Hereditary Colorectal Cancer Syndromes 2018

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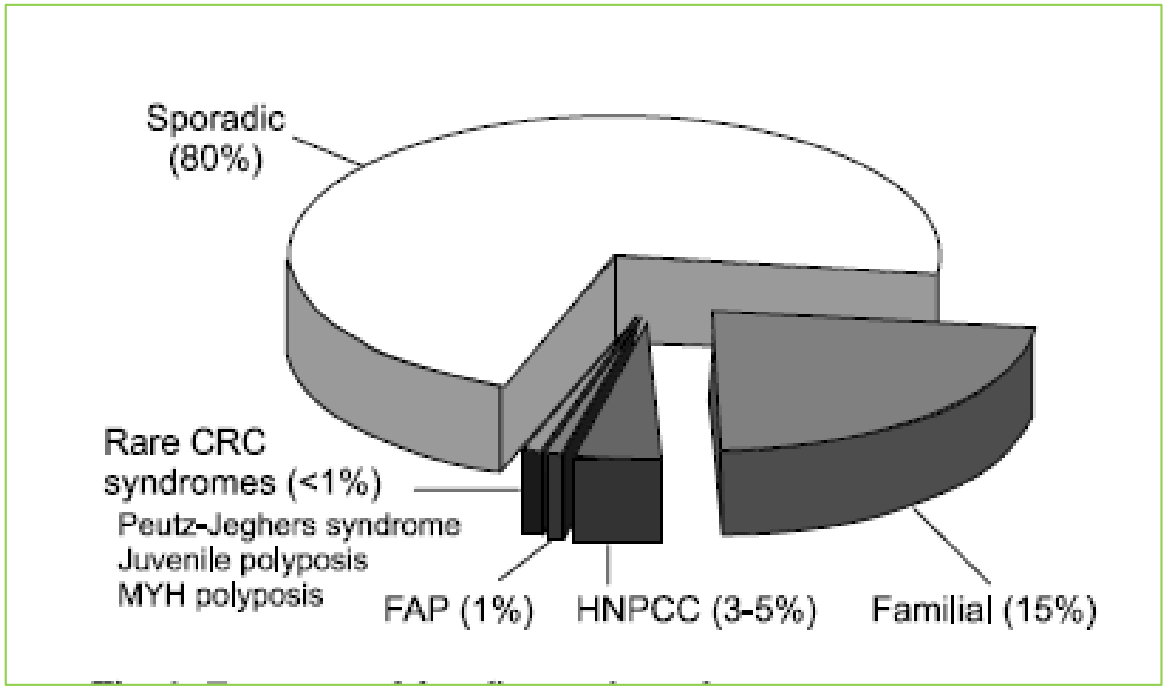
New Zealand Familial GI Cancer Service

Colorectal Cancer

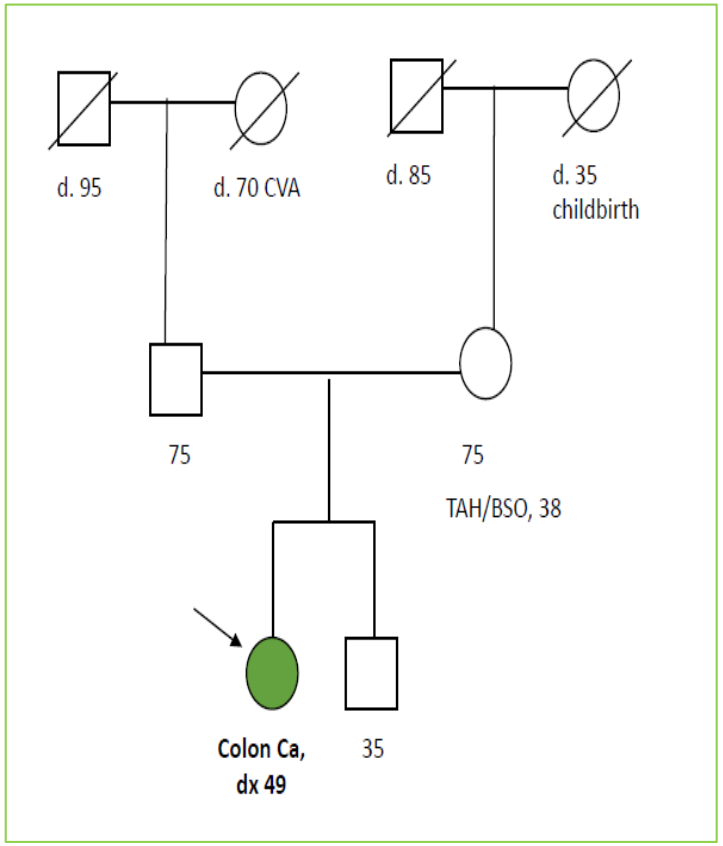
- Environmental factors dominant role in aetiology of most CRC
- Genetic factors are significant in 15-30% of cases
- In 5 % of all cases, CRC associated with a highly penetrant dominant or recessive inherited syndrome
- Most common Lynch Syndrome = 3%



