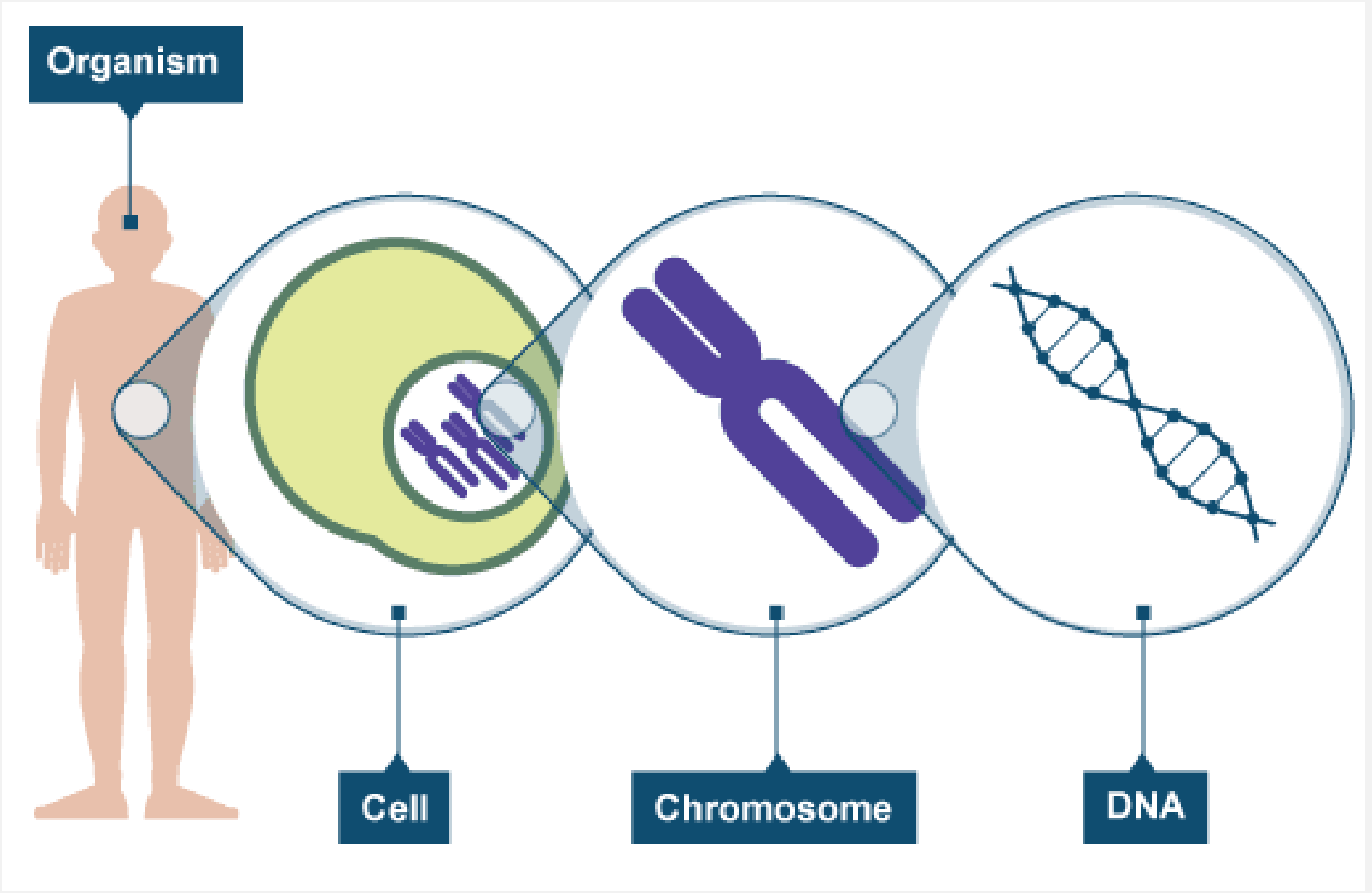
EVERYTHING YOU EVER WANTED TO KNOW ABOUT LFS BUT WERE AFRAID TO ASK….

Dr Helen Hanson

Consultant in Cancer Genetics

St Georges Hospital, South West Thames Regional Genetics Service

TP53 TESTING

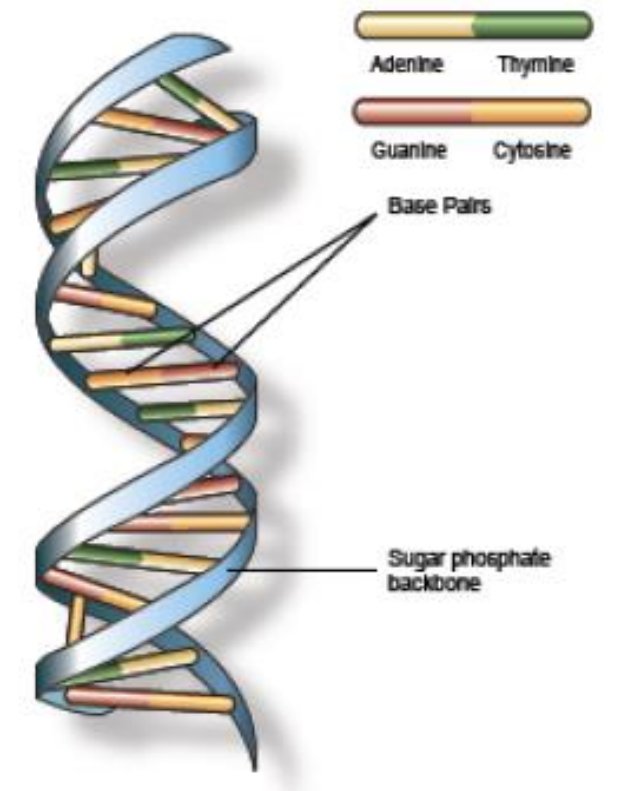

Organism
Cell
Chromosome
DNA

DNA AND THE GENETIC CODE

- Made up of 4 nucleotides or “bases”
  - A = Adenine
  - T = Thymine
  - C = Cytosine
  - G = Guanine

