Genetics

23 pairs of chromosomes

25,000 genes

5-10% of ovarian + breast cancer is hereditary

FAP = familial adenomatous polyposis
HNPPC = hereditary non-polypoid colon cancer

Cancer arises from genetic mutations (mutations in egg or sperm) or somatic mutations (i.e. mutations in breast, brain...)

Somatic mutations = NON heritable

Oncogenes = cancer genes i.e. genes with the potential to cause cancer

HNPPC = mutations in mismatch repair gene = excess of colorectal, endometrial, urinary tract, ovarian and gastric cancers

= prevention by coexpression

= mainly tumours of proximal colon

BRC1, 1+2 = breast + ovarian cancer in females

BRC2 in males = risk of breast + prostate cancer

Genetic testing allows early detection and prevention but does not detect ALL mutations.

1st relatives = parents + brothers + sisters

2nd relatives = grandparents + aunts + uncles

3rd relatives = second cousins

Li-Fraumeni syndrome = Autosomal dominant

RARE cancer hereditary condition

Syn: SBTLA syndrome = sarcoma, breast, leukemia, Adrenal gland sarcoma.

Genetic counselling = awareness of symptoms + risk factors, screening and prophylactic surgery.

BRC1 - breast cancer surveillance + mammography and MRI in high risk

Prophylactic mastectomy removes most but not all breast tissue, significantly reduces breast cancer risk down to 5%.

Endometrial cancer, look for post menopausal bleeding.

Do transvaginal ultrasound.

MULTI SYSTEM DISEASE

Due to germ line genetic variation present in every cell in the body.

New mutations are possible or modes of inheritance:

- Chromosomal imbalance
- Somatic and biallelic, deleterious mutations
- Single gene disorders i.e. NF, dystrophic epidermolysis

Multifactorial genetic conditions: more than one genetic change.

Commonly with multi-system diseases there is causality within and between faculties for the same disease but it allows screening + prevention.
Neurofibromatosis Type 1 (NF1)

Autosomal dominant

Diagnostic criteria - 2+ required for diagnosis:
- Cafe au lait spots ≥ 6 of them
- Neurofibromas ≥ 2 of them
- Axillary and groin freckling
- Optic glioma
- FH
- Hypertrophy of long bone cortex
- Lisch nodules - specks on iris seen by slit lamp

50% due to new mutations
- Short stature
- Epilepsy
- FB
- Learning difficulties
- Hypertension
- Pseudoarthrosis of the tibia
- Management: BP control
- Annual review - space for ankles, hands for unusual angulation, visual acuity + visual fields, education assessed, unusual symptoms.

NF1 and NF2 are completely separate disorders.

Neurofibromatosis Type 2 (NF2)

Autosomal dominant

Chromosome 22
- Acoustic neuromas (bilateral) 2. CNS + spinal tumours 3. Cafe au lait spots

Tuberous Sclerosis (TS)

2 genes on 2 different chromosomes causes it, with identical mutations: TSC1 + TSC2

Autosomal dominant

Classical triad: 1. Epilepsy - infantile spasm/mayocose seizures
2. Mental handicap
3. Skin lesions - angiofibromas (fibrous plaques, forehead, malar areas, nose)

Hamartomas in different organs:
- Retinal hamartomas
- Kidneys, cysts
- Lung hamartomas
- Phakomas in eye (benign unless in macula)

Surveillance + genetic counselling
- Cardiac CT
- Renal CT
- Echocardiogram

Myotonic Dystrophy

Autosomal dominant

Bilateral late onset cataract
- Muscle weakness
- Hypertonia
- Heart block
- Bowel problems
- DM

Death post anaesthesia if not monitored as respiratory failure.

Congenital myotonic dystrophy = death/severe muscle + brain disorder

Pre-disposition to Adult onset disease

Pregnancy - predictive testing

Genetic = Huntington's disease
- Osteoporosis imperfecta
- Spasticity
- Dementia

Family motor neuron disease - AD

Ethics

- Autonomy
- Beneficence
- Non-maleficence
- Justice

Test information must be weighed for prevention or treatment.
- Must tell them adequate information about uncertainty.
- Pre-natal testing requires counselling.
- Children + adolescents should only be tested if there are potential medical benefits.

Avoid penalties ie insurance/employers should have no access.
Diagnosis of a genetic condition implies risk for relatives & testing of them.

Motor neuron disease: amyotrophic lateral sclerosis
- no cure
- no satisfying treatment
- 10% inherited, generally sporadic mutations
- progressive muscle weakness, wasting, + reflexes
- upper + lower Motor neuron signs
- Death due to respiratory failure

Superoxide dismutase (SOD) ~ 20% of familial cases.
- SOD1 = autosomal Cu/Zn chromosome 21
- SOD2 = autosomal Mn chromosome 6
- SOD3 = extracellular Cu/Zn chromosome 4

SOD presence protects many cells from free radical damage.
- SOD is important in oxygen + extreme tissue damage. Also protects cells from DNA damage.
- Progressive cell degradation.

Huntington's disease
- Adult onset, adult onset, CAG expansion
- NO CURE
- Late 30's, early 40's
- Unsatisfactory treatments
- Cognitive changes
- Personality change:
  - Poor planning + memory
  - Irritable
  - "A different person" + self-centred
  - Societal diminution
  - Disinhibition + loss of empathy
- Depression, paranoia, psychosis

If tested and +, it means you don't need to worry about your children having it.
- +, arrange for future?
  - Recessive? Depends on how many children were born etc...
- Would you test the children?

Can a diagnosis connect the whole family?