Genetic Counselling in Mitochondrial Disorders

Jacqui Robinson

Genetic and Metabolic Nurse Practitioner

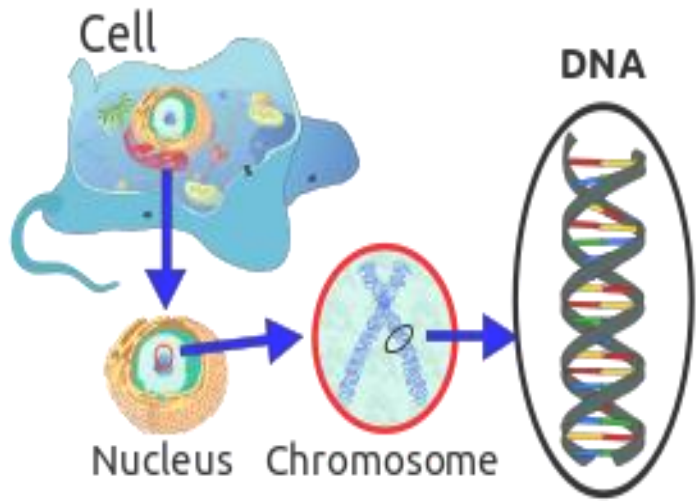
Sydney Children's Hospital, Randwick

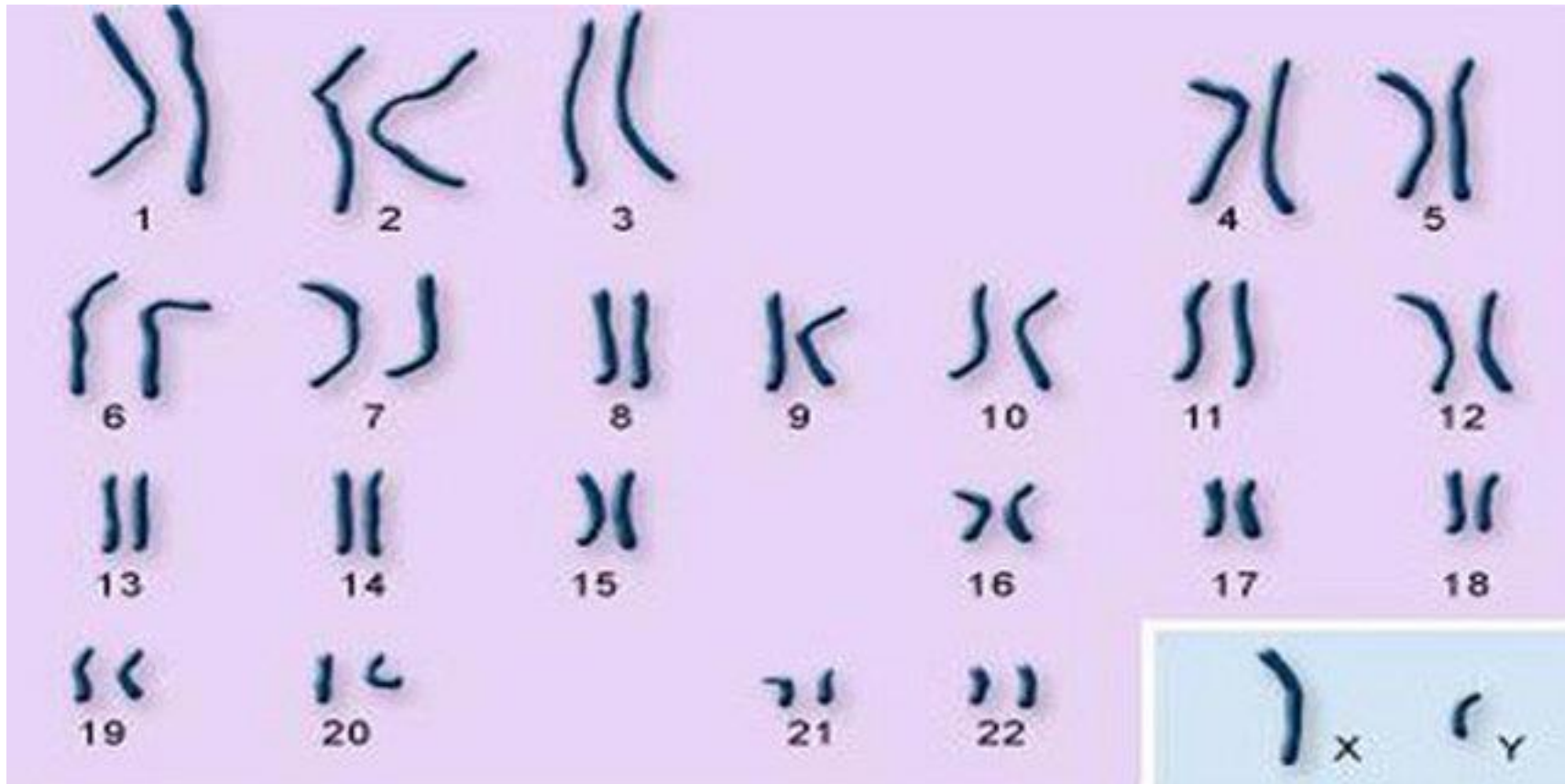
DNA

- The blueprint of life
- Recipe to make us who we are
- Inherited from our parents
- Shared with our relatives
- Sometimes the code is wrong
- Two types
  - Nucleic
  - Mitochondrial

Nuclear DNA

- Found in the nucleus
- Half from mum, half from dad
- Packaged as chromosomes
- 23 pairs
  - 22 pairs autosomes
