Great Ormond Street Hospital for Children NHS Foundation Trust

Genetics in PID and practical applications

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The child first and always

Primary immunodeficiency (PID)

- PID disorders are inherited conditions, which means the gene responsible for causing the disorder can be passed from parents to child
- Often caused by single –gene defect (mutation)
- Usually diagnosed during infancy or childhood
- Relatively rare but extremely diverse and serious
- Over 300 mutations have been identified so far
- PID diagnosis is life-changing in both the child affected and their families

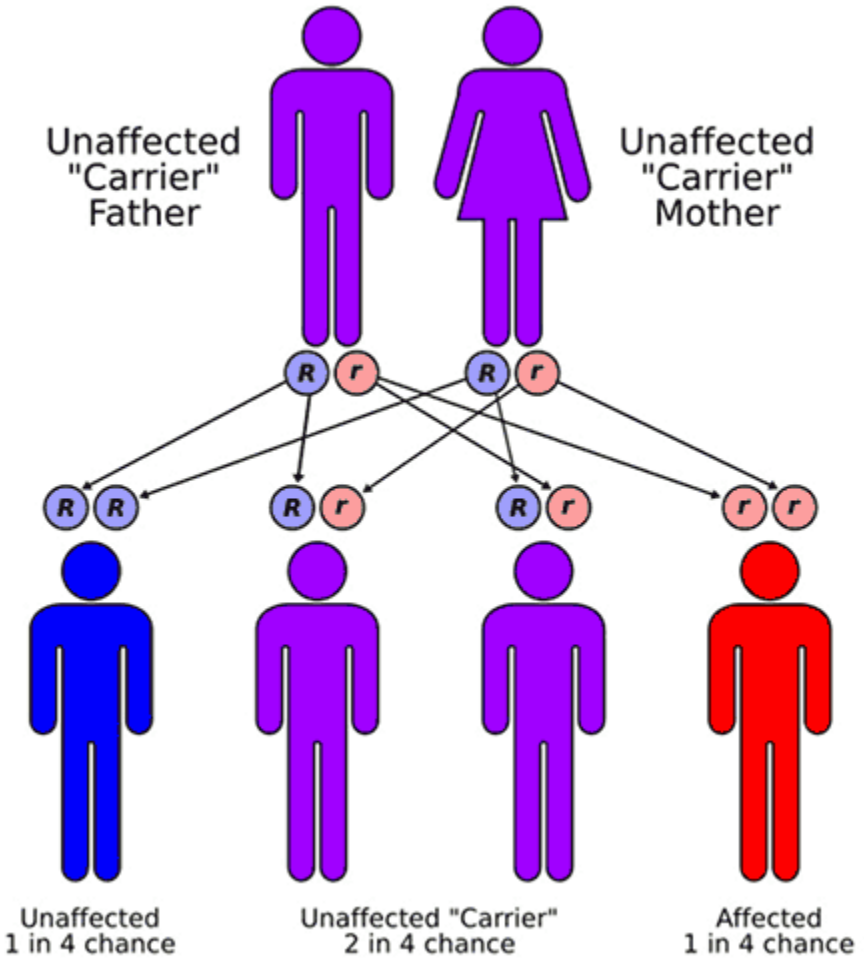
Pattern of inheritance

- Autosomal recessive inheritance
- X-linked pattern of inheritance
- Autosomal dominant inheritance
- De Novo mutation:
  - New mutation that occurred and that was not present in either parents

Autosomal recessive inheritance

- An individual, affected child, has inherited two abnormal copies of a gene, one from each parent
- Both parents are carriers of the faulty gene (mutation), they are also called heterozygous
- Autosomal recessive pattern of inheritance means that the condition can be passed on to both boys and girls
- Often no family history

Autosomal recessive inheritance



Autosomal recessive inheritance

Summary

- 1 in 4: 25% chance of having an unaffected and non carrier child
- 1 in 4: 25% chance of having an affected child
- 2 in 4 : 50% chance of having a carrier

