LENScience CONNECT
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NATIONAL RESEARCH CENTRE FOR GROWTH AND DEVELOPMENT

LENScience Senior Biology Seminar Series 2011

Aneuploidy and Biotechnology

Richard Fisher, Bert Stewart, Jenny Eaton, Jacquie Bay

12 May 2011

kordia
people & technology as one

FERTILITY associates | a better understanding
TE RAUHANGA O TE WHARETANGATA

THE UNIVERSITY OF AUCKLAND
INFORMATION TECHNOLOGY SERVICES

New Zealand Population

Wednesday, 11 May 2011 at 12:37:59 pm

4,410,930 people

Statistics NZ

New Zealand Population

Wednesday, 11 May 2011 at 12:37:59 pm

4,410,930 people

Thursday , 12 May 2011 at 12:37:59 pm

4,411,060 people

Statistics NZ

New Zealand Population

+ 130 people in 24 hours

- one birth every 8 minutes and 10 seconds
- one death every 20 minutes and 7 seconds
- a net migration gain of one New Zealand resident every 49 minutes and 51 seconds.

Statistics NZ

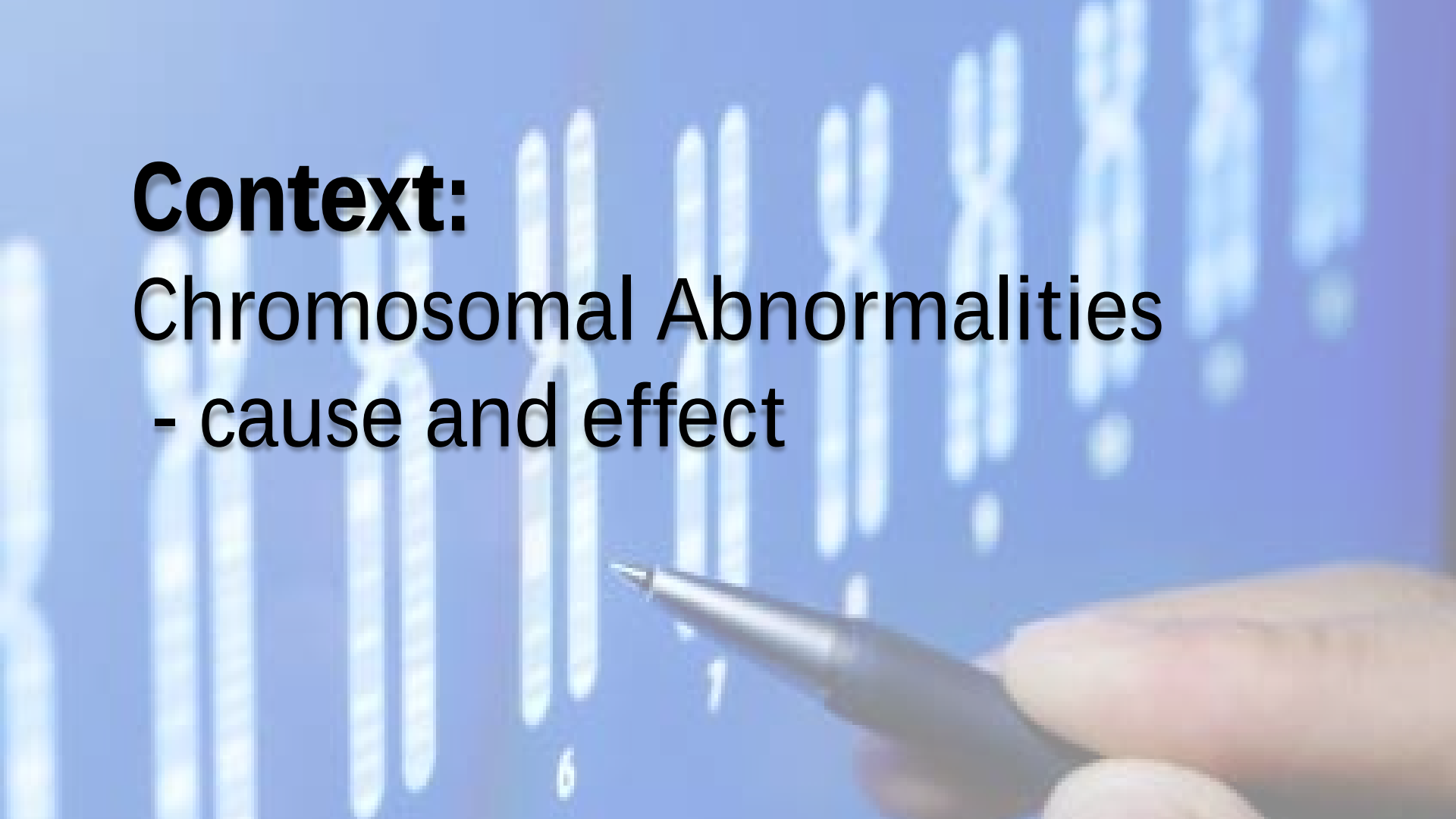

Conception


Healthy Pregnancies


Healthy Children

2-3% of infants are born with serious birth defects

15% pregnancies result in miscarriage



Context:

Chromosomal Abnormalities

- cause and effect

Meeting human need and demand

Genetic Screening & Diagnosis - application of biotechnology

Contemporary Issues.....

For achievement, students are expected to describe:

- biological concepts and processes relating to the issue
- implications of the issue, which can be biological, social, ethical, economic or environmental
- differing opinions or viewpoints.

Excellence requires evaluation, justification.....

Contemporary Issues.....

- What is the human need & demand?
- What knowledge is required to understand this situation?
- What are the technologies that are used to screen / diagnose genetic disorders?
- How do the technologies advance development of ways to meet human need & demand?

NCEA Level 3 Achievement Standards

3.1 – Ecological Niche

3.2 –Contemporary Biological Issue

3.3 – DNA and Gene Expression

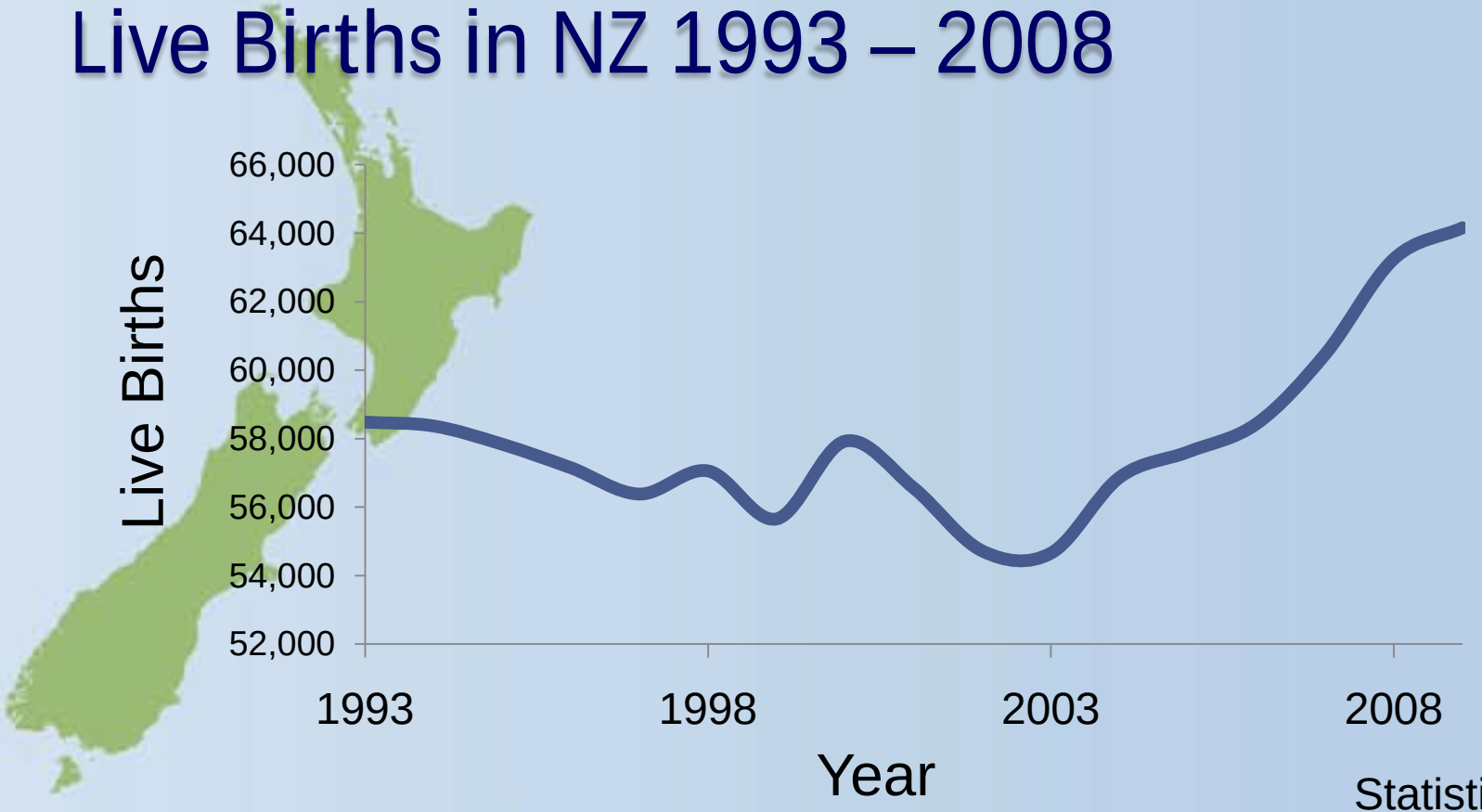
3.4 – Animal Behaviour & Plant Responses

