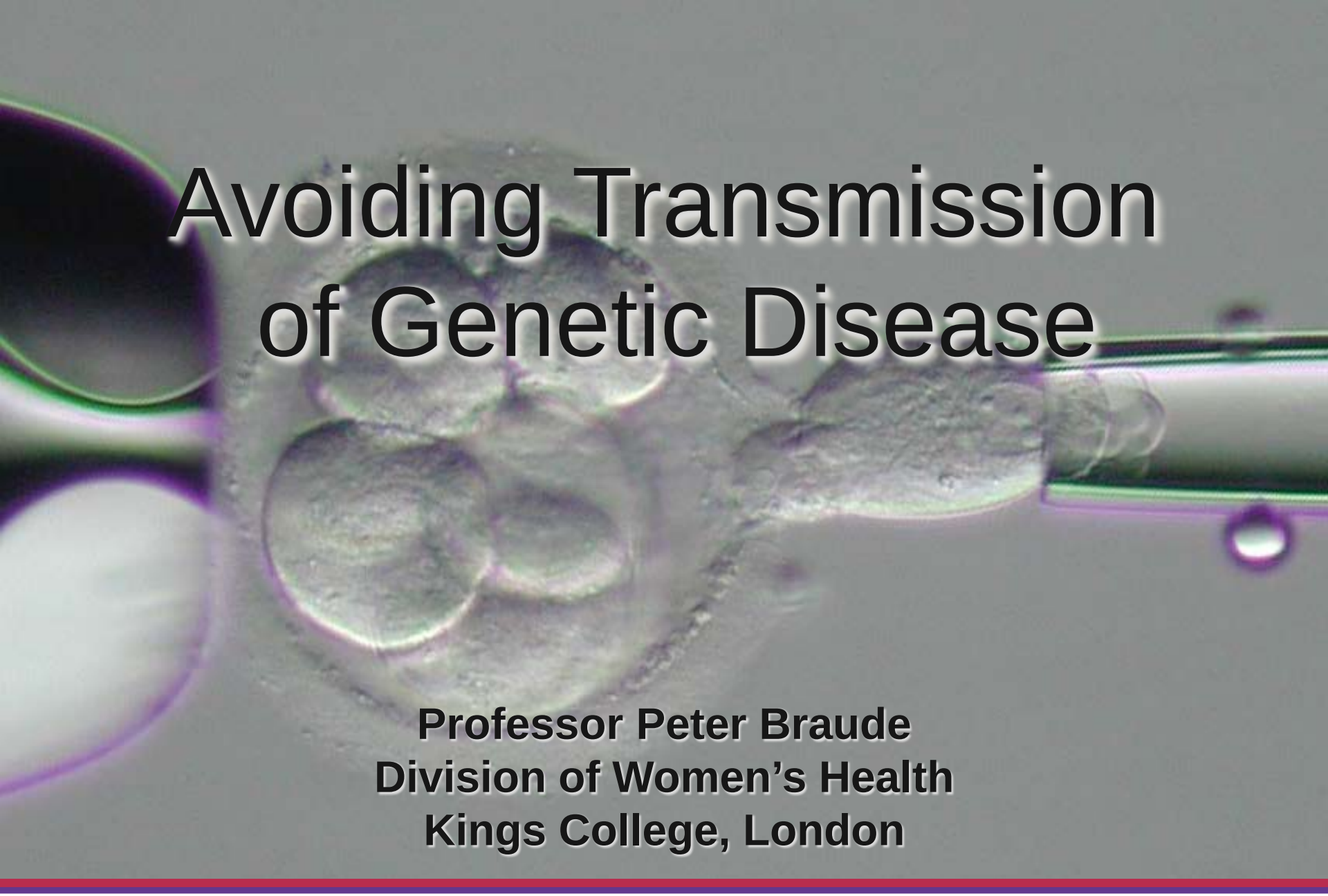


Avoiding Transmission of Genetic Disease

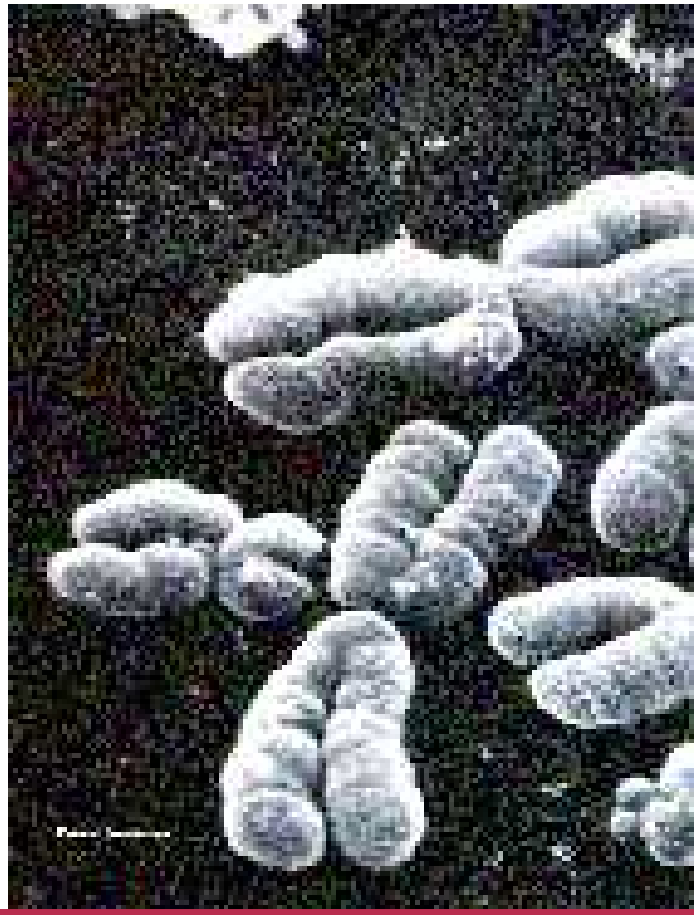
Professor Peter Braude
Division of Women's Health
Kings College, London

Avoiding Transmission of Genetic Disease

- **The health legacy of genetic disorders**
- **Reproductive options for couples with history of recurrent genetic risk**
- **For what conditions is PGD successful**
- **Options when PGD is difficult, inappropriate, or won't work**

Health legacy of genetic disorders

- Sporadic early embryonic loss
- Recurrent pregnancy loss
- Anatomical abnormality
- Mental disability
- Neonatal and childhood death
- Chronic disease and early demise
- Late onset disease



Two kinds of genetic risk

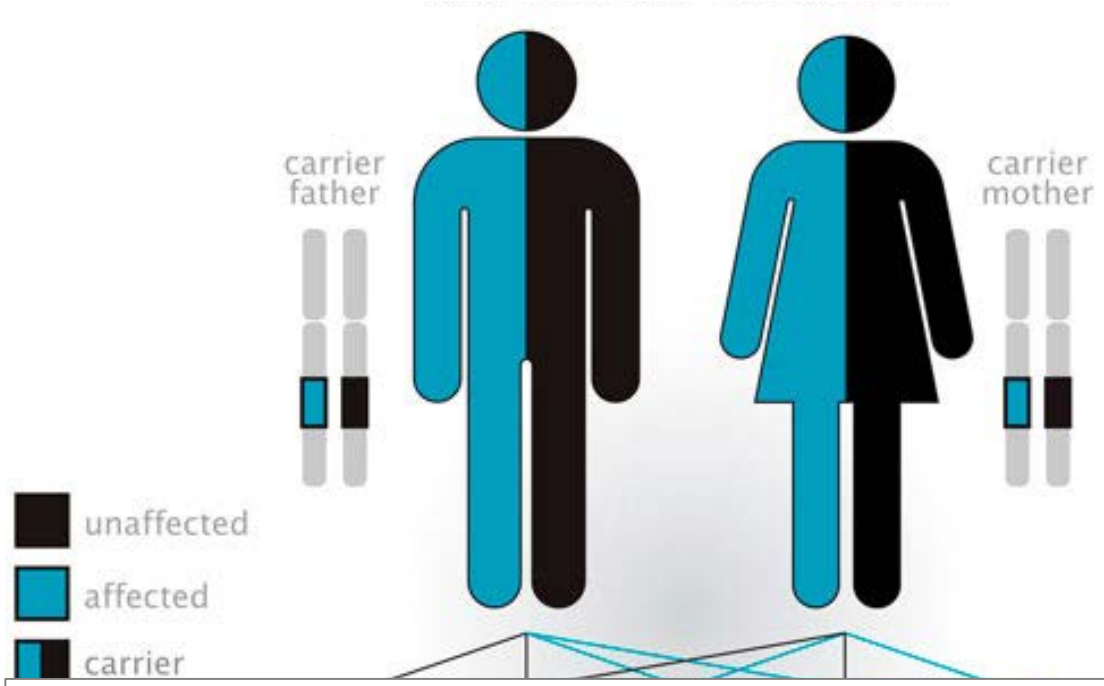
Recurrent:

As a result of inherited disorders

Sporadic:

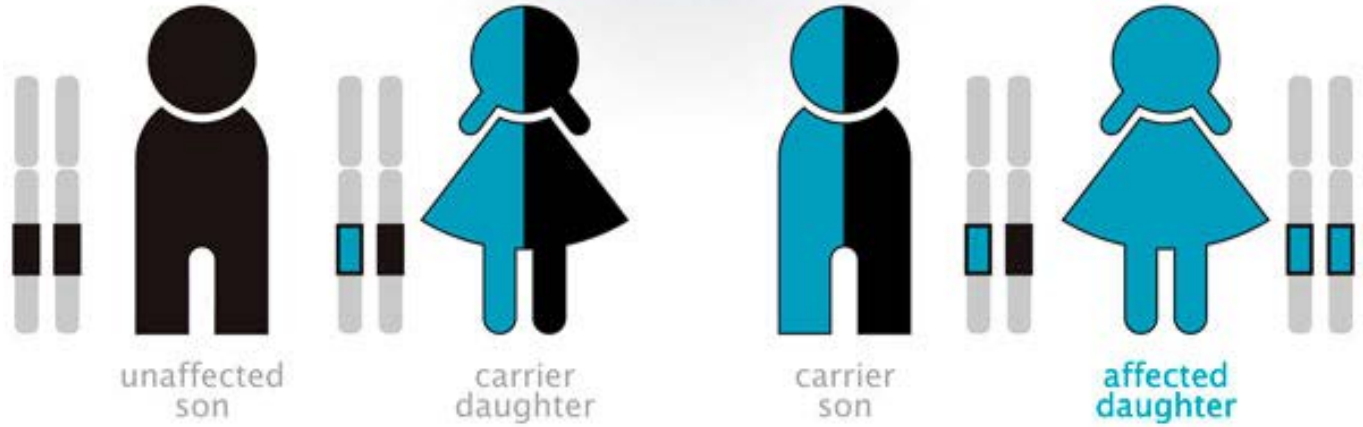
Random, often age related

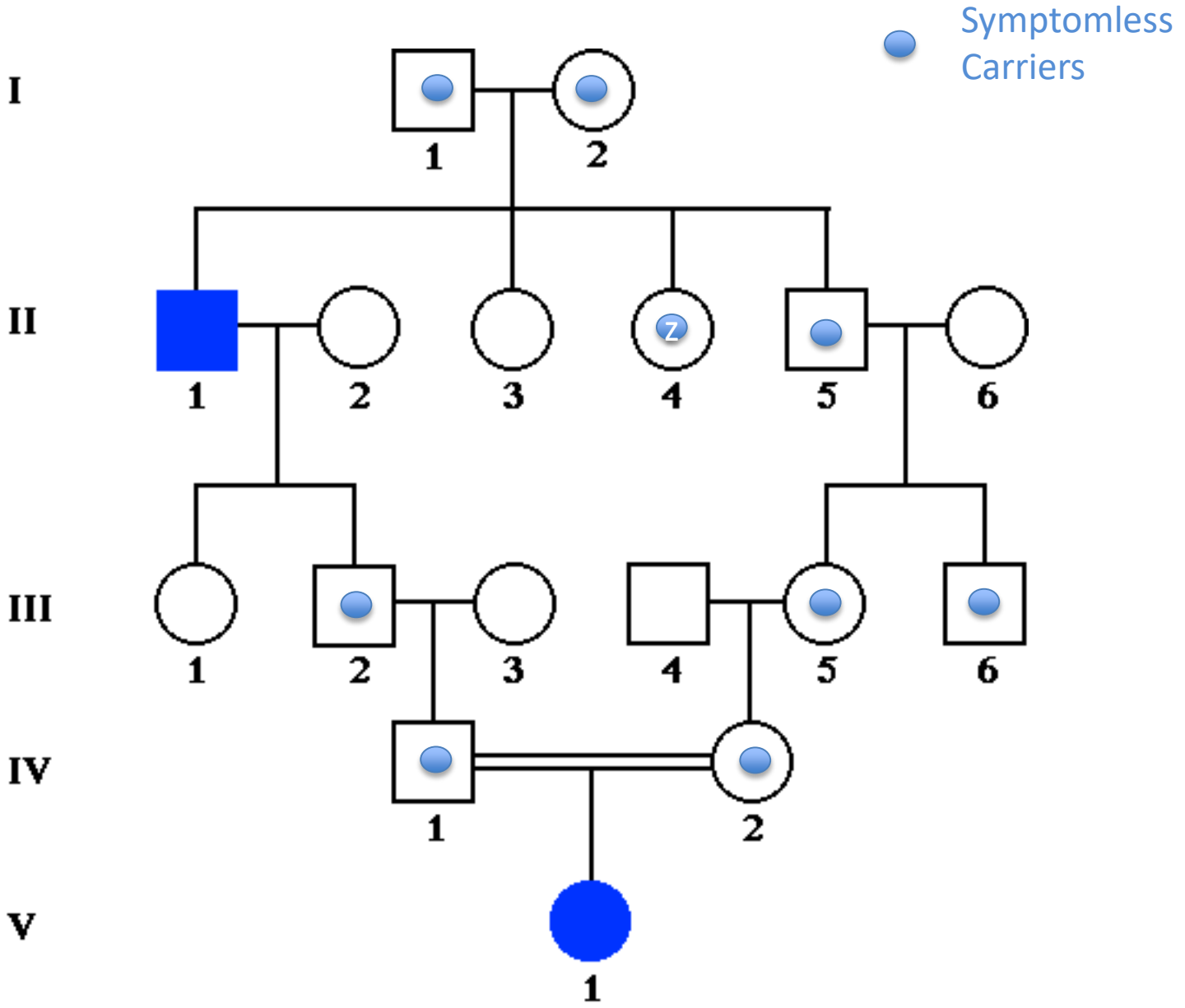
Autosomal Recessive Genetic Disease



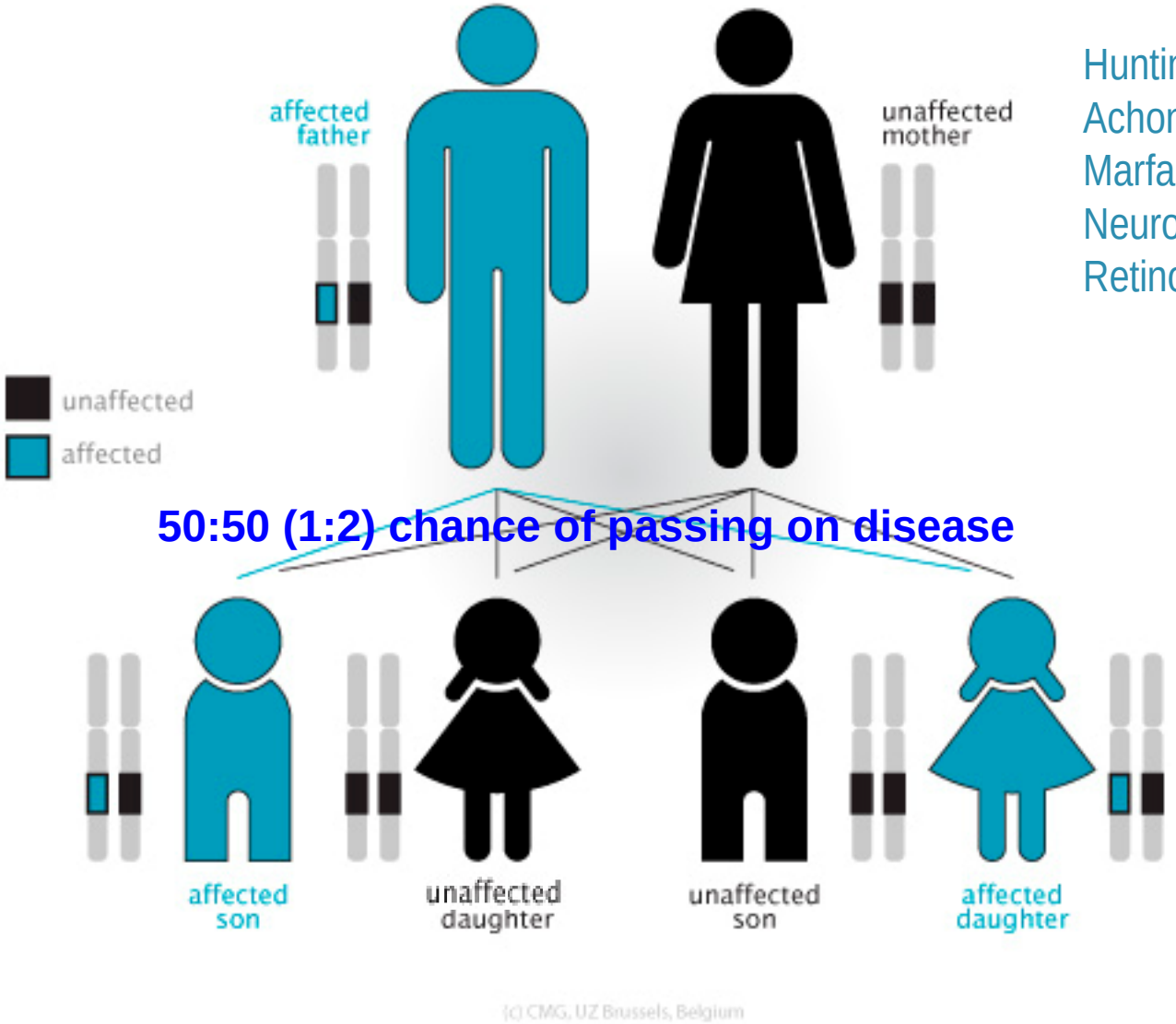
Cystic fibrosis
Spinal muscular atrophy
Sickle cell disease
Tay-Sachs disease
Fanconi Anaemia

1:4 free of disease; 1:2 carriers – but asymptomatic; **1:4 will be affected**

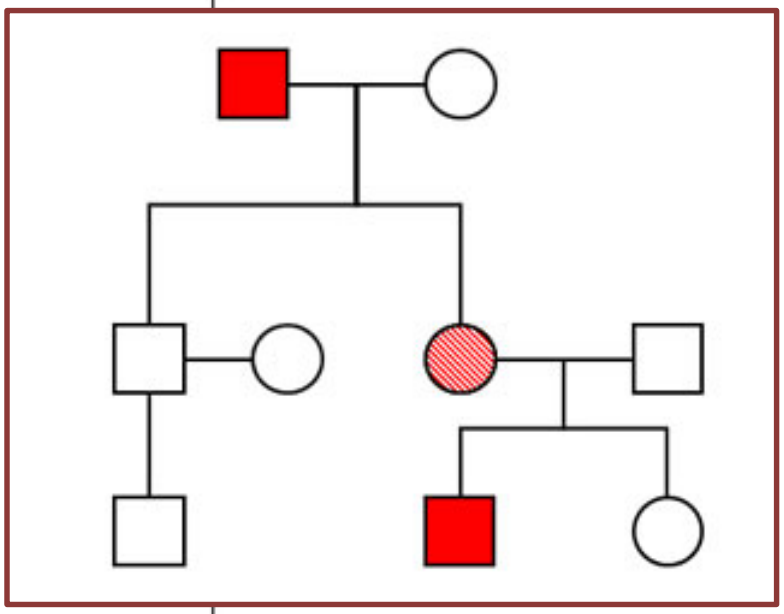



Symptomless Carriers
I
1
2
II
1
2
3
4
Z
5
6
III
1
2
3
4
5
6
IV
1
2
V
1

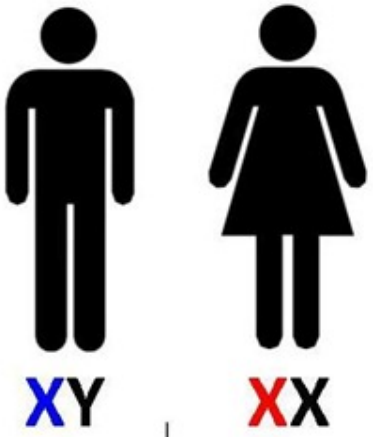
Autosomal Dominant Genetic Disease



Huntington's Disease
Achondroplasia
Marfan Syndrome
Neurofibromatosis
Retinoblastoma



