Advances in our approach to genetic testing for hereditary cancer predisposition syndromes

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Genetic Counsellor

Genetic Health Service NZ

Genetic Health Service New Zealand-GHSNZ

- National service established in 2012
- Three hubs based in
  - Auckland (Northern Hub)
  - Wellington (Central Hub)
  - Christchurch (South Island Hub)
- Providing
  - local and outreach clinics
  - specialist advice
  - education for professionals and support groups

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Welcome to Genetic Health Service NZ

Welcome to the Genetic Health Service New Zealand (GHSNZ). We provide expert genetic diagnostic and genetic counselling services, providing assistance, advice, and education in managing genetic conditions. We operate clinics throughout the country with our staff of Clinical Geneticists and Genetic Counsellors. Our services are publicly funded for NZ residents as we are part of New Zealand's public health system.

Genetic Counsellors also known as Genetic Associates have received the same training and provide the same role within a genetic service.

For patients referred to a clinic through a health professional, this website provides a guide to what to expect at your appointment. Read more

For health professionals, this website provides a list of our services and how we can assist in diagnosing genetic conditions and help support people with genetic conditions. Read more

Northern Hub

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Toll Free: 0800 476 123
Email: GenSec@adhb.govt.nz

Central Hub

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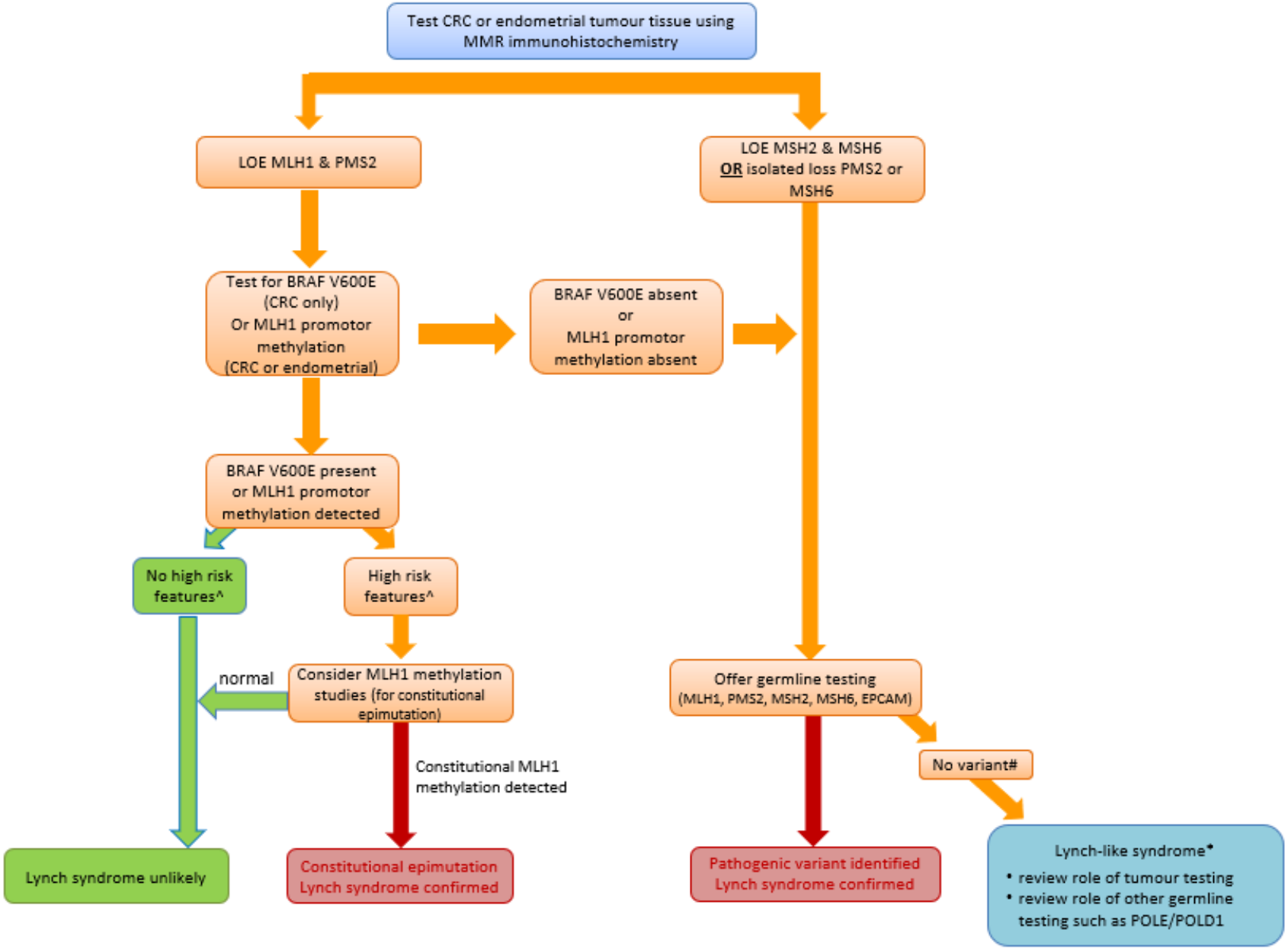
Hereditary Cancer Syndromes