5′-ATGTGCATGCTAGCT-3′

3′-TACACGTACGATCGA-5′



ATAAATGTATGAATACTCCATTTTTCTATTATCCTATATGGCCCCAGGTGTAATTGTATAGTATCTCTTT
TTACTGTTAAATGCTGCAATAAGACTCACATGCAAAAAGCTGTATCTCTAAGCACTTAATAATTTGTTTC
CCCAGGAGAGTGATTCGATGATGGTGGATCCAACCAATGACATCCGGATTATAGGCTCCATCACAGTGGT
GATTCTTCTAGGAATTTCAGTAGCTGGAATGGAATGGGAGGCAAAGGTAAATTTCTCAAAAATGATATTA
TCAACAGTGGCTGGTCAGGTCCTGAACAAATTGCAGGAGTAGAGGGAACTCCATATTCAAAAGGAATTGC
TGTTATTACCTGCTATGGTGAAATGAGCAGGCAAGTGCTAGGTGGAACACCAAGCCTGCAAAGCACGAAG
CCCAGGCAGTCATGATTCAGGGCTCACGAGTCACATGACTGCCGTATTTTGTCTCTCTGTGCTGTCACCA
AGGCGGCTGCCTTATGCACAGACCCCTTATGATCATAGCAGTGGTGCACGCTGGAAGCCTGGGTCTCTCA
ATCACAAACCCTGGTTCCTCTTTCAAGCTGCCTGTGGGTGCAAAAGCCCAAGAGAAATGGCAAGTGTGTT
GAGAACATAAGAGAGGCAAAAACTATCATTCTCATCTGAAAGCCAGTACTTCACCAGCAAATTTAGGCAC
ATCATAGGCTTTAGAACCAGAAAATCTCTGAGTTTAACTAGTGATAAAATGGATAGTAAATTTCCGAATG
ATGGGAAACATGTCTTTTGCCTCCTTTGTAATTCCCTCAAGTGACTGGTGCAATTGAAAATATTCCTACG
AGCCTGTGGATGAAGTAACTAGATCTCAAGCAGTCATGAGATGTGGAAAGACAGCCAAAGCCTCCCACCT
ATAAGTCAATAGAAAACATTCCTACATGGCATTTATTTGTAGATTATGCATTCACACATTCAACAAAAAT
TAAGTTAGTGCCTACCACATGTTGAGCATTCTTCTCGGCACTGATATGGACCTGTGACCAAAACAGGCCT
AATCCCTATATATGGTCTATGAAGAGATCAATAATAAGCAAGCAAATAAAGAAATAAATATAAAAAGAGA
ATTTGTGAAAATTAGTATCAACAGGACACTGTGATGAAAAAACACAGAACCCTACTTTAGATAACTTTAT
TCCCTGAGTGAGGCAATGAAGTTTAGTTAGCAGTAGAGGGTAGCATTTAAAGCTCCAGCTCTGTAGTTAG
AGTGCCTGAATTTGAATCCAGCTTATATCTCTGCAGCCTTTAGTAAATTATTTAACCTCTCGGTGCTTCA
GTGTCTTTACCTTTAAAATGAGGATAATAATATTGCCTACTCCATAAGGTTGTCAGTTTGTTGGTGGTAT
TATTTACCTAAAAGAATGCAGGGAAAGTAAATCTGCAACTGCTCTATTGTAAGCCCTCAGTGAACAGATA
GCTGTTATTATTTAAATGGGCCAGGCACGGTGGCACATACCTGTAATCCCAGCACTTTGGGAGGCTGAGG
CGGGCAGATCACGAGGTCAGGAGTTCGAGGCCAGCCTGGCCAACATGGTCAAACCCTGTCTCTATTAAAA
ATATAAAATTAGCCAGGGTGGCGTATGCCTGTAATCCCAGCTACTCAGGAGGCTGAGGCAGGAGAATTGC
TTGAACCCAGGAGGTGGAGGTTGCAGTGAGCCGAGATCGTGCCATTGCATTCCAGCCTGGGCGACAGAGT
GAGACTCCATCTTGGGAAAACAAAATAAAATAAAAAAACATAAAAGATTAAATTTTCAAGAAAGGCCCTC
TGAGGAGGTAACTAAGACTTAAAGGATGAAAAGAAGGAAATAGCTATGCAAGAAGTAGAGTGAAGTGCTT
TCCAGGTAAAGGAAACAGCATATGGCAACACCAAGCCATAAACACCTTGCAGCATTGGAGGGGCTGAAGG
AAGACCATCTGACCAGTCAACTTTGCAGACTGCTTGTGCTGAGCACACAGCGGCAGCCTGACGTCAAGTG
CACTGGGAATCACAGGAATTGTATTCATCATTCTGCATTCTCGAACTGCTGCAGTTAGCACTGGGAACAG
AAACAACCCATAAGTGCTCTGCTGAAAACAAACAAACAAAACCCCCCTCAAGTTTATCAGTGTTAAAACT
TTTGGCTTCCTTTACATTCCTGGGACAATGGTGGAAGTTACCCATCTGCTACTTAGAATGTTACAGAAAT

