Nicholas Angeles
BIOL 294
Critical Reading Assignment 3: Bioethics Paper
12/3/25

When determining whether or not mtDNA transfer to prevent mitochondrial disease is ethical and clinically acceptable, one must first understand mitochondrial gene disorders and their general inheritance. Mitochondrial gene disorders are inherited diseases from the mother that cause mutations in the so-called "cytoplasmic DNA" in the offspring germ-line cell mitochondria. The affected cells have their impact in later fetal development in any type of somatic cell which may have mutated mtDNA (i.e large deletions) that affect the somatic cell's overall ability to carry out proper oxidative phosphorylation and ATP production, hindering physiological processes of these cells, some of which rely heavily on mitochondrial function (i.e cardiac muscle cells, skeletal muscle cells, hepatocytes, etc.) which drives the somatic cells' overall loss of function. In understanding that inherited diseases caused by mtDNA mutations affect 1 in 5,000-10,000 children, it can be said and later supported that mitochondrial gene transfer **should** be implemented to treat disease from the germ-line.

Mitochondrial gene transfer involves using ART's (Assisted Reproduction Technologies) to replace mtDNA microsurgically in unfertilized oocytes via two different methods, Spindle Transfer (ST) and Pronuclear Transfer (PNT). ST implies isolating an unfertilized oocyte from the mother, with the mature oocyte in metaphase that has metaphase chromosomes, and isolate the spindle from the oocyte which is placed into an empty oocyte with an effectively empty cytoplasm which will be fertilized and transplanted into patient, clear of mtDNA from mother carrying disease. PNT on the other hand fertilizes a mother's oocyte and donor's oocyte, and removes pronuclei from the mother oocyte and the donor oocyte and inserts pronuclei from the fertilized mother's oocyte into the donor oocyte, which results in the parents nuclear DNA interacting with "healthy" mitochondrial DNA.

The method of mitochondrial gene transfer, which is considered a germline mediation, is criticized for many different reasons involving consequences of both ART techniques, respectively, due to concerns of challenges involved in ART's lack of clinical trials and lack of animal based research over its many years of exploration. Critics were also concerned that PNT and ST techniques would involve "carrying over" mtDNA bound to mother oocyte spindles or pronuclei, which would consequently carry the mutated mtDNA to the child and cause the specific mitochondrial disease. This, however, is a poor objection to the methodology, because in trial of ST and PRT techniques in human and mouse ST offspring, about 2% of mtDNA was carried over to donor oocyte, which is less than the estimated threshold of 60% mutated mtDNA required for "clinical manifestation." Another common concern of mitochondrial gene transfer is that it will be ineffective and children born having undergone these prenatal ART techniques will present with abnormalities due to "unmatched" nuclear and mitochondrial genomes, essentially lacking proper communication between the two and consequently interfering with mitochondrial and intracellular protein functions. This does not prove mitochondrial gene transfer ineffective,

however, as a study was conducted to test the long term effects of these ART techniques, specifically in Rhesus Macaque, where their ST offspring had combined mtDNA and native nuclear DNA which presented over long term studies with no significantly recognized abnormalities phenotypically postnatal and in early to later development.

Both the objections of mtDNA transfer due to “carry-over” mutant mtDNA and mtDNA incompatibility with nuclear DNA have proven to be false with animal and clinical trials, both resulting in safe and normal development of the mtDNA transfer offspring, which supports the idea that mtDNA from a clinical perspective should be used to mediate mitochondrial disease prenatal. With this being said, however, there is still ethical concern regarding mtDNA transfer, specifically in the sense of offspring legally having three parents: their mother, their father, and their mtDNA donor. This poses ethical concern due to family laws impacting the life of all parties involved, but is overcome by the identification that donor mtDNA appears to make up about 0.1% of total DNA of the offspring, which is understandable of concern but is still statistically less significant than the DNA of both parents in gene transfer offspring, affecting small biochemical phenotypes rather than large ones attained by the parents’ genes.

Given these bioethical objections, including their respective scientifically supported hurdles, it can be concluded that mitochondrial gene transfer should be implemented in prenatal treatment to inherited mitochondrial disease, due to its minimal consequences for both its’ clinical and ethical implications that have been given up to this point. It is not unreasonable to still be skeptic of mitochondrial gene transfer, however, because more still needs to be explored of this treatment method, such as more germline trials in human oocytes, with answers to other concerns such as the overall credibility of ART’s results due to its lack of such germline trials. Ethical implications of mitochondrial gene transfer as“normalized eugenics” also need refinement, as critiques claim that mitochondrial gene transfer, in its preventative efforts to mitochondrial disease, may lead to genomic editing to create “desirable traits” of a population rather than a sole attempt to ward off future disease. Of course more is to be researched and discussed of mitochondrial gene transfer, however its current clinical implications show promise into the future.