Family genetics: The future???

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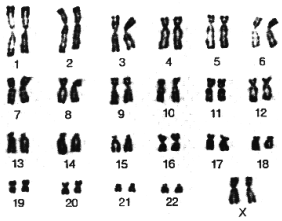
Learning objectives

- Understand how genetic problems may affect successful conception
- Consider the possible conditions and ethical considerations of counselling a healthy couple planning to conceive.
- Understand the modern technologies of genetic testing
- Understand the possibilities for non-invasive prenatal testing
- Understand the methodology of PGD and it's applicability.

"Here's my DNA sequence."

The traditional genetics



The new genetics

- Real time quantitative PCR for individual genes and chromosomes
- Array CGH (Comparative genomic hybridisation)
- Single nucleotide polymorphisms (SNP)
- Next generation sequencing

Genetics and reproduction in early 2015

- Genetic contribution to reproductive problems
  - Maternal side
  - Paternal side
  - Translocations
  - Miscarriage testing
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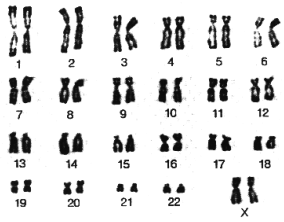
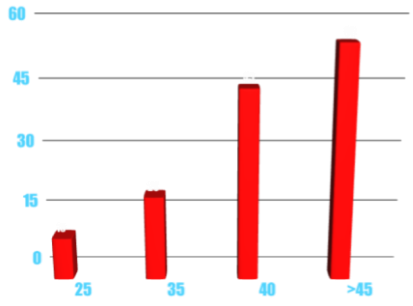
Maternal reproduction and chromosomes



Down syndrome and maternal age

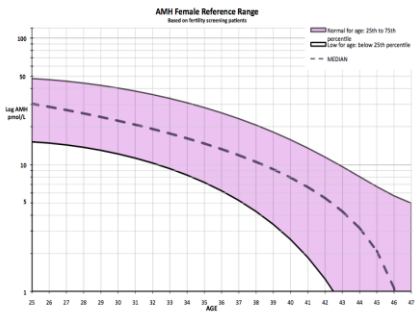
Maternal Age	Risk for trisomy 21 (Down syndrome)	Risk for all trisomies
20	1 in 1,667	1 in 526
25	1 in 1,250	1 in 476
30	1 in 952	1 in 384
35	1 in 385	1 in 192
40	1 in 106	1 in 66
45	1 in 30	1 in 21
49	1 in 11	1 in 8

Miscarriage rate & maternal age



Dew et al 1998

Ovarian reserve



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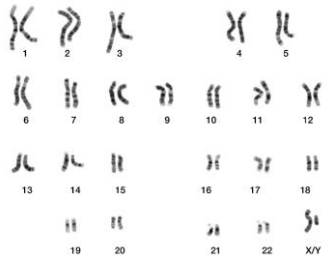
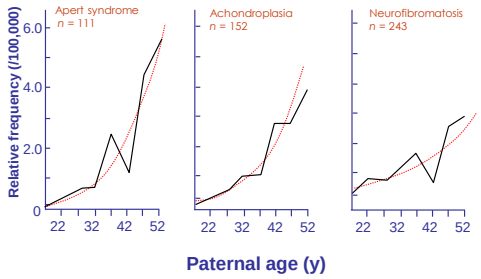


Genetic disorders of male reproduction

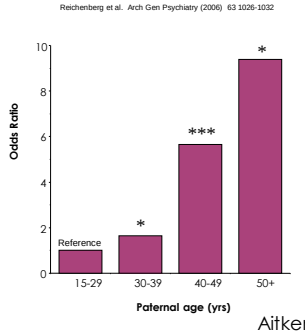
- Klinefelters syndrome
- Cystic fibrosis mutations
- Y-chromosome gene-deletions