THE GENETIC CODE IS ‘READ’ IN 3-LETTER WORDS…

TTCTCGGCACTGATATGGACC

TTC TCG GCA CTG ATA TGG ACC

Phe - Ser - Ala - Leu - Iso - Trp - Thr

TTCTCGGAGCTGATATGGACC

TTC TCG GAG CTG ATA TGG ACC

Phe – Ser – Glu – Leu – Iso – Trp - Thr

‘Missense’ mutation

TTCTCGGAGCTGATATGAACC

TTC TCG GAG CTG ATA TGA ACC

Phe – Ser – Glu – Leu – Iso – Stop

‘Nonsense’ mutation

TTC CGG CAC TGA TAT CGA CCT

Phe - Arg - His - Stop

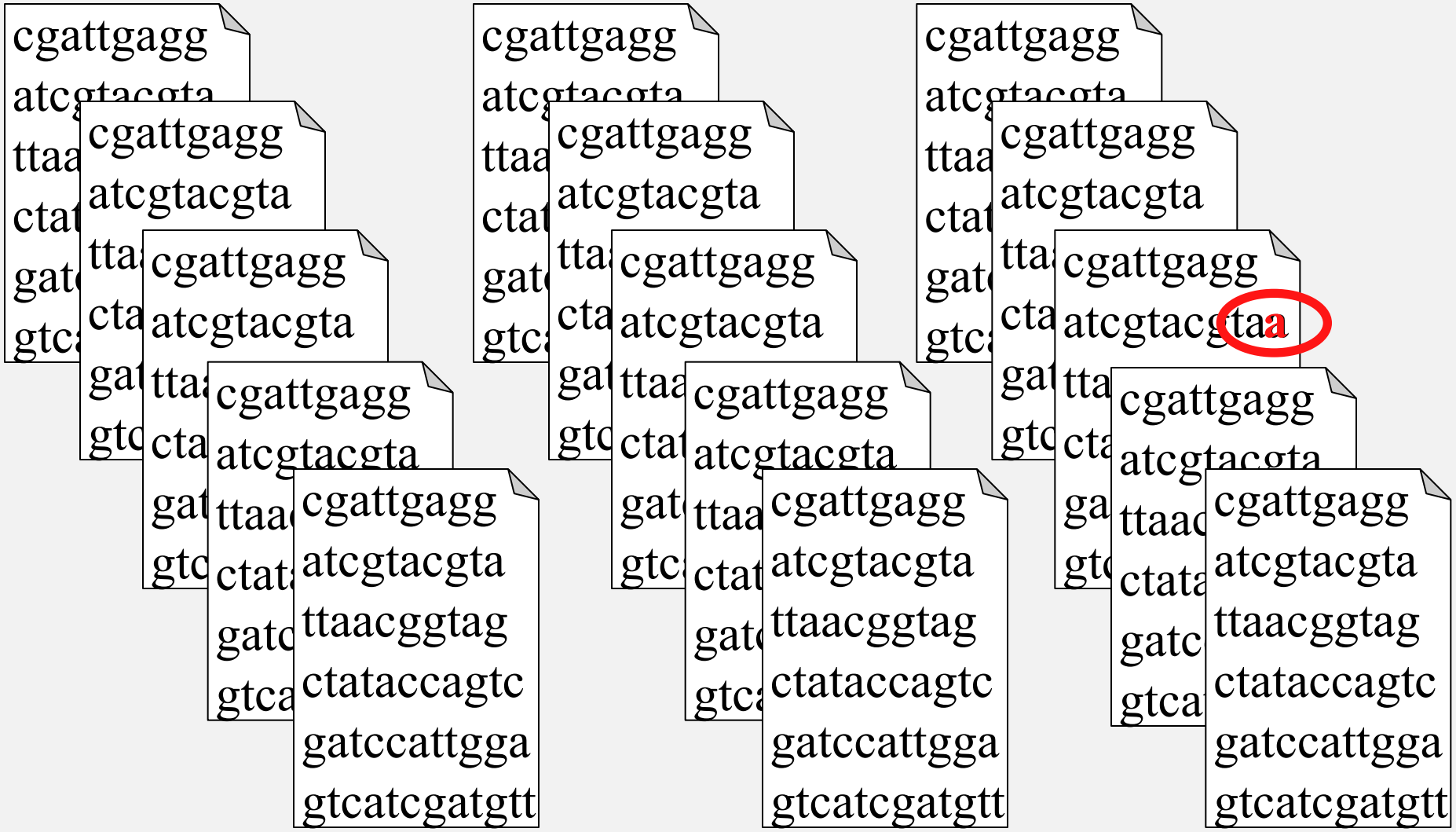
‘Frameshift’ mutation

CAN THERE BE DIFFERENT *TP53* MUTATIONS IN THE SAME FAMILY?

- There can not be different *TP53* mutations in the same family .....unless two separate families with LFS marry

- Once a mutation is identified in a family the test undertaken in other family members will always be for that specific mutation

DIAGNOSTIC VERSUS PREDICTIVE



IS THERE A REASON FOR DOING *TP53*-ONLY TESTS? DO YOU NEED TO DO SEPARATE *BRCA1/2* TESTS?

- **Sanger sequencing**

Test each gene individually

- **Next generation sequencing**

Tests multiple genes in parallel

Many labs starting to offer "cancer panel test" including *TP53*

IF A TEST RESULT FROM 10-YEARS AGO CAME BACK AS INCONCLUSIVE, DOES A PERSON NEED TO BE RETESTED NOW?

Depends on technique used - need to review genetic report and see what method used and check if large deletions or duplications of gene were looked at. If family history very suggestive of LFS probably worth repeating with newer technologies

MY TEST CAME BACK AS VARIANT OF UNKNOWN SIGNIFICANCE – WHAT DOES THAT MEAN IN TERMS OF SURVEILLANCE AND SCANNING?

TTCTCGGAGCTGATATGGACC

TTC TCG GAG CTG ATA TGG ACC

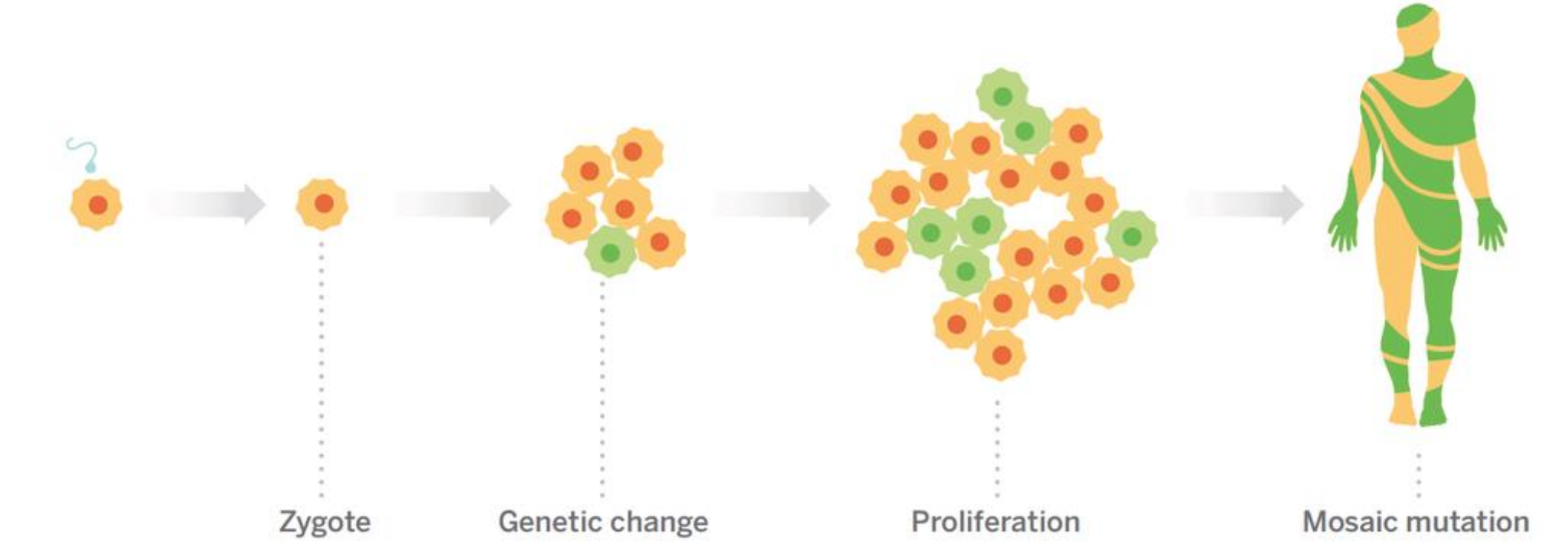
Phe – Ser – Glu – Leu – Iso – Trp - Thr

Variant of uncertain significance may be switch of one amino acid for similar one or at a location in protein that does not affect function

MY TEST CAME BACK AS VARIANT OF UNKNOWN SIGNIFICANCE – WHAT DOES THAT MEAN IN TERMS OF SURVEILLANCE AND SCANNING?

- Variant normally assessed in a “multidisciplinary meeting” with scientists and clinicians
- Look at whether variant occurs in a control population, the effect on protein structure and function and whether it has been reported before
- Some variants may be classed as “ not clinically significant” –manage according to family history
- Further work may be required – surveillance may still be offered but would not offer testing for variant to other family members is not certain cause of cancer in the family

WHAT IS A MOSAIC MUTATION AND DOES IT CARRY THE SAME CANCER RISKS?



