Prenatal Diagnosis

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Aims of Lecture

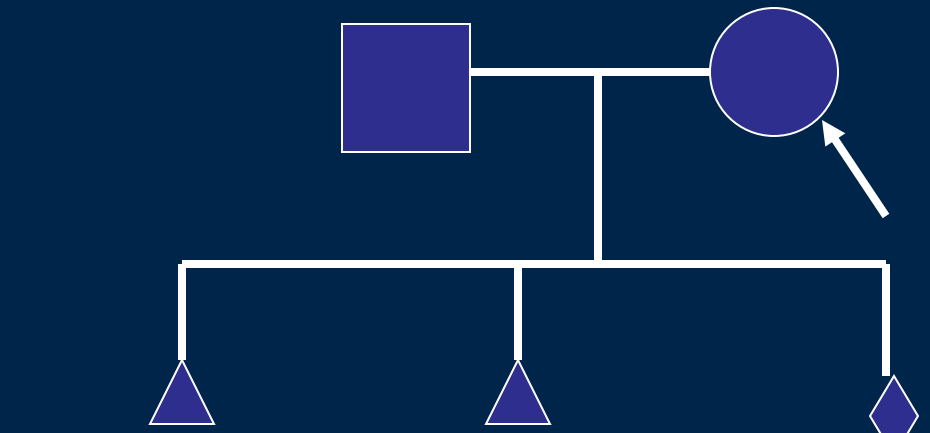
- Use case studies to illustrate the approach to genetic problems identified before or during pregnancy
- Show the difference between an antenatal screening test and an antenatal diagnostic test
- Show how molecular and cytogenetic results can be used by patients to make informed decisions

- NOT- TO MAKE YOU LEARN DETAILS OF RARE SYNDROMES!

Antenatal care in Lothian

- GP appointment following positive pregnancy test
- Booking appointment with midwife 8 - 10 weeks including dating ultrasound scan and haemoglobinopathy screening (Thal +/- Sickle)
- First trimester screening offered (nuchal translucency; hCG; PAPP-A) 11-14 weeks
- If late booker second trimester screening offered for T21 and NTD 14-18 weeks (hCG; AFP)
- Detailed second trimester ultrasound scan
- Monitoring in primary care throughout

Case 1



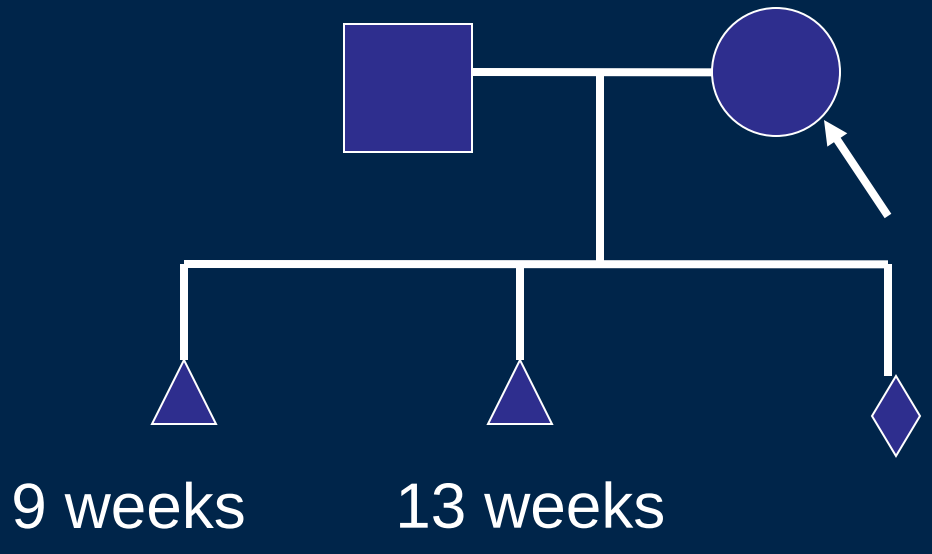
9 weeks

13 weeks

Hannah Brown

28 years

Case 1



9 weeks

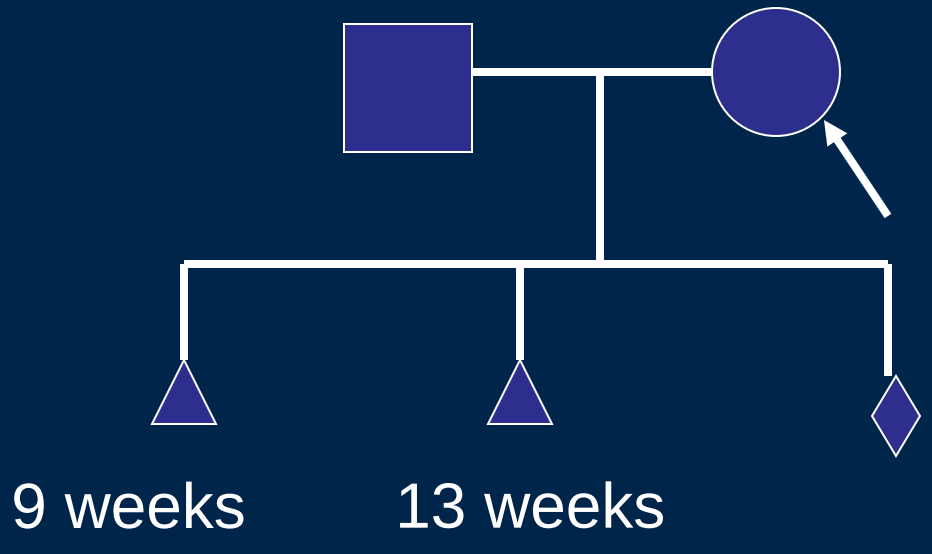
13 weeks

Hannah Brown

28 years

Ultrasound at 8 weeks - normal

Case 1



Ultrasound at 14 weeks- abnormal

- Post-axial polydactyly
- Encephalocoele
- Echogenic kidneys

Case 1

What do the couple want to know?