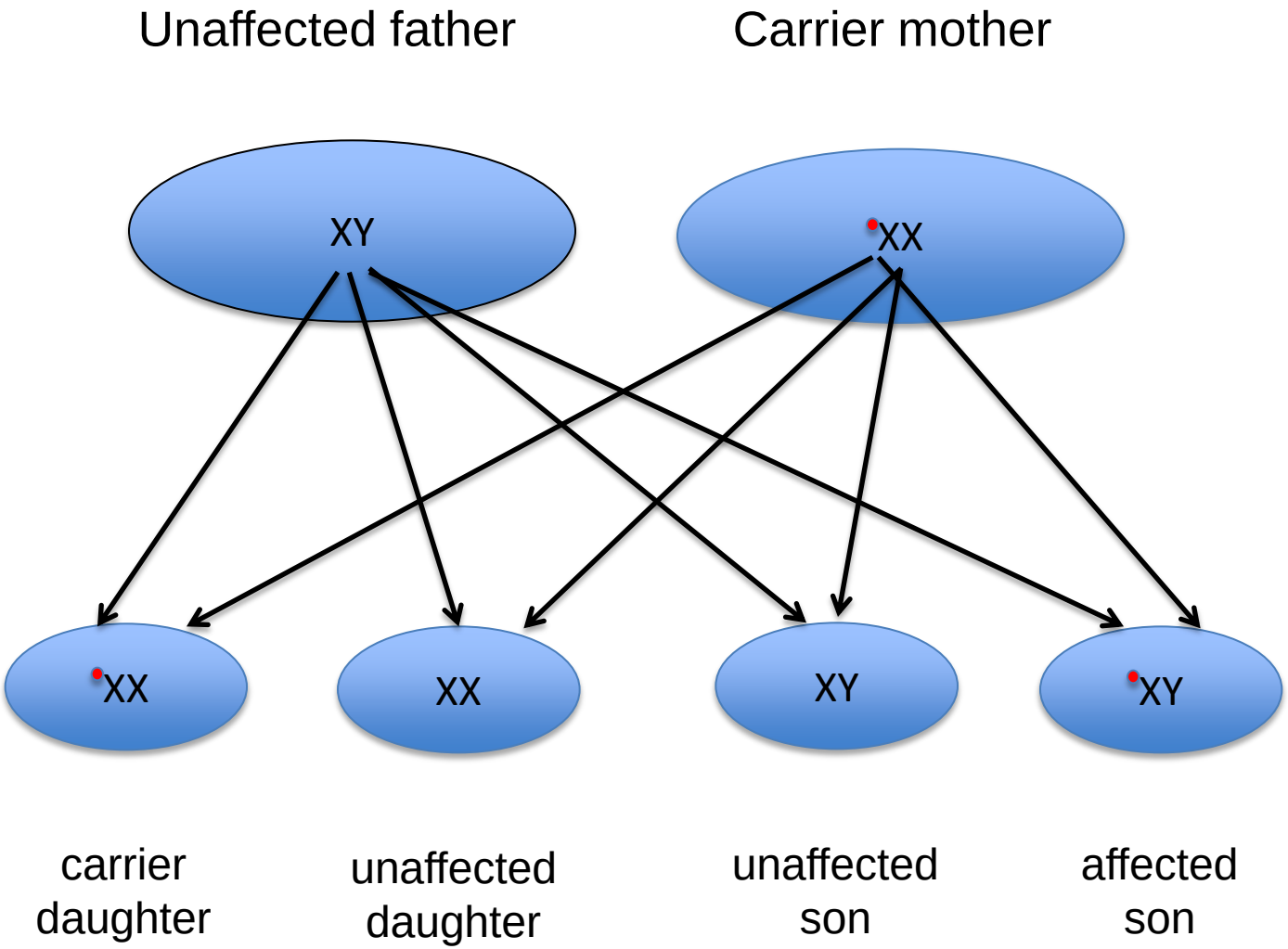
Autosomal recessive immunodeficiencies

- Several forms of severe combined immunodeficiency, ADA, PNP, RAG, JAK3, IL7R
- Several forms of Chronic granulomatous disease (CGD), p22,p47,p67 and p40
- Cartilage hair hypoplasia (CHH)
- LRBA (lipopolysaccaride responsive beige-like anchor protein
- Leucocyte adhesion deficiency (LAD)
- Familial forms of haemophagocytic lymphohistiocytosis (HLH)
- Ataxia-Telangiectasia