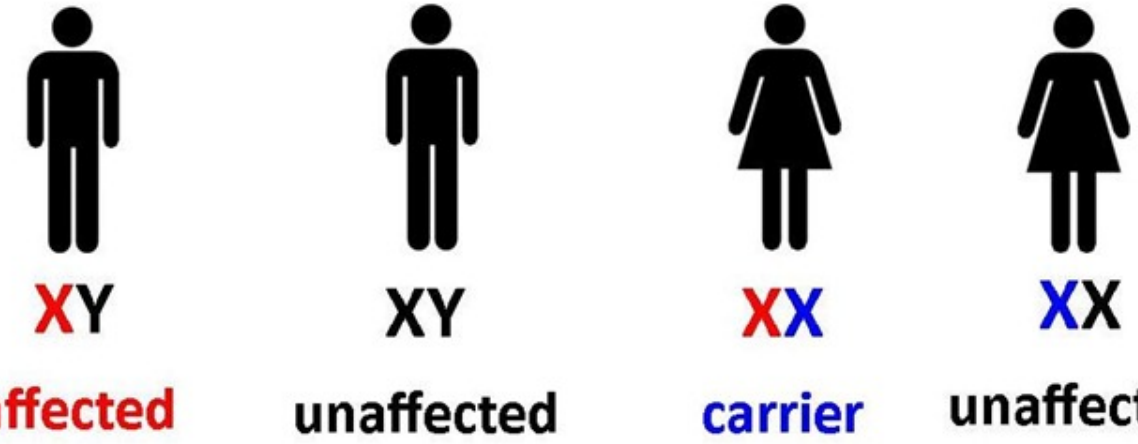
X-linked Genetic disease



X = Haemophilia

X = normal gene from mom

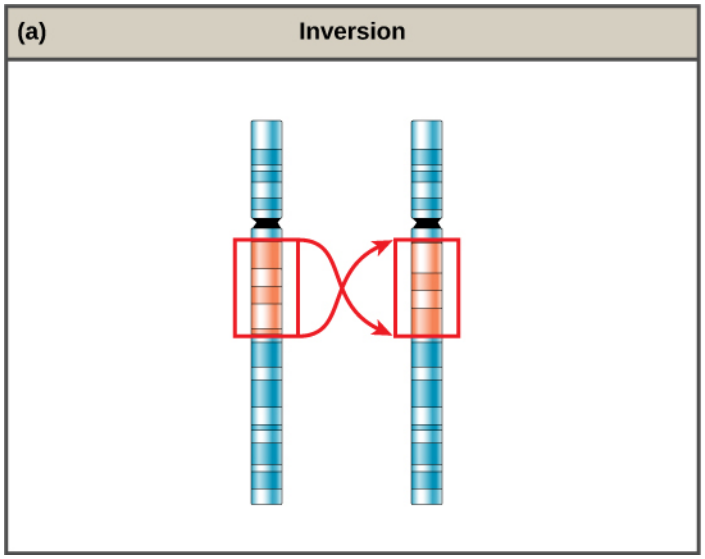
X = normal from dad

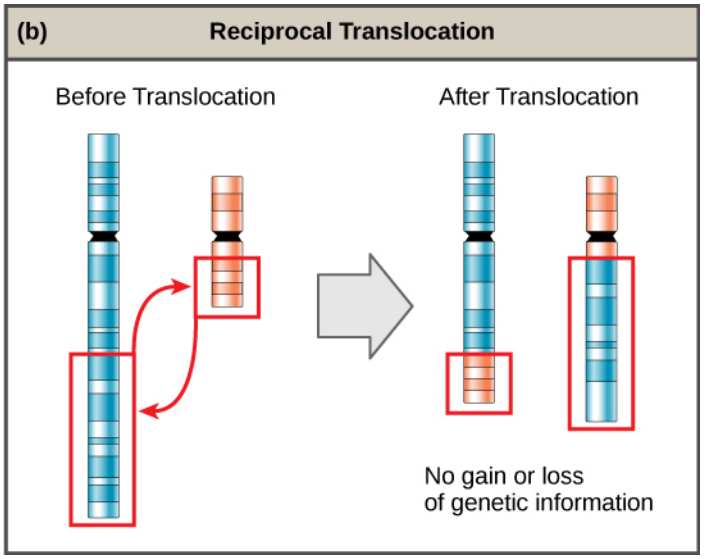


Women are carriers but generally don't have symptoms; only males affected

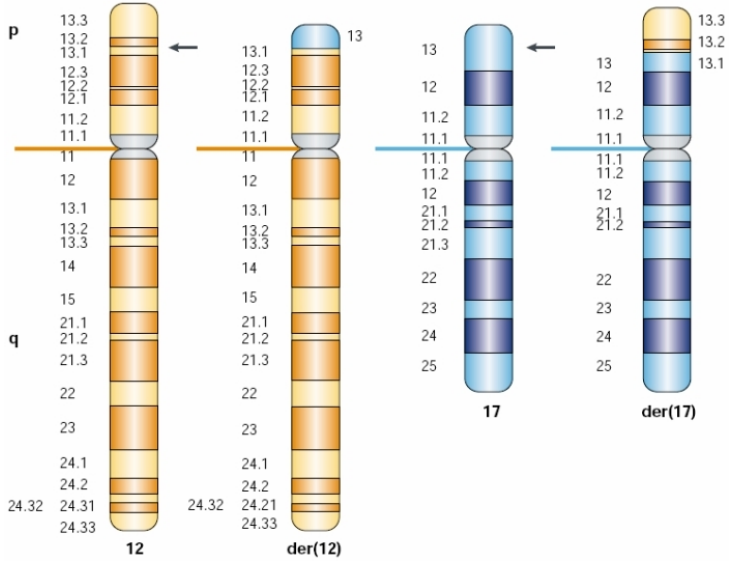
Chromosome Rearrangements

Inheritable but pattern random



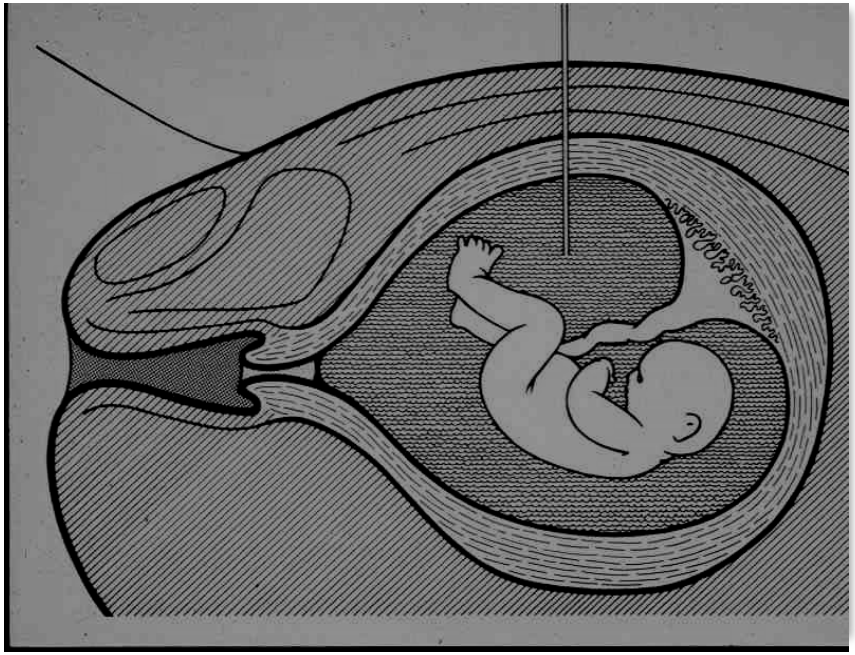


46,XX,t(12;17)(p13;p13)

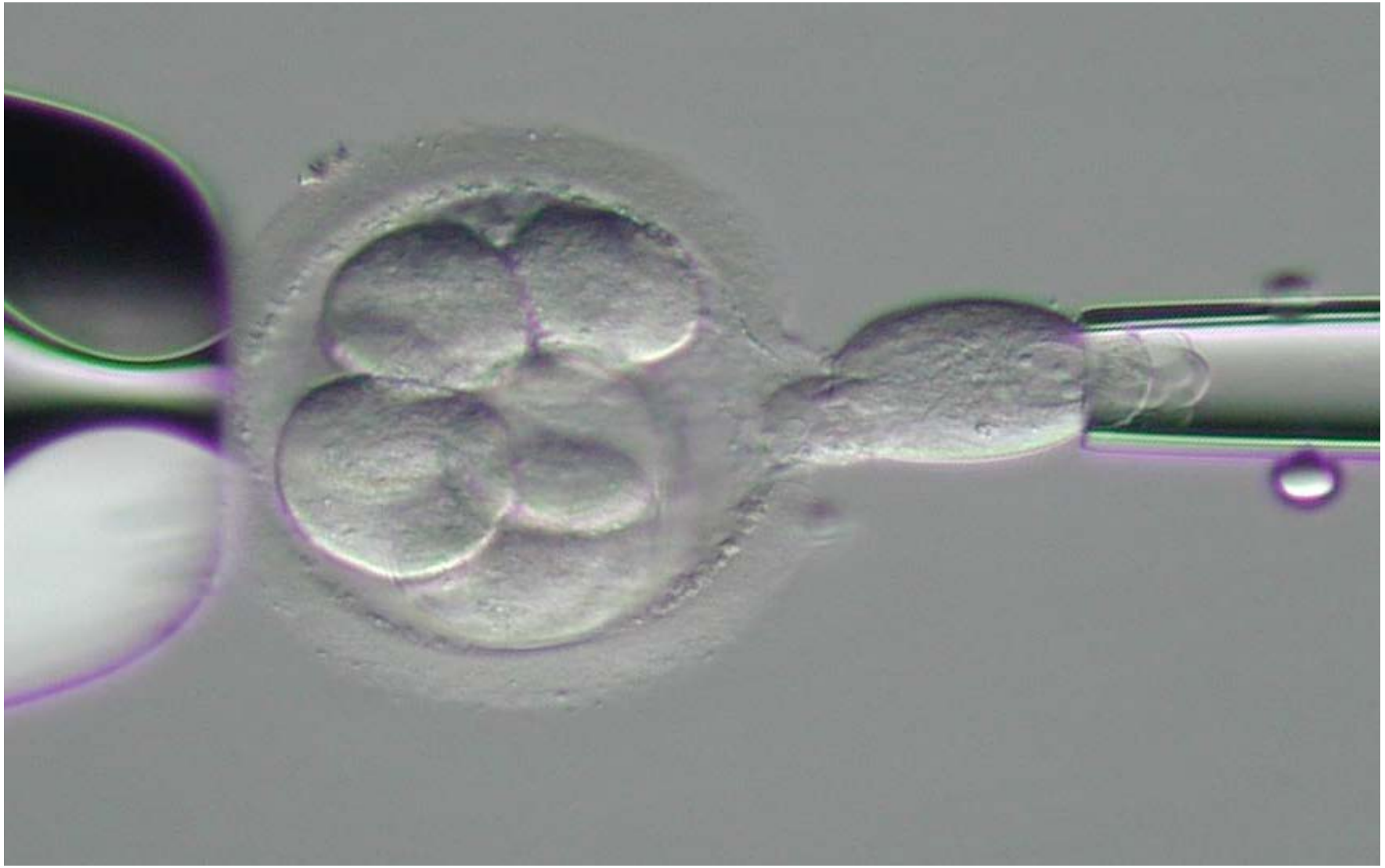


Reproductive options for those with serious recurrent genetic risk

- Reproductive roulette
- Gamete donation
- Adoption
- Remain childless
- Prenatal diagnosis and termination of pregnancy



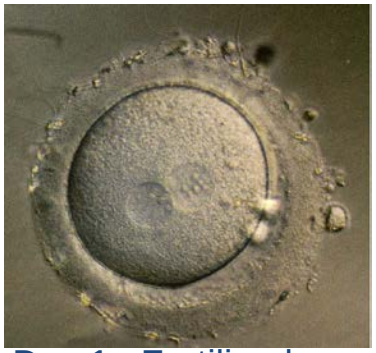
Preimplantation Genetic Testing



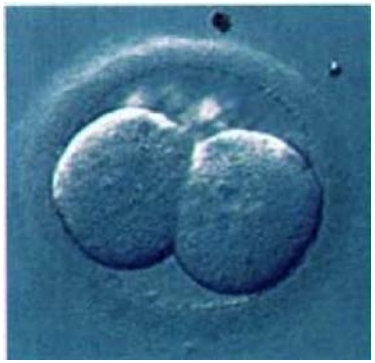
Preimplantation Genetic Testing

Detection of genetic information in an embryo made by examining a representative sample taken at a preimplantation stage of development