Burt et al Gastroenterology 2000

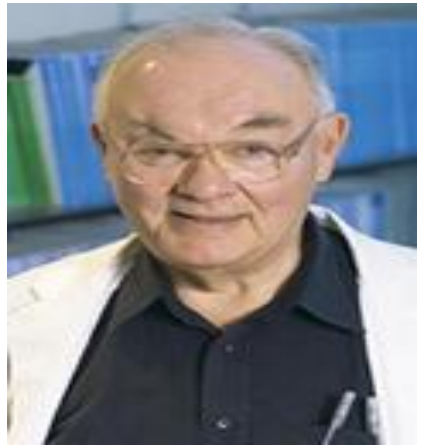
Hereditary Colorectal Cancer
An Update 2018

- Lynch Syndrome (Presumed Lynch, HNPCC)
  - Genetics
  - Clinical
  - Patient Management
  - Diagnosis
- Molecular Testing of Colorectal Cancer in NZ 2018
- FAP, Adenomatous polyposis, oligopolyposis
- Multi gene panel testing for Hereditary GI cancers
  - Implications for patient management



Hereditary Non Polyposis Colorectal Cancer

- 1913 - First described by Dr Scott Warthin
- His seamstress predicted her death from gynaecological or CRC…. and was correct
- 1960's -Dr Henry Lynch - Condition termed HNPCC
- Clinical Criteria developed to help identify families
- 1990's - Cancers from these families found to have mutations in DNA mismatch repair (MMR) genes
  - MLH1, MSH2, MSH6 & PMS2



Lynch Syndrome – 'The Basics'

- Most common hereditary GI Cancer Syndrome
  - Autosomal Dominant
  - 3% of all Colorectal Cancers, 2% of all endometrial cancers
  - Estimated 1 in 279 prevalence in General population
- High lifetime risks of gastrointestinal, gynaecological & other malignancies
  - High penetrance (20-70% lifetime risk of any Lynch associated cancer)
  - Often multiple cancers (metachronous or synchronous)
  - Early onset cancers hallmark but not always the case
- Defined by germline mutation in one of the DNA mismatch repair (MMR) genes
  - MLH1, MSH2 (and EPCAM), MSH6 or PMS2

Lynch Syndrome - Genetics

1. Loss of protein expression (of the 4 genes) can be shown with Immunohistochemistry (IHC)
   - Expression (or absence) is usually paired
   - MLH1/PMS2
   - MSH2/ MSH6

2. Tumours have Microsatellite instability (MSI)
   - Microsatellite Stable (MSS) or Microsatellite Instability – High (MSI-H)