3.5 – Processes & Patterns of Evolution

3.6 – Applications of biotechnological techniques

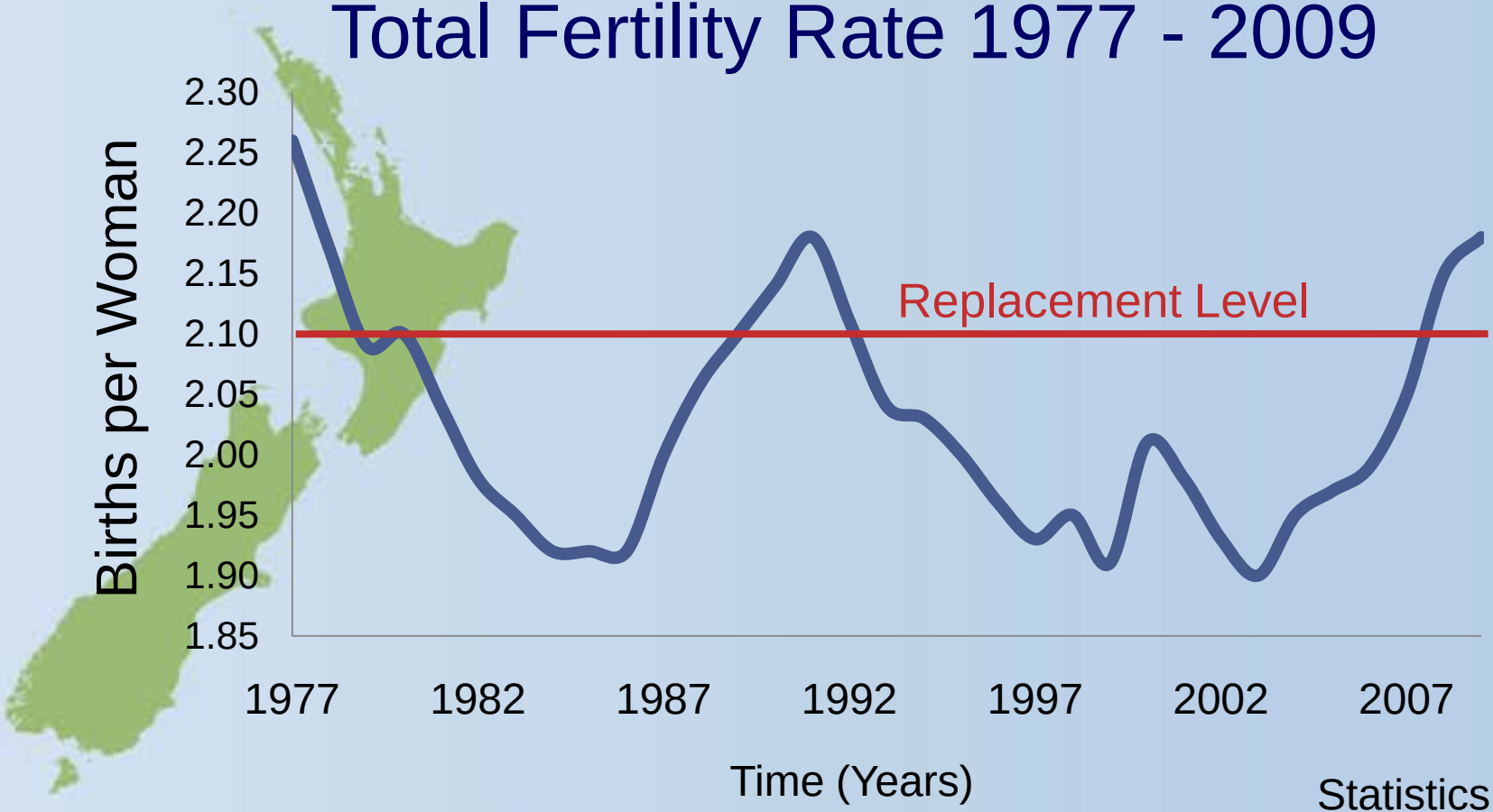
3.7 – Trends in Human Evolution

Live Births in NZ 1993 – 2008



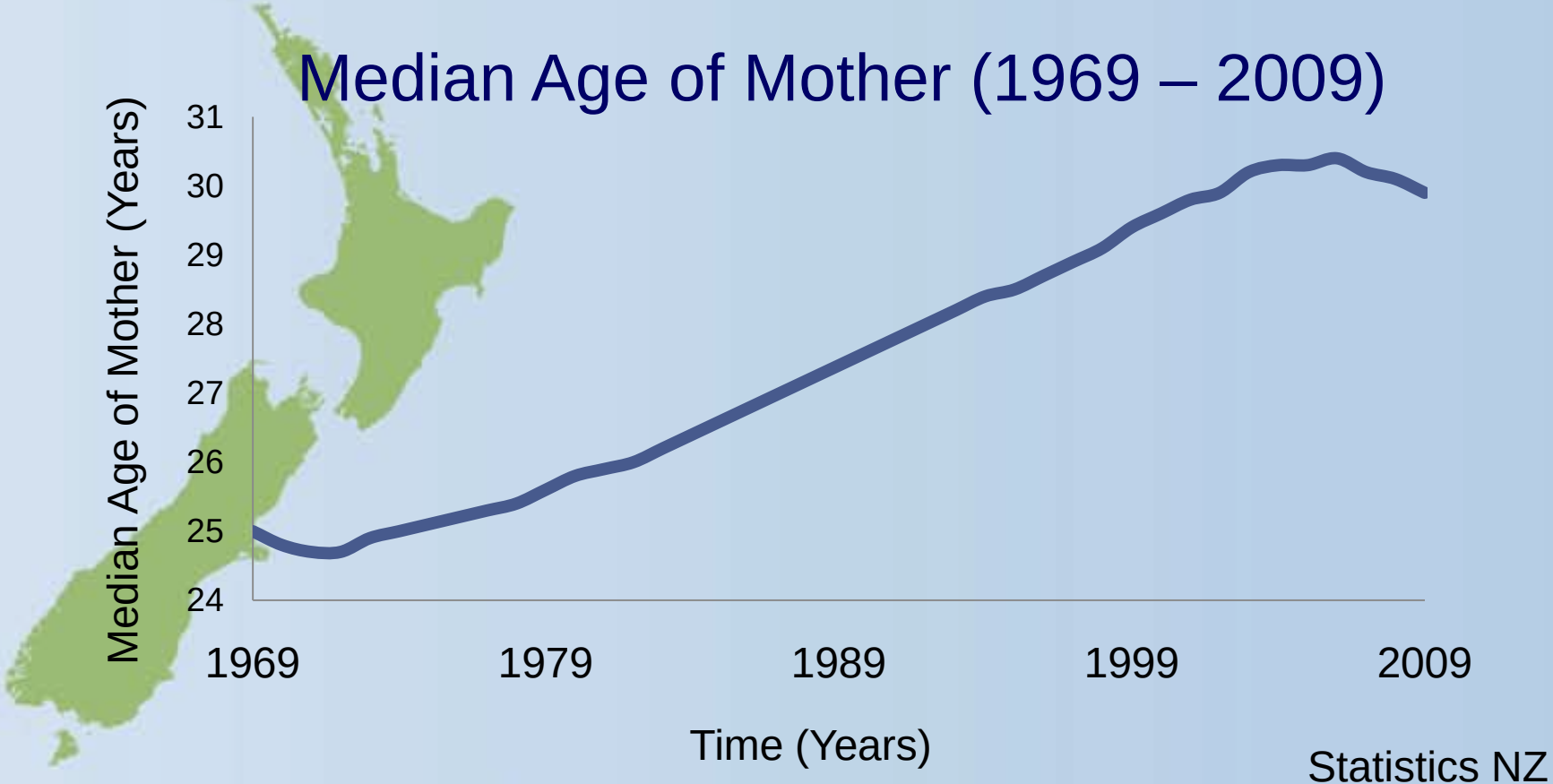
Statistics NZ

Total Fertility Rate 1977 - 2009



Statistics NZ

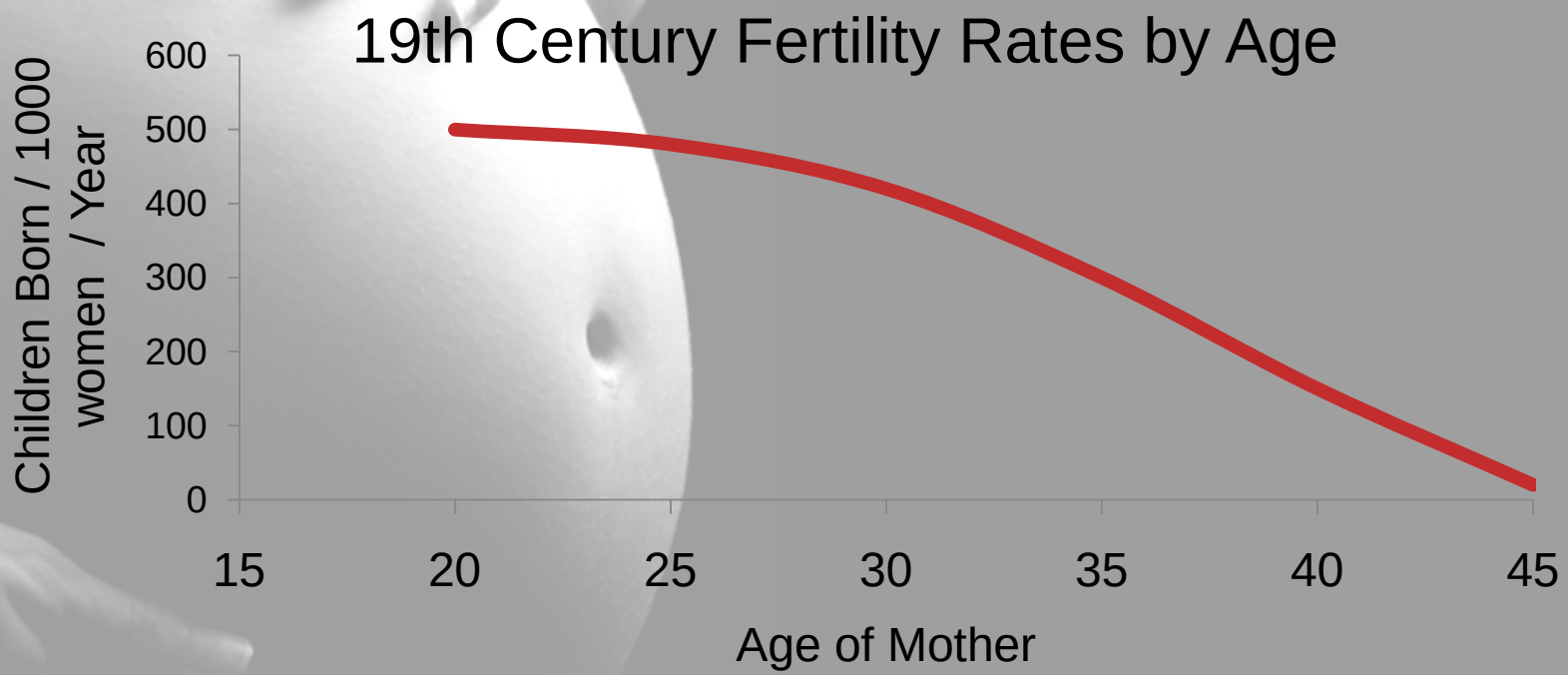
Median Age of Mother (1969 – 2009)



Statistics NZ

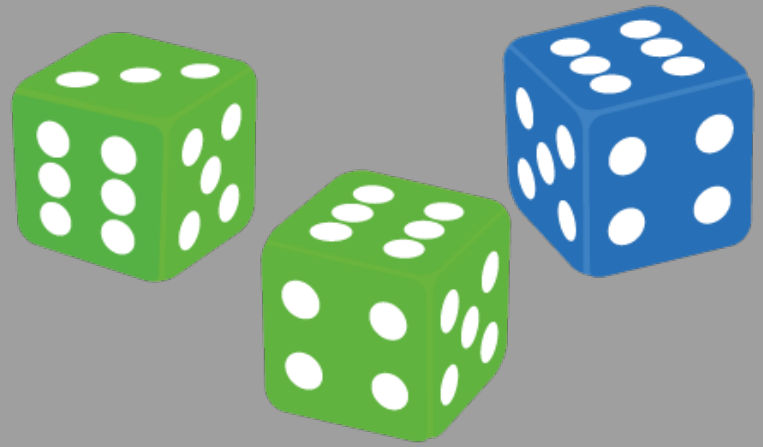
What can we learn from History?

Children born per 1000 women per year. (Menken et al, 1986)



Fertility Rate Decreases with Age

Age (Years)	Monthly Fertiliy rate (%)
25	25
30	20
35	16
37	11
40	6
42	4
44	2



Biological Clock™

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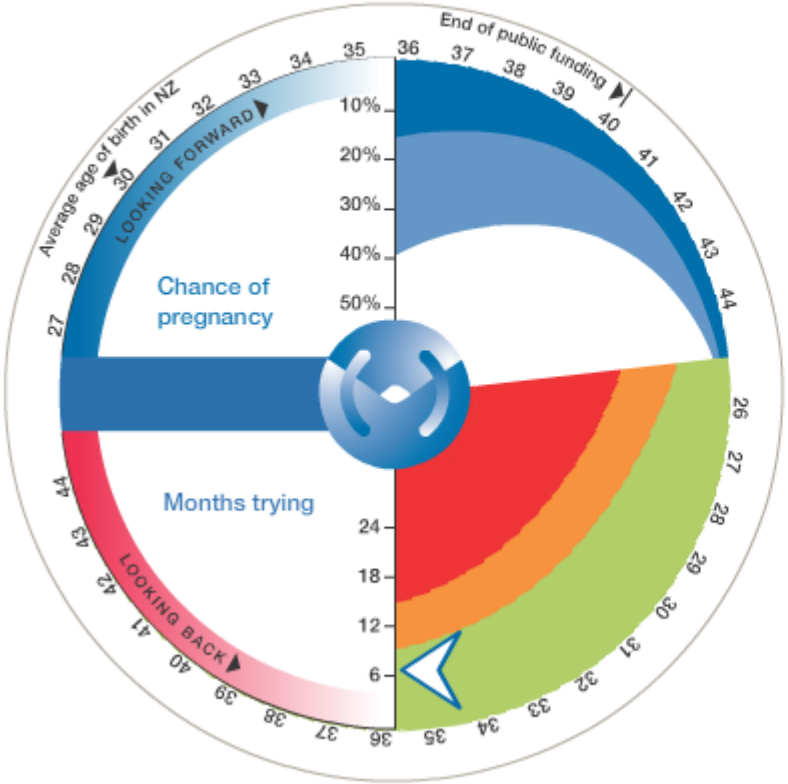


Chance of pregnancy

Chance of having a child per month of trying for fertile couples

15%

Chance of having a child from one IVF cycle for people experiencing infertility

38%

Months trying

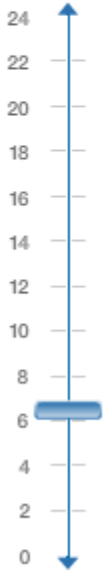
- Time to act
- Time to start thinking about seeing your GP or fertility specialist
- OK to wait, except under circumstances noted here

Age

35

Months Trying

6



Miscarriage Rate Increases with Female Age

Female Age (Years)	Miscarriage Rate (%)
Less than 30	10 – 15%
30 – 40	15 – 20%
More than 40	40%

Effect of smoking in females

- Reduces chance of conception per month to 60% of non smoker

- Doubles the risk of early pregnancy loss

Fertility Reduces with Male Age

Male Age (Years)	Pregnancy Chance relative to Female Age
< 25	1.0
30 – 34	0.62
35 – 39	0.50
> 40	0.51

Ford: Human Reproduction

Older Fathers

– Increases rate of miscarriage

- If the father is older than 35, there is a 2.33 times higher chance of miscarriage

(Ford et al)

Effect of smoking in males

- Smoking affects sperm production, motility, morphology and increases DNA damage

- A child born to a father who smokes has 4 x risk of childhood cancer.

Older fathers are linked to .....

Schizophrenia in the offspring

Father > 45 odds ratio 3.0 – 1 in 46 chance

(Malaspina 2001)

Increase in Autism

Compares with 30 years

> 40 – 3 x the risk

> 50 – 5 x the risk (Reichenberg 2006 and others)

Increase in Achondroplasia (short stature with short limbs).

Why?

Chromosomal Abnormalities

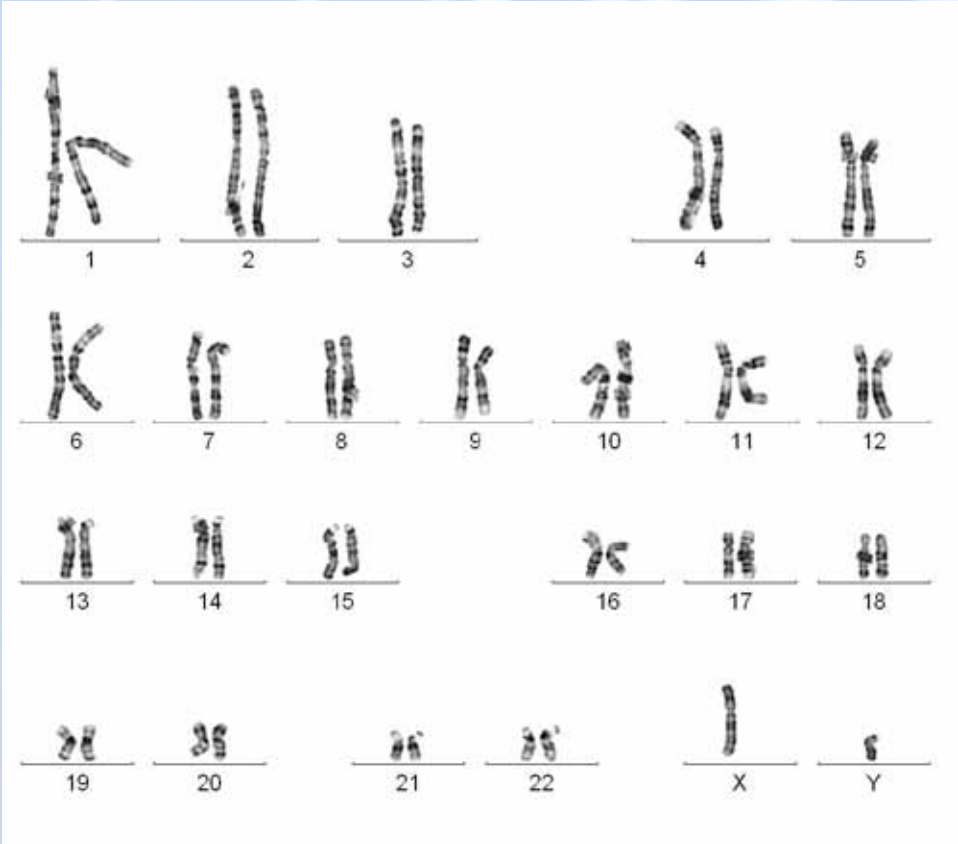
Most common cause of miscarriage

Affect multiple genes

- Deletion
- Duplication
- Inversion
- Translocation

Normal Karyotype

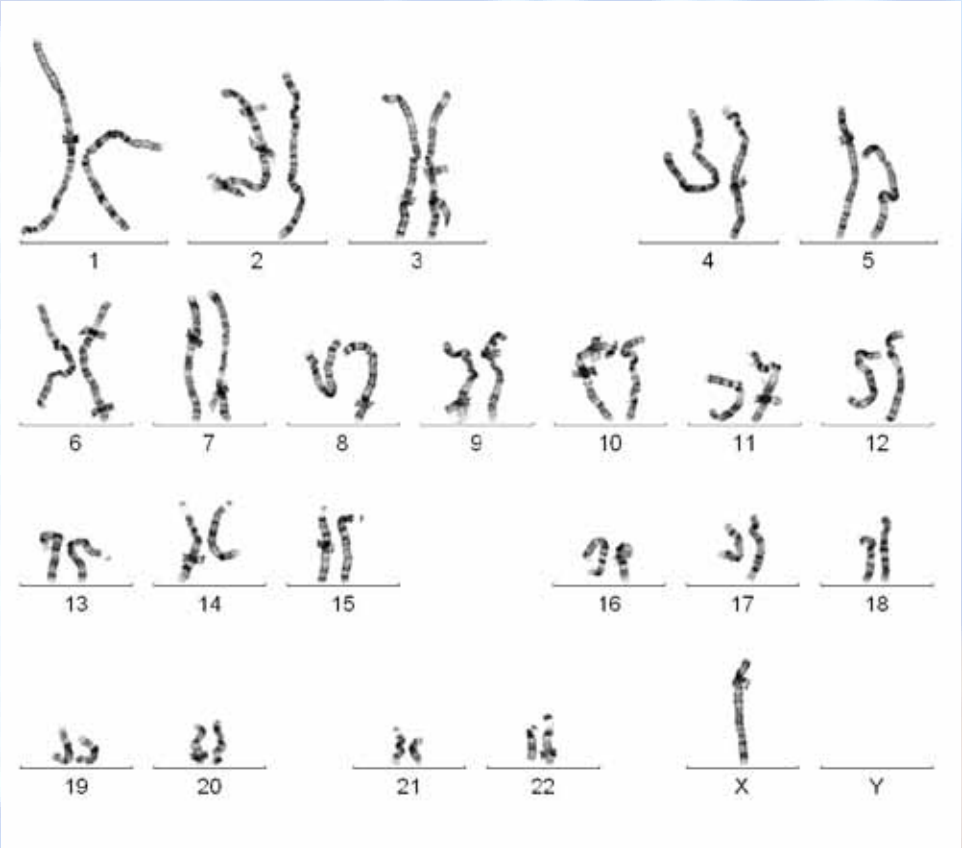
2n = 46



Aneuploidy

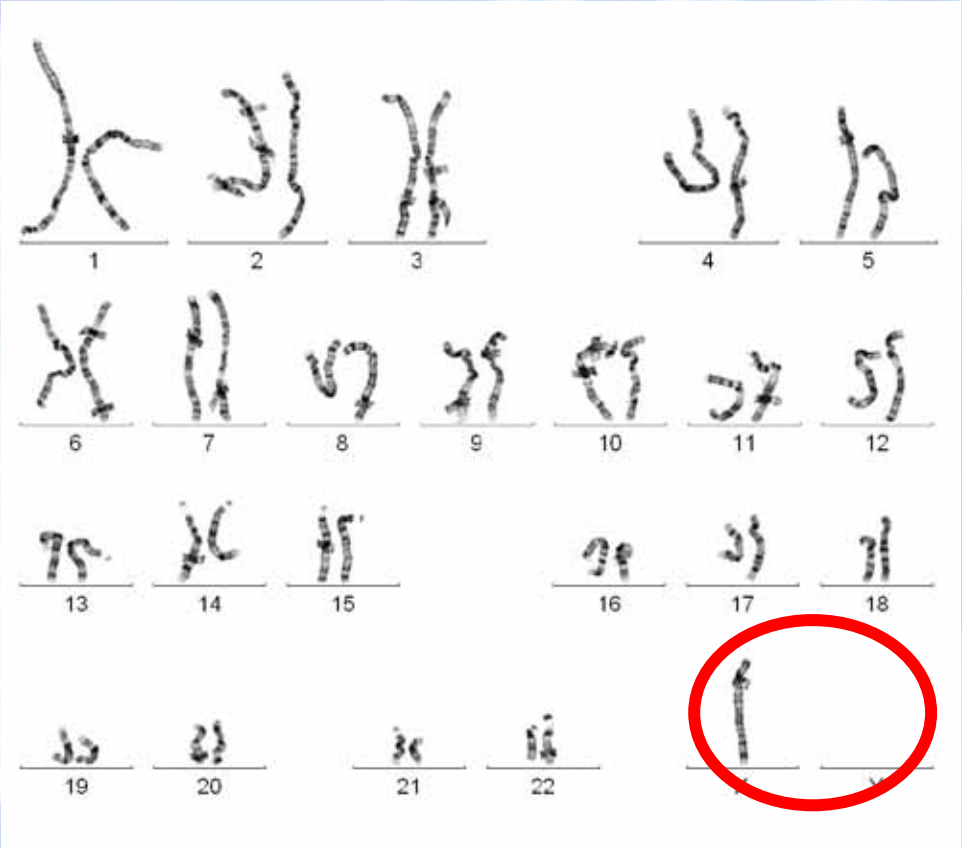
- Variation in chromosome number
- Most commonly identified chromosomal abnormality in humans
- 5% recognised pregnancies (Hassold and Hunt, 2001)
- 0.3% of live births
- Most common cause of intellectual disabilities