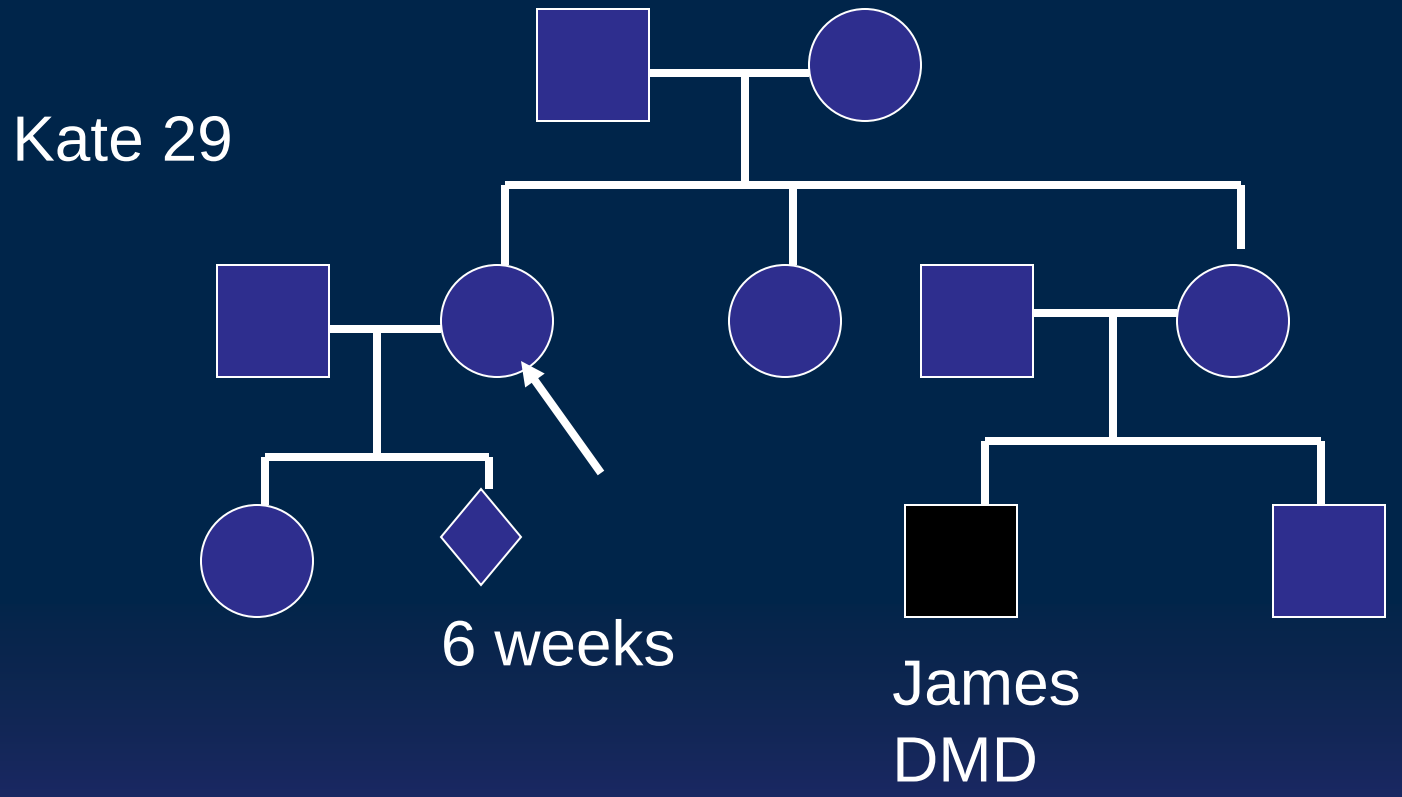
- What do these findings mean?
  - Possible diagnoses
    - Trisomy 13
    - Meckel Gruber syndrome
- Could you have made a mistake?
- What do we do now?
- What would you do?