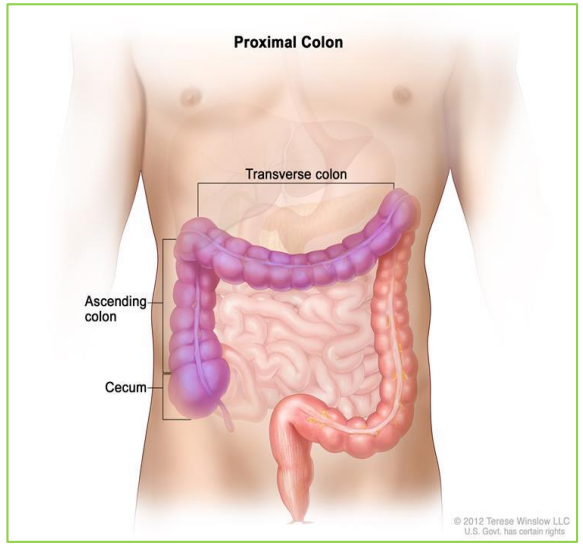
- BUT… MSI / loss of MLH1 expression can be found in 15% of sporadic CRC & caused by silencing of MLH1 gene by promoter abnormalities
- BRAF mutation or MLH1 promoter hypermethylation can detect this indicating NOT due to Lynch Syndrome

Diagnosis: What's in a Name?

- **Lynch Syndrome** – confirmed mutation in one of the MMR genes
- **Presumed Lynch** - abnormal IHC/ MSI – uninformative genetic testing
- **HNPCC** – meet Amsterdam criteria – no genetic test available
- Meet criteria – evidence of normal MMR genes (normal IHC &/or MSI) **Familial CRC Syndrome X**

Lynch Syndrome-associated colorectal cancer

- Predilection for the proximal colon, but can be seen In any part
- Often poorly differentiated / mucinous/ signet ring histology
- Arise from ‘traditional‘ adenomas– display accelerated carcinogenesis
- Classically ‘younger’ patients
- Almost Universally display abnormal MMR protein expression by immunohistochemistry (IHC) and microsatellite instability (MSI)



Lifetime Risk of Cancer across different Lynch Genotypes

Lifetime risk of cancer

Cancer	MLH1 to age 70 yrs[1,2,3]	MSH2 to age 70 yrs[1,2,3]	MSH6 to age 70 yrs[2,4]	PMS2 to age 70 yrs[5]	Lynch syndrome to age 70 yrs*	General population to age 85 yrs**
Colorectal (male)	34%	47%	22%	20%	38%	9%
Colorectal (female)	36%	37%	10%	15%	31%	6.3%
Endometrial	18%	30%	26%	15%	33%	2.3%
Gastric	6%	0.2%	Insufficient data	-	6%	1.1%
Ovarian	11%	15%	Low	-	9%	1.2%
Urothelial	0.2%	2.2%	0.7%	-	<3%	1.4%
Small bowel	0.4%	1.1%	Insufficient data	-	<3%	0.1%

**This data does not take into account the impact of surveillance.*

***Australian Institute of Health and Welfare 2017. Cancer in Australia 2017. [Accessed December 2017]*

EviQ Risk Management for Lynch 2017

Management of Individuals with Lynch Syndrome (1)

- Cancer Screening
  - CRC screening by annual colonoscopy in confirmed mutations carriers from age 25years
  - Baseline gastroscopy at 35 years, examine duodenum, *H.Pylori*
  - Consider annual endometrial biopsy and transvaginal USS from age 35years
  - Insufficient data to recommend screening for pancreaticobiliary, urological or CNS
- Surgical Management
  - Colectomy with ileorectal anastomosis is the preferred surgical treatment (or extended resection) of Lynch Syndrome CRC
  - Hysterectomy and bilateral salpingo-oophorectomy offered to women 40-45yrs on completion of family

Vasen et al Gut 2013;62:812-23
Burn et al Lancet 2011;378:20817

Management of Individuals with Lynch Syndrome (2)

- Medical Management
  - Chemoprevention : CAPP2 study – RCT of Aspirin 600mg vs placebo in Lynch Syndrome [1]

"2 aspirin a day for 2 years reduces risk of CRC by 2/3 after 5 years'

  - CAPP3 ongoing…
  - Lifestyle measures
  - OCP [2]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1. Burn et al Lancet 2011;378:20817
2. Dashti et al JAMA 2015

Diagnosis: Molecular Testing of Colorectal Cancer in NZ

- Previously performed only in CRC patients <50yrs or those who met Amsterdam criteria
  - Fails to identify up to 40% of Lynch Syndrome patients [1]
  - Implications for managing initial tumour
  - Implications for subsequent screening of individual & family members
- Molecular testing useful for both prognostic and predictive reasons
  - BRAF mutation is an independent prognostic factor for poor outcome in MSS Cancer
  - Benefit of 5FU adjuvant chemo limited to normal MMR Stage II colorectal cancers [4,5]
- Internationally Universal tumour Testing for MMR deficiency now recommended[2,3]

