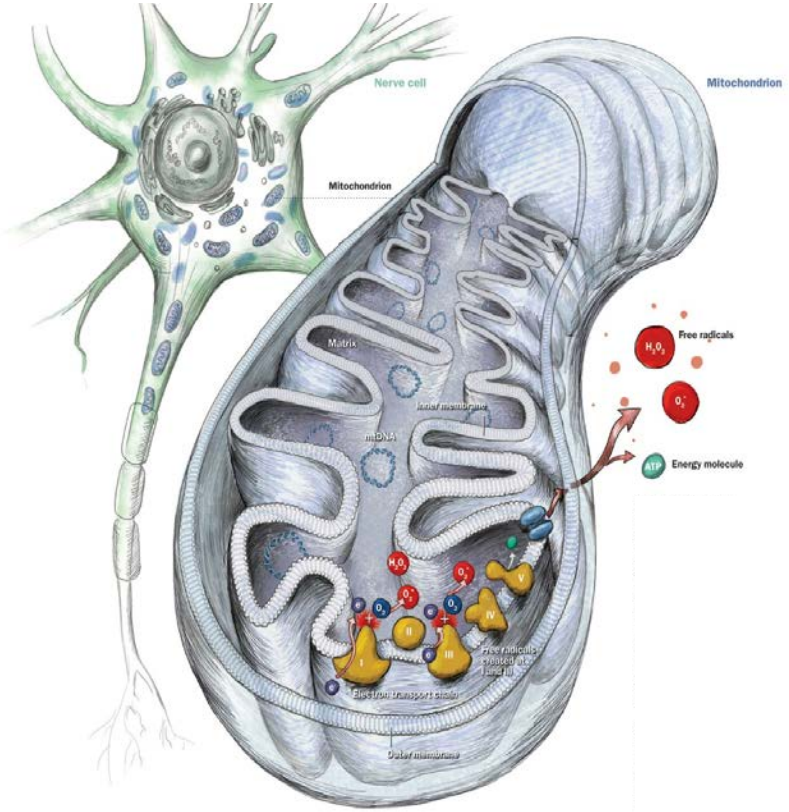
Achieving 3-person embryos

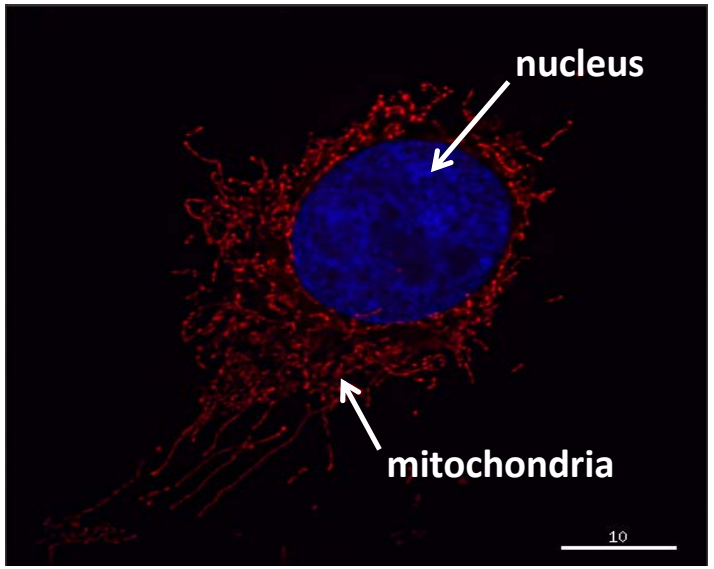
Clinical application of mitochondrial donation in the UK