Case 1

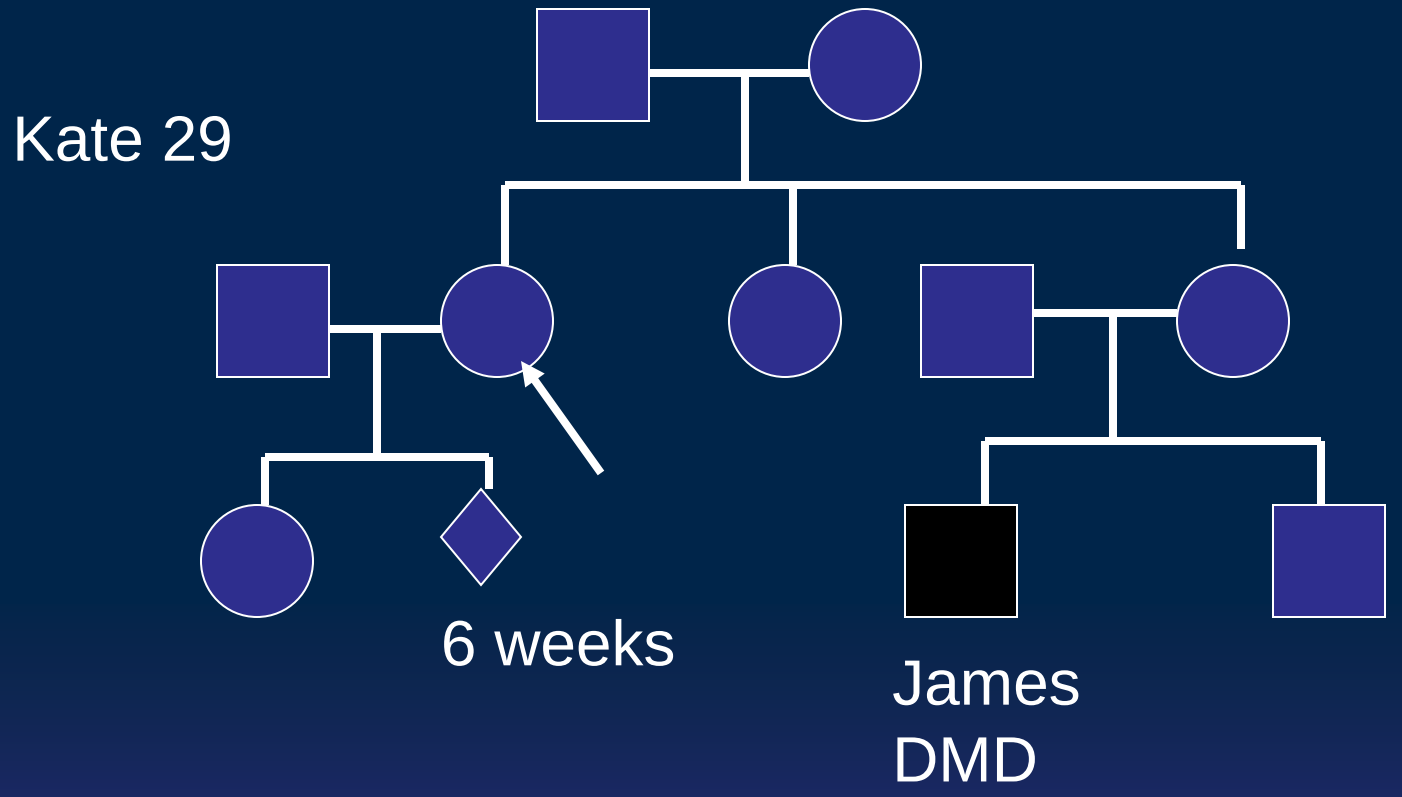
Post termination genetic counselling

- Was the diagnosis confirmed?
- Why did it occur?
- Can we ever have a normal baby?
- What tests are available in a future pregnancy?
- Did we make the right decision?

