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UNIVERSITY OF CALIFORNIA,
IRVINE

An Assessment of the Mitochondrial Disease Community's Knowledge and Perception of the
“Three-Person Baby,” or MRT, and the Impact of the Media Debate that Surrounds this
Technique

THESIS

submitted in partial satisfaction of the requirements
for the degree of

MASTER OF SCIENCE

in Genetic Counseling

by

Ashlynn Nicole Fiss

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2016

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ABSTRACT OF THE THESIS

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University of California, Irvine, 2016

Professor Virginia Kimonis, MD, MRCP, Chair

This study was designed to assess the mitochondrial disease community's knowledge, attitude and perception of mitochondrial replacement therapy (MRT) and determine how the media can impact such perception. MRT in conjunction with in vitro fertilization (IVF) has the ability to prevent inheritance of mitochondrial DNA (mtDNA) mutations from mothers to their offspring by using a donor egg's mtDNA. The Federal Drug Administration (FDA) is considering human trials for MRT, dubbed "three-parent IVF" by the media. Approval relies heavily on the mitochondrial disease community's willingness to participate; however, the community's perceptions of risks, benefits and limitations associated with MRT have not been adequately addressed.

An anonymous survey was distributed online to individuals within the mitochondrial community; 165 individuals completed the survey and comprised the study population. The majority of individuals found MRT ethical, agreed with FDA approval for human clinical trials, and would be willing to use MRT if clinically appropriate and available. However, almost half were unaware that MRT is only useful if a mtDNA mutation has been previously identified.

Many respondents knew this technique does not change physical or personality traits of offspring; however, those who believed it did also felt more strongly that this technique is “designing babies”. Interestingly, the majority did not believe that the children born using MRT have three parents, so the media’s use of “three-parent baby” may be unnecessarily sensationalized. Our results provide evidence that the mitochondrial disease community is forward-thinking about MRT; however, may not be adequately aware of MRT’s risks or limitations.

I. INTRODUCTION

1.1 Overview of mitochondria

Mitochondria are complex cellular organelles which take in nutrients and break them down to form usable energy via oxidative phosphorylation (Jonckheere, Smeitink, & Rodenburg, 2012). Five complexes made from various proteins control this process. They are named complex I, II, III, IV and V and are located in the inner mitochondrial membrane. Their collective role is to create adenosine triphosphate (ATP), the cell's main energy source, through a metabolic pathway where electrons flow through the protein complexes and protons are pumped out of the mitochondrial matrix (Berg, Tymoczko, & Stryer, 2002). Due to their function they are nicknamed the powerhouse of the cell, responsible for creating over 90% of the body's energy supply. Many of the functions of mitochondria are programmed by genes encoded in DNA that is unique to the mitochondria, called mtDNA. It is estimated that each cell carries between 500-10,000 mtDNA molecules in multiple mitochondrial organelles (Smeets, 2013) each with its own genome consisting of 37 genes, all of which are essential for typical mitochondrial function. The majority of these genes provide instructions for making molecules called transfer RNA (tRNA) and ribosomal RNA (rRNA), which help assemble amino acids into functioning proteins (Wolf, Mitalipov, & Mitalipov, 2015). Thirteen of these genes provide instructions for making enzymes involved in oxidative phosphorylation, but importantly the majority of the genes involved in oxidative phosphorylation are not encoded by the mitochondrial DNA (mtDNA) but are encoded by nuclear DNA.

Based on mitochondria's role in the body, typical tissues that are affected most by mitochondrial disease are often those that require the most energy including the brain, liver, heart, central nervous system and muscle. When less energy is created in cells, cell injury and

death can occur. When this is systemic throughout the body, whole systems can begin to fail. Depending on which systems are affected, symptoms of mitochondrial disease may include diabetes, blindness, muscle weakness, and heart, liver and kidney failure, among others (Amato, Tachibana, Sparman, & Mitalipov, 2014). The clinical spectrum of mitochondrial disease is expanding but currently there are no curative treatments for mitochondrial disorders.

1.1.1 Mitochondrial disease

The most common mitochondrial diseases include Leber's hereditary optic neuropathy (LHON) which includes loss of vision; Leigh syndrome (subacute necrotizing encephalomyelopathy); mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS) syndrome; neuropathy, ataxia and retinitis pigmentosa (NARP syndrome); and myoclonic epilepsy with ragged red fibers (MERRF) syndrome (Smeets, 2013). Severity and age of onset have a wide range, but onset can be as early as the neonatal period, with some babies presenting with profound lactic acidosis and multi-organ failure.

These conditions can be caused by alterations in mtDNA, which is entirely maternally inherited via mitochondria in the cytoplasm of the egg (Amato et al., 2014). The ability to recognize the involvement of mtDNA in disorders is partly due to the availability of sequencing the mitochondrial genome, but the ability to interpret the pathogenicity of sequencing results is still a looming challenge, leaving many patients with uncertainty. There is also no doubt that many patients with mtDNA mutations go undiagnosed for years and many are probably never recognized (Taylor & Turnbull, 2005). When pathogenic mutations are identified they can take the form of large rearrangements, copy number variants or point mutations. Genetic defects of the human mitochondrial genome were first described in 1988 and arose from the investigation

of two syndromes — Kearns–Sayre syndrome (KSS) and LHON (Holt, Harding, & Morgan-Hughes, 1988; Wallace et al., 1988). In patients with KSS, single, large-scale mtDNA deletions (usually sporadic) were detected in muscle biopsies. For patients with LHON, a maternal pattern of inheritance was evident and point mutations involving the assortment of genes that code for complex I of the oxidative phosphorylation chain, which mitochondria use to make ATP, were identified. Since the late 1980s, several mutations of the mitochondrial genome have been identified and associated with disease (Taylor & Turnbull, 2005).

While mtDNA mutations are a known cause of mitochondrial disease, most instances of mitochondrial disease are actually caused by mutations in nuclear DNA. The nuclear DNA is inherited from both of an individual's parents. Half of an individual's nuclear DNA is inherited from their biological mother and half from their biological father, which is in contrast to the strictly maternal inheritance of mtDNA. The nuclear genome is comprised of over 20,000 genes and contains the instructions for bodies to grow and develop. The nuclear genome is robust, and for most individuals with mitochondrial disease the cause is a mutation in their nuclear DNA. Examples of mitochondrial conditions which are inherited due to mutations in nuclear DNA include mitochondrial recessive ataxia syndrome, which is marked by encephalopathy, ataxia, epilepsy and involuntary movement, Alpers-Huttenlocher syndrome, which is characterized by spasticity, blindness, liver dysfunction, and seizures and Carnitine deficiency, which includes cardiomyopathy, failure to thrive, and coma (Smeets, 2013). When combined, nuclear and mtDNA mutations cause mitochondrial disease in around 1 in 4,000 individuals (Taylor & Turnbull, 2005).

1.2 Preventing inheritance of mtDNA mutations

Once an individual has an identified mutation(s) that leads to mitochondrial disease certain approaches geared toward preventing the transmission of mtDNA mutations become available. This is partly due to the fact that there is no cure for mitochondrial disease. Supportive treatments may help with the signs and symptoms of mitochondrial disease, but cannot repair the molecular defect that causes disease. Some physicians prescribe a combination of vitamins and supplements, called a mitochondrial cocktail (Parikh et al., 2009), however evidence for its efficiency is lacking. Researchers understand the mechanisms of prevention far better than the mechanisms of treating mitochondrial disease. Mitochondrial conditions as a collective whole are common, but the incidence of each specific mitochondrial disease etiology is relatively rare (Parikh et al., 2015). This adds to the difficulty of diagnosis, accurate recurrence risk information, and treatment. Another very poignant reason many researchers are focusing on preventing transmission is that the phenotypic presentation of mtDNA mutations is unpredictable.

Unaffected individuals are typically homoplasmic, meaning all of the mitochondria in their cells share identical mtDNA copies. However, it is possible for some of the mitochondria in an individual's cells to have changes, or mutations, in their mitochondrial genetic code. This individual would be heteroplasmic due to their mix of mutated and wild type mtDNA and their ratio of mutated to wild-type mtDNA often affects presentation of illness (Amato et al., 2014). The proportion of mutated mtDNA (also known as mutant load) may range widely in different cells and tissues within the same individual. A certain proportion of abnormal mtDNA must be present to cause clinical disease, known as the threshold effect. The proportion of mutated mtDNA that will be passed down from mother to child is impossible to predict and is affected by

segregational bottleneck. When an egg is made the mtDNA molecules become the founders of all of the 100,000-600,000 mtDNA molecules in the mature oocyte (Smeets, 2013). This creates unpredictability of the level of heteroplasmy during oogenesis and subsequent offspring. Due to the inability to predict which mtDNA molecules get passed down, it is also unpredictable as to which will be the founders from which the rest will develop. Further, even within families with the exact same mutation mitochondrial disease can look completely different.

There are several factors that are important to remember when considering inheritance of mitochondrial disease. It is important to distinguish that an affected male will not pass down his mtDNA to the next generation, therefore the mtDNA mutation will not affect the next generation in the same way it would if the mutation is maternally inherited. It is also important to distinguish if the mutation leading to the symptoms of mitochondrial disease is in the nuclear DNA. As a person passes down half of their nuclear DNA in each pregnancy it is only a 50% chance of passing down the mutation and thus only up to a 50% chance of having an affected offspring; there are also nuclear DNA mutations that typically do not produce symptoms unless both parents carry the mutation and pass them down to their offspring, which is why the chance is not always 50% and is often less.

1.2.1 Oocyte donation

Presently oocyte donation is a reliable method to prevent the transmission of mitochondrial disease caused by mtDNA mutations (Smeets, 2013). With egg donation a child shares a genetic relationship with a donor and the intended father, should his sperm be used to fertilize the donor egg. In this mode of prevention the intended mother shares no genetic link to her child. This option has the possibility to reduce a child's risk of a mitochondrial disease to the

general population risk but it also creates a child that is only genetically related to the father not the mother. Oocyte donation thus may have an overarching impact on defining and redefining parenthood in a time where that word has many different meanings. Parenthood may refer to a genetic relationship between parent and child, or may be limited to the performative aspects of being a parent. If it is merely defined by the latter, then having an egg donor takes away the genetic link between mother and child but has no effect on parenthood, the reason being is parenthood is linked to performativity (Garasic & Sperling, 2015). If the former defines it, then oocyte donation creates a dilemma. The importance of preserving the genetic link between mother and child is just one reason some women with mitochondrial disease do not choose this technique to have children. Other reasons may include cost due to the fact that insurance companies typically do not cover this procedure. Further, individuals may face an ethical dilemma when it comes to using *in vitro* fertilization (IVF) (Johnson, 2016). IVF is a procedure where the sperm and donated egg are combined outside of the body and then implanted into the intended mother or surrogate. IVF is the underlying technique in many options for preventing the transmission of flawed mtDNA, including oocyte donation, and those opposed to IVF may take issue because it involves the destruction of at least one egg or embryo (Johnson, 2016).

This is also sometimes referred to as third-party reproduction, where there are players other than just the intended mother and father (Greenfeld, 2015). This technique began in the 1970s and since then robust research has been conducted to assess the outcomes of children who are products of IVF, ranging from investigating rates of imprinting disorders, to psychosocial and emotional affects, to the parent-child relationship observed (Colpin & Soenen, 2002; Raoul-Duval, Bertrand-Servais, & Frydman, 2009; Somjate Manipalviratn, 2009). Imprinting disorders are a group of rare congenital disorders that do not involve changes to the sequence of the gene,

but rather affect whether the maternal or paternal copy of a gene is expressed. Imprinted genes comprise a small subset of the genome whose epigenetic reprogramming in the germline is necessary for subsequent normal embryonic development. There have been conflicting studies assessing the possible association of imprinting disorders with assisted reproductive techniques (Paoloni-Giacobino, 2007). There is still a need for large-scale long term health studies on individuals born using assisted reproductive technology, but current research has not identified a direct link between assisted reproduction treatment and poor health outcomes in offspring (Fauser et al., 2014).

1.2.2 Prenatal diagnosis

Another available solution for preventing mitochondrial disease in subsequent generations is prenatal diagnosis. Prenatal diagnosis involves testing some of the cells from the developing fetus. The process is invasive and can be done by chorionic villus sampling or amniocentesis (Taylor & Turnbull, 2005). This testing relies on testing very few cells and extrapolating those results to the entirety of the developing fetus. What makes this process so difficult is in its interpretation in regards to mitochondrial disease. Due to the aforementioned concept of heteroplasmy it is possible for a percentage of mitochondria to have changes in their genomes that others do not, this is called mutant load (Wolf et al., 2015). Determining the mutant load of a developing fetus is not widely practiced. There are little data to support the idea that the mutant load is stable during embryonic development and across various tissues (Monnot et al., 2011). Even conceding that the mutant load can be measured accurately the interpretation and real world application of a clinical picture to give the mother carrying that fetus is shrouded in unknowns. The variability associated with mitochondrial disorders adds another burden for

parents who are deciding to continue or terminate a pregnancy (Smeets, 2013). There are exceptions to every rule and one exception is a very particular mutation that prenatal diagnosis can reliably predict the phenotype for, such as m.8993T>G which is associated with Leigh syndrome and NARP (neurogenic weakness, ataxia, retinitis pigmentosa). A mutant load of under 20% is thought to be a guarantee for an unaffected offspring, whereas a mutant load of over 60% would give a 25% chance of a severe outcome (White et al., 1999). With this information a potential couple still must decide their course of action, and there is still a gray area between 20% and 60% mutant load that inconclusive results exist. A similar study conducted in 2007 (Steffann et al., 2007) found that individuals with the m.8993T>C mutation and NARP or Leigh syndrome have a mutant load >80%. Most people with the m.8993T>G mutation and severe NARP or Leigh syndrome have mutant loads of $\geq 75\%$. However, patients with this mutation and “mild” NARP phenotype (problems with night vision and proximal muscle weakness) may have mutant loads ranging from 10 to 90%.

1.2.3 Preimplantation genetic diagnosis

A major difference between prenatal diagnosis and the frequently debated preimplantation genetic diagnosis (PGD) is that PGD involves IVF with testing for the genetic defect in an eight cell embryo prior to implantation into the uterus (Hoozemans, Schats, Lambalk, Homburg, & Hompes, 2004). This is merely a risk reduction strategy, as there is no way to tell if the mutation load from a single cell at the eight cell stage is consistent throughout the embryo and what threshold should be considered when discussing the specific case by case clinical interpretation. If PGD is used it is possible for a child to be born with a mutant load under the threshold for symptoms to show; however, it is no guarantee. Additionally, if that

child is female when she goes to have children she will be in the same situation as her mother and will be subject to the genetic bottleneck that may sway her oocytes' heteroplasmy levels (Taylor & Turnbull, 2005). PGD may not be an available option for mothers with high levels of heteroplasmy and, independently, also brings up a similar discussion of sex selection as mitochondrial donation.

It was hypothesized in 2013 that PGD may lead to the selection of male embryos over female embryos simply to try to eliminate the disease risk for future offspring because a male does not pass down his mtDNA (Smeets, 2013). A recent report from the National Academies of Sciences, Engineering and Medicine advised in February 2016 that the US Food and Drug Administration (FDA) should approve human clinical trials of the use of donor mtDNA, but only to create male embryos. This important caveat was included because male offspring do not pass down their mtDNA and thus the donor mtDNA would not have cross-generational effects. They did also consider expanding to include female offspring once the technique was deemed safe in the male offspring (Reardon, 2016).

1.3 Research on germline genetic modification

The limitations of the currently available techniques of oocyte donation, PGD and prenatal testing for the transmission of mitochondrial conditions include not maintaining the genetic link between mother and child, uncertainty of mutant load, likelihood of clinical disease, and inability to stop the inheritance of mitochondrial mutations for generations to come. Due to what these techniques lack, a new wave of scientific advancement is focused on merging the nuclear DNA of the intended mother, the mtDNA of a donor, and sperm from the intended father. Two different approaches have been proposed, each with the same end, a child with

nuclear DNA from both parents and healthy mtDNA from a donor. This technique creates germline changes that will be passed on and on, and if done successfully, healthy mtDNA will be passed on and on (Wolf et al., 2015).

It is important to discuss what steps were made in the past in order to open the door for the two approaches being researched today. The idea of combining DNA from three individuals for a fetus is not new, but rather began with cytoplasmic transfer (CT) in the 1990s (Garasic & Sperling, 2015). CT involves the injection of cytoplasm from a donor egg into an egg with compromised mitochondria, which is then fertilized with sperm. This technique was initially used twenty years ago to help couples struggling with infertility. It was believed when Jacques Cohen and his team at the Institute for Reproductive Medicine and Science at Saint Barnabas Medical Center in New Jersey performed CT that it would boost the mother's egg to develop into a viable egg for IVF (J. Cohen, Scott, Schimmel, Levron, & Willadsen, 1997; Connor, 2014). An unintended consequence of early work with CT was the creation of two or more different cell lines in at least two of the seventeen children born using this technique. This was the first instance of germline mtDNA changes and in 2002 the US FDA began requiring IVF clinics to complete an Investigational New Drug (IND) protocol before continuing germline modification, which essentially halted all applications of this technique in IVF clinics (Connor, 2014). Nearly 10 years have passed since this FDA ruling and currently the FDA is circling back to reexamine this therapeutic twist on IVF (Craven et al., 2010).

1.3.1 Mitochondrial replacement therapy

Mitochondrial replacement therapy (MRT) is known by many other names including three-parent IVF, mitochondrial transfer, mitochondrial donation, and three-person embryos

(Baylis, 2013; Poulton et al., 2010; Masahito Tachibana et al., 2012). These names all refer to the same principal of nuclear DNA from an intended mother and mtDNA from a donor being combined with sperm from the intended father to prevent the transmission of a mtDNA mutation from mother to child (Roberts, 1999). MRT and three-parent IVF will be used to describe the technique from this point on. The concept of manually replacing mutated mtDNA with donor mtDNA is the core principal in MRT. There are two different approaches for this, maternal spindle transfer and pronuclear transfer (Garasic & Sperling, 2015).

Maternal spindle transfer involves the maternal spindle, which is the structure that contains the nucleus of the egg before it is fertilized. The nucleus is home to the nuclear DNA, the vast majority of genetic material in a cell that determines how a body grows and develops. In this technique the maternal spindle of the intended mother's egg is removed and placed into a donor's enucleated egg (M. Tachibana et al., 2009). The result is an egg cell with the nuclear DNA of the intended mother and the mtDNA of the donor egg. It is then ready to be fertilized by sperm and implanted in the intended mother (Garasic & Sperling, 2015).

Pronuclear transfer begins with fertilization of the donor's egg and intended mother's egg with sperm from the intended father. After the eggs are fertilized, the pronuclei (the combination of the nuclear DNA from the intended parents) are removed and similar to the prior technique placed where the pronuclei of the donor embryo (the combination of the nuclear DNA from the intended father and donor) once was. The embryo will thus have nuclear DNA from its intended mother and father and mtDNA from the donor (Craven et al., 2010). The key is that these techniques are shown to not interrupt developmental competence of said egg or embryo (M. Tachibana et al., 2009).

In the past researchers used mouse models to experiment with combining nuclear DNA and donor mtDNA. These experiments produced mixed results, some progeny were heteroplasmic having both donor and maternal mtDNA, while others were homoplasmic normal in the first generation. On average the reconstructed zygotes contained 19% mtDNA of maternal origin (Connor, 2014). Moreover researchers found that in third and fifth generation mice heteroplasmy was still evident, revealing that while for some it takes few generations to become homoplasmic, others pass down stable amounts of both origin and donor mtDNA leading to persistent heteroplasmy (Meirelles & Smith, 1997). Researchers are establishing preclinical models for MRT using mature nonhuman primate oocytes. They are using the maternal spindle transfer technique reconstructing oocytes by MRT prior to fertilization. Four infant rhesus monkeys have been born so far and importantly there was only evidence of mtDNA from the donor (M. Tachibana et al., 2009). The percent heteroplasmy of the four monkeys (Mito, Tracker, Spindler and Spindy) was measured in cord blood at birth and skin at 19 months (Wolf et al., 2015). All were essentially at the level of detection and did not change significantly over time. Importantly, it is essentially impossible to ensure there is no cytoplasm transferred along with the genetic material from intended mother to donor cell. Extraordinary precision is required to remove a maternal spindle, though the intent is to solely transfer the DNA material it is possible for some cytoplasm containing mitochondria and thus mtDNA to be transferred in the process as well. Though the heteroplasmy levels in these monkeys was right at the level of detection (<3%), the same cannot be guaranteed should the technique be used in humans. Growth curves for these four monkeys also showed they were in the normal range for the first 30 months of their lives, but that is all the information published about them. This technique is currently being put forward as a reliable method to avoid transmission of mtDNA diseases in humans.

MRT is the only proposed technique that enables the mother and father to sustain a genetic relationship with their child while preventing the transmission of faulty mtDNA from mother to child. Thus it brings up a similar discussion of the definition of parenthood as oocyte donation. Again parenthood may refer to a genetic relationship between parent and child, or may be limited to the performative aspects of being a parent. If it is merely defined by the latter, then having three genetic contributors doesn't make three parents. If the former defines it, then adoption creates a dilemma. When a child is adopted social dynamics dictate that the child then receives adoptive parents. The reason being is parenthood is linked to performativity (Jacques Cohen & Alikani, 2013). In the case of MRT a mtDNA donor will have a genetic relationship to that child, and if the definition of parenthood rested solely on genetic connection, then that person is a parent. However, if parenthood is more than genetics and is truly linked to performativity, then calling an mtDNA donor a parent and calling MRT three-parent IVF may be misnomers. This requires deep thought and consideration because the definition of parenthood and family is a moving target in today's world and the simple addition of one mtDNA donor and an intended couple equals three parents is an oversimplification. What ties a family together, genetics or experience and can there be one without the other?

A useful parallel to discuss is the use of a sperm donor, where individuals similarly have a genetic contribution from an outside source to create a child. Again the definition of parent differs, "One person's DNA is another person's dad" (Mahlstedt et al., 2010). To many individuals wanting to have children, conception is the first step. To the couple that has experienced infertility, conception is the goal and represents the end of a possibly very grueling process. To specialists in reproductive medicine, conception means success of treatment. To the

“hoped-for children,” however, conception is the beginning of their lives (Mahlstedt et al., 2010).

Putting the safety of the future child is paramount before considering implementation or approval for clinical trials by the FDA (Powledge, 2014). There is, however, a model to learn from, as the United Kingdom is to become the first country to allow this technique to prevent the transmission of mtDNA mutations by creating babies with genetic contributions from three people. The British Parliament’s House of Lords approved legislation for DNA replacement therapy in February 2015 (Dimond, 2015). It is possible that children in the UK will be born using this technique as early as 2016 and an estimated 150 could be born each year. Prime Minister David Cameron was quoted, “We’re not playing God here, we’re just making sure that two parents who want a healthy baby can have one” (Gallagher, 2016). The method, which was developed in Newcastle, should aid women like Sharon Bernardi, from Sutherland, who lost all seven children of her children to mitochondrial disease. She watched her first three children pass away within hours of being born due to metabolic acidosis and her last three each die before turning two. Her fourth child, her son Edward, survived the first few hours of life. He could walk, talk, laugh, and met all of his milestones on time. It was at age two that the seizures began. In 1994, at age 4 he was diagnosed with Leigh’s disease, a mitochondrial condition that primarily affects the central nervous system. Ms. Bernardi believes that MRT may help other women with mitochondrial disease and it will help keep Edward’s legacy alive (Callaway, 2014).

1.3.2 Media debate surrounding MRT

With the ability to impact families such as the Bernardis, it may come as a surprise that patients, journalists, scientists and ethicists are fiercely divided over this technique. Many individuals took to the media to express their arguments for and against the US FDA taking the steps to approve MRT. It stands to reason that these arguments are helping shape the way individuals in the mitochondrial community see it. And if the media is supplying false information it can cause widespread misconceptions about the technique, the first being about the utility (Cussins, 2013). Due to the relative frequency with which babies are born with a mitochondrial disease, about one in 200 each year, it would seem plausible that this technique would be a common practice (Cussins, 2013). This quoted number represents all mitochondrial disease and here a very important distinction must be made. As reviewed in detail above, mitochondrial disease can be caused by mtDNA mutations, which this technique may have the power to aid, but the majority of mitochondrial disorders are caused by mutations in a person's nuclear DNA. Because nuclear DNA is still being passed down from mother and father to child when MRT is used, this technique would be futile if the disease causing mutation is in the nuclear DNA of either parent. In short, this technique would help only a minority of individuals with mitochondrial disease (Taylor & Turnbull, 2005). This detail is not being explained in many media sources, leading individuals to miscalculate whom this technique can help and whom it cannot.

Another interesting media perspective is centered on the contribution of the egg donor. The percent of DNA the donor will contribute to the child is 0.1%. And that 0.1% is potentially enough to prevent the child from having a difficult disease. It is a number easy to downplay and thus has been so in the media but one that should not be as easily brushed over. Many individuals

argue that because the contribution is mtDNA, which doesn't affect the visible traits of the person, it thus doesn't affect their identity. But identity is far more than what can be seen on the outside. Identity is a combination of constructed beliefs, desires, traits, and emotions (Baylis, 2013). It is thus difficult to assess whether a person without a mitochondrial disease and a person with a mitochondrial disease will have the same identity. Going beyond the idea of healthy and ill, a person with mitochondrial disease and one without may have a difference in perspective, may have a different community of support, and may have a different view of family planning (Bredenoord & Braude, 2010; Garasic & Sperling, 2015; Smeets, 2013).

Another major point of contention being debated in the media is the way that MRT is being dubbed a cure and/or treatment. This is leading individuals to believe that MRT has powers to affect the lives of those currently affected with a mitochondrial disease. This is simply untrue. MRT only has the ability to prevent the transmission of a previously identified mtDNA mutation with the help of an egg donor, MRT and IVF. MRT does not help any individual with the devastating effects of a mitochondrial disease. In addition, many women with mitochondrial disease are not healthy enough to plan a family using MRT. Many women with an mtDNA mutation are living each day with symptoms of mitochondrial disease and they are concentrating on maintaining their own health, not their reproductive options. Some individuals see money and time being spent on MRT as secondary, at best, to the real struggle of mitochondrial disease, the disease itself. If MRT is receiving attention it does benefit the overall awareness of mitochondrial disease and it is a positive thought that this attention may bring with it attention to finding a cure, but that may be overly optimistic and misguided.

Another critical subject debated frequently pertains to the safety of this technique. Safety is an obvious concern, but one not so obvious caveat is whose safety merits concern. There is the

safety of the intended mother, the egg donor, and the child conceived by this technique, but there is also the need to protect the safety of the members of subsequent generations. This is the first technique to produce a germline change, one that will be passed from generation to generation. It truly has the potential to affect generations to come in ways we currently cannot predict (Baylis, 2013; Bredenoord & Braude, 2010; Garasic & Sperling, 2015). This issue brings up the discussion of autonomy. When an individual decides to make a decision that impacts their life they are doing so because they have the autonomy, or the right to decide what occurs in their future. Here the discussion of autonomy centers on making medical decisions. By introducing a germline change, each time a female child conceived via MRT reproduces the mtDNA from the donor will be passed down. This takes decision of whether or not to become a product of MRT away from subsequent generations (Darnovsky, 2013). This can constitute a loss of autonomy because it leaves someone without a choice. A counter argument is that one does not choose their genetic material regardless of their mode of conception so no autonomy is being lost in this process. A recommendation is thus to give consideration to the potentially overarching impact of this technique, beyond merely one generation.

A final topic hotly debated in the media is called the “designer baby argument” (Johnson, 2016). This spells out that choosing mtDNA for a child is choosing or designing preferable characteristics of a future child. MtDNA modification is one of the most scrutinized techniques in recent history because by approving MRT it may open the floodgates to gene editing. Will it be soon be possible for affluent parents to pick out every trait down to their child’s eye color or musical skill? This is what ethicists call a ‘slippery slope’ (Darnovsky, 2013; Dimond, 2015; Johnson, 2016; Powledge, 2014). It is difficult to predict how much power individuals’ will have over genetics, but many are cautious that MRT it a powerful first step. On the other hand, many

feel that it would be unethical to take a precautionary stance against MRT. Scientists do not work in a social vacuum. There must be technological advancement guided by a moral compass. In the end, the FDA will be in charge of approving clinical trials for mitochondrial modification and setting the boundaries for the ways they should be conducted (Powledge, 2014).

1.4 Aim of the present study

Currently the FDA is considering the approval of human trials using MRT with IVF. The United Kingdom's House of Lords and House of Commons voted to approve legislation in 2015 allowing MRT to produce children from two biological parents and a mtDNA donor (Gallagher, 2016). The United Kingdom is the first country to explicitly allow this procedure. This technique allows the ability to prevent individuals inheriting mtDNA mutations from affected mothers, however it is controversial because the donor mtDNA may be passed down from generation to generation. This technique has been vehemently debated in the media due to ethical and legal concerns. There is, however, a lack of research analyzing the perspectives of individuals this technique is designed for. To address this gap, members of the mitochondrial disease community were surveyed for their knowledge and perception of MRT, their attitudes toward the process, and the overarching impact of the media debate that surrounds this technique.

1.5 Statement of hypothesis

My hypothesis is twofold: (1) there is a lack of knowledge in the mitochondrial disease community of the technique's possible benefits and limitations and (2) the way the media

shapes the technique has the potential to alter individual's perceptions and thus possibly their future actions.

1.6 Significance

The connection between this assisted reproductive technology and the mitochondrial community will be healthcare professionals. As individuals specifically trained to help people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease, genetic counselors in particular must be aware of the benefits and limitations of the techniques being marketed and debated in the mitochondrial disease community. This will allow them to share a balanced, truthful and comprehensive summary of MRT with their patients. The mitochondrial disease community has much to gain from this scientific advancement but due to a lack of a balanced amount of published information focusing on both the benefits and the limitations of this technique this community may have misguided notions or beliefs about mitochondrial modification.

II. MATERIALS AND METHODS

This study was evaluated and classified as exempt research by the Institutional Review Board of the University of California, Irvine (HS# 2015-2404)(Appendix D).

2.1 Recruitment

Participants were recruited to partake in an anonymous web-based survey that was created on SurveyMonkey, a free, online survey development company. No researcher had any direct contact with the participants. Enrolment was exclusively through online avenues, including posting the link to the survey on the lead researcher's Facebook page. Also the lead researcher made a partnership with Cristy Balcells, the director of MitoAction: Mitochondrial Disease Action Committee (Appendix B). An electronic flier (Appendix C) with information regarding the survey, contact information for all researchers, as well as the direct link to the survey was generated for distribution through MitoAction's email lists.

2.2 Participants

The participant population included American individuals 18 years of age or older who considered themselves part of the mitochondrial disease community. For purposes of this survey, membership of the mitochondrial disease community included individuals either personally affected by a mitochondrial disease or suspected mitochondrial disease or who have an affected friend, spouse or family member. As the survey was only available in English, the participants were required to read and understand English. All other population characteristics were accepted. There was no discrimination based on gender, race/ethnicity, age or education level.

2.2.1 Protection of participants' privacy

The privacy of participants was a priority throughout the data collection process. There was no patient identifying information collected for this research. There was no direct contact between the researchers and the participants nor were there any known harms or discomforts associated with the study aside from the potential of emotional stressors that may arise from answering the questions, which are not thought to be beyond those encountered in daily life. All research data was stored confidentially and securely through a password protected account on SurveyMonkey.com.

2.3 Informed consent

Informed unwritten consent was obtained via the use of an IRB-approved study information page that served as the initial page of the online survey. By choosing the “Next” option, the survey participant gave consent as a research participant. The information page contained the purpose of the study, some general background on the topic of MRT, the eligibility requirements and the research team’s contact information. The participant also had the opportunity to exit the survey at any time as well as to choose to skip any question that would bring them discomfort by answering. It was possible that the survey questions could bring anxiety or a fear of judgment or invasion of privacy, due to the questions about personal relationships and health and thus the opportunity to exit the survey was always available.

2.4 Survey

This research questionnaire was created using SurveyMonkey.com and the direct link was <http://www.surveymonkey.com/r/MITOSurvey>. The entire survey can be viewed in

Appendix A. The survey consisted of 30 questions across 17 pages. Of the 30 questions, 2 were fill-in answer, 19 were multiple-choice, and 9 were questions with sub-questions. The total time required to complete the survey was between 10-20 minutes. The major themes addressed throughout the survey included: 1) the awareness and knowledge of the MRT technique, 2) the accessibility of genetic testing, 3) the general approval trend of the technique, 4) the ethical debate swarming around the technique in the media, and 5) how this technique affects parenthood and the future for individuals in the mitochondrial community. This survey relied upon skip logic technology in order to route the participants to specific questions based on their previous answers so as to not ask them questions that did not apply to them. The questions were all developed and edited by the research team; they were not adapted from previous survey tools.