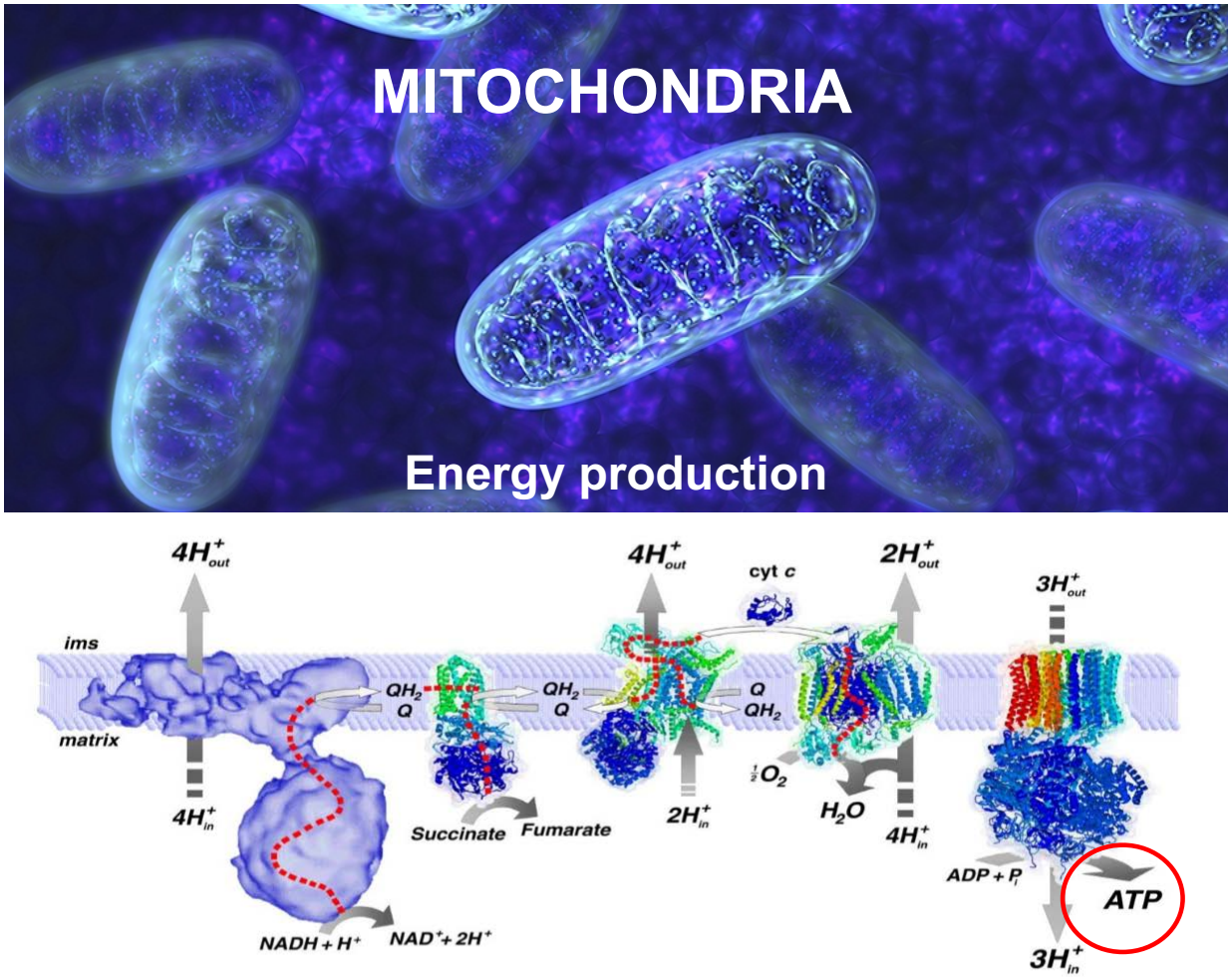
Dr Lyndsey Craven, 23 March 2018

39th BSRM Scientific Meeting

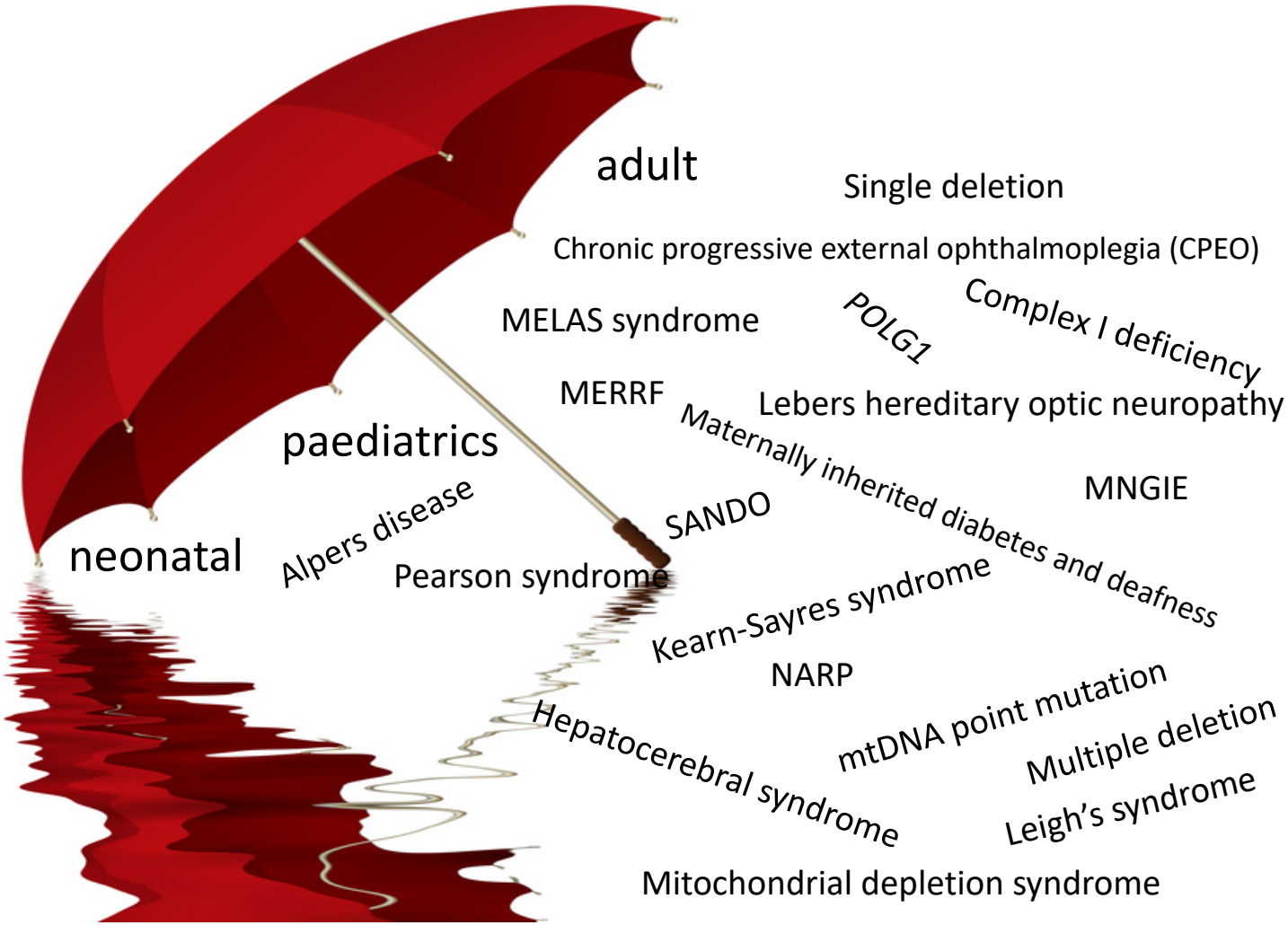
What are mitochondria?





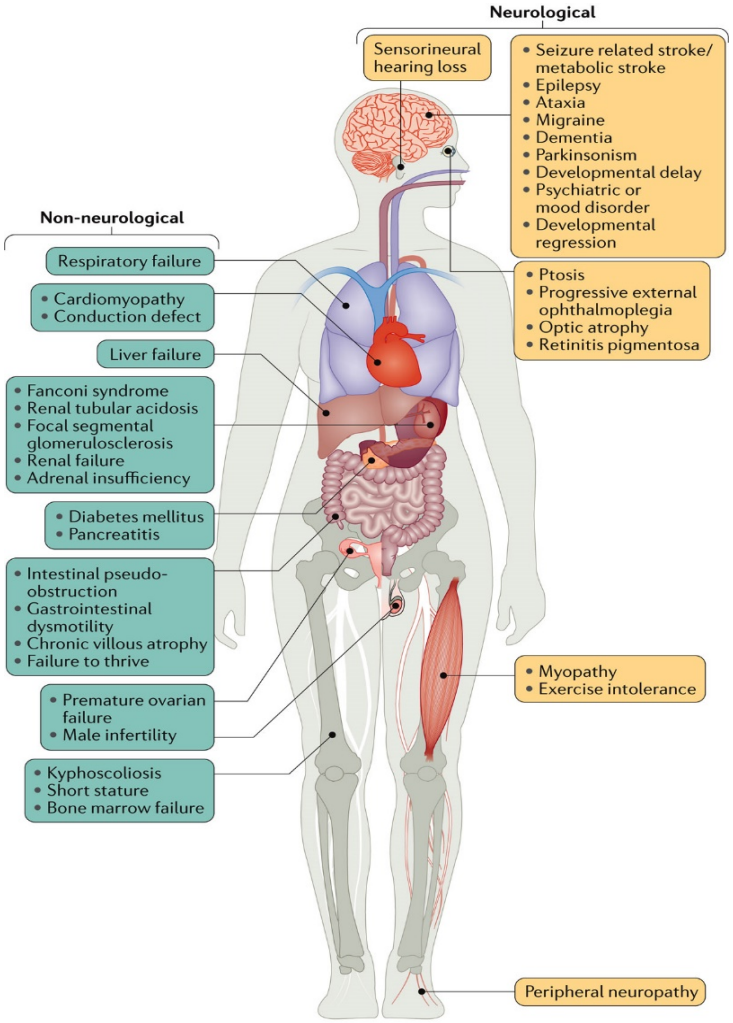

MITOCHONDRIA
Energy production
$4H^+_{out}$
ims
matrix
QH_2
Q
$4H^+_{in}$
NADH + H+
NAD+ + 2H+
Succinate
Fumarate
$4H^+_{out}$
cyt c
$2H^+_{in}$
$2H^+_{out}$
$\frac{1}{2}O_2$
H_2O
$4H^+_{in}$
$3H^+_{out}$
ADP + Pi
ATP
$3H^+_{in}$