Mosaic mutations arise after egg is fertilised and so are **not** present in every cell in body

CANCER RISK FOR MOSAIC MUTATIONS

- No clear data
- Risk will depend on the extent of mosaicism and the cells in which *TP53* mutations are present

TP53 TESTING IN CHILDREN

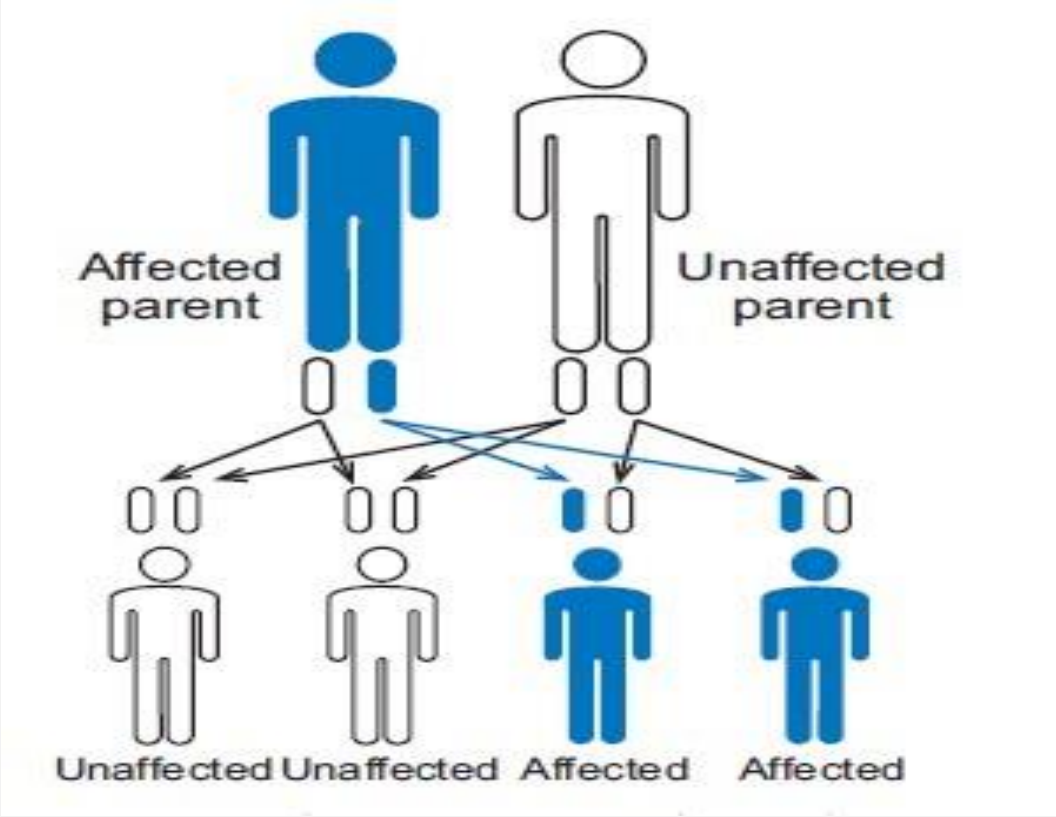
DIAGNOSTIC TESTING IN CHILDREN

- Adrenocortical cancer at any age
- Choroid plexus cancer at any age
- Rhabdomyosarcoma below 5 yrs
- Multiple childhood tumours
- Childhood cancer and suggestive family history

WHY AREN'T ALL CHILDREN WITH CANCER *TP53* TESTED?

- Low chance of mutation detection for many childhood cancer
- May be increased testing in future or picked up through genetic testing of the tumour