- Hereditary Breast and Ovarian Cancer Syndrome - breast, ovarian, prostate (BRCA1 and BRCA2)
- Hereditary Breast CHEK2 PALB2 ATM
- Lynch Syndrome: Bowel, endometrial, ovarian,(MMR genes – MLH1, MSH2, MSH6, PMS2, EPCAM)
- FAP, AFAP and MAP: bowel (APC and MYH)
- Hereditary Diffuse Gastric / Breast Cancer : Stomach and breast(CDH1)
- Paraganglioma Syndromes: Mostly benign neuroendocrine tumours (SDHB,C,D)
- Cowden Syndrome : Breast, thyroid, benign and malignant tumours (PTEN)
- Li-Fraumeni Syndrome : Childhood and adult cancers (TP53)

Tumour testing in suspected Lynch syndrome

- **Providing appropriate treatment to family members after an informative genetic testing evaluation**


Test CRC or endometrial tumour tissue using MMR immunohistochemistry
LOE MLH1 & PMS2
LOE MSH2 & MSH6 OR isolated loss PMS2 or MSH6
Test for BRAF V600E (CRC only) Or MLH1 promotor methylation (CRC or endometrial)
BRAF V600E absent or MLH1 promotor methylation absent
BRAF V600E present or MLH1 promotor methylation detected
No high risk features^
High risk features^
normal
Consider MLH1 methylation studies (for constitutional epimutation)
Constitutional MLH1 methylation detected
Offer germline testing (MLH1, PMS2, MSH2, MSH6, EPCAM)
No variant#
Lynch syndrome unlikely
Constitutional epimutation Lynch syndrome confirmed
Pathogenic variant identified Lynch syndrome confirmed
Lynch-like syndrome*
• review role of tumour testing
• review role of other germline testing such as POLE/POLD1

