“Ethical issues in mtDNA replacement”

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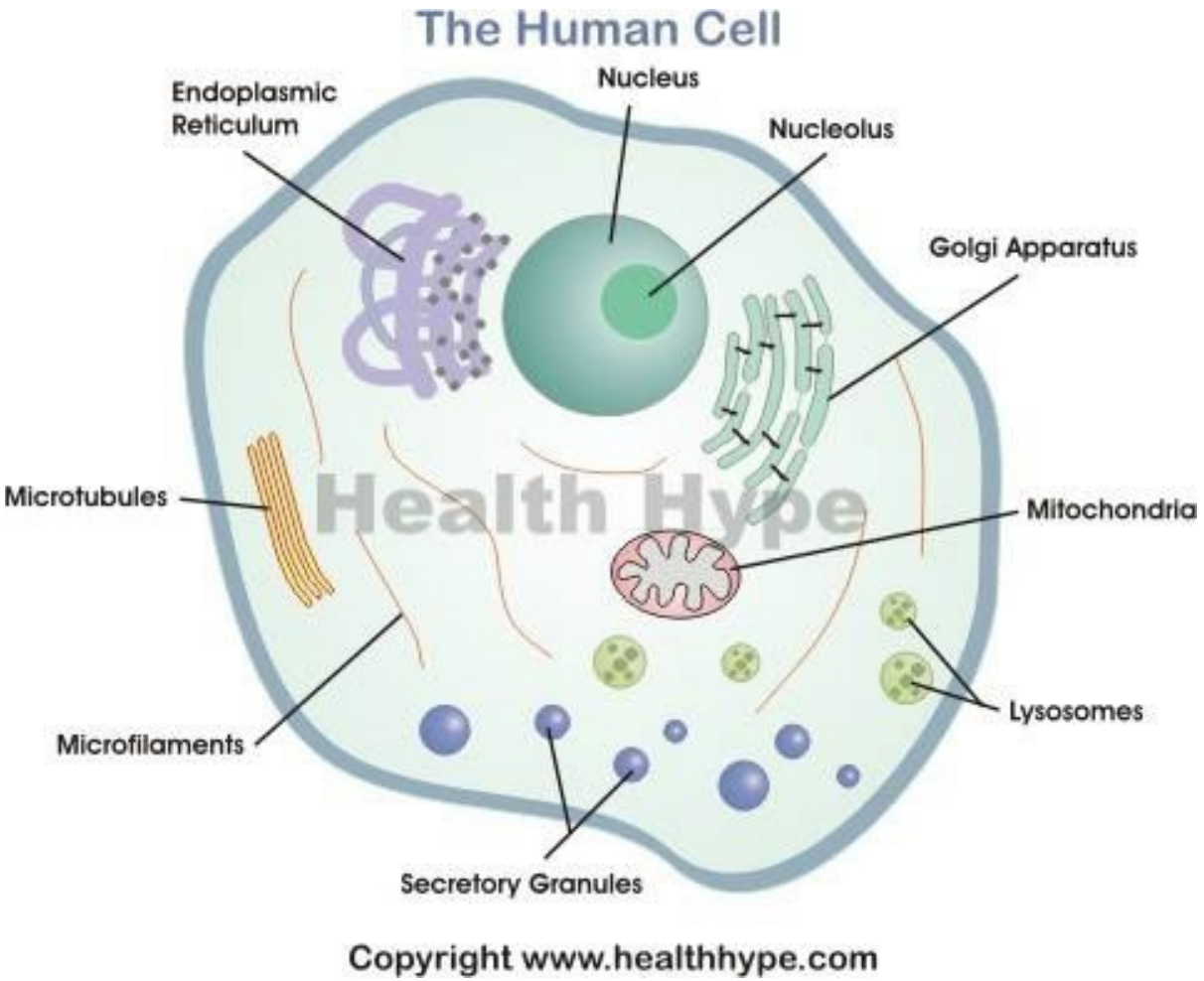
Overview

- Background Biology
- The ‘Right to Know’ identifying information about one’s donor
  - HFEA and Nuffield arguments (do not succeed)
  - Other disanalogies
- Mandatory Sex Selection
  - Question is trickier than it might seem, but the policy is unlikely to be defensible