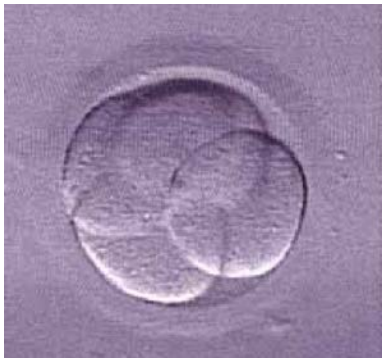
Early human development *in vitro*



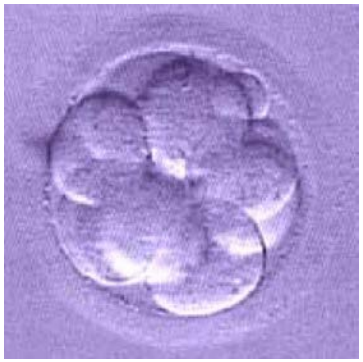
Day 1 Fertilised egg



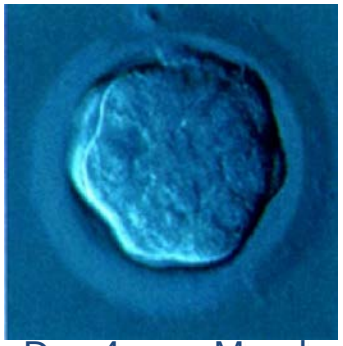
Late Day 1 2-cells



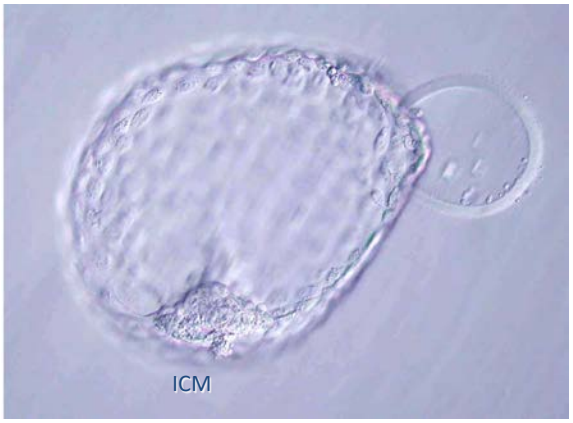
Day 2 4-cells



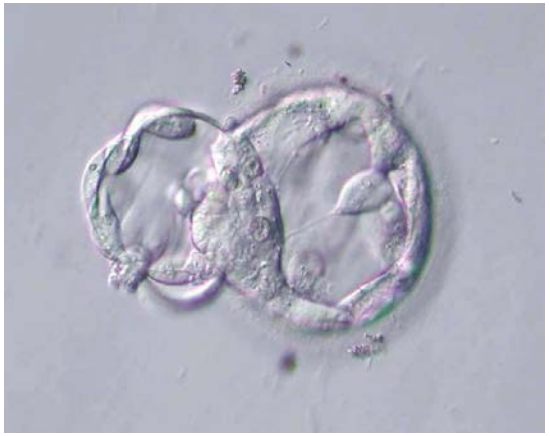
Day 3 8-cells



Day 4 Morula



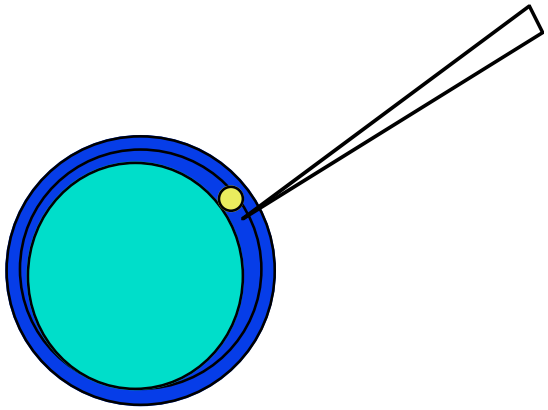
Late Day 6 Hatched blastocyst



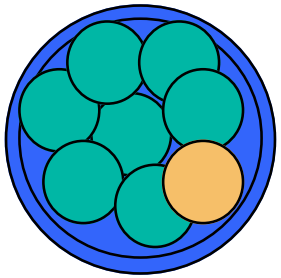
Day 6 Hatching blastocyst

Day 5 Blastocyst

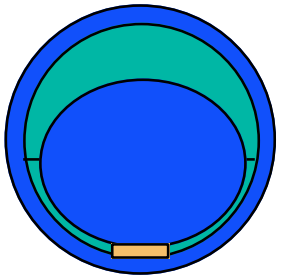
Tissues for Preimplantation Biopsy



egg



cleavage stage

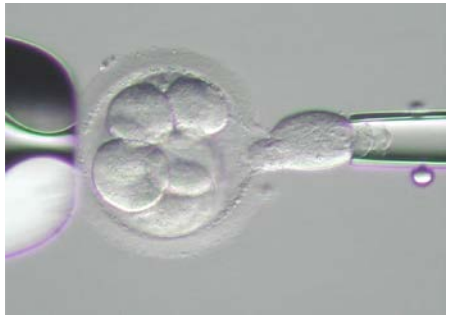


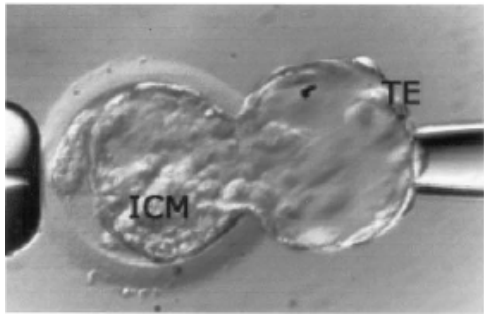
blastocyst

Polar Body

Blastomere

Trophectoderm





Two kinds of genetic risk
Two kinds of genetic test

Recurrent: **PGD**

As a result of inherited disorders

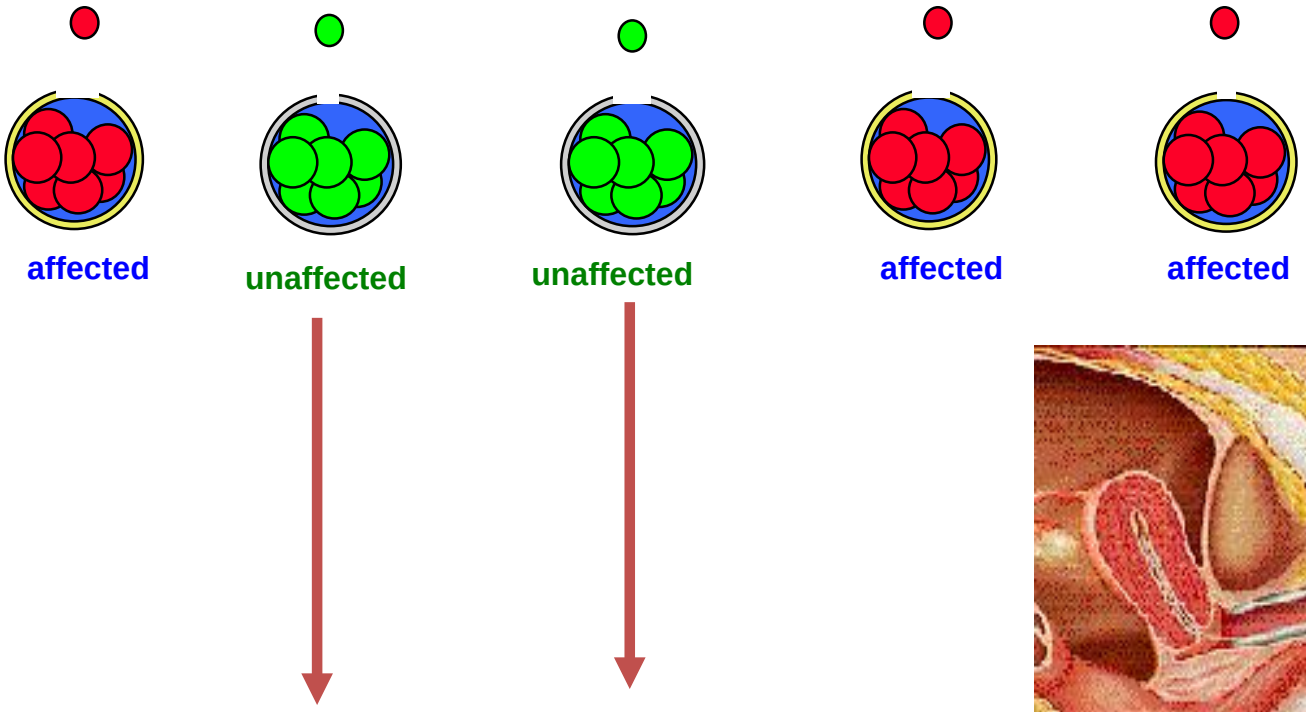
To diagnose known genetic condition

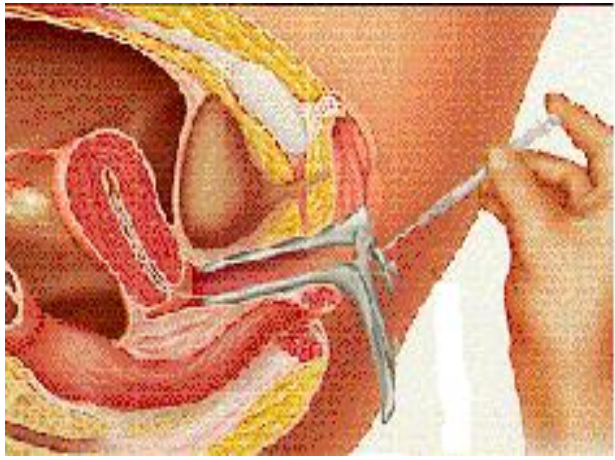
Sporadic: **PGS**

Random, often age related

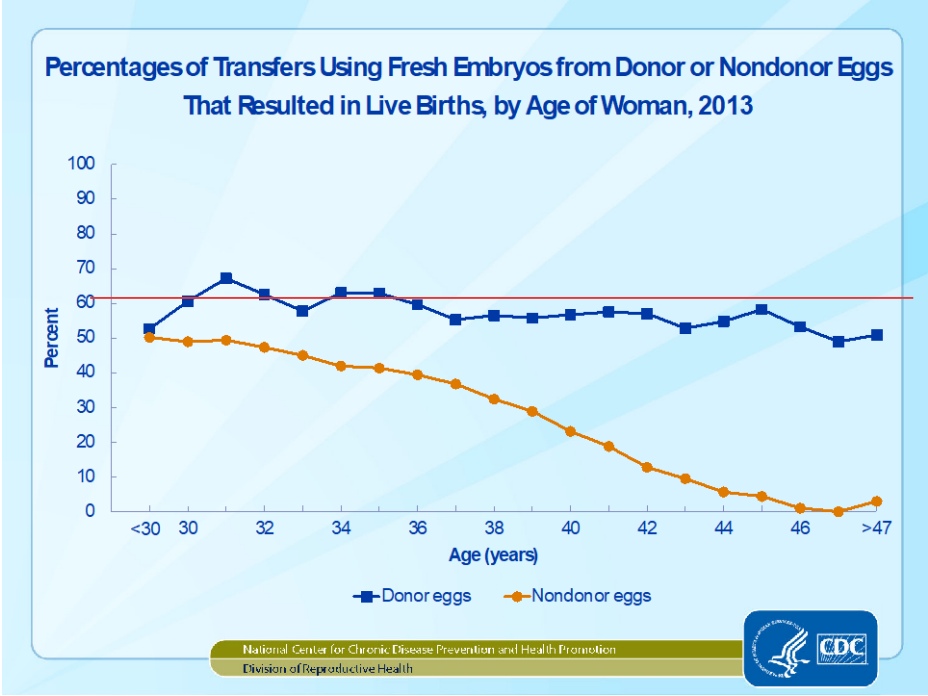
To screen for random aneuploidy to improve infertility outcome