Monosomy (2n-1)



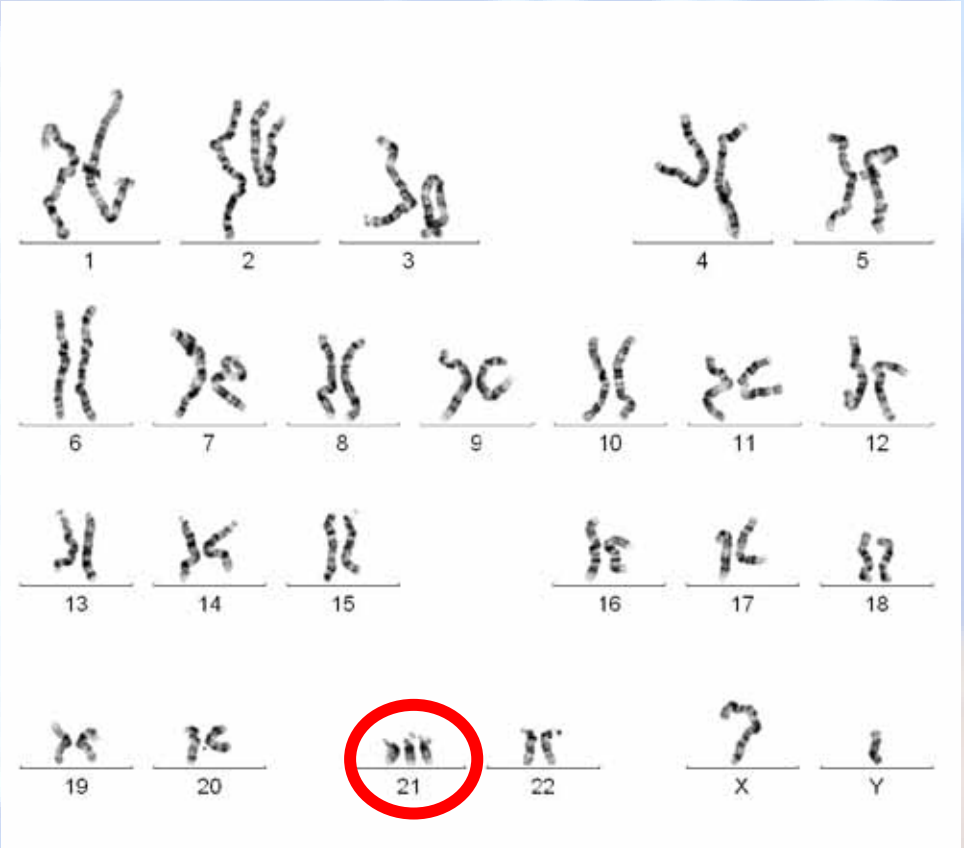
Monosomy (2n-1)

Turner Syndrome (XO)



Trisomy (2n+1)

Down Syndrome

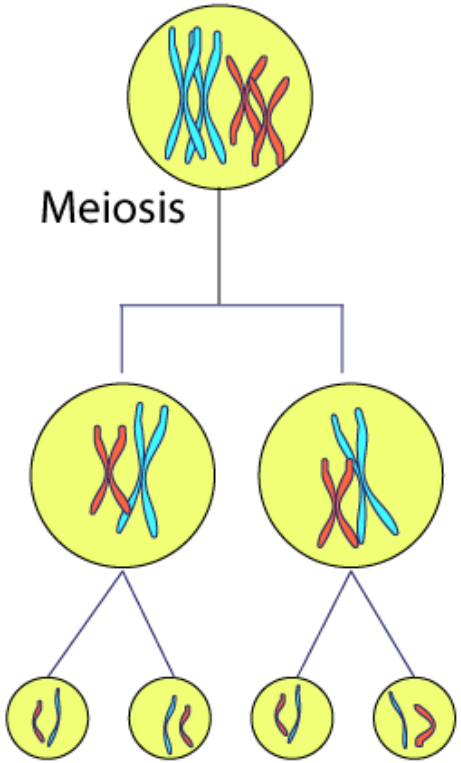


Causes of Trisomy (2n+1)

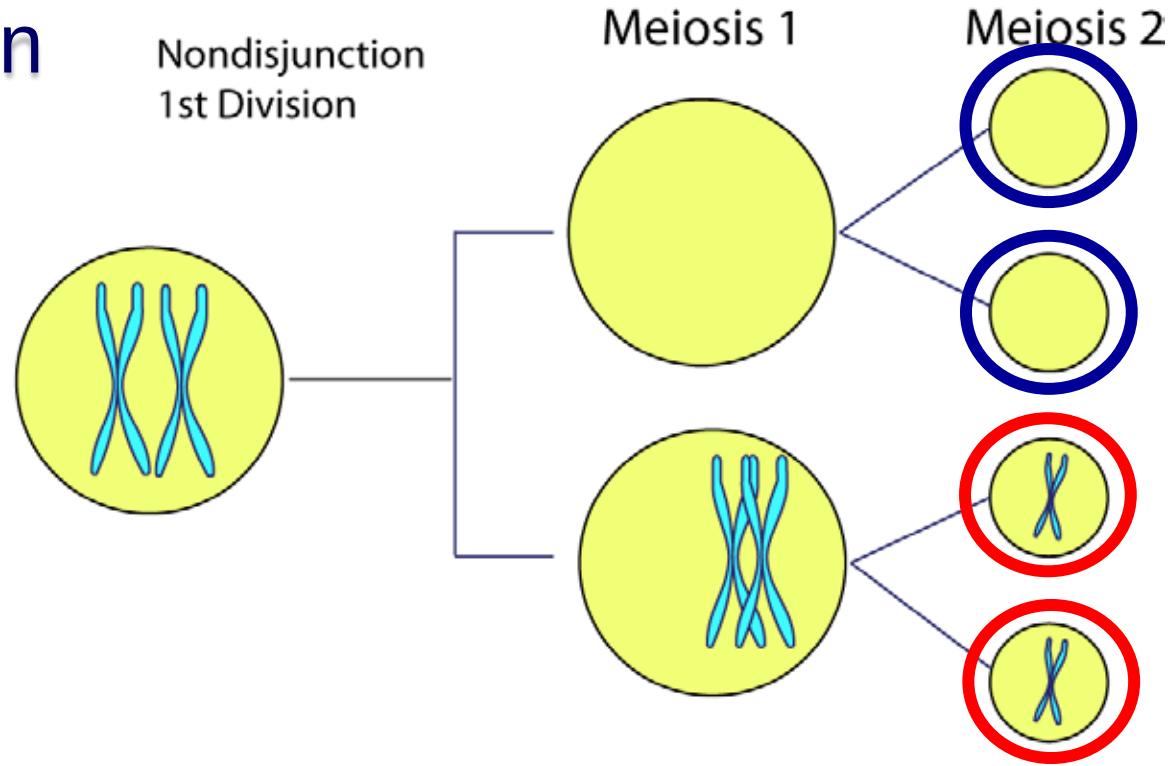
- Non-disjunction during Meiosis
- Non-disjunction during Mitosis in the early embryo
- Translocation