Background Biology



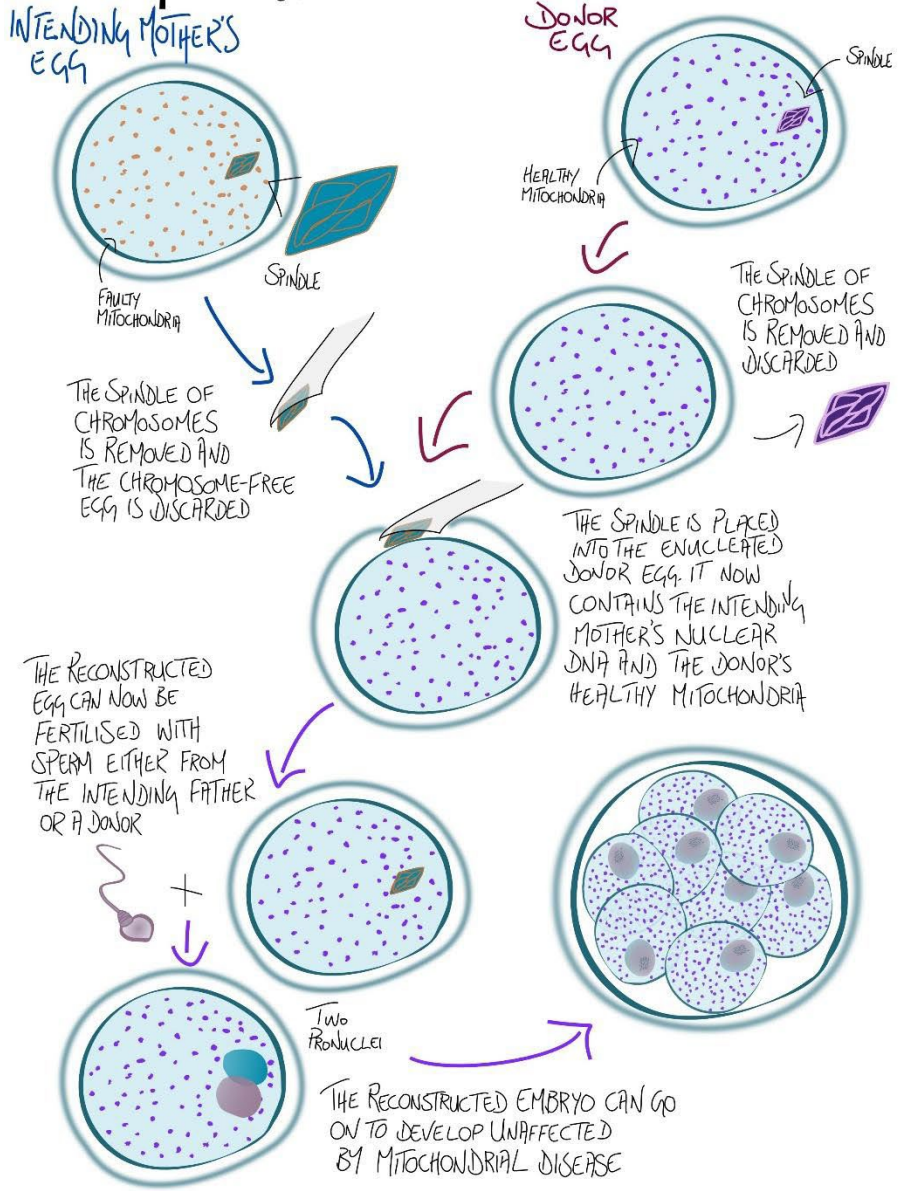
Background: Biology

Key differences:[1]