Medical and Family History

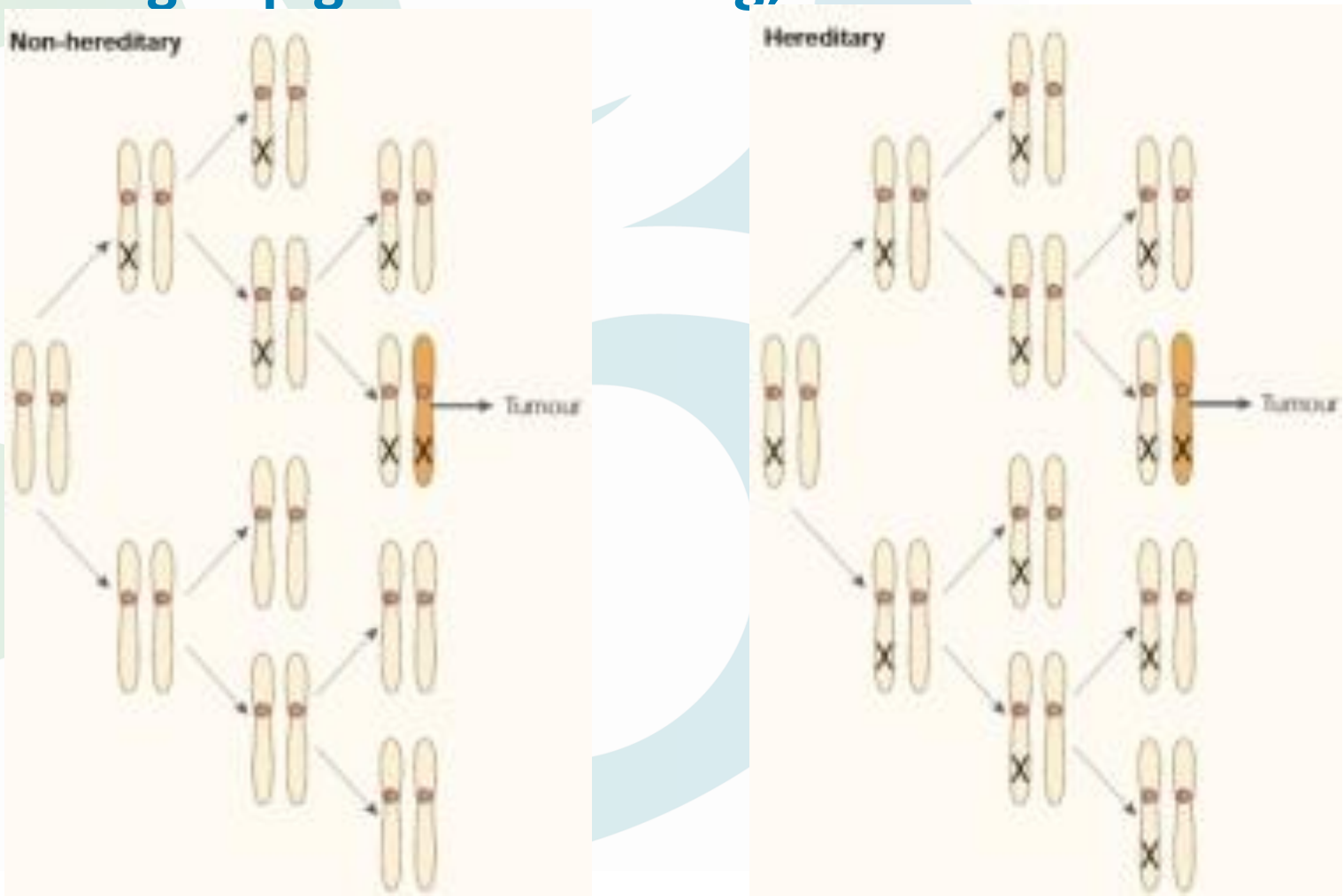
- JG, diagnosed CRC age 70
- IHC: LOE of MSH2 and MSH6 MMR proteins
- Referred to genetics by regional oncologist
- Family history
  - Three children in 40s, well
  - Two brothers in 60s, well
  - Parents diseased, mother diagnosed pancreatic cancer age 88
  - No other family history of cancer

Testing

- Lynch panel performed on peripheral blood: no mutations detected (refer to flow chart)
- Tumour sample sent for Lynch testing
  - Two variants in MSH2 detected
    - Pathogenic c.1386+1G>A (allelic frequency 20.4%)
    - Likely pathogenic c.2168_2187del (allelic frequency 9.7%)
- Explanation for abnormal (LOE) of MSH2/6 in tumour IHC screen

Cancer Development: Knudsen's two-hit hypothesis

Tumour suppressor genes require both alleles to be inactivated, either through mutations or through epigenetic silencing, to cause a phenotypic change.