Mitochondrial disease



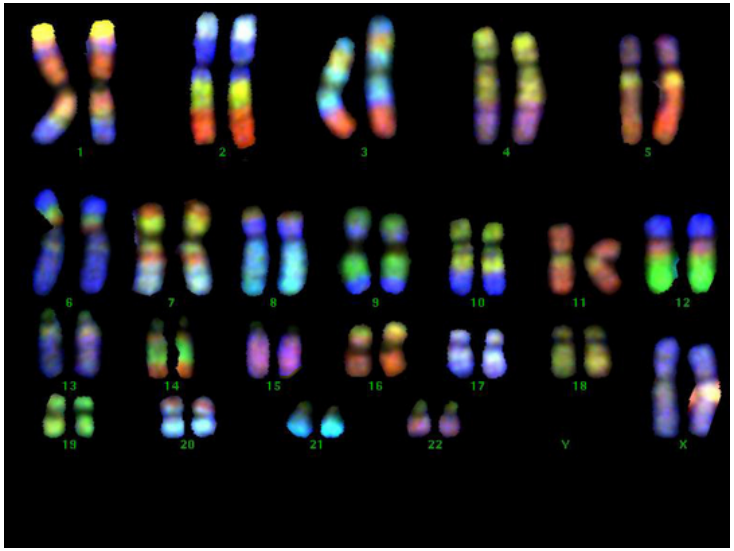
Dr Yi Ng

Clinical features of mitochondrial disease



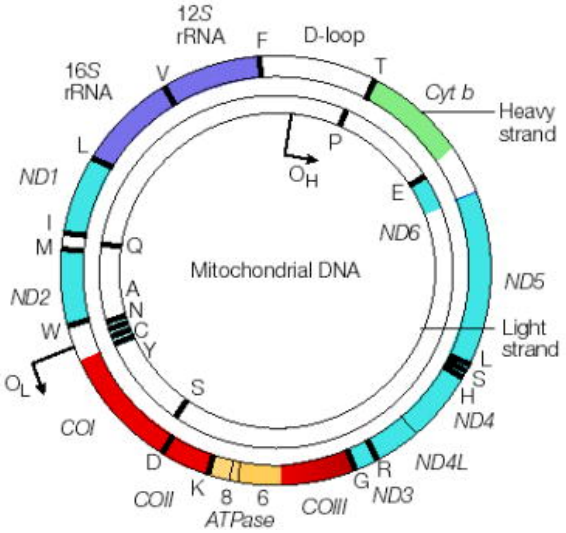
Nature Reviews | Disease Primers

Genetic causes of mitochondrial disease



Nuclear DNA: 3,000,000,000 bp

~1300 mitochondrial proteins

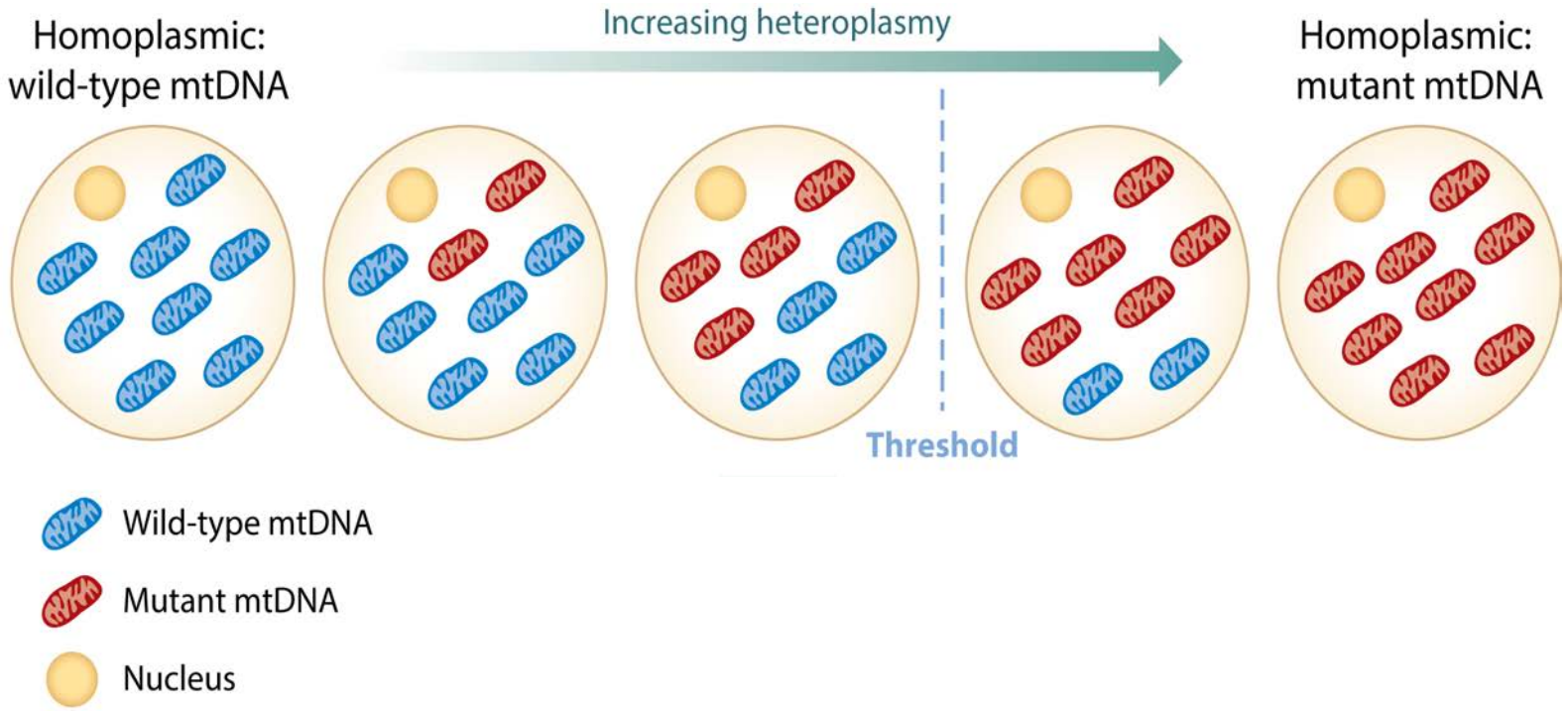


mtDNA: 16,569 bp

13 mitochondrial proteins

<u>>300 different disease-causing mutations</u>

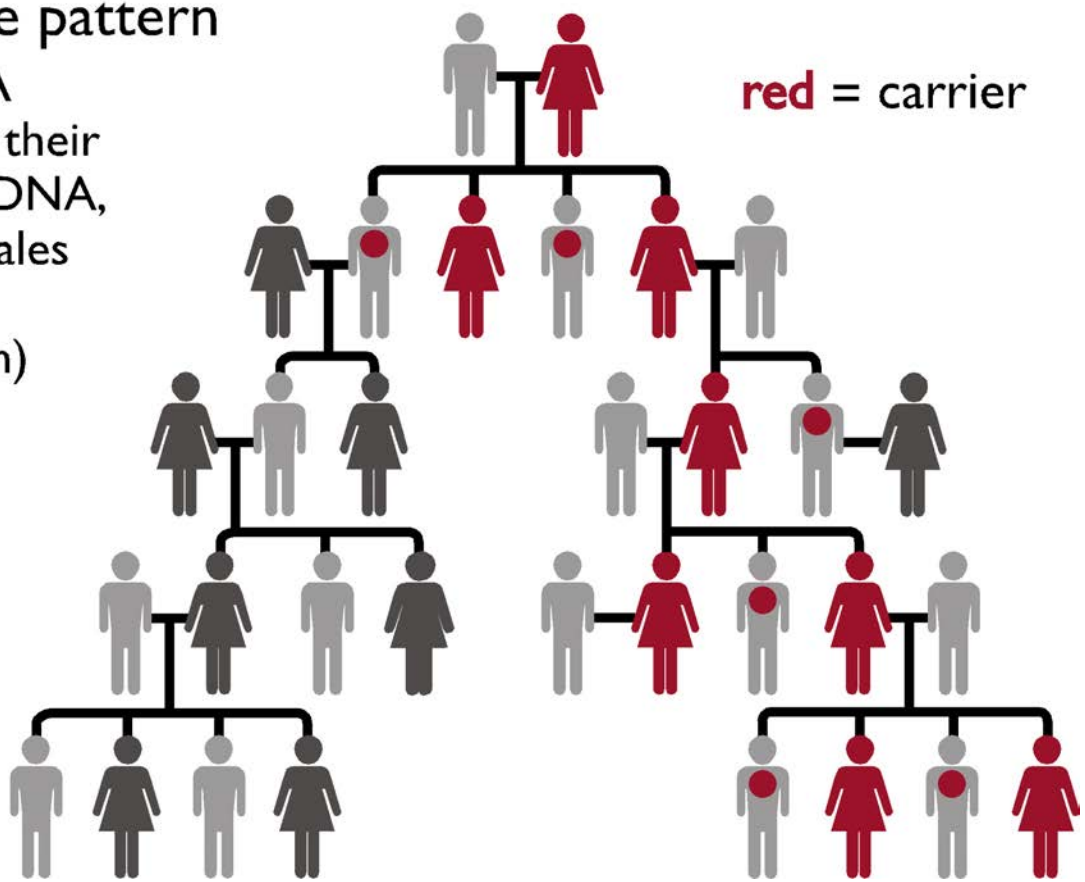
Mitochondrial Genetics: heteroplasmy and the threshold effect



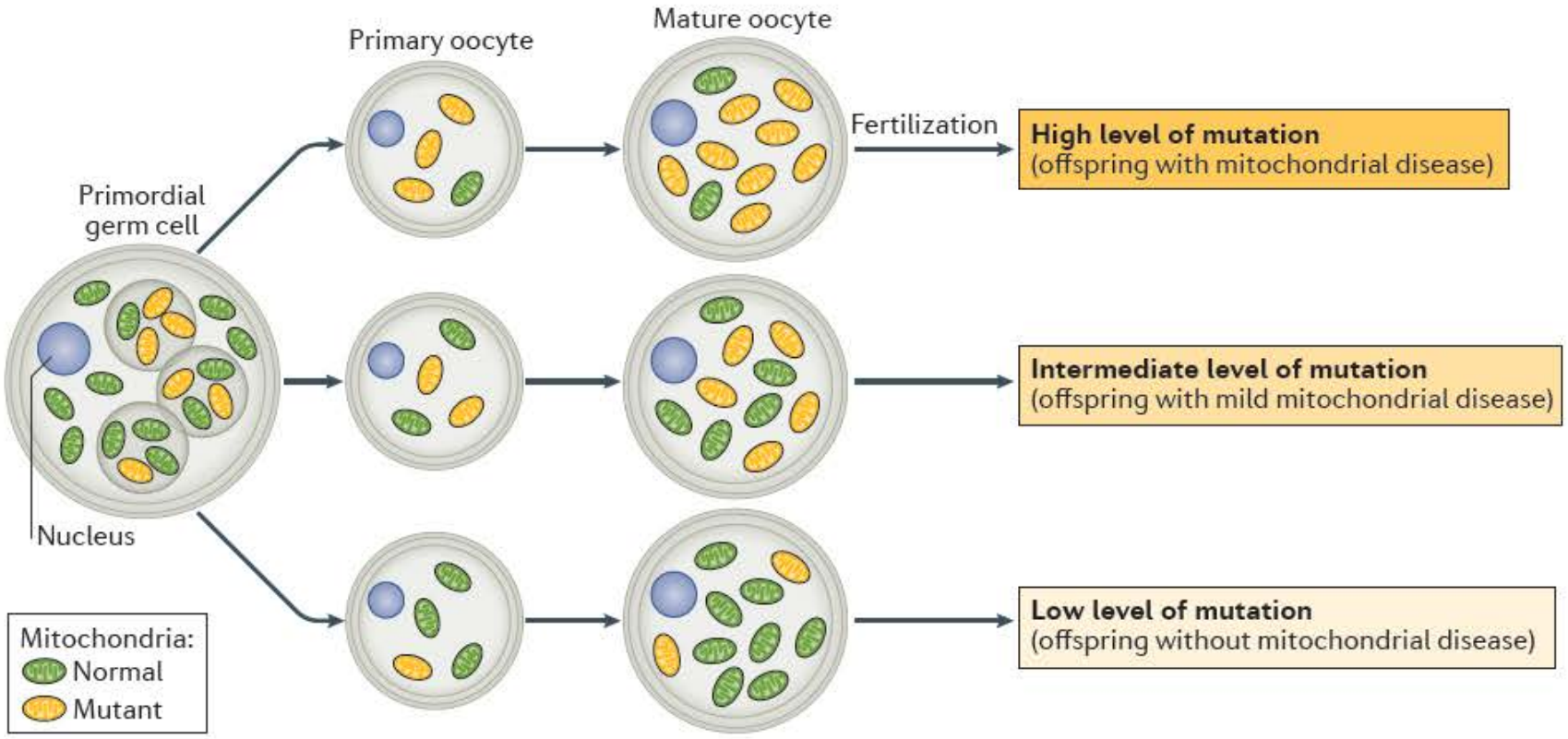
Craven L, et al. 2017.
Annu. Rev. Genom. Hum. Genet. 18:257–75

Mitochondrial Genetics: maternal inheritance

Inheritance pattern of mtDNA
(males carry their mother's mtDNA, but only females pass it on to their children)



Mitochondrial Genetics: the bottleneck



'I've lost six newborn babies'

Sharon Bernardi tells new! about the curse that has robbed her of six children

When she first fell pregnant 25 years ago, Sharon Bernardi had no idea of the nightmare ahead.