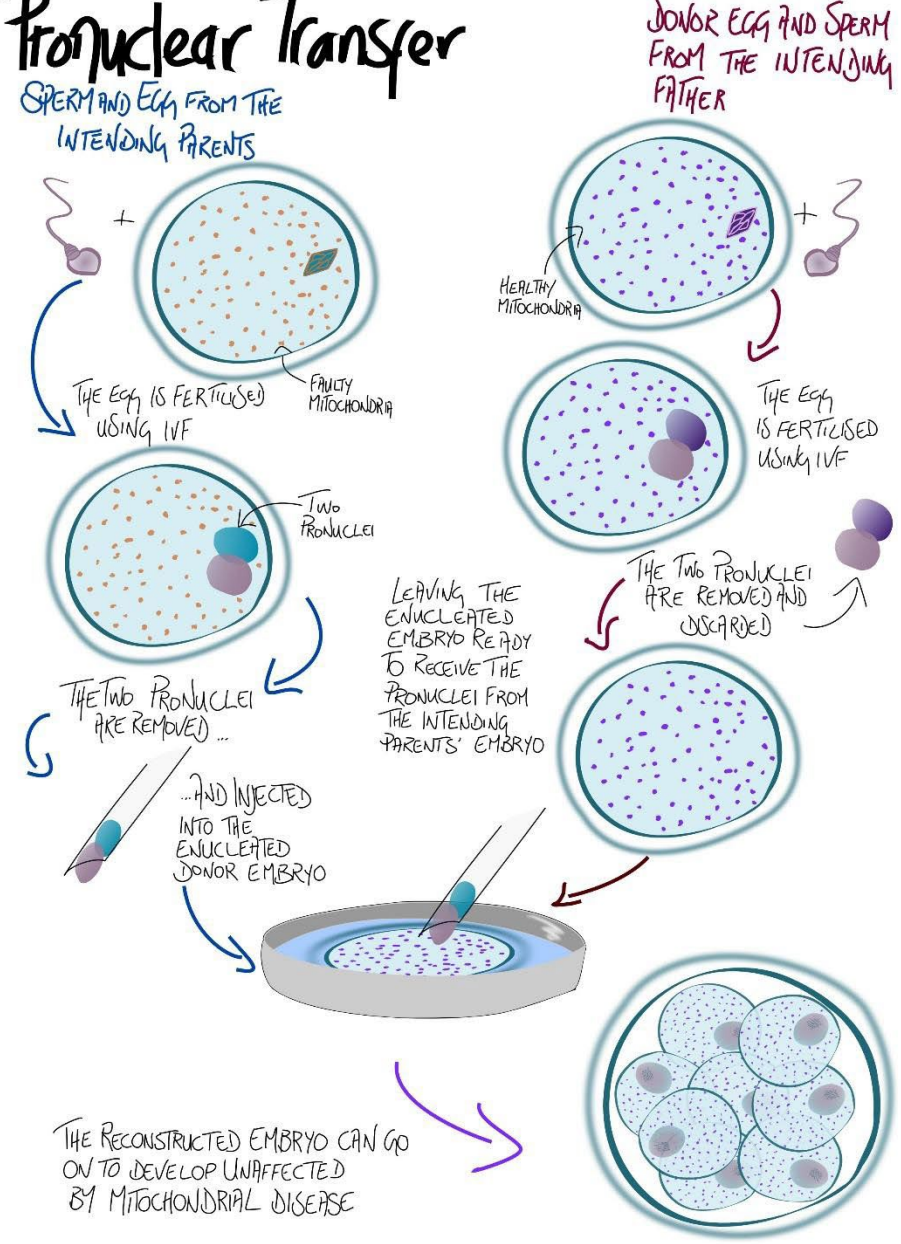
	nDNA	mtDNA
Size/location	Nucleus, 20,000 – 30,000 genes	Mitochondria, 37 genes
Ubiquity of gene products	Universal	All but one constrained to mitochondria[2]
Copies per cell	1	1000s
Inheritance	Paternal and maternal	Strictly maternal*
Variation within organism	Almost none	Universal heteroplasmy[3]

1. Taylor, Robert W., and Doug M. Turnbull. "Mitochondrial DNA mutations in human disease." *Nature Reviews Genetics* 6.5 (2005): 389-402
2. Kariya, Shingo, et al. "Effect of humanin on decreased ATP levels of human lymphocytes harboring A3243G mutant mitochondrial DNA." *Neuropeptides*39.2 (2005): 97-101.
3. Payne, Brendan AI, et al. "Universal heteroplasmy of human mitochondrial DNA." *Human molecular genetics* 22.2 (2013): 384-390.

Maternal Spindle Transfer



Pronuclear Transfer



Background Biology

The resulting child thus inherits DNA from three individuals:

- Nuclear DNA from sperm
- Nuclear DNA from the ova of the woman undergoing the treatment
- Mitochondrial DNA from a donor

This is where the media phrase ‘three parent’ babies comes from

The Right to Know

Is there parity between mitochondrial donation and gamete donation when it comes to the right to know?