21

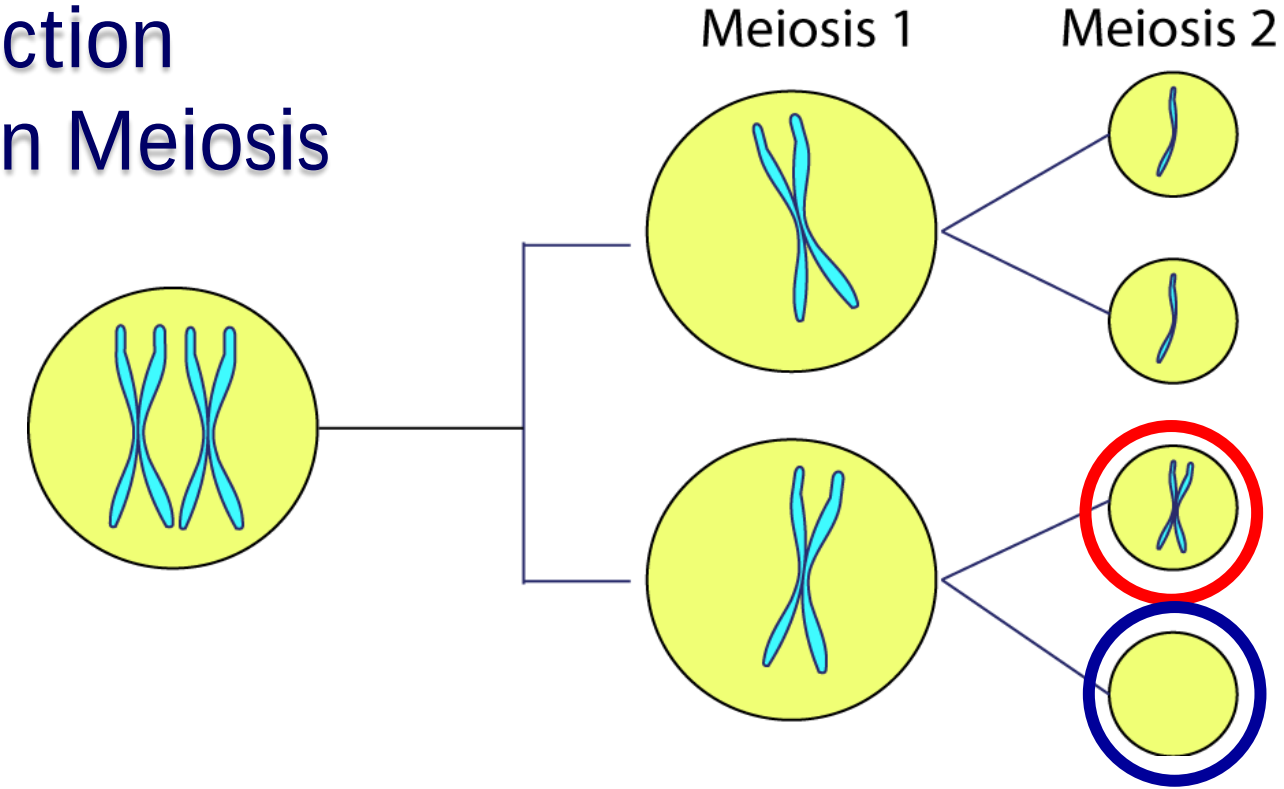
Meiosis



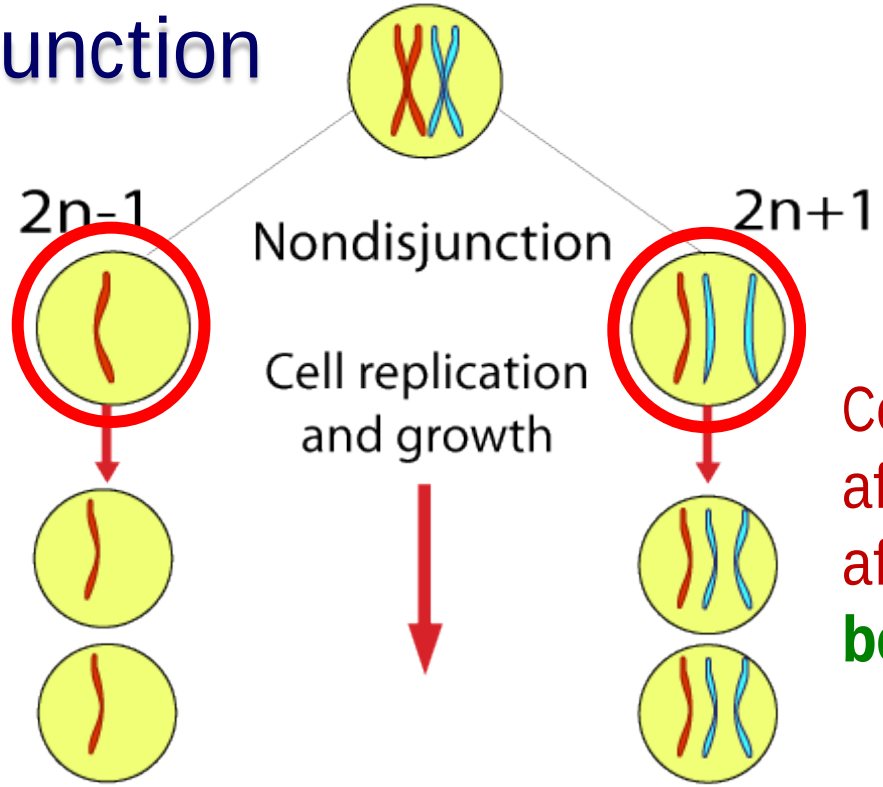
Nondisjunction 1st Division Meiosis



Nondisjunction
2nd Division Meiosis

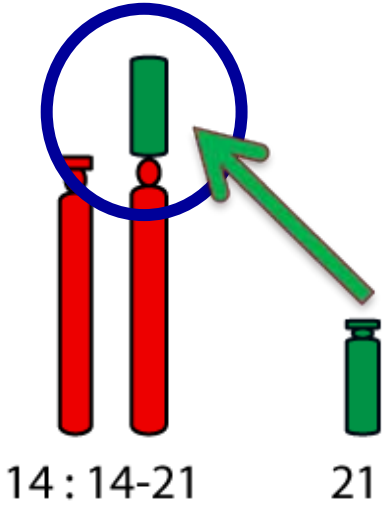


Nondisjunction
Mitosis

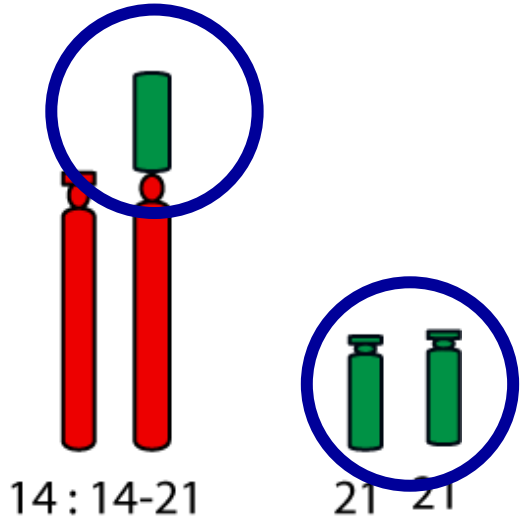


Cells arising from affected cells will be affected, **others will be normal**

Translocation



Balanced Translocation– unaffected



Translocation– affected

Trisomy 21 - Down Syndrome

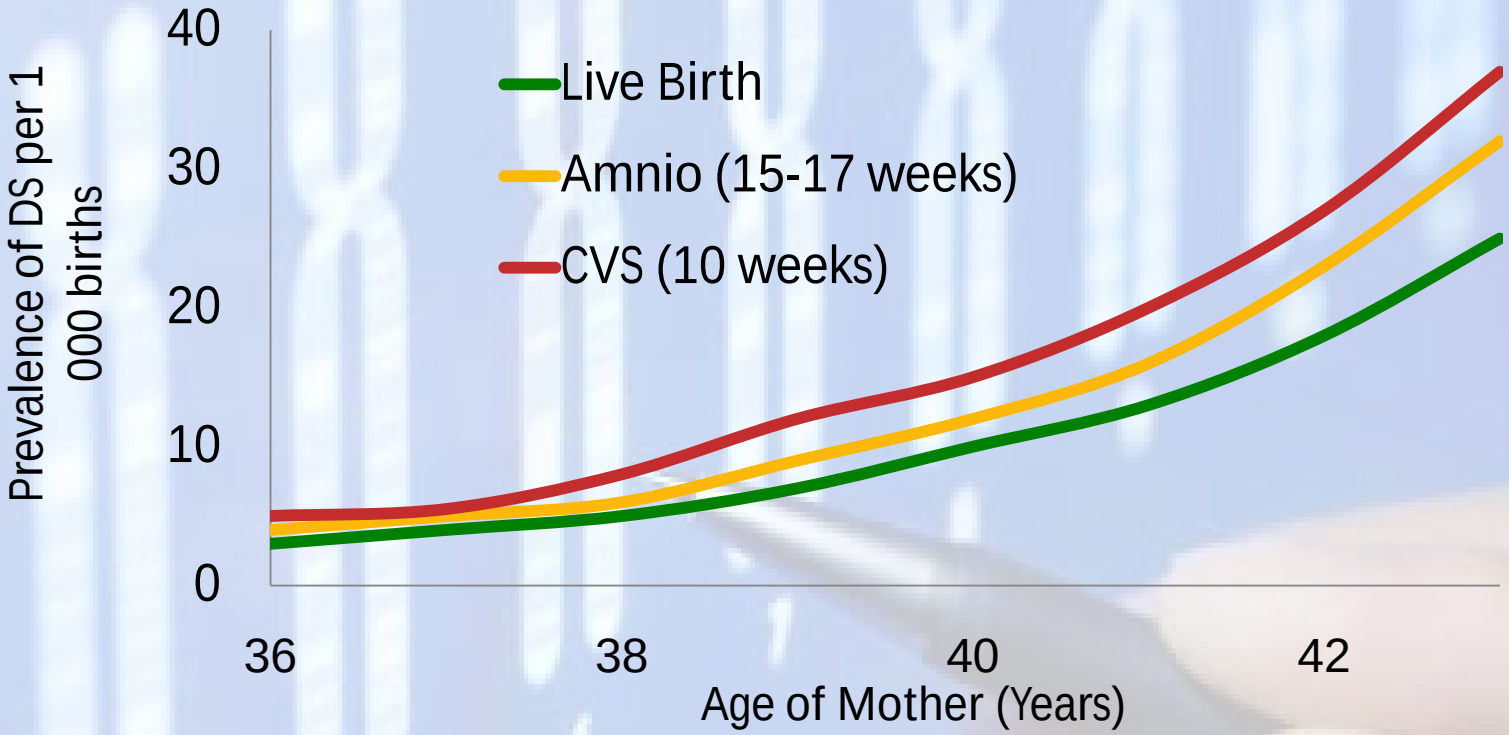
- Affects approximately 1 in 400 pregnancies
- Affects approximately 1 in 700 live births
- Increases with Maternal Age

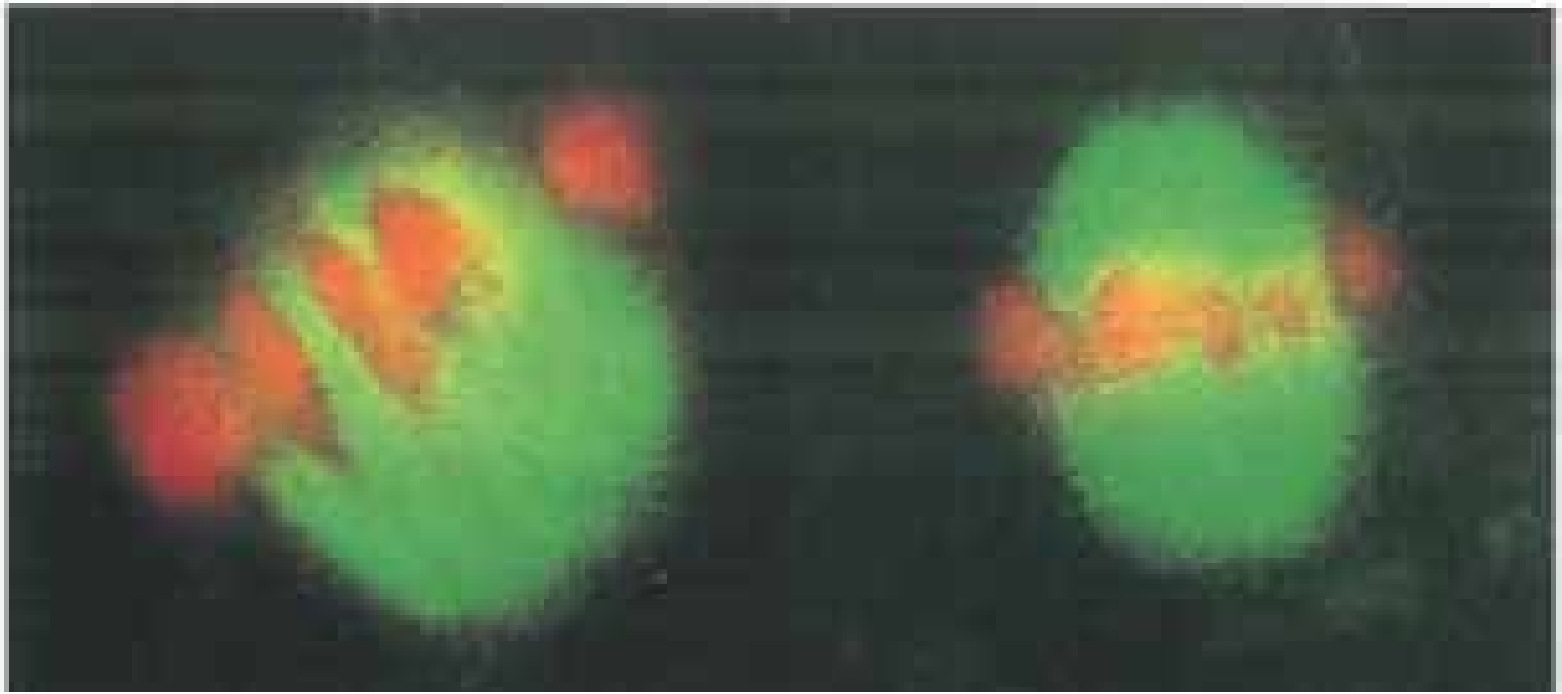
Trisomy 21 - Down Syndrome

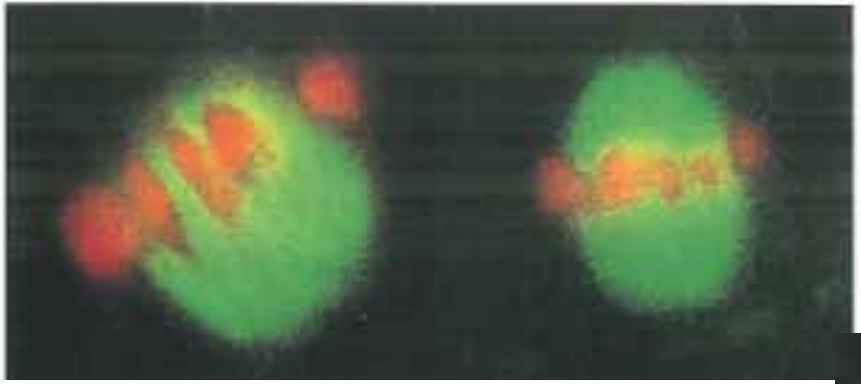
- Mild:
  - Intellectual impairment
  - Able to participate in society
- Severe:
  - Severe intellectual impairment
  - Severe health problems

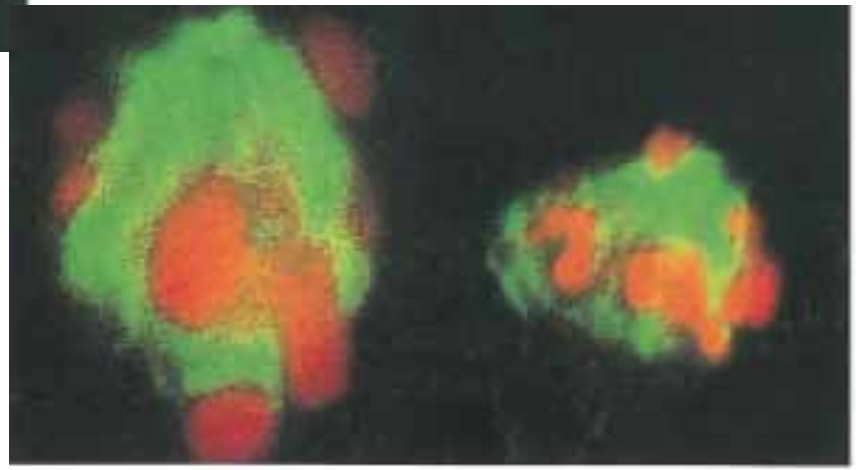
Prevalence of Down Syndrome for Maternal Age

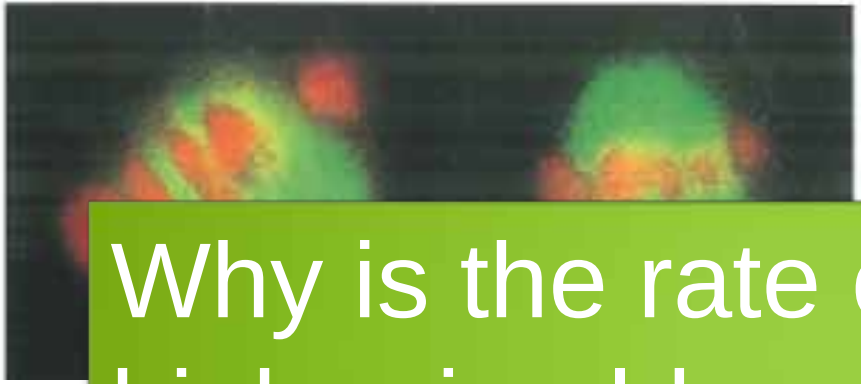
Halliday et al 1995



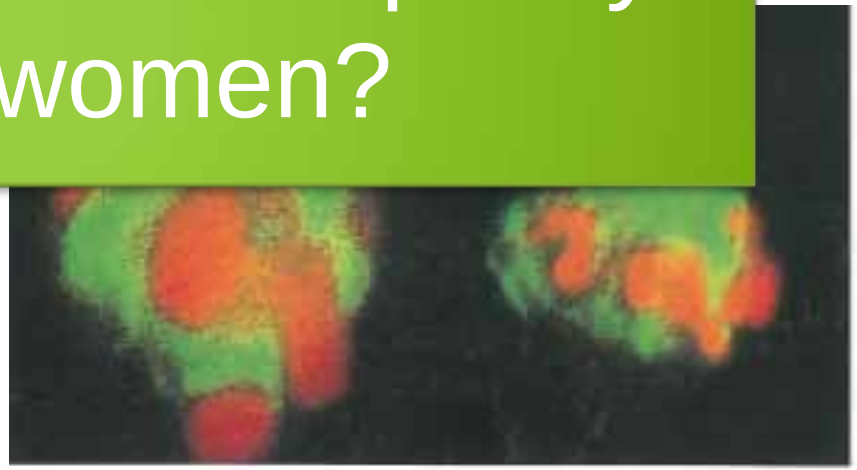








Why is the rate of aneuploidy higher in older women?



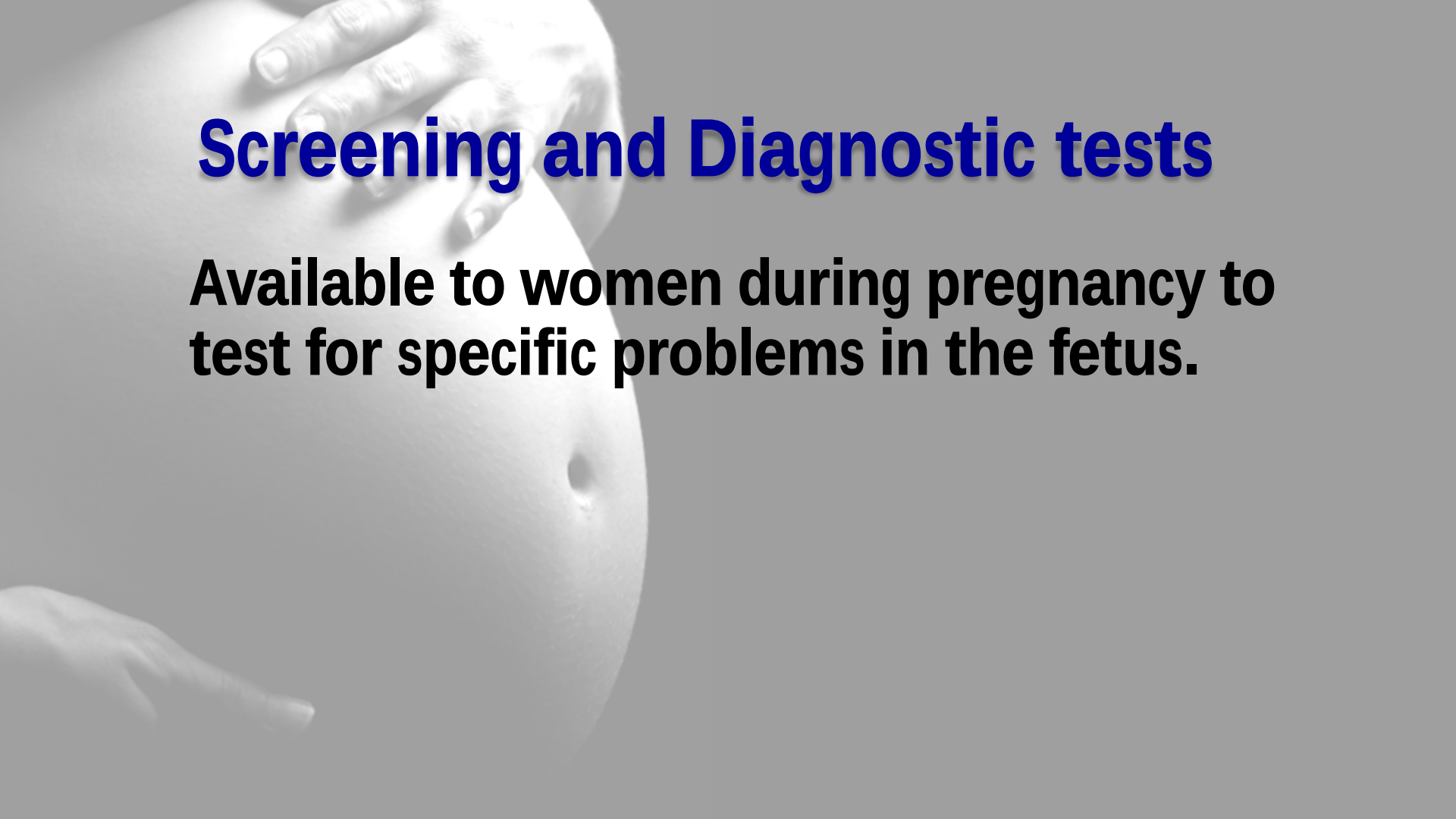
Screening vs Diagnostic testing during pregnancy

Screening

- Indicates relative risk

Diagnosis

- Definite answer



Screening and Diagnostic tests

Available to women during pregnancy to test for specific problems in the fetus.