2.4.1 Survey scoring

Perceived knowledge of the MRT technique was scored on a 5-point scale: 5=I could explain MRT to a medical professional; 4=I understand the process of MRT but don't know all the details; 3=I still have a lot of questions but understand the general topic; 2=I have limited knowledge of MRT; 1=I know almost nothing about MRT. The higher an individual scored the higher their perceived knowledge of MRT. The individual also had a perceived knowledge score of mitochondrial disease. This was also calculated on a 5-point scale: 5=I could explain mitochondrial disease to a medical professional; 4=I understand mitochondrial disease more than most people but don't know all the details; 3=I still have a lot of questions but understand the general topic; 2=I have limited knowledge of mitochondrial disease; 1=I know almost nothing about mitochondrial disease. The perceived knowledge scores were compared to see if individuals with greater perceived knowledge of mitochondrial disease in general also had a

greater perceived knowledge of MRT. Then the individuals were placed into quartiles (defined by median) based on their perceived knowledge scores about MRT. Group one had the lowest perceived knowledge score and group four the highest. The true/false questions measured actual genetic knowledge (Appendix A, Question 15); correct responses were scored as 1 and incorrect responses were scored as 0. The higher the total score, the greater that person's actual knowledge of MRT and mitochondrial disease as a whole. The individuals were then divided into quartiles (defined by median) based on their actual knowledge scores about MRT and mitochondrial disease as a whole. Similarly, group one had the lowest actual knowledge score and group four the highest.

Attitudes toward MRT were also scored. These questions included both positive attitude statements and negative attitude statements. The positive statements were scored on a 5-point scale: 5=Strongly Agree; 4=Agree; 3=Neutral; 2= Disagree; 1=Strongly Disagree. The negative statements were scored on a 5-point scale using reverse scoring: 1=Strongly Agree; 2=Agree; 3=Neutral; 4= Disagree; 5=Strongly Disagree. A higher score correlated to more favorable attitudes. Participants were then grouped into either favorable or unfavorable attitude categories based on their total scores, split at the median. Attitudes toward the media portrayal of MRT were also scored. These questions included both positive and negative attitude statements (Appendix A, Question 20). The positive statements were scored on a 5-point scale: 5=Positive; 4=Somewhat Positive; 3=Neutral; 2= Somewhat Negative; 1=Negative. An individual's higher score correlated to more positive attitudes despite the different media perspectives. Participants were then grouped into either positive attitude or negative attitude categories based on their total scores, split at the median.

2.5 Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) Version 23. This is a descriptive study of perceived mitochondrial disease risk, attitudes and knowledge of MRT, and the media's ability to bias perceptions. Prior to analysis, several new variables were created. Knowledge scores were created by summing the number of correct responses within the set of true/false questions. High, mid and low knowledge groups were composed using a quartile split on the sum score of all knowledge items. A 5-point Likert ordinal scale was used to measure the extent to which a respondent agreed or disagreed with various questions (as detailed above). Individual attitude scores were created from these responses by summing the point total over 12 questions. High, mid and low attitude groups were composed using the same approach.

Chi-square analysis was used to test for association between nominal (categorical) variables. Relationships among self-reported mitochondrial disease knowledge, actual knowledge, and attitudes toward MRT were investigated. Goodman and Kruskal's gamma was used to test for association between the ordinal variables knowledge and attitude (each scored as 'high', 'mid', and 'low'). Goodman and Kruskal's gamma was also used to examine the relationship between reported knowledge of mitochondrial disease and reported knowledge of MRT. A one-way analysis of variance (ANOVA) was used compare the mean knowledge scores of respondents grouped by categorical variables such as age group, education level, mitochondrial community connection, and others. ANOVA was also used to test for a significant effect of these categorical groupings on other continuous variables (such as attitude score). P-values of less than 0.05 were considered statistically significant. No correction was made for multiple comparisons.

III. RESULTS

3.1 Sample characteristics and demographic information

A total of 210 study respondents began the survey, 41 respondents were ineligible to complete the survey because they held no connection to the mitochondrial community (neither affected themselves nor had a family member or friend affected). Of the 169 eligible respondents, 165 completed the entire survey and those exclusively were used for analysis. Females represented 89.7% of respondents and males 9.1%, 1.2% of respondents preferred not to answer. Further, 50.3% of individuals were married while 26.7% were single. The majority of respondents, 81.8%, reported Caucasian ancestry, 3.0% African American, 6.1% Hispanic, 4.8% Asian etc. as noted in Table 1. Age groups were divided as follows: 3.0% were 18-20, 29.1% were 20-29, 20.6% were 30-39, 20.6% were 40-49, 17.0% were 50-59 and 9.7% were over the age of 60. For data analysis the individuals aged 18-20 and 20-29 were grouped as one category because of small sample sizes.

Individuals were asked about how they were connected to the mitochondrial community. The options included: being affected with a mitochondrial disease or suspected mitochondrial disease, being affected and having a family member affected, having a child affected, having a sibling affected, having a spouse affected, having a parent affected, having an extended family member, having a friend affected or none of the above (Figure 1).

TABLE 1: CHARATERISTICS OF 165 ENROLLED RESPONDENTS	Total	
	N	%
Age		
18 to 29	53	32.1%
30 to 39	34	20.6%
40 to 49	34	20.6%
50 to 59	28	17.0%
60 or older	16	9.7%
Gender		
Female	148	89.7%
Male	15	9.1%
Prefer not to answer	2	1.2%
Level of education		
Less than high school degree	3	1.8%
High school graduate or equivalent (e.g., GED)	15	9.1%
Some college, no degree	40	24.2%
Associate degree	17	10.3%
Bachelor degree	65	49.4%
Graduate/professional degree or equivalent	25	15.2%
Relationship status		
Married	83	50.3%
Widowed	2	1.2%
Divorced/Separated	15	9.1%
In a domestic partnership	5	3.0%
Single, but cohabitating with a significant other	16	9.7%
Single, never married	44	26.7%
Ethnicity/race		
Caucasian	135	81.8%
Black or African American	5	3.0%
Hispanic	10	6.1%
Asian	8	4.8%
Native Hawaiian or Pacific Islander	2	1.2%
Native Indian or Native Alaskan	1	0.6%
Prefer not to answer	4	2.4%

Table 1 shows the breakdown of demographic information of the 165 survey respondents. Respondents were characterized based on age, gender, level of education, relationship status and ethnicity/race.

FIGURE 1: CONNECTION TO THE MITOCHONDRIAL COMMUNITY

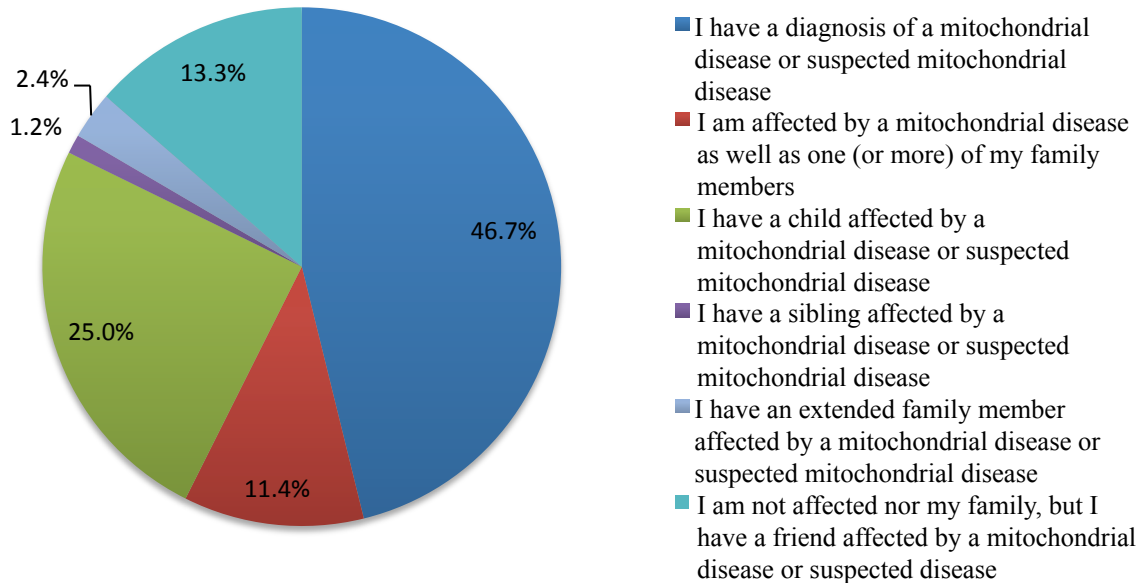


Figure 1 shows the 165 respondents' connections to the mitochondrial community.

3.2 Genetic counseling and genetic testing

Individuals were asked if they (or the affected individual) had ever had an appointment with a genetic counselor. The majority (72.8%) answered that they had met with a genetic counselor to discuss genetic testing for mitochondrial disease, 22.4% had not and 4.8% answered unsure/unknown (Figure 2).

FIGURE 2: GENETIC COUNSELING APPOINTMENT

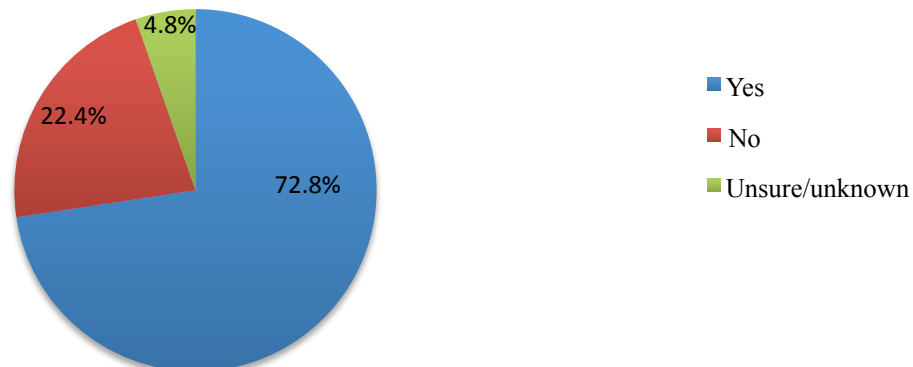


Figure 2 is a depiction of the answer breakdown to the question, "Throughout the diagnosis process, has the individual with a mitochondrial disease or suspected mitochondrial disease (either yourself or another individual) ever had an appointment with a genetic counselor to discuss genetic testing for mitochondrial disease?" All 165 respondents answered this question.

Then the respondents were asked if they (or the affected individual) had genetic testing to identify a disease causing mutation. The majority, 69.1% of those surveyed, responded 'yes' while 18.2% responded 'no' and 12.6% answered 'unsure/unknown' (Figure 3A). Those who met with a genetic counselor were significantly more likely to have undergone genetic testing ($p < 0.001$). Among the group that had genetic counseling, 84.4% of respondents received genetic testing, whereas of the group who did not receive genetic counseling, only 35.1% received genetic testing.

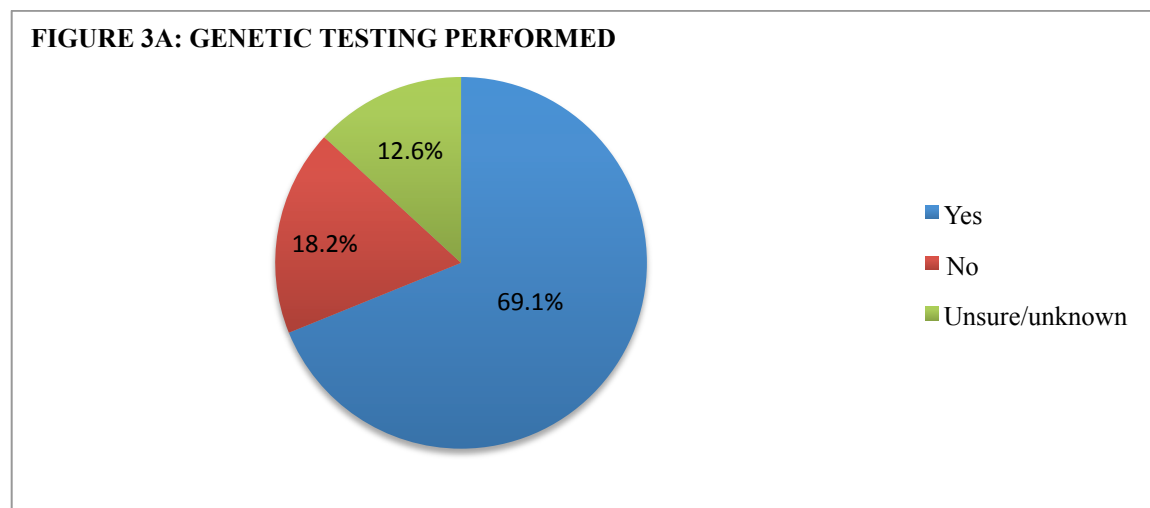


Figure 3A is a breakdown of 165 respondents' answers to the question, "Did the person with a mitochondrial disease or suspected mitochondrial disease (be it yourself or another individual) have genetic testing to identify a disease causing mutation(s)?"

The respondents who reported receiving genetic testing were asked if genetic testing revealed a disease-causing mutation and if so, to indicate the type of mutation. Of the 116 individuals who had genetic testing, 63 (53.9%) reported that a disease-causing mutation was identified. Of the 63 whose mutations were identified, 36 (56.5%) had a mtDNA mutation, 20 (32.2%) had a nuclear DNA mutation, and 7 (11.3%) were unsure of the mutation status (Figure 3B).

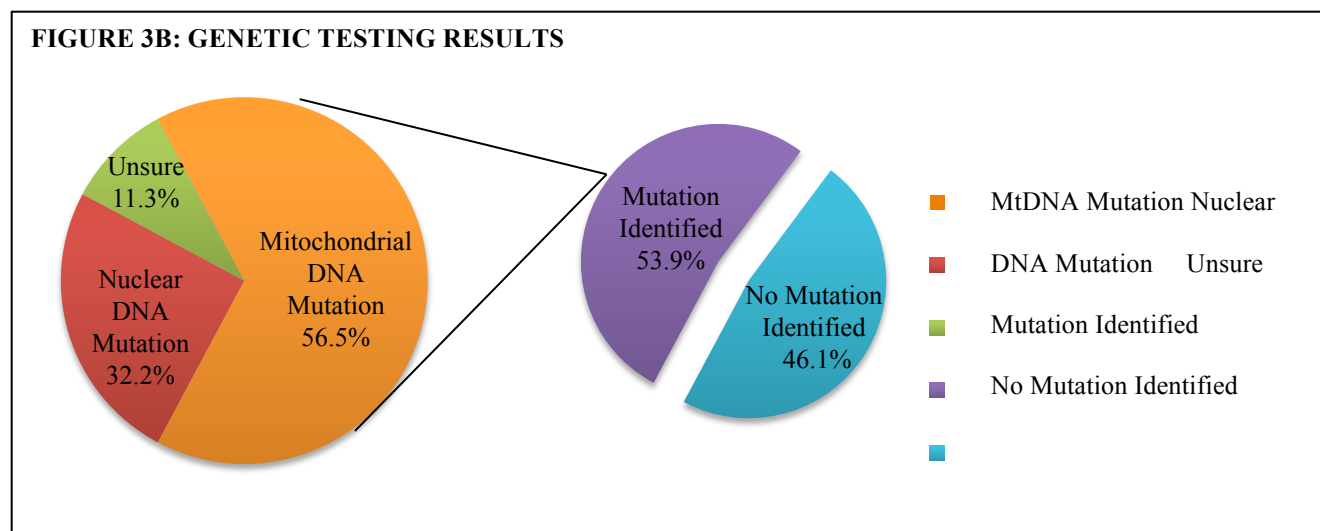


Figure 3B is a graphic representation of the different types of DNA mutations identified through genetic testing. 116 individuals underwent testing, and 63 had a mutation identified.

3.3 Accessibility of information on MRT

Respondents were asked to detail if they had prior knowledge of MRT to help gauge the accessibility of information regarding the MRT technique (Appendix A, Question 11). The majority of respondents (71.5%) had heard of the MRT technique prior to this survey. Among those who had heard of the technique and those who had not, no statistically significant difference in age ($p=0.625$) or education level ($p=0.641$) was identified. However, there was statistical significance when examining the connection with the mitochondrial community and prior knowledge of MRT ($p=0.039$). Among individuals affected by mitochondrial disease ($n=96$), 74 (77.1%) had heard of MRT. Of individuals with a family member affected ($n=47$), 33 (70.2%) had prior knowledge of the technique while among individuals with a friend affected, ($n=22$) 11 (50.0%) had heard of the technique prior to the survey.

When respondents were asked where they had first heard of the technique, an overwhelming majority (78.0%) of individuals answered a media source, including a news

program or Facebook/some other website, 10.2% from foundation information/meeting, 6.8% from word of mouth, 4.2% from a doctor and 0.8% from a genetic counselor (Figure 4).

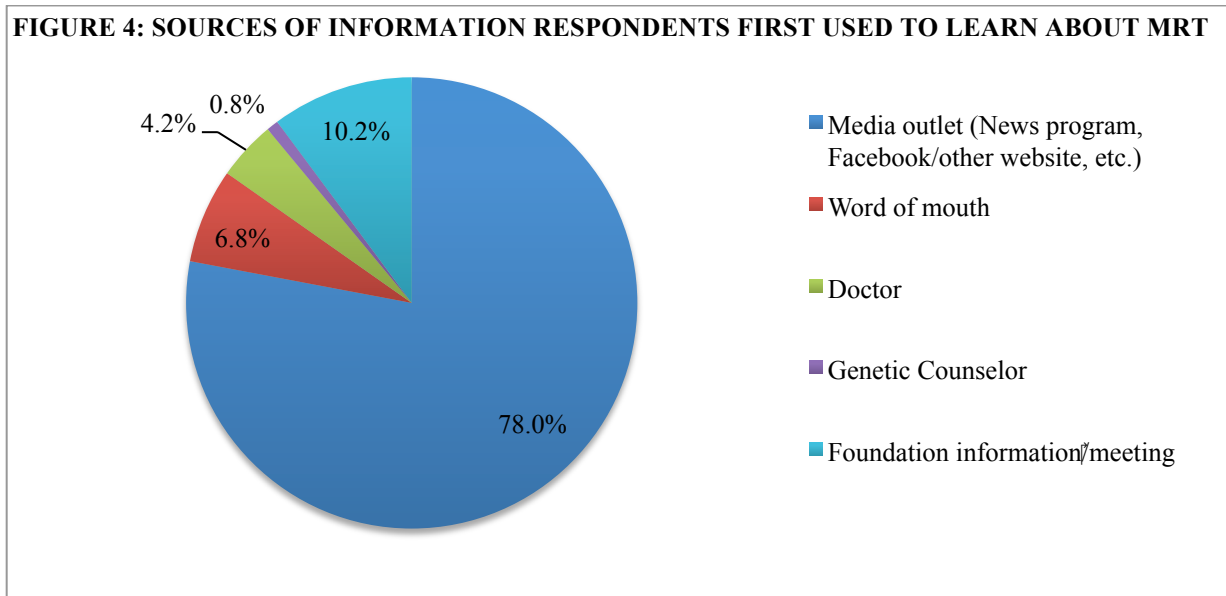


Figure 4 lists the sources for information on MRT for the 118 individuals who had prior knowledge of the technique.

3.4 Calculated knowledge of mitochondrial disease and MRT

Individuals were then asked to state their own personal knowledge of both MRT and mitochondrial disease as a whole prior to a series of six true/false questions about mitochondrial disease and the replacement technique. The results of their personal assessment of their knowledge are in the tables below (Table 2, Figure 5).

TABLE 2: SELF-REPORTED KNOWLEDGE OF MRT AND MITOCHONDRIAL DISEASE		
Self-reported knowledge of MRT	N	Percent
I know almost nothing about MRT.	20	12.1%
I have limited knowledge of MRT.	20	12.1%
I still have a lot of questions but understand the general topic.	30	18.2%
I understand the process of MRT but don't know all the details.	73	44.2%
I could explain MRT to a medical professional.	22	13.3%
Self-reported knowledge of Mitochondrial Disease	N	Percent
I know almost nothing about mitochondrial disease.	4	2.4%
I have limited knowledge of mitochondrial disease.	5	3.0%
I still have a lot of questions but understand the general topic.	19	11.5%
I understand mitochondrial disease more than most people but don't know all the details.	58	35.2%
I could explain mitochondrial disease to a medical professional.	79	47.9%

Table 2 shows the 165 respondents' self-reported knowledge of both MRT and mitochondrial disease

Figure 5 below is a visual representation of respondent's self-reported knowledge. As the bar graph shows, many individuals clustered around knowing about both mitochondrial disease and replacement. Goodman and Kruskal's gamma was run to determine the association between knowledge of mitochondrial disease and knowledge of MRT among the 165 respondents. There was a strong, positive correlation between self-reported knowledge of mitochondrial disease and knowledge of MRT, which was statistically significant ($G=0.708$, $p<0.001$).

FIGURE 5: SELF-REPORTED KNOWLEDGE OF MRT AND MITOCHONDRIAL DISEASE

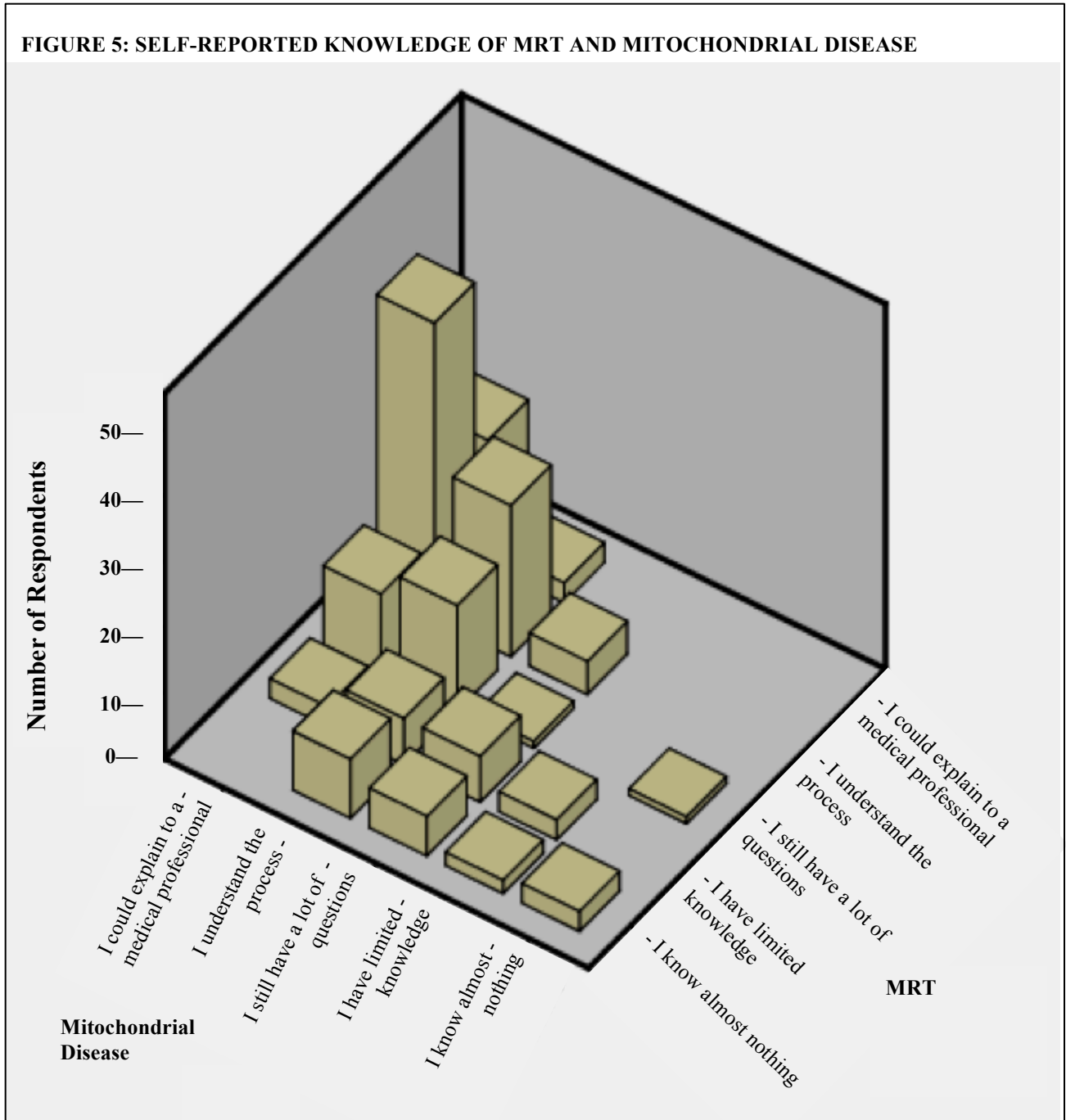


Figure 5 displays the distribution of self-reported knowledge of both MRT and mitochondrial disease. There was a strong, positive correlation between self-reported knowledge of mitochondrial disease and knowledge of MRT, which was statistically significant ($G=0.708$, $p<0.001$).

Overall knowledge scores were calculated for each individual. One point was given for each correct true/false question answered correctly, with zero points for incorrect answers (Table 3A).

The maximum possible score was six and minimum score was zero. Table 3B shows the mean, median and mode of 5.0 (Table 3B).

TABLE 3A: KNOWLEDGE OF MITOCHONDRIAL DISEASE AND MRT		% Answering Correctly
<i>Mitochondrial Disease Questions:</i>		
1. Mitochondria are responsible for producing energy for our bodies		99.4%
2. There are treatments but currently no cure for mitochondrial diseases		84.8%
3. A man passes down his mtDNA to all of his children but a woman does not pass on her mtDNA to any of her children		97.0%
Average subsection score		93.7%*
<i>MRT (MRT) Questions:</i>		
4. MRT can help prevent mitochondrial diseases in the offspring of all individuals affected with mitochondrial disease		51.5%
5. If a couple successfully pursues MRT, then the donor mtDNA in their children can be passed down to subsequent generations		78.2%
6. MRT has the potential to prevent certain mitochondrial diseases		93.3%
Average subsection score		74.3%*
Overall Average score		84.0%**

Table 3A displays the respondents' answers to true/false questions about mitochondrial disease and MRT. Responses were used to calculate knowledge score. All 165 individuals answered all of these questions.

*Average percent of correct answers per subsection. **Average percent of correct answers overall.

TABLE 3B: KNOWLEDGE SCORE BREAKDOWN		
Mean		5.0
Median		5.0
Mode		5.0
Std. Deviation		0.91
Percentiles	33.3	5.0
	66.7	6.0

Table 3B displays the statistical information used to group the 165 respondents based on their calculated knowledge score

Actual knowledge scores were compared across individuals' connections to the mitochondrial community. Individuals were grouped based on if they were affected themselves (affected + family member affected also), if they were unaffected but had a family member affected, or if they were unaffected but had a friend affected. The affected group had a total of 96 individuals (58.2% of total), the family member affected group had a total of 47 (28.5% of total) and the friend group had a total of 22 individuals (13.3% of total). Among individuals with a

family member affected the affected individual was a child in 85.7%, a sibling in 4.1%, and an extended family member (aunt, uncle, cousin etc.) in 10.2%. The average knowledge scores for each group are shown in Table 4. The mean knowledge score for affected individuals was slightly higher than for individuals with an affected family member, whose scores were slightly higher than those with a friend affected. However there was no statistically significant difference between the knowledge scores of the three groups ($p=0.403$, Table 4).

We also examined if there was a difference in knowledge scores when considering whether or not individuals met with a genetic counselor. The knowledge scores of affected individuals who met with a genetic counselor to discuss mitochondrial disease were higher than those who did not meet with a genetic counselor (5.14 vs. 4.76, $p=0.016$, Table 4).

Knowledge scores were also compared across age groups and education levels. The ages were grouped as shown in Table 1. The average knowledge score was highest for individuals between 40-49 years old (5.21) and lowest for individuals 30-39 years old (4.80), but no statistical significance was found between age group and knowledge score ($p=0.351$, Table 4). When considering education level, individuals who had less than a high school degree and those who had a high school degree or equivalent were grouped ($n=18$, mean=4.61). The remaining categories were: some college, but no degree ($n=40$, mean=4.95), Associate degree ($n=17$, mean=4.82), Bachelor's degree ($n=65$, mean=5.01), and those with a Graduate/professional degree ($n=25$, mean=5.52). This difference in means was statistically significant ($p=0.014$, Table 4).

TABLE 4: COMPARISON OF MEAN KNOWLEDGE SCORES BY DEMOGRAPHIC CHARACTERISTICS				
Respondent demographics	N	Mean Score	SD	p-value
Age				0.351
18 to 29	53	5.04	0.88	
30 to 39	34	4.79	1.04	
40 to 49	34	5.21	0.88	
50 to 59	28	5.00	0.98	
60 and over	16	5.25	0.68	
Level of education				0.014
Less than high school degree/High school degree or equivalent	18	4.61	0.92	
Some college, no degree	40	4.95	0.93	
Associate degree	17	4.82	0.81	
Bachelor degree	65	5.08	0.96	
Graduate/professional degree or equivalent	25	5.52	0.65	
Connection to the Mitochondrial Community				0.403
Affected (+/- affected family member)	96	5.10	0.91	
Family member affected	47	5.00	0.88	
Friend affected	22	4.82	1.00	
Met with a Genetic Counselor				0.016
Yes	120	5.14	1.10	
No	37	4.76	0.81	

Table 4 shows the differences in knowledge scores among the 165 respondents when compared to various demographic information, connection to the mitochondrial community and genetic counselor involvement.

Individuals were then grouped based on their knowledge score. Individuals with a score of 3/4 (no one scored lower than a 3) were placed into the “Low Knowledge Group”, those who scored a 5 were placed into the “Mid Knowledge Group” and those who scored a 6 were placed into the “High Knowledge Group” (Table 5).

TABLE 5: KNOWLEDGE SCORE GROUPS			
Knowledge Score	Knowledge Group	Frequency	Percent
3/4	Low	42	25.5%
5	Mid	63	38.2%
6	High	60	36.4%

Table 5 displays the frequency and percent of individuals in each knowledge subgroup and their corresponding knowledge score. All 165 respondents were placed into a knowledge group based on the number of true/false questions they answered correctly (out of six).

3.4.1 Perceptions of the limitations of MRT

Question 4 (Appendix A) proved to be the most challenging (Table 3A). The true/false question stated: “MRT can help prevent mitochondrial diseases in the offspring of all individuals affected with mitochondrial disease.” Nearly half of individuals (48.5%) incorrectly indicated that this was true; the statement is actually false because the technique is only designed to work for individuals who have mitochondrial disease due to an identified mtDNA mutation. When the ability to answer this question correctly was broken down by age group, there was no statistically significant difference among age and those who answered it correctly or incorrectly ($p=0.369$). Similarly, when analyzed based on having a genetic counseling appointment or not individuals with an appointment were no more likely to answer this question correctly ($p=0.815$). Affected individuals were also statistically no more likely to answer this question correctly compared to those who have a family member or friend affected ($p=0.531$). Those with a higher education level were also no more statistically likely to answer this question correctly ($p=0.123$). Those

with an identified mtDNA mutation were no more likely to choose the correct answer than those with a nuclear DNA mutation ($p=0.297$).

However, when compared to individuals' self-reported knowledge of MRT, there was a statistically significant difference in ability to answer this question correctly (Figure 6A, $p<0.001$). Further, when comparing respondents' self-reported knowledge of mitochondrial disease and the ability to answer this question correctly, there was an overall statistically significant difference (Figure 6B, $p=0.010$). Generally, those with higher self-reported knowledge of both MRT and mitochondrial disease performed better on this true/false question, showing that they may more fully understand a major limitation of MRT, a lack of universality. All individuals with mitochondrial disease cannot use this technique because it requires an identified pathogenic mtDNA mutation in the family.