  - 1 pair sex chromosomes
- 20,000 pairs of genes
- Mutations can cause mitochondrial disorders


Cell
DNA
Nucleus
Chromosome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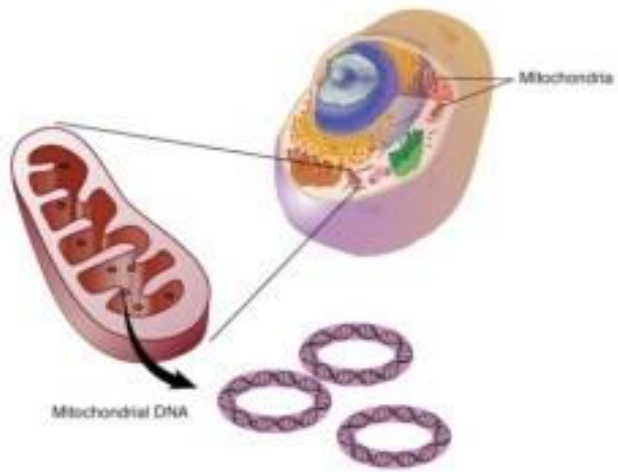
22
X
Y

Mitochondrial DNA

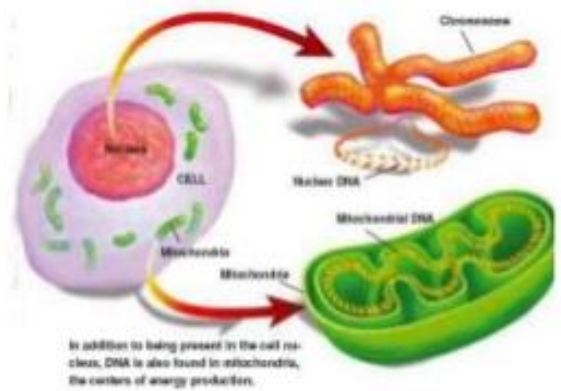
- Mitochondria have their own DNA (mtDNA)
- Inherited from mum
- Circular chromosome
- Mutations can cause mitochondrial disorders
- 37 genes
- Most cells contain 1000 mtDNA molecules distributed among hundreds of individual mitochondria