1 Hartman et al 2013, 2 NICE Guidelines 2017, 3 Syngal et al 2015,
4. Jover et al 2009, 5. Sargent et al 2008 6 Ogino et al 2012

Molecular testing of Colorectal Cancer in NZ

1. All newly diagnosed colorectal cancers should be tested for Mismatch repair (MMR) deficiency
   - IHC or MSI
2. Tumours with loss of MLH1 straining should undergo BRAF mutation or MLH1 promotor hypermethylation analysis to rule out sporadic (non Lynch) MMR – deficiency
3. BRAF mutation analysis in all Stage IV colorectal cancers

→ If abnormal refer to NZFGICS

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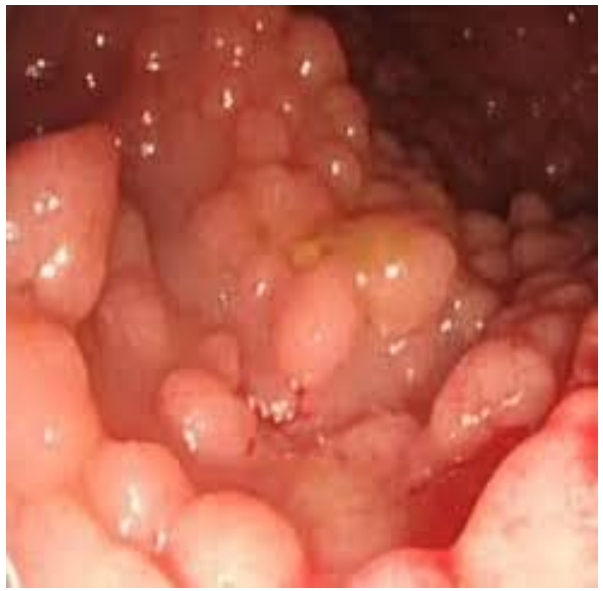
https://www.health.govt.nz/publication/molecular-testing-colorectal-cancers-new-zealand-minimum-standards-molecular-testing-newly-diagnosed June 2018

Clinical Features of Classic FAP

- Autosomal Dominant
- 1 in 7000 to 10,000 births
- Almost 100% risk of developing CRC
- Recognition of phenotype is easy
- Risk of extracolonic tumours – upper GI, desmoid, thyroid, osteoma, brain…
- Due to germline mutation in APC gene on Chromosome 5
- Clinical presentation depends on location of mutation



MUTYH-associated Polyposis (MAP)

- Autosomal recessive – biallelic inheritance of MUTYH gene mutation
- Wide spectrum of polyp burden and CRC risk
  - >50% of MAP patients with CRC have < 10 lifetime adenomas at the time of CRC diagnosis
  - Dozens, not 100's of adenomas
  - Later onset
- Mono-allelic carrier – unclear risk

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- If > 20 lifetime adenomas or 10 adenomas at one colonoscopy, think of referring
- Other oligopolyposis being investigated and defined more clearly…

Guarinos C et al Clin Cancer Res 2014;20:1158-68

Management of Individuals with FAP/MAP

- Surgical Management
  - Appropriately timed colectomy – usually late teens, early 20's
  - For attenuated polyposis, annual colonoscopy may delay / ?? avoid colectomy
- Cancer Screening
  - Surveillance of J Pouch annually
  - Upper GI tract surveillance as per Spiegelmans criteria
  - Annual thyroid examination
- Medical Management
  - Chemoprevention : Celocoxib reduces polyp burden
  - Desmoids – Sulindac & Tamoxifen

Samadder NE JAMA Oncol 2018
Giardiello Gastroenterology 2002

Welcome to the Future… Panel Testing

Traditionally:

Syndrome specific testing.