Case 2

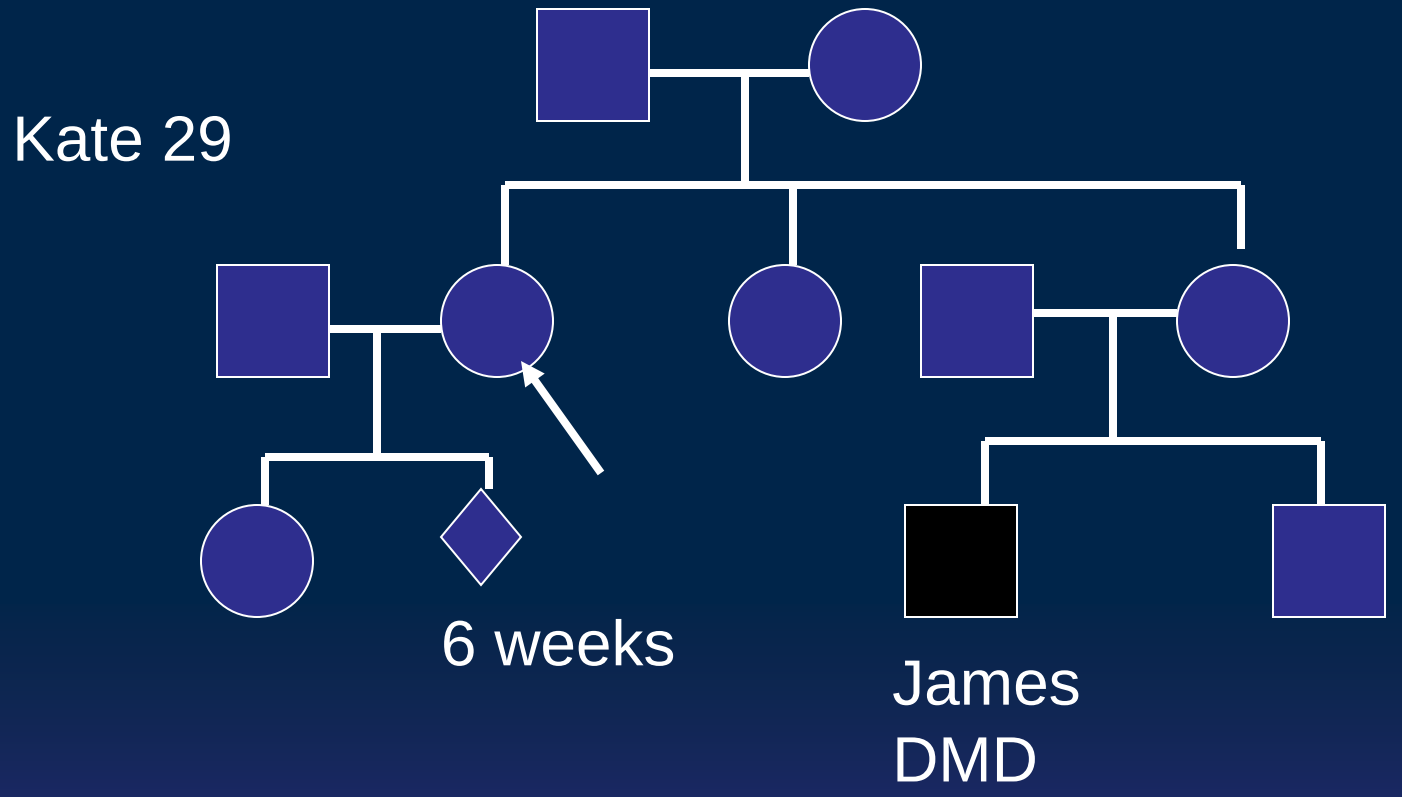


Case 2



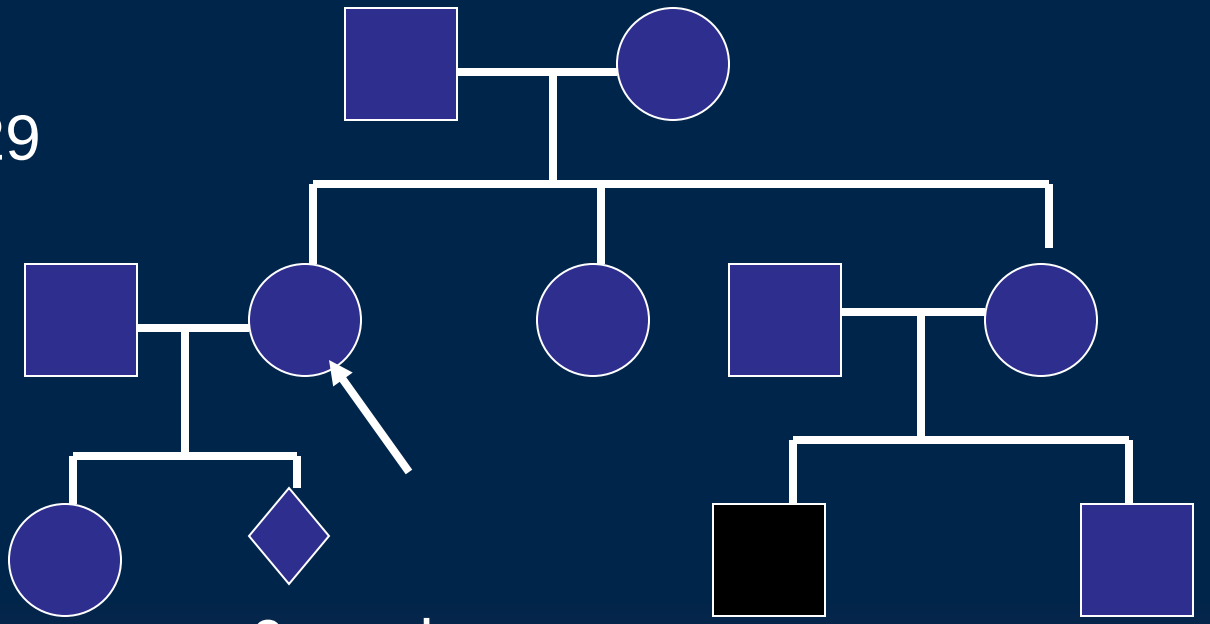
What is Kate’s risk of being a DMD carrier?

Case 2



How can Kate’s carrier risk be clarified?

Case 2



Chorionic villus sampling

- Out patient procedure
- Performed at 10.5-12 weeks gestation
- Miscarriage risk 1.5 - 2%
- Transabdominal

Foetal sexing on maternal blood

Cell free foetal DNA (cffDNA)

- 5-10% of total cell free DNA in maternal plasma
- Originates from trophoblast
- Detectable from 4-5 weeks gestation
- Levels increase with gestation period
- Fragmented DNA
- Cleared from circulation rapidly after delivery

- Provides a means for non-invasive foetal sexing

cffDNA

Challenges of non-invasive foetal sexing

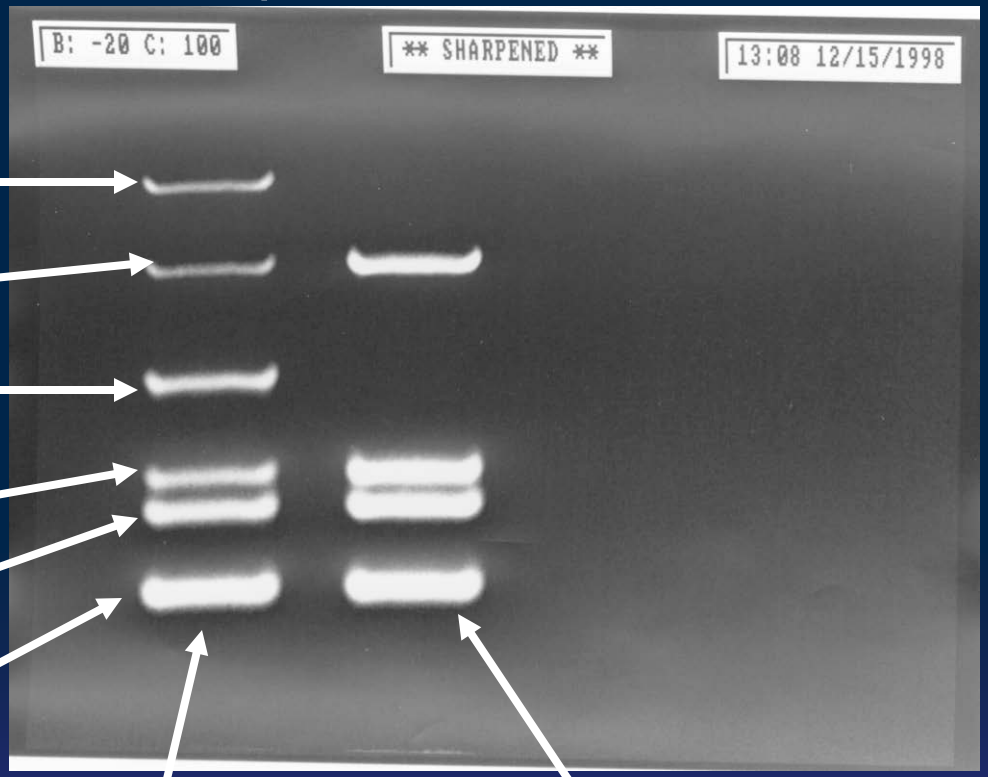
- Technically problematic
  - Very low DNA concentrations
  - High levels of maternal DNA ‘background’
- **Reliable** detection of cffDNA only possible from ~9 weeks gestation; must confirm by scan
- Not applicable in twin pregnancies, including vanishing twins
- Samples need to be extracted quickly