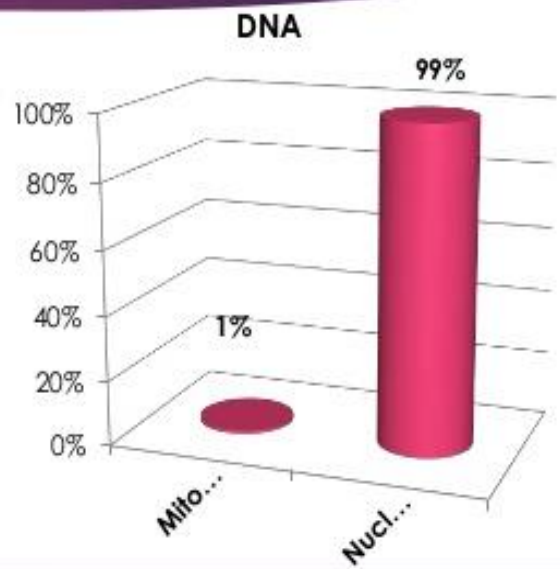
Mitochondrial DNA



Talking Glossary of Genetic Terms
NATIONAL HUMAN GENOME RESEARCH INSTITUTE
NATIONAL INSTITUTES OF HEALTH | genome.gov
Illustration by Darryl Leja, NHGRI

NUCLEAR DNA VS MITOCHONDRIAL DNA



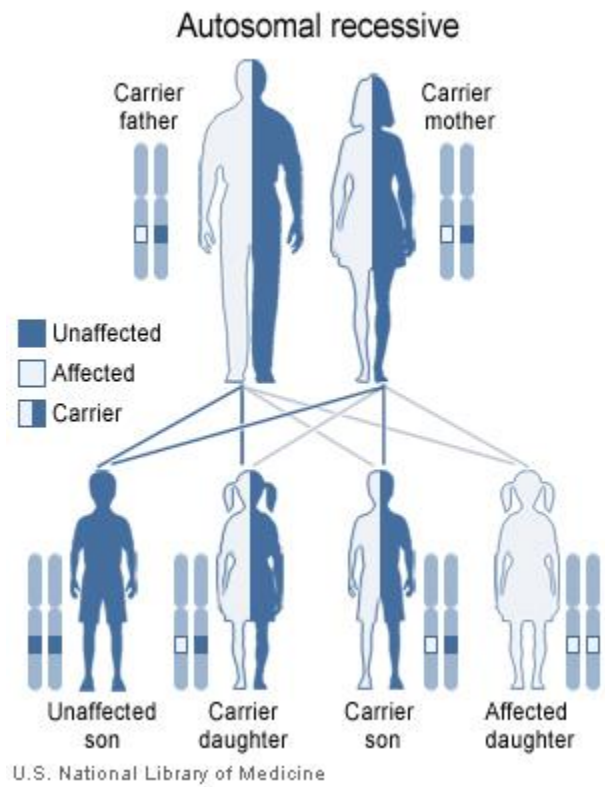


Inheritance of Mitochondrial Disorders

- Can be caused my mutations in both nuclear DNA and mtDNA
- Can be caused by different types of inheritance
- Need to know the exact genetic change for accurate genetic counselling

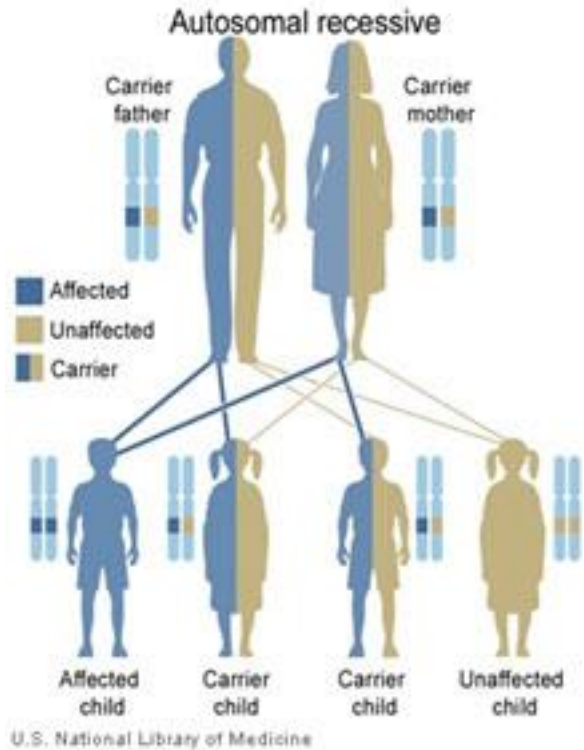
Autosomal Recessive Inheritance

- Nuclear DNA
- Need mutations in both copies of the gene to have the disorder
- Parents are both healthy carriers
- Equally likely for boys and girls to be affected
- 25% recurrence risk
- Usually no family history
- Probably the most common inheritance in mitochondrial disorders