Individuals undergo testing for a given syndrome if their personal / family history fulfil criteria

- Lynch Syndrome testing for MMR deficient colon cancers
- APC/ MUTYH testing if multiple adenomas

The Future:

Multi gene panel testing

- Next generation germline sequencing of numerous ‘cancer genes’
- Each commercial lab has their own panel of genes & new genes added…

Coming to a clinic near you…

- Gene panel testing available in NZ starting at $399….

Inherited Cancer Panel
Our Inherited Cancer Panel specifically looks for inherited gene mutations in over 130 different genes associated with a wide range of hereditary cancers (including BRCA1, BRCA2 & MLH1). This screening test can be used to identify gene mutations responsible for hereditary cancers and to clarify the genetic risk for individuals with a family history of these hereditary cancers. It is a powerful tool that can help you reduce your risks or undertake measures that will help you detect hereditary cancers as early as possible.

Multi-gene panel testing in young Onset CRC

- 450 individuals with CRC< 50yrs
  - 72 (16 %) had a germ line mutation
  - 13% with mutations in genes linked to CRC
    - 8.4% Lynch Syndrome
    - 1.1% FAP
    - 0.9% MUTYH associated polyposis
    - Others - SMAD4, TP53
  - 33% of mutation carriers did not meet clinical criteria for the gene / syndrome they had
  - 3% mutations in genes not linked to CRC - BRCA1/2 in (1.3%)
  - 1/3 of patients had Variant of Uncertain significance (VUS)

Pearlman et al JAMA Oncol 2016
Stoffel et al Gastroenterology 2018

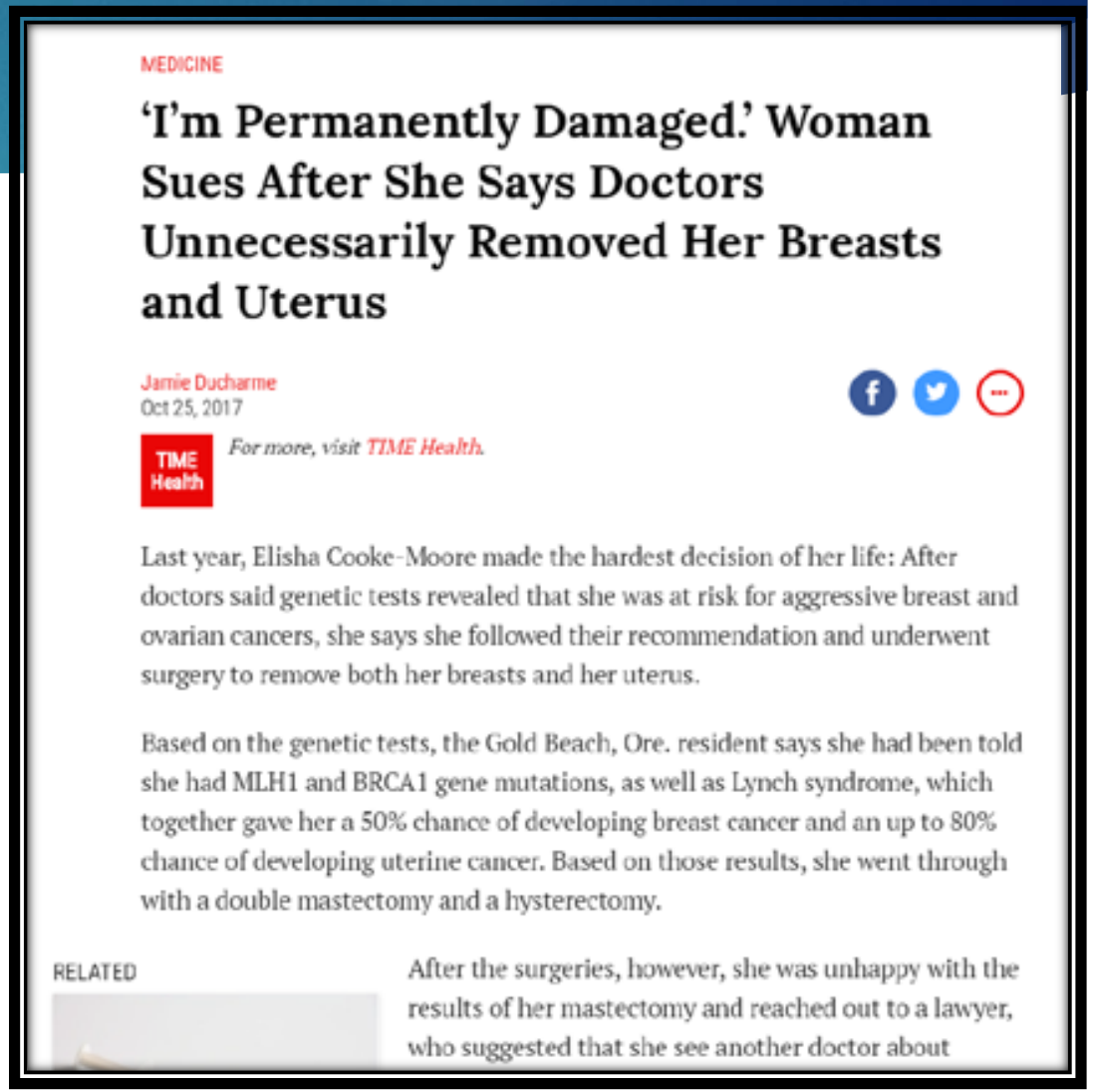
Multi-gene panel testing in Unselected CRC