The future: non-invasive prenatal diagnosis

Case 2

Duchenne Muscular Dystrophy

PCR amplification of exons 35, 36, 39, 47, 48, 50,

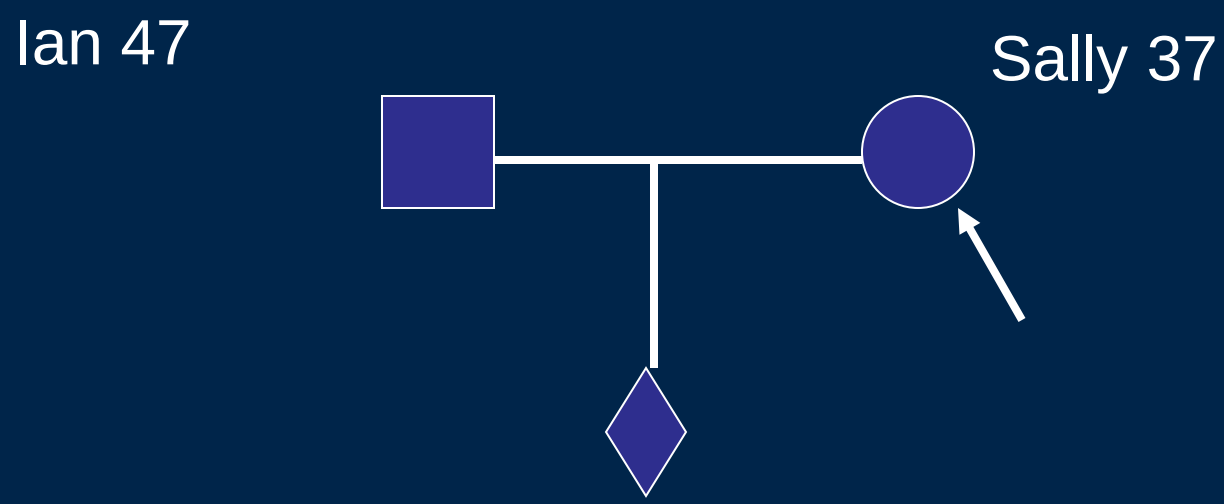


Criteria to receive NHS funded PGD in Edinburgh

- Known genetic condition which conveys a "significant risk of a serious genetic condition being present in the embryo" (HFEA Code of Practice)
- No living unaffected child* as a couple
- Female age < 39 yrs
- Anti mullerian hormone (AMH) ≥ 6 or antral follicle count > 8
- Female BMI < 30
- Both partners non-smokers for > 3 mths
- Couple living at same address for > 2 yrs
- Both partners must be eligible for NHS treatment

* If have unaffected child, may also have treatment if fulfilling other criteria but would need to self-fund

Case 3



Booked at 12 weeks
7 years unexplained infertility
First trimester screening declined

Case 3

- Sally is admitted to the ward because of vaginal bleeding at 17 weeks
- The bleeding settles but an ultrasound scan is performed

Case 3

USS Findings

- Lemon shaped head
- Banana shaped cerebellum
- Abnormal spine with sac protruding

Spina Bifida

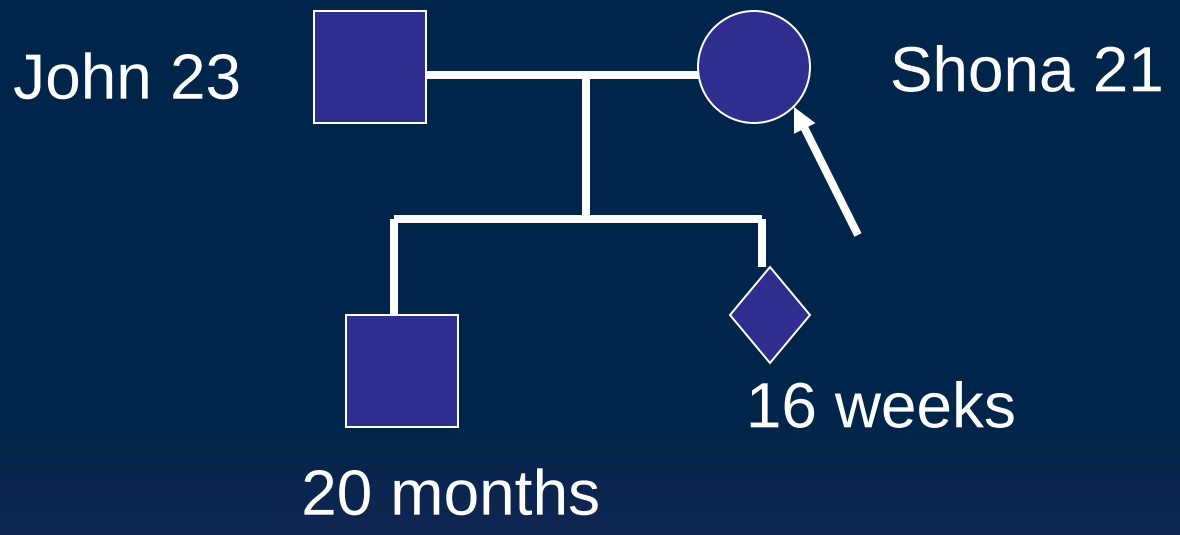
Neural Tube Defects

- Neural tube closure occurs early in pregnancy; from cervical spine distally day 18-28
- Outcome varies from spina bifida to anencephaly
- Incidence 1/300 N.Ireland – 1/1000 USA
- Polymorphisms in MTHFR
- mostly multifactorial but can be syndromic, chromosomal or teratogen-induced