Screening and Diagnostic tests

Optional and Voluntary

Decisions.....

- **Information allows people to make an informed choice about testing**

- **People consider their moral, religious, ethical and personal views on termination and disability.**

The beginning of screening

- 1970's
- Karyotyping technology
- Only for high risk women >35

A history of advances

- MSS (2nd trimester blood test)
- NT alone (from about 2000)
- Integrated testing using 1st trimester blood test and NT ultrasound available to women of any age (From 2009)

Screening tests

- Carry no risk to the pregnancy
- Give an “increased” or “decreased” risk of the baby having a chromosome problem usually in comparison to the mothers age related risk.

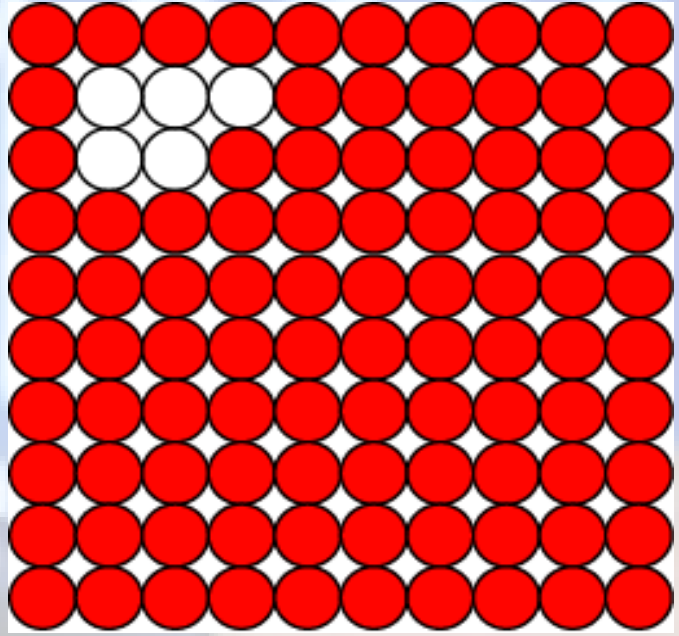
Screening tests

- Approximately 5% of pregnancies tested will receive an increased risk result

- Most of these **won't** have a chromosome problem

Screening tests

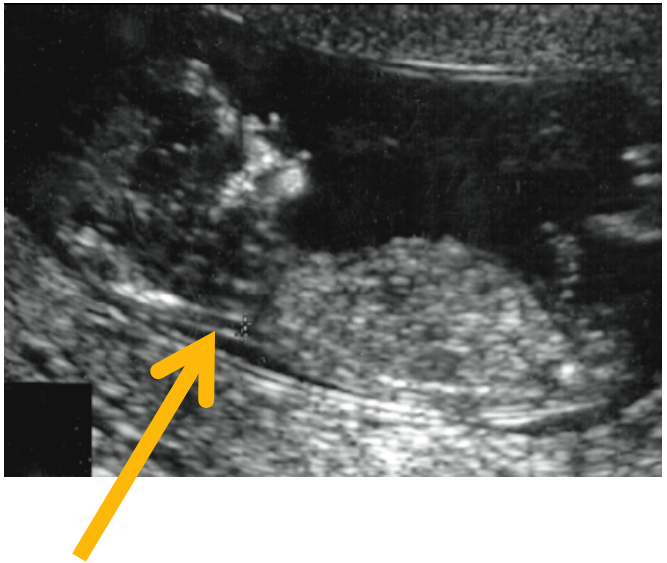
- Approximately 5% of pregnancies tested will receive an increased risk result
- Most of these **won't** have a chromosome problem



NT ultrasound

- 11 – 13 weeks of pregnancy

- Give a risk figure
  e.g. 1 in 135 risk compared with an age related risk of 1 in 320

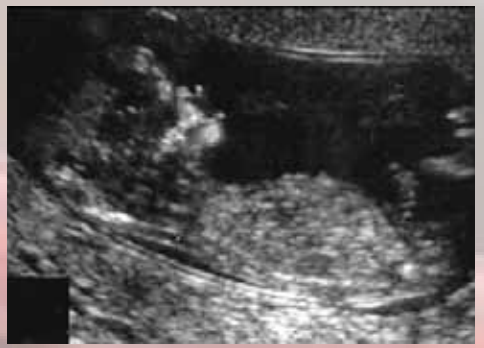


Nuchal Translucency

Maternal Serum Screen

- 11 – 14 weeks or 15 – 17 weeks
- Measures the levels of specific proteins in the mothers blood
- Gives a “high” or “low” risk result

Integrated test



1st Trimester

- Blood test and NT ultrasound

2nd trimester

- Blood test combined with the maternal age to give a risk figure.

Integrated test

	Maternal Serum Screen	Nuchal Translucency	NT + blood test
Detection rate	60%	~75%	~80-90%
False negative rate	40%	~25%	~10-20%

Screening tests

Cannot say whether the pregnancy is affected with a chromosome problem, just whether it is **more or less likely to be**.

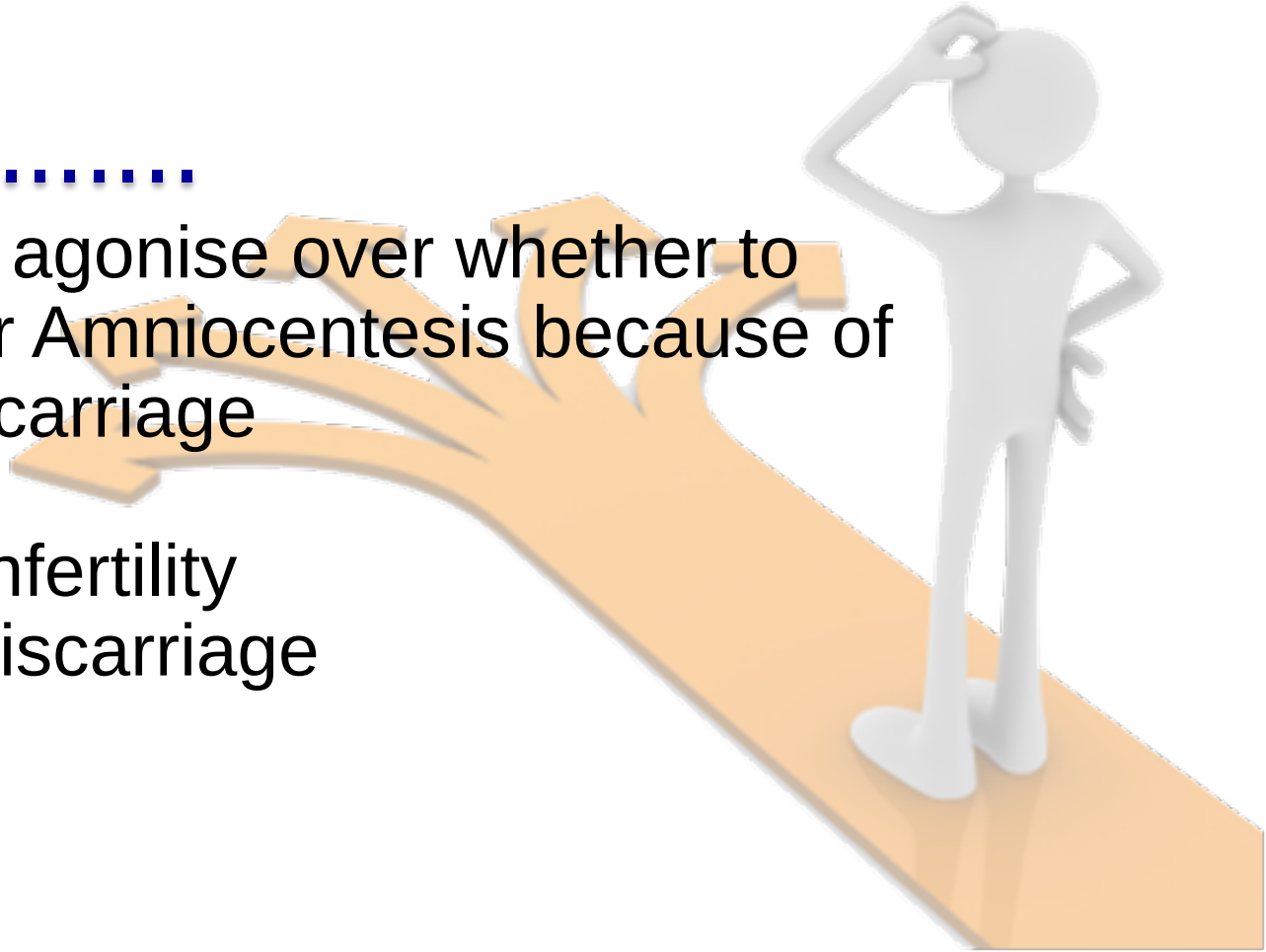
Screening tests

- A “high risk” result can be extremely anxiety provoking for the couple while they decide how to proceed.
- Couples may have a reassuring screening test and go on to have a child affected with a chromosome problem.

Decisions.....

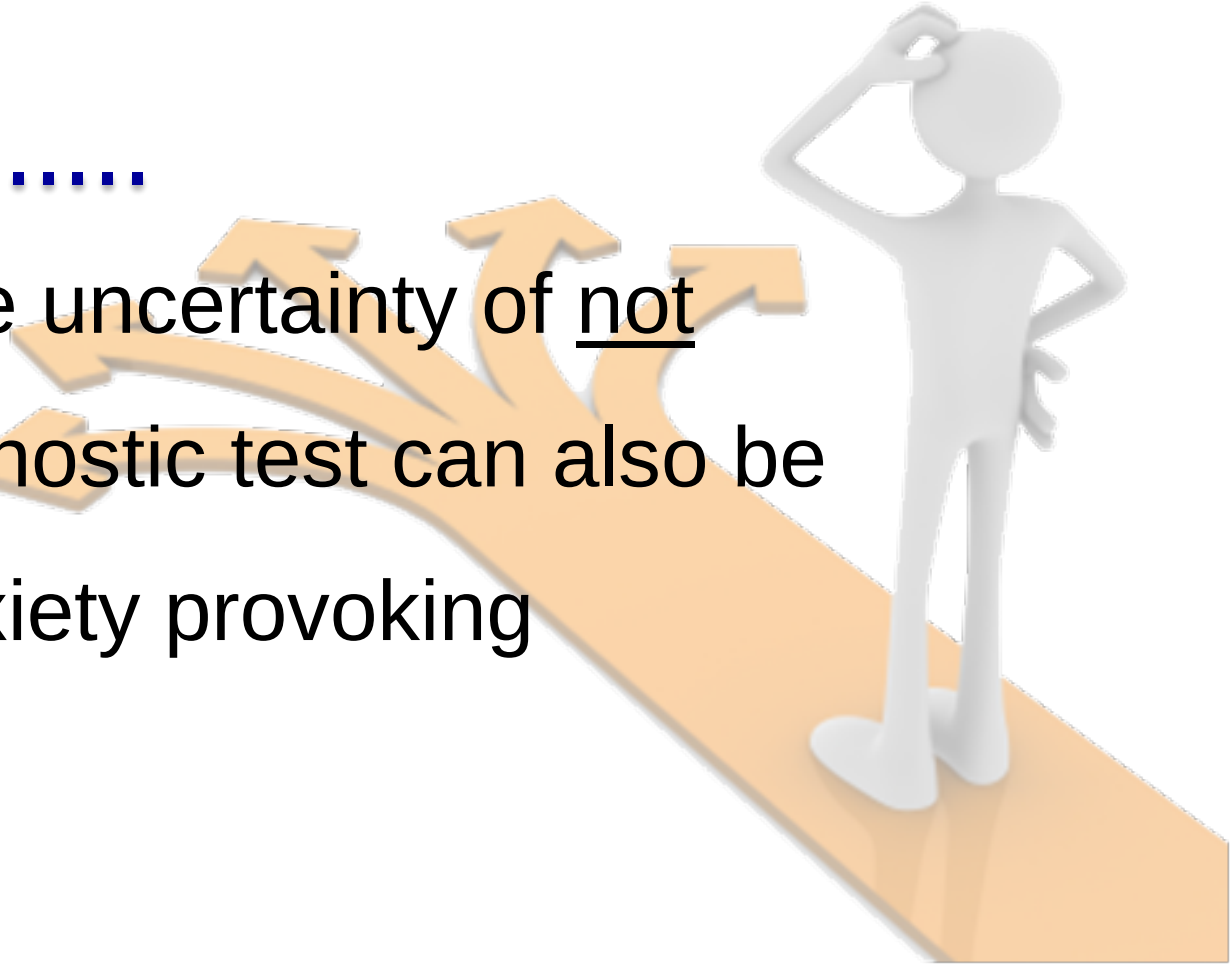
Couples often agonise over whether to have a CVS or Amniocentesis because of the risk of miscarriage

- History of Infertility
- Previous miscarriage
- Age



Decisions.....

Living with the uncertainty of not having a diagnostic test can also be extremely anxiety provoking

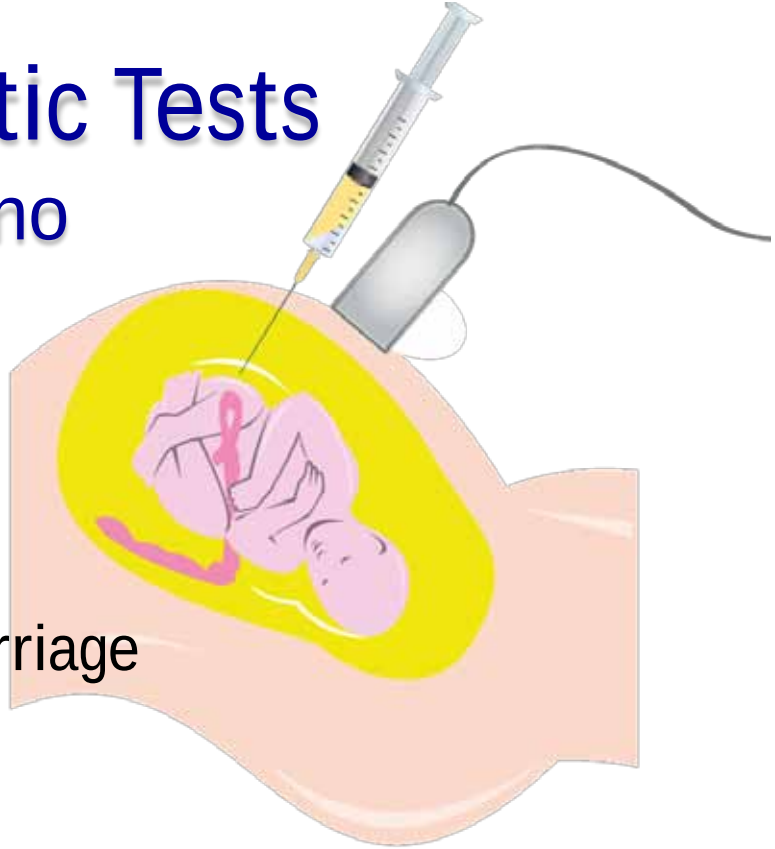


Genetic Counselling

- Help provide an opportunity to discuss
  - What the result means for the parents/family
  - Options available
  - Advantages & disadvantages of further testing
  - Parent's attitude toward disabilities and termination
  - The course of action the couple think they may take
- In a non-judgement, supportive environment

Prenatal Diagnostic Tests

Not maybe, but yes or no



Amniocentesis

- 15 – 17 weeks gestation
- Remove 10 – 20 mL fluid
- 0.5% to 1% risk of miscarriage