Consequences for screening/assessment

- Without genetic tumour testing, family would have been considered “Lynch-like” and all FDR would have been offered 2 yearly screening from age around age 40.
  - Five individuals with ongoing colonoscopy, possibly 10+ years
- With genetic tumour testing (informative results), family can be put into “sporadic” category, with assessment for FDR as slightly above population average risk
  - Manage five individuals with population risk screening

- Somatic mutations provide an alternative explanation for MMRd in approximately 69% of cases
- Confirmation of homozygous, pathogenic variants within the tumour (not detected on germline), supports a sporadic tumour in the absence of other high risk features
- Reassurance for families and better targeting of screening colonoscopies
- Prospective look at 40 cases since mid 2020 at the Wellington office of GHSNZ since offering this tumour testing for uninformative “Lynch-like” families, with a significant number being informative.

Family history is still important

- Technical limitations may mean that a pathogenic variant is missed in a known gene, or an as yet unidentified gene.
- Polygenic conditions are likely
- Testing may fail due to poor preservation of DNA, or low yield
- Patients with unexplained MMRd and no high risk features, should be reviewed in the future as they are more likely to have sporadic cancer
- Negative Lynch screen does not exclude other conditions such as MUTYH

Tumour testing in HGS ovarian cancer

- Providing appropriate treatment to an individual after an informative genetic testing evaluation
- Similar issues; current approach is mainstreaming
- Case: 65 yr old with HGSO cancer
- Peripheral blood sent for testing; BRCA1 mutation found
- Tumour testing shows: BRCA1 mutation
- Implications: funded PARP inhibitor treatment (Olaparib)
  - Note: While Pharmac requires germline (hereditary) cause to be identified, we know all tumours with BRCA mutations may be sensitive to Parp inhibitors. Implications for testing in the future (this is the goal of the current program), as well as other tumours in the BRCA spectrum.

How do PARP inhibitors work?