X-Linked inheritance

- Mutations are in a gene on the X chromosome
- Almost exclusively affect boys only, as males have only one X chromosome
- Females are unaffected carriers (with some exceptions like XCGD)
- Females are unaffected because their second X chromosome carries the normal gene and compensates for the affected gene
- No male - to - male transmission

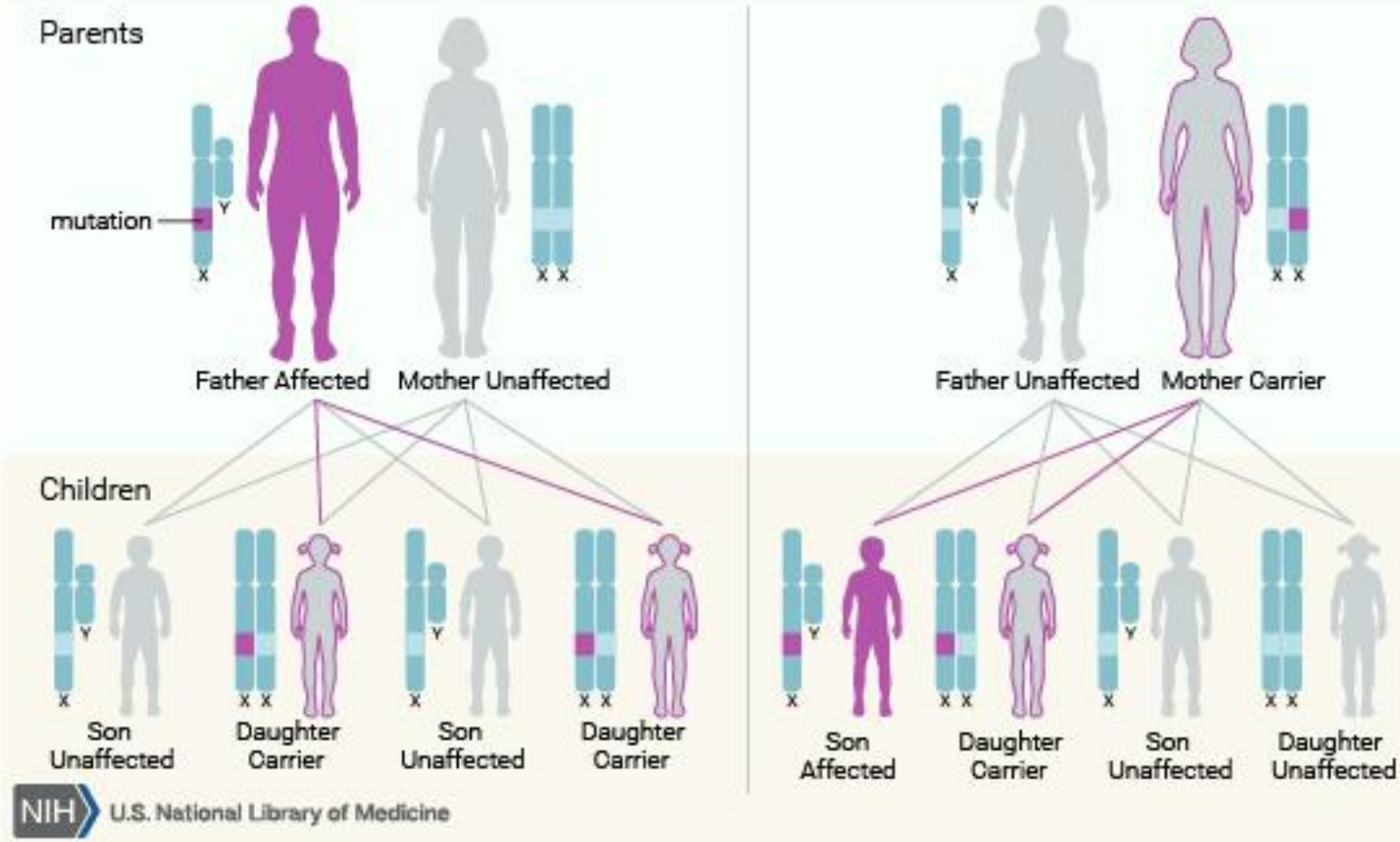
X-linked inheritance



X-linked inheritance

- Carrier female: 1 in 4 or 25% chance
- A non carrier or Normal female: 1 in 4 or 25% chance
- A heathy male 1 in 4 or 25% chance
- **An affected boy: 1 in 4 or 25% chance**