Relative frequency of affected children of normal parents



Aitken et al., 2014

Impact of paternal age on Autism



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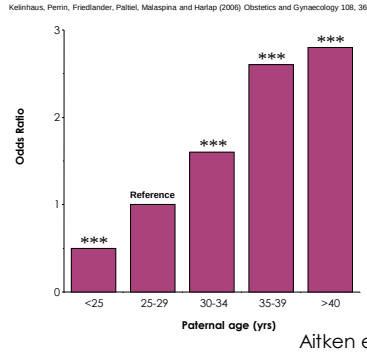
Impact of paternal age on miscarriage



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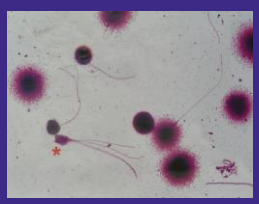
Excessive Sperm DNA Fragmentation

- Can be assessed clinically by carrying out SCSA or TUNEL on a semen sample
- Gives an indication of overall level of damage to DNA in sperm cells
- Excessive damage linked to infertility and recurrent miscarriage
- Mostly thought to be due to oxidative damage from locally-produced free oxygen radicals

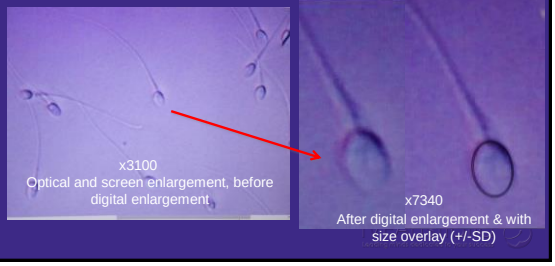


Treatment of abnormal DNA fragmentation in sperm

- Simple anti-oxidants (Menevit, Men's Performance Multi)
  - Readily available
  - Evidence of efficacy limited
- Frequent ejaculation at fertile time
  - Thought to limit the exposure to endogenous oxygen radicals
- Obtaining sperm direct from the testis
- Selection of sperm for ICSI through digital high magnification

Digital High Mag IMSI – Sperm Selection

x400 standard ICSI sperm size (if use 40x objective, not the x20 objective)



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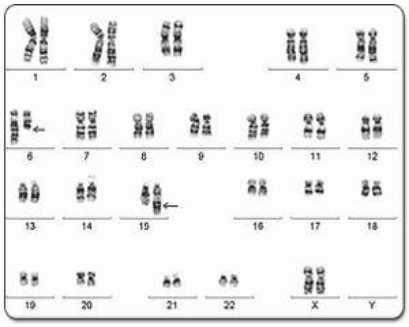
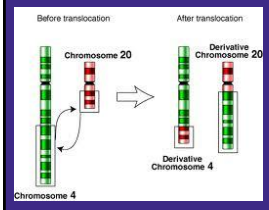
Balanced translocation



Translocations



- Associated with reproductive problems
- Can be linked to livebirth of child with problems
- What to do?

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Investigation for genetic causes of recurrent miscarriage

- Karyotypes in both partners
- Sperm DNA fragmentation
- AMH level
- Karyotype products of conception where possible

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Pre-conceptional genetic testing in healthy families?

The present:

Discussion of:

- Cystic Fibrosis
- Fragile X
- Spinal muscular atrophy (SMA)
- Haemoglobinopathy
- Autosomal recessive for (Ashkenazi) Jewish background

Pre-conceptional genetic testing in healthy families?

The future???