Otherwise put, should children have access to identifying information about their mtDNA donor? (especially in jurisdictions that recognize the right to know)

The Right to Know

In the UK the answer was **no** for two reasons:

1. Mitochondrial DNA does not affect personal characteristics

2. 2. Mitochondrial transfer does not result in a unique genetic connection between donor and child since the donor's mitochondrial DNA would be indistinguishable from that of any in her maternal line

   - Unclear why having mitochondrial disease wouldn't count
   - Empirically not well founded
     - Mitochondrial DNA has been linked to variation in personality (though this is quite tenuous) psychiatric disorders, propensity for neuro-degenerative diseases

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The Right to Know

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What is a 'unique genetic connection'?

a. Epistemic claim – we wouldn't be able to identify the donor from amongst others in her maternal line

- But what about identical twins?

b. Ontological claim –it would be impossible (or highly unlikely) for an individual to have the same genetic makeup but a different donor

- But what about heteroplasmy?

The Right to Know

Neither of the reasons offered for disparity in recognizing the right to know succeed

- There are reasons to think that mitochondrial DNA affects 'personal characteristics'
- At least on one plausible account, it seems that there is a unique genetic bond between mitochondrial donor and resultant offspring

But there are other reasons why me might treat mtDNA donation differently

- Self-knowledge (Velleman) – still raised by genetic parent(s)
- Medical information – less relevant in the case of mtDNA
- Genetic bewilderment – evidence it is socially constructed

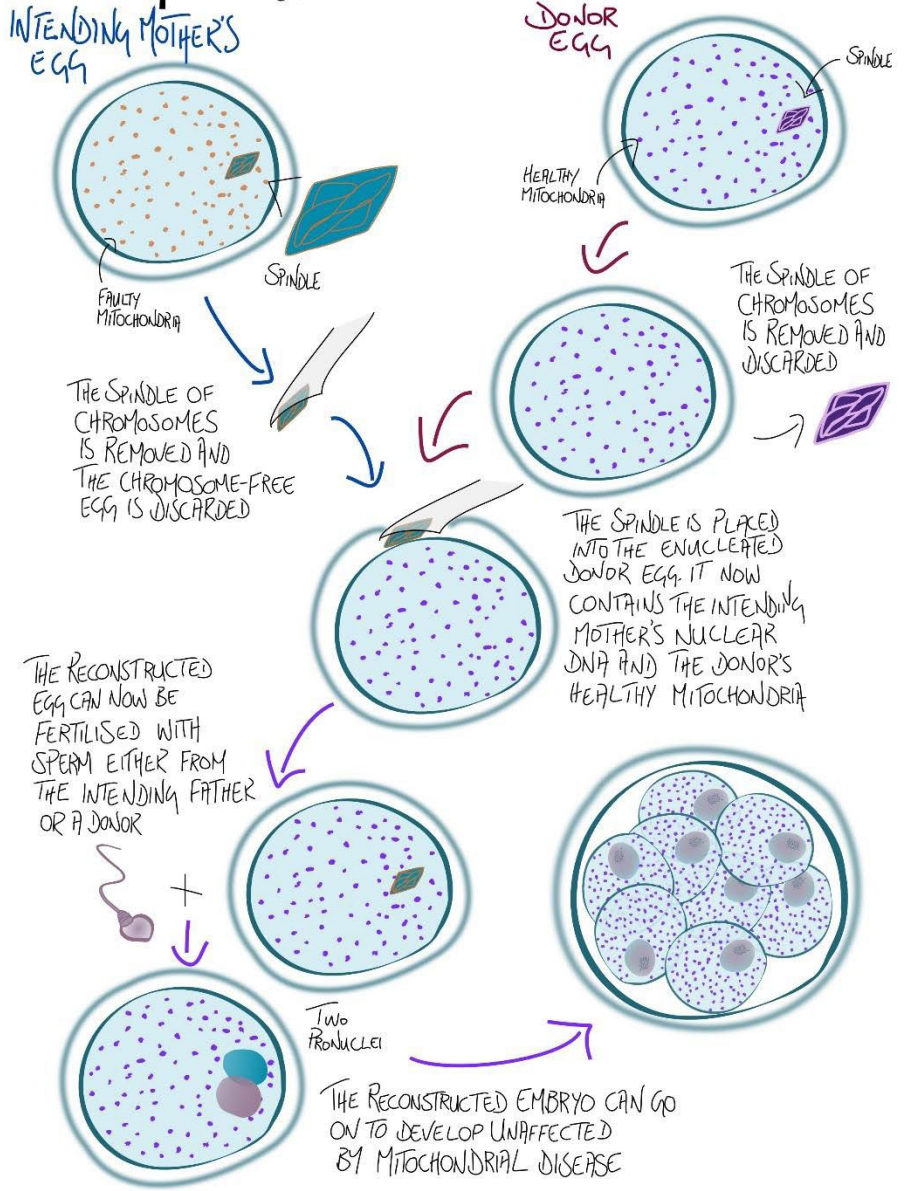
Given the different impacts, the balance between the child's interests and those of the donors/parents could very well come out differently