Autosomal recessive
Carrier father
Carrier mother
Unaffected
Affected
Carrier
Unaffected son
Carrier daughter
Carrier son
Affected daughter
U.S. National Library of Medicine

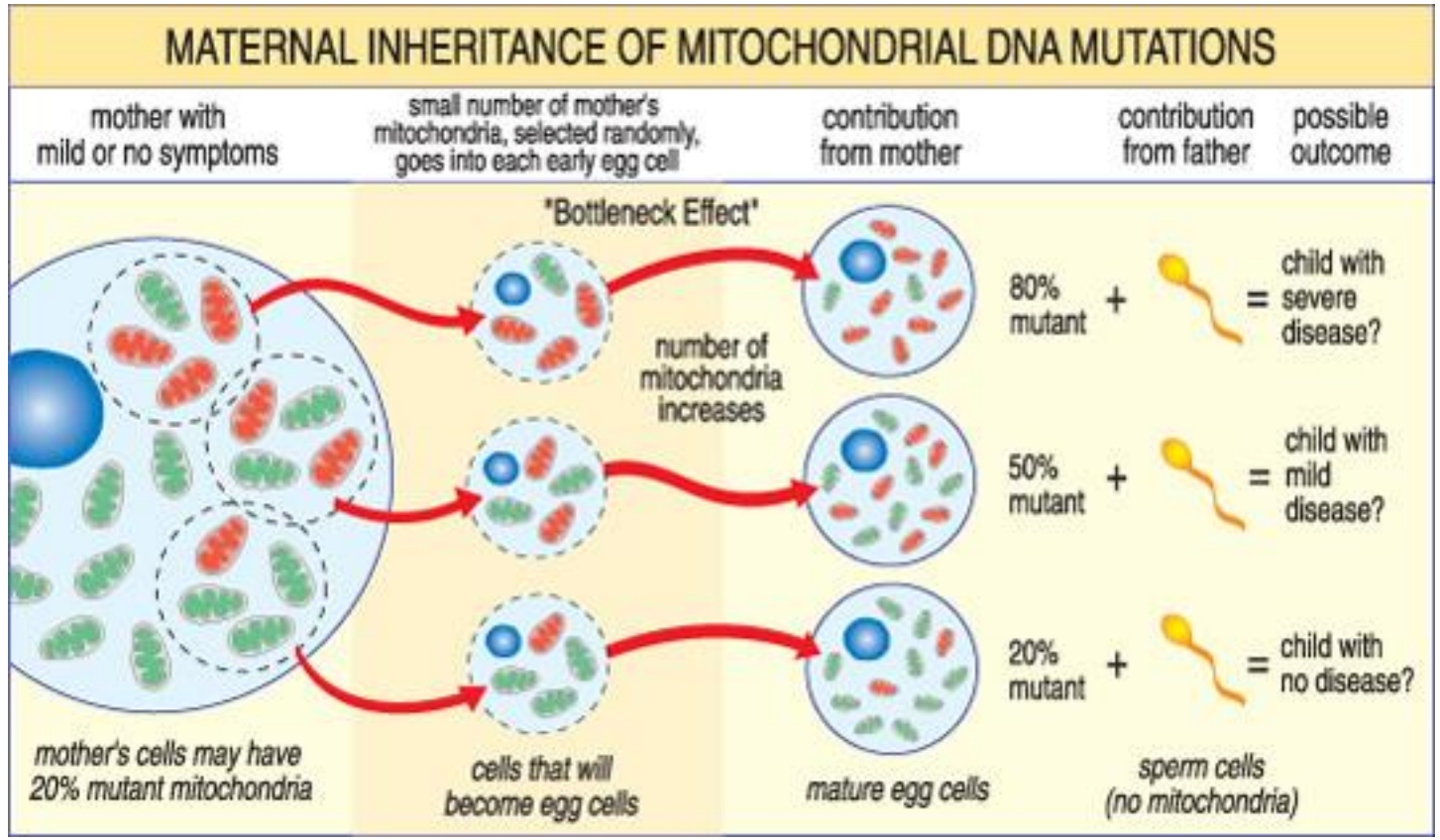
Autosomal Dominant Inheritance

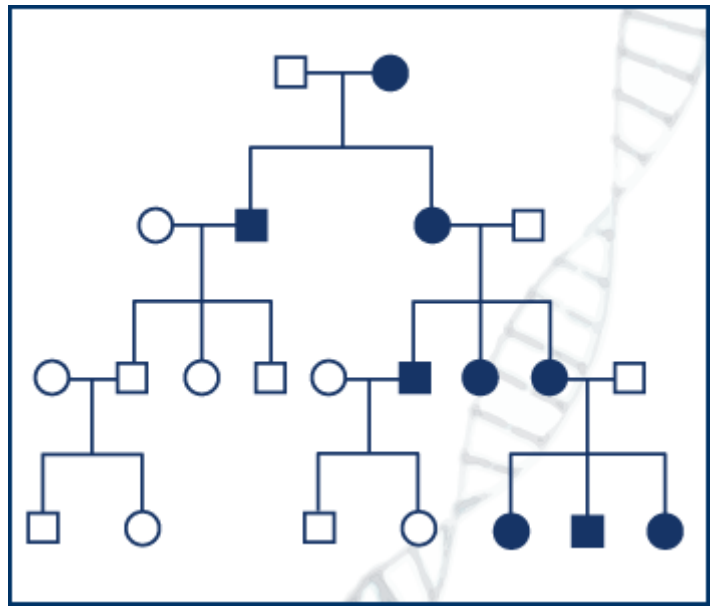
- Nuclear DNA
- Need a mutation in only one copy of the gene (mutation is *dominant* over the good copy)
- Usually one parent is affected or can be a new mutation (de novo)
- Equally likely for boys and girls to be affected
- Up to 50% recurrence risk
- Often a family history
- Not very common in mitochondrial disorders


Autosomal recessive
Carrier father
Carrier mother
Affected
Unaffected
Carrier
Affected child
Carrier child
Carrier child
Unaffected child
U.S. National Library of Medicine

Mitochondrial Inheritance

- Maternal inheritance
- Men can not pass it on to their children
- Mother can either be affected herself, have a very low mutant load, or it is a de novo mutation
- Very variable between affected people in the family
- Recurrence risk up to 100%