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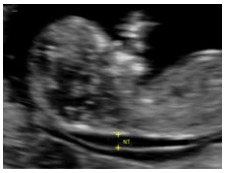
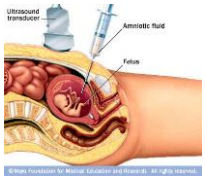
Prenatal testing for genetic disorders

Prenatal testing

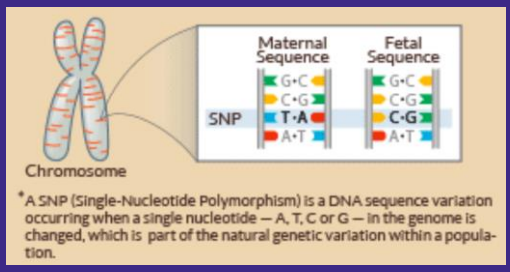
- 1970s – amniocentesis >35years
- 1980s – chorionic villus sampling
- 1990s - nuchal translucency screening
- 2000 - nuchal translucency plus biochemistry

Current prenatal testing



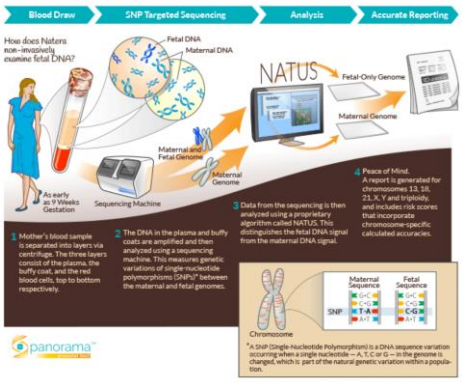


Non-invasive prenatal testing



*A SNP (Single-Nucleotide Polymorphism) is a DNA sequence variation occurring when a single nucleotide — A, T, C or G — in the genome is changed, which is part of the natural genetic variation within a population.

How does Natera non-invasively examine fetal DNA?



Non-invasive prenatal testing

- Requires minimum amount of fetal DNA in circulation
- Usually present after 9 weeks gestation
- Can assess commonest 5 abnormalities + sex
- 2 week turn around
- Not MBS listed –cost $400-900

Where does NIPT fit in routine antenatal care?

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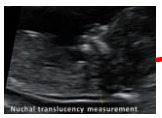
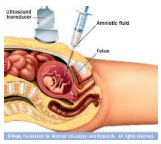
Low risk?

High risk?



panorama™ prenatal test



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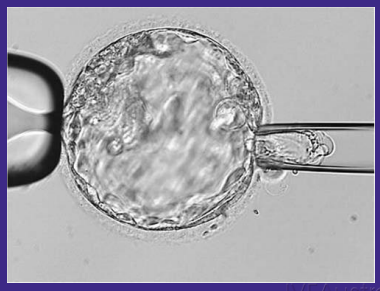
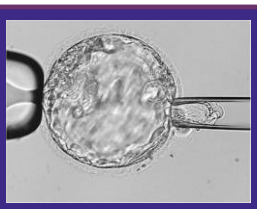
Preimplantation Genetic Diagnosis



Preimplantation Genetic Diagnosis



Test the cells

Replace only the unaffected embryos

Preimplantation genetic diagnosis methods

Chromosome structures

- FISH
- Array CGH

Single genes

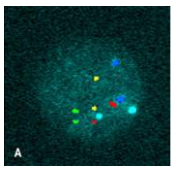
- Real-time PCR
- Karyomapping

Everything

- Next generation sequencing

Testing for chromosomal problems

FISH



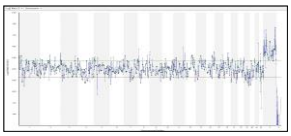
Array CGH

Test DNA Amplified Labelled

Reference DNA Labelled

Hybridised

Automated analysis



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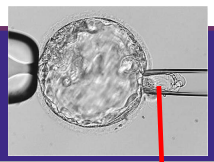