RISK TO CHILDREN IF PARENT AFFECTED

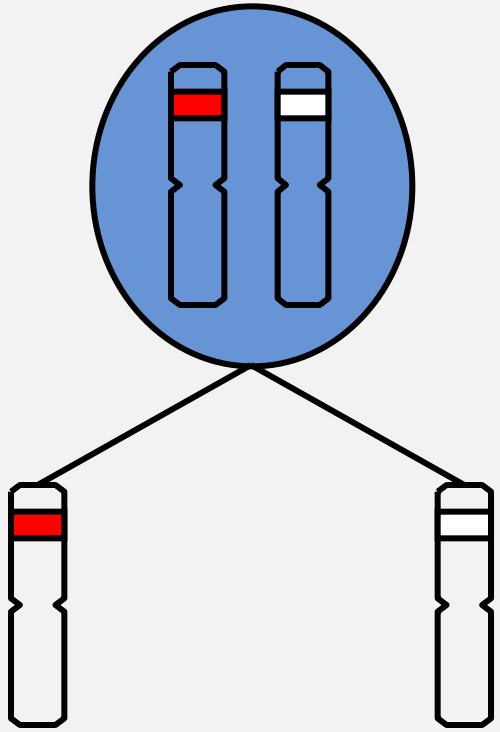


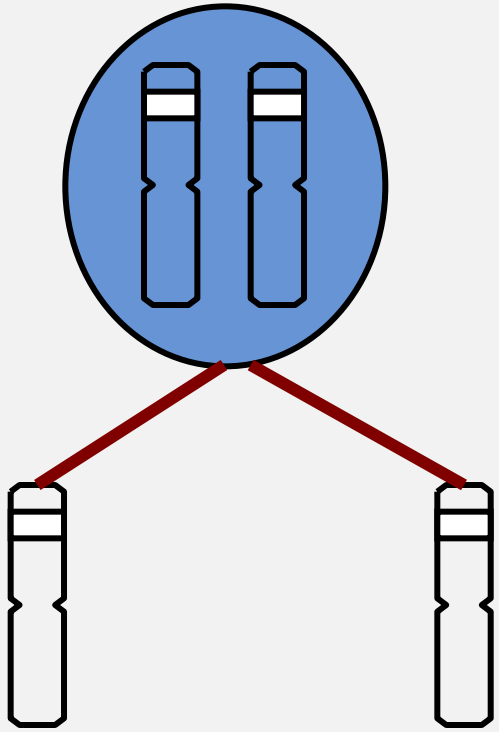
AUTOSOMAL DOMINANT INHERITANCE

Parents

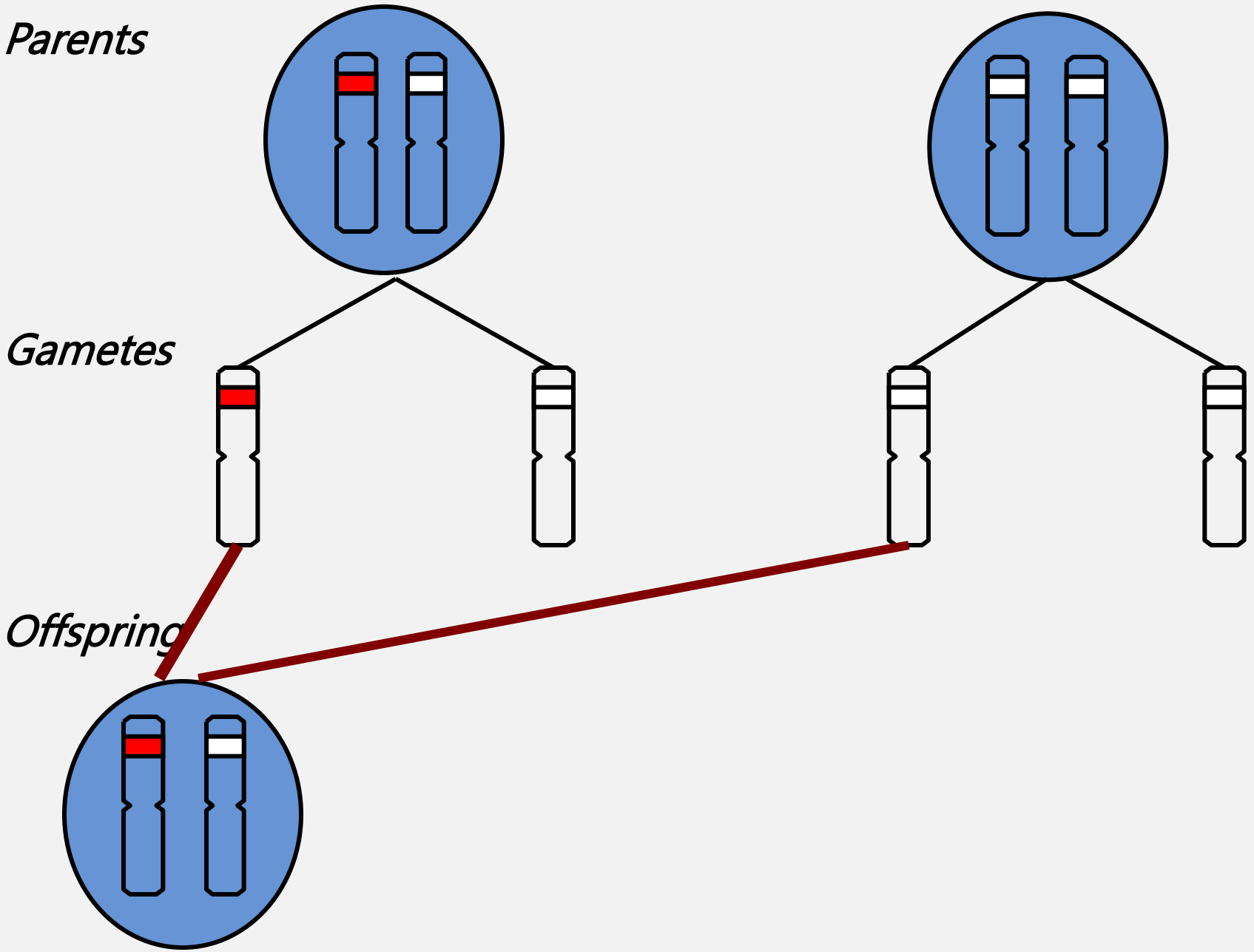
Gametes

egg/sperm

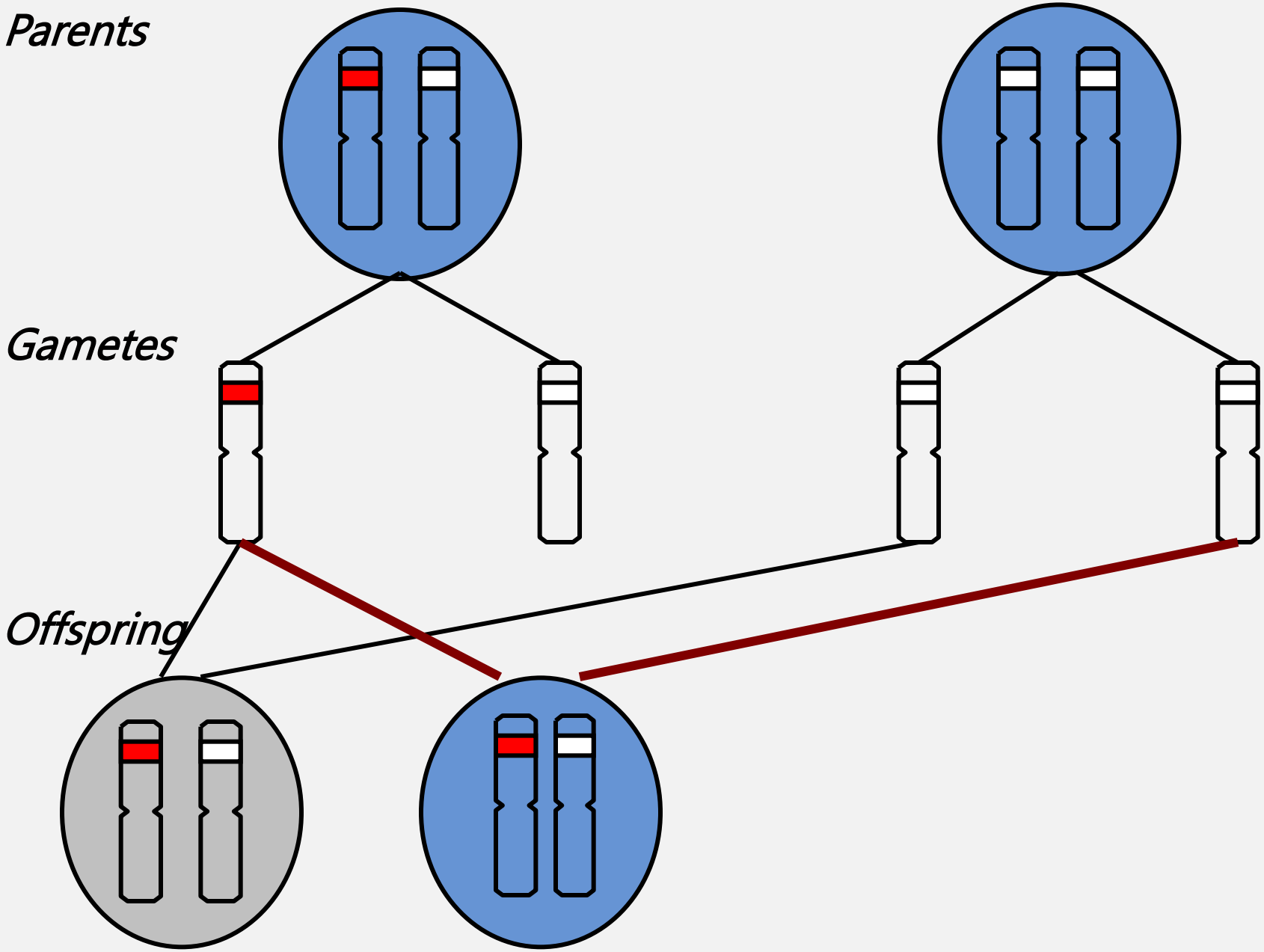




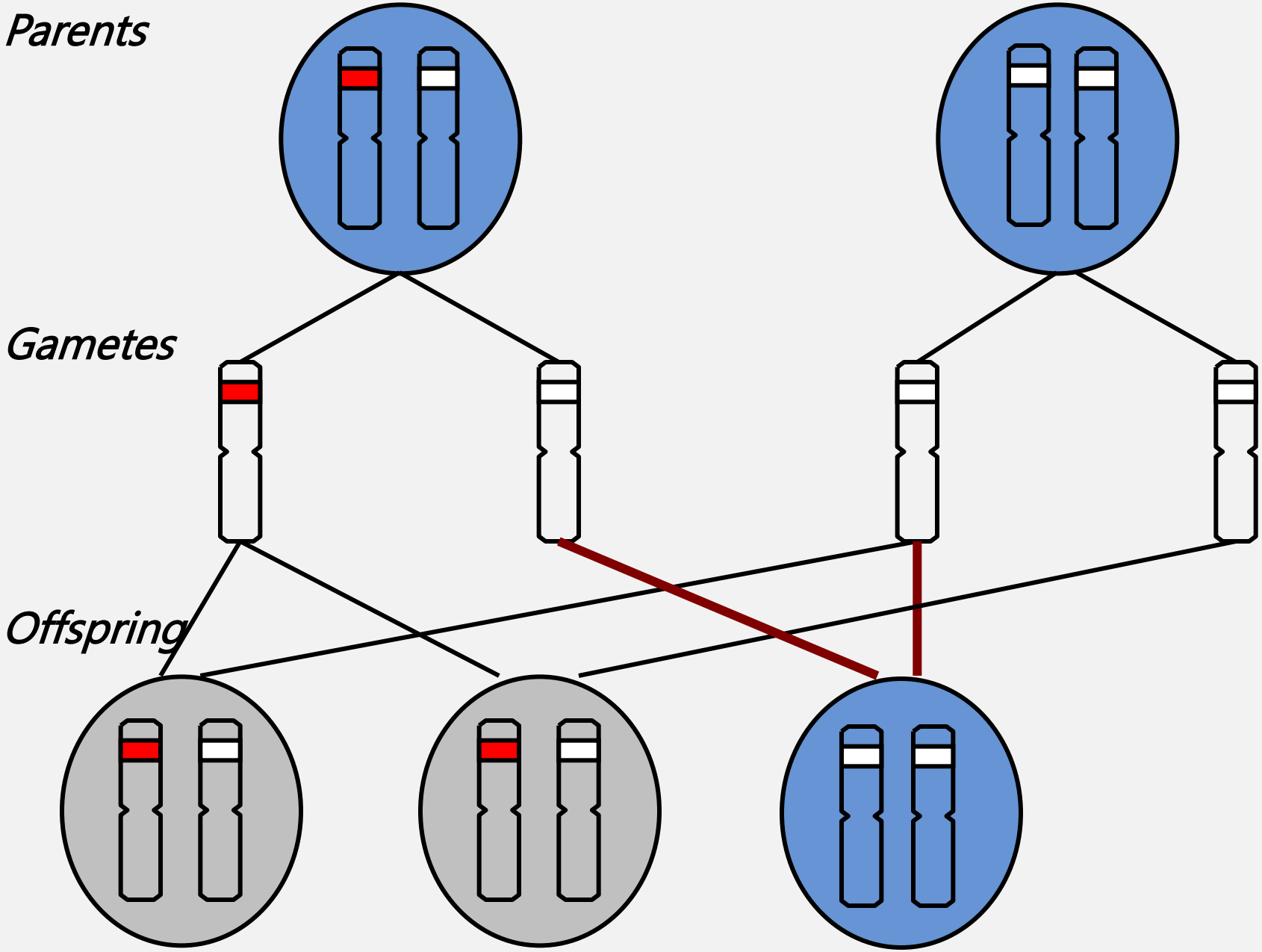
AUTOSOMAL DOMINANT INHERITANCE



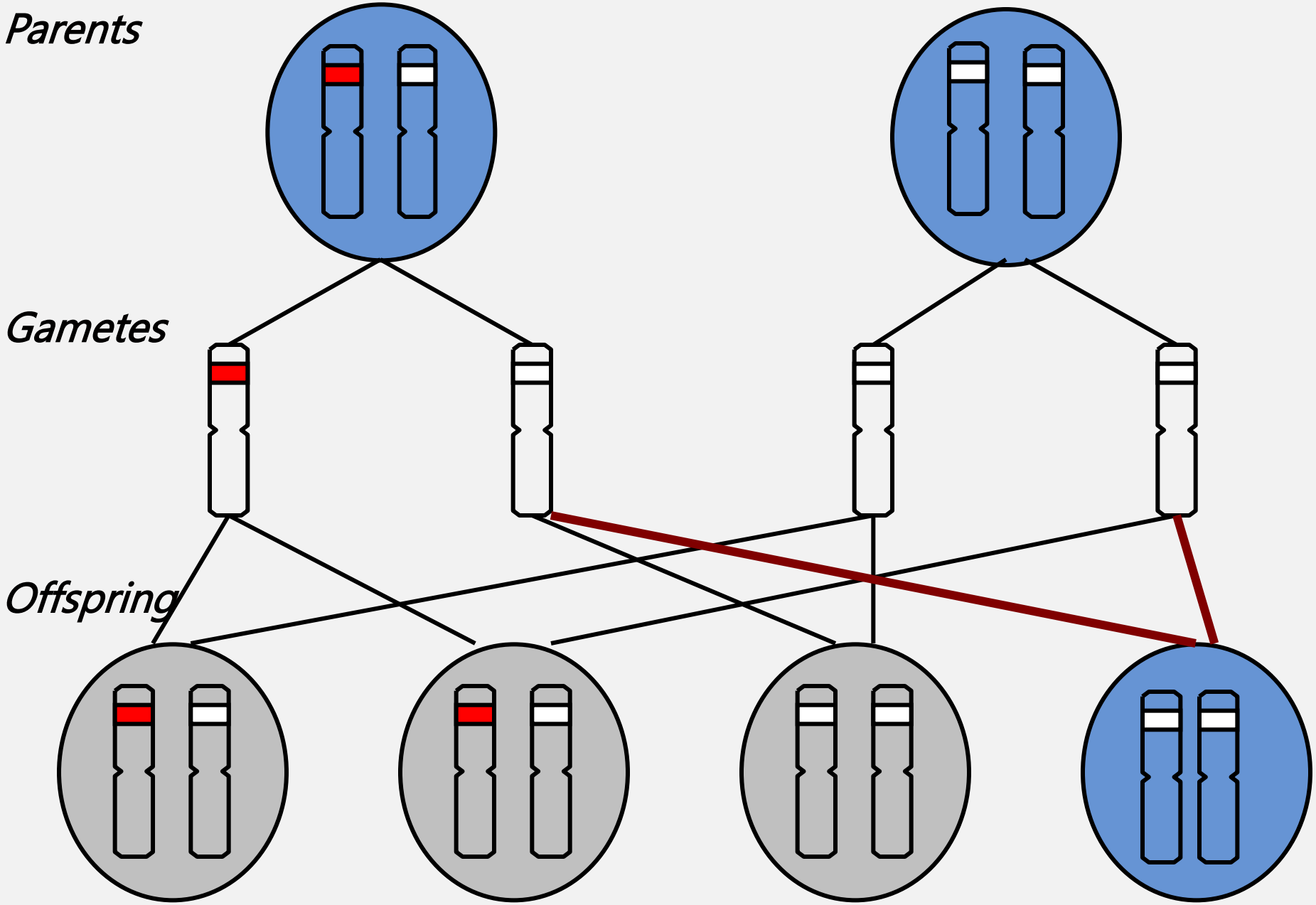
AUTOSOMAL DOMINANT INHERITANCE



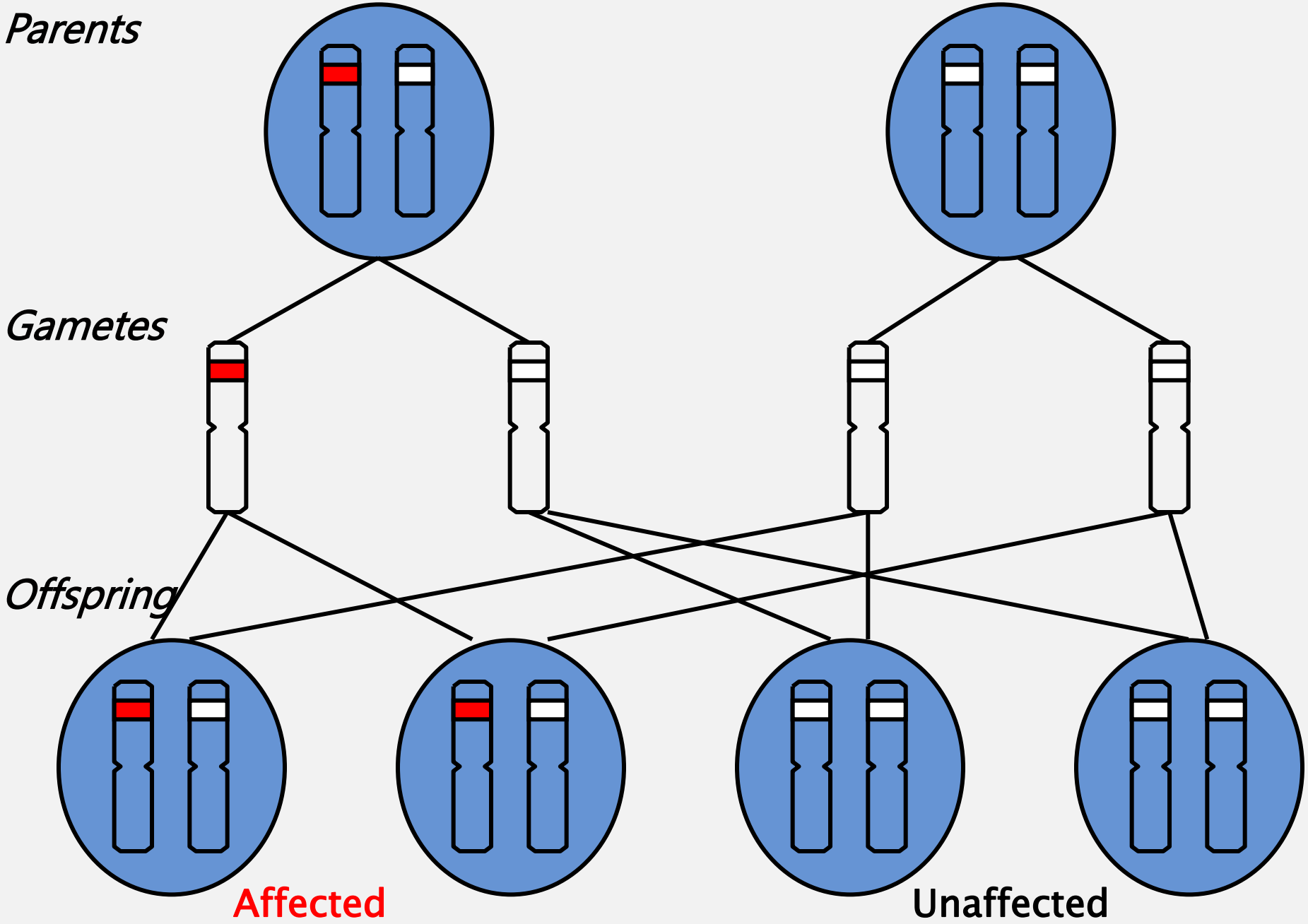
AUTOSOMAL DOMINANT INHERITANCE



AUTOSOMAL DOMINANT INHERITANCE



AUTOSOMAL DOMINANT INHERITANCE



AT WHAT AGE CAN MY CHILDREN BE TESTED FOR LFS?

- ICR/Pan-London guidelines are that children can be tested at any age, providing there has been appropriate counselling
- In general genetics professionals largely counsel families against testing children for adult-onset cancer predisposition, an approach supported by professional society guidelines
- testing for conditions in childhood with no actionable management options poses a number of ethical dilemmas