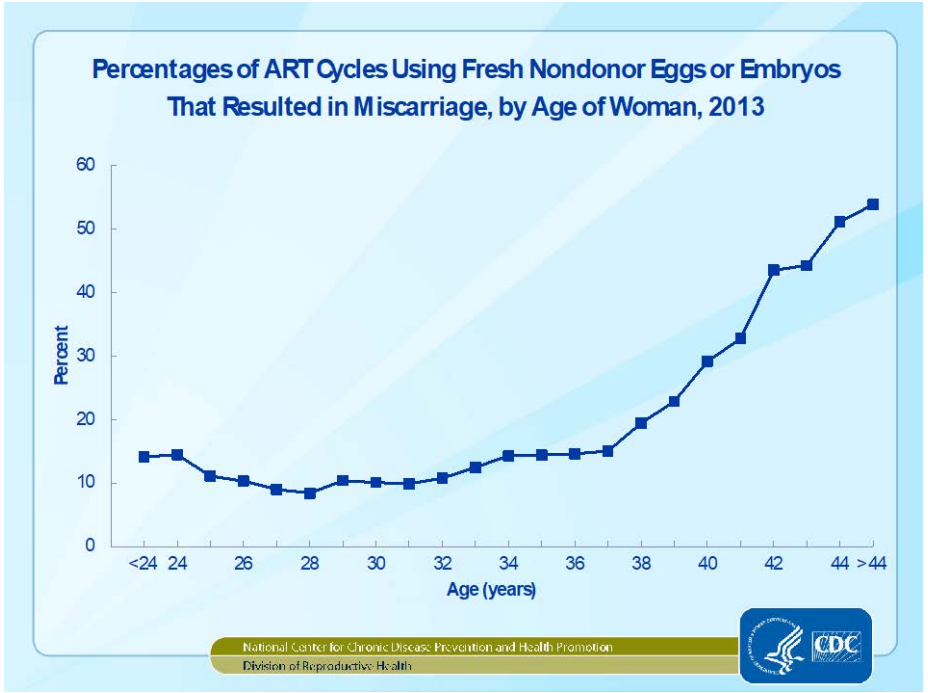
The principle of PGD





Sporadic Genetic Risk & Infertility Theory for use of PGS





To improve chances of conception through IVF for women of older age and for those with IVF failure or repeated miscarriage by screening for random aneuploidies

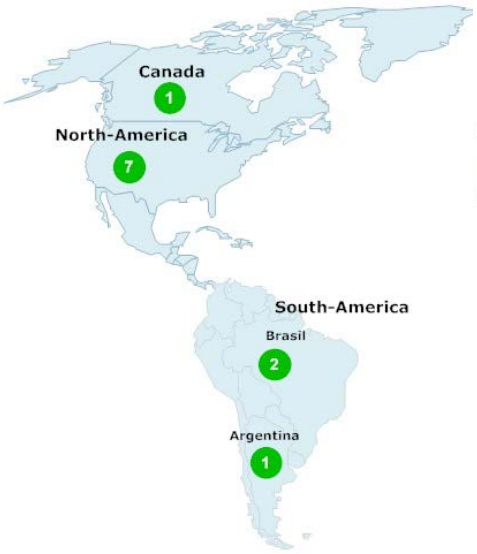
“The extent to which beliefs are based on evidence is very much less than what believers suppose.”

Bertrand Russell

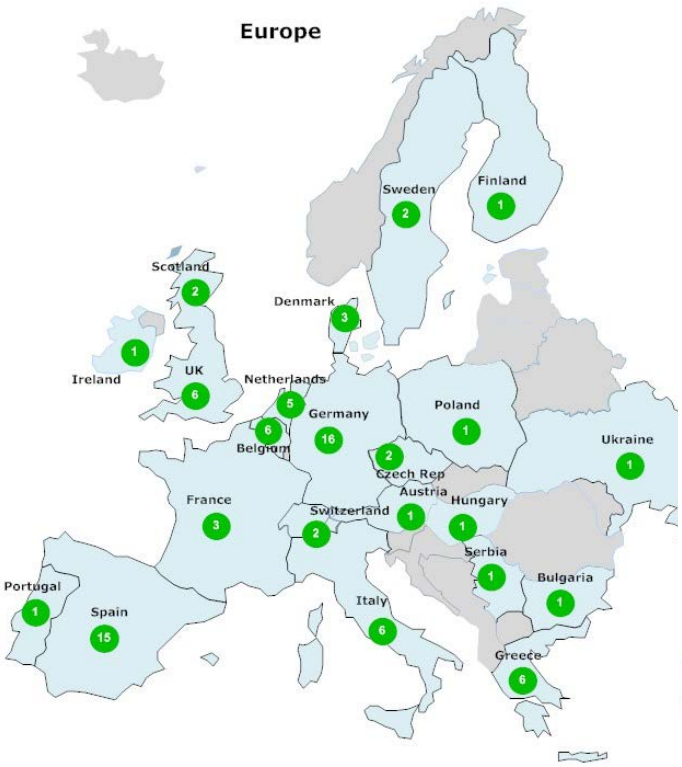
ESHRE PGD Consortium members by country

(June 2015)

Total number of centres: 124



number of centres: 11



number of centres: 86

number of centres: 27

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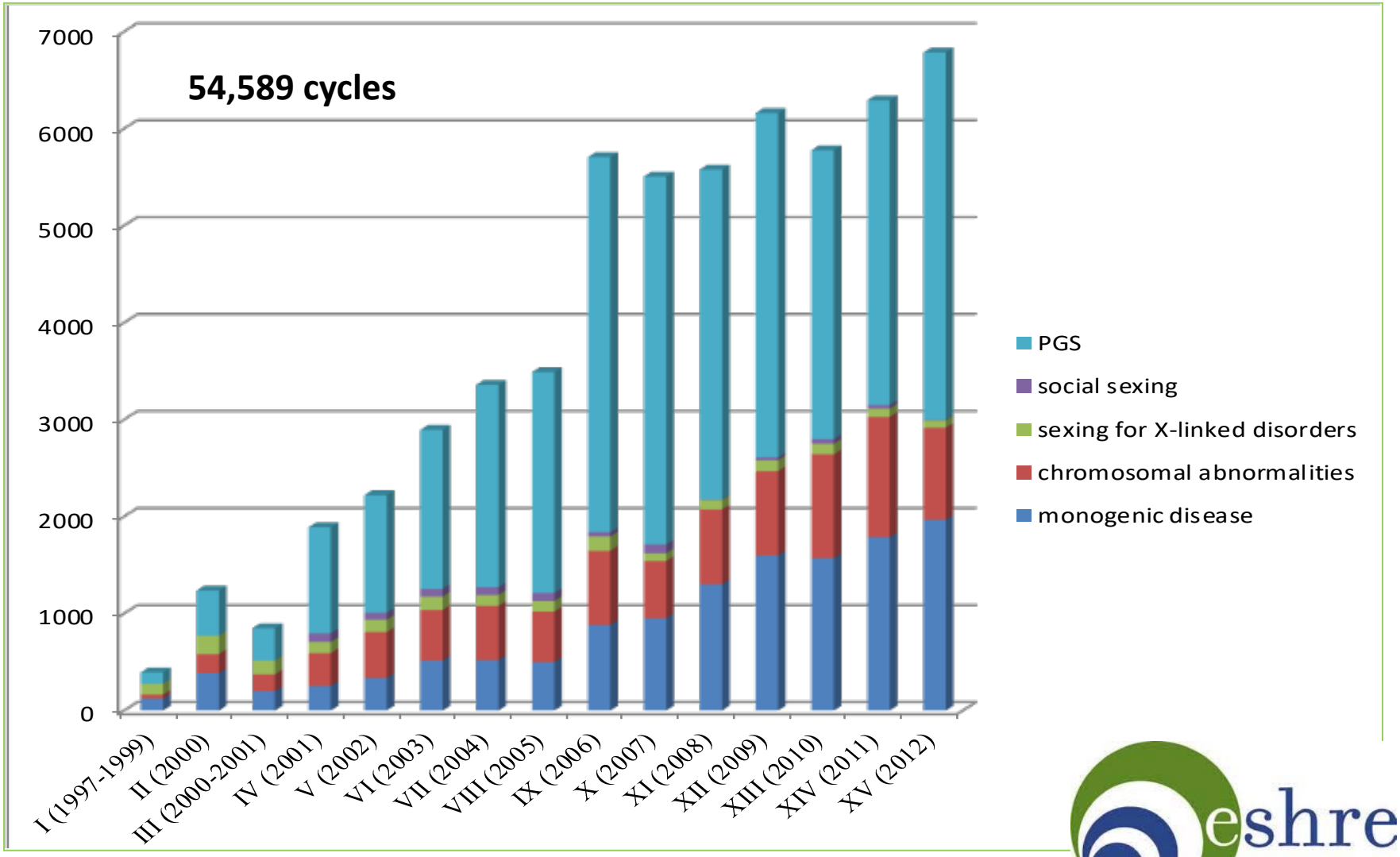
MOVING SCIENCE