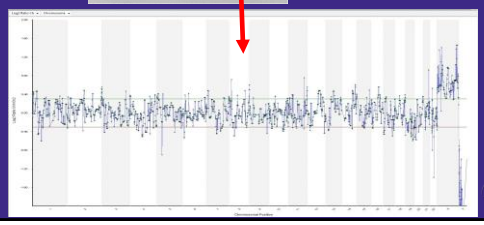

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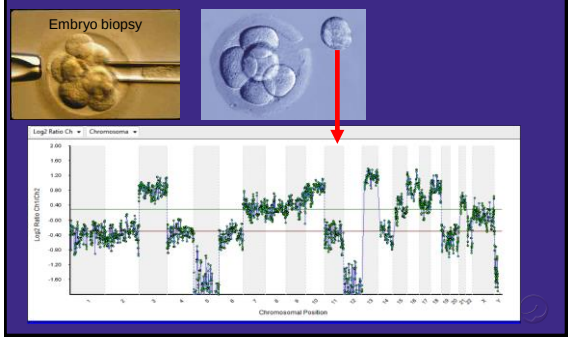

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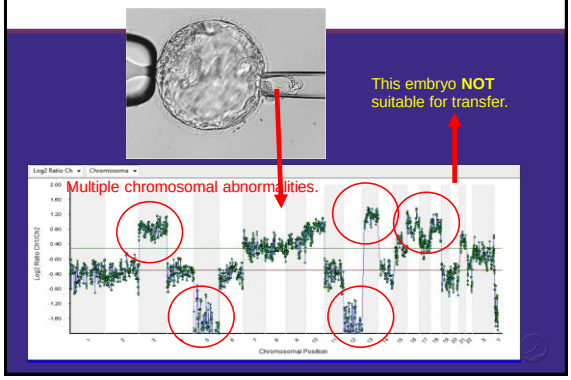

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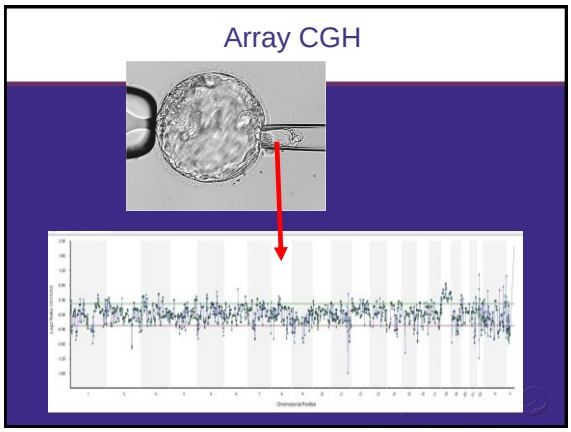

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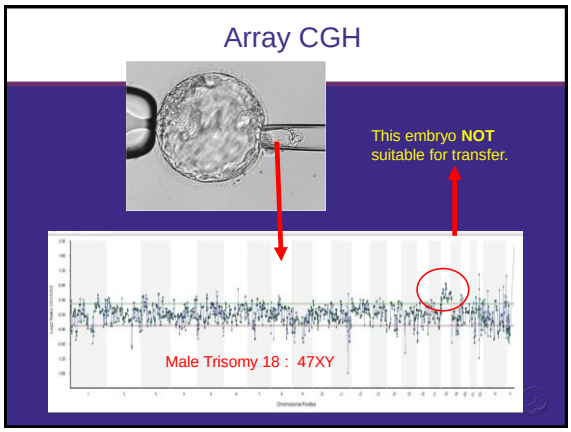

PGD for known single gene disorders

- Past: sequencing the mutation.
  - Effective but needs extensive preparation.
  - Can take six months to prepare
- Current: Karyomapping
  - Based on SNP variation (DNA fingerprinting).
  - Uses automatic algorithms to pick from which parent, the sequence has come
  - Immediate
  - Will, eventually, be able to test multiple sites

So what's the role of PGD in 2015?

- Testing for known single gene disorders
- Identifying health embryos where there's a translocation
- Preventing miscarriage?
- Improving success rates for IVF?
- Others?????

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- “Designer babies” ??? – Not the big issue
- Exponential growth in testing for future possibilities
- More worry
- Longer consultations…