Hereditary Colorectal Cancer

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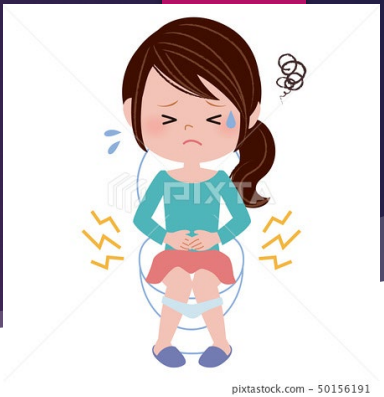
Disclosures

None

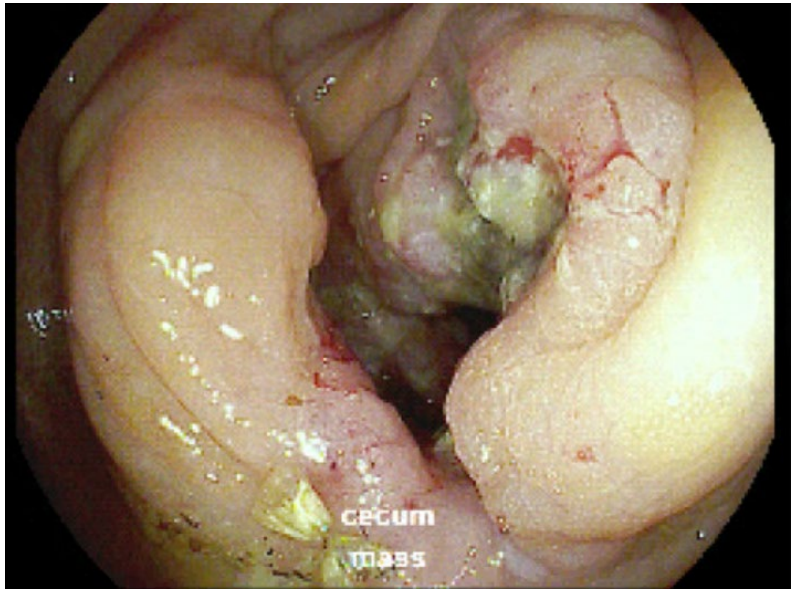
Objectives

- Introduction to hereditary colorectal cancers
- Basics of genetic testing
- Criteria for referral for genetic testing

Ms J



- 35 yr old woman with constipation x 12 months
- Family history- Mother with CRC at age 49
- Advised to start Colonoscopy at age 39



Diagnosis: Lynch Syndrome

- Named after Henry Lynch
- Most common hereditary colorectal cancer syndrome
- Due to germline mutation in Mismatch repair genes

Lynch syndrome

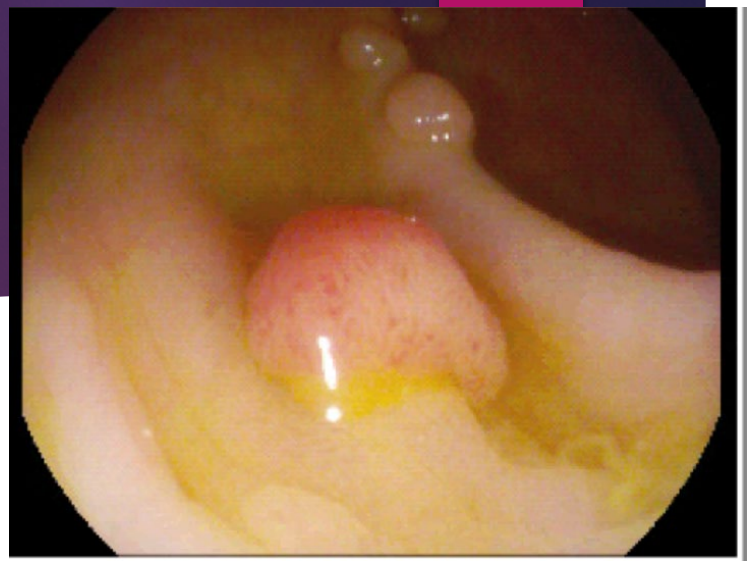
Gene	CRC risk by age 80	Age to start CRC surveillance	Frequency
MLH1	40-61%	20-25 Y	1-2 years
MSH2(EPCAM)	33-52%		
MSH6	10-44%	30-35 Y	
PMS2	8-20%		

How common is Lynch syndrome in the general population?