Indications PGD & PGS



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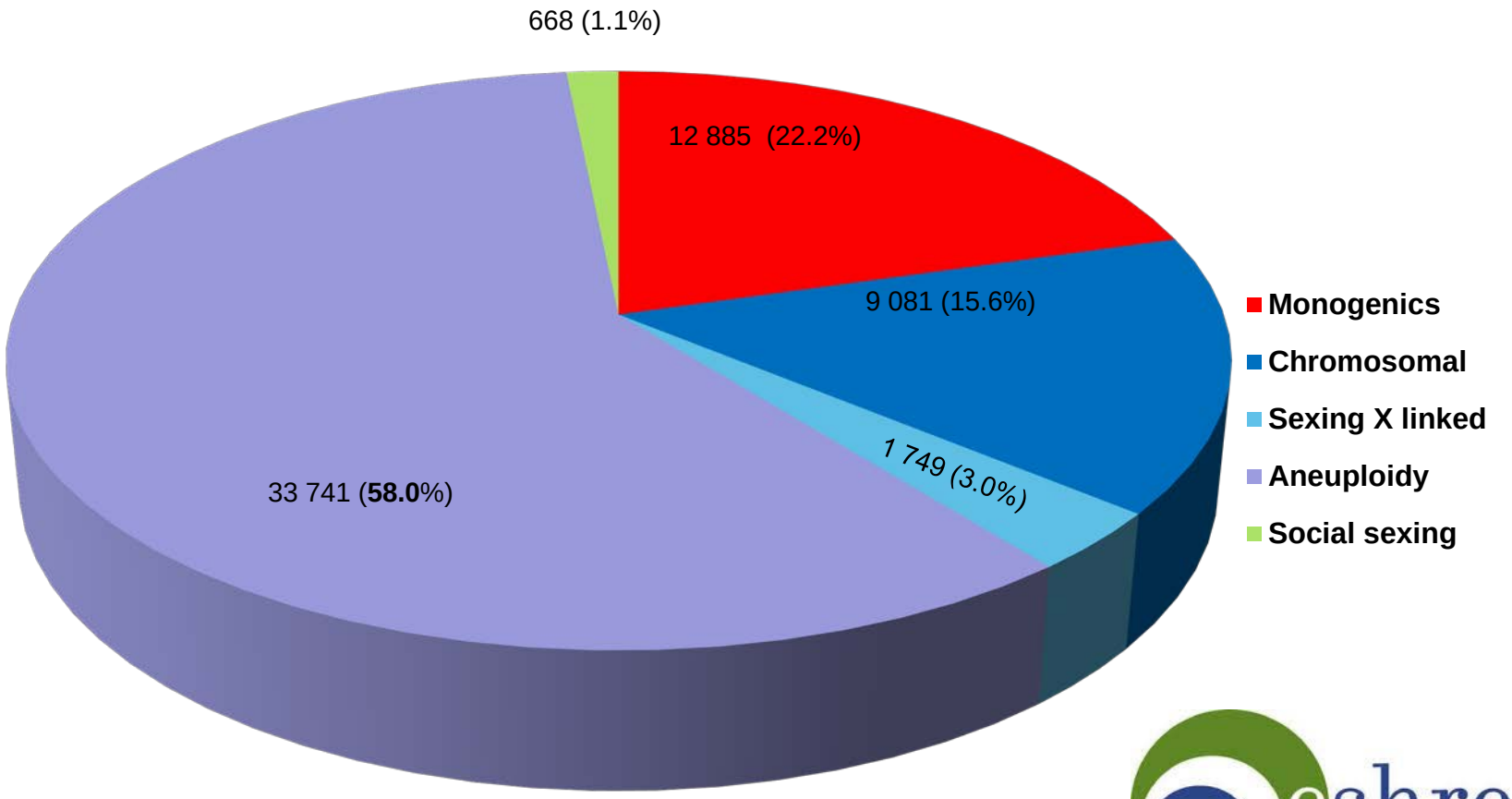
ESHRE 2015 Coonen: Unpublished and still to be verified data

REASONS FOR EMBRYO BIOPSY

ESHRE Consortium data I-XV

Based on 54,589 cycles



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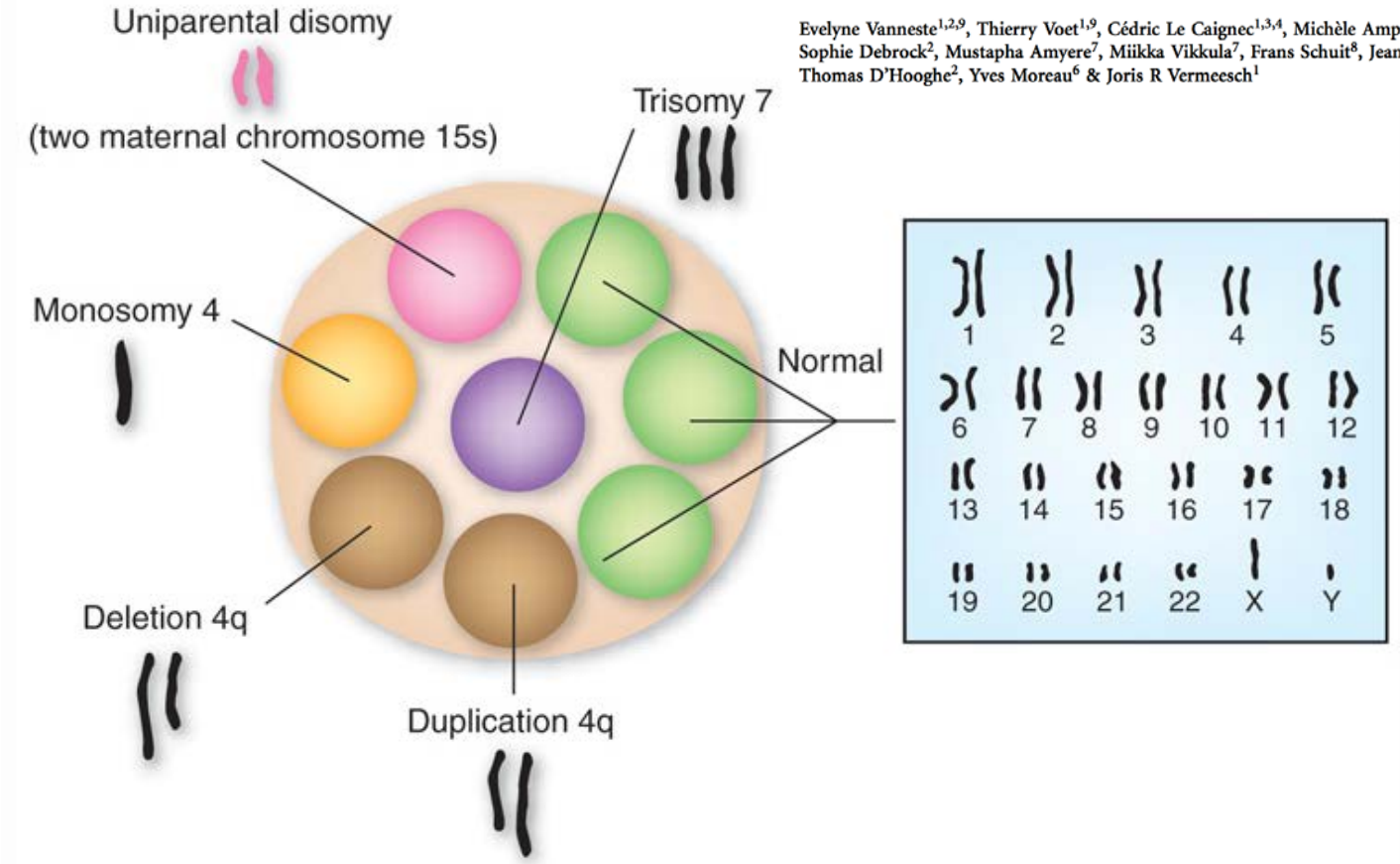
ESHRE 2015 Coonen: Unpublished and still to be verified data

Cleavage stage mosaicism

Chromosome instability is common in human cleavage-stage embryos

Evelyne Vanneste[1,2,9], Thierry Voet[1,9], Cédric Le Caignec[1,3,4], Michèle Ampe[5], Peter Konings[6], Cindy Melotte[1], Sophie Debrock[2], Mustapha Amyere[7], Miikka Vikkula[7], Frans Schuit[8], Jean-Pierre Fryns[1], Geert Verbeke[5], Thomas D'Hooghe[2], Yves Moreau[6] & Joris R Vermeesch[1]



Chaos in the embryo

David H Ledbetter

The chromosomes of human embryos seem to be more unstable than previously thought. An analysis of embryos derived from *in vitro* fertilization reveals high rates of structural abnormalities (pages 577–583).

nature medicine

15, 490 - 491 (2009)

B. K. BANGASH/AP

SEISMOLOGIST DELAYED EN ROUTE TO PAKISTAN
Quake researcher fights for access to rare data in the stricken Himalayas.
www.nature.com/news

Biologists forced to reassess embryo test

MONTREAL

A technique for detecting genetic abnormalities in embryos is itself coming under the microscope. Preimplantation genetic diagnosis (PGD) is used in fertility treatment to check the condition of an embryo before it is implanted in a mother's womb. But studies now suggest that there is still much to learn about the procedure.

The findings suggest that genetically 'abnormal' embryos could still give rise to normal embryonic stem-cell lines. And they lend urgency to a newly launched effort to track the safety of the procedure, which is becoming increasingly popular but is regulated differently around the world.

In PGD, a cell is taken from the embryo at the eight-cell stage and tested for genetic abnormalities. If the cell is given the all-clear, the embryo is implanted in the mother's uterus. Babies born after the procedure seem to be fine, but few data have been collected on the children later in life.

genetic abnormalities in younger women who donate eggs to infertile couples. That led some specialists, such as Jeffrey Nelson of the Huntington Reproductive Center in Pasadena, California, to suggest that the technique should be used more widely. "You can make an argument that PGD should be done in younger women", not just older women, he says.

But the most intriguing findings presented at the conference suggest that embryos diagnosed as abnormal might be able to correct their genetic defects as they grow. A team including Santiago Munné of Reprogenetics, a company specializing in PGD based in West Orange, New Jersey, grew 55 embryos previously diagnosed as abnormal to the preimplantation stage, called the blastocyst. They found that many of the embryos' cells were genetically normal. One embryo contained 76% normal cells after 12 days in culture. On

48% of cells tested normal at blastocyst stage

"These results suggest that we could get normal stem cells from abnormal embryos."

could get normal stem cells from abnormal embryos," says Munné. "These embryos will never implant, so this is ethically the best way of making them."

But the results also raise questions about whether cells that are not directly sampled by PGD are actually defective. If they aren't, the potential of these embryos remains unclear. "These really are all important data we have to get from PGD," says Paulette Browne, a reproductive endocrinologist at the Shady Grove Fertility Center in Virginia. "It could be that some of the cells are abnormal and some are not, and we're starting to collect the rest of those data right now."

Together, the latest studies highlight the importance of a new effort to accumulate data on PGD, described at this week's meeting. Scientists and policy analysts announced the creation of a US database to track the safety of