X-Linked Recessive



X-linked immunodeficiencies

- X-CGD
- X-SCID
- Wiskott-Aldrich syndrome (WAS)
- X-linked hyper IgM (CD40 ligand)
- X-linked inhibitor of apoptosis (XIAP) disease
- X-linked lymphoproliferative disease (XLP)
- X-linked agammaglobulinemia (XLA)

Autosomal dominant inheritance

- Rare
- One abnormal gene is sufficient to cause the disorder
- Both boys and girls are equally affected
- Variable penetrance
- Examples:
  - Hyper IgE syndrome due to STAT3 mutation,
  - Autoimmune lymphoproliferative syndrome (ALPS), FAS mutation

Carrier and Prenatal Testing

- Non-invasive testing
  - Ultrasound scanning
  - **Free fetal DNA analysis**
- Invasive testing
  - Chorionic villus sampling (CVS)
  - Amniocentesis
  - Fetal tissue biopsy e.g blood, skin muscle (these tests are uncommon)

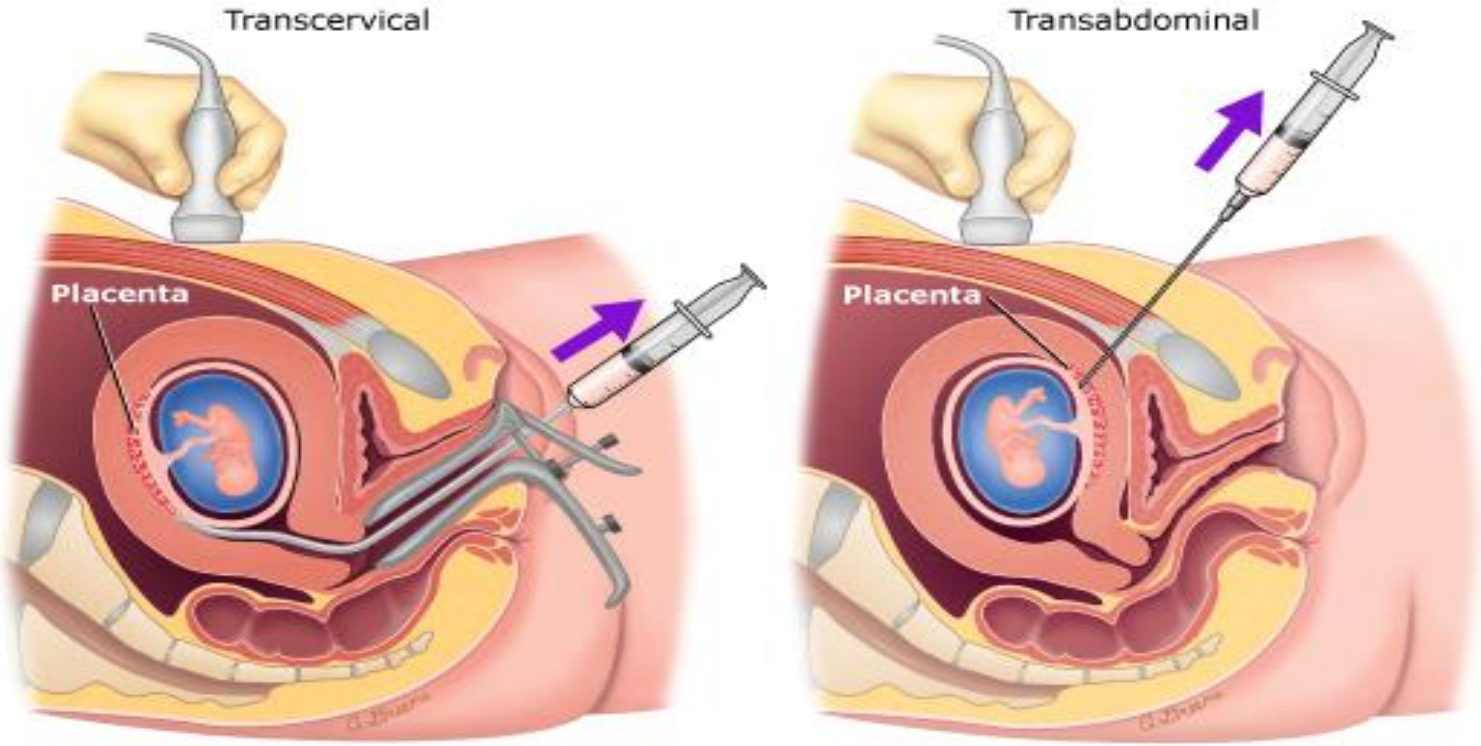
Free fetal DNA analysis

- Non invasive
- Maternal blood can be taken as early as 8-9 weeks of gestation
- Usually performed in conjunction with ultrasound scan
- 99% reliability results
- Its not widely available
- Benefit to carrier mothers for an x-linked disorder only

Chorionic villus sampling

- CVS is usually scheduled at 10-13 week of pregnancy, most centre perform this around just over 11 weeks
- A small sample is taken from the developing placenta tissue which directly arises from the growing foetus
- Transabdominal CVS,
- Transcervical CVS
- *Results usually are back within three days*
- Very accurate results
- Risk of miscarriage, 0.5%-1%