THE ETHICAL DILEMMA: POINTS TO CONSIDER

❖ **Autonomy**

- Remove child's future right to an informed decision about when to test. Privacy.
- Parent's autonomy for making decisions about children, as they would for other reasons.

❖ **Capacity**

- Very young children not able to understand the information and make a decision.

❖ **Beneficence**

- Who does testing benefit, child or parents? Best interest of child – who decides, health professional or parents? Short and long term benefits?
- Reassurance: parental anxiety is present anyway, may be reduced if negative and remove need to discuss with children and worry about them throughout childhood.
- Reducing uncertainty and taking back control

THE ETHICAL DILEMMA CONT'

- **Nonmaleficence – 'do no harm'**

- Negative impact on relationships in future – e.g. siblings with different results? Resentment of parents by child? Parenting style, differential treatment of children?
- How will result affect decisions in future, careers, partners etc

WHAT IF I WANT MY CHILD TESTED?

- Speak to your Genetics team and work with them
- Each centre will have experienced Consultants and Genetic counsellors who can work with each family

- BBC Inside the Ethics Committee Series 9 Episode 3

SURVEILLANCE IN LFS

CURRENT GUIDELINES

- Open door policy (can be with a general paediatrician or paediatric oncologist for children).
- Breast cancer risk management should include:
  - Practice of breast self-awareness and self-examination
  - annual MRI age 20-50 yrs, review at age 50 (UK NICE guidelines)
  - discussion of risk-reducing mastectomy
- No targeted surveillance is recommended or of proven benefit other than for breast cancer.

- ICR guidelines based on International LFS Working Group Guidelines

HOW CAN I ACCESS ANNUAL WHOLE BODY MRI SCANS FOR MY FAMILY?

Not currently available as standard practice. Evaluated as part of research study –SIGNIFY.

Professor Gareth Evans discussing this afternoon

IS IT SAFE FOR ME TO HAVE X-RAYS AT THE DENTIST?