The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

Healthy Babies after Intrauterine Transfer of Mosaic Aneuploid Blastocysts

N Engl J Med 2015; 373:2089-2090 | November 19, 2015 | DOI: 10.1056/NEJMc1500421

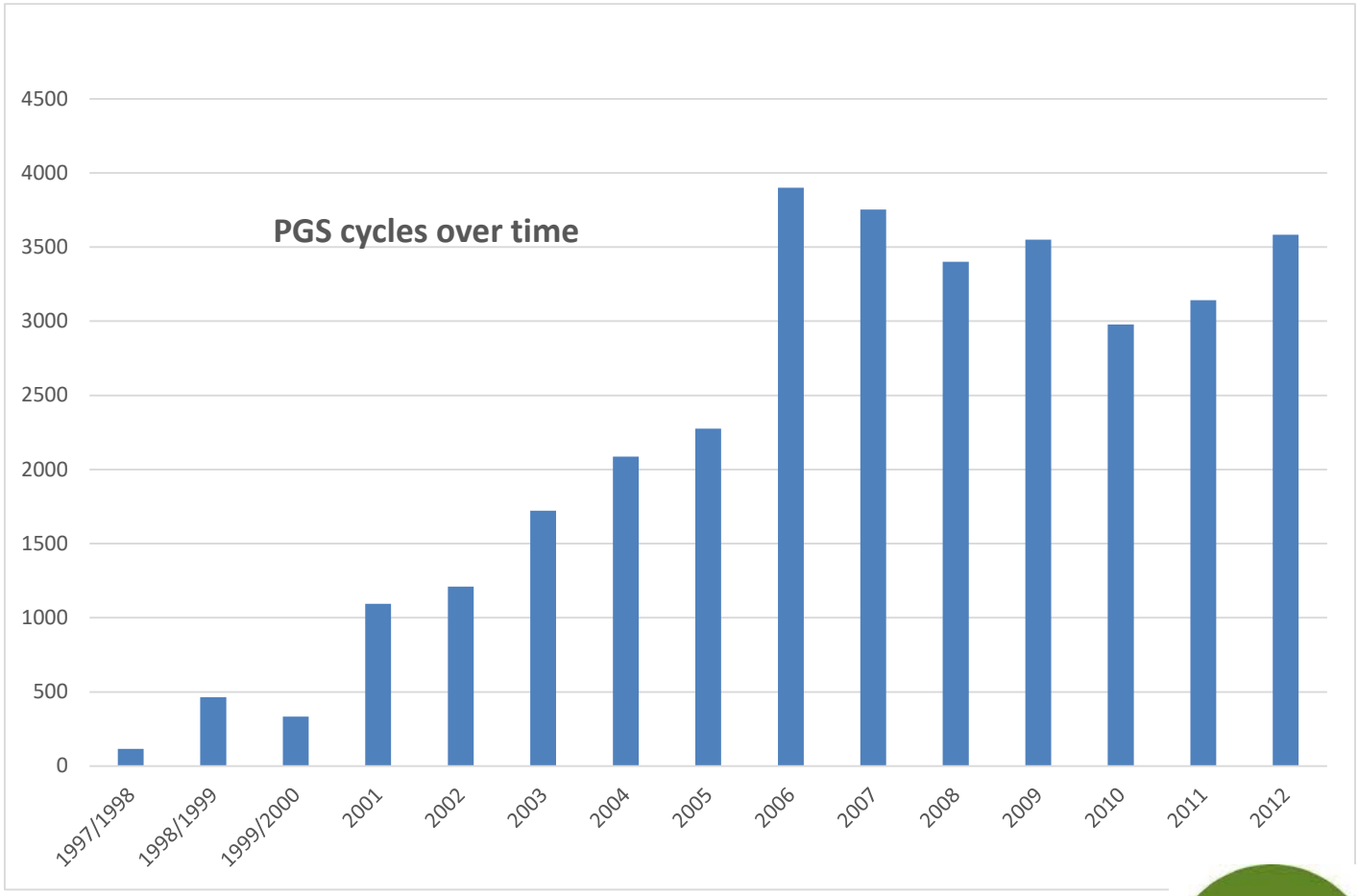
Ermanno Greco, M.D.
Maria Giulia Minasi, M.Sc.
Francesco Fiorentino, PhD.
European Hospital & Genoma Molecular Genetics Laboratory
Rome, Italy

In the light of recent re-evaluations of the risk benefit ratio, it seems that PGS has been oversold

"Rather than improving outcome for childless couples, PGS encourages the waste of healthy embryos which are excluded from transfer to the uterus."

"The procedure just appears to increase costs and complexities of IVF. Its utilization, at present, should therefore be acknowledged as highly experimental and refuted in routine IVF care."

Number of PGS cycles reaching a plateau?



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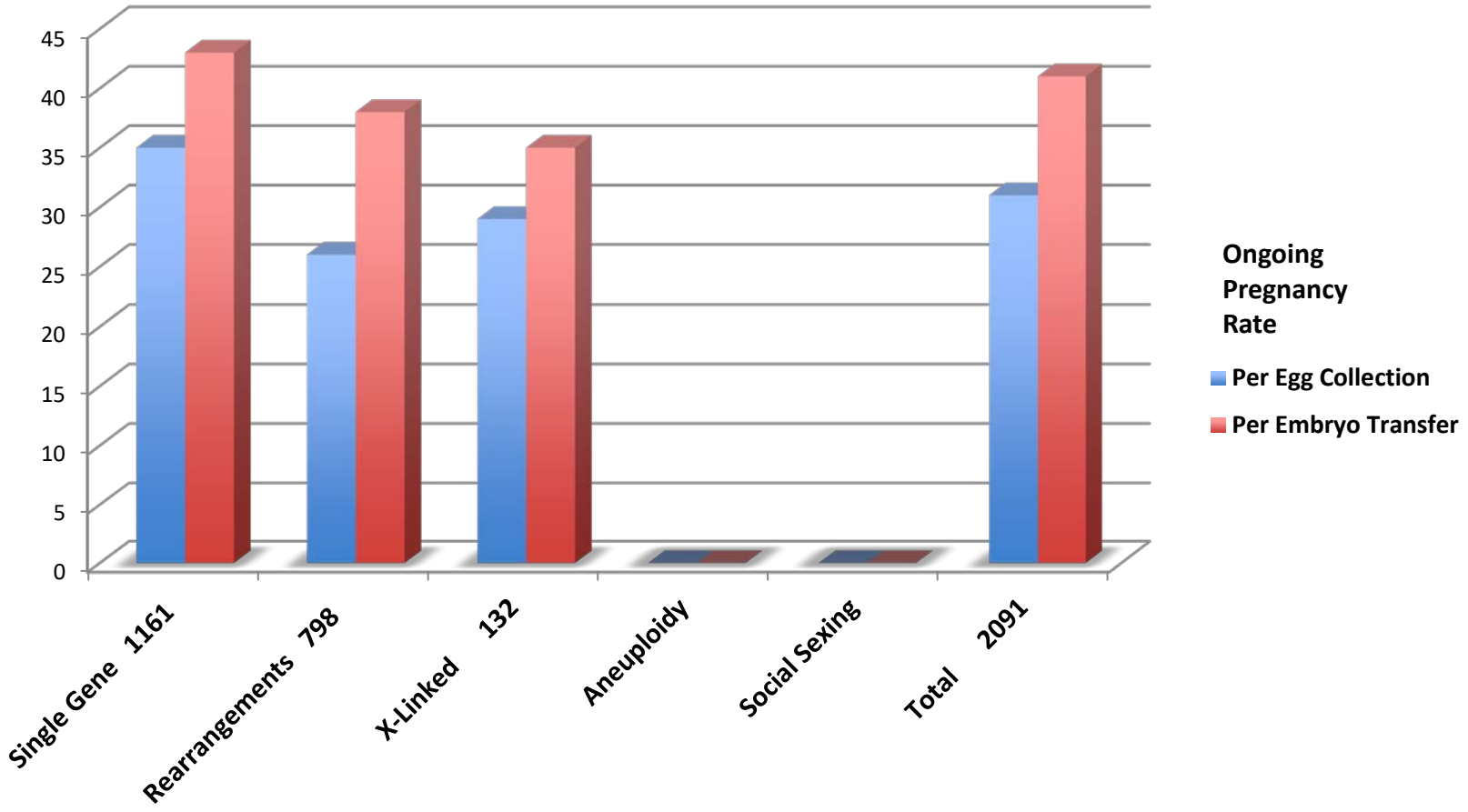
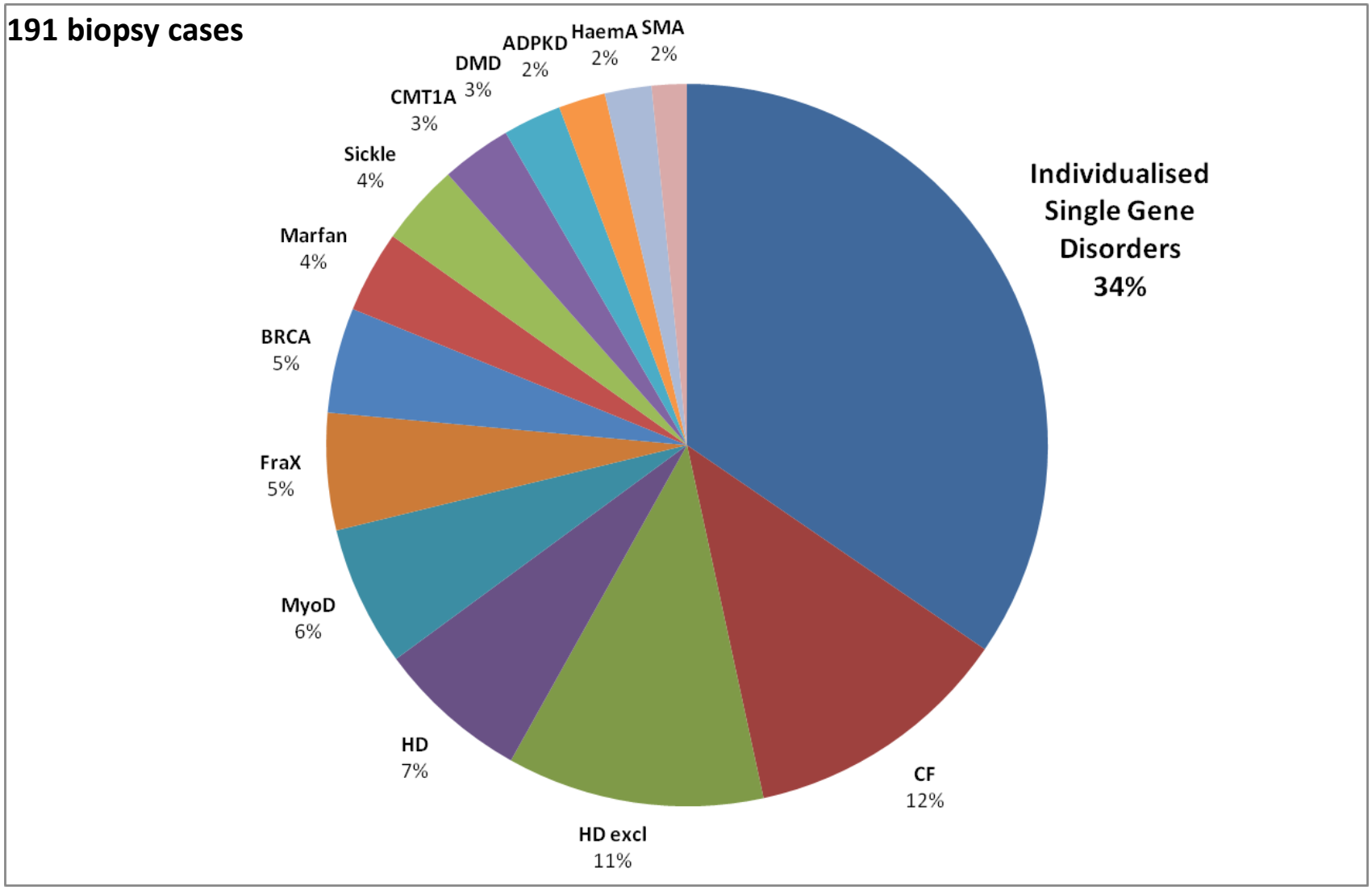
ESHRE 2015 Coonen: Unpublished and still to be verified data