- 1058 pts – all CRC – no preselection
- 105 (9.9%) with pathogenic mutation
  - 3.1% Lynch Syndrome
  - 7% non Lynch Syndrome Mutations – MUTYH, APC, TP53
  - Of those >1/3 lacked clinical histories suggestive of their mutation
- 1.1% BRCA1/2 mutation
- 31% with germline Variant of Uncertain significance (VUS)
- More Answers but more questions…

Yurgelun et al J Clin Oncol 2017

Variants of Uncertain significance (VUS)

'...doctors misinterpreted a line in the results which said that there were 'variants of Uncertain significance' associated with the MLH1 gene...'



MEDICINE

'I'm Permanently Damaged.' Woman Sues After She Says Doctors Unnecessarily Removed Her Breasts and Uterus

Jamie Ducharme
Oct 25, 2017

TIME Health *For more, visit TIME Health.*

Last year, Elisha Cooke-Moore made the hardest decision of her life: After doctors said genetic tests revealed that she was at risk for aggressive breast and ovarian cancers, she says she followed their recommendation and underwent surgery to remove both her breasts and her uterus.

Based on the genetic tests, the Gold Beach, Ore. resident says she had been told she had MLH1 and BRCA1 gene mutations, as well as Lynch syndrome, which together gave her a 50% chance of developing breast cancer and an up to 80% chance of developing uterine cancer. Based on those results, she went through with a double mastectomy and a hysterectomy.

RELATED

After the surgeries, however, she was unhappy with the results of her mastectomy and reached out to a lawyer, who suggested that she see another doctor about

Conclusion

- Lynch Syndrome
  - Most common hereditary GI Cancer Syndrome, 3% of all CRC
  - Defined by germline mutation in MMR gene, different gene, different cancer penetrance
  - Management including intensive colonoscopic surveillance, chemoprophylaxis & don't forget gynaecology
- All new Colorectal cancers should have Molecular Testing for IHC/ MSI
- Polyposis & Oligo polyposis – think of it & refer
- The Future… multi gene panel testing