After a normal pregnancy, she gave birth to a healthy girl. But only 28 hours later, her baby was dead. Doctors could give no explanation and Sharon, 42, was baffled and devastated. This tragic tale repeated itself five more times, as each of Sharon's babies lived for just a few hours. Only one, Edward, survived.

Having just celebrated Edward's 18th birthday, full-time mother Sharon, who lives with partner Neil Smith, 38, in Sunderland, tells new! how she's coped with the loss of six babies.

Clockwise from top: Sharon, Edward and Neil are taking every day as it comes; Holly; Caroline; Olivia

"Aside from some terrible morning sickness, my first pregnancy was uneventful. It was only after the delivery that things began to go wrong. My daughter, Gemma-Louise, was born a perfect pink, chubby baby. But half an hour later, she developed breathing problems and was whisked to intensive care. After 28 hours, she died.

"This was meant to be the happiest day of my life. Instead, I was mourning my baby's death and preparing myself for her burial. It was heartbreaking. The doctors could give no explanation, but I knew that I wanted to be a mother and didn't hesitate to try again.

"A couple of years later, in 1984, I gave birth to another baby – a boy, Iain. This time I was more anxious. I knew that while my baby was still inside me, he was safe. I was almost scared of giving birth. I had a Caesarean section because he was breech. I was under general anaesthetic and woke up, two hours after, to be told my son had died.

"Again, there was a postmortem and, again, I was given no explanation why Iain died. The babies were perfectly healthy on delivery but just didn't seem able to survive on their own. As there seemed to be no medical reason, I was never warned against trying for more children.

"Three years later, in 1987, I had Geoffrey, again born by Caesarean. As the hours went by and nurses came in and out, doing checks, I started to feel hopeful. Each minute I didn't hear anything, I took as a positive sign – it meant my baby was still alive. But 30 hours after the birth, the doctor's footsteps came – and so did the news I was dreading. Geoffrey, like the two babies before him, had died."

family curse

"I began asking myself if it was my fault. That's when my mum admitted that she had been through a similar heartache. She had four babies, the first three of whom died a few hours after birth. I was the fourth – the lucky one. It made me wonder if it was something I had inherited from her, but it also gave me hope. I'd survived – maybe one day I'd have a baby that would live.

"Edward, my fourth child, born two years later in 1989, would be that survivor. He was terribly poorly and I was warned his chances of survival were slim, but the hours turned into days, then weeks. The doctors didn't know why he was different to the other babies, but after a blood transfusion and time on a ventilator, he made it. Five weeks after he was born, I took him home.

"Finally, I was the mother I'd longed to be. Edward was a bonny baby, reaching all his milestones – walking by 14 months and talking as normal. Then, when he reached four, he began falling over a lot. Experts ran tests and scoured my medical history. It was then that Leigh's disease was mentioned. I learned it was a rare, inherited disorder that caused degeneration of the central nervous system. Symptoms could include a lack of muscle control and breathing, and heart problems. It was likely that my mum had passed the abnormal gene on to me and as a carrier, I had passed it on to my first three babies – and now Edward."

The mum has come to terms with only one child surviving (Edward, right, aged one)

only child

"Doctors didn't think Edward would make it to his fifth birthday. But he was a fighter. I learned that although there was no cure, Leigh's disease could be managed by diet and medication. The disease has limited Edward's quality of life – he is confined to a wheelchair and suffers with epilepsy. But he was a happy child with lots of friends and a great sense of humour.

I'd leave hospital exhausted, with no baby to show for it – instead, I'd have a funeral to arrange

"I learned to accept what I had in Edward. But I didn't want him to be an only child and I knew that there was a chance I could have another baby that would survive. I was aware of the risks, but I wanted to try for more children. I had Holly in 1991 and Olivia in 1995, but neither survived.

"In 1996, I split from my husband. I met Neil in a club two years later. We had one baby together, Caroline, in 2000 but she died after 29 hours. It never got easier. I'd leave hospital exhausted from the births – especially if I'd had a Caesarean – and didn't even have a baby to show for it. Instead, I'd have a funeral to arrange.

"After Caroline, I decided to stop trying for my own health reasons. As a carrier of Leigh's, I was on a lot of medication, and doctors warned my heart might not be strong enough to cope.

I feel sad that Edward never had a brother or sister to play with, but he's aware of the brothers and sisters he never knew. We've got photos of my lost babies round the house and if anyone asks, I tell them I have one child – but I've had seven.

"Neil has been supportive but as a mother, losing your children is something you never get over. I think about them every day, and have kept their photographs and fingerprints. They're a part of my family history. I can't afford to break down – because of Edward. I need to be strong for him, and it's important that he enjoys a good quality of life. If it gets too much or I feel upset, I'll deal with it privately.

"Of course, sometimes I wish I'd had another child or that I could make Edward perfectly healthy – but I know now that it just wasn't meant to be. So, although I'll always remember my six other children, writing cards and lighting candles on each of their birthdays, I also appreciate what I've got.

"Edward has just celebrated his 18th birthday. Most kids with Leigh's disease die between the ages of two and eight, so he's done so well to get this far. We don't know what the future holds, but we take each day as it comes.

"Maybe one day, he could have his own family. If so, as a male he won't pass on the condition – and we will finally have broken the family curse." ◻

WORDS: Helen O'Brien PHOTOS: North News & Pictures

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Mitochondrial DNA Disease

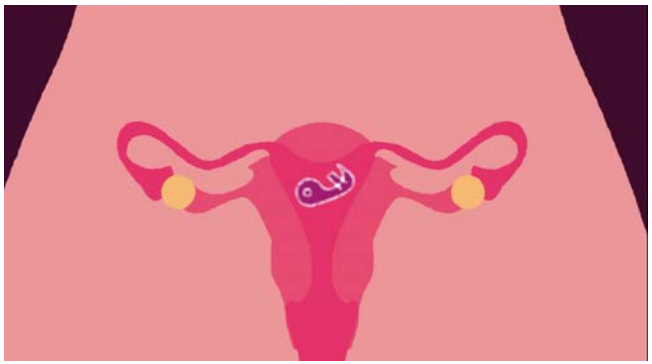
- Estimated that ~2500 women of child bearing age are at risk of transmitting mtDNA disease in the UK
- Currently few effective treatments and no cure for mtDNA disease
- Many couples seek reproductive advice to reduce the risk of having an affected child

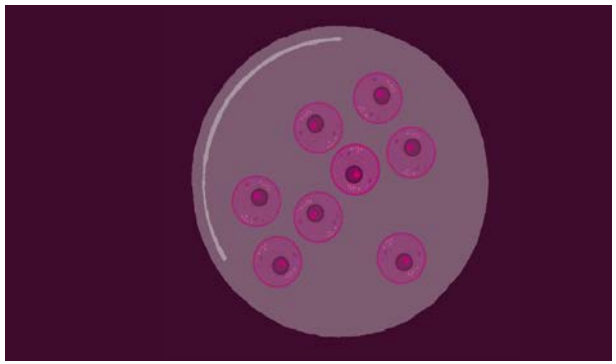
Mitochondrial DNA Disease

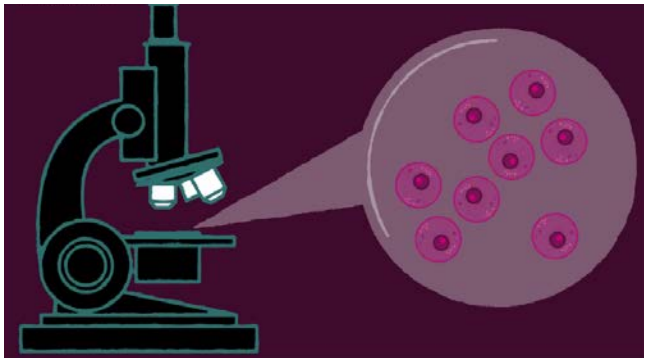
- Several options for women who carry an mtDNA mutation:

  - voluntary childlessness
  - adoption
  - egg donation
  - prenatal testing
  - preimplantation genetic diagnosis
  - mitochondrial donation