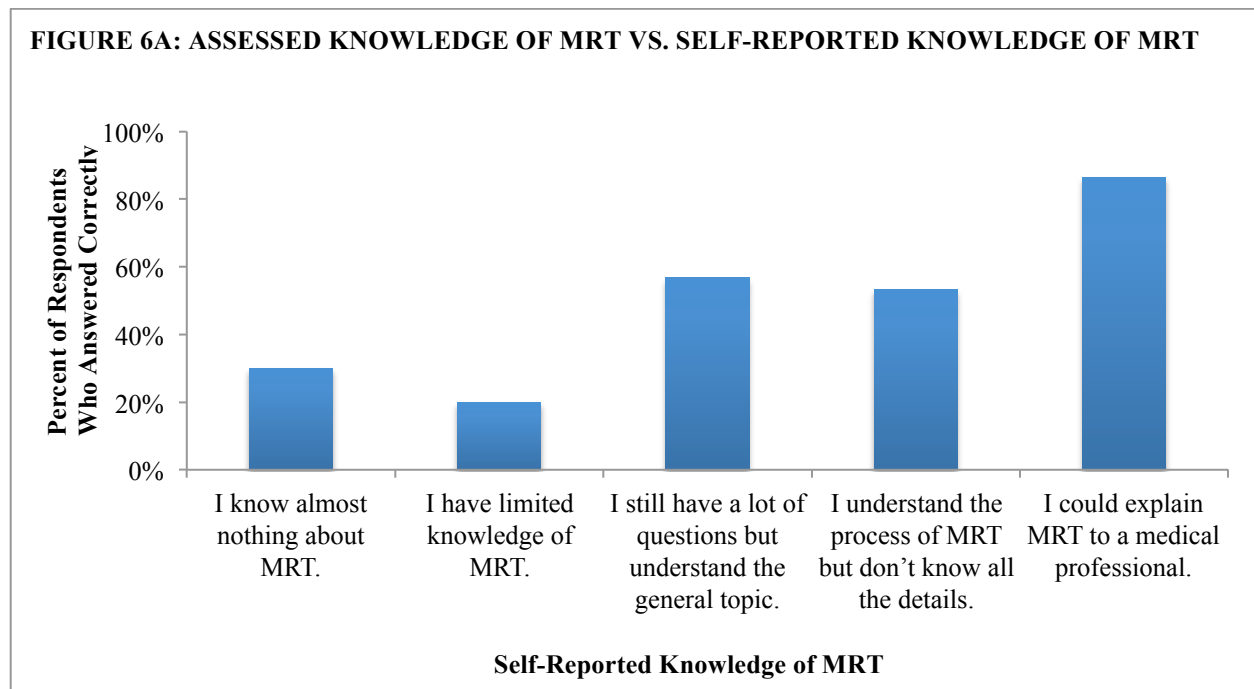


Figure 6A displays the distribution of self-reported knowledge of MRT and the ability to answer the following question correctly, "MRT can help prevent mitochondrial diseases in the offspring of all individuals affected with mitochondrial disease." A statistically significant difference was seen overall, as those with more self-reported knowledge were more likely to also correctly assess MRT's limited utility.

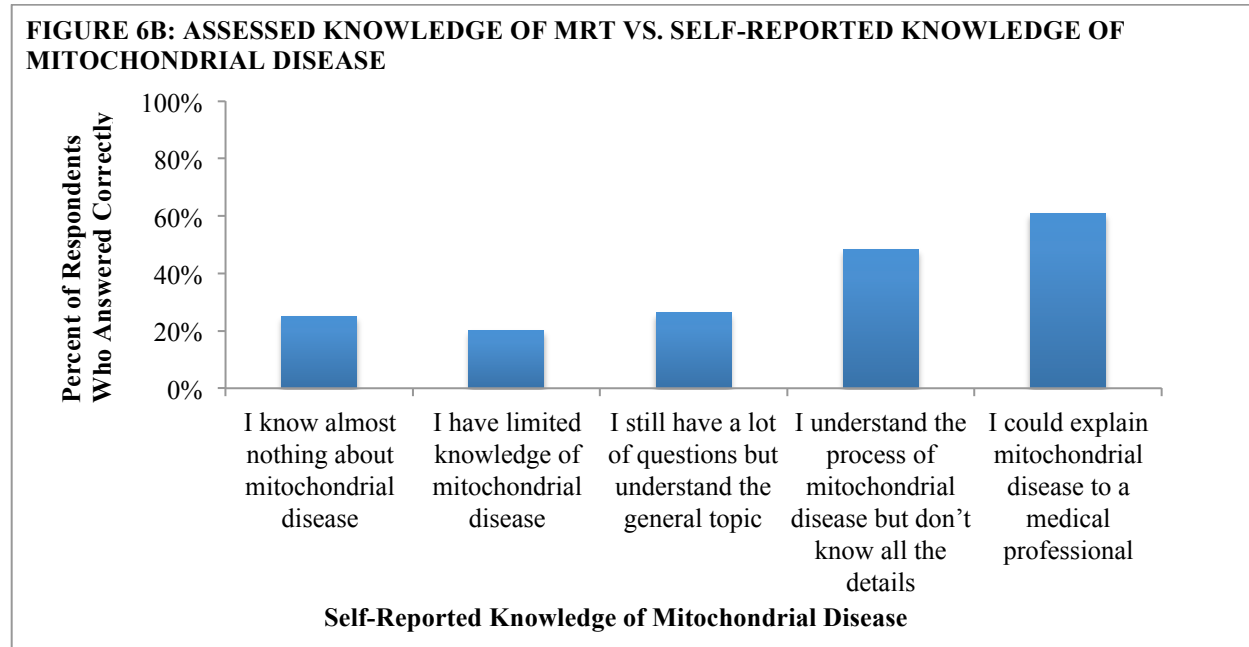


Figure 6B displays the distribution of self-reported knowledge of mitochondrial disease and the ability to answer the following question correctly, “MRT can help prevent mitochondrial diseases in the offspring of all individuals affected with mitochondrial disease.” A statistically significant difference was seen overall, as those with more self-reported knowledge were more likely to also correctly assess MRT’s limited utility.

3.5 Summed attitude scores

Individuals were asked a series of survey questions in order to help gauge their outlook on MRT (Questions 16 A-E, Questions 18 A-E, Question 21 A-B, Appendix A). The questions in their entirety and the percentage breakdown for the respondents’ answers to the 12 survey questions are compiled in Table 6. Each question was scored and then summed to give individual overall attitude scores. For favorable statements respondents were given 5 points for choosing strongly agree, 4 for agree, 3 for neutral, 2 for disagree, and 1 for strongly disagree.. Statements in the oppositional attitudes section were reverse coded, 1 point for strongly agree, 2 for agree, 3 for neutral, 4 for disagree, and 5 for strongly disagree. The maximum attitude score was 60 (5 points for each of 12 questions) and the minimum score was 12 (1 point for each question). The higher the score the more the respondents agreed with the positive statements about MRT and the more they disagreed with the negative statements about the technique (Figure 7, Table 6).

TABLE 6: ATTITUDES TOWARD MRT	Strongly Agree/Agree	Neither Disagree Nor Agree	Disagree/Strongly Disagree
<i>Favorable Attitudes</i>			
If I were to have a child, they would be at risk to have a mitochondrial disease	70.3%	11.5%	18.2%
If I were at risk to have a child with a mitochondrial condition I would use mitochondrial replacement to have unaffected children in the future if it were clinically available.	64.3%	17.5%	18.2%
There is already enough proof available to show that mitochondrial replacement is safe for the mtDNA donor, the intended couple and their children	40.6%	41.3%	18.1%
The FDA should approve human clinical trials of mitochondrial replacement	73.9%	16.5%	9.6%
Mitochondrial replacement should be covered by health insurance	81.2%	13.3%	5.5%
I personally consider mitochondrial replacement an ethical practice.	71.5%	13.3%	15.2%
I The media's portrayal of mitochondrial replacement is accurate.	21.3%	49.6%	29.1%
Introducing mitochondrial replacement into clinical practice will have a positive impact on the mitochondrial community.	67.3%	23.6%	12.1%
<i>Oppositional Attitudes</i>			
If I were at risk to have a child with a mitochondrial condition I would not pursue mitochondrial replacement because it requires <i>in vitro</i> fertilization, a technique that I would not consider using.	12.2%	13.9%	73.9%
If I were to pursue mitochondrial replacement it would have a negative impact on my relationship with the mitochondrial disease community.	4.8%	37.0%	58.2%
Dozens of countries and various international human rights documents express concern about changing a person's genetic code because our genes are passed from generation to generation and the impact of changing them cannot truly be known.	35.8%	30.3%	33.9%
The "designer baby argument" questions the right of parents to choose which genetic characteristics are best for their children. Mitochondrial replacement is "designing a baby," because it allows parents to choose their child's genetic make-up in the same way as choosing a baby's gender or eye color.	14.5%	18.8%	66.7%

Table 6 shows the statements and responses used to calculate individual attitude scores. All 165 respondents answered these questions and received a summed attitude score.

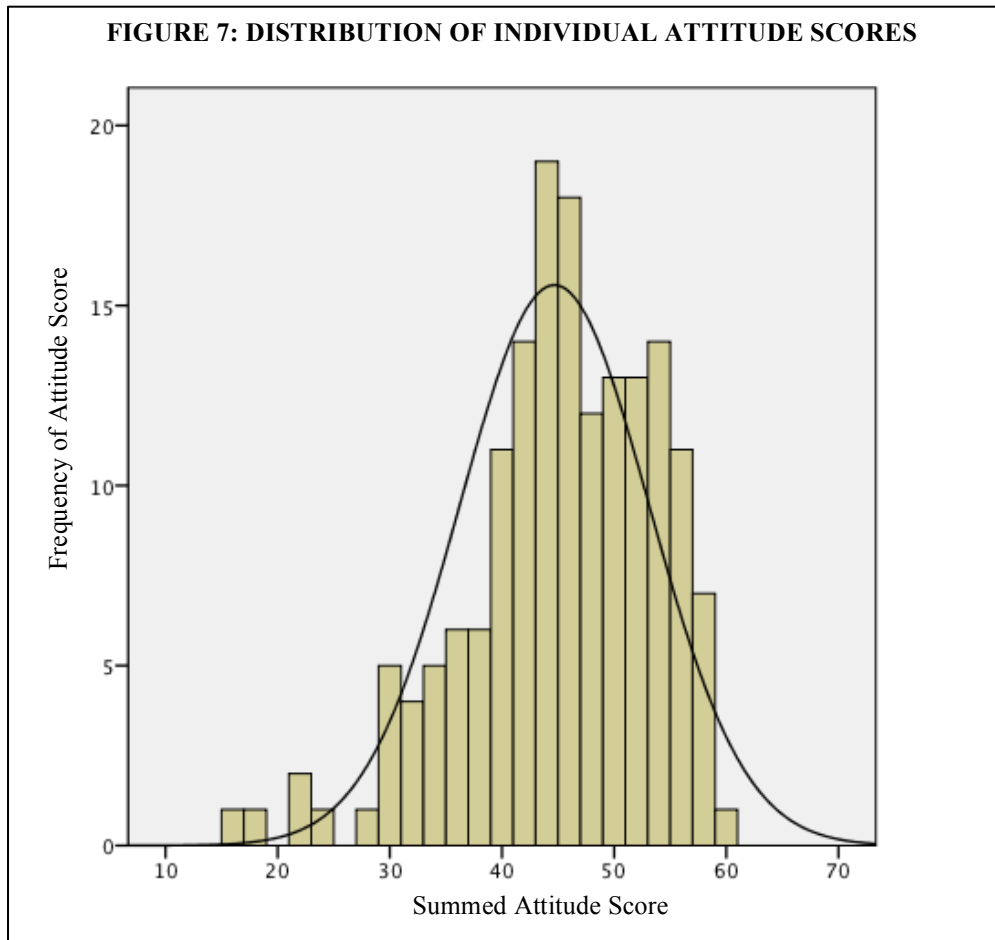


Figure 7 is a histogram showing frequency of attitude score across all 165 respondents. The mean score was 44.7 and the standard deviation was 8.5. The highest possible score was 60. The superimposed curve represents the best-fit line.

In addition to overall attitude score, answers to individual questions were analyzed. The respondents were asked if their child was at risk for a mitochondrial disease and whether they would pursue MRT (Appendix A, Question 18B, see Appendix F and G respectively for individual free-response explanations). Participants were stratified based upon their position within the mitochondrial community (affected vs. family/friend affected). The majority of responders (66.7% for affected and 61.0% for friend/family affected) strongly agreed or agreed that they would undertake MRT if it were clinically available. There was not a statistically significant difference between an individual's connections to the mitochondrial community and whether or not they would use MRT ($p=0.766$, Figure 8).

FIGURE 8: RESPONDENTS' WILLINGNESS TO UNDERGO MRT IF CLINICALLY APPROPRIATE AND AVAILABLE

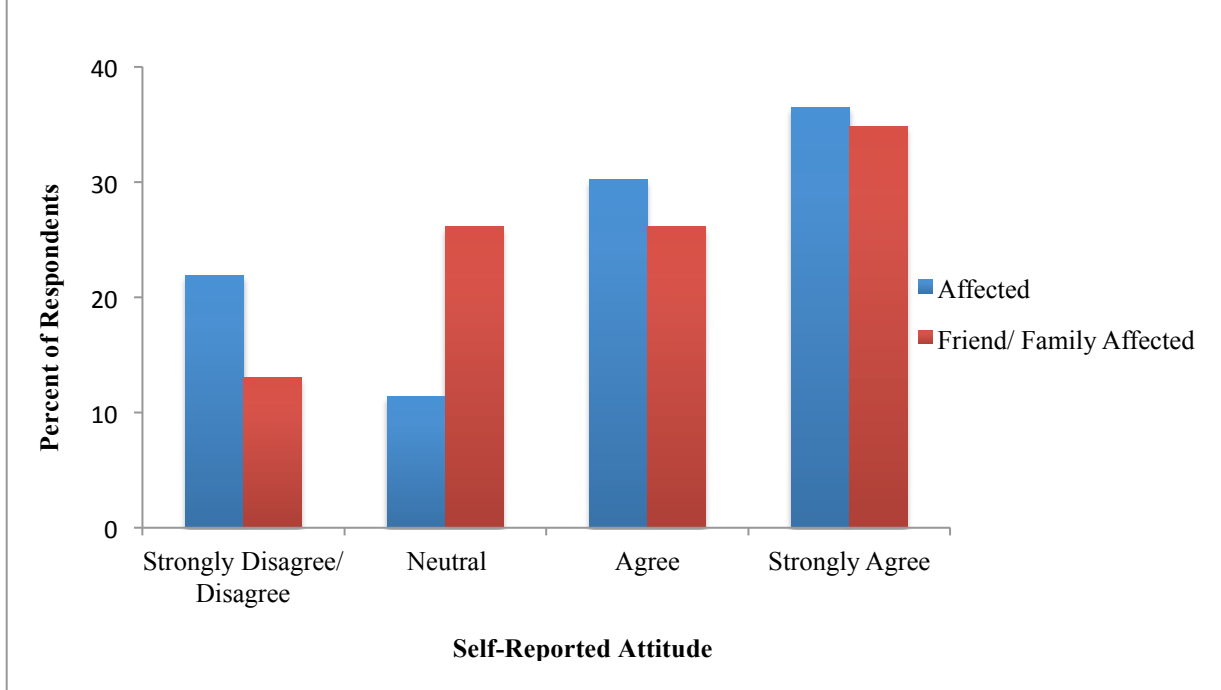


Figure 8 represents the breakdown of respondents' answers to the question, "If I were at risk to have a child with a mitochondrial disease I would use MRT to have unaffected children if it were clinically available." Responses of those who are affected versus those who have a friend/family member affected are compared side by side. No statistically significant differences were seen between responses and connection to the community.

Similarly agreeable trends were seen when a question was posed about the FDA approving clinical trials of MRT (Appendix A, Question 16B). Participants were asked, "The FDA should approve human clinical trials of MRT." Among those personally affected 73.0% agreed or strongly agreed with FDA approval; among those with a friend or family member affected 75.4% agreed or strongly agreed. There was not a statistically significant difference between an individual's connection to the mitochondrial community and whether or not the FDA should approve clinical trials, ($p=0.905$). However, only 39.5% of those affected and 42.0% of those with a family member or friend affected agreed or strongly agreed that there is already enough data showing the MRT technique is safe for the mtDNA donor, the intended couple and their children.

Individuals were then asked what was the most important to them when personally considering MRT. The majority of individuals, 52.7%, stated that the safety of MRT was most important, followed by considering the technique ethical, followed the ability to have the procedure covered by health insurance and FDA approval (Figure 9, see Appendix E for individual free-response explanations).

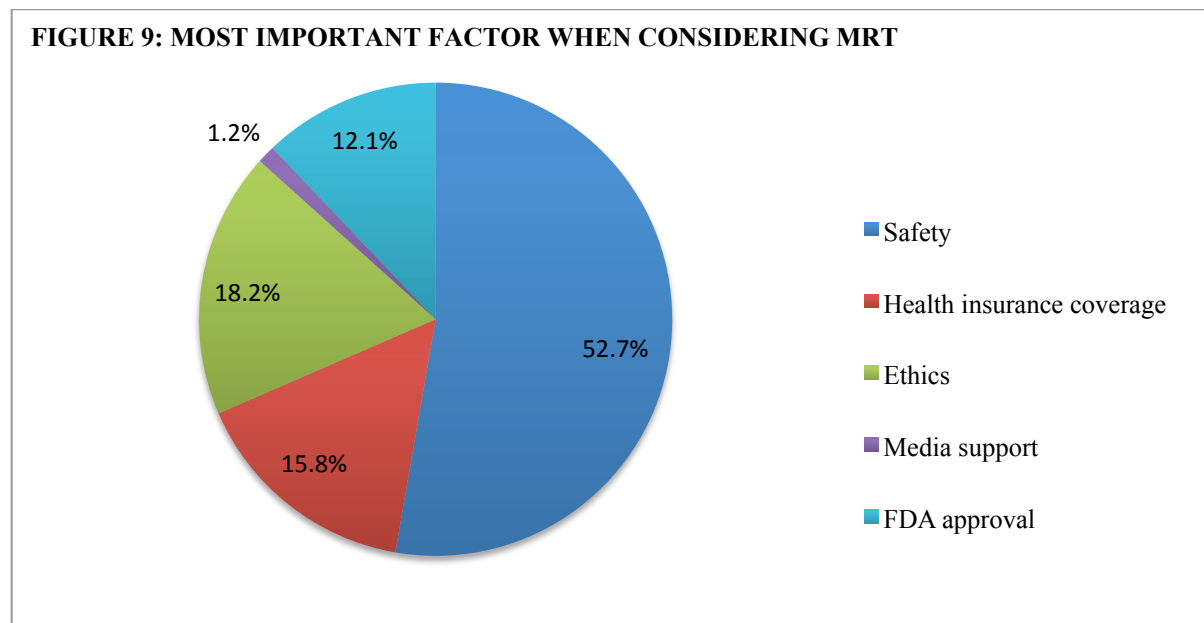


Figure 9 displays participant preference for what is most important to them when considering MRT. All 165 participants answered this question.

3.5.1 The ethics of MRT

The majority of respondents overall (73.9%) believed that the MRT process is ethical. Those who agreed or strongly agreed MRT was ethical were unsurprisingly also statistically significantly more likely to be willing to use MRT if it were clinically available ($G=0.647$, $p<0.001$). Addressing MRT's reliance on IVF was explored via the following statement: "If I were to have a child at risk for a mitochondrial disease I would not pursue MRT because it relies on IVF, a technique I would not consider using." The majority of individuals (73.9%) disagreed

or strongly disagreed that IVF was a deterrent (Appendix A, Question 18B, free-response explanations in Appendix H). Even when stratified by membership within the mitochondrial community the trend of disagreeing/strongly disagreeing with the statement continued (69.8% of those affected and 79.7% of those with a family member or friend affected). Individuals were also asked whether they felt this technique was ethical, 46.1% of individuals strongly agreed this technique was ethical while an additional 25.5% agreed it was ethical. When stratified by membership within the mitochondrial community connection similar trends were observed (Table 6).

Individuals were also asked about the ‘designer baby’ argument that is prevalent when this technique is discussed in the media. The designer baby argument details that individuals who pursue MRT are ‘choosing’ or ‘designing’ the traits of their children. Again, as seen in Table 7, the majority of individuals (66.7%) disagreed or strongly disagreed with the validity of this argument. In a separate question individuals were asked if they believe that MRT will alter the traits of the offspring including hair color, personality or height. MtDNA does not have the ability to alter the visible traits of the offspring; however, 21% of the respondents believed that the use of MRT would impact the child’s traits (Table 6, see Appendix L for individual free-response explanation). Respondents who believed this technique can alter traits also were statistically more likely to feel that this technique was “designing babies” ($p=0.001$). Also individuals who answered that the traits are not affected by MRT had a significantly higher mean knowledge score than those who believed traits would be affected by this process (5.2 vs. 4.5, $p<0.001$).

3.5.2 *Variation in attitude score*

As displayed in Table 7, attitude scores varied by age with a statistically significant difference in attitude score by age group ($p=0.043$). The lowest attitude score was among those aged 40-49 years (score 42.1) and the highest score was among those over 60 years (score 50.0). Attitude scores were then compared to education level of the respondents. There were differences in average attitude scores across levels of education but none were statistically significant ($p=0.326$, Table 7), indicating that the variation in scores cannot be explained by education level.

Differences in attitude scores were also analyzed based on membership within the mitochondrial community. Individuals with a family member affected had the highest mean attitude score of 45.7, individuals who were affected (+ or – a family member) had a mean attitude score of 44.6 and individuals with friends affected had a mean score of 42.6. There was no statistically significant difference between the attitude score of the three groups ($p=0.343$, Table 7). This shows there is variation in the means of attitude scores that cannot be explained by mitochondrial community connection. The attitude scores of those who were affected and met with a genetic counselor were compared to those who did not meet with a genetic counselor. The attitude scores of affected individuals who met with a genetic counselor to discuss mitochondrial disease were higher (45.4 vs. 43.0). The difference in attitude scores between the two groups was not statistically significant ($p=0.126$, Table 7).

TABLE 7: DIFFERENCES IN ATTITUDE SCORES AMONG DIFFERENT PARTICIPANT GROUPS				
Respondent demographics	N	Mean Score	SD	p-value
Age				0.043
18 to 29	53	44.57	7.58	
30 to 39	34	45.18	8.86	
40 to 49	34	42.06	9.26	
50 to 59	28	44.39	8.97	
60 and over	16	50.00	5.47	
Level of education				0.326
Less than high school degree/High school degree or equivalent	18	44.22	8.57	
Some college, no degree	40	45.10	8.01	
Associate degree	17	40.76	10.37	
Bachelor degree	65	45.65	8.43	
Graduate or professional degree or equivalent	25	44.44	7.58	
Connection to the Mitochondrial Community				0.343
Affected (+/- family member)	96	44.64	9.06	
Family Member Affected	47	45.74	8.41	
Friend Affected	22	42.55	4.98	
Meeting with a Genetic Counselor				0.126
Yes	120	45.43	8.44	
No	37	43.00	8.33	

Table 7 shows the differences in attitude scores among the 165 respondents when compared to various demographic information, connection to the mitochondrial community and genetic counselor involvement.

3.6 Overall attitude scores vs. knowledge scores

In order to compare attitude and knowledge scores, both sets of scores were divided into three groups (high, mid, and low). Beginning with attitude score, the average attitude score was 44.7, the minimum was 16 and the maximum was 59. The attitude scores were divided into three groups based on percentiles cut at 33.3% and 66.7%. There were 57 individuals who scored between 16-42 and were in the lowest attitude group, 55 individuals scored between 43-49 and were in the mid attitude group and 53 scored between 50-59 and were in the high attitude group.

The knowledge scores were divided into three groups based on percentiles cut at 33.3% and 66.7%. There were 42 individuals who scored either three or four correct answers and were in the lowest knowledge group, 63 individuals scored five correct answers and were in the mid attitude group and 60 scored all six questions correct and were in the high attitude group. Goodman and Kruskal's gamma was run to determine the association between grouped attitude score and knowledge score among the 165 respondents. There was a mild, positive correlation between grouped attitude score and knowledge score, which was not statistically significant ($G=0.130$, $p=0.178$). There was not an observed statistically significant trend of individuals in the high knowledge score group also belonging to the high attitude score group.

The mean overall attitude score was examined in each knowledge group as well. The lowest knowledge group had a mean attitude of 44.0, the mid knowledge score group had mean 44.3 and the highest knowledge group had a mean attitude of 45.5. There was not a statistically significant difference between the mean attitudes of the different knowledge score groups. As seen in Figure 9, there was some variation among the mean attitude scores, but it is not explained by statistically significant difference in knowledge ($p=0.620$).

FIGURE 10: COMPARISON OF KNOWLEDGE ABOUT AND ATTITUDE TOWARDS MRT

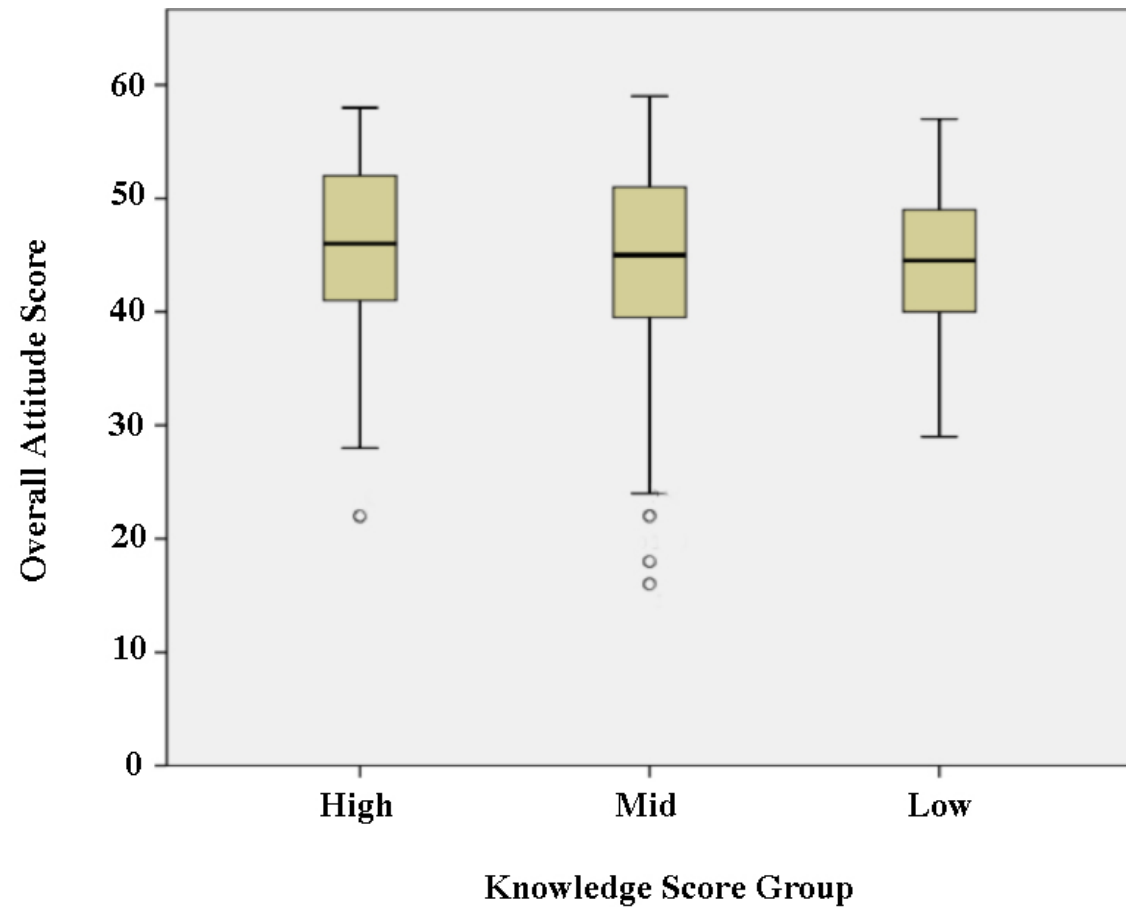


Figure 10 is a graphic representation of the similarity between mean and distribution of attitude score compared to knowledge subgroups (mild outliers, between an inner and outer fence, are marked with circles)

3.7 Comparison of summed attitude score and self-reported attitude score

As an independent measure of the accuracy of the summed attitude scores individuals were separately asked to choose the option that best matched their attitude towards MRT (Figure 11). To determine how these self reports compared to our inferred attitude scores described in detail above, we assigned points to these responses based on the following system: positive (5 points), somewhat positive (4 points), neutral (3 points), somewhat negative (2 points) and negative (1 point). The majority of individuals felt positively (55%) or somewhat positively

(23%) about MRT. Eleven percent felt neutral, eight percent felt somewhat negatively about MRT, and three percent responded feeling negative about MRT (Table 8, Figure 11).

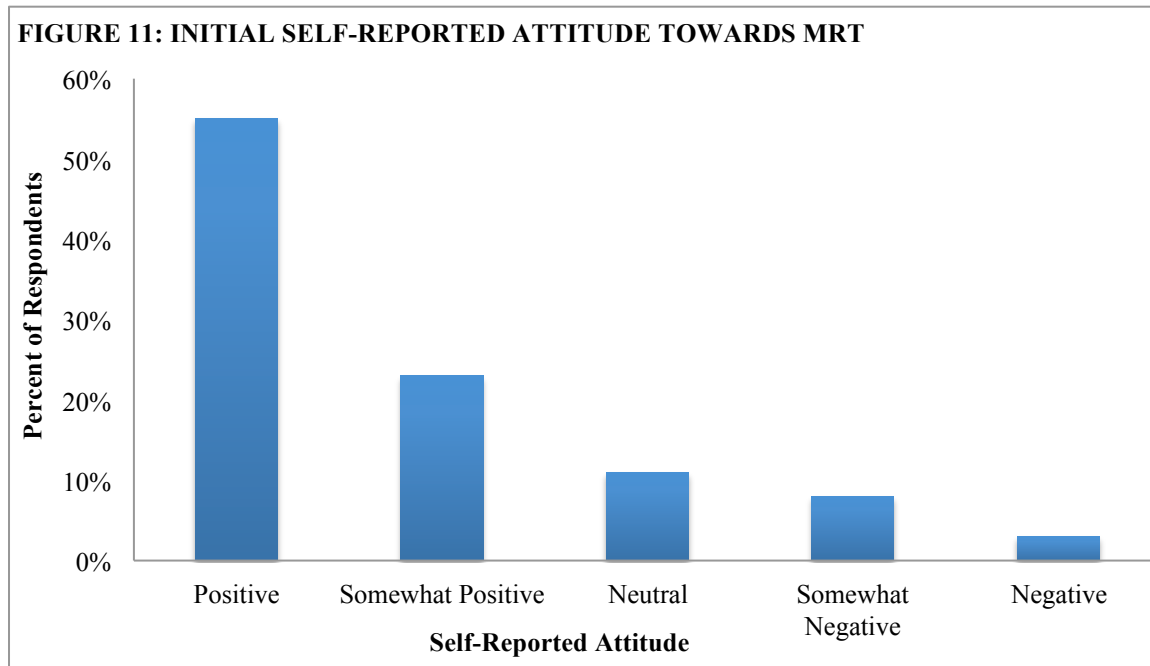


Figure 11 shows percent of respondents in each self-reported category of general attitude towards the MRT technique.

The mean attitude score for each of these groups (positive, somewhat positive, neutral, somewhat negative, negative) was calculated as an independent measure of the accuracy of the overall attitude score calculated agreement/disagreement with 12 survey questions (Table 6). The self-reported attitude score is an independent control to assess the validity of the individual summed attitude scores out of a total of 60 points. Individuals who self reported a negative attitude toward MRT had the lowest mean attitude score (29.4), followed by somewhat negative (31.1), followed by neutral (37.7), followed by somewhat positive (42.1) and positive (50.0) ($F=64.951$, $df: 4-160$, $p<0.001$). This check on internal consistency helps to validate the accuracy of the individuals' summed attitude scores.