Neural Tube Defects

- If couple has one affected child, increased chance of another (5%)
- Recurrence risk can be decreased by high dose Folic acid (5mg)
- Pre-conceptual Folic acid important for all women – 400 micrograms, 2months prior to conception and up to 12 weeks of pregnancy

Case 4



Book at 16 weeks - serum screening
“to be sure everything is OK”

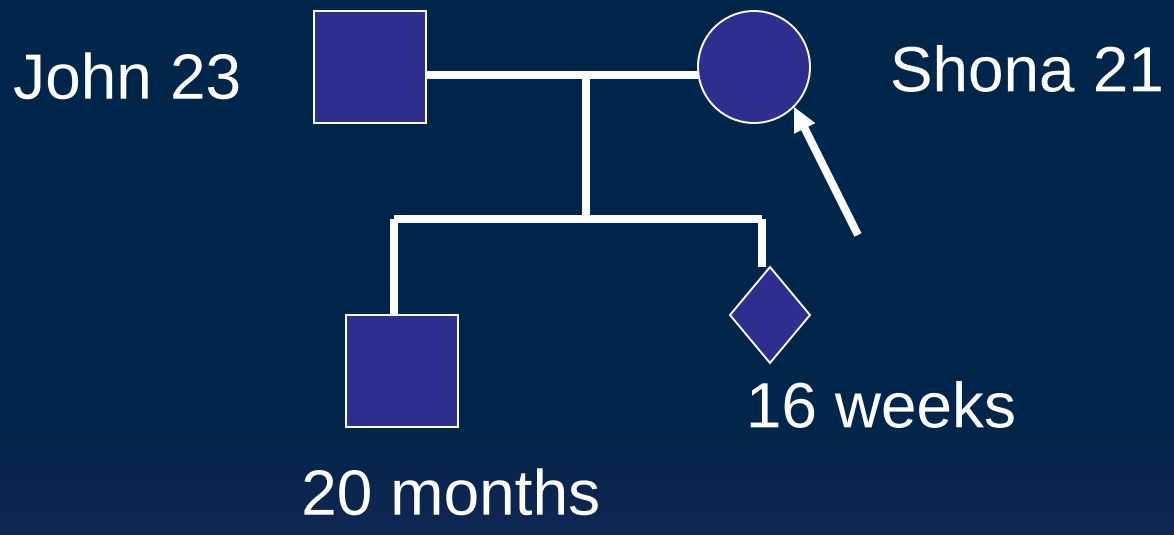
Screening for Down syndrome and Neural Tube Defects

- First trimester screening (nuchal translucency; hCG; PAPP-A) offered 11 – 14 weeks
- Second trimester screening offered to late bookers for T21 and NTD 16-18 weeks (hCG; AFP)

- Down syndrome
  - Low AFP / PAPP-A
  - Raised hCG
  - Increased nuchal translucency
- Neural Tube defect
  - Raised AFP > 2MoM