Prenatal Testing



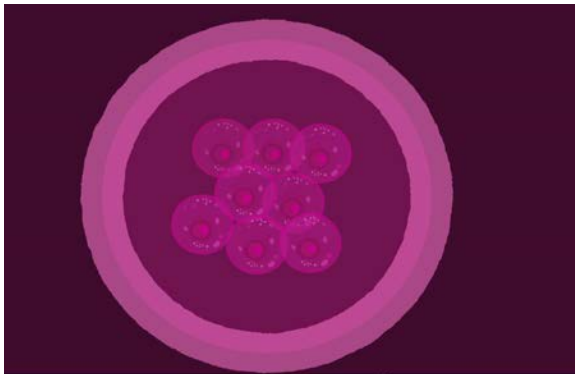


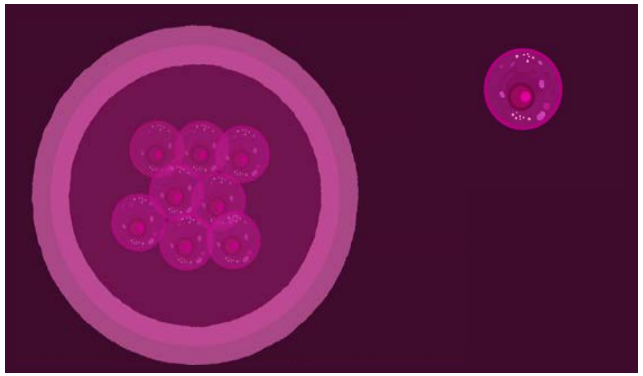


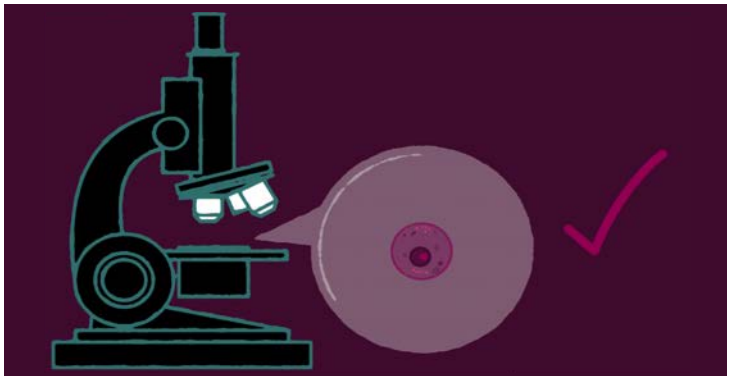
Couple conceive naturally and the heteroplasmy level determined in cells removed from the pregnancy.

Will only reduce the risk of mtDNA disease when a patient has low levels of faulty mitochondria within her eggs.

Preimplantation Genetic Diagnosis





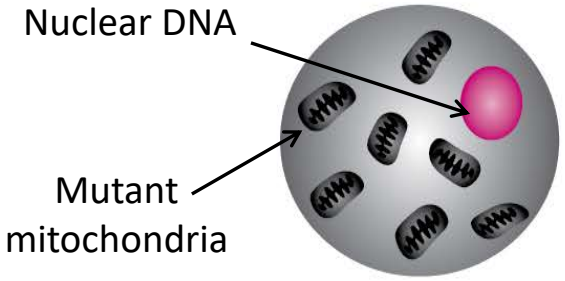


Couple undergo an IVF cycle and the heteroplasmy level determined in cell(s) removed from the developing embryo.

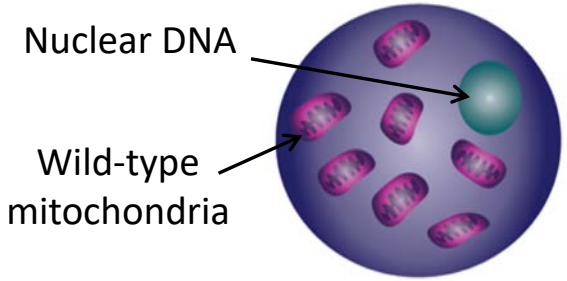
Will only reduce the risk of mtDNA disease when a patient has low levels of faulty mitochondria within her eggs.