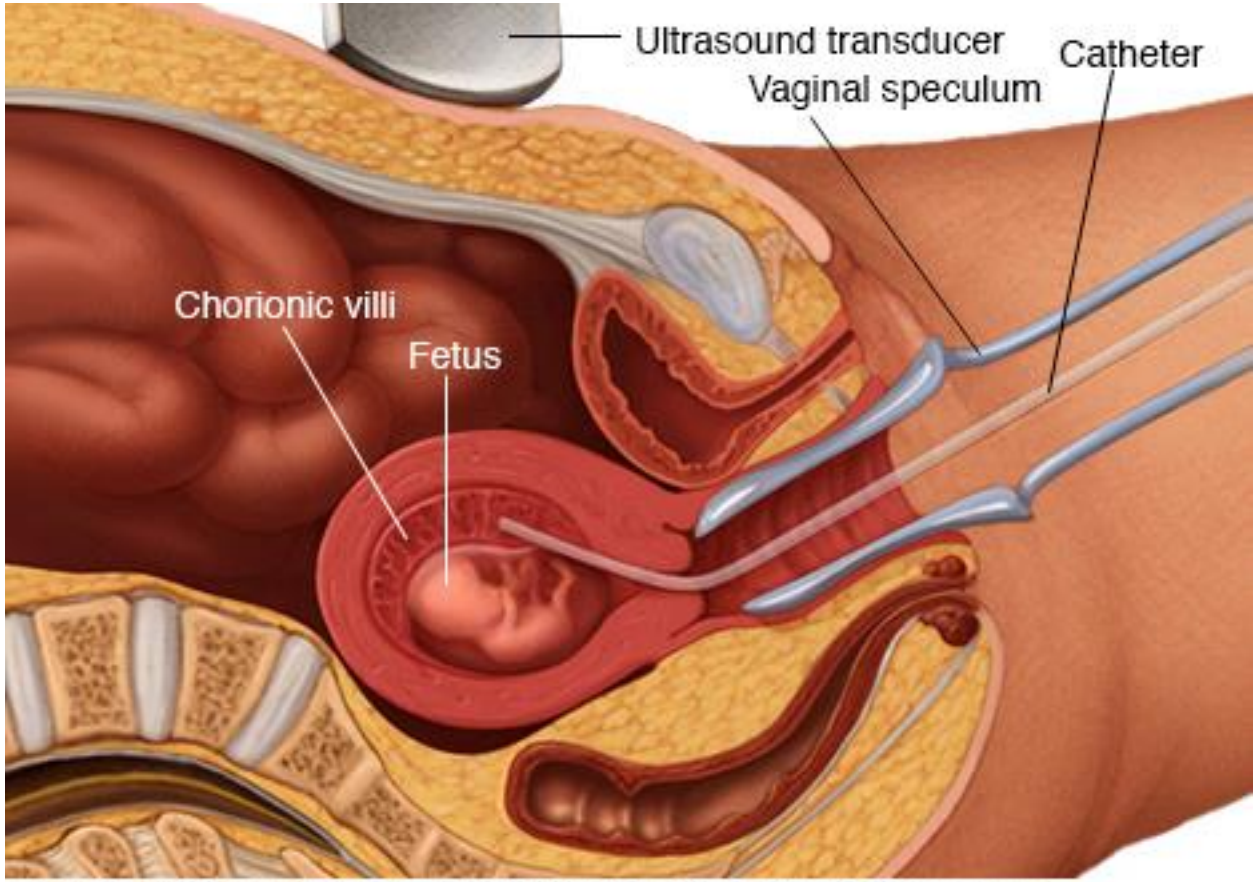

MATERNAL INHERITANCE OF MITOCHONDRIAL DNA MUTATIONS
mother with mild or no symptoms
small number of mother's mitochondria, selected randomly, goes into each early egg cell
contribution from mother
contribution from father
possible outcome
"Bottleneck Effect"
number of mitochondria increases
80% mutant + = child with severe disease?
50% mutant + = child with mild disease?
20% mutant + = child with no disease?
mother's cells may have 20% mutant mitochondria
cells that will become egg cells
mature egg cells
sperm cells (no mitochondria)