Chorionic Villus Sample

- 11 – 13 weeks gestation
- Removal 10 – 25 mg of tissue
- 1 – 3% risk of miscarriage

Advances in Biotechnology

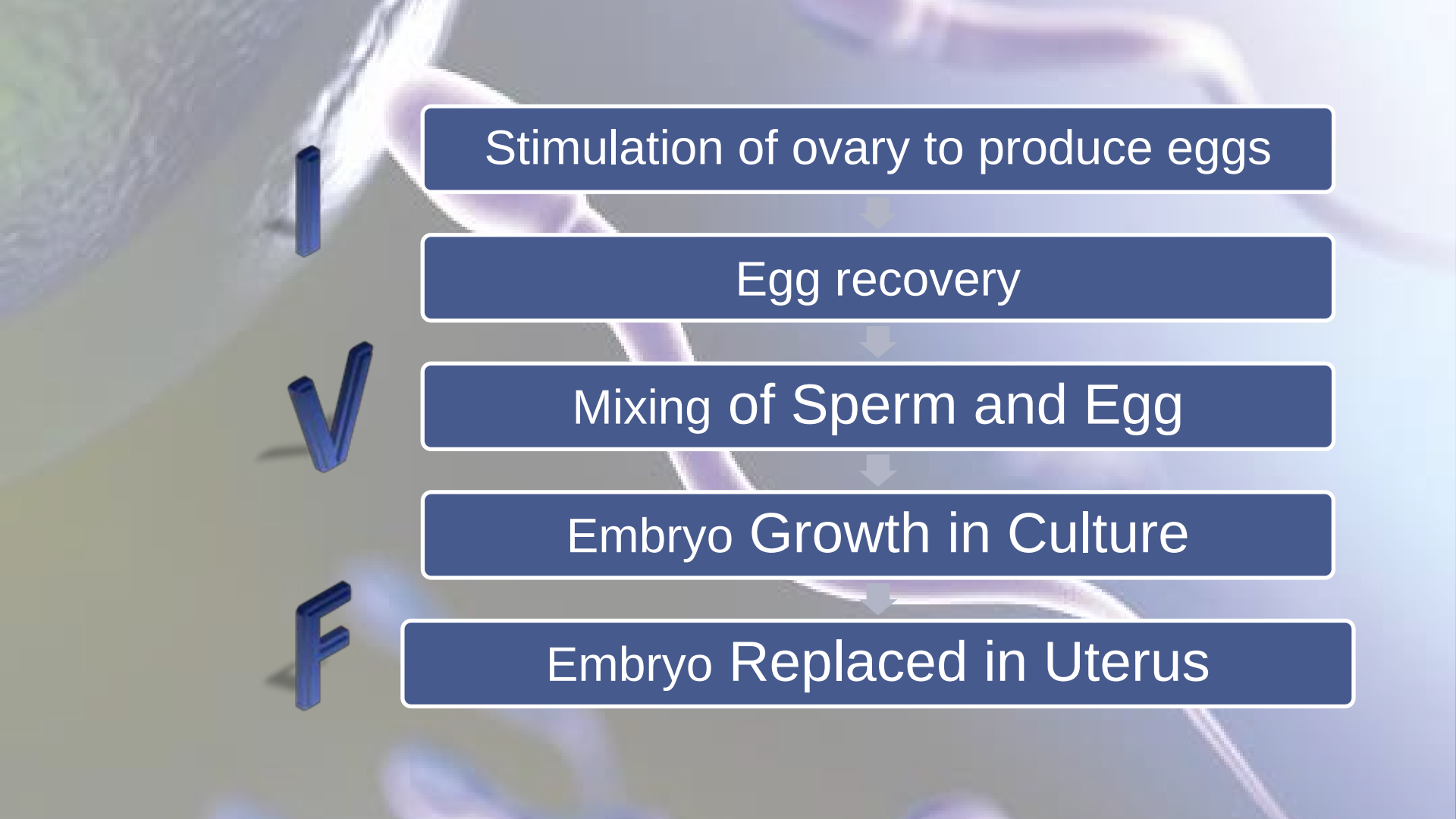
- Pre-implantation genetic Diagnosis
  - Screening for aneuploidy
  - Diagnosis for inheritable disease
  - Offers the opportunity to detect in the embryo before pregnancy is established

Preimplantation Genetic Diagnosis

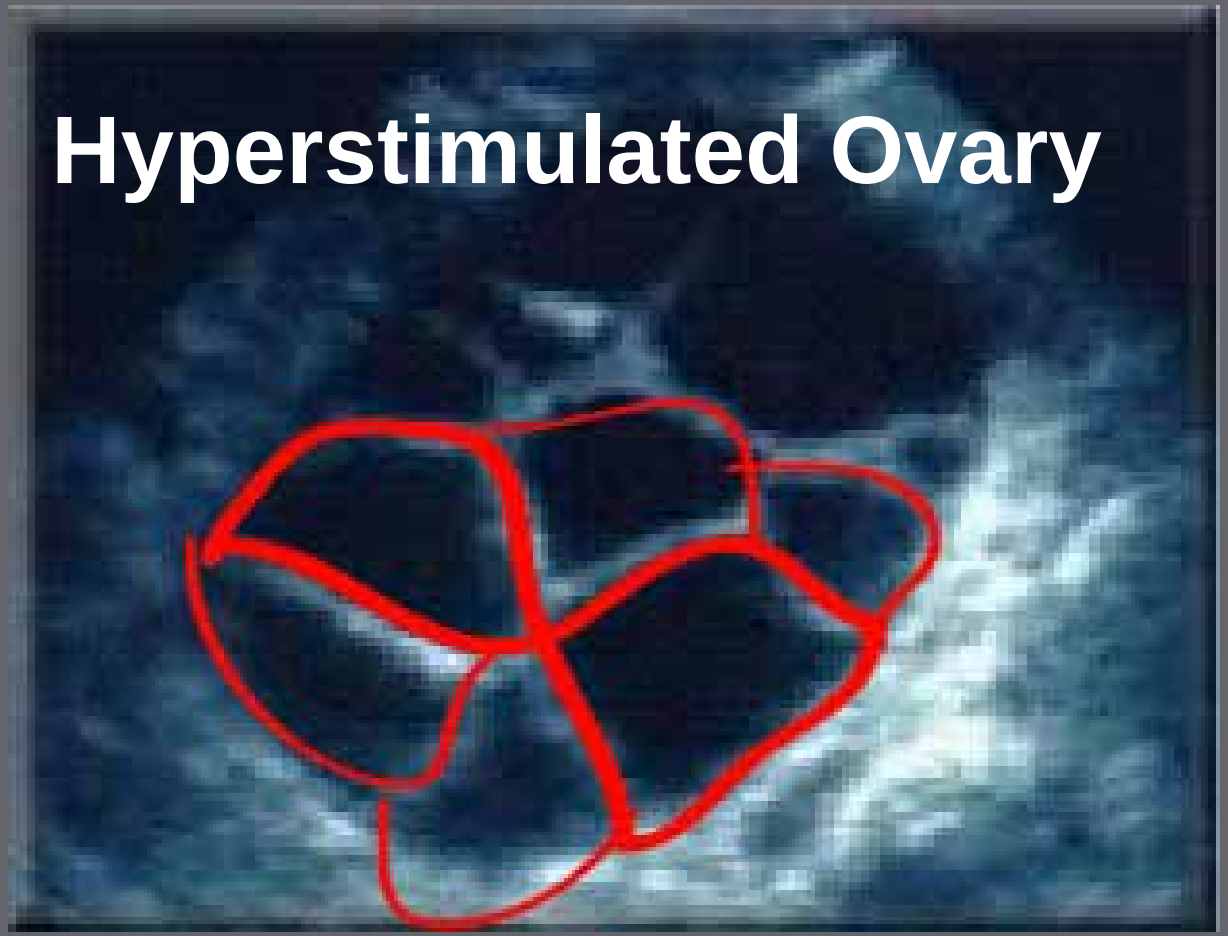
P — Generate Embryo via IVF

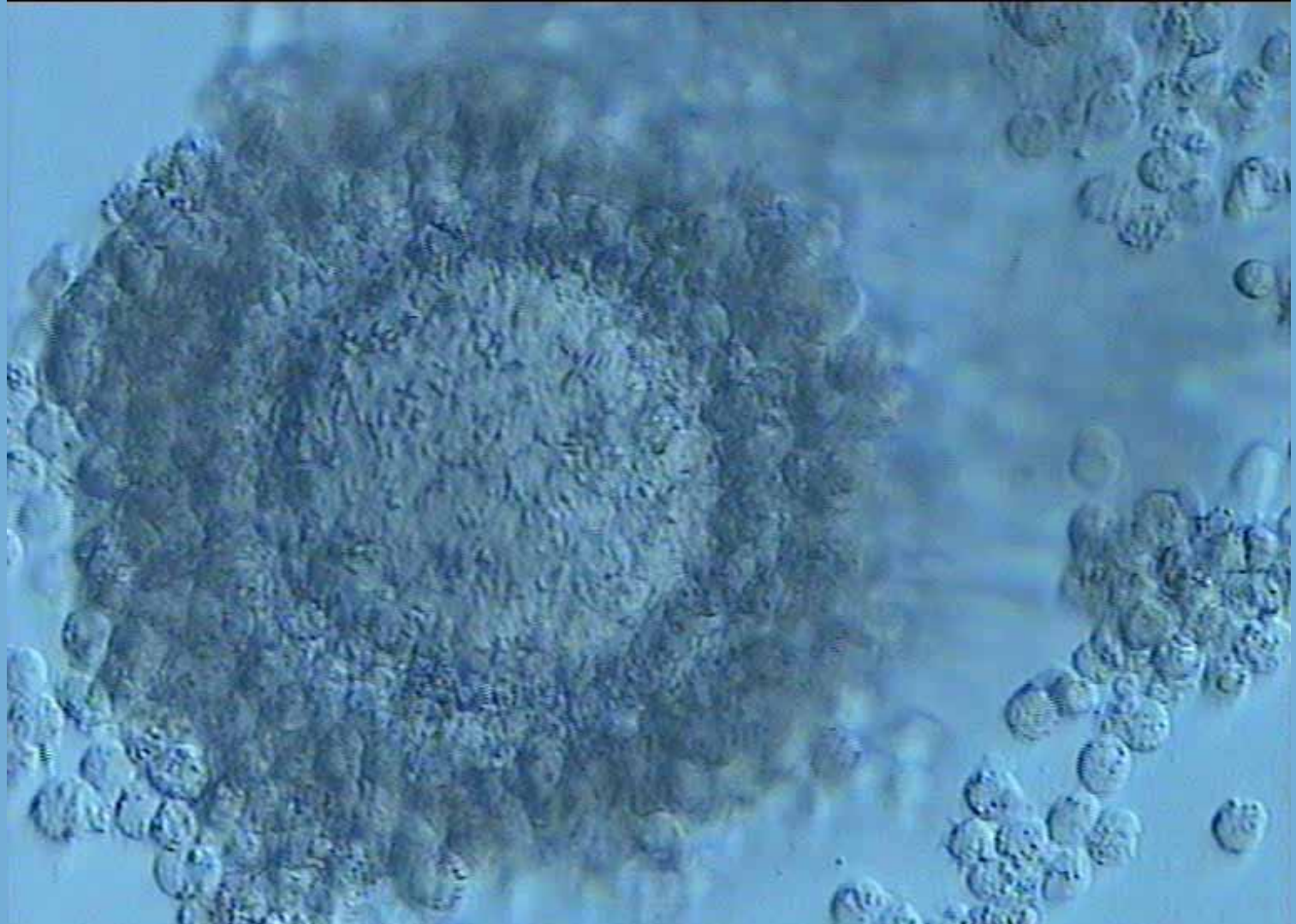
G — Screen Embryo
Biopsy and Diagnostic Screening

D — Implant unaffected embryo


I
Stimulation of ovary to produce eggs
Egg recovery
V
Mixing of Sperm and Egg
Embryo Growth in Culture
F
Embryo Replaced in Uterus