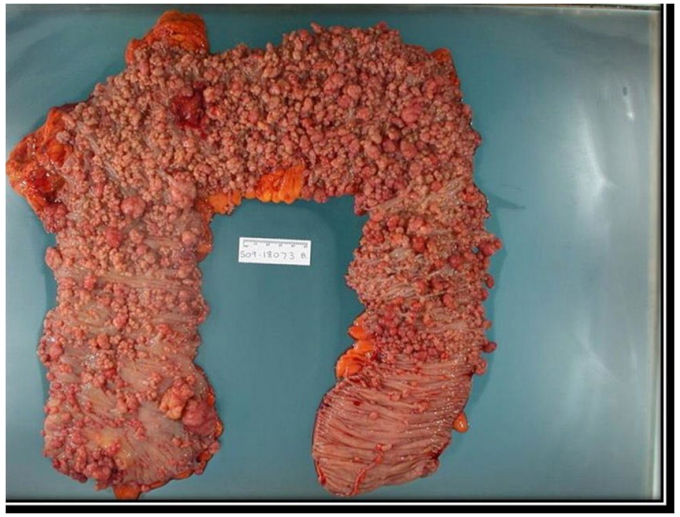
Mr Y

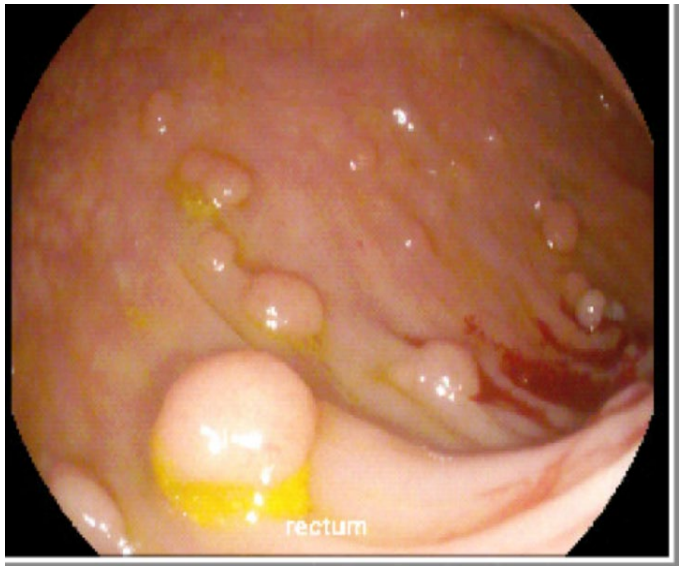
- 20 yr old M with intermittent rectal bleed
- No family history of colon cancers
- Managed as hemorrhoids

Mr Y: Diagnosis FAP

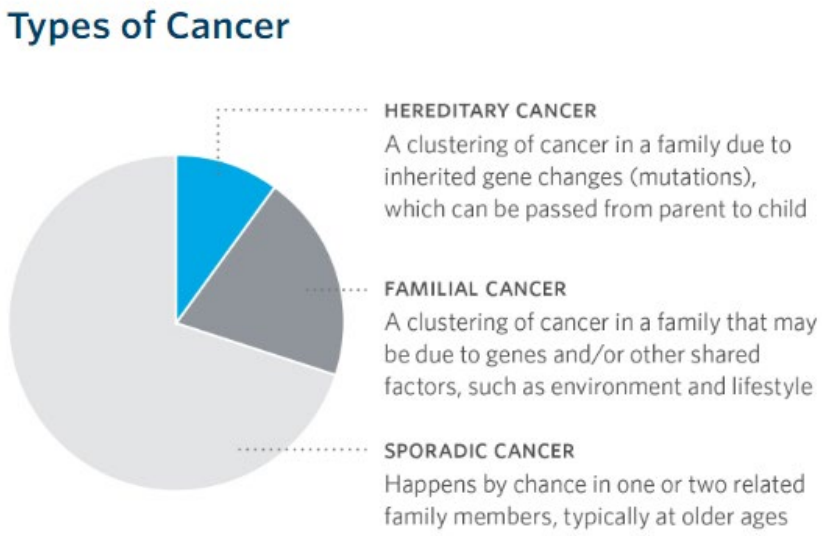


- Familial adenomatous polyposis
- Due to germline mutation in APC gene
- Risk of colon cancer-~100%
- 25% can be de novo
  - (no family history)