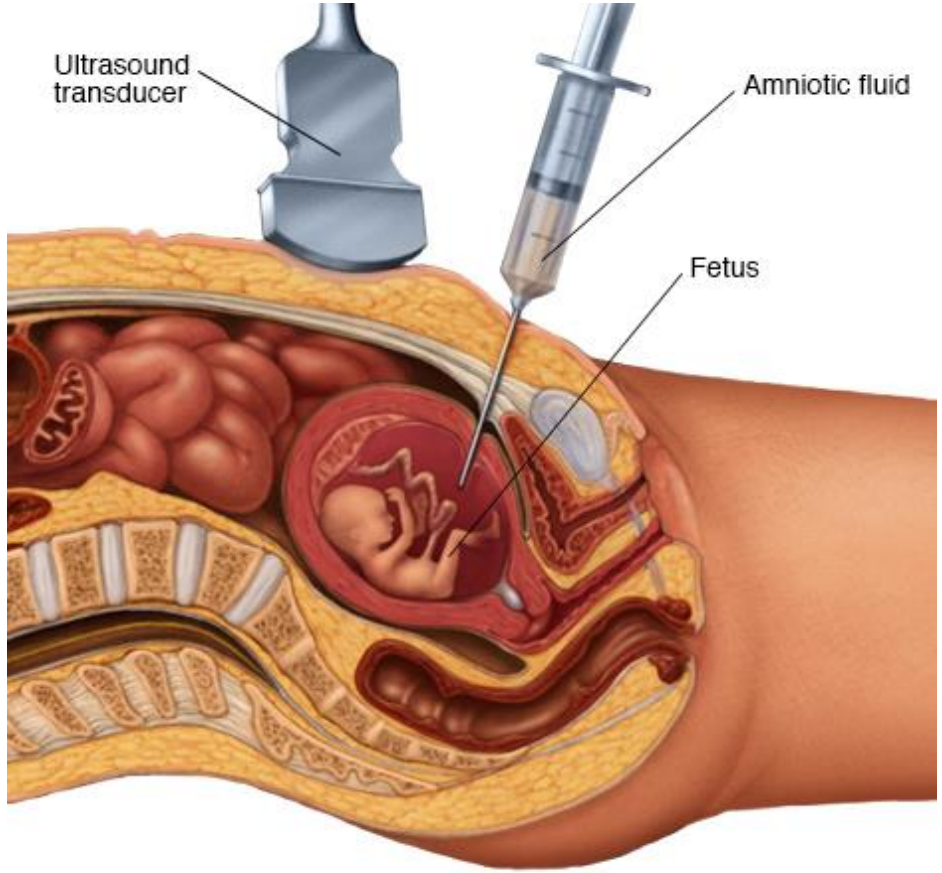
Options for future pregnancies

- Natural Conception
  - Do nothing
  - Do CVS
  - Do amniocentesis
- IVF pregnancy
  - PGD
- Donor
  - Donor egg
  - Donor sperm
  - Donor mitochondria

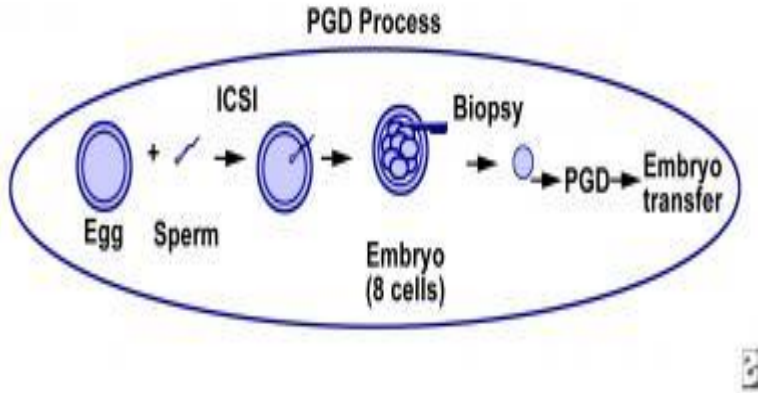
Chorionic Villus Sampling



Amniocentesis



Pre-implantation Genetic Diagnosis



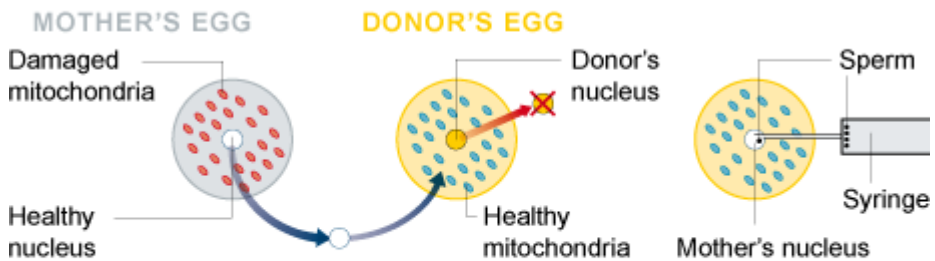
Donor Gamete

- Helpful for when you don’t know the genetic mutation
- Best to use donor egg because it also rules out mtDNA
  - Don’t use a female relative!
- Easier to get sperm donor than egg donor
- Disadvantage is that one parent will not be a ‘biological’ parent

Mitochondrial Donor

- Transfer the mother’s nucleus into the donor’s egg
- Retains mother’s nuclear DNA but uses mutation free mtDNA
- So called 3 parents
- Approved in UK but not done here in Australia yet
- Don’t use a female relative

CREATING A THREE–PARENT FAMILY



1 Healthy nucleus is extracted from mother's defective egg

2 Nucleus removed from healthy donor egg and replaced with mother's nucleus

3 Egg carrying genetic material of two women fertilised by male sperm and implanted into mother