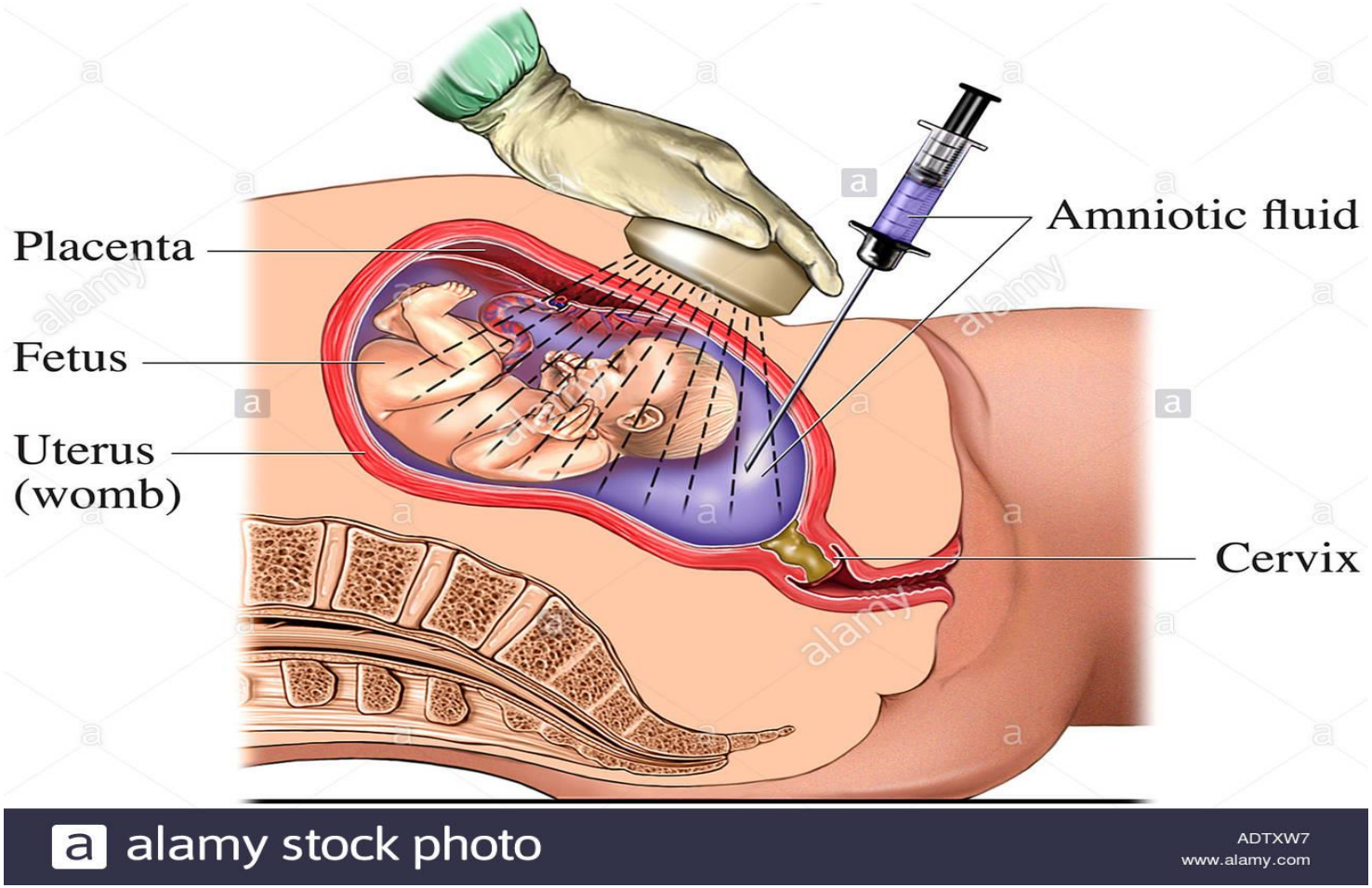
CVS testing



Amniocentesis

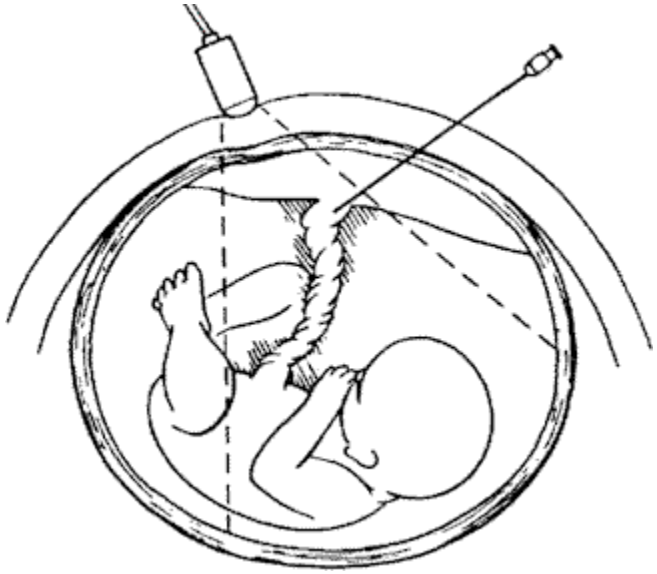
- It’s usually done in second trimester from 15 weeks and beyond
- A sample is taken from amniotic fluid which surrounds the growing foetus which contains foetal cells
- Results are very accurate,
- Amniocentesis also carries a risk of miscarriage, which estimated to be 0.5% to 1%

