investigation of 'mitochondrial replacement techniques' was distinguishable from the modification of nuclear DNA and could be carried out under strict conditions. Due to a Congressional appropriations bill rider in effect that prohibits the FDA from considering applications for clinical trials intended to create genetically modified embryos, however, US researchers are currently unable to apply for FDA approval to conduct NGT clinical trials.[27] Other countries, including Canada and Australia, are under some pressure to explore shifts to more lenient policies.[28]

As noted above, NGT techniques are clearly linked to germline gene editing in the minds of several researchers and fertility doctors. This is evident in Zhang's earlier quoted statement that, 'Everything we do is a step toward designer babies.' Another example is Shoukhrat Mitalipov, Senior Scientist and Professor at Oregon Health and Science University. Until recently, Mitalipov was best known for primate cloning research, including the first reported success in using somatic cell NGT to create a cloned human embryo. The technical skills developed for those projects, along with their reliance on recruitment of women as egg providers, likely assisted his development of the NGT (MST) technique.

Mitalipov, like Zhang, hoped to use MST beyond cases of mitochondrial disease, to treat age-related infertility. Seeking to accomplish this, he applied to the FDA to conduct clinical trials for the latter purpose in 2015 (Connor 2015), and a week later teamed up with disgraced South Korean cloning researcher Hwang Woo-Suk and the Chinese company Boyalife to conduct clinical trials in China.[29] In 2017, Mitalipov and his team published an article in the journal *Cell Stem Cell* advocating the use of another NGT (MST) technique they had developed, polar body transfer, as a fertility treatment (Ma *et al.* 2017a).

[27] https://www.congress.gov/bill/114th-congress/house-bill/2029.
[28] For Canada, see CBC News 2017; for Australia, see Johnston 2016.
[29] See Shanks 2015 and Lowthorp 2016c. The U.S. Congress does not permit the FDA to consider applications for the propose ofngenetically modifying human embryos.

Mitalipov recently achieved even wider notice when he and his team became the first U.S. researchers to use CRISPR gene editing on human embryos. Their controversial and disputed study, published in *Nature* in early August 2017, created 58 gene-edited human embryos via IVF, claiming greater accuracy than previous studies published by Chinese researchers (Ma *et al.* 2017b).[30] The work had a clear clinical aim—to prevent the transmission of hypertrophic cardiomyopathy, a heterozygous heart condition—and Mitalipov has been explicit to the press about his desire to move to clinical trials.[31] It is important to note here, however, that hypertrophic cardiomyopathy is one of the many diseases for which PGD offers a safe, effective option for transmission prevention. Jennifer Doudna, a co-discoverer of CRISPR-Cas 9, recently told *Science* magazine that the study made her uncomfortable, saying, 'It's not about research, I don't think. It's about how we get to a clinical application of this technology' (Servick 2017b).[32]

Despite the technological differences between the techniques, both Zhang and Mitalipov seem to consider NGT a technological precursor of germline gene editing. Zhang envisions that his clinic will first offer NGT for the purpose of treating age-related infertility, and subsequently offer germline gene editing as an add-on procedure. Mitalipov's work in cloning and NGT forms the foundation underlying his subsequent research on human germline editing. As Françoise Baylis (2017) has argued, NGT 'provides scientists with "a quiet way station" in which to refine the micromanipulation techniques essential for other human germline interventions and human cloning.'[33] The two technologies are bound together by the fact that they are both forms of germline modification, and explored by several of the same researchers. It is therefore important to consider the close relationship that NGT and human germline modification have had, and continue to have, over time.

Interrogating legacies

Neither NGT nor germline gene editing would be possible without IVF, a forty year old technology that has helped millions around the world to have children. IVF—the process of fertilizing embryos outside a woman's womb—is not a germline modification technique. However, it is a required step in implanting genetically altered embryos created through either NGT or germline gene editing. It also has a widely unacknowledged legacy of eugenics. Robert Edwards is one of the pioneers of IVF, along with Patrick Steptoe and the oft forgotten Jean Purdy.[34] After his death, it emerged that Edwards had been an active member of Britain's Eugenics Society (Obasogie 2013). As Osagie Obasogie (2013) points out,