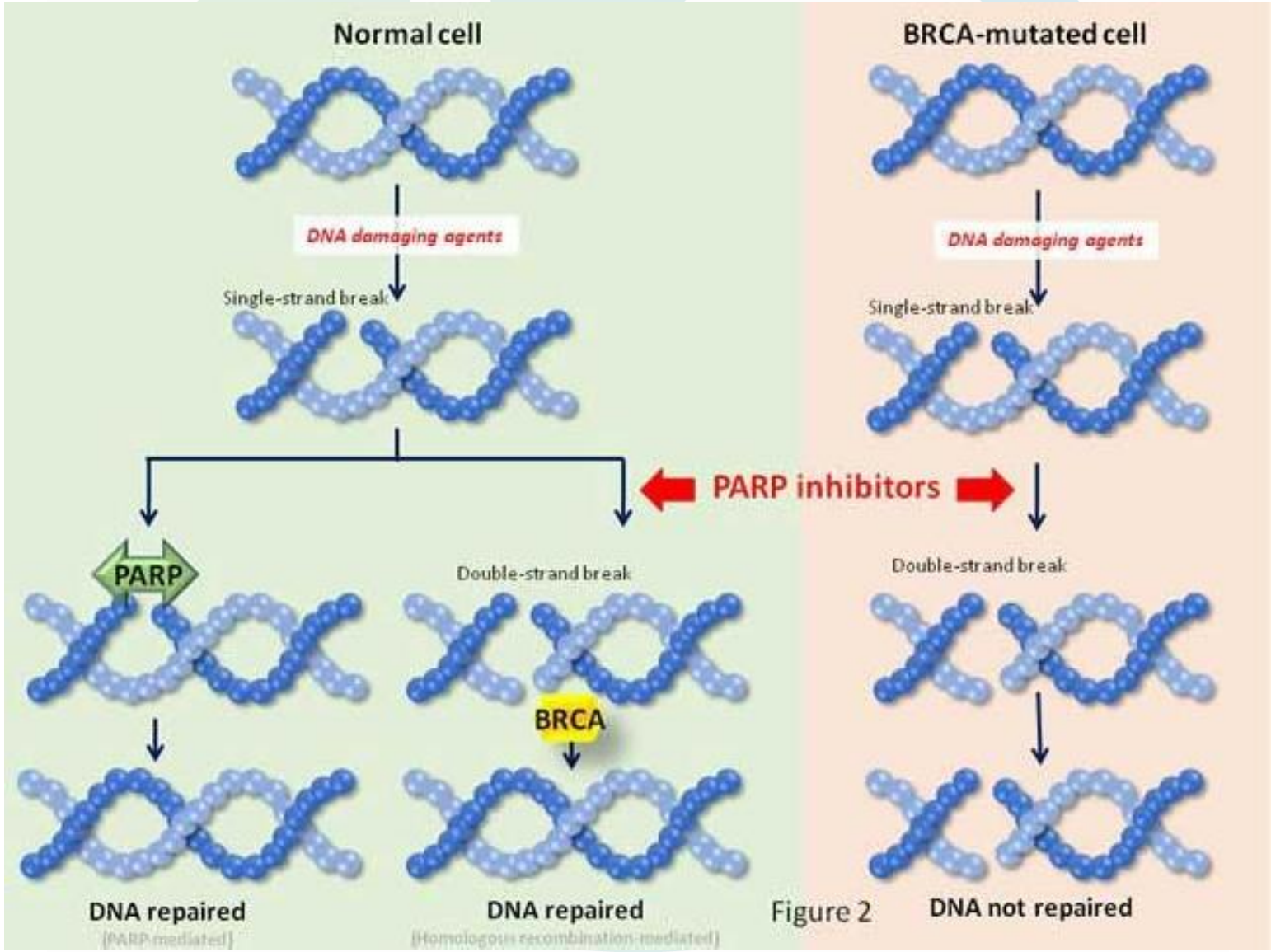


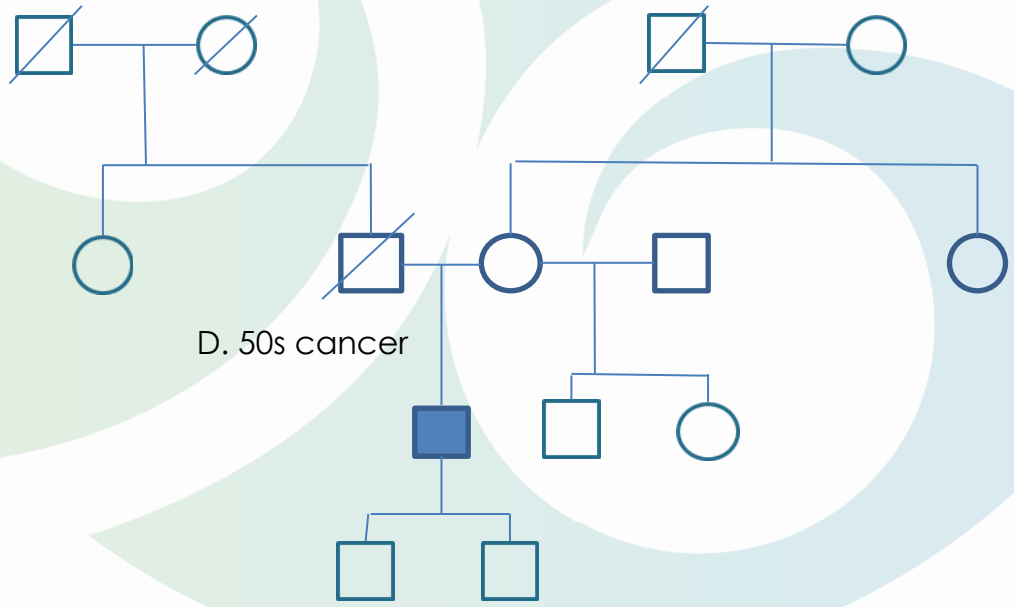
Figure 2

Tumour testing in HGS ovarian cancer

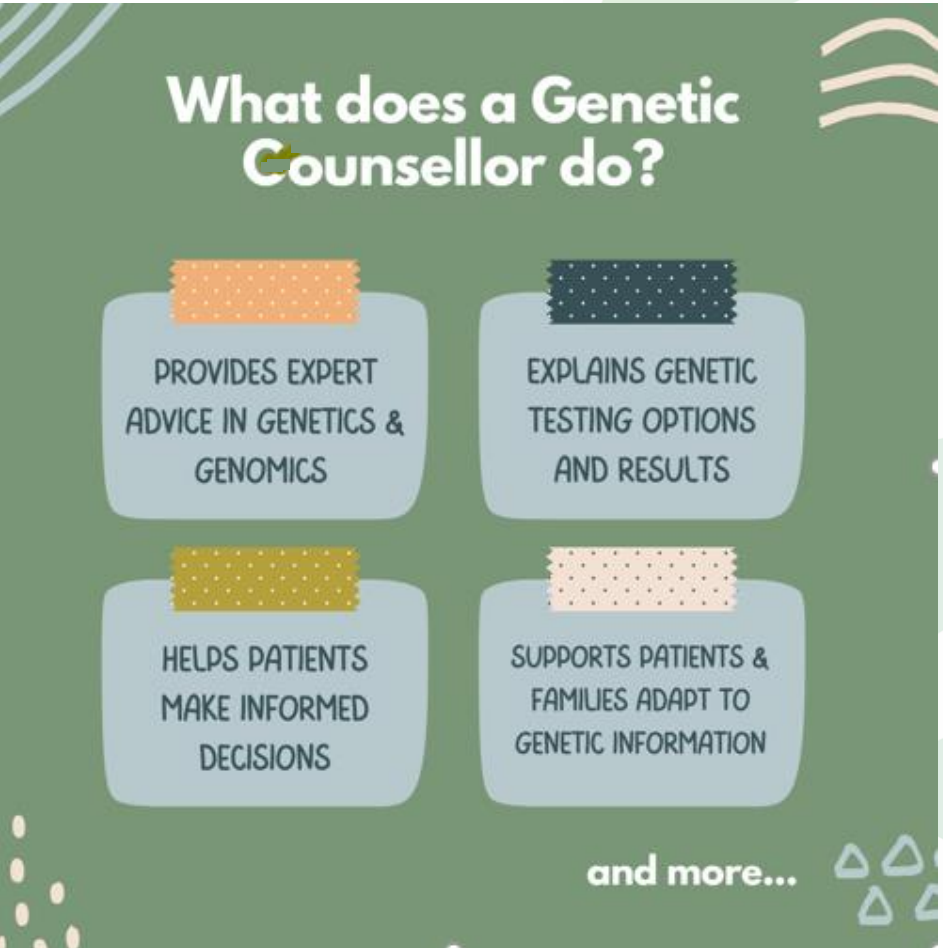
- Somatic testing currently available to Central Hub patients; goal is to offer this nationally.
- Wellington Regional Genetics Laboratory: working towards accreditation.
- Ideally: offer somatic testing first, followed by germline testing only if a P/LP variant is identified.
  - Limitation: large dels/dups aren't tested for in tumour, so germline testing needed
- Lynch Syndrome: if there is ovarian and a FDR with bowel cancer then LS germline testing offered
  - IHC is sometimes carried out on ovarian tumours, which can be helpful too