- Plus detailed second trimester ultrasound scanning

Case 4



Down syndrome serum screening risk 1 in 47

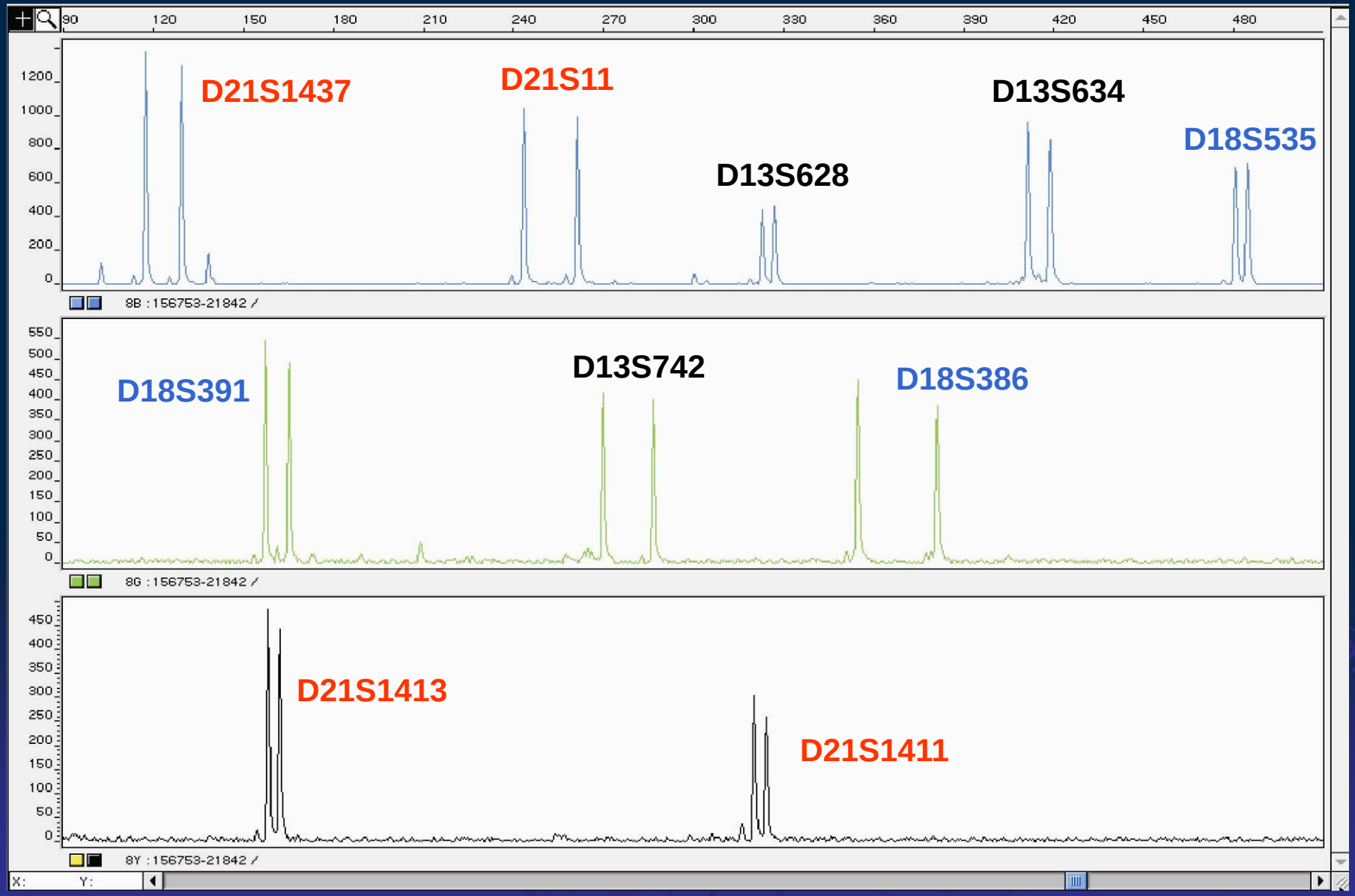
Amniocentesis

- Performed between 14 and 16 weeks gestation
- 15-20mls amniotic fluid aspirated
- Small risk of membrane rupture
- Associated miscarriage rate 0.5-1%
- Rapid aneuploidy screen for Trisomy 21, 13 and 18

QF-PCR

- Quantitative fluorescence polymerase chain reaction
  - Amplification of chromosome-specific short tandem repeats (STRs)
  - Sample DNA is amplified by PCR using fluorescent primers
  - Products can be visualised and quantified as peak areas of the respective repeat lengths
- for chromosomes 21, 13, 18, sex chromosomes

Rapid aneuploidy screen trace

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D13S628
D13S634
D18S535
9B :176753-21847 /
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D18S391
D13S742
D18S386
9G :176753-21847 /
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9Y :176753-21847 /
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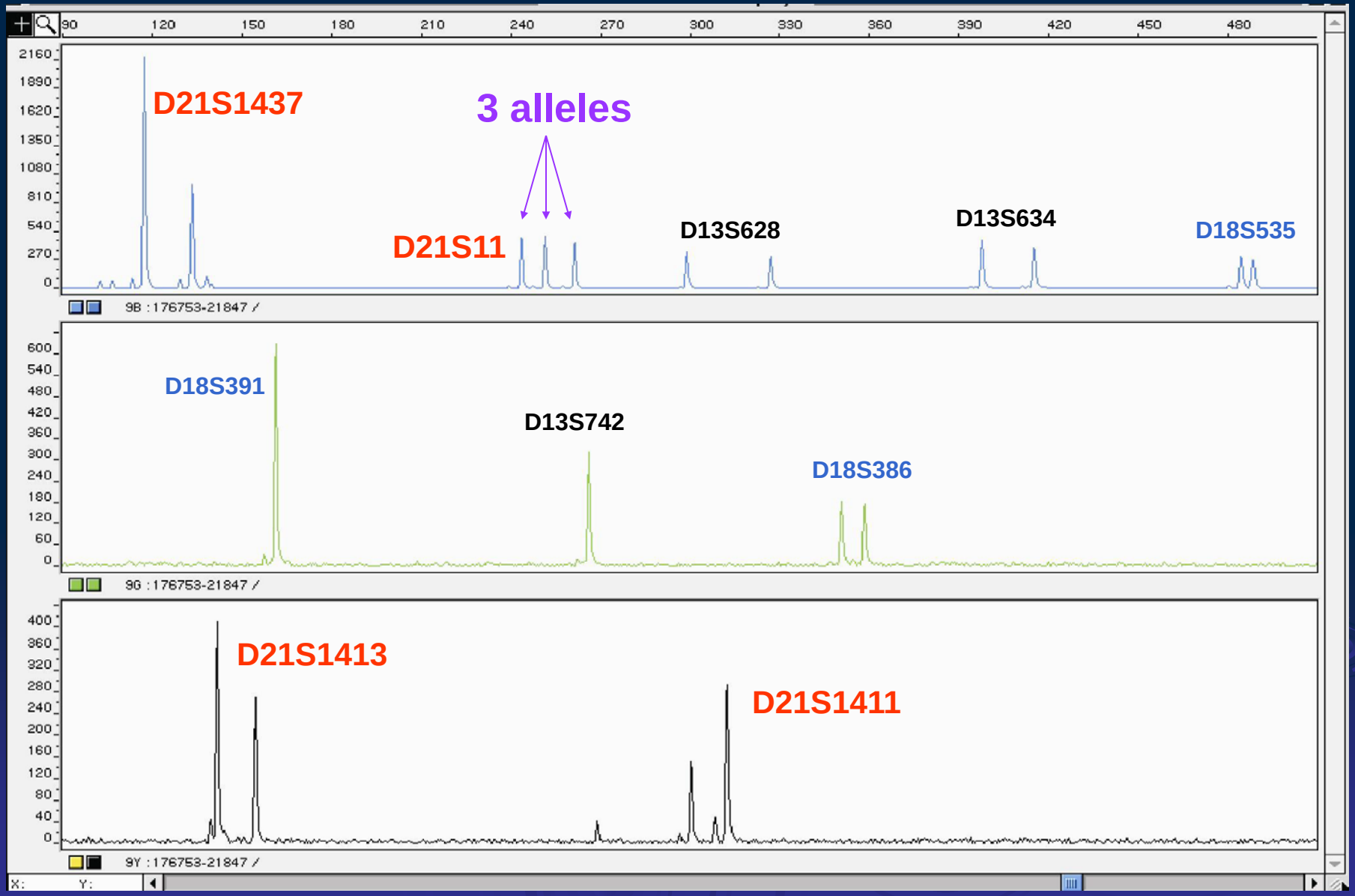
Downs Affected Amnio