Hyperstimulated Ovary





Normal embryo development


D1


D1-2

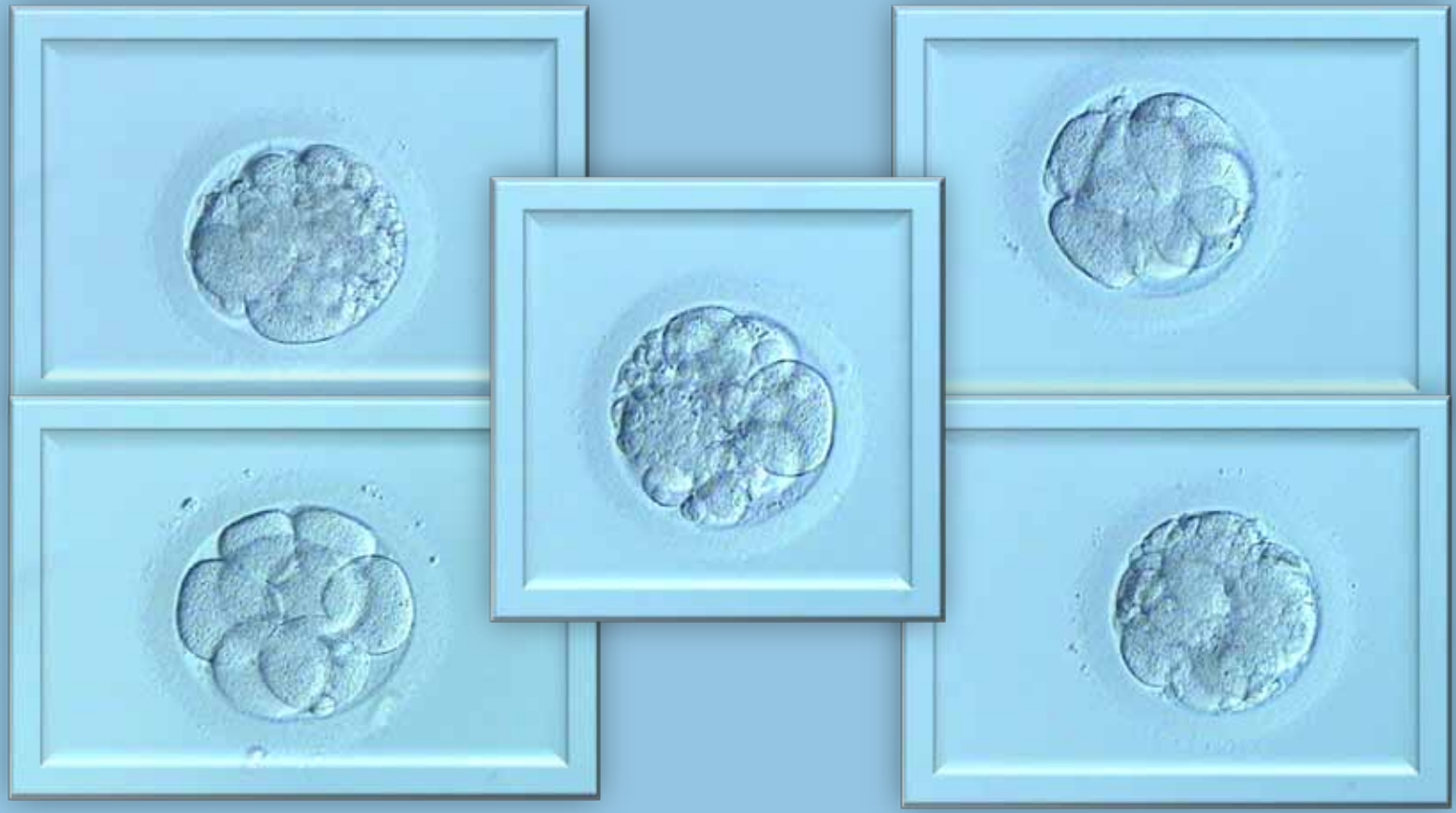

D2

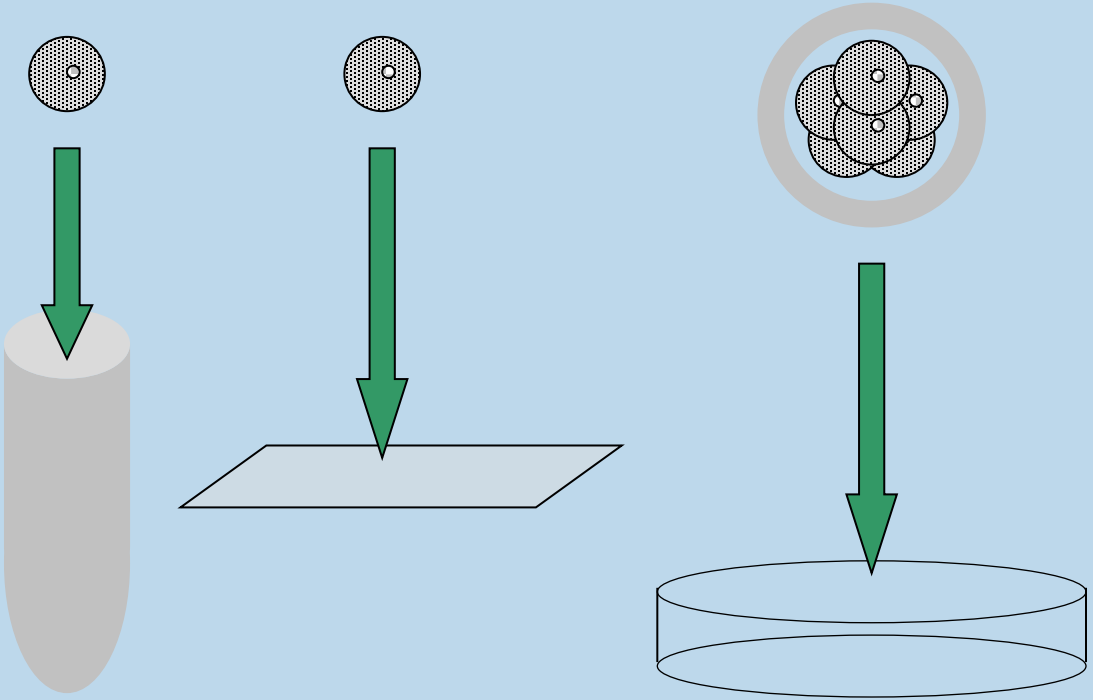

D3


D4


D5


D6

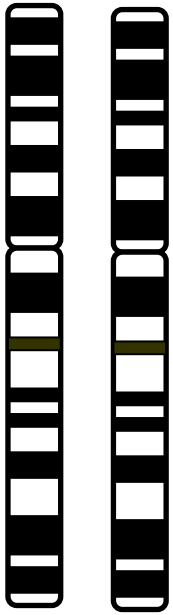




PCR tube glass slide culture dish

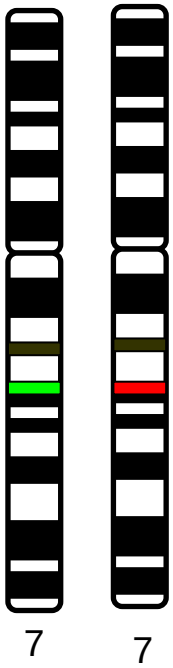
Identifying Inheritable Genetic Disorders

Polymerase Chain Reaction (PCR)



Identifying Inheritable Genetic Disorders

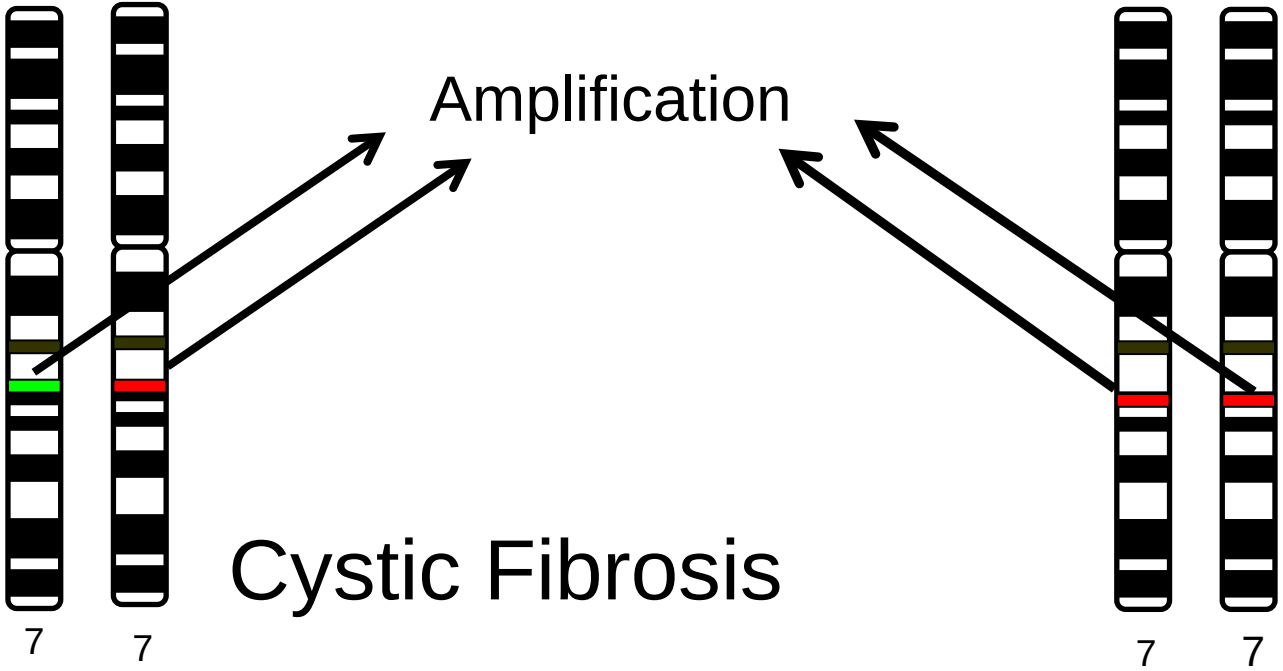
Polymerase Chain Reaction (PCR)



Cystic Fibrosis

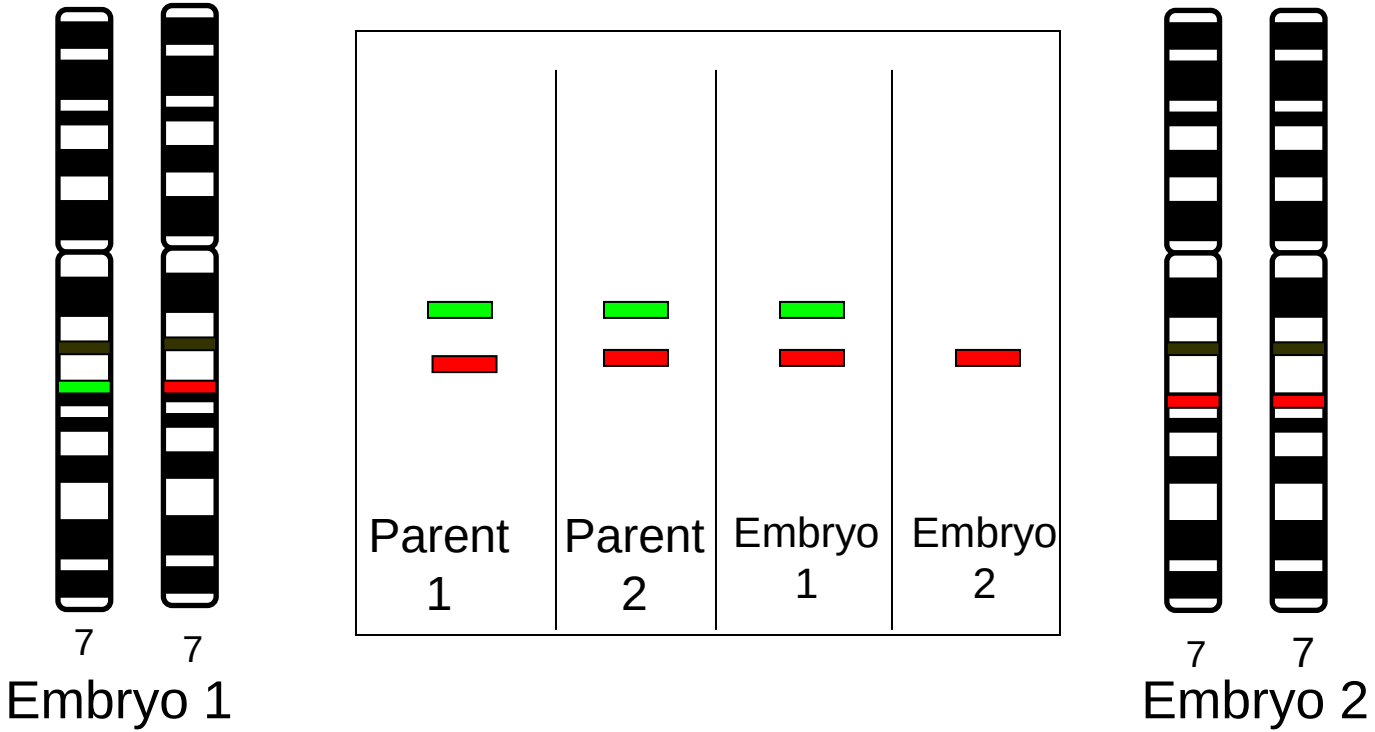
Identifying Inheritable Genetic Disorders

Polymerase Chain Reaction (PCR)

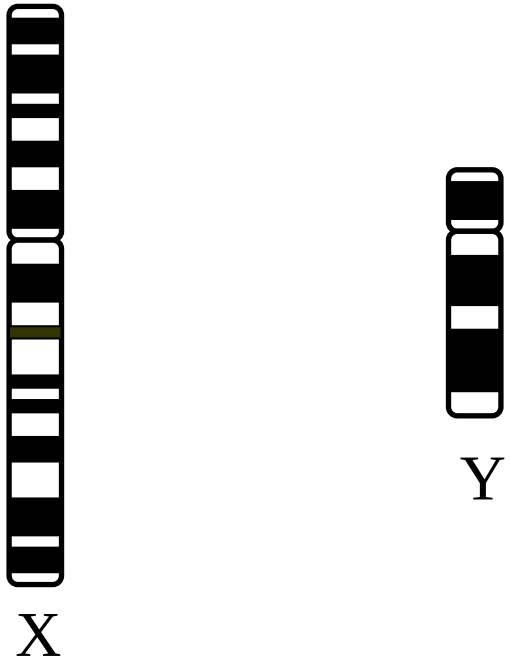


Identifying Inheritable Genetic Disorders

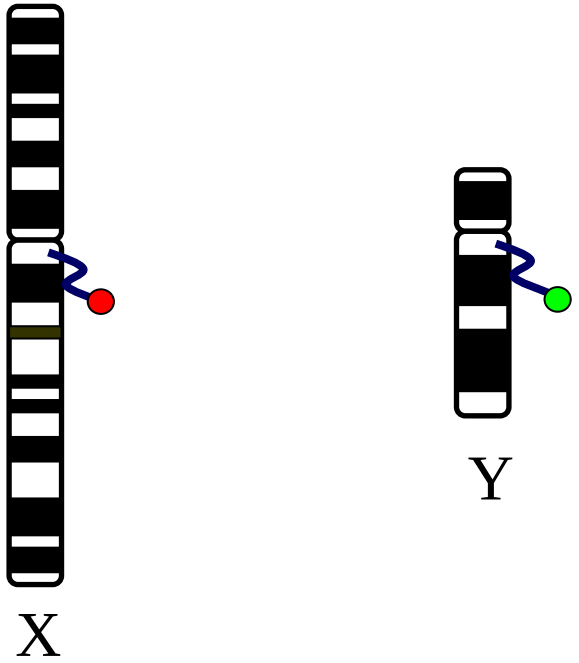
Polymerase Chain Reaction (PCR)