Amniocentesis testing



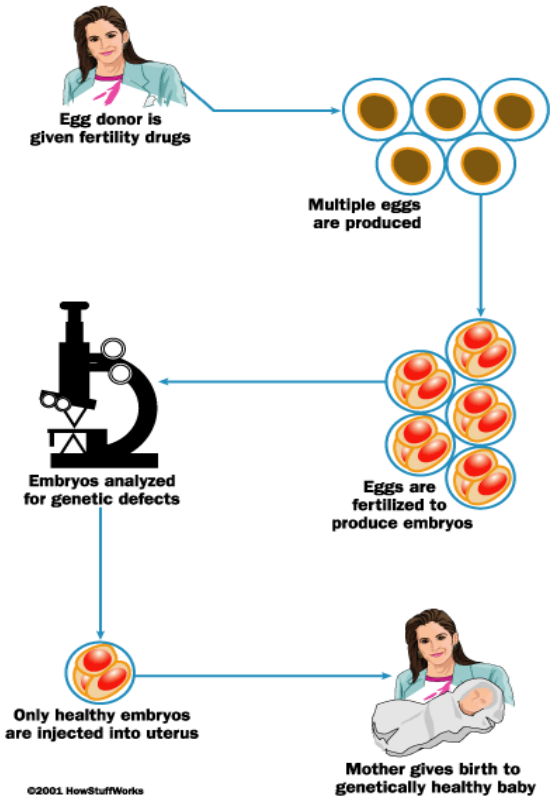
Prenatal testing

- Fetal Blood sampling



Preimplantation genetic diagnosis (PGD)

- Using IVF technique to create embryos and then be tested for the genetic disorder
- Only unaffected embryos are transferred back to the uterus
- The number of conditions can be tested using PGD in increasing and various from centre to centre
- Each condition needs to have a licence issued by the licensing body, the Human Fertilisation and Embryology Authority (HEFA)