Reproductive options: mitochondrial donation

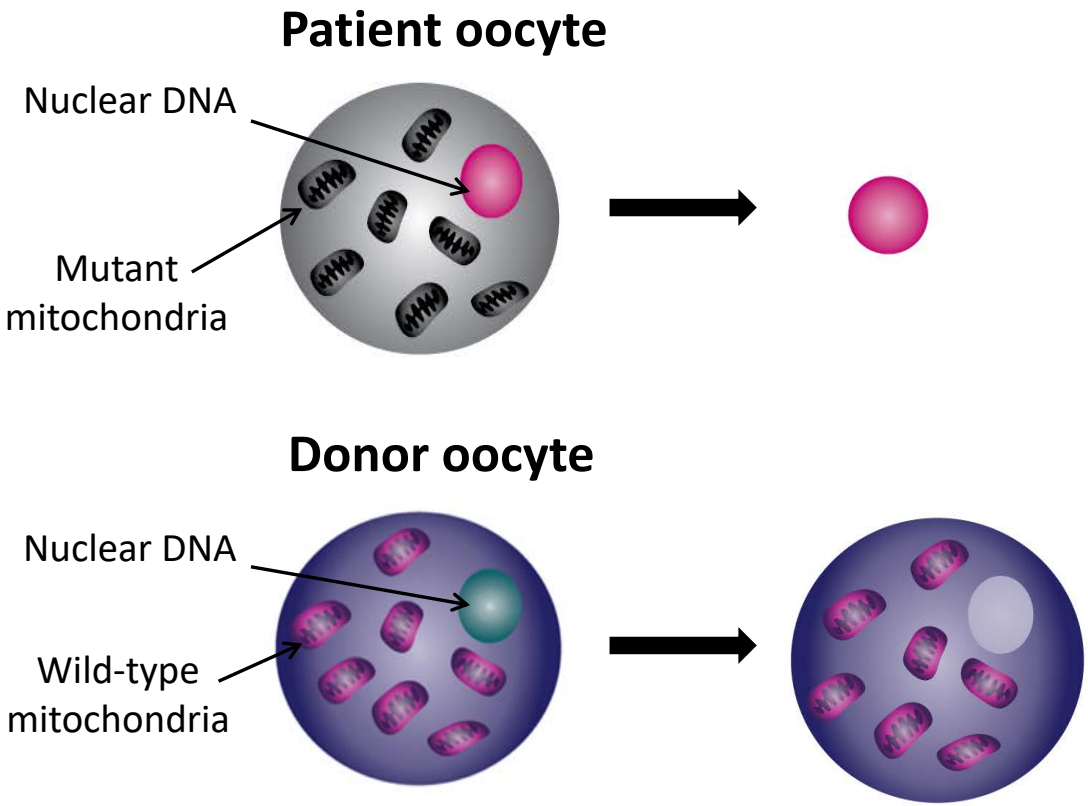
Patient oocyte



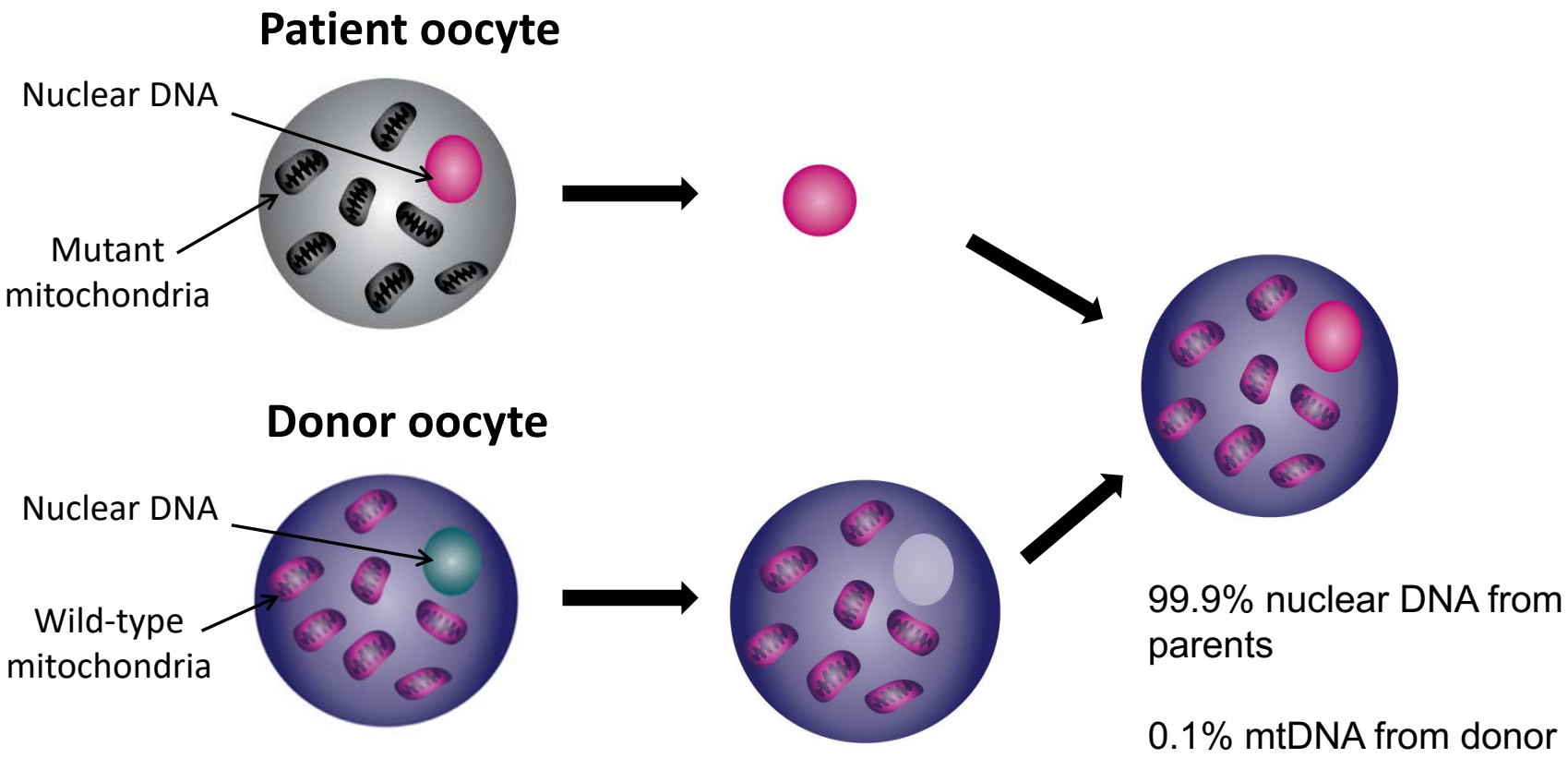
Donor oocyte



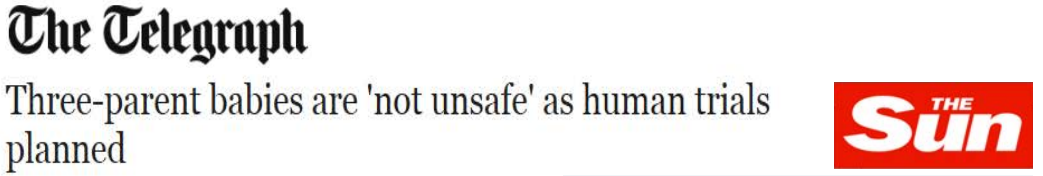
Reproductive options: mitochondrial donation



Reproductive options: mitochondrial donation



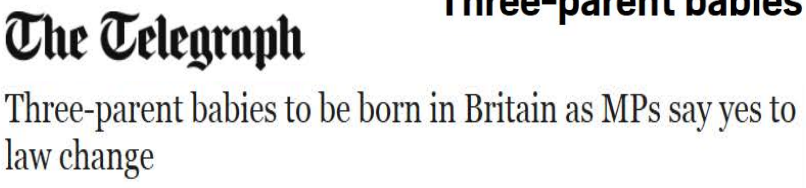
September 2005

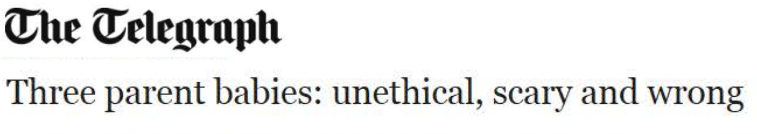


UK approves three-person babies

Three-parent babies 'could be a reality within two years' after report finds controversial IVF techniques are 'not unsafe'

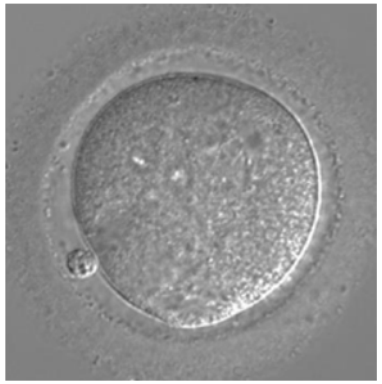
Three-parent babies 'safe' to be born



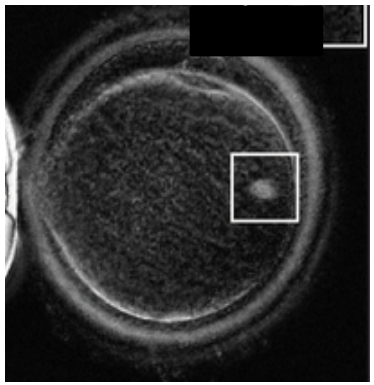


Reproductive options: mitochondrial donation

Germinal Vesicle Transfer (GVT)

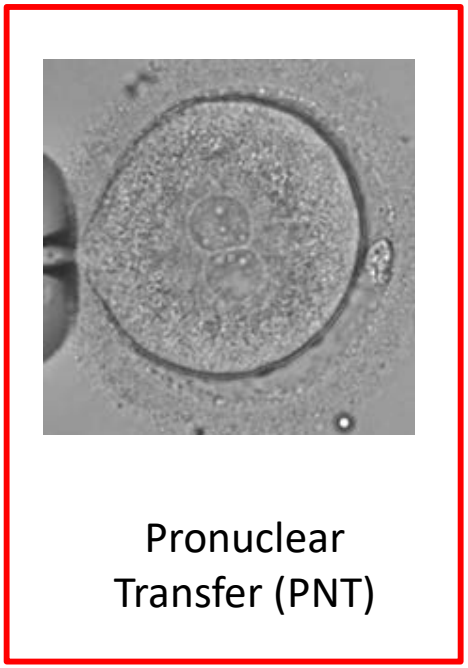


Polar Body Transfer (PBT)



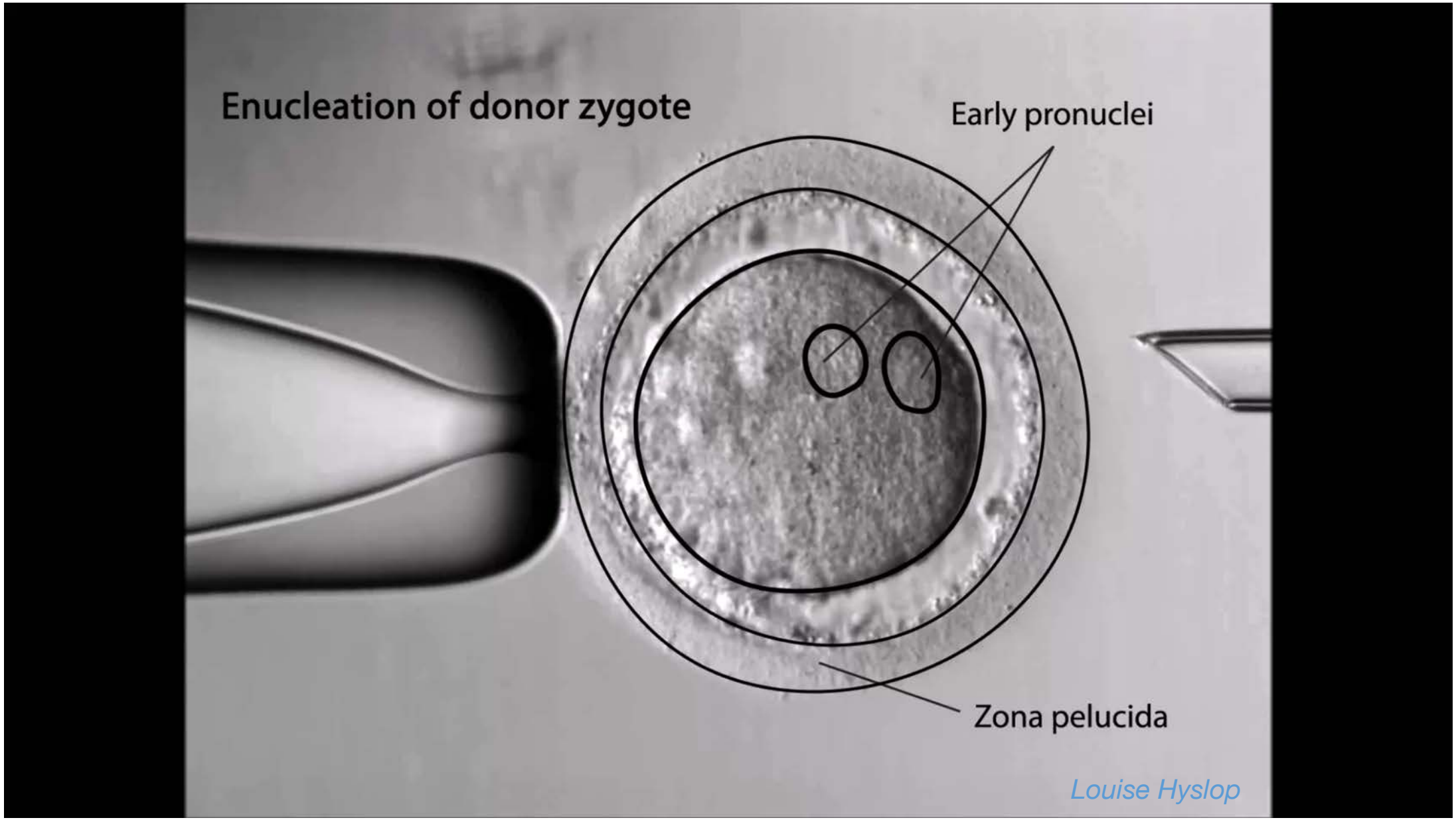
Greggains *et al*, Sci Rep. 2014 Jan 24;4:3844