FIGURE 12: COMPARISON OF SELF-REPORTED AND CALCULATED ATTITUDE SCORE

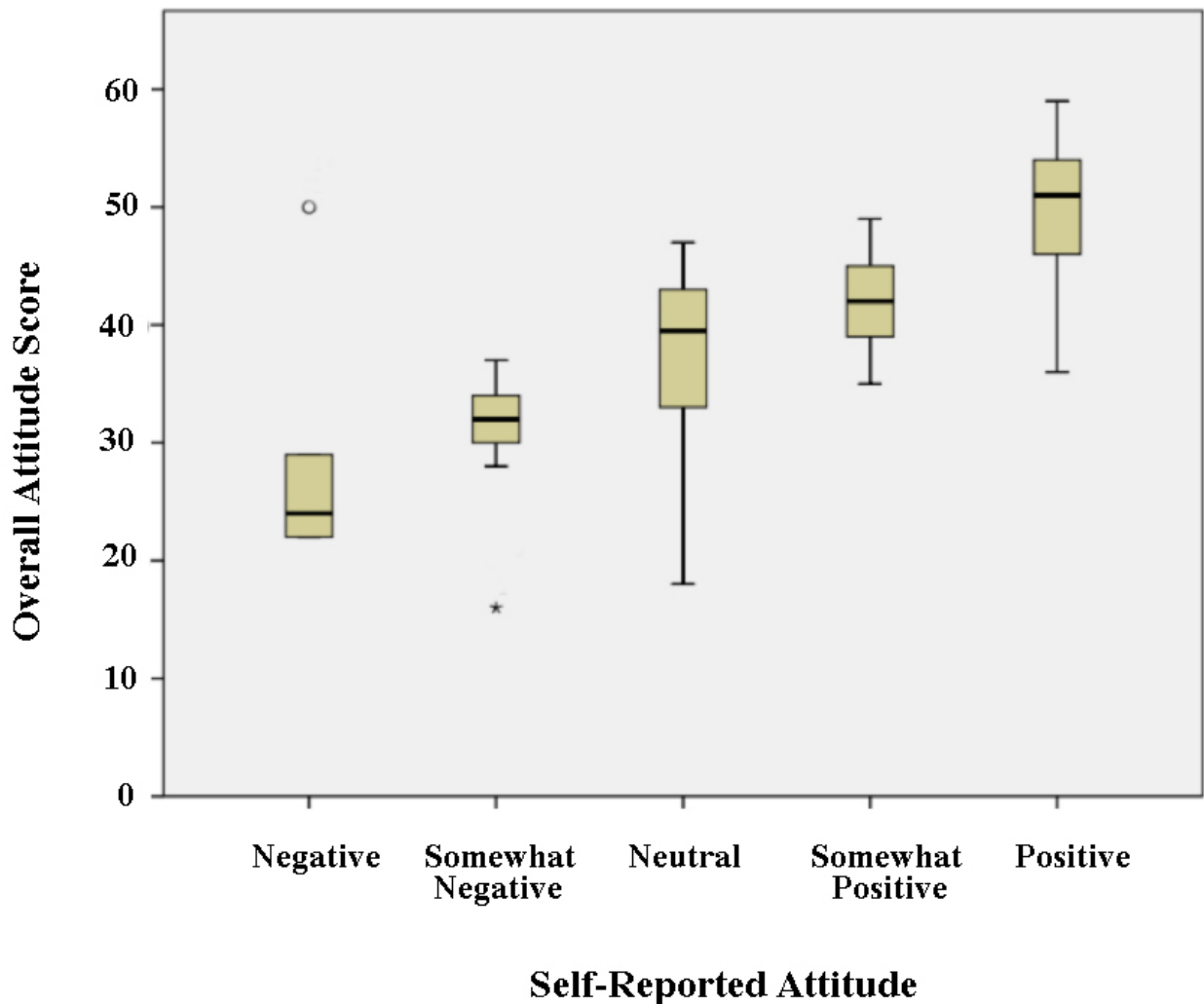


Figure 12 shows the trend of self-reported attitude score and mean calculated attitude score (mild outliers, between an inner and outer fence, are marked with circles and corresponding respondent number, extreme outliers, beyond one of the outer fences are marked with an asterisk).

3.8 Community effects

Two questions in Table 6 discuss the impact that MRT may have on the mitochondrial disease community (Appendix A, Questions 18D and 18E). Most respondents believed this technique will have a positive impact on the mitochondrial community and that their personal relationship with the community will not be negatively impacted by the decision to use the technique (Table 6, see Appendix I, J respectively for individual free-response explanations).

3.9 Media impact on attitude

A series of survey questions were used to help gauge the media's ability to sway the way individuals regarded MRT (Appendix A, Question 20). Individuals read headlines from media articles published on MRT. They were also given a link to read the full article, if desired. After reading the headline (or headline plus full article) individuals were asked again to rate their general attitude towards this technique. The goal of this question was to determine whether or not the media (through these articles) has the power to change the opinion of the survey respondents (Table 8).

TABLE 8: MEDIA IMPACT ON ATTITUDE TOWARD MRT					
	Positive	Somewhat Positive	Neutral	Somewhat Negative	Negative
My general attitude towards MRT is:	54.5%	23.6%	10.9%	7.9%	3.0%
After reading the headline below from an online science magazine my attitude towards MRT is: "U.K. Parliament approves controversial three-parent mitochondrial gene therapy"	42.4%	26.1%	20.0%	7.3%	4.2%
After reading the quote below from the MitoAction website, my attitude towards MRT is: "We decided to try and develop this IVF technique to prevent the transmission of mtDNA disease after one of our patients lost 7 children"	57.0%	20.0%	16.4%	3.6%	3.0%
After reading the headline below from the Bioethics Project my attitude towards MRT is: "MRT: is this the beginning of the end?"	32.7%	16.0%	28.5%	15.8%	6.7%
After reading the headline below from an online Catholic news source my attitude towards MRT is: "Catholic and Anglican church leaders oppose three parent babies"	32.1%	16.4%	23.6%	14.5%	13.3%

Table 8 displays the media headlines, which all respondents were asked to read and then choose the option that best represented their attitude toward MRT.

FIGURE 13A: SELF-REPORTED ATTITUDE FOLLOWING READING, “U.K. PARLIAMENT APPROVES CONTROVERSIAL THREE-PARENT MITOCHONDRIAL GENE THERAPY”

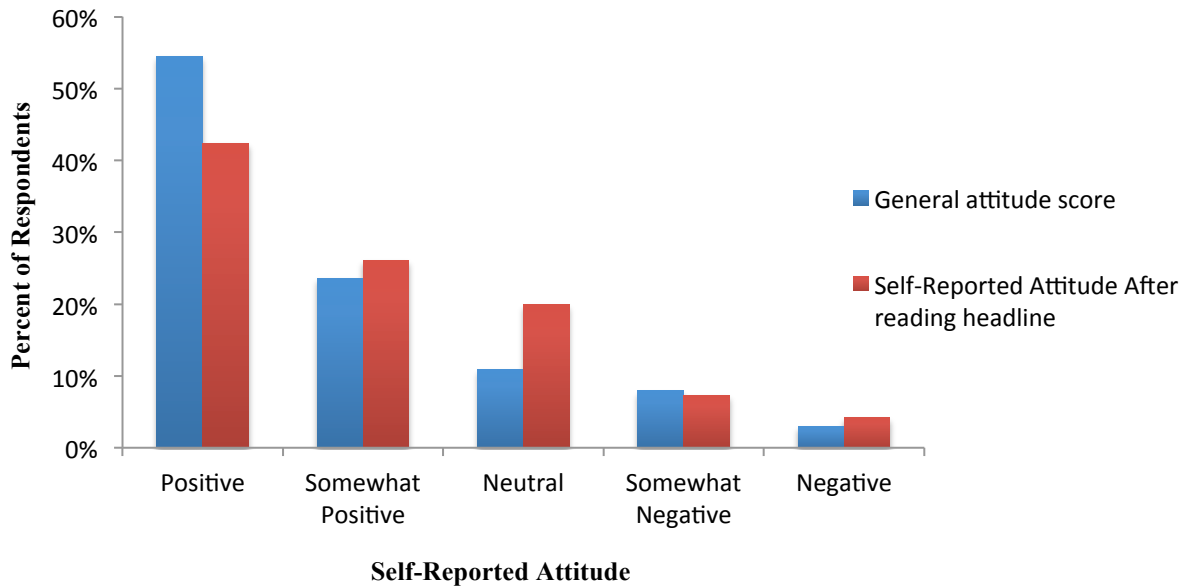


Figure 13A shows the breakdown of respondents' general self-reported attitude toward MRT before reading any media headlines and after reading the headline, “U.K. Parliament approves controversial three-parent mitochondrial gene therapy.”

FIGURE 13B: SELF-REPORTED ATTITUDE FOLLOWING READING, “WE DECIDED TO TRY AND DEVELOP THIS IVF TECHNIQUE TO PREVENT THE TRANSMISSION OF MTDNA DISEASE AFTER ONE OF OUR PATIENTS LOST 7 CHILDREN”

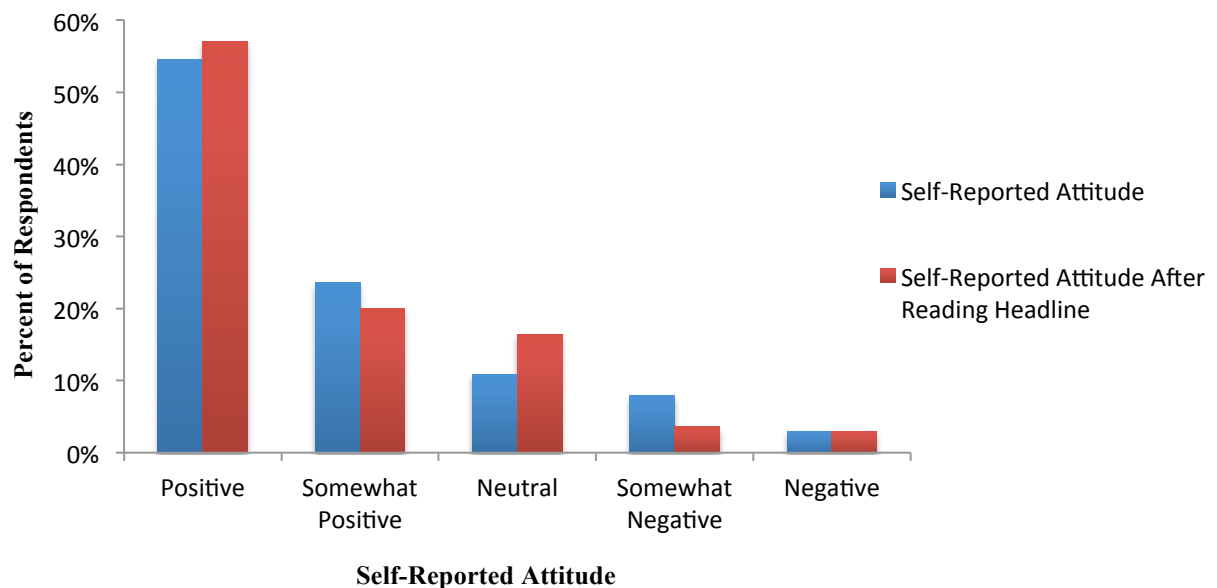


Figure 13B shows the breakdown of respondents' general self-reported attitude toward MRT before reading any media headlines and after reading the headline, “We decided to try and develop this IVF technique to prevent the transmission of mtDNA disease after one of our patients lost 7 children.”

FIGURE 13C: SELF-REPORTED ATTITUDE FOLLOWING READING, “MRT: IS THIS THE BEGINNING OF THE END?”

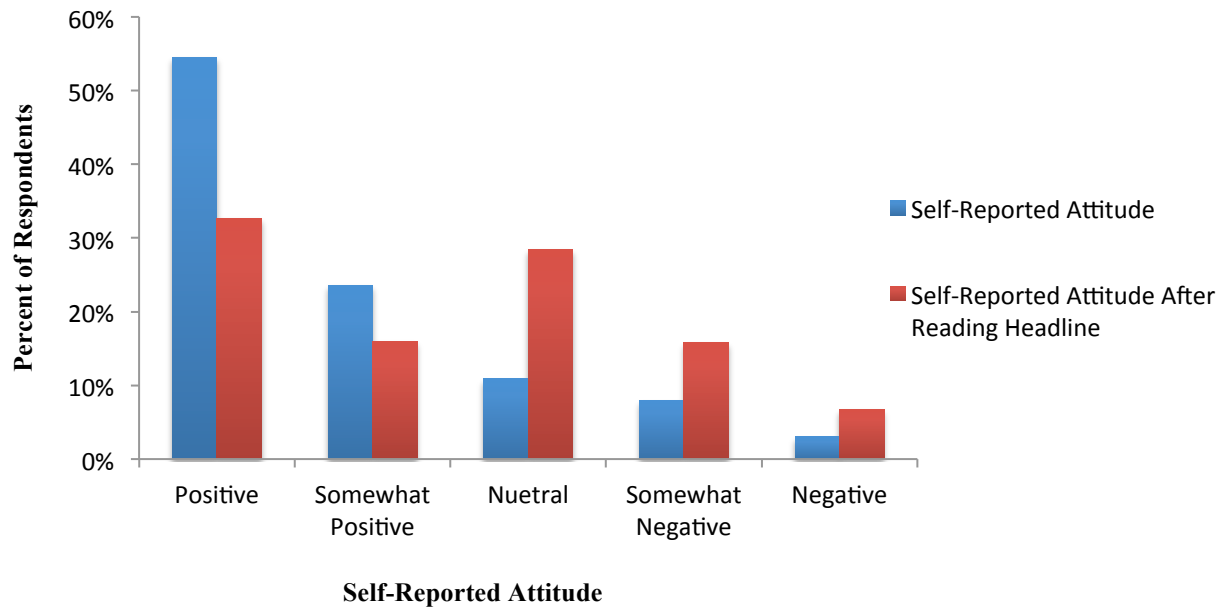


Figure 13C shows the breakdown of respondents’ general self-reported attitude toward MRT before reading any media headlines and after reading the headline, “MRT: is this the beginning of the end?”

FIGURE 13D: SELF-REPORTED ATTITUDE FOLLOWING READING, “CATHOLIC AND ANGLICAN CHURCH LEADERS OPPOSE THREE PARENT BABIES”

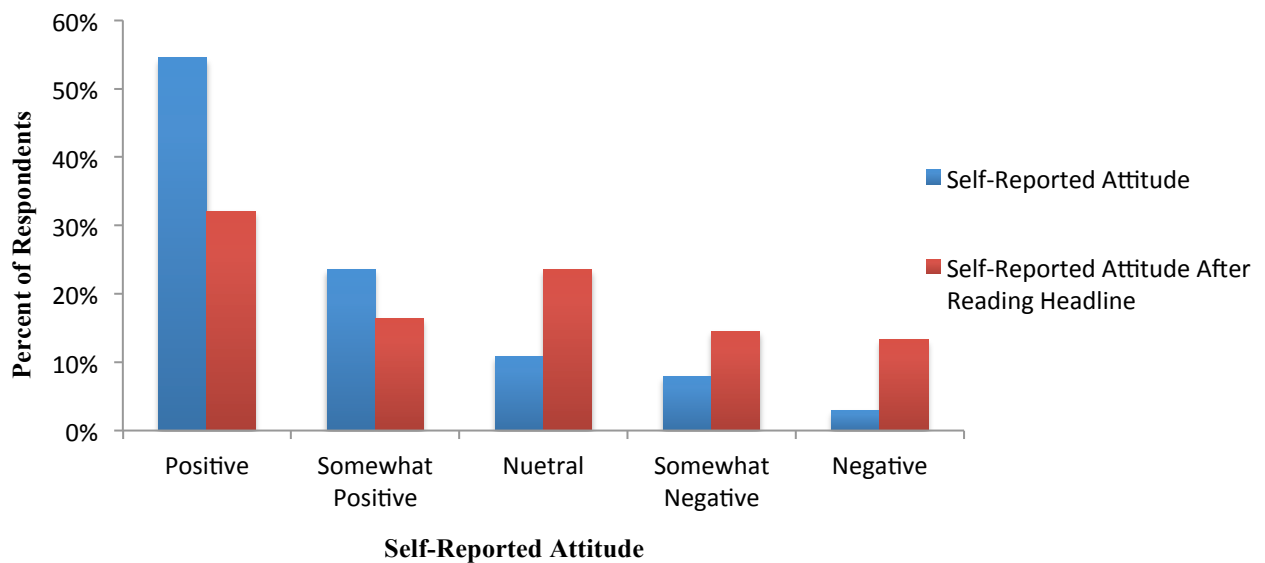


Figure 13D shows the breakdown of respondents’ general self-reported attitude toward MRT before reading any media headlines and after reading the fourth headline, “Catholic and Anglican church leaders oppose three parent babies”

As seen in Figures 13C and 13D, negative headlines showed the highest deviation from self-reported attitude indicating that negative headlines rather than positive were the most likely to bias individuals.

3.9.1 Fluctuation in attitude score

We then determined a total fluctuation score for each individual. If a person initially felt positive, then after reading the next question felt somewhat positive they had a 1-point change in attitude. If they then felt neutral after reading the next headline they got one point added to their fluctuation in attitude score etc. until a total change in attitude score was calculated after the fourth headline was read. Table 9 shows the fluctuation in attitude score observed across study participants after reading all four headlines. If the change in attitude score was zero, it means their attitude did not fluctuate over the four questions. For 36.4% of individuals attitude did not change after reading the headlines, but the majority (63.6%) showed fluctuation (ranging between 1-12 points) (Figure 14A, Table 9).

TABLE 9: Fluctuation in Attitude Score After Reading Headlines		
Change in Attitude Score	Frequency	Percent
0	60	36.4%
1	13	7.9%
2	27	16.4%
3	14	8.5%
4	29	17.6%
5	5	3.0%
6	8	4.8%
7	4	2.4%
8	2	1.2%
9	2	1.2%
12	1	0.6%

Table 9 shows the variability in attitude toward MRT after reading the selected media headlines.

As shown in Figure 14A, we created three categories of fluctuation in attitude: small fluctuation (1-2 point change), mid fluctuation group (3-4 point change), and large fluctuation group (5-12 point change).

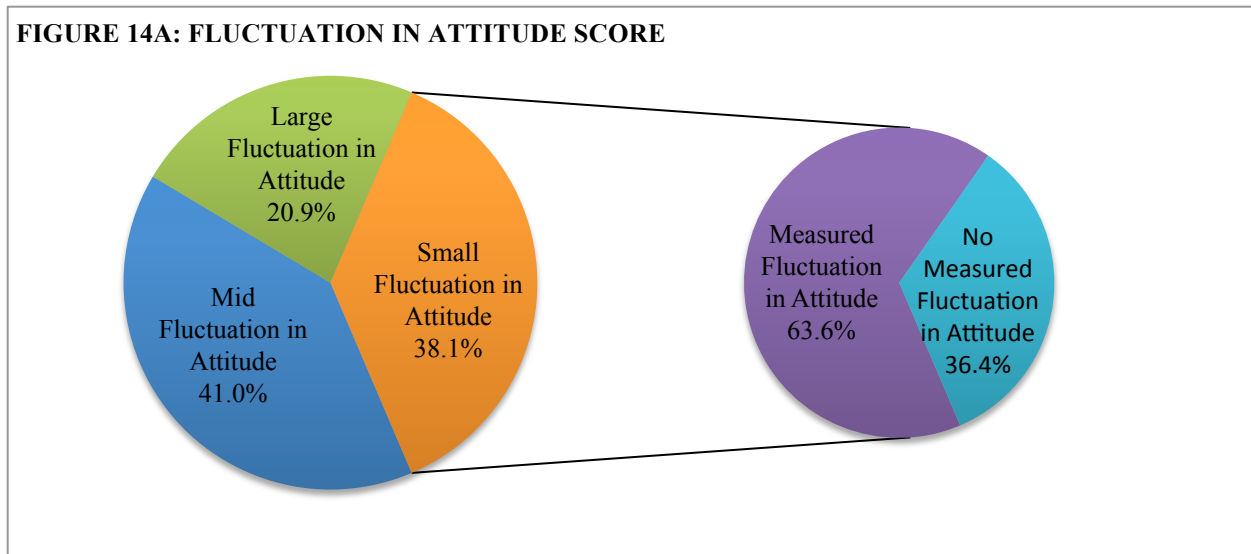


Figure 14A shows the categories of fluctuation respondents were grouped into based on their change in attitude score.

These three groups (small, mid and large attitude change) were then analyzed to identify what may have caused these differences in changes in attitude scores. The mean knowledge score for individuals with a large change in attitude score was 5.2, individuals with a mid attitude change had a mean knowledge score of 5.2, and those with a small change in attitude had a mean knowledge score of 4.9; this was not a statistically significant difference ($p=0.367$). Further, there was no statistical significantly difference in attitude change among individuals who had met with a genetic counselor and those who had not ($p=0.889$), nor was there a statistically significant difference in mean fluctuation scores across age groups ($p=0.868$). Figure 14B is designed to display the groups of fluctuation in attitude broken down by age group.

FIGURE 14B: DIFFERENCES IN CHANGE IN ATTITUDE ACROSS AGES

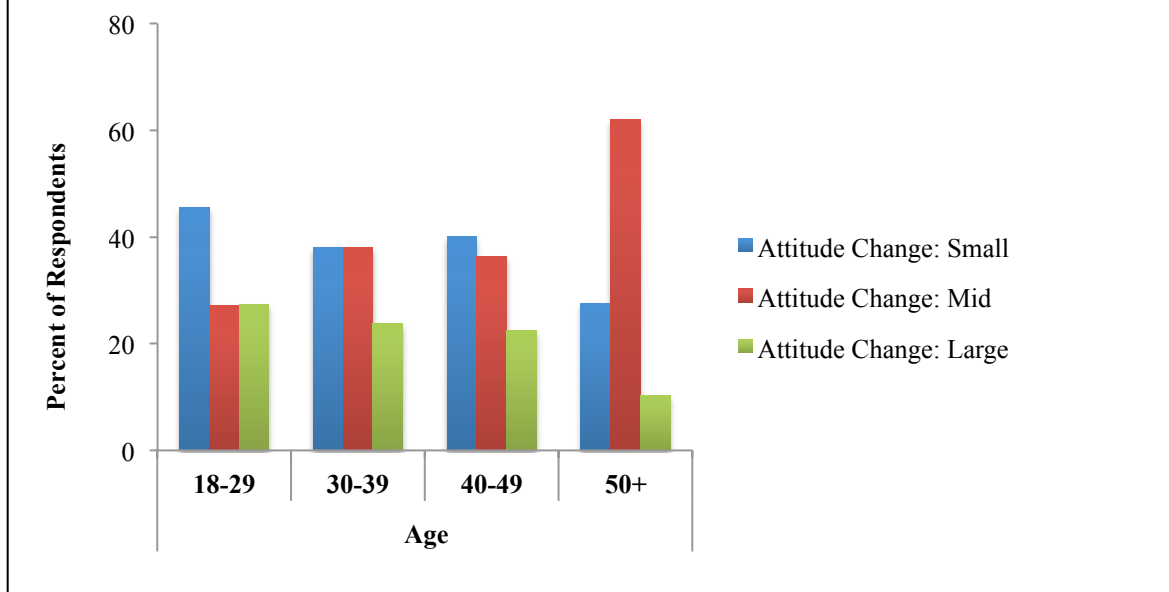


Figure 14B shows the degree of change in attitude stratified by age category of the respondent.

3.10 MRT's impact on relationships and family structure

Respondents were also asked to weigh in on whether they would prefer a mtDNA donor they knew or were personally related to (Appendix A, Question 22, see Appendix K for individual free-response explanations). Many individuals were concerned that having a related donor would open up their children to health risks because of the shared DNA of family members and had other concerns that led 46.7% of individuals to not prefer a related donor, however the majority (53.3%) were open to the idea of a known donor. The respondents were pressed further to decide if the child born using MRT would then have the right to find out the identity of their mtDNA donor (Appendix A, Question 24, see Appendix M for individual free-response explanations). Those who were more likely to choose a related donor were also statistically more likely to believe that the child has the right to know their mtDNA donor ($p=0.004$). Individuals were also asked whether they believed that children born as a result of

this technique had three parents (Figure 15, see Appendix N for individual free-response explanations). The majority of individuals (69.7%) did not agree that a child born using MRT would have three parents. Respondents who did not believe that children born as a product of MRT will have three parents had a higher mean knowledge score than those who believed resultant offspring did have three parents (5.2 vs. 4.6, $p < 0.001$).

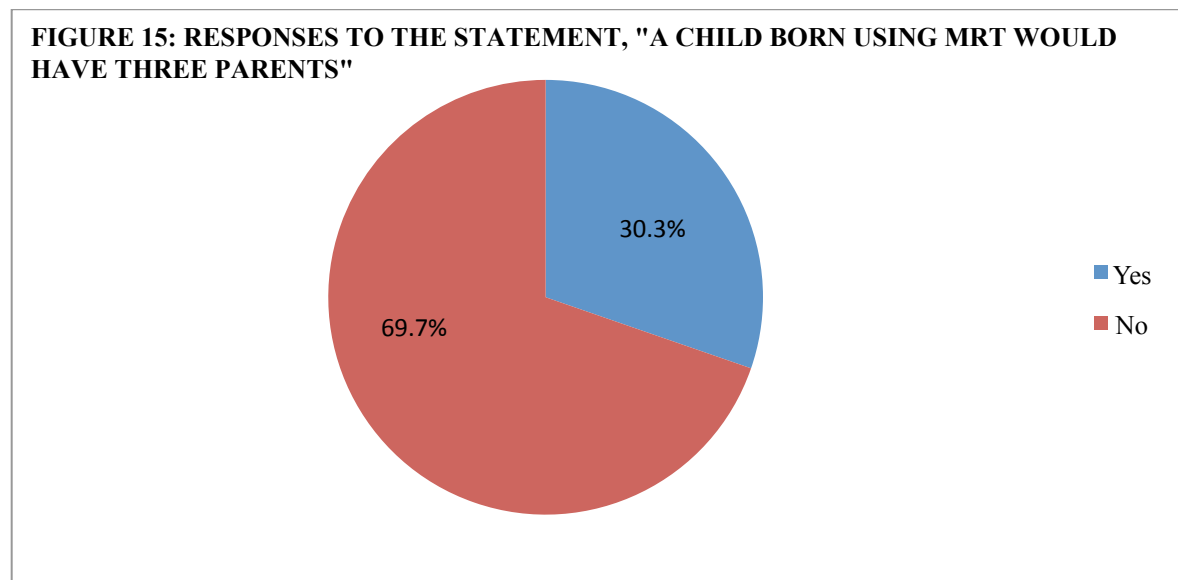


Figure 15 shows the percent of the 165 respondents who agree and disagree that a child born using MRT would have three parents.

3.11 Potential benefits and limitations of MRT

Respondents were asked to describe what they saw as potential benefits and limitations of MRT. Their answers were in free text (Appendix O, P) and then coded by hand into different categories based on content (Figures 16 and 17). A wide variety of responses were provided and there did not seem to be one prevailing topic that was most important to everyone.

FIGURE 16: BENEFITS OF MRT

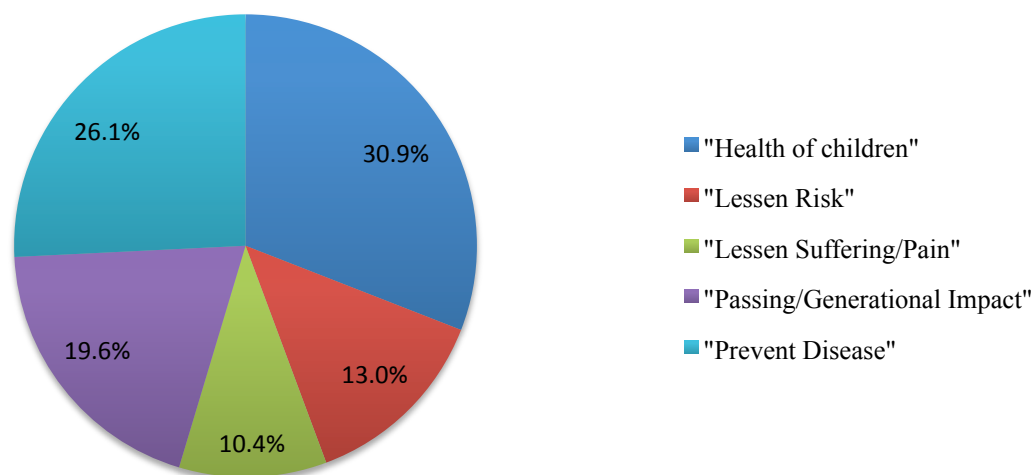


Figure 16 shows possible benefits of MRT as reported by 97 survey respondents (categories defined by investigator) – see Appendix O for actual responses.

FIGURE 17: LIMITATIONS OF MRT

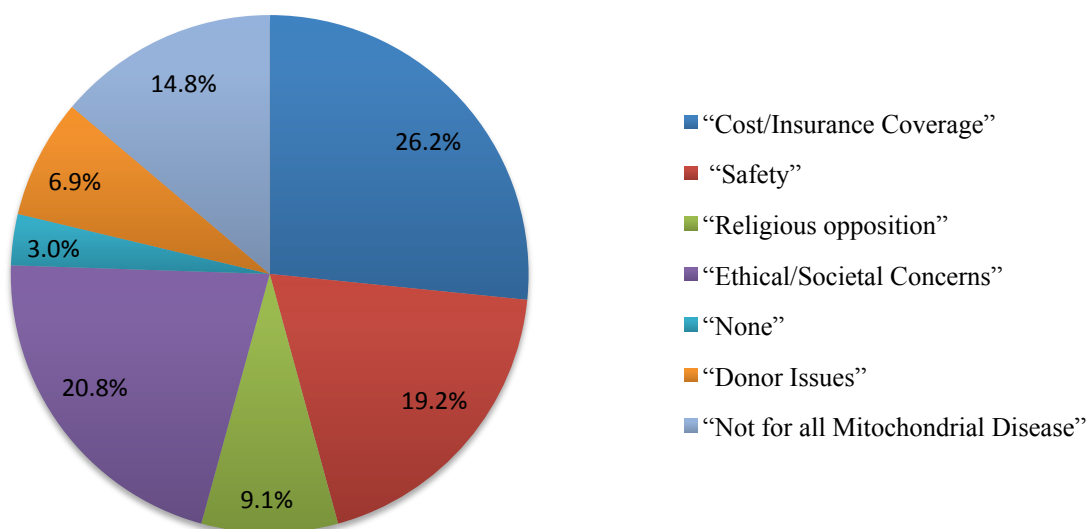


Figure 17 shows possible limitations of MRT as reported by 94 survey respondents (categories defined by investigator) – see Appendix P for actual responses.

IV. DISCUSSION

The technique of MRT is being developed in conjunction with IVF in order to prevent the transmission of mtDNA mutations from mother to child. Its process includes utilizing an egg donor's mtDNA and the intended mother's nuclear DNA. Currently the FDA is considering approval for human clinical trials for this technique. Approval relies heavily on the mitochondrial disease community's willingness to participate; however this population's attitudes, knowledge, and their perception of the risks associated with this procedure have yet to be adequately addressed. The purpose of this study was to determine the mitochondrial disease community's perception of MRT and the impact the media has on that perception. The tested hypotheses included that not many individuals would have prior knowledge of MRT, that the media headlines (regardless of positive or negative) would not impact the opinions of the respondents, and that those with a higher knowledge score would also have a higher attitude score and be more willing to pursue MRT if clinically available and appropriate.

In general the majority of respondents felt they had strong knowledge of mitochondrial disease, and we found that perceived knowledge of mitochondrial disease was highly correlated with the respondent's perceived level of knowledge of MRT. This technique had overall high marks of approval across the mitochondrial community, with the majority of respondents indicating both support for FDA approval and willingness to use it if clinically available. As hypothesized, those who were affected with a mitochondrial disease were more likely to feel their children were at risk for a mitochondrial disease than were those who had a family member or friend affected. However, those who were affected did not express more or less willingness to undergo MRT than those with a friend or family member affected. These results indicate

additional factors may be important when considering MRT beyond solely risk for offspring to have a mitochondrial disease.

4.1 Prior knowledge of MRT in the mitochondrial community

Under the first hypothesis, it was assumed that this survey would be the first introduction to MRT for the majority of individuals in the mitochondrial disease community. This was proven incorrect as the majority of the respondents had prior knowledge of MRT. There were no differences in the age or education level of the respondents who had or had not heard of MRT; however, those who were affected with a mitochondrial disease were statistically more likely to be versed in MRT. Respondents' self-reported knowledge of MRT and mitochondrial disease was highly correlated, as a person who reported higher knowledge about mitochondrial disease also reported higher knowledge about MRT.