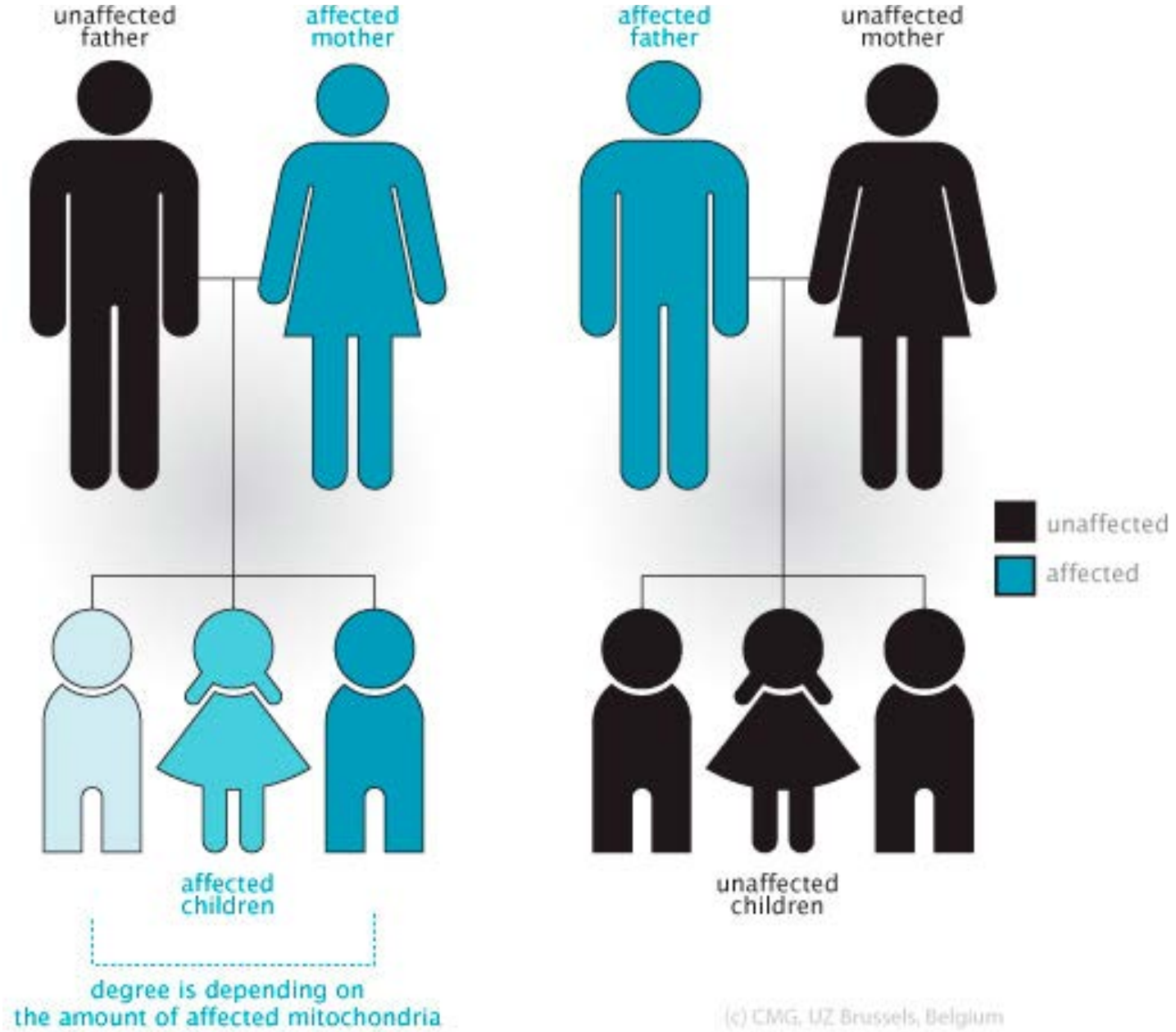
Results of 2091 cycles in one PGD only centre (1998 -2014)

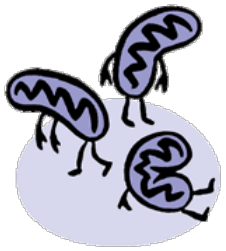


Range of SGD Cases for 2014



Genetic disease due to mtDNA mutations (maternally inherited – in the egg)

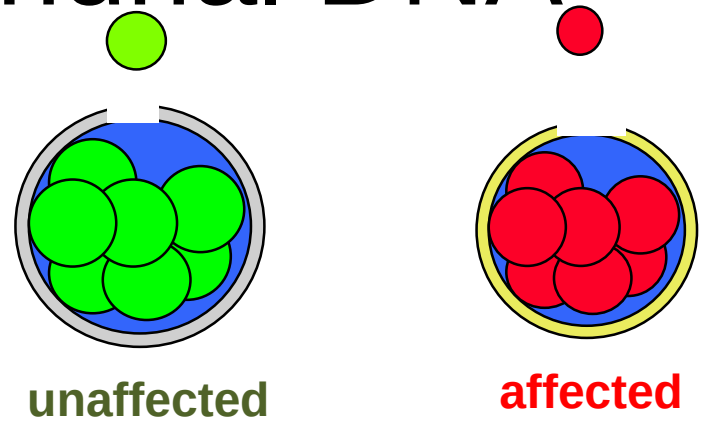




PGD for Nuclear DNA is Different from testing Mitochondrial DNA

Nuclear DNA

Bad gene present or not present

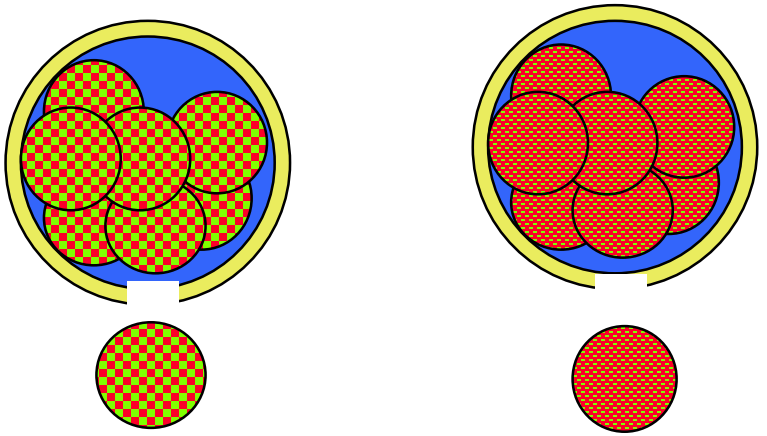


unaffected

affected

Mitochondrial DNA (mtDNA)

Mixture of mutated and normal mtDNA (heteroplasmy) in each cell

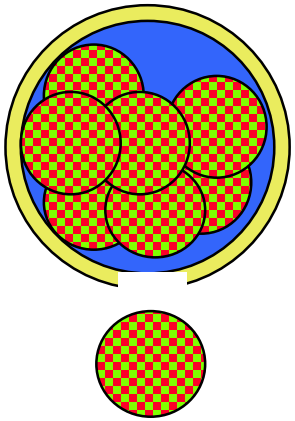


Less likely to be affected

More likely to be affected

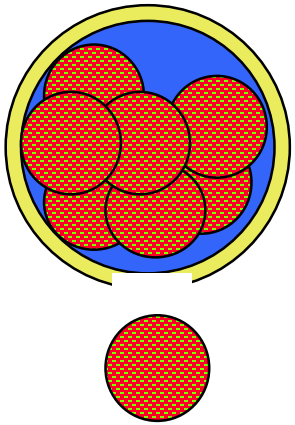
PGD for mtDNA mutations

PGD can work in heteroplasmy



Less likely to be affected

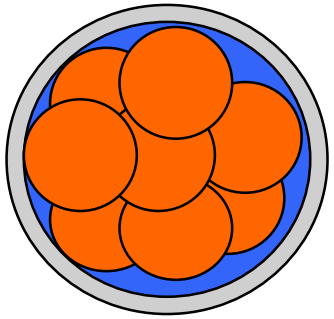
Unlikely <20%



More likely to be affected

Variable 20-50%

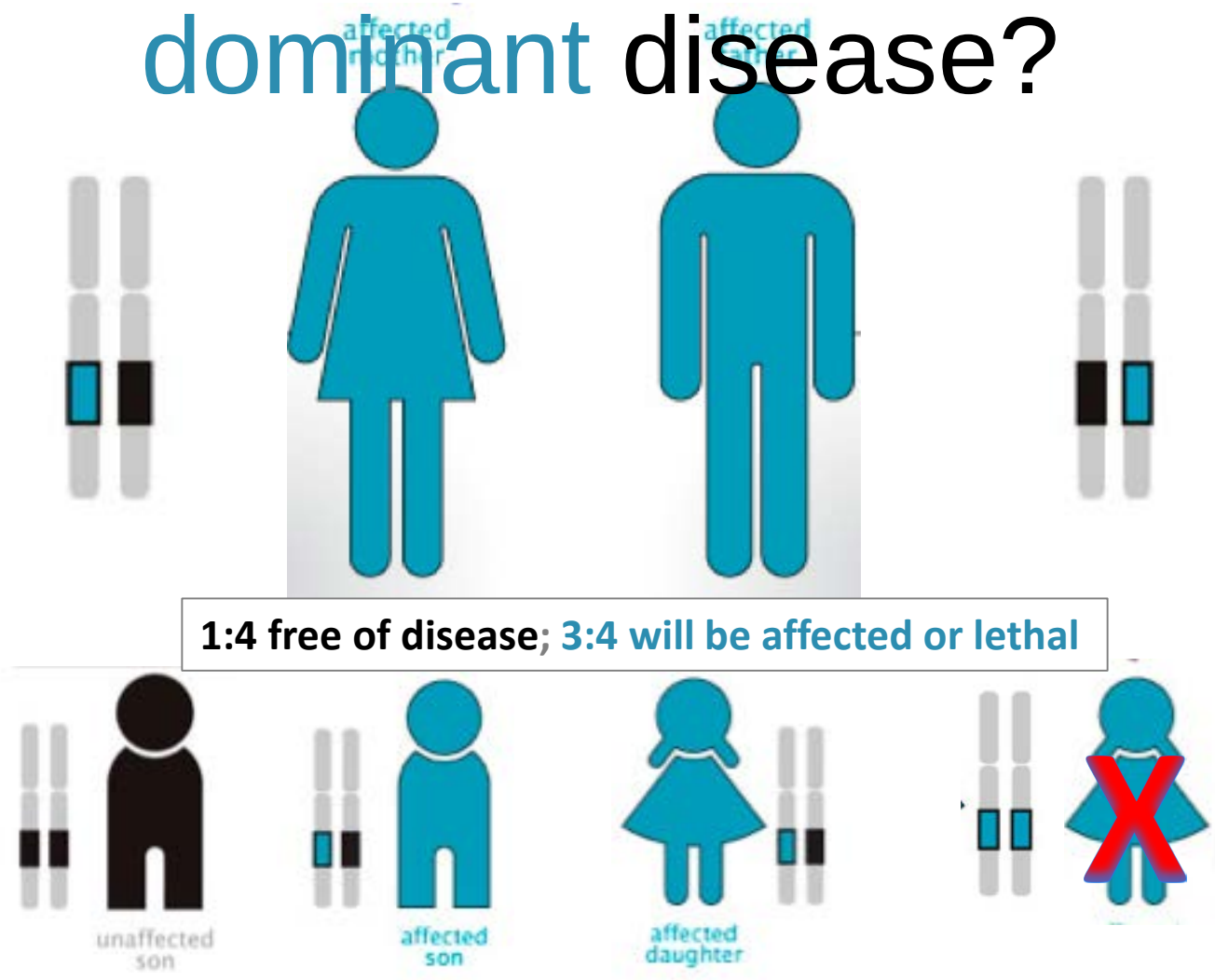
PGD inappropriate in homoplasmy



All children will be affected

What happens when both parents are affected by genetic disease?

What happens when both parents are affected by dominant disease?



What happens when both parents are affected by recessive disease?

Sickle cell disease, Cystic fibrosis, Spinal muscular atrophy, Fanconi Anaemia, Tay-Sachs disease