Maternal Spindle Transfer (MST)



Pronuclear Transfer (PNT)

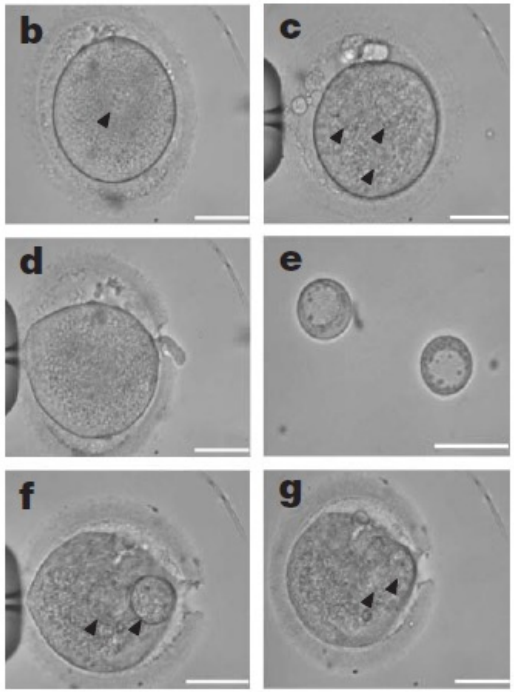
Fertilisation

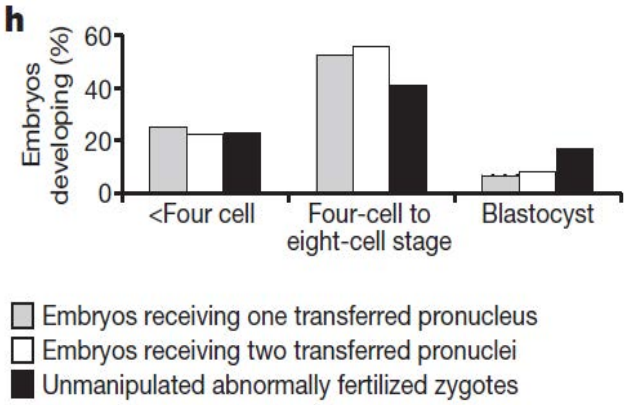

Enucleation of donor zygote
Early pronuclei
Zona pelucida
Louise Hyslop

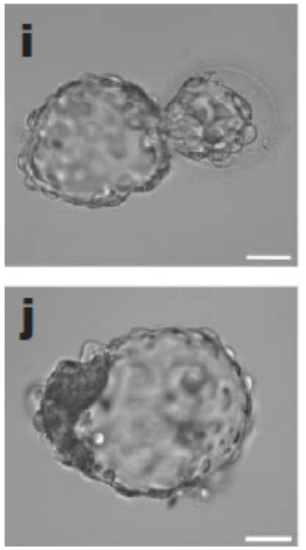
Pronuclear transfer: proof of principle

Pronuclear transfer in human embryos to prevent transmission of mitochondrial DNA disease

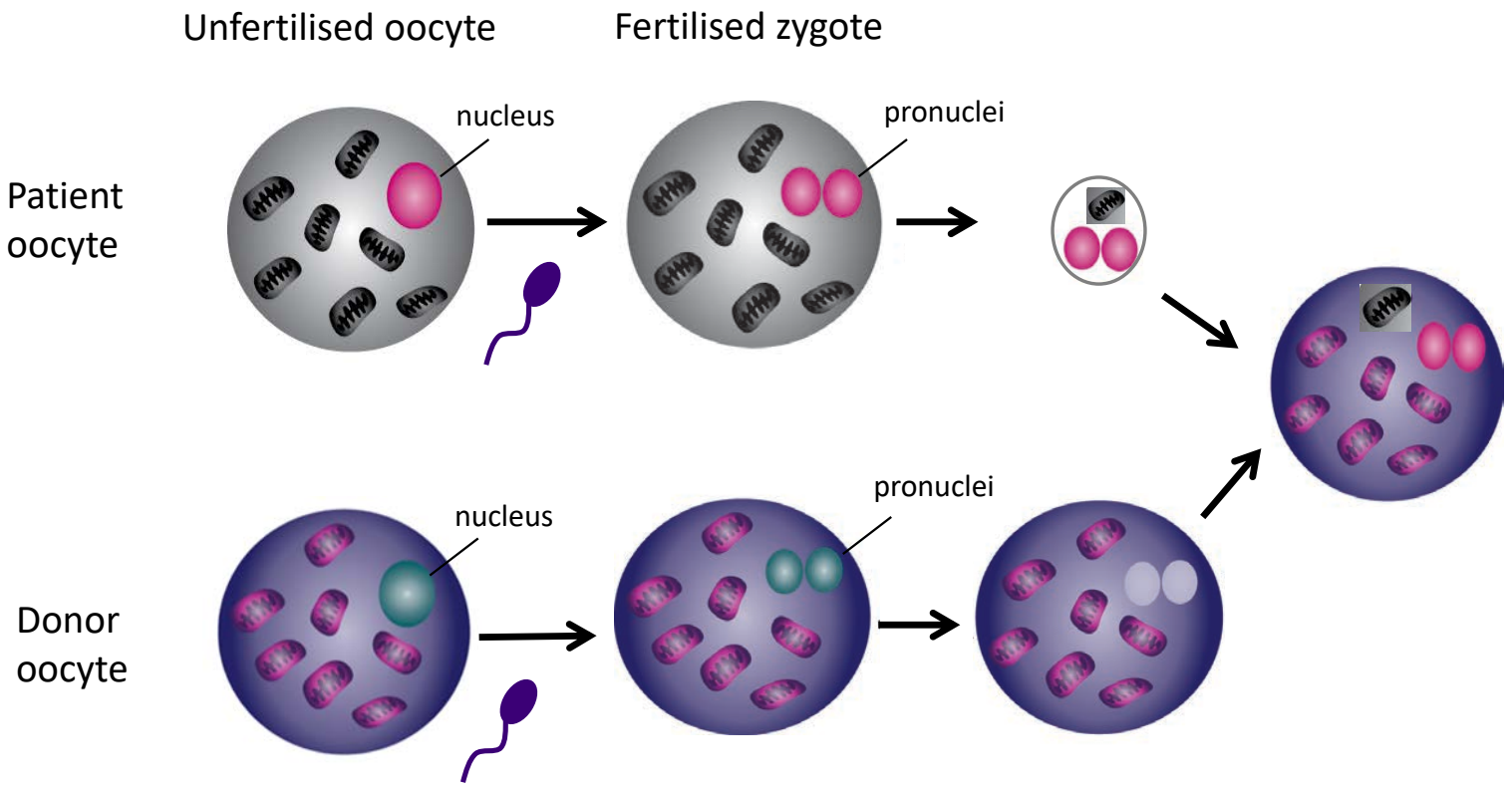
Lyndsey Craven[1], Helen A. Tuppen[1], Gareth D. Greggains[3,4], Stephen J. Harbottle[3], Julie L. Murphy[1], Lynsey M. Cree[1], Alison P. Murdoch[3,5], Patrick F. Chinnery[1], Robert W. Taylor[1], Robert N. Lightowlers[1], Mary Herbert[3,4,5] & Douglass M. Turnbull[1,2,5]