4.1.2 Sources of information about MRT

Where respondents found out about MRT was also assessed in this study. The majority of respondents, nearly 80%, had looked to the media (news program or Facebook/some other website) for information about MRT. Although almost 73% of individuals met with a genetic counselor (or their friend or family member did), only 0.8% of respondents first heard about MRT from their genetic counselor. This study supported the notion that genetic counselors play an important role in accurately communicating health information, as those who met with a genetic counselor had a significantly higher knowledge score compared to those who did not. However, a genetic counselor was not the primary source of information about MRT for many of the respondents. A genetic counselor is an educator, who can present a balanced view of the

benefits and limitations of MRT, which is less likely to occur through an Internet search. A genetic counselor informing patients and their support system about innovative, disease preventing measures can reduce the possibility of misinformation and thus prevent misunderstandings. As many individuals in the survey showed prior knowledge of MRT, it is important for a genetic counselor's role to not only include assessing accuracy of prior knowledge, but building an accurate picture of MRT for the future as well. Genetic counselors should be knowledgeable of the gaps in information published in the media and to help clarify the possible misconceptions surrounding MRT.

4.2 Genetic testing among participants

Those who met with a genetic counselor were also statistically more likely to have had genetic testing than those who did not. Indeed, out of 122 respondents who met with a genetic counselor, 103 (84.4%) had genetic testing, whereas out of 37 who did not meet with a genetic counselor, only 13 (35.1%) had genetic testing. It is reassuring to see the important role a genetic counselor has in both explanation and coordination of genetic testing. Importantly, in approximately half of the respondents a mutation was reported. A total of 36 mtDNA mutations and 20 nuclear DNA mutations were reported among the cohort. Identification of a disease causing mutation in mtDNA is one requirement prior to utilizing MRT so it is crucial to understand on average how often a mutation is identified when mitochondrial disease is suspected. Therefore, only a minority of respondents, those with reported mitochondrial mutations (36, or 21.8% of total respondents) would meet this criterion. When further delineated by gender and childbearing age the number of respondents eligible for MRT was calculated to be 16. Of those 16, 12 agreed or strongly agreed that they would use MRT if it were clinically

available. However, this analysis only includes two major criteria, willingness and mtDNA mutation status, it does not include discussion of any other barriers surrounding this technique, such as access, cost, willingness and ability to withstand the physical challenges of pregnancy, or burden of proof of safety.

4.3 Understanding limitations of MRT

Nearly half of respondents believed that MRT could be used for any individual with mitochondrial disease to prevent their offspring from being similarly affected, which unfortunately is incorrect. As detailed above, this technique is designed for a very specific and potentially very small subset of patients diagnosed with mitochondrial disease. Individuals who were affected were statistically no more likely to answer this question correctly than were those with a friend or family member affected, suggesting that many of those who have interest in MRT are unaware of a large limitation of the technique. Currently the media is so preoccupied with debating the ethics of MRT, they are missing the logistics and not creating a balanced picture of MRT. An important step for the media to take is to give an appropriate idea of all of MRT's requirements, which will put into perspective how limited the scope of MRT truly is currently. This presents an opportunity for the media and genetic counselors to join forces. By utilizing a media platform such as a Facebook, or another social media site, podcast or National Public Radio, genetic counselors could present a balanced view of MRT to a nationwide audience. In this way the members of the National Society of Genetic Counselors can help shape the perceptions of MRT in addition to clarifying the inevitable misconceptions.

4.4 Fluctuation in attitude based on media headlines

To understand the impact of media portrayal, respondents were asked to self-report their attitude (i.e. positive, somewhat positive, neutral, somewhat negative, or negative) toward MRT after reading headlines about MRT that gathered attention in the media. No demographic predictors of fluctuation in attitude were identified in this study. We hypothesized that younger individuals would be more likely to have their opinions swayed by what is published in the media, but this trend was not observed. The majority of respondents did fluctuate in attitude throughout their analysis of the headlines presented. Although many individuals stayed positive throughout, a general trend of feeling less rather than more favorable about the technique after reading the headlines was observed. This may be due to the fact that most respondents' attitudes were positive to begin with and thus the only way to change was to lose favor; however this change was most significant when the headlines themselves were negative. The headline that garnered the biggest shifts in attitude was the one that stated Anglican and Catholic Church leaders oppose this technique, reflecting the influence of religious beliefs on opinion regarding MRT.

4.5 The ethical debate surrounding MRT

Over 70% of respondents agreed or strongly agreed that MRT is ethical. Not surprisingly, those that agreed or strongly agreed MRT is ethical were statistically more likely to be willing to use the technique if clinically available. In the minority of respondents who, disagreed or strongly disagreed that MRT is ethical, we attempted to identify factors influencing this response. To pursue one possibility, we asked about the technique's reliance on IVF. Of the 25

individuals who felt that this technique was unethical, about half reported that this feeling was due to the reliance of MRT on IVF.

The first baby born after conception by IVF was Louise Brown, born in July of 1978. Through the work of Patrick Steptoe and Robert Edwards, the world dubbed Ms. Brown the first “test-tube baby”. According to 2013 estimates more than five million people have been born through IVF (Adamson et al., 2013) but in the 1970s it was extremely controversial. Many believed that Ms. Brown would be “born without a soul”, and her family was bombarded with hate mail. In November of 1978, Pope Francis said the process promoted children as "a right rather than a gift to welcome", and IVF was "playing with life" (Eley, 2016). In our study we noted that opposition to IVF remains almost forty years after this process was first introduced, as about 10% of respondents overall opposed MRT because of its reliance on IVF.

Prior to the introduction of IVF and preimplantation methods such as PGD, reproductive options for carriers of hereditary mutations were limited. The use of prenatal testing such as CVS or amniocentesis were available to potentially detect if a fetus was affected, giving the couple information to help make a plan for the future; however, with a genetic diagnosis by these methods the only options available to a couple were pregnancy termination or continuation with the knowledge that the child would be affected. PGD was first performed by a team of researchers at the Institute of Obstetrics and Gynaecology in the UK (Handyside et al., 2016). The team counseled five couples that were at risk of passing on an X-linked recessive syndrome such as Lesch-Nyhan syndrome and Duchenne muscular dystrophy. In this study sex of the embryos was identified prior to transfer and based on the X-linked recessive form of disease only female embryos were transferred (X-linked recessive disorders are symptomatic in males but female carriers are generally asymptomatic). Later this technique become more widespread and

advanced, and the embryos were tested for a specific familial mutation and thus unaffected embryos, regardless of sex, could be transferred.

The beginning stages of PGD used sex selection as the means of transferring only unaffected embryos; in the beginning stages of MRT there is also a discussion of sex selection. As many individuals are concerned with the cross generational effects of MRT, i.e. passing down the donor's mtDNA from generation to generation, it has been proposed to use sex selection with MRT. Since males do not pass down their mtDNA to their offspring, allowing only male embryos to be transferred mitigates the potential for a cross generational impact. The idea of implementing sex selection along with MRT may alter the decision making of couples and add to the already growing debate on MRT and the concept of “designing babies”. This idea is that through MRT parents would be choosing or “designing” the traits of their offspring, even though mtDNA does not play a role in personality or physical traits. In this study two-thirds of respondents did not believe that MRT was a form of “designing babies”. However, those who incorrectly believed that mtDNA would impact the physical or personality traits of offspring were significantly more likely to believe that MRT was a form of “designing babies”. This shows that the fuel behind this misconception of designing babies is possibly due to a lack of understanding about mtDNA and its role in the body rather than a factual critique of MRT.

4.6 Redefining parenthood

MRT seems to be sensationalized as ‘three-person IVF’ in the media due to its novelty; it is the first technique that brings together DNA from three individuals to create offspring. It has other similar titles in the media including the “three-parent baby”. This use of the word “parent” rather than “person” is a leap, as only around 30% of our respondents believed that MRT will

create a child with three parents. Many respondents explained their objection to this idea based on the role a parent plays in the life of their offspring. One respondent commented, “Parenthood comes from nuclear DNA and the act of raising the child.” Another noted, “Genetically yes, realistically no.” Many also compared the donated mtDNA to a sperm/egg donation, comparing the fact that other donors are not considered parents, so why would a mtDNA donor be a parent? Others compared MRT to an organ donation or blood transfusion, considering it something that helps solve a health problem but is otherwise not creating a lasting bond/relationship. However, others disagreed and said a child resulting from MRT does have three parents. One respondent stated simply that the reason the child does have three parents is: “math”.

Is parenthood defined by genetic contribution alone without qualifying the role of a parent or a cut off for biological contribution? The phenomenon of assisted reproductive technology raising questions about the preconceived definition of parenthood and family is not new or isolated to MRT. Another example of biological contributions from three individuals being involved in reproduction includes gestational surrogacy. Gestational surrogacy is where a contract is made with a woman to gestate a child for a couple and then to relinquish him/her after birth (Brinsden, 2003). The surrogate’s biological material is used to nourish the baby and the pregnancy could not continue without it, however the surrogate is not considered a parent to the child. Our study respondents seemed to agree with this line of thought, and did not agree that individuals born through MRT have three parents. So while the “three-parent baby” is impressive at garnering media attention, it may be a misnomer that does not truly describe how the mitochondrial community sees MRT.

4.7 Limitations of the study

This study was limited by selection bias due to the survey's language and mode of distribution. The survey was available only in English, which limited the number of individuals that could participate in the survey due to a potential language barrier. The survey was also distributed electronically barring individuals with a lack of access to, or familiarity with, the Internet. Additionally, the majority of participants were recruited through social media sites, including Facebook support groups which may have contributed to our ascertainment of mostly female, younger, more highly educated individuals than is expected in the general population. The study population was also almost 90% female (with a similar proportion of females among the affected respondents), limiting our ability to compare across genders, which is especially important given that only females pass on mtDNA to their offspring. Investigators of future studies should be encouraged to try to recruit more males given our significant limitation.

We used six true/false style questions to assess knowledge. Three were used to address knowledge of mitochondrial disease and three for MRT. This limited number of questions did not enable a thorough analysis of their knowledge. A larger, more detailed set of questions addressing knowledge of both MRT and mitochondrial disease would have allowed the research team to analyze important differences in knowledge and potentially identify major misconceptions about MRT and mitochondrial disease in this community. Such analyses may lead to design of educational tools to eliminate misconceptions surrounding this technique.

Our use of an anonymous survey without written consent made it impossible to determine respondents' disease severity and exact mtDNA mutations, which made it difficult to fully understand the connection between mutation type and willingness to pursue this technique. It is possible that individuals with more severe disease and more severe mutations may be more

interested in this technique than those who are more mildly affected. An understanding of whether the individual was heteroplasmic or homoplasmic would have also helped to get a better sense of perceived risk of recurrence and its connection with interest in pursuing MRT.

4.8 Future studies

While results of this study show the mitochondrial disease community's willingness and general approval of human clinical trials for MRT, it confirmed that only a small number of individuals will be both eligible and willing to pursue this technique. It will be important in the future to analyze the logistical, ethical and legal considerations of MRT. Analysis of further barriers individuals may face if they truly decide to pursue this technique, such as cost, insurance coverage, safety concerns, and mitochondrial community response, was outside the scope of this study. On the surface the attitudes and willingness to pursue MRT are positive, but these and other barriers must be considered in the future.

Further studies on the potential indications for MRT are imperative. The idea that this technique may also include selection of only male embryos in an attempt to mitigate the cross generational impact of using donor mtDNA and the associated impact on the mitochondrial community and their approval of the concept is also a vital area of research. Another area of research would be to assess how the family/parental structure may be impacted, if at all, by having three different biological contributions to a child rather than two. There are parallels in this area from gamete donation and surrogacy.

This study also did not address the screening measures for potential mtDNA donors or whether the burden of proof of safety has been met for all parties involved for the FDA to approve human clinical trials for MRT. This is a preliminary report of the consensus of a small

number of individuals in a quickly expanding and knowledgeable community. Though small, it was an attempt to show the feelings of the mitochondrial disease community as a whole but upon examination of the demographic characteristics of respondents it does not appear that the study population was a good representation of the mitochondrial community at large. In the future, larger studies should be able to better capture and elicit more respondents and identify more subtle differences in opinion and perception.

4.9 Conclusion

This study provided evidence and insight into the attitudes of the mitochondrial disease community about MRT; a newly presented assisted reproductive technique that can prevent the transmission of mitochondrial disease from mother to offspring. The study included 165 members of the mitochondrial disease community. The purpose of the study was to understand this population's attitudes, knowledge, and perception of MRT in a crucial time before it becomes clinically available. Additionally this study aimed to prove how perception of the technique can be crafted and transformed by the media and thus emphasize the importance of an accurate media portrayal.

The majority of individuals surveyed found MRT ethical and were willing to use it if it were clinically available. Almost half however, were unaware that MRT can only be used when a mtDNA mutation has been previously identified in the mother. The majority thought the FDA should approve MRT and cited that safety was their top concern, but paradoxically only a minority thought there was enough evidence already published proving its safety. The majority was aware that this technique does not change physical or personality traits of the offspring and those who believed that it did were also more likely to believe that this technique is for

“designing babies”. Many respondents’ attitudes were impacted after reading media headlines published on MRT; however, those who were younger were no more easily swayed, as we had hypothesized. In fact, no predictors of change in attitude were identified in this study. There was also no significant trend found between increased knowledge of mitochondrial disease and MRT and more positive attitudes toward MRT. Overall this study showed that members of the mitochondrial disease community are forward thinking and generally have positive attitudes toward MRT, but may not understand its many limitations.

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APPENDIX A: Thesis Survey

Knowledge and Perception of the "Three-Person Baby," or Mitochondrial Replacement Therapy and the Impact of the Media Debate that Surrounds this Technique.

Welcome! Please read the summary below:

You are being asked to participate in a research study. The purpose of this research study is to determine the mitochondrial disease community's knowledge and perception of the "three-person baby," also known as mitochondrial replacement therapy. Specifically, the study focuses on attitudes toward the mitochondrial replacement process, and how the media debate over the technique affects individuals' views of it. Information on the perspective of the mitochondrial disease community on techniques being marketed and debated in the community will allow genetic counselors to better assist their patients.

Summary of Mitochondrial Replacement Therapy:

- Currently the Food and Drug Administration is considering the approval of human trials for Mitochondrial Replacement Therapy (MRT).
- MRT is a new in vitro fertilization technique, where sperm from one man and eggs from two different women are combined in a laboratory procedure to prevent mitochondrial disease in the resulting baby.
- MRT allows women with mitochondrial DNA mutations to have a child without mitochondrial DNA mutations by utilizing an egg donor's mitochondrial DNA (which is thought to be free of mutations).
- This technique is intended for women who have mitochondrial disease due to identified mitochondrial DNA mutations.
- Mitochondrial DNA is found only within the mitochondria, which are tiny organelles within each of our bodies' cells. Mitochondrial DNA is inherited solely from mother to child (men do not pass on their mitochondrial DNA) and has a very limited amount of genetic information compared to nuclear DNA.
- Nuclear DNA includes over 20,000 nuclear genes, while mitochondrial DNA includes only 37 mitochondrial genes. So the donor contributes less than 1% of the total genetic material for the child.
- This technique has the potential for a couple to have a child who is a >99% genetic match and not have the same mitochondrial DNA mutation as his/her mother.
- This technique can only be used to prevent disease when the cause of the mitochondrial disease is a mitochondrial DNA mutation. It cannot prevent mitochondrial disease in the offspring of the majority of individuals with mitochondrial disease because the majority of people with

mitochondrial disease either have mutations in their nuclear DNA, or have not had any mutations identified.

You are eligible to participate in this study if you are at least 18 years of age and a member of the mitochondrial disease community, which includes those who are affected with a mitochondrial disease or suspected mitochondrial disease, and those with a family member or friend affected with a mitochondrial disease or suspected mitochondrial disease.

Please click next in order to agree to participate in this survey.

Knowledge and Perception of the "Three-Person Baby," or Mitochondrial Replacement Therapy and the Impact of the Media Debate that Surrounds this Technique.

Welcome to My Survey

The research procedure involves an electronic anonymous survey. The survey will take approximately 10-20 minutes to complete.

There are no known harms or discomforts associated with this study beyond those encountered in normal daily life. The possible risks and/or discomforts associated with the procedures described in this study can include: anxiety, embarrassment, social stigma and invasion of privacy. If you feel discomfort talking about your perceptions and beliefs you are free to exit at any time during the survey. At no time will you be expected to answer a question that you are not comfortable with.

There are no direct benefits from participation in the study. However, the results from this study may benefit the mitochondrial disease community as a whole by allowing genetic counselors a better understanding of the community's opinions and knowledge of mitochondrial replacement and its role in mitochondrial disease prevention.

You will not be compensated for your participation in this research study.

All research data collected will be stored securely and confidentially. Research data will be stored electronically on a password protected laptop computer. As this survey is anonymous, the study team may not be able to extract or delete any specific data provided, should you choose to withdraw from the study. As part of the completion of this survey, you are agreeing to the "Terms of Use" for 'SurveyMonkey,' the entity administering the survey. The data you provide may be collected and used by SurveyMonkey as per its privacy agreement. While the research team will make every effort to keep your personal information confidential, it is possible that an unauthorized person might see it. We cannot guarantee total privacy.

If you have any comments, concerns, or questions regarding the conduct of this research please contact the researcher listed on the bottom of this form. Please contact UCI's Office of Research by phone, (949) 824-6662, by e-mail at IRB@research.uci.edu or at 5171 California Avenue, Suite 150,

Irvine, CA 92697 if you are unable to reach the researchers listed at the bottom of the form and have general questions; have concerns or complaints about the research; have questions about your rights as a research subject; or have general comments or suggestions.

Participation in this study is voluntary. There is no cost to you for participating. You may refuse to participate or discontinue your involvement at any time without penalty. You are free to withdraw from this study at any time.

By clicking "Next" you are indicating you consent as a research participant.

For more information please contact:

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Knowledge and Perception of the "Three-Person Baby," or Mitochondrial Replacement Therapy and the Impact of the Media Debate that Surrounds this Technique.

Welcome and thank you for your participation!

1. What is your age?

- ☐ 17 or younger
- ☐ 18-20
- ☐ 21-29
- ☐ 30-39
- ☐ 40-49
- ☐ 50-59
- ☐ 60 or older

2. Are you male or female?

- ☐ Male
- ☐ Female
- ☐ Prefer not to answer

3. Which of the following best describes your current relationship status?

- ☐ Married
- ☐ Widowed
- ☐ Divorced
- ☐ Separated
- ☐ In a domestic partnership or civil union
- ☐ Single, but cohabiting with a significant other
- ☐ Single, never married

4. Ethnicity origin (or Race): Please specify your ethnicity.

- ☐ Caucasian
- ☐ Black or African-American
- ☐ Hispanic
- ☐ Asian
- ☐ Native Hawaiian or other Pacific Islander
- ☐ American Indian or Alaskan Native
- ☐ Prefer not to answer

Other race (please specify)

5. What is the highest level of school you have completed or the highest degree you have received?

- ☐ Less than high school degree
- ☐ High school degree or equivalent (e.g., GED)
- ☐ Some college but no degree
- ☐ Associate degree
- ☐ Bachelor degree
- ☐ Graduate degree

6. Please pick the option(s) that best apply to you.

- ☐ I have a diagnosis of a mitochondrial disease or suspected mitochondrial disease
- ☐ I have a spouse/significant other affected by a mitochondrial disease or suspected mitochondrial disease
- ☐ I have a child affected by a mitochondrial disease or suspected mitochondrial disease
- ☐ I have a parent affected by a mitochondrial disease or suspected mitochondrial disease
- ☐ I have a sibling affected by a mitochondrial disease or suspected mitochondrial disease
- ☐ I have an extended family member (aunt, uncle, cousin, grandparent, etc.) affected by a mitochondrial disease or suspected mitochondrial disease
- ☐ I am not affected nor is anyone in my family, but I have a friend affected by a mitochondrial disease or suspected mitochondrial disease
- ☐ None of the above
- ☐ Other (please specify)

Knowledge and Perception of the "Three-Person Baby," or Mitochondrial Replacement Therapy and the Impact of the Media Debate that Surrounds this Technique.

7. Throughout the diagnosis process, has the individual with a mitochondrial disease or suspected mitochondrial disease (either yourself or another individual) ever had an appointment with a genetic counselor to discuss genetic testing for mitochondrial disease?

- ☐ Yes
- ☐ No
- ☐ Unsure/Unknown

8. Did the person with a mitochondrial disease or suspected mitochondrial disease (be it yourself or another individual) have genetic testing to identify a disease causing mutation(s)?

- ☐ Yes
- ☐ No
- ☐ Unsure/Unknown

Knowledge and Perception of the "Three-Person Baby," or Mitochondrial Replacement Therapy and the Impact of the Media Debate that Surrounds this Technique.

9. Did the genetic test identify a disease causing genetic mutation(s)?

- ☐ Yes
- ☐ No
- ☐ Unsure/Unknown
- ☐ Other (please specify)

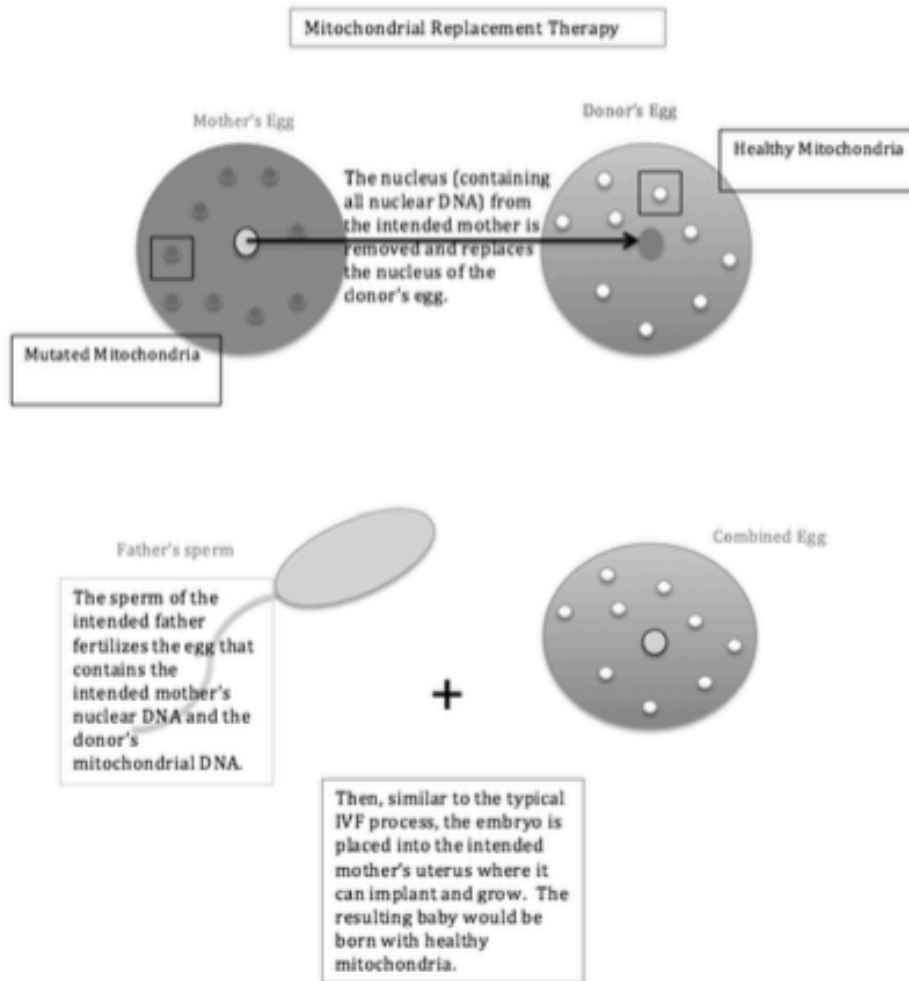
Knowledge and Perception of the “Three-Person Baby,” or Mitochondrial Replacement Therapy and the Impact of the Media Debate that Surrounds this Technique.

10. To the best of your knowledge, the mutation(s) is which of the following?

- ☐ A nuclear DNA mutation (either autosomal dominant, autosomal recessive, or X-linked)
- ☐ A mitochondrial DNA mutation
- ☐ Unsure/Unknown
- ☐ Other (please specify)

Knowledge and Perception of the “Three-Person Baby,” or Mitochondrial Replacement Therapy and the Impact of the Media Debate that Surrounds this Technique.

Below is a Graphic of Mitochondrial Replacement Therapy



11. Had you heard of mitochondrial replacement therapy prior to this survey? (The technique goes by many names including: "mitochondrial transfer," "mitochondrial donation," "three-person embryos," "three-parent babies," "three-person in vitro fertilization (IVF)," and "nuclear genome transfer.")

- ☐ Yes
- ☐ No
- ☐ Unsure/Unknown

Knowledge and Perception of the "Three-Person Baby," or Mitochondrial Replacement Therapy and the Impact of the Media Debate that Surrounds this Technique.

12. Where did you first hear about the mitochondrial replacement technique?

- ☐ Media outlet (News program, Facebook/other website, etc.)
- ☐ Word of mouth
- ☐ Doctor
- ☐ Genetic Counselor
- ☐ Foundation information/meeting
- ☐ Book
- ☐ Other (please specify)

Knowledge and Perception of the "Three-Person Baby," or Mitochondrial Replacement Therapy and the Impact of the Media Debate that Surrounds this Technique.

13. Compared to the general public, how would you compare your level of knowledge of mitochondrial replacement?

- ☐ I could explain mitochondrial replacement to a medical professional.
- ☐ I understand the process of mitochondrial replacement but don't know all the details.
- ☐ I still have a lot of questions but understand the general topic.
- ☐ I have limited knowledge of mitochondrial replacement.
- ☐ I know almost nothing about mitochondrial replacement.

14. Compared to the general public, how would you compare your level of knowledge of mitochondrial disease?

- ☐ I could explain mitochondrial disease to a medical professional.
- ☐ I understand mitochondrial disease more than most people but don't know all the details.
- ☐ I still have a lot of questions but understand the general topic.
- ☐ I have limited knowledge of mitochondrial disease.
- ☐ I know almost nothing about mitochondrial disease.

Knowledge and Perception of the "Three-Person Baby," or Mitochondrial Replacement Therapy and the Impact of the Media Debate that Surrounds this Technique.

15. Please indicate if the following statements are true or false:

	True	False
Mitochondria are responsible for producing energy for our bodies.	☐	☐
There are treatments but currently no cure for mitochondrial diseases.	☐	☐
A man passes down his mitochondrial DNA to all of his children but a woman does not pass on her mitochondrial DNA to any of her children.	☐	☐
Mitochondrial replacement can help prevent mitochondrial diseases in the offspring of all individuals affected with mitochondrial disease.	☐	☐
If a couple successfully pursues mitochondrial replacement, then the donor mitochondrial DNA in their children can be passed down to subsequent generations.	☐	☐
Mitochondrial replacement has the potential to prevent certain mitochondrial diseases.	☐	☐

Knowledge and Perception of the "Three-Person Baby," or Mitochondrial Replacement Therapy and the Impact of the Media Debate that Surrounds this Technique.

16. How strongly do you agree or disagree with the following statements?

	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
There is already enough proof available to show that mitochondrial replacement is safe for the mitochondrial DNA donor, the intended couple and the resulting children.	☐	☐	☐	☐	☐
The FDA should approve human clinical trials of mitochondrial replacement.	☐	☐	☐	☐	☐
Mitochondrial replacement should be covered by health insurance.	☐	☐	☐	☐	☐
I personally consider mitochondrial replacement an ethical practice.	☐	☐	☐	☐	☐
The media's portrayal of mitochondrial replacement is accurate.	☐	☐	☐	☐	☐

17. Which of the following is most important to you when personally considering mitochondrial replacement?

Please explain your choice

Knowledge and Perception of the "Three-Person Baby," or Mitochondrial Replacement Therapy and the Impact of the Media Debate that Surrounds this Technique.

18. How strongly do you agree or disagree with the following statements?

	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
If I were to have a child, they would be at risk to have a mitochondrial disease.	☐	☐	☐	☐	☐
Please explain your response					
If I were at risk to have a child with a mitochondrial disease I would use mitochondrial replacement to have unaffected children if it were clinically available.	☐	☐	☐	☐	☐
Please explain your response					
If I were at risk to have a child with a mitochondrial disease I would not pursue mitochondrial replacement because it requires in vitro fertilization, a technique that I would not consider using.	☐	☐	☐	☐	☐
Please explain your response					
Introducing mitochondrial replacement into clinical practice will have a positive impact on the mitochondrial community.	☐	☐	☐	☐	☐
Please explain your response					
If I were to pursue mitochondrial replacement it would have a negative impact on my relationship with mitochondrial disease community.	☐	☐	☐	☐	☐

Strongly Agree Strongly Disagree

Please explain your response

19. Which option below would be your first step to learn more about mitochondrial replacement?

- ☐ Media Outlet (News program, Facebook/other website, etc.)
- ☐ Doctor
- ☐ Genetic Counselor
- ☐ Family member/friend
- ☐ Internet Source
- ☐ Support Group
- ☐ Library/Book
- ☐ Religious Leader
- ☐ Foundation Information/Meeting
- ☐ Other (please specify)

Knowledge and Perception of the “Three-Person Baby,” or Mitochondrial Replacement Therapy and the Impact of the Media Debate that Surrounds this Technique.

20. Please choose the option that best describes your attitude towards mitochondrial replacement

	Positive	Somewhat Positive	Neutral	Somewhat Negative	Negative
My general attitude towards mitochondrial replacement is:	☐	☐	☐	☐	☐

	Positive	Somewhat Positive	Neutral	Somewhat Negative	Negative
After reading the headline below from an online science magazine, my attitude towards mitochondrial replacement is:	☐	☐	☐	☐	☐
"U.K. Parliament approves controversial three-parent mitochondrial gene therapy"					
After reading the quote below from Mitoaction, my attitude towards mitochondrial replacement is:					
"We decided to try and develop this IVF technique to prevent the transmission of mitochondrial DNA disease after one of our patients lost 7 children"	☐	☐	☐	☐	☐
After reading the headline below from the Bioethics Project my attitude towards mitochondrial replacement is:	☐	☐	☐	☐	☐
"Mitochondrial replacement therapy: is this the beginning of the end?"					
After reading the headline below from an online Catholic news source my attitude towards mitochondrial replacement is:	☐	☐	☐	☐	☐
"Catholic and Anglican church leaders oppose three parent babies"					

Please click on any of the links below to read more:

[Online Science Magazine Article](#)

[Mitoaction Article](#)

[Bioethics Project Blog](#)

[Online Catholic News Source](#)

Knowledge and Perception of the "Three-Person Baby," or Mitochondrial Replacement Therapy and the Impact of the Media Debate that Surrounds this Technique.

21. Please choose the statement that best describes your reactions to the following statements:

	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
Dozens of countries and various international human rights documents express concern about changing a person's genetic code because our genes are passed from generation to generation and the impact of changing them cannot truly be known.	☐	☐	☐	☐	☐
The "designer baby argument" questions the right of parents to choose which genetic characteristics are best for their children. Mitochondrial replacement is "designing a baby," because it allows parents to choose their child's make up.	☐	☐	☐	☐	☐

Knowledge and Perception of the "Three-Person Baby," or Mitochondrial Replacement Therapy and the Impact of the Media Debate that Surrounds this Technique.

22. If you were to pursue mitochondrial replacement, would you prefer your mitochondrial DNA donor to be someone you know personally or are related to?

☐ Yes

☐ No

Please explain your choice

23. Do you think that having donor mitochondrial DNA will alter the traits (for example: hair color, height, personality) of any resulting child?

☐ Yes

☐ No

Please explain your choice

24. Do you think a child conceived with donor mitochondrial DNA would have a right to know the identity of the woman who has provided her mitochondrial DNA?

☐ Yes

☐ No

Please explain your choice

25. Do you believe that a child resulting from the use of a mitochondrial DNA donor has three parents?

☐ Yes

☐ No

Please explain your choice

Knowledge and Perception of the "Three-Person Baby," or Mitochondrial Replacement Therapy and the Impact of the Media Debate that Surrounds this Technique.

26. What do you see as benefits of mitochondrial replacement?

27. What do you see as limitations of mitochondrial replacement?

Knowledge and Perception of the "Three-Person Baby," or Mitochondrial Replacement Therapy and the Impact of the Media Debate that Surrounds this Technique.

Thank you so much for completing this survey!