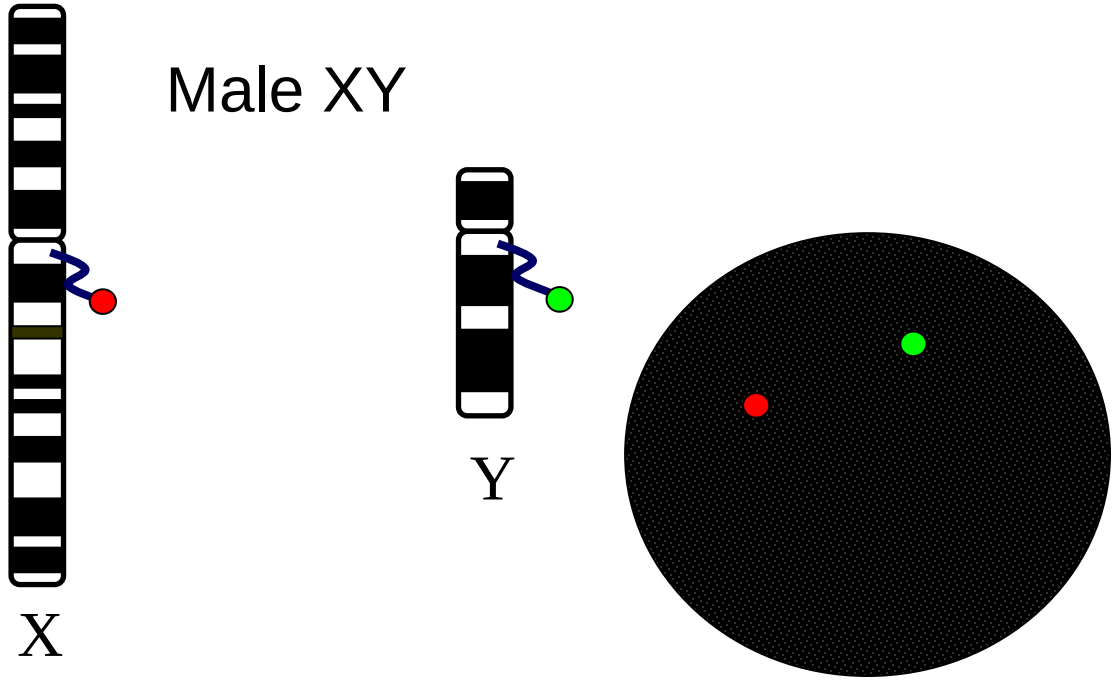
Aneuploidy - Chromosomal Rearrangement



Fluorescense *in situ* hybridisation FISH

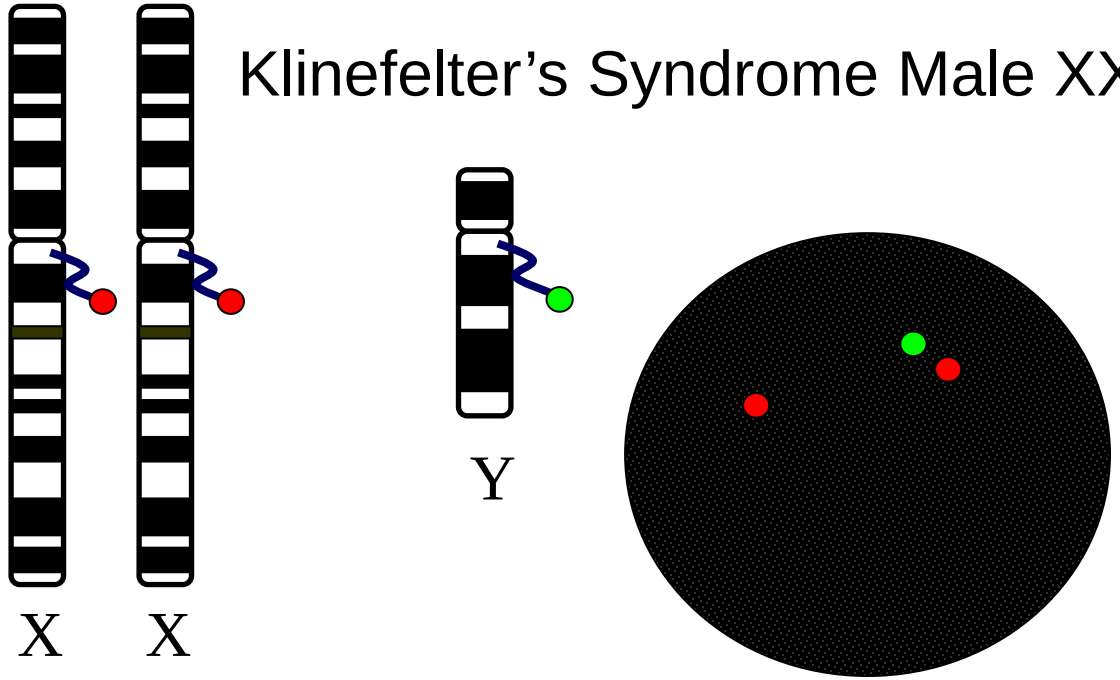


Fluorescense *in situ* hybridisation FISH

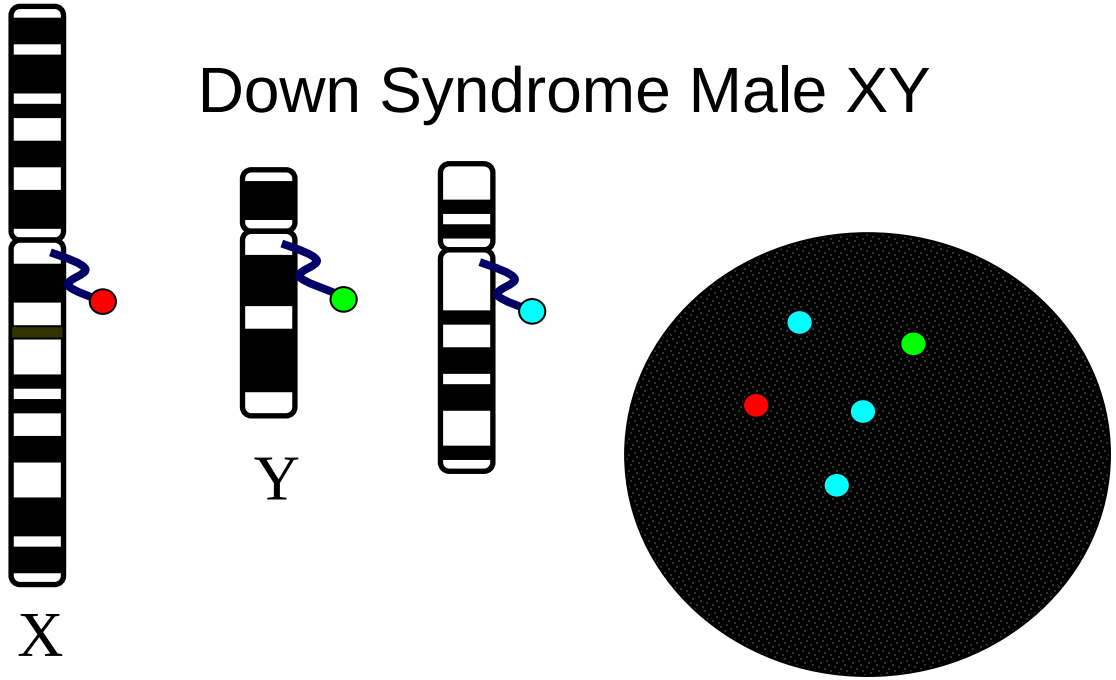


Fluorescense *in situ* hybridisation FISH

Klinefelter’s Syndrome Male XXY



Fluorescense *in situ* hybridisation FISH



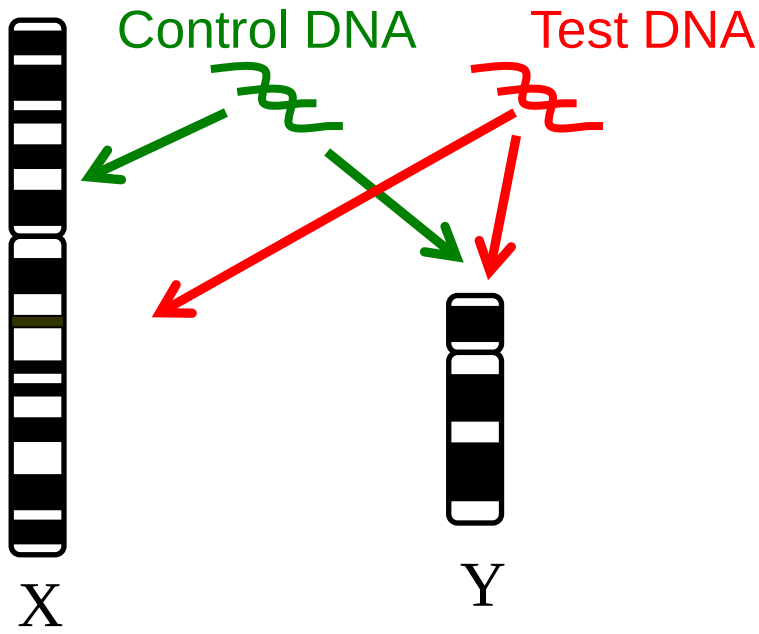
Limits of FISH

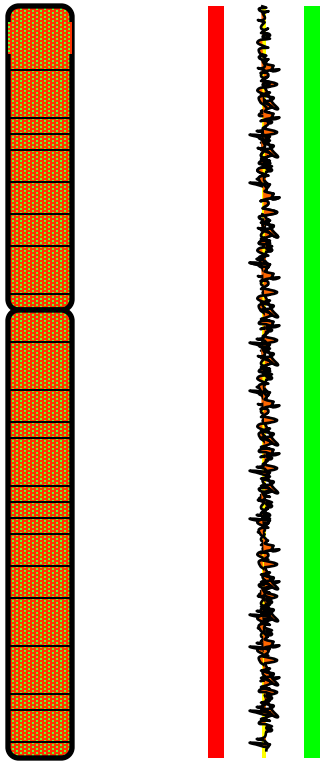
Can only look at ~ 10 chromosomes

Leaves ploidy of 14 autosomes unknown

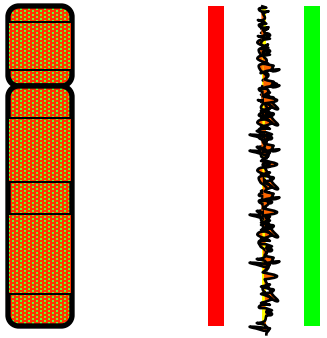
90% accuracy from a single cell

Comparative Genomic Hybridisation (CGH)



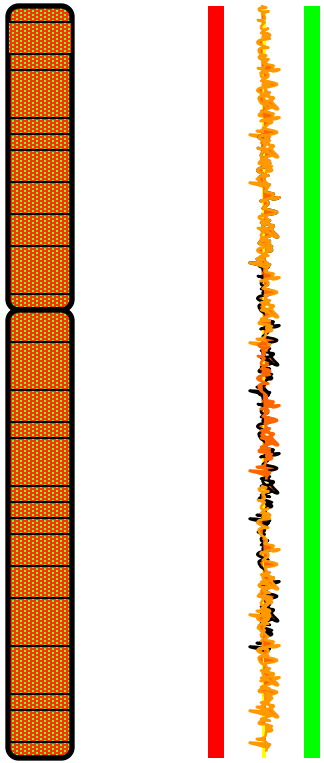


X

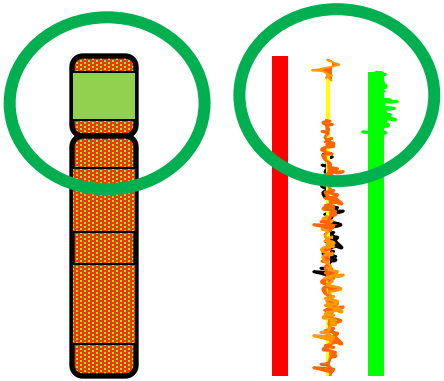


Y

Normal Male

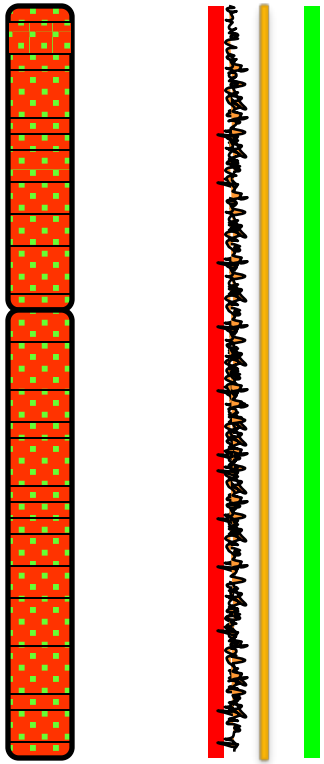


X

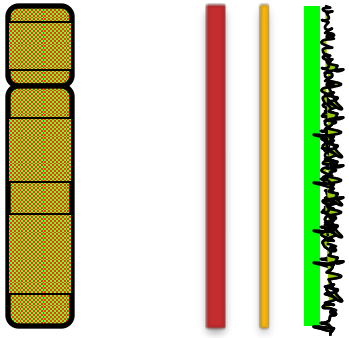


Y

Male with Y-deletion



X



Y

Normal Female

How does one make the decision to proceed?

Numbers are easy

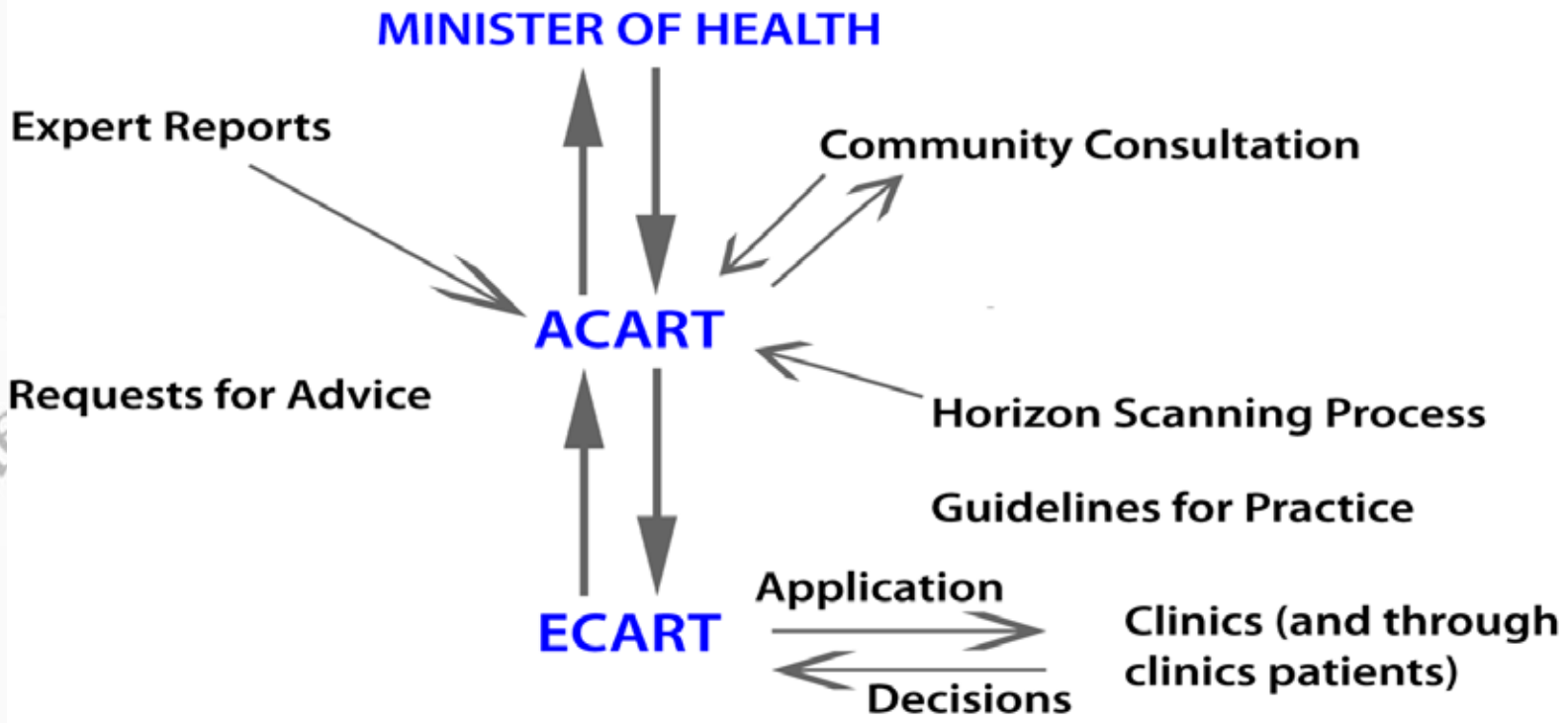
Values are difficult

Does it always go right

2 - 3% of all babies are born with some congenital abnormality


Ethics
Standards
Duty
Integrity
Values
Principles
Duty
Morals

HUMAN ASSISTED REPRODUCTIVE TECHNOLGIES ACT

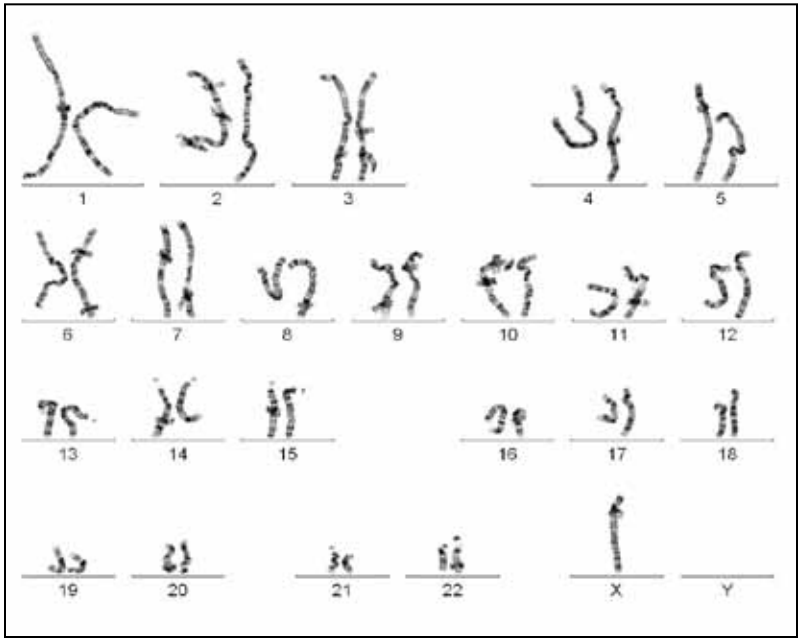


The HART Act and PGD

- **What is a ‘serious disorder’?**
- **What grounds is the decision made on?**
- **Who makes the decision?**
- **Is a ‘serious disorder’ one that presents only at birth?**
- **What would you think of selecting for a disability?**

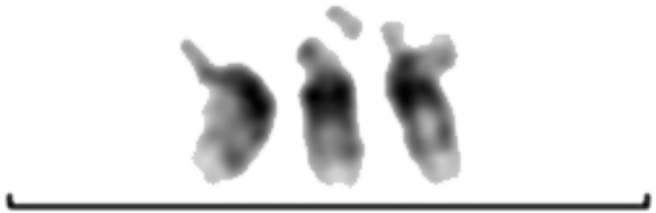
Challenge 1 Aneuploidy

Aneuploidy resulting in the loss of an entire chromosome usually results in a non-viable embryo. However, if the chromosome concerned is the X-chromosomes the embryo may live. Explain why the loss of an entire **autosome** is almost always lethal but the loss of the **X-chromosome** may not be lethal.



Challenge 2 Trisomy 21

Compare and contrast the three possible mechanisms by which Trisomy 21 can arise.



21

Challenge 3 Contemporary Issues

Discuss how the use of named **biotechnologies** have enabled scientists to develop effective methods of ***diagnosing genetic abnormalities in embryos*** and how these technologies have met a human need or demand.

Challenge 4 Contemporary Issues

Pre-natal Diagnosis – DURING pregnancy
Preimplantation genetic diagnostics – BEFORE pregnancy

- Identify the technologies used
- Define the human need and demand that led to technological developments
- Discuss the ethical issues arising in each situation

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