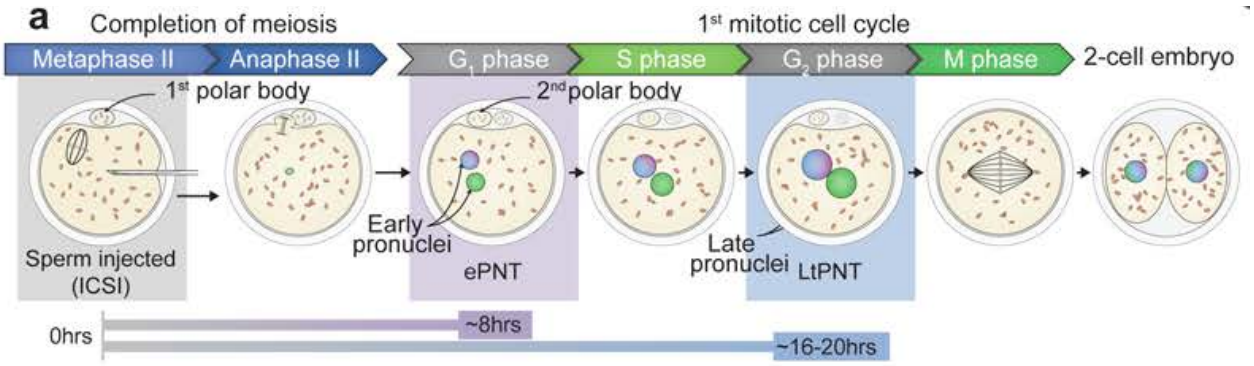
Pronuclear transfer: proof of principle

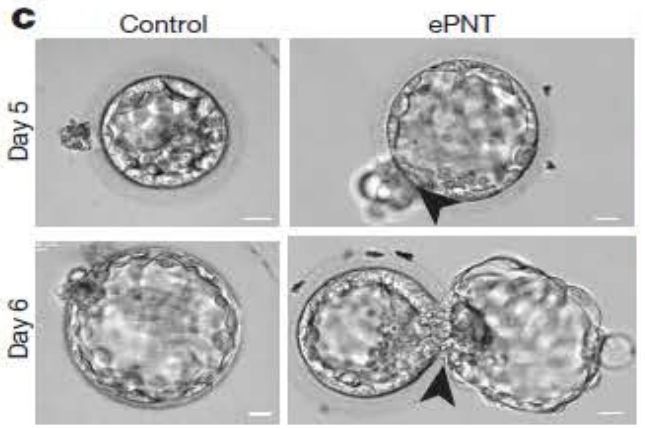


Average level of mtDNA carryover <2%

PNT has the potential to prevent transmission of mtDNA disease in humans

Pronuclear transfer: preclinical study





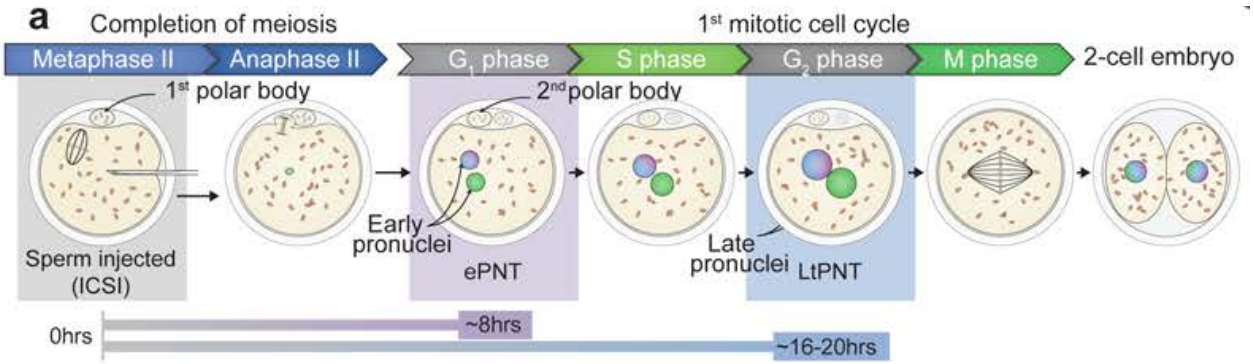
Good quality embryos that are likely to result in a pregnancy

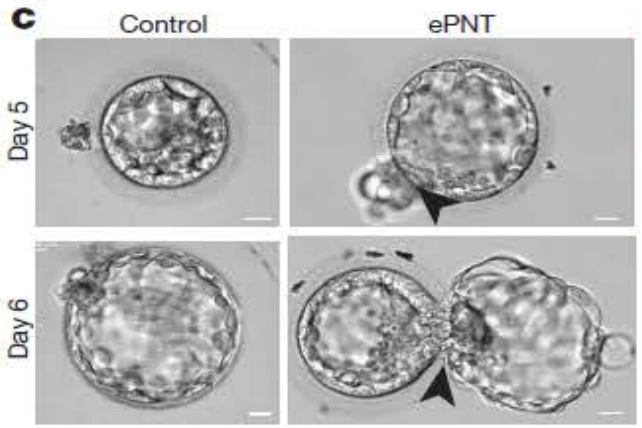
Low levels of mtDNA carryover (<2%)

mtDNA carryover increased over time in a limited number of stem cell lines

Hyslop et al, 2016

Pronuclear transfer: preclinical study



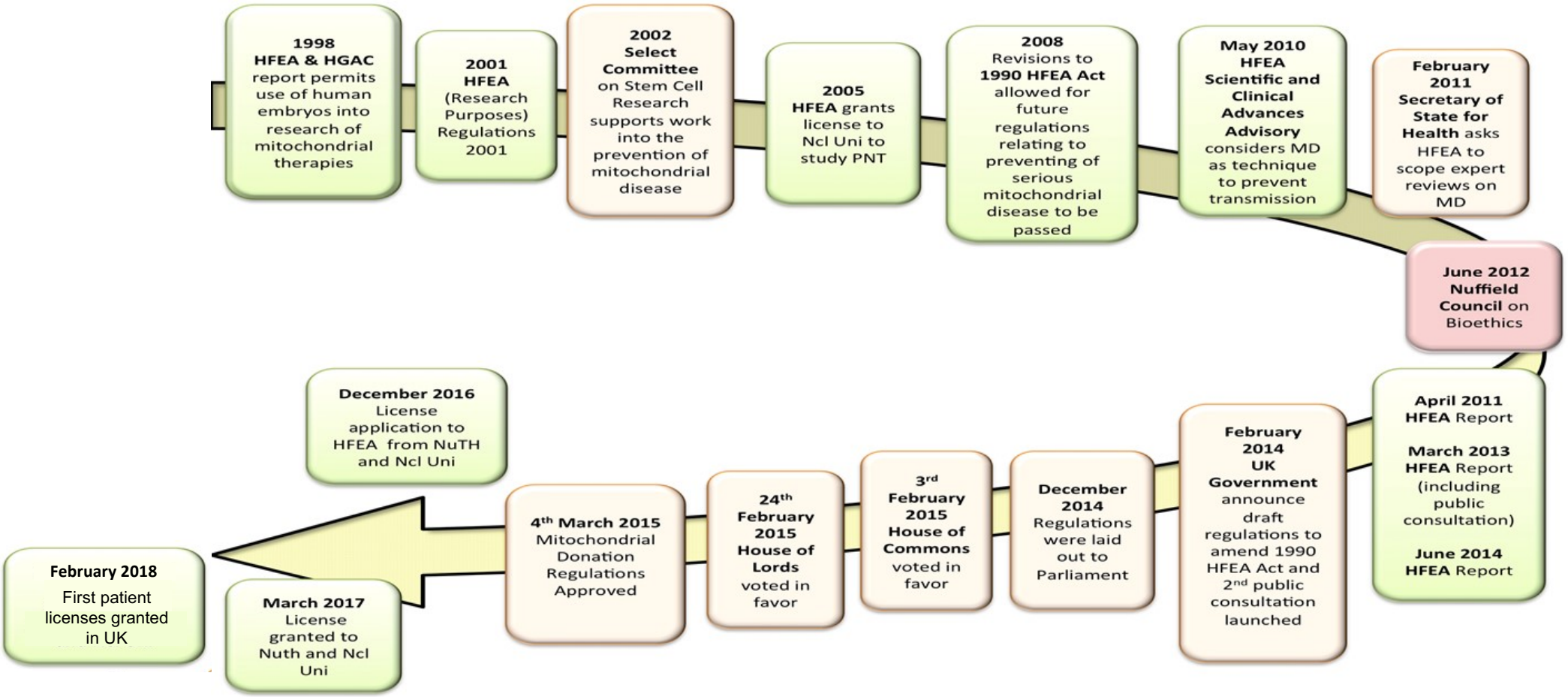


Mitochondrial donation can reduce the risk of mtDNA disease but may not guarantee prevention

Mitochondrial donation should be offered in combination with prenatal testing

Hyslop et al, 2016

Mitochondrial Donation: changing policy



Mitochondrial Donation: scientific review

Scientific review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception: 2016 update

- It is appropriate to offer mitochondrial donation to carefully selected patients when preimplantation genetic diagnosis (PGD) would not be suitable

- Patients who become pregnant following the use of mitochondrial donation should be offered prenatal testing

- All patients should be encouraged to participate in long-term follow-up of children born from the use of mitochondrial donation

Mitochondrial Donation: changing policy

December 2016

HFEA permits cautious use of mitochondrial donation in treatment, following advice from scientific experts

The Human Fertilisation and Embryology Authority (HFEA) has today approved the use of mitochondrial donation in certain, specific cases.

March 2017

HFEA statement on mitochondrial donation

Read our statement as we approve the first application by Newcastle Fertility at Life for the use of mitochondrial donation to treat patients.

Mitochondrial Reproductive Advice Clinic

- Risks of inheritance
- Fitness for pregnancy
- Reproductive history questionnaire
- Reproductive options
- Care of mother through pregnancy
- Psychological support

The Pathway


Mitochondrial
Reproductive Advice
Clinic
&
Mitochondrial
Reproductive Options
Clinic


wellcome trust centre for
Mitochondrial Research
Newcastle
University
Lily
MRC
Medical
Research
Council
NHS
Newcastle upon Tyne Hospitals
NHS Foundation Trust

Thank you!

http://www.newcastle-mitochondria.com/

http://www.thelilyfoundation.org.uk/

http://mitochondrialdisease.nhs.uk/

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Lyndsey.butterworth@ncl.ac.uk