To learn more about mitochondrial replacement therapy, please click either of the links below:

<http://www.mitoaction.org/blog/mitochondrial-donation-or-3-parent-embryos>

http://www.umdfrg.org/site/c.8qKOJ0MvF7LUG/b.9166823/k.2E25/Mitochondrial_Replacement_Therapy.htm

For more information about mitochondrial disease please visit www.umdfrg.org and www.mitoaction.org

To find a genetic counselor near you please visit www.nsgc.org

APPENDIX B: Request for Survey Distribution Blurbs

Facebook Status blurb:

Hey guys! Please take a moment and help me out with my thesis project by taking this anonymous survey. Pass it on to all your family and friends in the mitochondrial disease community. I really appreciate it. Thank you!

{Flier inserted here}

Blurb for MitoAction and United Mitochondrial Disease Foundation (UMDF):

My name is Ashlynn Fiss, and I am currently working on my master's degree in Genetic Counseling at the University of California, Irvine. I have been able to counsel many patients with mitochondrial diseases and throughout my training I have cultivated a special interest in this subset of genetic conditions. I am working on turning my passion for mitochondrial disease into a graduate thesis.

Specifically I want to distribute a survey that investigates the idea of the "three-person baby" that has been the topic of much debate.

Please take part in the anonymous survey titled, "An Assessment of the Mitochondrial Disease Community's Knowledge and Perception of the "Three-Person Baby," or Mitochondrial Replacement Therapy, and the Impact of the Media Debate that Surrounds this Technique." This technique is currently being considered by the FDA in the United States and determining knowledge/interest in the mitochondrial community is crucial.

{Flier inserted here}

Blurb for the public Facebook groups dedicated to the mitochondrial disease community:

My name is Ashlynn Fiss, and I am currently working on my master's degree in Genetic Counseling at the University of California, Irvine. I have been able to counsel many patients with mitochondrial diseases and throughout my training I have cultivated a special interest in these subset of genetic conditions. I am working on turning my passion for mitochondrial disease into a graduate thesis.

Specifically I want to distribute a survey that investigates the idea of the "three-person baby" that has been the topic of much debate.

Please take part in the anonymous survey titled, "An Assessment of the Mitochondrial Disease Community's Knowledge and Perception of the "Three-Person Baby," or Mitochondrial Replacement Therapy, and the Impact of the Media Debate that Surrounds this Technique." This technique is currently being considered by the FDA in the United States and determining knowledge/interest in the mitochondrial community is crucial.

{Flier inserted here}

APPENDIX C: Flyer



Your opinion matters!

Please share your opinion in this anonymous survey titled:
"An Assessment of the Mitochondrial Disease Community's Knowledge and Perception of the "Three-Person Baby," or Mitochondrial Replacement Therapy and the Impact of the Media Debate that Surrounds this Technique."

Link to be inserted here.

<i>For more information please contact:</i> Lead Researcher Ashlynn Fiss, Genetic Counseling Graduate Student UCI Department of Pediatrics 101 The City Drive, ZC 4482 Orange, CA 92668-3298 (714) 456-5837 or afiss@uci.edu	Specifically, the study focuses on attitudes toward the mitochondrial replacement process, and how the media debate over the technique affects individuals' views of it. You are eligible to participate in this study if you are at least 18 years of age or older and a member of the mitochondrial disease community, which includes those who are affected with a mitochondrial disease or suspected mitochondrial disease, and those with a family member or friend affected with a mitochondrial disease or suspected mitochondrial disease. There are no direct benefits from participating in the study; however information on the on techniques being marketed and debated in the mitochondrial community will allow genetic counselors to better assist their patients. The research procedure involves an electronic anonymous survey. The survey will take approximately 10-20 minutes to complete. You will not be compensated for your participation in this research study.
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CONFIRMATION OF EXEMPT RESEARCH REGISTRATION

December 11, 2015

ASHLYNN NICOLE FISS DEPARTMENT OF PEDIATRICS

RE: HS# 2015-2404 *An assessment of the Mitochondrial Disease community's knowledge and perception of the "three-person baby," or MRT, and the impact of the media debate that surrounds this technique.*

The human subjects research project referenced above has been registered with the UC Irvine Institutional Review Board (UCI IRB) as Exempt from Federal regulations in accordance with 45 CFR 46.101. This exemption is limited to the described activities in the registered UCI IRB Protocol Narrative and extends to the performance of such activities at the sites identified in your UCI IRB Protocol Application. Informed consent from subjects must be obtained unless otherwise indicated below. UCI IRB conditions for the conduct of this research are included on the attached sheet.

Information provided to prospective subjects to obtain their informed consent should, at a minimum, consists of the following information: the subject is being asked to participate in research, what his/her participation will involve, all foreseeable risks and benefits, the extent to which privacy and confidentiality will be protected, that participation in research is voluntary and the subject may refuse to participate or withdraw at any time without prejudice.

Questions concerning registration of this study may be directed to the UC Irvine Office of Research, 5171 California Avenue, Suite 150, Irvine CA 92697-7600; 949-824-6068 or 949-824-2125.

Level of Review: Exempt Review, Category 2

Determinations as Conditions of Exemption:

Informed Consent Requirements:

1. Signed Informed Consent Not Required a. Study Information Sheet Required

Matthew Kinder, CIP IRB Administrator

Registration valid from 12/11/2015 to 12/10/2020 UCI (FWA) 00004071, Approved: January 31, 2003

UNIVERSITY OF CALIFORNIA

UCI IRB CONDITIONS FOR ALL UCI HUMAN RESEARCH PROTOCOLS

UCI RESEARCH POLICIES: All individuals engaged in human-subjects research are responsible for compliance with all applicable UCI Research Policies

(<http://www.research.uci.edu/compliance/human-research-protections/hrp-policy-library/hrppPolicies.htm>).

The Lead Researcher of the study is ultimately responsible for assuring all study team members adhere to applicable policies for the conduct of human-subjects

research.

LEAD RESEARCHER RECORDKEEPING RESPONSIBILITIES: Lead Researchers are responsible for the retention of protocol-related records. The following web pages should be reviewed for more information about the Lead Researcher's recordkeeping responsibilities for the preparation and maintenance of research files: <http://www.research.uci.edu/compliance/human-research-protections/researchers/lead-researcher-recordkeeping-responsibilities.html> and <http://www.research.uci.edu/compliance/human-research-protections/researchers/preparation-maintenance-research-audit-file.html>.

PROTOCOL EXPIRATION: The UCI IRB expiration date is provided on the exempt registration letter. **All exempt protocols are registered for a maximum period of 3 years.** If the study will continue beyond 3 years, a new Application for IRB review is required. No annual continuing renewals are required.

MODIFICATIONS & AMENDMENTS:

No changes are to be made to the registered protocol or the approved, stamped consent form without the prior review and approval of the UCI IRB. All changes (e.g., a change in procedure, number of subjects, personnel, study locations, new recruitment materials, study instruments, etc.) must be prospectively reviewed and confirmed by the IRB before they are implemented.

APPROVED VERSIONS OF CONSENT DOCUMENTS, INCLUDING STUDY

INFORMATION SHEETS: Unless a waiver of informed consent is granted by the IRB, the consent documents (consent form; study information sheet) with the UCI IRB approval stamp must be used for consenting all human subjects entered into this study. Only the current approved version of the consent documents may be used to consent subjects. **Approved consent documents are not to be used beyond their expiration date.**

ADVERSE EVENT & UNANTICIPATED PROBLEMS REPORTING:

All unanticipated problem involving risk to subjects or others or serious adverse events must be reported to the UCI IRB in accordance with Federal regulations and UCI policy. See <http://www.research.uci.edu/compliance/human-research-protections/researchers/reporting-of-adverse-events-unanticipated-problems-and-violations.html> for complete details.

CHANGES IN FINANCIAL INTEREST: Any changes in the financial relationship between the study sponsor and any of the investigators on the study and/or any new potential conflicts of interest must be reported immediately to the UCI Conflict of Interest Oversight Committee (COIOC). If these changes affect the conduct of the study or result in a change in the required wording of the approved informed consent document, then these changes must also be reported to the UCI IRB via a modification request.

CLOSING REPORT: An electronic closing report should be filed with the UCI IRB when the research concludes. See <http://www.research.uci.edu/compliance/human-research-protections/researchers/closing-a-protocol.html> for complete details.

APPENDIX E: Full List of Free-Responses for Survey Question 17 about the Most Important Aspect of MRT

Full List of Free-Responses about the Most Important Aspect of MRT
<i>"I do not think it is ethical"</i>
<i>"If FDA approved, that means enough researching was done"</i>
<i>"No matter the cost or approval by the media and the FDA, if the procedure isn't safe to myself or to future generations it's not worth it."</i>
<i>"Each of the other options is an opinion/view of the procedure. The actual safety of it will possibly affect a human life."</i>
<i>"My biggest concerns come from how privilege affects those who have access to treatment. If it is covered by health insurance, then I would hope this is less of an issue."</i>
<i>"I feel like it is most important to me that the person with Mito actually wants to use 3 person IVF and isn't pressured into it as that quickly leads to eugenics."</i>
<i>"I worry that health insurance would not cover this, thus preventing people from using it due to high prices."</i>
<i>"If the fda doesn't approve it, other shit won't matter because it won't be done. In the other hand I don't really understand fda so I could be wrong"</i>
<i>"I don't really know which is most important but out of the choices it seems like the next logical important one."</i>
<i>"I think the safety of it can lead to the other parts of it being good. If it's proven safe, media portrayal will be better, insurance companies will be more likely to cover it, it will be more ethical, and the FDA will be more likely to approve it."</i>
<i>"The entire point of doing MRT is to protect my children so my biggest concern would be the safety of the procedure that I would be using to make that happen."</i>
<i>"I do not because of my religion"</i>
<i>"Want the procedure or be safe for mother and unborn child. Would also hope for FDA approval, but know that may take years of testing to achieve."</i>
<i>"Safety is crucial"</i>
<i>"I don't what anyone else goes though what my daughter goes through."</i>
<i>"I have had to fight my insurance for coverage from an established mitochondrial specialist."</i>
<i>"MRT is a way for a woman who's mtDNA is defective to conceive and deliver a baby who is not afflicted with the defect. Ethically, I believe it is the ONLY way a woman who KNOWS that she has defects in her MDNA should reproduce. Mitochondrial disease, in almost all its incarnations, is painful, debilitating and incurable. To bring a child into the world with the knowledge that there is a 50% chance or more that the child will be afflicted, is NOT acceptable. This IS my personal belief."</i>
<i>"I understand what three parent replacement is. I love the idea. How can we be sure the 3rd person has healthy DNA? I haad a friend who had Marrow replacement and at 7 years he developed ALS. Theory was it was from stress on the body and DNA from the donor. My friend was in his 70's. It would be less ethical to put parents and children through an accidental cone mistake than getting what they would normally get without intervention."</i>
<i>"If safety cannot be certain within the uncertainty of any medical application (ex: tonsil surgery is safe, yet there are risks...), then the insurance costs, media perceptions, ethics issues, and so forth aren't even worth debating. Unless something can be safe (within reason), then nothing else particularly matters..."</i>
<i>"I would want it to be safe for all 5hose involved; especially the baby."</i>
<i>"It's a great idea, to the extent that it will work in a given case, has been shown to decrease the likelihood of a mito disorder in the child, and has been shown to not induce other problems that outweigh its benefits."</i>
<i>"Its most important to be sure that it's safe for the resulting children and not create a different more harmful mutation"</i>
<i>"We do not have a specific diagnosis for my 11 year old, I would need tons of info before we went this</i>

<i>route, if he has a diagnosis”</i>
<i>“I live in Ontario, Canada and my cocktail is covered by the government”</i>
<i>“I struggled between answering safety & health insurance coverage. I think safety should be of the utmost importance because these are human lives we are talking about & since the reason for this procedure is to have a healthy child, then it needs to be done safely. However, I wouldn't want to see parents not be able to go ahead with this simply because they could not afford it & then give birth to a child affected by mito because MRT wasn't covered, meaning the child could have had a healthy life but from an expense standpoint will cost more to insurance & out of pocket medical care than having MRT in the first place.”</i>
<i>“My family's Mitochondrial Disease is mtDNA, this procedure would stop the disease in future generations.”</i>
<i>“I had 2 children that passed away at the age of 7 and 8 from the same maternally inherited mutation (T8993C) that I also have and experienced the devastation. I cannot have any more children and will not due to the risk to my children. I think this is a great way to allow couples the possibility of having a health child. The safety of the therapy is and should be the most important aspect to consider, but the possibility of having a healthy child would be amazing . My children, like most suffered tremendously in their short life because of my being unaware of my condition and genetic mutation.”</i>
<i>“I feel if the FDA approved then much easier for all other organizations/facilities to be involved.”</i>
<i>“It must be safe for the mother and the embryo”</i>
<i>“Safety comes first!!”</i>
<i>“I would pick ethics but not an option”</i>
<i>“I haven't heard too much of the downside of MRT.”</i>
<i>“Then it could begin in the states and we could begin preventing this horrible disease in some people which is amazing!”</i>
<i>“I would want to make sure mito replacement would not have any negative effects on my fetus/child.”</i>
<i>“I want the choice to become available to everyone that needs it.”</i>
<i>“It's ruling out Mito but there are so many other conditions as well”</i>
<i>“desire for safety for the mother and baby, particularly knowing the any unintended consequences of mtDNA replacement”</i>
<i>“None, I think it crosses a moral and ethical boundary.”</i>
<i>“If you cannot afford it how can it even be an option”</i>
<i>“My fear is that a woman with Mito would be put in a potentially life threatening situation.”</i>
<i>“Concerns with the practice of playing God and things going too far with the idea of creating perfect people.”</i>
<i>“Safety is #1 concern, but by the point we'd have to worry about FDA approval safety would already be demonstrated. FDA approval is often a huge stumbling block for potentially very useful treatments and interventions”</i>
<i>“I would like healthy grandchildren and based on my current knowledge of using fertility treatments, this sounds expensive. If insurance would cover this, healthy children could be born without the expense of a lifelong potentially debilitating disease.”</i>
<i>“I disagree with in vitro fertilization itself due to the production of multiple embryos that are often not implanted but are frozen or destroyed.”</i>
<i>“I am against creating surplus embryos that might not be used (ie. discarded) for any reason. I believe an embryo is a life. So while I believe that MRT is ok for families affected by mito, I understand that the in vitro process creates as many embryos as possible. So if all the embryos were to be used, I would fully support it. But since I know that this is not always the case, it is sometimes unethical in my view. However, since embryos are created for many families that pursue in vitro/MRT, mito families should not be restricted any more than another person pursuing in vitro for any other reason.”</i>
<i>“I have concerns about it being part of a slippery slope regarding genetically engineered humans. I wonder if in the future it could be used to genetically select for whatever the people in power deem important ”</i>

<i>"Safety in the sense that the child produced would not suffer from the same disease that I do."</i>
<i>"When making a decision regarding whether or not to engage in a controversial medical treatment, I weight my personal feelings regarding the morality of the treatment higher than other considerations."</i>
<i>"Health insurance should cover everything!"</i>
<i>"If in vitro is covered, so should this be. The FDA should not be involved at all because they are industry shills who do not care about public safety at all. "</i>
<i>"Health Insurance gives options to those interested but allows you a choice if that is not the right option for you."</i>
<i>"I think it is useless to most people unless people can afford it. I do think Safety is equally important probably way more, but insurance will never cover it unless it is safe (relatively) to begin with."</i>
<i>"If the process is safe for all parties involved, and if MRT produces healthy children that can reproduce future generations of healthy children, I am more than happy to support, advocate and consider MRT. If this process proves dangerous, especially for the offspring, there is no way I would ever feel comfortable with MRT."</i>
<i>"Once MRT is approved, health insurance coverage is important so individuals that would need to opt for the replacement in order to avoid passing potential disorders down to their offspring aren't inhibited from doing so by the cost. MRT has the potential to do a lot of good in the world by reducing these types of disorders but it needs to be available for the average American without causing extreme financial problems."</i>
<i>"The safety of the couple, the donor, but most importantly the resulting child, is of the utmost importance. All the other factors, such as insurance coverage, media support and the ethics of the procedure itself mean nothing if the future health of the child is compromised."</i>
<i>"For me, even if it is proven to be safe, unless I can use this method and afford to use this method then it would be useless to me. Also, for me unless I wish to have more children This does not help me either. As of right now, we have 2 children both with Special needs, for me to take the risk of having another child and using this method with the hopes that it works and having a normal child. Is a lot to ask, I do not see this as the end all to a treatment for Mito. I see this as a band-aide. And that is not taking into consideration the risks of having IVF at all because not all viable embryos take and become pregnancies. There are risks all over the place. And to add that IVF is not completely safe for the resulting child even with Genetic testing and Counseling Things can randomly go wrong or if something was not considered resulting in another even greater problem. All of this is still rather new and many that are at pregnancy age do not know that they have a Mito problem. So, I think that it would only aid in a very small population. And on top of that would need to be covered by all insurance to make it even an option."</i>
<i>"Unless FDA approves, MRT will not be recognized as safe or insurable in the USA. In the UK, both levels of government have passed the procedure."</i>
<i>"If it were unsafe, it would be irrelevant to me whether insurance covers it or whether it has media or FDA support."</i>
<i>"Due to the fact that those of us who have Mitochondrial Disease already have many health issues as it stands, I want to know that the process of MRT will not make us more sick than we already are. I also would like to know more in depth facts about how those babies who have been born using MRT are doing health wise. I would like to know that the process of replacing mitochondria has truly made these children free of being born with no presence of Mitochondrial Disease."</i>
<i>"We have EDS as well as possible mito issues. I hope my children can have healthy children one day. We suffer so much and I feel guilty I passed this down."</i>
<i>"I think it is too late for my 18-year-old child."</i>
<i>"Safety of the donors & the offspring is the most important aspect."</i>
<i>"I don't believe we should be doing any INVF."</i>
<i>"Though I have no plans personally to have this procedure done due to my health, age, and being single, I certainly would if things were different. I volunteer in every clinical trial and study I can to help along the search for a cure."</i>
<i>"Considering its an invasive procedure the safety would be the most important aspect to me"</i>

<i>"It will help couples have a child free from mitochondrial disease"</i>
<i>"I wanted to choose all of the above, however I think that safety should be the top priority of any medical procedure."</i>
<i>"I don't think it's something I'd re-locate for or do on the black market, so FDA approval is essential."</i>
<i>"It is vitally important that people with mitochondrial disease have access to this important option for having children."</i>
<i>"I believe it is ethical and It obviously has to absolutely be a know. safe procedure. However, just knowing the extreme cost of genetic testing, I am sure this procedure would be astronomically higher. Treatments for the resulting disorders I currently have are already a huge burden with health insurance coverage, so I know treatments of this nature must be covered by insurance to be even remotely feasible."</i>
<i>"Simply, if it is not 100% safe for all involved, it should not happen"</i>
<i>"Safety in any procedure is paramount & not debatable. The remaining issues are personal & ethical."</i>
<i>"I have no doubts about the ethics of the procedure. I think that this is relatively new science/medicine and overall safety will only be determined by longitudinal studies."</i>
<i>"I would like to see this move forward as an option for women with mitochondrial disease."</i>
<i>"I have concerns regarding the health of the potential fetus. My family's mtDNA defect was diagnosed in 2006. I have nDNA defects that were not identified until 2013. If I had had a baby using my nucleus within a donor's egg, I would have been given a false sense of security, since I had been told that the mutation that was responsible for my daughter's death was definitely from mtDNA. She never had nDNA testing after she was diagnosed with Leigh's."</i>
<i>"It needs to be affordable"</i>
<i>"I will not consider MRT as my mitochondrial mutations reside in the nuclear DNA. To the best of my understanding this does not affect me as it is replacing mitochondria and there are no mitochondrial mutations to my knowledge. I also do not feel MRT should exist....not only from a safety perspective (do these children run the risk of having cancer or other diseases) but I strongly feel we should not be playing God. The existence of these technologies also seem to imply that if someone does have mito, their lives do not matter and they should be snuffed out of the gene pool because they are not perfect. This technology seems like a form of eugenics."</i>
<i>"I do not approve of the use of a fertilised donor egg but have no objections to the use of an unfertilised donor egg."</i>
<i>"I feel that the procedure is safe, ethical, and should be approved and available. Media approval is irrelevant, as it is a personal choice that should be weighed in on only by people who know what it is. If this procedure was approved, it would be difficult to get insurance to cover it"</i>
<i>"I don't consider it ethical"</i>
<i>"I'm considering this because my sister has the disease. So to have a way to ensure my kids do not have it I fully support this."</i>
<i>"Replacement therapy likely would be costly, and as a result would not be obtainable for many individuals without insurance."</i>
<i>"I don't think this is ethical and could not support it."</i>
<i>"I want my children's health safeguarded."</i>
<i>"I believe as long as it is safe for everyone it should be an okay choice."</i>
<i>"Needs to be safe"</i>
<i>"FDA approval, because it vouches that it is safe, but is also supposedly should be covered by insurance."</i>
<i>"Interested and willing to learn more, but ultimately health insurance could possibly prevent me from ever receiving MRT"</i>

APPENDIX F: Full List of Free-Responses for Survey Question 18A about Child's Risk for Mitochondrial Disease

Full List of Free-Responses about Child's Risk for Mitochondrial Disease
<i>"I am a male- I don't pass it"</i>
<i>"I don't have any problems with mitochondrial disease"</i>
<i>"Without knowing the genetics it's hard to say, but it's a definite possibility."</i>
<i>"I do not have mito."</i>
<i>"Don't have mito"</i>
<i>"I do not have mito, I think."</i>
<i>"I have suspected mito"</i>
<i>"Idk. My niece and nephew have it but I was adopted as an infant so A. I'm not in their gene pool but B. I have no family medical history at all so the gene could run in my bloodline as well, Idk. But I never had children so it doesn't matter."</i>
<i>"I have no family history of mitochondrial disease"</i>
<i>"I'm not affected, my friend is. For her the answer would be strongly agree"</i>
<i>"I am not affected with mitochondrial disease (unless I am mosaic) so my children would not be at an increased risk."</i>
<i>"Strong family history. Have had 4 miscarriages."</i>
<i>"I have one child with it and 2 children without it but they have different father."</i>
<i>"My mito specialist says my type (MT DNA Deletion) is not transferable from one generation to another."</i>
<i>"I am long past child-bearing age. My child's Mitochondrial disease did not present until early adulthood and took a long time to diagnose. Genetic testing that was done on me during the diagnostic phase of my child's condition, did not show know significant nuclear DNA mutations; however, mDNA was not specifically sequenced."</i>
<i>"Both my daughters have it. I lost the one who was most fragil and the oldest daughter is more sick than I am. I will pass in my 60's. my mom make it to 76, my grandmother to 81...I took Anthro. I understand how environmental adaptation works."</i>
<i>"I have two children; one is diagnosed with the disease and one also very likely has the disease. I have the disease."</i>
<i>"I am male, so mito gene issues would not be in play, but some mito issues are caused by issues in the nuclear DNA."</i>
<i>"I want to be relatively sure that my offspring would be safe"</i>
<i>"I have a child who most likely has mito, I am thinking it could happen to any other kids I could have had. Though only 1 out of my 3 kids show any signs"</i>
<i>"Knowing I have 6 unknown mutations as well as a brother that passed with suspected mito (but no genetic work up), I feel the chances would be high to pass the illness on & would never want to put anyone else through the illness & pain I've been in throughout my life."</i>
<i>"Mine is spontaneous"</i>
<i>"I am a woman with adult onset mitochondrial disease. Family history implies previous generations of women may have experienced mitochondrial disease. My children could inherit mitochondrial disease."</i>
<i>"Our disease is in the mtDNA"</i>
<i>"I am a woman do my children receive their mtDNA from me. I have four children, two girls and two boys. Both boys are diagnosed."</i>
<i>"I have been diagnosed after the loss of both my children. They were diagnosed after autopsy with the T8993C mutation and I have experienced this myself."</i>
<i>"There other Mitochondrial decease!!"</i>
<i>"I have one affected child. The other we think is unaffected."</i>
<i>"I am a woman and have some symptoms of mito but not confirmed."</i>

<i>"It is maternally inherited."</i>
<i>"Because I did."</i>
<i>"I adopted my children who have the disease and I do not have the disease. Not to mention it is very unlikely I would have a child at this stage of life. It is possible though to have a child with first generation mutation."</i>
<i>"We know that I have a genetic mitochondrial disease that I am capable of passing to my children."</i>
<i>"I have mitochondrial disease, as do all 3 of my biological children."</i>
<i>"I have a DNA mutation thats recessive but there."</i>
<i>"My daughter has mito"</i>
<i>"I suspect my mitochondrial disease is due to mutations in my mtDNA, which I could pass down to my children"</i>
<i>"I have three children and only one is affected by a mitochondrial disease."</i>
<i>"Even though genetic testing showed myself and one out of three children as not affected by the disease I am still skeptical"</i>
<i>"I HAVE MITOCHONDRIAL MYOPATHY"</i>
<i>"I was told by my genetic specialist that I would not be able to carry a fetus to term. A pregnancy would be life-threatening for mother and child."</i>
<i>"My son's was a spontaneous rather than inherited mutation"</i>
<i>"Two out of three of my children are severely affected."</i>
<i>"I believe we have an mtDNA defect in my maternal family line."</i>
<i>"Genetic counselors told us our risk would be 25% affected for future offspring."</i>
<i>"I have a suspected nuclear DNA mutation, which is much less likely to be passed on to my children, but can still be transmitted."</i>
<i>"I have had two children. Both inherited a mitochondrial disease. Our care team is considering the possibility that the disease is inherited in an Autosomal Dominant fashion, making the risk of inheritance significant."</i>
<i>"I am female and have mtDNA mutations that in combination with the nuclear DNA mutations cause my mitochondrial disease. It is my understanding that in so far as at least the mtDNA is concerned that is passed down to any biological offspring of mine in all cases."</i>
<i>"Because my mtDNA is likely missing some chunks."</i>
<i>"Too old to have children."</i>
<i>"I was advised it was over a 50% chance since it's mtdna."</i>
<i>"I have been told by a doctor who specializes in MELAS that any child I have could have between 1 and 100 percent mutation for MELAS."</i>
<i>"I have been treated for a suspected mitochondrial or genetic like disease and we have evidence to prove that this has already been passed down through the family."</i>
<i>"There is no history of mitochondrial disease in my family's history. However, I'm sure it can happen to anyone even without the history or known history."</i>
<i>"My son has maternally inherited mitochondrial disease so any children I have or had are at risk."</i>
<i>"I am symptomatic and my son has Mito and my daughter is suspected to have mito. I have mito so any children that I have may have mito."</i>
<i>"Mt DNA has been tested and negative for me and my sons. However ... there have been cases where Mt DNA has been passed from the male to his children even though this fact is not widely known!"</i>
<i>"Mine are nuclear DNA variants. I could contribute a normal x or a variant x."</i>
<i>"Since women pass on mtDNA, my child would be more at risk of having a mitochondrial disease."</i>
<i>"yes We have EDS, GP and POTS for sure. My children suffer."</i>
<i>"Since I, a female am strongly believed to have a mitochondrial disease any child of mine would as well"</i>

<i>"That is what I was told by doctors once I gave birth to a child who was later diagnosed with a mito disease."</i>
<i>"2 of my 3 children are affected with Alper's Syndrome, 1 of which has passed."</i>
<i>"I have a non mtDNA mutation and i believe there would be 25-50% of passing along my mutation. I have never directly inquired because I do not plan to have children"</i>
<i>"I have MELAS and with a higher percentage point would certainly pass the disease on to a child, if I were even able to conceive and have a full-term pregnancy."</i>
<i>"Being I have mito, my child would be at risk"</i>
<i>"I have mitochondrial mutation A3243G, and while I have it to fairly low percentage myself, I am aware that I can pass on a much higher percentage to any children. My mother has similar levels present to me, around 15%, but my brother has around 77%."</i>
<i>"My son had MELAS now we are trying to see if my daughter could have passed it down to her grandson?"</i>
<i>"I am not aware of any mitochondrial mutations in my genetics, but I have never been tested."</i>
<i>"I am a woman with mitochondrial disease that we believe to be caused by an mtDNA mutation (I have a VUS that is probably pathogenic)."</i>
<i>"I have 3243 mutation, therefore my child would be at risk"</i>
<i>"From my knowledge the statement is incontrovertible."</i>
<i>"I am a carrier of a nuclear DNA gene that causes mitochondrial disease."</i>
<i>"It's only logical that since I have mitochondrial disease I can pass it to my children."</i>
<i>"I have both confirmed mtDNA and nDNA mutations which are recognized as disease-causing mutations. I passed on these mutations to all three of my children: my youngest passed away at age 3 due to complications from Leigh's. My oldest child has symptoms. My middle child is asymptomatic but has mtDNA mutations that she could pass on to her own children."</i>
<i>"I have a child with mito. It's a 25/100 chance after that"</i>
<i>"Assuming I actually have one (strongly suspected but not confirmed as yet) it's true that children would be at risk of inheriting it from me."</i>
<i>"I do not have a mitochondrial condition, and they are relatively rare without a family history."</i>
<i>"I have two children (I had both before I knew what I had was genetic). One tests negative for the mutation, the other tests positive and is symptomatic at a young age"</i>
<i>"I have four children. I have passed on the mutation to all of them, but at differing levels."</i>
<i>"My husband and I have been genetically confirmed to be carriers of a Mito disease that causes MtDNA Depletion."</i>
<i>"I have had 3 children all with mitochondrial disease"</i>
<i>"My family most likely has A maternal inheritance disorder."</i>
<i>"There is a hereditary component/risk to many forms of Mito. The probability of passing it down may vary based on the variant of mitochondrial cytology, but to knowingly take that chance, is unethical in my view."</i>
<i>"I already have one child with mitochondrial disease and one with autism"</i>
<i>"Because I do not know what kind of Mitochondrial Mutation I have (if that is what I have) I wouldn't really be able to say yes or no."</i>
<i>"I've discussed this with doctors and researched it."</i>
<i>"My younger sister has it"</i>
<i>"We have four children with mito"</i>
<i>"I am a known carrier and suspected patient."</i>
<i>"I have a sporadic mtDNA mutation which has only been seen in my muscle tissue. There is a risk of me passing on my mito DNA mutation but it is very low."</i>
<i>"My mutation is in my mt-DNA, so it's quite likely I would pass it to my children."</i>
<i>"I suffer from Cyclic Vomiting Syndrome, believed to be a mitochondrial disease, and as a woman I am</i>

aware that there is a possibility that I could pass down my mitochondrial mutation to my children.”