Trisomy 21

- 1 in 650 births
- Maternal age effect
- Risk > population risk by mid 30's
- Recurrence risk is 1 in 100 or twice the risk for age if due to non-dysjunction (~95%)
- Mosaicism
- Robertsonian translocation

Case 4

Issues for Shona and John

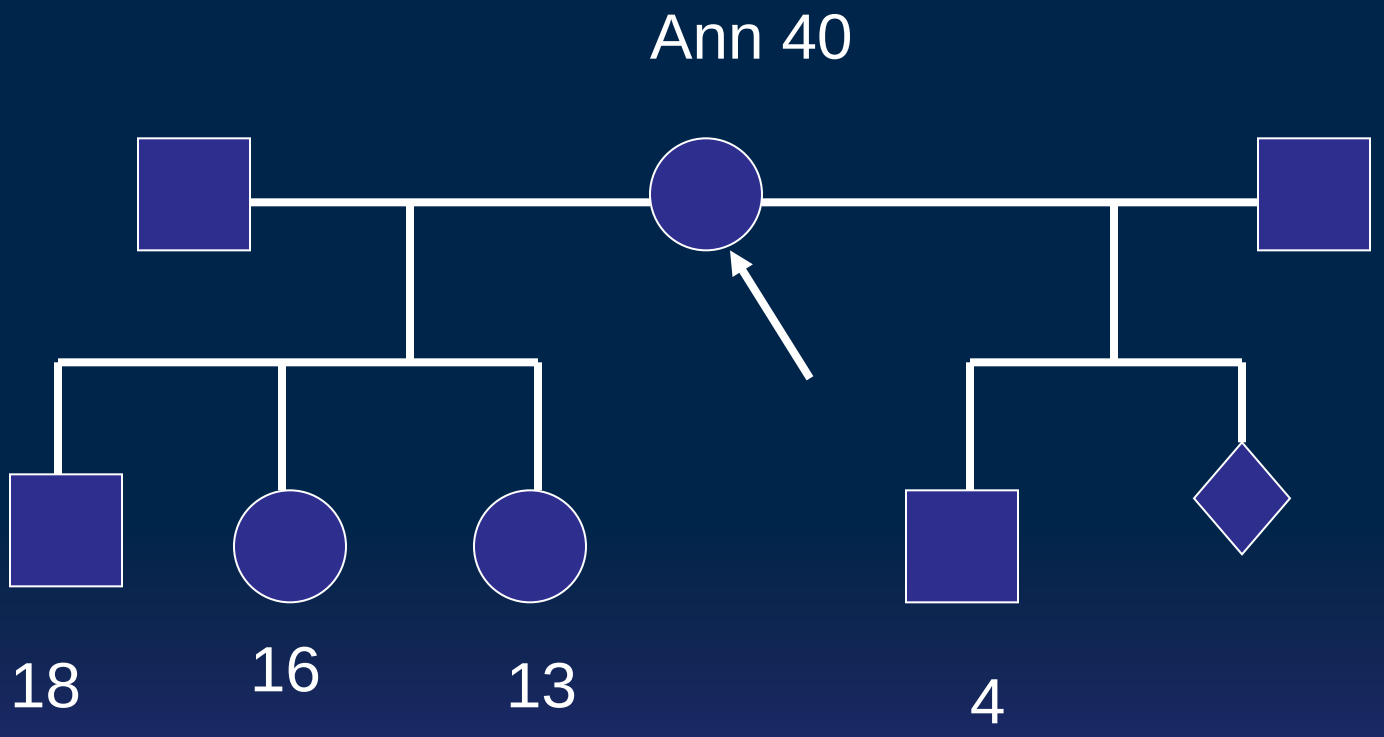
- How confident are you about the results of the test?
- How will Down syndrome affect our baby?
- What happens if we decide to continue the pregnancy?

Case 4

Issues for Shona and John

- How confident are you about the results of the test?
- How will Down syndrome affect our baby?
- What happens if we decide to continue the pregnancy?
  - detailed scan for cardiac and other defects

Case 5



Booked at 15 weeks requesting amniocentesis

Case 5

- Amniocentesis performed
- Amnio-pcr result “No trisomy detected”
- Full karyotype report 12 days later

Case 5

Results of final karyotype

- Marker chromosome present in both cultures
  - Is it inherited?
  - Is it significant
    - does it contain coding material?
    - Can the chromosomal origin be identified?

Case 5

Interpretation

- Unbalanced karyotype
- Phenotypic effect unknown

Case 5

- Opt to terminate pregnancy
- Post-mortem shows the fetus to have facial dysmorphism and a cardiac outflow tract defect.

- Some people believe that terminating the pregnancy will reduce their suffering. It will not. No matter what you choose, the pain will be high. The Bad Thing has happened. There is no way you can turn back the clock and make life the way it was before. The question is, if you have to pay a price, what do you want in return for it? Termination gives you no gifts, just pain, guilt, and questions for the rest of your life. Carrying to term gives something back that is totally unexpected. When your baby is first diagnosed, you will not be able to foresee what your child can give you, even during a few more months of pregnancy. Because you have not yet lived with this hardship, you won't be aware of how you will grow through it.

- I initially thought I would "be brave" and continue my pregnancy. But I came to realize that ultimately it wasn't about how strong I could be, how deeply I wanted this baby or what important lessons he could teach me. It was about what **he** would experience in his short life. Given his diagnosis, he would have known only suffering. As his mother, I couldn't allow that to happen.

Summary

- Use case studies to illustrate the approach to genetic problems identified before or during pregnancy
- Show the difference between an antenatal screening test and an antenatal diagnostic test
- Show how molecular and cytogenetic results can be used by patients to make informed decisions