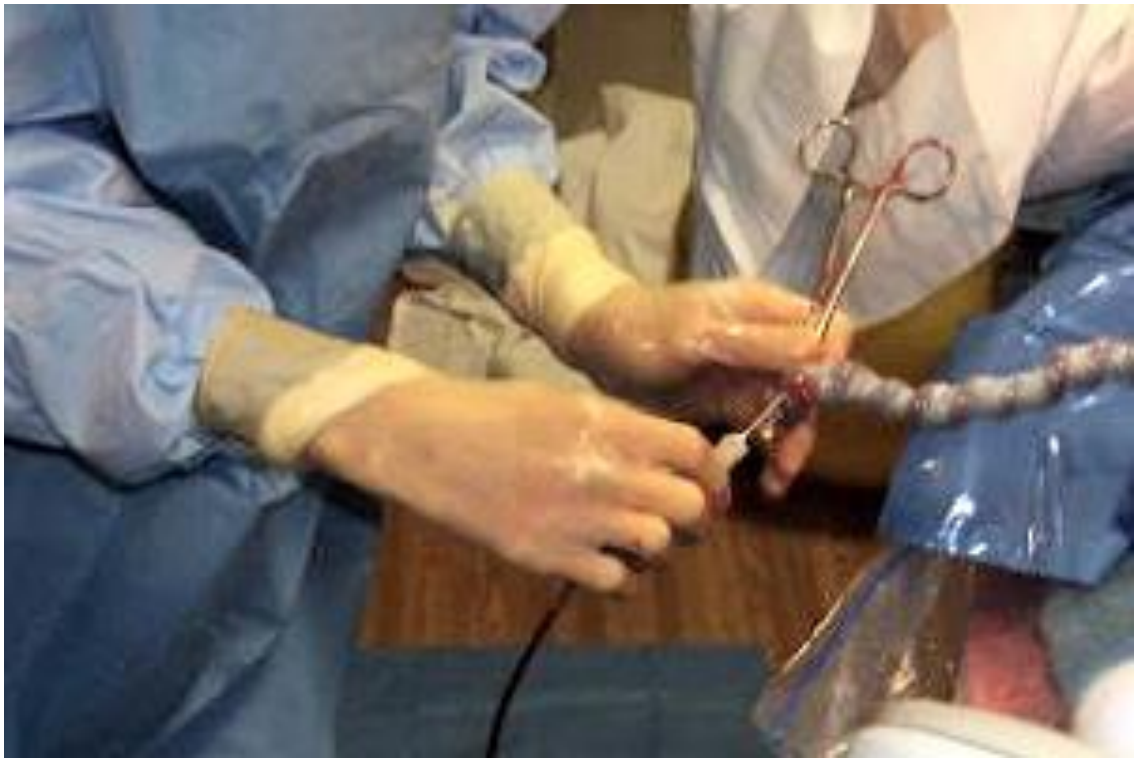


PGD cont'd

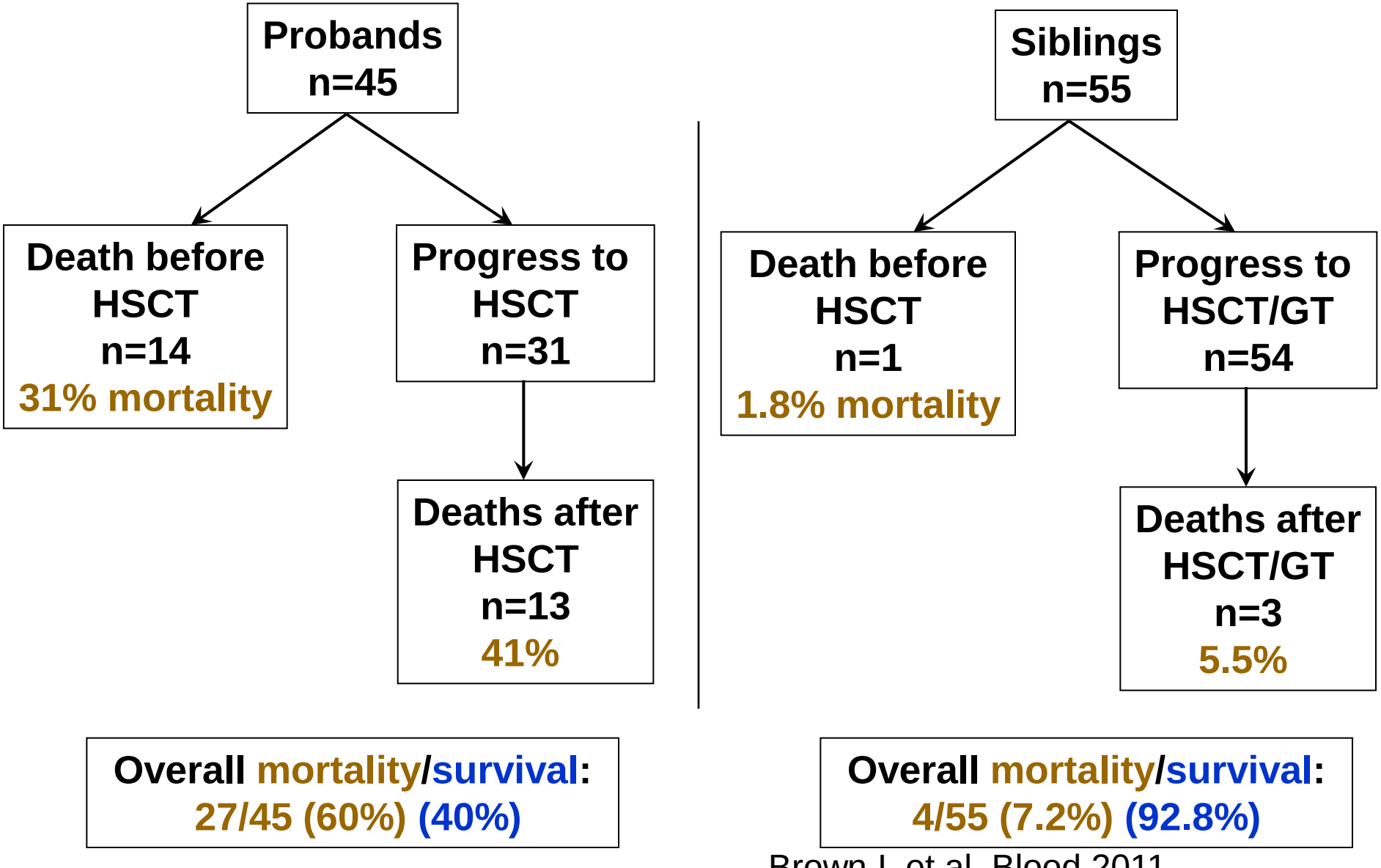
- Usually up to 2 embryos are transferred back to the uterus
- ***Embryos can also be tested to exclude the genetic disorder and selected to be the tissue typing match for an affected sibling***
- Funding is not available to all couples requesting PGD,
- Highly regulated by the HFEA
- Limited centres offer PGD treatment in the UK

Cord blood collection

- Diagnose at birth on cord blood
- Cord bloods collection and storage



Comparison of overall outcomes



Brown L et al. Blood 2011

Any Questions?