APPENDIX G: Full List of Free-Responses for Survey Question 18B about Use of MRT

Full List of Free-Responses about Use of MRT
<i>"I don't think I would because of cost"</i>
<i>"If I decided having children who were genetically related to me was important to me, I'd consider surrogacy with mtDNA replacement therapy."</i>
<i>"I'm not sure I want children, but if I decide I do, I would want the treatment"</i>
<i>"I suffer from a rare autoimmune disease and am terrified of passing it to a child."</i>
<i>"Mito can be deadly and extremely painful for babies or young children. I would not want them to suffer"</i>
<i>"Unlike my other disabilities, mito can kill. I wouldn't put a kid at risk"</i>
<i>"That's just way above my pay grade since having a child was never in my plans and I'm old now. I can't even fathom decisions like that."</i>
<i>"Not sure, has MRT been tested yet?"</i>
<i>"I'm not sure. I've seen how a friend has been affected by it, and while it does change her life, she also has a great community of other people it affects. This makes me think of something like "if you knew your kid could have Down Syndrome and you had a way to prevent it, would you?" I'm pretty neutral, but leaning slightly towards no."</i>
<i>"If I wanted a child I would use MRT"</i>
<i>"If it were possible and safe I would likely opt for MRT because the effects of mito are so variable and unpredictable."</i>
<i>"I would not want to give my child mito. Having a healthy child is the main objective"</i>
<i>"Yes but I wish there was other test out there to know about first."</i>
<i>"I don't know enough about the replacement therapy to have an opinion yet."</i>
<i>"If my mtDNA was defective, I would certainly use MRT or I would not have children."</i>
<i>"If I knew I was at risk"</i>
<i>"If I had known my own diagnosis and the issues of having children, I would have considered both having children and what types of measures I could have taken."</i>
<i>"Although I a male, if I was female, I would certainly consider it."</i>
<i>"would need to know"</i>
<i>"I don't think my body would be healthy enough to have a child in the first place, but if I did choose to have a baby, I would want to give that baby their best chance at a healthy life."</i>
<i>"Mine can not be passed on"</i>
<i>"Absolutely. If I could use replacement and know for sure that my child would not have a mitochondrial disease I would definitely do it. Watching your child suffer with this disease is not anything that I would want."</i>
<i>"If it were determined that my children were at risk of being born with mitochondrial disease that would also be handed down through subsequent generations and that the replacement therapy was safe and reliable, I would use MRT."</i>
<i>"It would be wonderful to know my child had 0 chance of inheriting my disease."</i>
<i>"Mito at its best is life challenging but at its worst life threatening."</i>
<i>"What I know now!!"</i>
<i>"I don't have a known pathogenic mtDNA mutation. Only a polymorphism has been identified."</i>
<i>"And if I had a known mtDNA mutation."</i>
<i>"If I could prevent what my boys go through I would. It is horrible."</i>
<i>"Yes, If we could confirm that my mutation was in mtDNA. Currently my geneticist believes it more likely to be a nDNA mutation but we cannot currently get insurance coverage to finish my genetic testing. I do have some mtDNA variants as well but it is unknown if they are disease causing. My dx is MDS by muscle biopsy."</i>

<i>"I would not want my children to have mitochondrial disease if I could prevent it."</i>
<i>"DNA mutation not Mdna"</i>
<i>"Unsure of the safety and reliability of the therapy at this point"</i>
<i>"No, I believe it crosses a moral and ethical boundary."</i>
<i>"Still need to do more research"</i>
<i>"Possibly."</i>
<i>"This would have allowed us to have more children."</i>
<i>"I am unsure due to ethical considerations."</i>
<i>"I have already faced this choice and it was not a consideration for me."</i>
<i>"I feel it would be a violation of my ethics to do so."</i>
<i>"If MRT were shown to be an option in preventing my family's mitochondrial disease from being inherited I would consider MRT, but I currently am undecided if I would consider personally engaging in the practice to be moral."</i>
<i>"If I were to have a child, I would use replacement therapy. That is the only condition under which I would have a biological offspring."</i>
<i>"I would be wanting a daughter and this would improve the genome down the line. As it is, I have sons so they won't be passing on my mutation."</i>
<i>"I recently lost my child to this genetic mutation and if I wanted to have more kids this would be one of my only options."</i>
<i>"I would definitely use this if available. I am even considering moving to the UK eventually to have this option. Hopefully it will not come to that."</i>
<i>"Again, if the process was proven safe, I would be all for MRT to prevent passing down such a progressive, debilitating disease to my children."</i>
<i>"I have seen what happens to people with mitochondrial disease and I would never wish that upon my own children or anyone else's children."</i>
<i>"Living with someone who is severely affected by mitochondrial disease, I know the heartbreak of watching your child decline and lose abilities. No parent should have to experience this, especially if a procedure like MRT could allow a woman to have a healthy child."</i>
<i>"To me it would be worth the risk to have a healthy child."</i>
<i>"I would take measures to prevent pregnancy if I were of child-bearing age. Unless covered by health insurance I would not be able to afford the procedure."</i>
<i>"I would if proven safe and if my husband was in agreement."</i>
<i>"I think if it is an option to safely remove the bad mtDNA and therefore have a child who would be unaffected, I would greatly consider using MRT as a means to make sure my child would be as healthy as possible in regards to the passing on of a mitochondrial disease."</i>
<i>"I can't stand watching my kids in pain. No one should be in pain"</i>
<i>"I would not want my child to suffer as I have"</i>
<i>"I do not believe in INVF"</i>
<i>"I would not want to have anyone, much less my own child, to have this disease if I could prevent it."</i>
<i>"It would have to be more known about it to be certain"</i>
<i>"I would not risk having biological children without MRT. I believe any resulting medical side effects (potential changes to life span, etc) would have less impact than the mutation I carry."</i>
<i>"I sure would. I would have loved to have a healthy child"</i>
<i>"I'm not sure about this one. I have a reproductive disorder and may be using IVF in the future. I feel as though this inhibits my response as I would already be having the best embryo's chosen. However, I have not fully decided on if I would want to use IVF treatments or if I would adopt instead."</i>
<i>"Personally, I would much rather adopt children that need homes than go to such lengths to have children. Pregnancy would also be difficult for my health. Also, I'm a lesbian, so that aspect is challenging too!"</i>

<i>"Still not sure of my personal ethical stance."</i>
<i>"I would, should I still be at child bearing age, have no hesitation in using the procedure to minimise the difficulties my child would have to face in life."</i>
<i>"I am past child bearing age and have other unaffected children. I would not have additional children. I would want available for others to use."</i>
<i>"Why not insure my child health?"</i>
<i>"I would have the procedure only if disease-causing nDNA defects could be ruled out. Testing and analysis is not sophisticated enough to provide this information at this time."</i>
<i>"If it were proven that (a) I have mito and (b) my mito is a result of an MtDNA mutation then yes, I'd use it if it were available and I was going to have a biological kid."</i>
<i>"Depends on severity of condition and cost of procedure."</i>
<i>"If I had known I had a genetic disease, I would not have had children. I would not wish upon them what I have gone through. If the option to have unaffected children had been possible at the time, I would have strongly considered it"</i>
<i>"I could not afford it."</i>
<i>"If the form of Mito that I passed on was mtDNA and not nuclear then yes, I would use MRT."</i>
<i>"I feel this is not ethical and is a step towards allowing all sorts of other unethical procedures."</i>
<i>"I don't think its fair or ethical to experiment on children that have not given informed consent."</i>
<i>"Absolutely! If it were possible to eliminate, or significantly decrease the risk that my child would have Mito, I would do anything to protect them from getting it."</i>
<i>"I'm not sure, but I would like the option"</i>
<i>"I've had a surgery that resulted in me never being able to carry a child."</i>
<i>"I would be all for a way to ensure my kids will not have the disease."</i>
<i>"It's not ethical"</i>
<i>"As above. If there was an option to have MRT and take away the risk of passing on my mutation I would definitely do it."</i>
<i>"If there is a possible way to have children without mitochondrial disease, I would do it."</i>

APPENDIX H: Full List of Free-Responses for Survey Question 18C about Opposing IVF

Full List of Free-Responses about Opposing IVF
<i>"I have no ethical issues with IVF."</i>
<i>"I have nothing against IVF."</i>
<i>"I feel neutral about IVF"</i>
<i>"I don't care how the conception happens. Are there really people who disapprove of ivf?"</i>
<i>"The fact that it uses IVF would have nothing to do with that decision"</i>
<i>"I have no qualms with IVF assuming I have the money to get the procedure done."</i>
<i>"IVF is a perfectly acceptable method of conceiving a child."</i>
<i>"I would consider in vitro fertilization. Although my formal faith (Catholic) does not support this and I am very much a follower of the religion, I differ in views. I believe that God gives us the technology through science, doctors, and so forth to use this knowledge for the greater good."</i>
<i>"I support the use of ivf"</i>
<i>"In my opinion In vitro is ethical"</i>
<i>"as above"</i>
<i>"I see nothing wrong with IVF, it has been done successfully for decades."</i>
<i>"My understanding is that in vitro fertilization is relatively safe. I have not ethical objections to IVF."</i>
<i>"I have two boys with mito. Do I need to say more. It's not easy to watch them struggle."</i>
<i>"I would not have ivf. I am ethically opposed to it"</i>
<i>"I have no negative feelings about using vitro fertilization if I was a candidate for the procedure."</i>
<i>"Prevent suffering and have a longer life."</i>
<i>"I would consider using this procedure if it were not too much risk to my health."</i>
<i>"If I had an MdnA mutation I would in a heartbeat."</i>
<i>"I have no qualms about in vitro fertilization"</i>
<i>"Within three months of being diagnosed, my doctors put an IUD in me to prevent a life-threatening pregnancy. I was told that since I can't get enough nourishment myself the fetus would never make it."</i>
<i>"I would absolutely pursue MRT."</i>
<i>"I pursued adoption as well as using a donor embryo. In the end, we used a donor embryo that was surplus from another family. This embryo was already in existence and was not created for me specifically."</i>
<i>"I would use in vitro, but only under certain circumstances."</i>
<i>"It would depend on the type of IVF. I am not in favor of generating multiple embryos that would be discarded, destroyed, or used in research, but I might consider single embryo creations for use through IVF."</i>
<i>"I am not opposed to IVF."</i>
<i>"I would have done it in order to have a girl 30 yrs ago!"</i>
<i>"If you have a mitochondrial kid you would understand and make the sacrifice to ensure the health of your next child."</i>
<i>"If in vitro were proven to be safe for me, I would consider MRT."</i>
<i>"I do not have any ethical reservations about using IVF. I think it's a beneficial procedure that has helped so many people have children who would not have been able to otherwise."</i>
<i>"I had to go through infertility treatments to have children in the first place so this would be no different."</i>
<i>"I would consider using the technique rather than have a child with Mitochondrial Disease. This technique would stop the passing down of faulty Mt DNA to my following generations. I have no problem with in vitro fertilization except COST unless covered by insurance"</i>

<i>"I have no issue with in vitro fertilization."</i>
<i>"I believe that if the process is done in a safe and ethical way I would absolutely use MRT."</i>
<i>"Why pass on bad genes?"</i>
<i>"I do not believe we should play God"</i>
<i>"The cost could be an issue but I have no moral issues with this."</i>
<i>"It would depend on safety"</i>
<i>"I have no issue with IVF and believe it to be a legitimate and essential tool for people who have infertility issues. I am aware that some people view it as killing, due to the process creating several embryos before implantation, but I personally do not view it as such."</i>
<i>"I would do anything to have a healthy child"</i>
<i>"See above answer"</i>
<i>"I'm very happy for others to have the option-- I just don't personally want to use expensive techniques to have kids, when there are other children out there in need of homes."</i>
<i>"As above"</i>
<i>"As above. Any process to minimise hardship for a child is worth undertaking."</i>
<i>"I have no issue with in vitro fertilization and believe it to be safe."</i>
<i>"I have no religious hang-ups about IVF."</i>
<i>"I am not opposed to IVF and pre-implantation genetic testing in order to ensure that any implanted embryos were free from specific genetic mutations."</i>
<i>"I have no issues with IVF."</i>
<i>"Depends on cost."</i>
<i>"I have no problems with IVF"</i>
<i>"this is not a valid argument to me"</i>
<i>"Again, if my child was at risk for having Mito, I would do everything possible in hopes they would not have it."</i>
<i>"I would do this so that I could have kids"</i>
<i>"IVF is not a problem for me."</i>
<i>"IVF is a trusted technology."</i>
<i>"I don't have any problem with MRT ethically."</i>

APPENDIX I: Full List of Free-Responses for Survey Question 18D about MRT's Positive Impact on the Mitochondrial Disease Community

Full List of Free-Responses about MRT's Positive Impact on the Mitochondrial
<i>"At the very least it gives hope to the community."</i>
<i>"Patients of mito suffer enough. This option would empower their futures and options for creating healthy families. If safe conception of healthy children is an option, it should be a crime to withhold it."</i>
<i>"The mito community is not a monolith. They may all feel differently."</i>
<i>"There's definitely a dear about passing this disease onto children. This could make people with mito feel safer having kids"</i>
<i>"I'm not sure about this one either. As I've seen, the mitochondrial community is a very strong, close-knit one, similar to the Deaf community. I'm thinking this might have a similar affect to the cochlear implant, which some Deaf/HoH people embraced, and some (most) shunned."</i>
<i>"I feel like many in the mito community may think of this technology as a means to eradicate the disease, which may be a huge part of their identity, and I could see how they might view this as a personal attack."</i>
<i>"Disease prevention is key when it is available"</i>
<i>"Yes it would."</i>
<i>"It provides a method for a woman who has defective mDNA to conceive and deliver a baby free of her mtDNA defects. It creates the possibility for her to have children, period. I do not believe that a woman who KNOWS she has defective potentially disease-creating Mdna should reproduce without MRT. Again, this is my personal belief based on my observation and knowledge."</i>
<i>"Too many children are dying"</i>
<i>"It is yet to be seen to say "agree." I am hopeful. However, to my knowledge, it has not yet been widespread to say it will be a positive impact. Promising...yes!"</i>
<i>"Remains to be seen - insufficient data at this point."</i>
<i>"Less babies born with mito would be an excellent thing. My only concern or perhaps part I don't understand is the chances that the donor material may inadvertently have an unknown mito defect or that the mito could still be passed down through the fathers genetic material (the mitochondrial portion he got from his own mother), which if I understand correctly is found in the nucleus & is then missed by MRT. I don't know how much of an exact science MRT is or if it eliminates mito diseases 100% of the time. I definitely think vastly reducing the number of children born with mito disease would be a great thing!"</i>
<i>"MRT can prevent terrible suffering."</i>
<i>"It could stop some Mitochondrial Disease."</i>
<i>"HOPE for future generations and the potential to end or slow down the spread of the disease."</i>
<i>"Many people in the mito community would probably jump at the chance. Do we know enough yet?? Will ethical issues be well explained?"</i>
<i>"It would give those patients who carry a mtDNA mutation the opportunity to have a family free of the disease."</i>
<i>"Again it will prevent the passing on of this killer disease. It impacts generations."</i>
<i>"It will give many mito patients the opportunity to have children when otherwise they would not."</i>
<i>"Because we would be able to have a lot more agency in our lives."</i>
<i>"It could potentially prevent the disease in children, giving parents hope, but risks are still not fully known"</i>
<i>"I would not be surprised to see a divide in the community. Those who don't have hope will feel more hopeless."</i>
<i>"It elevates the dna"</i>
<i>"It has the potential to eliminate the disease."</i>
<i>"This would be a great option for many families. Adoption is very time consuming and costly. PGD for</i>

<i>in vitro</i> is also an option that comes with risk of false results. People should have this option available to them regardless of my personal views.”
“Explained previously.”
“I predict it would offer hope to patients with mtDNA-based diseases, and that this hope would spur greater interest in correctly diagnosing all patients, and hopefully in generating more treatment options.”
“It will enable parents who wish to reproduce the ability to do so safely.”
“It will reduce the number of cases due to an mDNA mutation.”
“Knowledge is power.”
“I think it would give many people hope. I don't see any negatives to this at all.”
“If proven safe and used specifically for the reason advertised and not for unnecessary personal genetic modifications.”
“It will give hope to those with family members affected by mitochondrial disease. It will give hope to those that would love to have children but have opted not to in order to avoid passing the mitochondrial disorders to their children.”
“I would have strongly agreed this question, but MRT will not be helpful for those with nuclear DNA mutations so there is a significant population of the mitochondrial community who will not benefit from the procedure. However, for those who can take advantage of MRT and have healthy children, it will have a positive impact.”
“I think that it may, but the population is so small I do not think that It would be noticed all that much.”
“Absolutely ... however, it would only represent a "cure" for those with Mt DNA deletions ... roughly 20% of the mitochondrial community are affected by Mt DNA deletions.”
“reduce the passing on of devastating diseases: win for families, win for child, win for society”
“I think introducing MRT into clinical practice is just one step forward into more awareness of this disease. The more that the public (doctors included) knows about mitochondrial disease and MRT, the better. One step more towards a cure, in my opinion.”
“More help and answers”
“It would prevent some future cases but it could also stop funding for research for already affected individuals”
“If other people want to use the therapy that is their choice and in the long run we might see less mTDNA disease causing mutations.”
“For those that really want their own child and are at a point in their lives to do so, except for having an mtDNA diagnosis in the female, then this is a true opportunity.”
“I feel it may definitely be beneficial bit we don't know enough yet”
“Being able to give life to a child without passing on all of the issues that mitochondrial disease presents is a godsend.”
“Healthy children are most important that is life to outlive there parents”
“I think if a parent chooses to use this technique that is fine. It should be up to each individual family”
“The more options the better!”
“Yes, I think most of the mito community see this as a positive advancement”
“This process appears principally controversial due to misuse. If it were correctly safeguarded & presented, then I see nothing but a positive impact”
“Many parents would welcome the opportunity to have biological children that are free of mitochondrial disease.”
“Lessening that community is the most positive impact that can be made.”
“More research on the interplay of mtDNA and nDNA defects needs to be done before MRT could be considered a sure-fire way to avoid mitochondrial myopathies.”
“I do think that some people find it is something that gives them hope and that having biological kids is important to them, so it would be positive for those people. Unfortunately there are so many mito sufferers internationally who it wouldn't be available to that it would be rough on them.”

<i>"Many mutations could be nearly eradicated in the span of a generation"</i>
<i>"Research should be based at the medical and environmental factors that cause Mito to start with"</i>
<i>"Hopefully, over time we would see a decline in the incidence and possibly severity of Mito cases."</i>
<i>"It adds options"</i>
<i>"It would make it so people could have kids, and hopefully weed out the disease."</i>
<i>"This is going too far."</i>
<i>"We need options!"</i>
<i>"This has the potential to be life changing for many adults/families with mitochondrial disease, which is caused by a known mtDNA mutation which may have been in many generations of a family. Potentially eradicating it from their family line."</i>
<i>"I think more people with mito would be willing to have children. Since some of us have very mild cases of mito, we are well enough to take care of a child, but fear having children since we might pass on the gene- and give our child mito (with the possibility of them having a severe case of mito)."</i>

APPENDIX J: Full List of Free-Responses for Survey Question 18E about MRT's Negative Impact on their Personal Relationship with the Mitochondrial Disease Community

Full List of Free-Responses about MRT's Negative Impact on their Personal Relationship with the Mitochondrial Disease Community
<i>"I don't think anyone would hold it against me."</i>
<i>"I am not a part of the mito community"</i>
<i>"I don't think my friends with Mito would feel negatively about me if I perused it but I haven't asked so I don't know."</i>
<i>"The mito community, unlike other disability communities, looks for a cure and treatments as it can kill. While other disabled communities may think that passing a disease/disability along to a child isn't bad (and would be right), there is a different attitude because mito can kill. I think the community would understand"</i>
<i>"It might. I could see the community seeing it as planning a child "not like us"."</i>
<i>"I do not think that my friend would judge or blame me in the slightest for engaging in MRT."</i>
<i>"There may be no community"</i>
<i>"I think we all want healthy children"</i>
<i>"No I would want a healthy kids"</i>
<i>"People who would otherwise benefit from MRT may have personal religious and otherwise beliefs that hinder their pursuit of MRT. However, it is my belief that their choice, in that event, MUST be NOT to reproduce."</i>
<i>"In the mito community that I am apart of (Mito Action, etc.), it appears that the overall approach is looking at a myriad of avenues as the 'future' and 'solutions' with no 'one-size-fits-all' approach."</i>
<i>"I would think the only negative impact would be that Drs would see children born with mito disease even less than they do now (a good thing) but it means that for those children, the Drs would possibly know even less than they do now making getting the appropriate health care even harder."</i>
<i>"This does not apply to me"</i>
<i>"I do not believe suffering makes one a better person. I believe that science should be used to relieve suffering. I do not believe that MRT is unethical."</i>
<i>"I would stay connected to provide support and maintain relationships as well as fundraising."</i>
<i>"I think my Mito friends who completely understand my choice. Mito is not easy."</i>
<i>"I don't know of any reason why it would have a negative impact on my relationship with the mito community but that may be because I am unaware of the community as a whole feelings about MRT. I do believe that wanting to eliminate the possibility of having children born with a mtDNA disease doesn't diminish the value of a child born with the disease."</i>
<i>"I believe most people would understand and I would still advocate and continue the fight to find a cure for ALL who suffer from the various types of Mitochondrial Disease."</i>
<i>"I think most people in the mito community support use of this technique. Particularly more so than the general public."</i>
<i>"The community wants this option"</i>
<i>"I have no relationship with the mito disease community at this point, knowing no one else with the condition and not yet part of a support group"</i>
<i>"I wouldn't pursue, so it does not apply."</i>
<i>"I feel supported and know that aside from a cure this is my next best option"</i>
<i>"I think the community understands how debilitating this disease is and what a positive impact replacing mtDNA would be."</i>
<i>"I don't know."</i>
<i>"I'm not certain it would affect my relationship with the community either positively, or negatively."</i>
<i>"Whaaaaat? Get outta' here!"</i>
<i>"Our community isn't big in judgement we are all affected."</i>

<i>"I see no negatives to MRT."</i>
<i>"I would seriously hope that the community would be understanding of this personal decision, but I wouldn't know how they would react until a decision like this was made."</i>
<i>"On the other hand, I would be a donor which would have a positive impact on the mitochondrial disease community."</i>
<i>"I feel that the mito community is very excepting and would not judge me on using this method or not. Besides it is none of there Business who I have children."</i>
<i>"If you live with mitochondrial disease, you would not wish to have your children suffer ... it is hard on the patient, the family and the medical system because it is not well understood. Those in the mitochondrial disease community, IF they understand the process, are united in support of the process. I would be encouraging others to look into whether the procedure would help them. I also suggest that women carrying faulty Mt DNA take measures to prevent pregnancy. This is not as widely accepted in the mitochondrial community."</i>
<i>"No one I have met in the mito community wants to see more ill and dying children. please."</i>
<i>"I don't believe that this is a true statement. Furthermore, it is my body and it would be my child. What I choose to do is my own personal choice. If others in the mitochondrial community disagree with or are against MRT that is their issue and their choice, not mine."</i>
<i>"more research done is for the better"</i>
<i>"It may but I don't know"</i>
<i>"Too abstract an idea for me."</i>
<i>"I suppose it could vary by individuals, but I believe if they understand the process they will be supportive."</i>
<i>"I don't feel it would"</i>
<i>"While it would allow me to have children without mito, it does not cure my own issues or those of my siblings and mother."</i>
<i>"I'm not sure, most responses within the community that I have seen have been positive. But there may be those that do not agree."</i>
<i>"I bet I'd be super popular in the mito community, to be honest-- many people would want to know my experiences."</i>
<i>"It may, with individuals who are still unsure of the ethical nature and personal belief systems"</i>
<i>"Only if I let it & if others were judgmental."</i>
<i>"That's just ridiculous. I don't know anyone who would judge me nor would I care."</i>
<i>"The welfare of my family is infinitely more important than the opinions of strangers on the Internet. The "Mitochondrial community" is not a true community: it is merely a subset of individuals whose lives are impacted by a specific group of genetic diseases."</i>
<i>"I don't see why it would be negative."</i>
<i>"I can't see how having a healthy child would have a negative impact"</i>
<i>"I do not see any connection with the two parts of the argument"</i>
<i>"It would need to be a highly personal decision. Yes, I can see it dividing some members of the community, but in the end everyone needs to do what's best for them and aligns with their values, ethics, beliefs, etc."</i>
<i>"Everyone in the mitochondrial community sticks together."</i>
<i>"I do not believe this would be the case. As far as I know the majority of the mitochondrial disease community support this technique and it would not change my relationship with them."</i>
<i>"It would not impact my relationship with the community in any way."</i>

APPENDIX K: Full List of Free-Responses for Survey Question 22 about an mtDNA Donor You Know Personally or are Related To

Full List of Free-Responses about an mtDNA Donor You Know Personally or
<i>"They may be affected too"</i>
<i>"Not that the 37 genes makes much of a difference, but since the child may one day want to look up that donor for the symbolic role they play I'd prefer it be someone I knew."</i>
<i>"No preference"</i>
<i>"It makes the process seem less terrifying and new"</i>
<i>"Not really sure."</i>
<i>"I guess it wouldn't matter"</i>
<i>"I'd just like this to be personal"</i>
<i>"I have no idea but it was an automatic, gut reaction. Only if there was a certain person that was special in our life or something."</i>
<i>"It doesn't matter to me, as long as the mtDNA is normal."</i>
<i>"I have adopted siblings, so I know personally how a genetic relationship is not necessary to loving a child"</i>
<i>"Assuming it was an unaffected relative, I would love to have a family member donate to try and keep my mtDNA line going."</i>
<i>"Probably but don't really care"</i>
<i>"No Preference"</i>
<i>"Yes.. but who is it really does not matter"</i>
<i>"Someone I know to feel like more part of the family"</i>
<i>"I would want the DNA from a stranger and don't think my immediates need to take part in the controversy"</i>
<i>"Not necessarily. I do not know all of the specifics, but just like any organ/tissue donor, I would want cells that would best meet the deficiencies identified in my cells. If it could come from a family member or known person...great. If not, so be it. I just would have liked to prevent the health issues both me and my son (and potentially daughter) are facing. Every major organ--except his kidneys and pancreas, have been impacted. I would have liked to have options--as imperfect as they are."</i>
<i>"Do not care at all - would. Want most appropriate mito for the child."</i>
<i>"I would just feel better with someone know"</i>
<i>"I wouldn't mind knowing the person but would not want to be related to the person since I know there is great deal of illness that runs in our family beyond mito & would feel that chances of a healthier child would be better with someone not related. I wouldn't have any issue simply knowing them as long as they were healthy."</i>
<i>"Does not apply to me"</i>
<i>"Only in that it might give me more information re: my baby's future health"</i>
<i>"Someone I know would be nice; I would not want a relative as the disease is in our MTDNA. I wouldn't want the risk."</i>
<i>"It would prevent me from wondering where the mtDNA came from."</i>
<i>"I would prefer no connection socially"</i>
<i>"why not."</i>
<i>"It only is the mitochondria. A stranger with healthy mitochondria is fine."</i>
<i>"I think having someone that you know and care about be a contributor to the IVF process is comforting and eases the process and the anxiety associated with undergoing these procedures."</i>
<i>"It wouldn't matter to me."</i>
<i>"I would not want to the of the person as part-mother of my child"</i>

"N/A"
"Could be helpful later"
"adopted"
"It doesn't matter as long as there were no mutations."
"I would want the child to be mine and not have another mother."
"If possible, I would prefer to keep my child's mtDNA as closely related to that of my own, as possible."
"That's just "messy" personally. Also wouldn't want to risk that they'd somehow attempt to establish parental rights to the child down the line."
"I want better DNA than my relatives have."
"I would prefer to not know."
"I have a slight preference towards that but only because my husband would want that. For me, it does not matter very much."
"I would not want a personal connection with a donor of any kind when it comes with my children. There is too much concern for transference and unhealthy attachments."
"If and when this gets approved, I will be the donor for my best friend so she can have her own baby. If our roles were switched, I would prefer my donor be someone I had a close relationship with."
"I would like the donor to just be the best person because it is just her mtDNA and not nuclear DNA"
"I would want the donor to have Mt DNA testing clear of problems. Related may have Mt DNA problems also. Probably best to be clear of friendships."
"As I am not and never will be in that predicament, I refuse to speculate but defend the right of each individual to determine what is best for their family."
"As long as I knew the donor was healthy I don't think it would matter much to me if it was someone I knew or was related to."
"No, They could also have health issues"
"Undecided - there are pros and cons to both."
"That seems awkward. I'd rather have prescreened anonymous donors."
"I'd prefer not to know as long as they'd been tested to have healthy mitochondria! If the donor was someone I knew there'd always be a sense of gratitude or debt to them."
"Personal preference"
"I do not have a preference. Whoever would be a good match, stranger or friend. Of course it would be nice to be able to involve a beloved friend or family member, but it is not essential."
"As long as it's healthy"
"I feel as though if you choose someone you are not related to you can just raise your child as is."
"It might be nice to have the donor from my dad's side of the family-- so it would still be my genes, in some way"
"If you know the person, you will have some knowledge in their genetic make up"
"If minimal characteristics are passed on, knowledge of the donor would be irrelevant."
"It would be easier to confirm the absence of genetic errors in the donated mtDNA."
"It would be nice but not necessary."
"I have no opinion regarding the decision between a known or anonymous donor."
"Just for emotional reasons, I think the kid would want to potentially know who that person is and have a relationship with them in the future."
"Less uncertainty about donor and hopefully cheaper?"
"I would not welcome any emotional involvement with the child from the donor."
"as long as the mitochondria are healthy, I would not care. It has no effect on the physical makeup of the child, only their ability to produce energy and be healthy"
"no comment"

<i>"I was adopted and my birth mother was adopted too"</i>
<i>"Keeping same family DNA makes things less confusing for kids, they know where they come from"</i>
<i>"I would rather it not be random if I had a choice."</i>
<i>"Would not pursue this course of treatment."</i>
<i>"I personally would prefer it to be anonymous."</i>
<i>"Why use the same family dna?"</i>
<i>"Since mitochondrial disease is generic you never know if they would have it as well."</i>
<i>"I think I would want it to be someone from my partner or I's family."</i>

APPENDIX L: Full List of Free-Responses for Survey Question 23 about mtDNA Donation Altering Traits

Full List of Free-Responses about mtDNA Donation Altering Traits
<i>"Only 37 genes, that we know don't play roles in those functions"</i>
<i>"I'm pretty sure most of those traits are coded for in the nucleus?"</i>
<i>"I'm guessing it's only a minuscule part of the child's genome and I don't think many phenotypic traits are carried by mito DNA, but I'm not positive."</i>
<i>"I'm guessing here"</i>
<i>"I am not qualified to say."</i>
<i>"Okay let's be honest I don't understand genetics"</i>
<i>"As far as I know (and I may be wrong, this is from brief genetics units in high school and college biology classes) these traits are not on the mtDNA"</i>
<i>"As far as I am aware mtDNA impacts cell function rather than actual traits. I suppose cell function could impact personality and I have known to be wrong but I would not be all that concerned about this."</i>
<i>"MtDNA have no or little impact on such physical features."</i>
<i>"mtDNA impacts the mitochondria within cells, nuclear DNA determines traits of the child."</i>
<i>"I think that donors might have a mix into a personality, but kids each have individual personalities and end up somewhat like their parents in most cases."</i>
<i>"I honestly don't know. I would hope that the science would allow that only the mito elements (the production of ATP and so forth) could be pinpointed and transferred, as opposed to all of the other hereditary issues. This is one of the things that I would need more info on in order to make an informed decision."</i>
<i>"No knowledge here - would prefer a don't know option on this Q"</i>
<i>"have no idea"</i>
<i>"If I understand genetics correctly, all of those traits are passed along in the nucleus part of the cell which is not being touched in MRT."</i>
<i>"Do not know much about this subject"</i>
<i>"I believe that MRT is being used so that parents with mtDNA can still have genetically related children"</i>
<i>"They are replacing only Mitochondria, not the genes that make the child mine."</i>
<i>"But I might be ignorant of this happening. Most of my thoughts about MRT have been focused on saving a child's life because some of the mtDNA causing mito diseases can be deadly, not necessarily what characteristics a child might acquire. I don't know of any personality genes good or bad. I guess I don't know a lot about mtDNA genes and how they contribute to a person's genetic makeup."</i>
<i>"Mitochondria do not control those traits."</i>
<i>"mtDNA does not carry DNA affecting phenotype. mtDNA solely affects the ability of our cells to make energy. Nuclear DNA is what carries information that determines traits and phenotype."</i>
<i>"at this point, it is unclear so I must assume it is possible"</i>
<i>"I don't believe the depth of the knowledge about MtDNA is fully known."</i>
<i>"Why wouldn't it"</i>
<i>"It's the same genes essentially for every person. It's not nuclear DNA."</i>
<i>"My understanding is that mtDNA is only concerned with energy production."</i>
<i>"mtDNA has not been shown to influence traits other than the production of ATP and the efficiency of other metabolic processes."</i>
<i>"I don't see how they could, genetically speaking."</i>
<i>"Those things are somatic DNA. Not having mito could make them taller and definitely healthier though."</i>