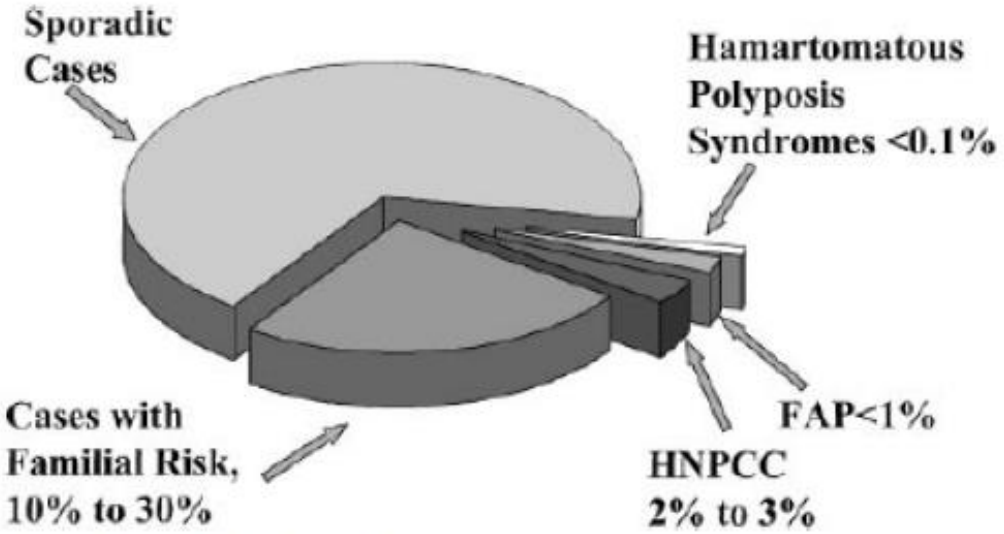
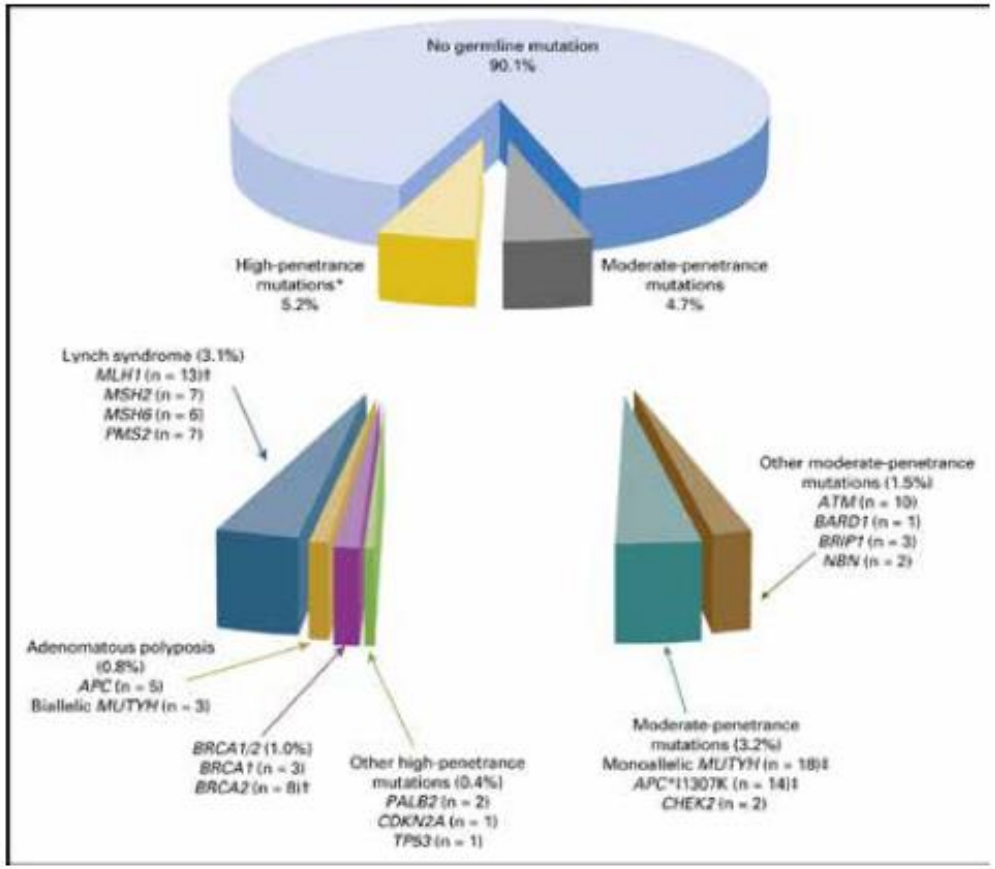


Figure 1. The fractions of colon cancer cases that arise in various family risk settings.



Burt RW. *Gastroenterology* 2000;119:837-53.
Yurgelun MB, et al. *J Clin Oncol*, 2017 ePub.