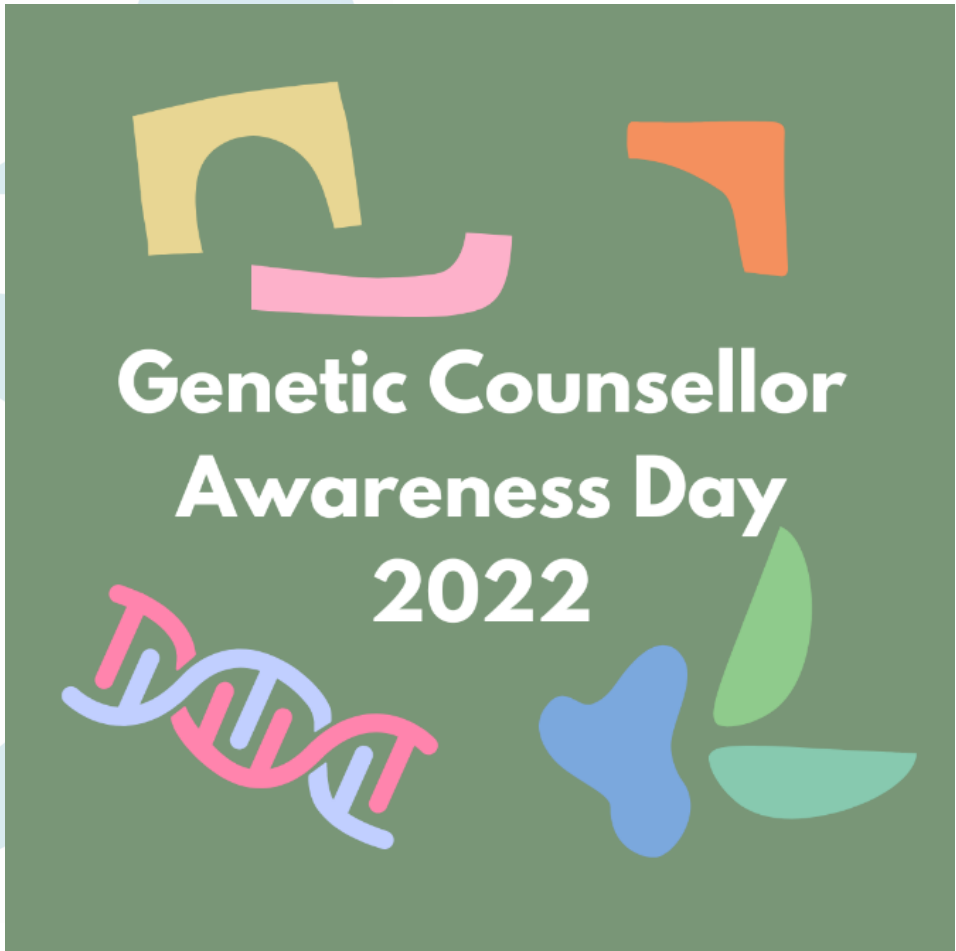
Desmoid tumour

Desmoid tumour dx. 49 Normal colonoscopy. Father died in his 50's .
Desmoid tumours are frequently sporadic, but are associated with mutations in APC (FAP). Genetic testing can be a cost effective approach to diagnosing FAP.
Testing on stored tumour tissue showed presence of CNN1B mutation, indicative of sporadic desmoid tumour. No family follow up required.



Questions?


What does a Genetic Counsellor do?
PROVIDES EXPERT ADVICE IN GENETICS & GENOMICS
EXPLAINS GENETIC TESTING OPTIONS AND RESULTS
HELPS PATIENTS MAKE INFORMED DECISIONS
SUPPORTS PATIENTS & FAMILIES ADAPT TO GENETIC INFORMATION
and more...


Genetic Counsellor Awareness Day 2022

Chromosome to Gene to Protein