- Radiation is measured in units called mSv (millisieverts)
- Many diagnostic exposures are less than or similar to the exposure we receive from natural background radiation
- For comparison, each person receives about 3.0 milliSieverts of radiation exposure from background sources every year
- No direct evidence that x-rays increase cancer risk for *TP53* carriers

Typical Effective Radiation Dose from Diagnostic xRay
---------- Single Exposure (Mettler 2008)----------

Exam	Effective Dose mSv (mrem)
Foot, Hand Radiograph	0.005 (0.5)
Dental Bitewing	0.005 (0.5)
Dental Panoramic	0.01 (1)
Full Mouth Series (FMX)	0.10 (10)
Chest	0.1 (10)
Skull	0.1 (10)
Cervical Spine	0.2 (20)
Mammogram (2 view)	0.36 (36)
Abdomen or Hip	0.6 (60)
Pelvis	0.7 (70)
Thoracic Spine	1.0 (100)
Lumbar Spine	1.5 (150)

Examinations and Procedures	Effective Dose mSv (mrem)
Abdomen Kidney, Ureter, Bladder (KUB)	0.7 (70)
CT Biopsy	1.0 (100)
Pacemaker Placement	1.0 (100)
CT Head	2.0 (200)
Calcium Scoring	2.0 (200)
Intravenous Pyelogram	3.0 (300)
Peripheral Vascular Angioplasties	5.0 (500)
Upper GI	6.0 (600)
Barium Enema	7.0 (700)
CT Chest	7.0 (700)
CT Abdomen/Pelvis	10.0 (1,000)
Whole-Body CT Screening	10.0 (1,000)

We all receive about 3.0 mSv (of radiation exposure from background sources every year.

Comparison of doses from sources of exposure

Source of exposure	Dose
Dental x-ray	0.005 mSv
100g of Brazil nuts	0.01 mSv
Chest x-ray	0.014 mSv
Transatlantic flight	0.08 mSv
Nuclear power station worker average annual occupational exposure (2010)	0.18 mSv
UK annual average radon dose	1.3 mSv
CT scan of the head	1.4 mSv
UK average annual radiation dose	2.7 mSv
USA average annual radiation dose	6.2 mSv
CT scan of the chest	6.6 mSv
Average annual radon dose to people in Cornwall	6.9 mSv
CT scan of the whole spine	10 mSv
Annual exposure limit for nuclear industry employees	20 mSv
Level at which changes in blood cells can be readily observed	100 mSv
Acute radiation effects including nausea and a reduction in white blood cell count	1000 mSv
Dose of radiation which would kill about half of those receiving it in a month	5000 mSv

https://www.gov.uk/government/publications/ionising-radiation-dose-comparisons/ionising-radiation-dose-comparisons

IS THE CONTRAST USED IN MRI SCANS SAFE FOR PEOPLE WITH LFS?

- Magnetic resonance imaging (MRI) is a type of scan that uses strong magnetic fields and radio waves to produce detailed images of the inside of the body.
- Gadolinium-containing contrast agent is sometimes administered during MRI to improve imaging. Because gadolinium is a metal, it is given in a form that is rapidly removed from the body, limiting side effects
- Has been some concern that gadolinium can cause side effects or long term problems –these are not substantiated and there is no evidence that gadolininum increases cancer risk
- Kidney function normally checked prior to contrast MRI
- SIGNIFY study whole body imaging did not use contrast

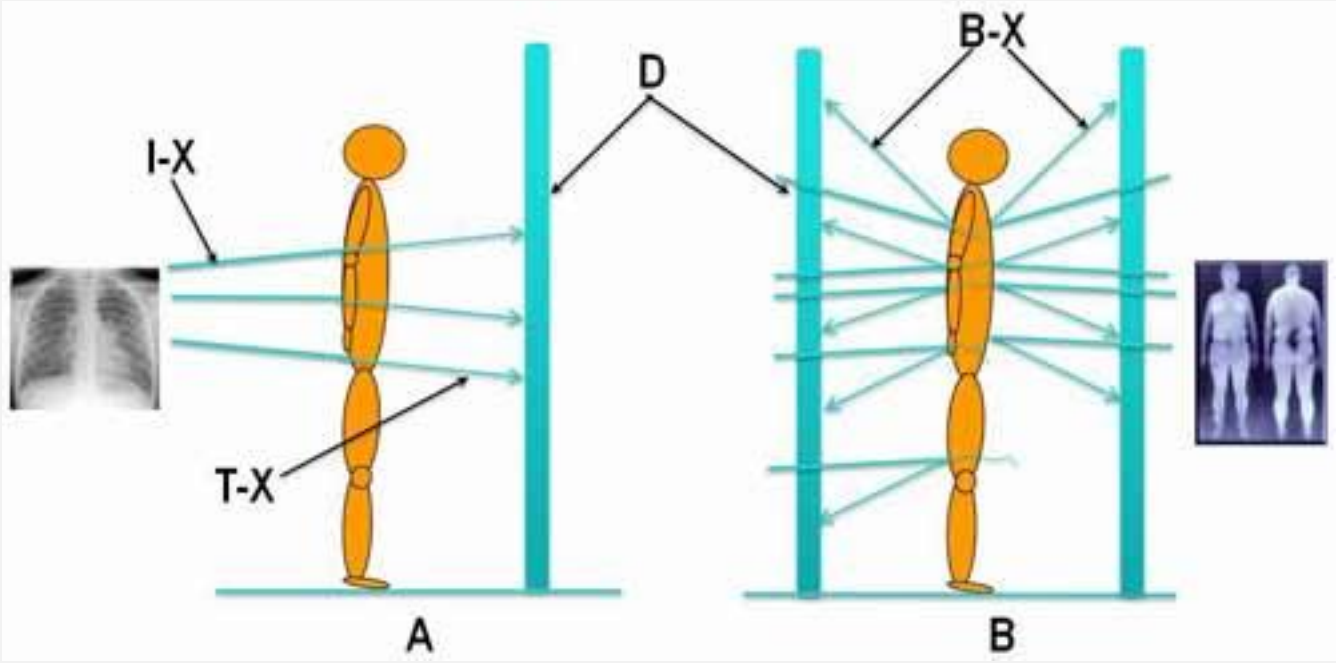
AIRPORT SCANNERS

Millimeter radio-wave scanners

- Stand in booth with arms raised. Inside booth, you are scanned with millimeter radio waves. Antennas then collect the reflected waves to generate images.
- Because this type of scanner does not use x-rays, but instead uses millimeter radio waves similar to radio waves produced in a cell phone, there is no concern about radiation.

Backscatter scanners

- Stand between two large boxes with arms raised. Inside the backscatter scanner is an x-ray source that produces low intensity x-rays. The scanner uses a low intensity narrow x-ray beam to scan at high speed taking 2-5 seconds
- Large detectors capture the backscatter x-rays to create images



In a backscatter x-ray system, the x-ray intensity is very low and not strong enough to penetrate or transmit through the body, even though a few of the x-rays may be absorbed by the body. However, the majority of the x-rays bounces off or scatters onto the surface. This is the reason for the two large detectors that collect the backscatter or scatter x-rays to create an image.

DO AIRPORT SECURITY SCANNERS REPRESENT A RISK?

- Radiation exposure for an individual scan is low.
- 100 to 200 backscatter scans is equal to one day of natural background radiation
- 1,000 to 2,000 backscatter scans to get a dose equivalent to a single chest x-ray.

- One backscatter scan is equivalent to
  - Two to four minutes of radiation received from air travel
  - 10 to 20 minutes of natural background radiation

ANY QUESTIONS?