<i>"I am unclear but can see a possibility."</i>
<i>"from what I understand it is only the mitochondria that will be altered so I am not worried about anything else. Plus it would be mostly my dna and my husband's."</i>
<i>"Anything is possible, but MRT is not used or designed to alter those characteristics."</i>
<i>"It is my understanding that mtDNA does not contain the genetic material that determines physical traits or personality."</i>
<i>"All of those traits are from your nuclear DNA which come from the original set of parents not the donor."</i>
<i>"there are 2 different DNA sources. the mtDNA is not in the Nucleus of the cell but in the mitochondria as way way back mito use to be what scientist feel bacteria which has its own DNA and over time developed a partnership with animal DNA and it produces energy that we need at the same time our cells produce what it needs to survive. It is the Nuclear DNA that provides the information for hair color, and eye color and things like that."</i>
<i>"Nuclear DNA governs traits of resulting child largely: Mt DNA is less than 1% of inheritance factor"</i>
<i>"Do not know about hair color or height. Personality is far too complex and has many factors based on nurture and environment, so obviously no. Height is also influenced by nutrition, or course."</i>
<i>"No, because as far as I know it would only be replacing the unhealthy part of the mtDNA which has nothing to do with a child's traits."</i>
<i>"It could but a healthy child is worth it"</i>
<i>"I do not believe those traits are passed through mTDNA"</i>
<i>"Those are from nuclear DNA, or personality from nature/nurture."</i>
<i>"I don't believe it would but not sure"</i>
<i>"MtDNA does not affect any of these things."</i>
<i>"I don't think that part to worry about its the mitochondrial that I worry about"</i>
<i>"This is silly, it's only fixing the mitochondrial problem. This does not affect any outward traits of the child."</i>
<i>"Maybe not, but I don't think the possibility should be dismissed completely-- given the mtDNA links of so many disorders, including mental illnesses, I don't think it's unreasonable to think it could affect personality"</i>
<i>"Maybe. I think it is a possibility, but not sure"</i>
<i>"One can only make decisions on current expert opinion. Such opinion negates this possibility."</i>
<i>"MtDNA dose not encode for anything except mitochondrial functions"</i>
<i>"It's possible but that should make no difference. Your child is your child."</i>
<i>"MtDNA contains information regarding a cell's internal function, not the characteristics of the resulting embryo. For example, exchanging high-output lithium batteries for generic inexpensive batteries in a toy would enable it to function longer and more reliably, but would not change a toy car into a toy airplane."</i>
<i>"Those come from nuclear DNA."</i>
<i>"The mtDNA does not contribute to any of these traits"</i>
<i>"those traits are determined by nuclear DNA"</i>
<i>"possibly"</i>
<i>"I it's not the primary intent but it would be a secondary effect. In other words, it would happen to some degree."</i>
<i>"I think those characteristics are on other DNA alleles"</i>
<i>"I'm not sure but that would be something I'd ask my genetic counselor."</i>
<i>"I do not entirely know if it would"</i>
<i>"From what I read the baby would still have the genetic make up of the parents."</i>
<i>"In some way it will alter the child. You can't mess with DNA and not cause changes whether tangible"</i>

<i>ones or not."</i>
<i>"MtDNA does not have any control over traits such as hair colour, height etc. These are all determined by the nuclear DNA which is not affected in anyway by this technique."</i>
<i>"Nothing is guaranteed."</i>
<i>"I honestly have no idea but I have thought about it a lot. It wouldn't make me love the child any less."</i>
<i>"I don't know enough about which traits are in which part of the DNA, but I don't think they are in the mitochondria. I could be wrong though."</i>

APPENDIX M: Full List of Free-Responses for Survey Question 24 about Children Knowing the Identity of their mtDNA Donor

Full List of Free-Responses about Children Knowing the Identity of their mtDNA
<i>"In the way that any child conceived with the participant of a donor has the right, even though it is such a tiny role they're playing."</i>
<i>"More donors will come forward if their anonymity is protected."</i>
<i>"Children should have the right to know the circumstances in which they are conceived"</i>
<i>"As long as the woman in question has OKed it, I think it would be akin to knowing the identity of one's birth mother."</i>
<i>"Not necessarily. Much like sperm donation, any genetic disease info should be communicated but if a don't does not want to be in contact that's okay. As long as the child knows they were conceived with mito replacement, I don't think there's a problem"</i>
<i>"Adopted and reg IVF children don't have any right to know id's of their bio or bio contributing parent. Is there a health related reason why 3-parent kids should be treated differently?"</i>
<i>"I don't think there's any situation in which a child would have "no right" to know a person who helped them be born. The donor may prefer to be anonymous, but I don't think that changes the basic right (the donor has rights too)"</i>
<i>"If the donor is willing and the child wants to then absolutely."</i>
<i>"Don't know, would assume same legal rights as for children from egg/sperm donors"</i>
<i>"Really in the middle on this one. I would not think the identity would be important, but the child may think it IS important and, therefore, I would respect that desire in others."</i>
<i>"Due to medical reasons"</i>
<i>"If the donor is properly screened, her contribution is mtDNA which determines the functioning of the mitochondria within the cells of the child's body."</i>
<i>"I would only want to know traits. I don't want a predominately African American surprise, or I want counseling about that. Otherwise I should adopt."</i>
<i>"Not necessarily. It's much like a sperm donor..."</i>
<i>"I see it much more as a therapy, not a gene question."</i>
<i>"Completely the parents choice although I believe it should be shared with the child"</i>
<i>"may need their history"</i>
<i>"Given that the child still shares over 99% of genetic material with the 2 biological parents that would be raising the baby, it's not as though they would be strangers to their parents or anything. Upon telling the child of their birth story, if the donor was known to me then it might be a nice way of saying thank you to let the child know as they got to an older & more appropriate age. I would see it as a privilege to say thank you (such as meeting an organ donor's family) but no; not as a right because this is a great gift that was donated but there would be no legal rights on the part of the donor."</i>
<i>"My mom had it when I was born and I do not know why I got it"</i>
<i>"This information could be available if future research deems it medically helpful"</i>
<i>"They are only receiving the mitochondria"</i>
<i>"If the genetic make up is only 1% inherited I would consider it the same as a organ transplant."</i>
<i>"Yes and no, if the woman wanted to meet the child whose life she changed the outcome of and the family were fine okay. To me though it is like donating blood to blood bank... You save lives and should be thanked in more global than individual way of that is the way the people wish it to be."</i>
<i>"Merely because I think the child will be grateful and may want to thank the donor."</i>
<i>"unsure, but an "anonymous" donation would be preferred"</i>
<i>"I believe everyone has the right to know where they come from."</i>
<i>"I need more information"</i>
<i>"See previous answer."</i>

<i>"She has a right to privacy, but the child should have a complete medical history."</i>
<i>"Actually, I am undecided. I would want to evaluate the reasons and context of the child's potential rights in this situation on a case-by-case basis, until the issues involved were more clearly realized."</i>
<i>"I think they are inclined to ask, if they are informed of the nature of their conception, however I don't think they are entitled to this knowledge. If the donor agrees, sure"</i>
<i>"It's up to the donor. There is no right."</i>
<i>"Medical needs pieces of the puzzle."</i>
<i>"It is one small part of the genetic makeup. So miniscule that it does not matter."</i>
<i>"Possibly. I would like to say there would be no need for a child to seek a mtDNA donor as in the case of a sperm/egg donor, but that decision would have to be up to the donor and the child per their rights to privacy."</i>
<i>"I think it would help having that information available in the case of a future health concern that might be caused by the donor mtDNA."</i>
<i>"I think it would depend on whether the donating woman was willing to have her identity known."</i>
<i>"to me I see this as something like a blood transfusion. should you get to know and meet everyone that has given you blood?"</i>
<i>"I can see NO reason why the donor identity should be available to the child."</i>
<i>"Only if both all both women consent"</i>
<i>"I do think the child should have a right but I believe it should be a decision the family makes together with the parents heavily involved in the decision."</i>
<i>"Case by case basis"</i>
<i>"Only if all 3 parties involved agreed to this arrangement."</i>
<i>"I can't see any reason they shouldn't have the right. They had no choice in how they were brought into this world so if they wanted to pursue that info, it should be available to them."</i>
<i>"This is not the same as adoption."</i>
<i>"It would really depend on the situation, but it's still the same mother, just do or mitochondria"</i>
<i>"There is no parentage. It is as if someone donated an organ."</i>
<i>"I don't think that would be important unless it was not healthy"</i>
<i>"For health purposes"</i>
<i>"If it was the child's choice, when they are at an age of understanding and consent, then yes"</i>
<i>"If the donor was willing. However I don't see the necessity."</i>
<i>"I see no reason the child would need to know this. I also see no reason for the child not to know at an appropriate age."</i>
<i>"Everyone has a right to know whose DNA they possess."</i>
<i>"I have no opinion."</i>
<i>"If it was someone close to family"</i>
<i>"I don't know whether there's any legal rule but I think they SHOULD have the right to know that person. The more we learn about the psychology of children conceived through donor egg and donor sperm the more we learn it's important to those kids to know who they came from, I think it's at least potentially possible they would feel the same about a mtDNA donor."</i>
<i>"While as a personal decision I would discuss it with them, I do not believe they would have a right to discover an anonymous donor. Feels more like organ(-elle) donation to me than parentage."</i>
<i>"Yes, because the child may be adversely affected if they think information is being withheld, but I would prefer that they did not know, as the contribution from the donor is so small and does not affect inherited traits apart from the mitochondrial mutation."</i>
<i>"it would seem irrelevant as the "third parent" provided no physical traits, only healthy mitochondria"</i>
<i>"no comment"</i>
<i>"No. This is different than adoption because in the case of adoption there's more of a want and the need"</i>

<i>to know the identity of the person who gave birth to you. Here the focus is unchanging the genetic makeup to eradicate disease.”</i>
<i>“We keep learning more science it could matter later”</i>
<i>“For medical reasons yes...”</i>
<i>“I think it would be good for the child to know everything about how they were created.”</i>
<i>“You should know what you are made of.”</i>
<i>“Only part of that donor is present in the child.”</i>
<i>“It's just like a surrogate or an adoption. If the child wants to know they can.”</i>
<i>“I think it is fair for them to know who's DNA they are made from.”</i>

APPENDIX N: Full List of Free-Responses about for Survey Question 25 MRT Creating Children with Three Parents

Explanation for Question: "Do you believe that a child resulting from the use of a mtDNA donor has three parents?"
<i>"Parent is who raised the child"</i>
<i>"I think who the "parents" are should be determined by the folks involved"</i>
<i>"This is no different than sperm and egg donors."</i>
<i>"If the parents and the children desire that, then yes"</i>
<i>"Yes, technically, but a child born of a surrogate mother is not considered to have three parents. I consider this to be similar to organ donation."</i>
<i>"On the end, parents are the ones who raised you."</i>
<i>"not really. Your parents are who raise you. And donor's are just that, donor's. Surrogates are surrogates. There's always really 2 bio parents- the 2 that came together to make the baby. Esp if they went to all that extra work to do it. The others are helpers."</i>
<i>"One of my adopted siblings used to like to say she has 4 parents: birth mother, foster mother, adoptive mother, and adoptive father. I think anyone who contributes to the child's being in the world or upbringing, no matter how small, is a parent. They might not be an active parent, but they're a parent in their own way. "</i>
<i>"Technically, yes. "</i>
<i>"I do not feel that the mtDNA changes the DNA that much. Just like getting a transplant, or transfusion, does not give you a third parent..."</i>
<i>"Just like any other reason why there are family like that now"</i>
<i>"The child has two parents and a helper which allows them to reproduce themselves, WITHOUT the significant risk of bringing a child into the world who is doomed with a disease which is incurable and wretchedly crippling painful, debilitating and fatal. We do the best with what we know; and when we know better, WE DO BETTER. Anything less is just negligent."</i>
<i>"not really. I think it's a descriptive term and alarming, but not reality in meaning."</i>
<i>"Not necessarily. It is my hope, as stated above, that the "impaired" elements of my DNA could be infused with the "healthy" elements of someone else's DNA to create a "healthier version" of my own DNA. Much like if I received an organ transplant...ex: a heart...and then went on to have a child. No one would question whether the child was mine or not b/c it was "powered" by the pumping of another person's heart. In the same way, I hope the process evolves as to use the two parents DNA, with the "third person's DNA" used to infuse into the mother's "impaired" DNA to make it "whole/healthy."</i>
<i>"Parentage comes from nuclear DNA and the act of raising a child."</i>
<i>"No it is a way of getting rid of this disease"</i>
<i>"Biologically yes, because it takes 3 people to make this child be able to be born healthy. Legally no, the child would only have the 2 legal parents."</i>
<i>"I don't believe that using MRT creates a parent/child bond."</i>
<i>"MtDNA should be no different than a stem cell transplant, or organ transplant."</i>
<i>"No, but you can't ignore the fact that part of the child's genetic makeup came from someone other than their two biological parents. I would consider the donor to be a biological donor but not a donor parent."</i>
<i>"It is only the mitochondria, nothing else that determines traits."</i>
<i>"Emphatically NO!!!"</i>
<i>"parents are the ones who birth, raise, and nurture a child"</i>
<i>"Not at all"</i>
<i>"I'm adopted & the people who raised me are my parents. The idea of a 3 person baby is similar to surrogacy. I feel that each couple should decide for what is best for them"</i>
<i>"Previous answer."</i>

<i>"mtDNA doesn't affect any of the genes that make us who we are, basically. they enable proper energy production of the physical host"</i>
<i>"Genetically yes, but realistically no."</i>
<i>"Technically, the child has directly inherited genetic material from three individuals."</i>
<i>"Mostly untrue. The percentage of the total genome from mDNA is so small."</i>
<i>"Parenting and conceiving are very different parts of life."</i>
<i>"No. It is such a tiny percentage. Perhaps biologically, but three parents don't need to go on the birth certificate."</i>
<i>"Just as a sperm/egg donor child does not have three parents, a mt dna donor child would not. Your parents are those that raised you, not those that biologically made you."</i>
<i>"The child does not get any genetic material from the donor mitochondria. His or her physical appearance and personality traits are completely determined by the regular DNA inherited by his or her parents."</i>
<i>"because as I said before this is more like a blood transfusion. Where the person is giving the other person a shell for there baby to grow but it is not going to change who that person grows into."</i>
<i>"A child resulting from Mt DNA donation has less than 1% of its DNA make up from donor: this doesn't represent parenting. However ... I pray that women with good Mt DNA will be encouraged to help the mitochondrial disease community by donating the mitochondria in their egg"</i>
<i>"As with adoption, the parent is the woman who raises the child."</i>
<i>"Technically, in the genetic world maybe this is true to some point but I believe that since only the unhealthy part of the mtDNA was being changed that the birth mother would be the child's only mother and the father would be the only father. Although, maybe, each family would have their own opinion based on their own beliefs. I do not believe that the child would have three parents though."</i>
<i>"parents are who love and raise you"</i>
<i>"Well I guess in a sense they have genetic traits from 3 people so sure."</i>
<i>"MtDNA is responsible for energy, etc. and not responsible in determining who a person is."</i>
<i>"They have a mother and father in my opinion."</i>
<i>"No because it would be a small tiny amount"</i>
<i>"To me it seems more like an organ transplant as opposed to three parents. "</i>
<i>"The mtDNA is so tiny it's barely a rounding error"</i>
<i>"It is similar to a person donating an organ. mtDNA does not affect looks or personality, and is not necessarily even unique from person to person."</i>
<i>"In a way. It is such an alien concept however"</i>
<i>"The mtDNA is such a small portion of the genome I do not think it constitutes parenthood."</i>
<i>"Surrogate babies are not considered to have three parents so why would it be the case in this instance? No one suggested the adopted parents of adopted children anything but parents. With transplants, which this to my mind is, the recipient of a donated body part is not considered as 'dual' person. Anyway it is more the role in the child's life, rather than the biological input, that make one a parent."</i>
<i>"Being a parent goes far beyond being a donor. Raising a child, loving them, takes so much more."</i>
<i>"A child conceived with an egg that has undergone nuclear transplantation is the product of two parents. The child would not be considered the product of three individuals, just as a person who receives a transplanted organ is not considered to be two individuals sharing one body."</i>
<i>"Because mitochondria r only the "power house" not your traits, etc. "</i>
<i>"Because mtDNA does not carry DNA that makes you "who" you are. It is purely for metabolism."</i>
<i>"Not really, but it's a semantic issue. It's clearly an edge case and you could argue either way. To me "Three parents" means "three donors of nuclear DNA" and I think that's the most obvious reading of the phrase so I'm answering "no" but the real answer would need to include a definition of "parent" and many other things."</i>
<i>"The donor contribution is more comparable to transplanted body parts or bone marrow"</i>

<i>"the third donor has not donated physical traits"</i>
<i>"I'm not sure....."</i>
<i>"YES"</i>
<i>"No. They are not raised by 3 people. They would still be raised find one or two parents just like anyone else. The donor is simply used to alter the DNA sequencing."</i>
<i>"From what I have read the baby doesn't have the genetics of the third parent"</i>
<i>"The amount of DNA from the donor egg is less than 1% so I do not believe this constitutes a 3rd parent."</i>
<i>"You are using three forms of DNA."</i>
<i>"Math."</i>

APPENDIX O: Full List of Free-Responses for Survey Question 26 about the Benefits of MRT

What do you see as benefits of MRT?
<i>"To fix the problem"</i>
<i>"Healthy children"</i>
<i>"Better Health"</i>
<i>"Hope, an option of a genetic connection for mothers with mito, another option to prevent future child loss, progress in research"</i>
<i>"Possibility of preventing children born with mitochondrial disease"</i>
<i>"Possibly decreasing frequency of mitochondrial disease"</i>
<i>"Eliminating mitochondrial disease which I have witnessed as being extremely debilitating"</i>
<i>"A child who is less at risk for a deadly disease"</i>
<i>"I'm not sure. I wish I knew if I got a couple answers on that quiz right cause if it could slowly cut out the disease completely that'd be amazing. But it'd give people the chance to have babies who otherwise would opt out and most importantly it would save so many lives."</i>
<i>"Prevents transmission of disease from parents to children"</i>
<i>"Possibility of having a child unaffected by mitochondrial disease"</i>
<i>"Among other things, I could see a mother wanting biological children, but not being able to have a safe pregnancy because of her mitochondrial disease, and also not wanting to pass her symptoms on to her children. In this case, she could use MRT, and a surrogate."</i>
<i>"Less babies affected with mitochondrial disease."</i>
<i>"Patients of rare disease suffer enough before worrying about passing illness to their children. Many patients are ignorant about their own illnesses and do not understand the risks of childbirth until it is too late, which must be incredibly psychologically damaging. This should be viewed as a treatment. Treatments allow patients to live more normally and that is exactly what this would do if doctors regularly discussed it with mito patients interested in having children."</i>
<i>"Preventing disease."</i>
<i>"Healthy children... less pain, suffering, deaths, and less expense to insurance companies and families."</i>
<i>"Healthy kids"</i>
<i>"Save lives of children"</i>
<i>"Healthy baby"</i>
<i>"As stated, repeatedly, it provides the possibility for a woman who has defects in her mtDNA to have a healthy child. There is no higher benefit."</i>
<i>"Putting a woman at ease in motherhood and reducing illness."</i>
<i>"Better health"</i>
<i>"Potentially, to either minimize or eradicate the passing of mito disease to offspring."</i>
<i>"Not a cure but a way to save all the kids that it would save from this"</i>
<i>"Healthy children, ending the cycle of passing along mutations."</i>
<i>"Life..."</i>
<i>"Healthy children to women that cannot produce a healthy child themselves and the possibility of rendering the mutation absent in future generations"</i>
<i>"Much less mitochondrial disease & the ability to have a healthy child (from a mito standpoint, I know that the child - like anybody's child - could still be one ill from something else but those are the chances that parents take when having a baby). If you know for a fact though that you are a carrier of a mito mutation & have in fact even given birth to children with mito disease; this is a great gift to be able to have a healthy child. I would think that if/when this becomes more widely available & accepted, it could branch out further possibly into other genetic diseases."</i>
<i>"Stopping faulty mitochondria in future generations"</i>

<i>"The ability for a couple to have a family without risking the suffering of a child when the mutation is detected."</i>
<i>"A potential to end this cruel disease."</i>
<i>"The elimination of horrific suffering and the ability of people to have genetically related children."</i>
<i>"If it works hopefully a healthy baby."</i>
<i>"Less Mito diseases in future generations"</i>
<i>"Saving lives."</i>
<i>"Ending the disease being pass from one generation to the next in certain forms of the disease."</i>
<i>"increase the odds of having a healthy child and descendants"</i>
<i>"Reducing disease"</i>
<i>"Women not fearing passing on the huge risk of mitochondrial disease to their children."</i>
<i>"Couples can have babies that are biologically their own, but without a terrible diagnosis."</i>
<i>"Agency, living the most out of human experience, safety of future children"</i>
<i>"We could prevent it"</i>
<i>"offers an option for healthy babies"</i>
<i>"NO MITOCHONDRIAL DISEASE"</i>
<i>"healthy babies/people"</i>
<i>"To lessen the suffering in patients and families."</i>
<i>"Healthy people!"</i>
<i>"Children not having to suffer from the effects of a mitochondrial disorder."</i>
<i>"Mito is a terrible and incurable disease. It has a major impact on all members of the family. If families choose to use this option as a way to expand their family without the guilt of passing along diseased traits, then I see that as a benefit."</i>
<i>"Allows parents to safely create healthy offspring."</i>
<i>"The cessation of a families maternally inherited mitochondrial disease."</i>
<i>"We'll eliminate one small source of birth defects in society."</i>
<i>"healthy children"</i>
<i>"Life"</i>
<i>"A couple can reproduce without the fear that their child will have a lifelong, crippling disease for which there is no treatment."</i>
<i>"The exclusion and possible eradication of mitochondrial disease is all you need as an answer. For parents to not lose their children, for children to not have to fight every day to survive. For siblings to never know grief and loss of another for this reason."</i>
<i>"People effected by mitochondrial disease can have their own children without the risk of passing a serious mitochondrial disease or disorder down to those children."</i>
<i>"If my daughter elected to use MRT to have children, it would mean that MERRF would end in my family. Future generations would be free from the mutation."</i>
<i>"That it has the potential of helping some people have health children free of Mito disease."</i>
<i>"Diseases of the mitochondria directly related to faulty Mt DNA would have a "cure" in future generations"</i>
<i>"To reduce the pain and burden of devastating disease."</i>
<i>"Those of us who have Mitochondrial Disease could possibly have children knowing that they would be born without the risk of having passed the disease onto them."</i>
<i>"Healthy babies"</i>
<i>"eradicating disease - or lessening frequency"</i>
<i>"Prevent people from dying young."</i>
<i>"Healthy, unaffected children who can live a full, meaningful life."</i>

<i>"Less children being born with a devastating disease."</i>
<i>"The possibility for women with an MtDNA diagnosis to have a healthy child."</i>
<i>"Not passing mitochondrial disease to the next generation."</i>
<i>"A huge impact on better health as mito can be life threatening and is life shortening."</i>
<i>"A healthy child"</i>
<i>"No more mitochondrial disease."</i>
<i>"Giving more options to women with mtDNA disorders. I have cousins who are asymptomatic but presumably carry the gene-- when they grow up it would be lovely to tell them that there's an option for them to have kids without rolling the dice."</i>
<i>"Elimination of a multitude of health problems that are result of mitochondrial defects."</i>
<i>"The ability of women to have healthy biological children."</i>
<i>"An easier life for the child. Less emotional/financially burden on the family - not solely the parents Less financial burden on the state."</i>
<i>"Reducing the number of children born with the disease is a huge benefit. Allowing a woman to have a wanted child otherwise denied by a few defective genes would be wonderful."</i>
<i>"Prevention of maternally inherited mtDNA defects, as well as an opportunity to screen for specific genetic diseases prior to implantation."</i>
<i>"Reducing the Mitochondrial Mutations being passed down subsequent generations"</i>
<i>"Kids and adults can live a full life with less limitations"</i>
<i>"It provides the ability to have a healthy child without risk of developing devastating mitochondrial diseases that are passed via mtDNA."</i>
<i>"Lets some people with screwed up mitochondria caused by screwed up mito DNA have kids without mito."</i>
<i>"Not passing on the mutation"</i>
<i>"healthy offspring"</i>
<i>"Healthy babies for couples who have or will face the overwhelming hardships and even death that Mito diseases will otherwise cause their children to have. And healthier generations for the future."</i>
<i>"Healthier kids"</i>
<i>"A normal and healthy life for my future child"</i>
<i>"Possibility for healthier children less suffering."</i>
<i>"It would put a stop to a horrible deadly disease."</i>
<i>"None"</i>
<i>"Eliminating or cutting down the incidence and possibly the severity of mitochondrial disease as it's passed on."</i>
<i>"People with a history of the disease could have children safely, and maybe types of the disease would be eradicated."</i>
<i>"Pain free life. No physical limitations. Longer life."</i>
<i>"It will allow many adults who carry known mtDNA mutations to be able to have a baby without the worry and anguish of passing on their mutation. It has the potential to eradicate mitochondrial disease from a family line."</i>
<i>"People with mito will be able to have children and not have to worry about passing the disease on to their children."</i>
<i>"I would be able to have a child without having to give them this awful disease that I have."</i>
<i>"My children wouldn't have to suffer from the negative effects of a mitochondrial disease"</i>

APPENDIX P: Full List of Free-Responses for Survey Question 27 about the Limitations of MRT

What do you see as limitations of MRT?
<i>"getting it approved by insurance companies"</i>
<i>"cost, ethics, there are other ways to have children- adoption etc. why go through this?"</i>
<i>"I am not sure if it is safe"</i>
<i>"embryos being created just to be destroyed"</i>
<i>"Cost"</i>
<i>"The risks"</i>
<i>"It only applies to such a small portion of the population - those with identified familial mtDNA mutations, and access to the resources to cover the procedure."</i>
<i>"Probably costly, not covered by insurance. Only works to prevent MD if the mutation was originally in the mtDNA"</i>
<i>"It's possible pregnancies in the mito community would increase and I have no concept of how safe pregnancy is for mito patients."</i>
<i>"Not possible for lower income families, negative public opinion"</i>
<i>"Not sure"</i>
<i>"Struggling for fda approval I guess"</i>
<i>"Idk them"</i>
<i>"Procedure might fail during transmission of mother's nucleus to the donor egg."</i>
<i>"Not being able to prevent disease in cases of mito not being caused by a mtDNA mutation"</i>
<i>"Among other things, There might be some negative reactions from the community, thinking that this "designer baby" is designed to not be like them."</i>
<i>"It is hard to determine with absolute certainty that it is completely safe and the risks might not be fully realized until it has been tried in humans which is scary."</i>
<i>"Expense... so only the wealthy can afford this therapy. Knowledge - misconceptions may keep some from seeking this therapy Religion - some religions may not think it ethical."</i>
<i>"The unknown"</i>
<i>"Social perception"</i>
<i>"Problems of other person / baby different from parent"</i>
<i>"It only successfully removes defects in mtDNA. If mutations in the nuclear DNA are involved, it obviously won't fix the problem."</i>
<i>"It is a new process...and I question the techniques and success of the outcomes overall at this point. As with any new technology at its "invention stages," it will take many people to test, make cost effective, safe, and so forth. It's one "arm" of the research that needs to be done. Selfishly, I would like to see more focus on medications and treatments for those with the disease as I am coping with the reality of having/living with the disease for myself and my children. However, I do understand the importance of being able to prevent it for the next generation. It's much like "polio" or other such diseases in their day...there's the treatment aspect, as well as the prevention. If you actually HAVE polio, you want to find treatments and therapies to cope. If you don't, you want to focus on prevention. :)"</i>
<i>"Unknown at this early stage."</i>
<i>"Only viable in specific instances"</i>
<i>"\$\$\$\$"</i>
<i>"None"</i>
<i>"The 2 things I don't know as much about MRT is what effect does this have on children that have a mito mutation that came through the father's lineage by way of his mother & I don't understand how the donor is screened & if it is guaranteed that the child will not be born with mito. In under the impression that during screening, they look for known genes in the donor but I don't think that we have identified every single gene or mutation yet that causes mito (such as the 6 mutations I have that are unknown) so that could be a limitation of being able to highly reduce the</i>

<i>cases of muto but not completely eradicate the disease in all its forms."</i>
<i>"It doesn't work for nuclear DNA"</i>
<i>"being 100% sure that the donor has healthy mDNA."</i>
<i>"Religious beliefs of a section of society"</i>
<i>"IVF does not always work for everyone. MRT will not guarantee offspring with no inherited health problems"</i>
<i>"Doctorz"</i>
<i>"Ethical issues. Just because we can do something doesn't mean we should"</i>
<i>"Making sure this procedure is safe"</i>
<i>"none"</i>
<i>"cost, possibility of unforeseen consequences"</i>
<i>"Controversy, many unknowns, potential negative results in trials, potential negative PR, cost"</i>
<i>"Financial costs, public perception"</i>
<i>"Cost, does not work for DNA mutations, and distress from religious communities."</i>
<i>"Its not letting god do his work"</i>
<i>"insufficient knowledge of potential unintended consequences"</i>
<i>"I do not think there is enough knowledge on the subject to make an assumption."</i>
<i>"Narrow minded people"</i>
<i>"some people few this as messing with nature"</i>
<i>"False hope"</i>
<i>"ethicists and conservatives and fda"</i>
<i>"Finding healthy donors."</i>
<i>"Non-scientific opinions based on beliefs."</i>
<i>"No one knows yet what horrible effects might result from altering mtDNA."</i>
<i>"no limitations that I can think of"</i>
<i>"overly litigious populations, idiotic religious groups, cost / insurance companies"</i>
<i>"It cannot address mitochondrial diseases inherited through the nDNA."</i>
<i>"Cost."</i>
<i>"Not enough is known in mitochondrial sciences."</i>
<i>"the cost both time and energy it takes for the patient to get it done"</i>
<i>"I feel it has the potential to be cost prohibitive for the average American. I also feel that it may not be 100% effective like people hope, random mutations in the mitochondria can still occur."</i>
<i>"Expense"</i>
<i>"That not all eggs will be viable. And that it will only help those wishing to have children and those with an identified mito mtDNA mutation. which is a small population."</i>
<i>"Religious bias, uneducated press, unaware medical community and cost"</i>
<i>"Many cases of mitochondrial disease are still undiagnosed."</i>
<i>"Many people have very strong religious or ethical beliefs that play a big part in their belief of using MRT. I think that is one of the biggest limitations of MRT along with the fact that I don't believe enough facts are known at this point about the actual outcome of having MRT."</i>
<i>"ignorant people stopping science."</i>
<i>"It won't prevent all mitochondrial diseases"</i>
<i>"funding, unforeseen medical implications, the slippery slope people see with designed babies in general"</i>
<i>"It cannot help my son who is now 18 years old."</i>

<i>"Some peoples' ethical views."</i>
<i>"It would only be good for the more limited mtDNA mutations and not cover nuclear DNA mutations."</i>
<i>"It only helps those with a definitive mtDNA diagnosis and healthy enough to carry a child to term, as well as possible costs and the difficulty of getting it passed by the FDA as current political situation in the United States."</i>
<i>"Expense"</i>
<i>"I'm not sure at this time"</i>
<i>"There's always someone who will take this and try and profit from it, possibly making it unethical."</i>
<i>"The science has been a bit rushed, it seems-- I would love more animal models before humans. This is a huge deal, and it is clearly important to get it right."</i>
<i>"We are not yet fully aware of the full role of mitochondria in the body. We could be altering a person's natural life span, for instance."</i>
<i>"Interfering with Creation - Not sure of future genetic implications to the child- Some Mito doctors encouraging, already unwell woman, to have children, purely for their own research interest (this has happened to me)"</i>
<i>"The cost and societal attitudes."</i>
<i>"Abuse of the procedures, specifically and generally. Lack of comprehensive & ethical policies, Emotional issues arising from media & social issues for respondents."</i>
<i>"I don't see any limitations yet."</i>
<i>"Limited medical knowledge related to the association between nDNA and mtDNA defects; in my own case, it is unknown if all identified nDNA defects would cause disease on their own, or if they only cause symptoms if working synergistically with mtDNA defects."</i>
<i>"They couldn't help ppl that r already affected"</i>
<i>"The health of the mother having the procedure may be at risk due to her mito disease. Due to the severity of my mito disease and the fact that my pregnancy 10 years ago triggered a severe decline in my symptoms, I would not be able to go through this procedure. Many mothers like me would need a surrogate to carry the baby and may not even be well enough to go through the egg retrieval process."</i>
<i>"Biggest limitation is not all mito disease is caused by mtDNA, so it won't work for all. There may be further as yet unknown limitations that will only come apparent as the first generation of kids conceived with replaced mitochondria have their own kids - there may be interactions/incompatibilities/compatibilities/etc. between MtDNA and nuclear DNA we don't understand yet."</i>
<i>"It is open to abuse of an ethical nature"</i>
<i>"ignorant people who take it out of context (designer babies, etc)"</i>
<i>"Unknowns in science"</i>
<i>"Possible symptoms"</i>
<i>"Struggles bring strength I'm proud to have mito but I wouldn't wish it in anyone else."</i>
<i>"Changing children from the people they were meant to be to the people who are more convenient for parents to have. I have four children with Mito. There are challenges for sure but I wouldn't trade them for the world."</i>
<i>"It will take time too perfect. It may take longer than we would like to see appreciable results. As with anything there can be, unintended negative effects as well. We we'll just have to see how it plays out over the long term."</i>
<i>"The only limitation I see is trying to find donors."</i>
<i>"Financial. Fear, for those so inclined."</i>
<i>"The cost would probably be incredible unless insurance covers it which I doubt."</i>
<i>"None at this time."</i>
<i>"Conservative media outlets spreading uneducated opinions about this potential life saving process."</i>