[30] The study also claimed to have no off-target effects or mosaicism. A number of prominent scientists have since raised doubts about the accuracy of the study's findings. See Egli *et al.* 2017; Servick 2017a.
[31] See Mullin 2017b.
[32] See also Hasson 2017.
[33] For an allied argument, see Darnovsky 2013.
[34] The British Fertility Society has called for Purdy, the world's first embryologist, to be recognized as IVF's third pioneer alongside Edwards and Steptoe on the 40th anniversary of IVF next year, see Photopoulos 2017. Edwards was awarded the Nobel Prize in Physiology or Medicine in 2010 for in vitro fertilization. Since the Nobel Prize is not awarded posthumously, Steptoe did not receive the recognition.

> it is important to think critically about the relationship between Edwards's development of IVF and his participation in an organization that was dedicated to promoting one of the most dangerous ideas in human history: that science should be used to control human reproduction in order to breed preferred types of people.

A common thought of the eugenics movement of the time was that 'unfit' people were having too many children. IVF was a tool some thought might better 'balance' that equation by allowing 'socially favored characteristics to be selected and bred into the population' (ibid).

With all the talk of 'designer babies,' it is easy to think that the only dangerous or concerning element of genetic modification technologies would be their potential use for some kind of human enhancement down the road. However, there is no clear policy line that could be realistically held that would Redundant distinguish health interventions from enhancement. The meaning of these technologies will also be significantly more multifaceted. We have greater technological means today with which to treat sex cells as a canvas for selection and modification abilities, but the idea of population control via reproductive technologies is not new. Back in 1999, Edwards guessed at the kind of social pressure this would exert over time: 'Soon it will be a sin of parents to have a child that carries the heavy burden of genetic disease. We are entering a world where we have to consider the quality of our children' (Obasogie 2013).

So when NGT researcher John Zhang said in 2017, 'Everything we do is a step toward designer babies,' it is shocking, but not entirely surprising. We cannot talk about NGT or gene editing in embryos as tools that would only mitigate disease propensity. There is significantly more social baggage than that. Ethical concerns about children's right to an open future, and for the parent/child relationship not to be reduced to an overt commercial transaction, do not hinge on intended use of modification technologies. The fact that NGT has already been used for infertility is a good example of how easily mission creep happens in our interconnected world, where the medical tourism market is now worth more than $61,172 million (Allied Market Research 2017). Existing reproductive technologies like IVF already tell these stories. When we look for that complexity, and not just convenient, static models, it is clear that germline gene editing cannot claim a morally neutral ground. The project of modifying humans must contend with these interconnected histories.

Conclusion

Policymakers around the world will increasingly be required to contend with technological possibilities for human germline genetic modification. The most comprehensive model the world has to date is the UK's legalization process of nuclear genome transfer ('mitochondrial replacement'), but as we have outlined here, there were notable flaws in that process, with both safety/efficacy and social/ethical concerns seen as isolatable variables that could be overcome. Euphemistic language and inaccurate claims of 'saving lives' were widely used in an attempt to sway public opinion in favor of the technology. From the widespread use of the

editing metaphor to pictures of smiling happy babies, similarities in media portrayals of CRISPR have already become common.

As we have demonstrated here, there are numerous important parallels between NGT and germline gene editing, not least because they involve many of the same people, including researchers, fertility doctors, and bioethicists. While different both politically and technologically, we have nevertheless seen how NGT techniques have been clearly linked to germline gene editing by policy-makers, the researchers who work with these technologies, and the media. In our view, the UK's legalization of NGT should have limited effect on what has been an international policy consensus about the appropriate limits of technologies that alter the human germline, and it should not be looked to as a model, particularly when it comes to germline gene editing. Opening the door to the modification of nuclear DNA would be hugely consequential, exacerbating global disparities and likely taking structural inequality to a new, molecular level. Germline modification sold as an 'add-on' at fertility clinics could all too easily establish a system of consumer-based eugenics. Highly limited use of NGT need not be the undoing of a broad societal consensus against modifying the genomes of our descendants. The human genome remains the shared heritage of humanity (UNESCO 1997), and any policy decisions to allow permanent changes to our shared genetic code should only be decided through open and transparent dialogue among us all.

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