Mandatory Sex Selection

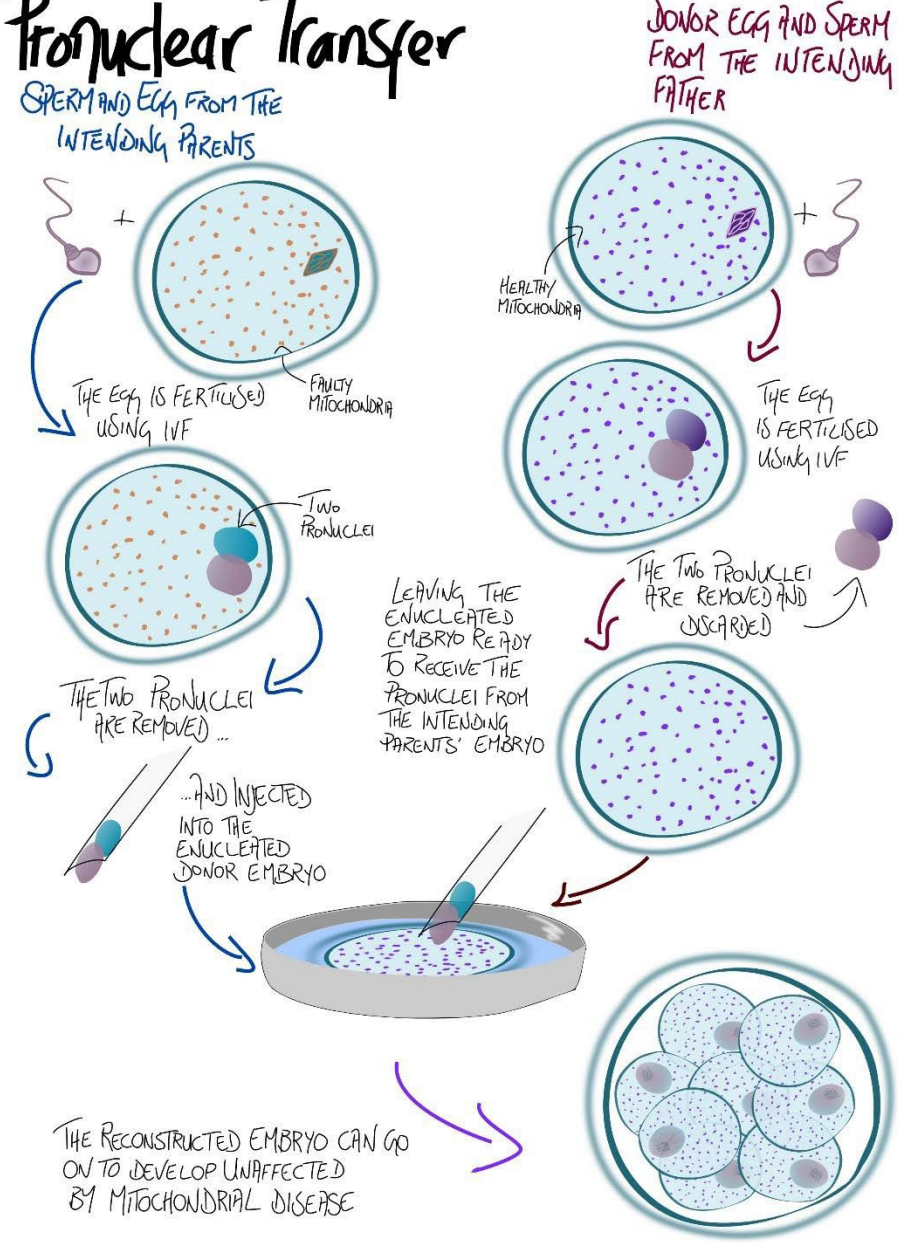
Mitochondrial replacement techniques are not perfect:

- There is a risk that some pathological mtDNA will get transferred along with the nuclear DNA

Maternal Spindle Transfer



Pronuclear Transfer



Mandatory Sex Selection

Mitochondrial replacement techniques are not perfect:

- There is a risk that some pathological mtDNA will get transferred along with the nuclear DNA
- While the small amount of pathological mtDNA is unlikely to cause mitochondrial disease in children created via use of the technology, there is a plausible chance that mitochondrial disease could reemerge in future generations
- In response at least one philosopher has called for mandatory sex selection against female offspring created using mitochondrial transfer until the extent of the risk is better understood (a view endorsed by the Academy of Medicine (formally the IOM) in the US)

Mandatory Sex Selection

Putting aside non-identity concerns, the argument pits intending parent's interests in reproductive autonomy against the interests of offspring to be free of mitochondrial disease

It's worth noting that the argument put forward by Appleby is quite poor. He states,

"considering how few prospective parents would likely be granted clinical access to MRTs (the chances are that it would be <10 cases each year), it is hard to imagine how bringing only males into existence would…cause suffering to the prospective parents."

Clearly, the *number* of prospective parents affected has no bearing on whether those individuals in fact suffer

Mandatory Sex Selection

But we can easily put aside this problem, and argue that while it does infringe on the autonomy of prospective parents, this harm is outweighed by the benefit to future individuals

There are two problems with this argument:

1. Pragmatic – individuals carrying mitochondrial disease who are intent on reproducing might opt to simply forgo making use of mitochondrial replacement, placing future generation at even higher risk

2. Theoretical – Upon reflection, accepting Appleby's basis of sex selection would entail a drastic revision to the kind of reproductive practices we consider morally acceptable

Mandatory Sex Selection

Theoretical – Upon reflection, accepting Appleby's basis of sex selection would entail a drastic revision to the kind of reproductive practices we consider morally acceptable

- We're not restricting reproductive autonomy for the sake of the child that may be created using mitochondrial replacement – that child is likely to be disease-free

- The justification for the ban is that if *the resultant child is female*, they may reproduce in a risky manner in the future

Mandatory Sex Selection

- Such offspring could:
  - Themselves make use of mitochondrial transfer technology
  - Use donor gametes
  - Forgo biological parenthood
- There is always a chance that offspring may reproduce in a risky manner
- Even in the case of genetic disease, we tend to consider it acceptable for individuals to reproduce in a manner that produces asymptomatic carriers
  - Consider the Tay-Sachs registries
- At a minimum, the policy is highly revisionary, and out of keeping with existing norms
- Why be stricter on those taking steps to reduce the transmission of disease than those who do not

Appleby's Reply:

"if we extend Brandt's account of eugenics to everyday life, then his view appears to be that anyone making a decision that will result in creating one type of offspring over another (this could be as simple as picking a donor based on their looks or even setting preferences for physical appearance on a dating app) amounts to a harmful and dangerous form of eugenics. This not only seems absurd, but it also erodes the work done by the concept of eugenics to highlight genuine atrocities across history, such as those that occurred at the hands of the Nazis in WW2. Brandt's criticism misconstrues the original argument put forward, fails to appropriately deploy the concept of eugenics in a meaningful narrow sense, and makes an uncompelling case against the use of sex selection"

John B. Appleby, Chapter 14 - The ethical issues of mitochondrial transplantation and transfer, Editor(s): Sergej M. Ostojic, Gokhan Burcin Kubat, Oner Ulger, Serdar Gunaydin, In Translational and Applied Bioenergetics, Mitochondrial Transplantation and Transfer, Academic Press, 2024,

Summary

- When it comes to the right to know, reasons offered to date for disparity between gamete donation and mitochondrial donation have not been compelling, yet there are other reasons to think this disparity is justifiable

- There are pragmatic and theoretical reasons for rejecting mandatory sex selection in the initial rollout of mitochondrial replacement technologies