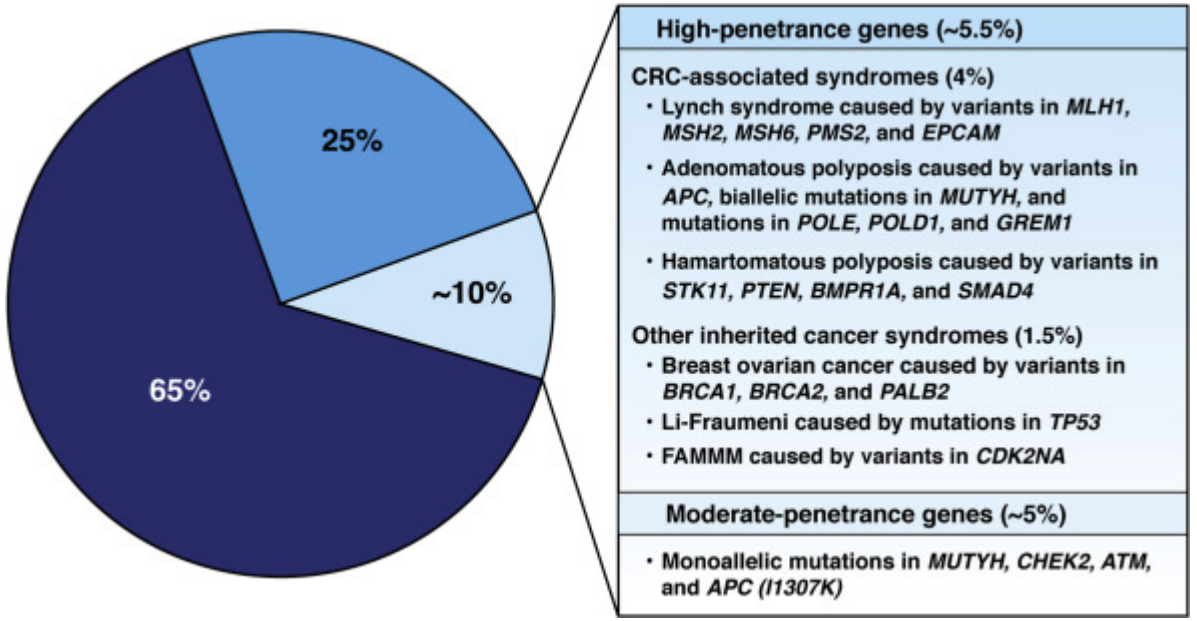




Sporadic Vs Hereditary Cancers

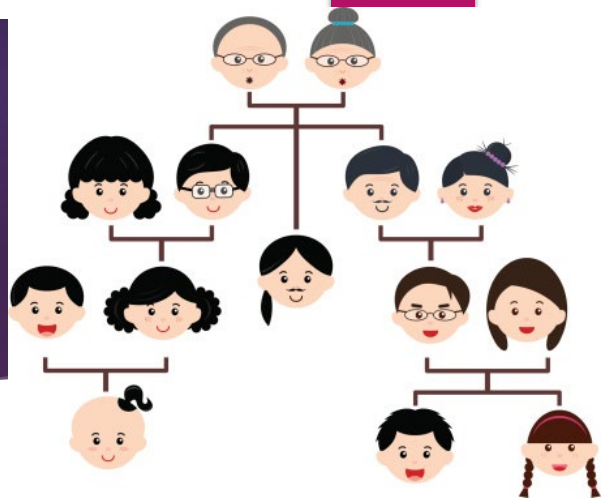


10% of CRC patients have hereditary syndromes



Kastrinos et al, Gastroenterology,2022

Family history matters



Family History	Absolute Risk (%) of CRC by Age 79 y
No family history	4
1 FDR with CRC	9
>1 FDR with CRC	16
1 FDR with CRC <45 y	15
One FDR with colorectal adenoma	8

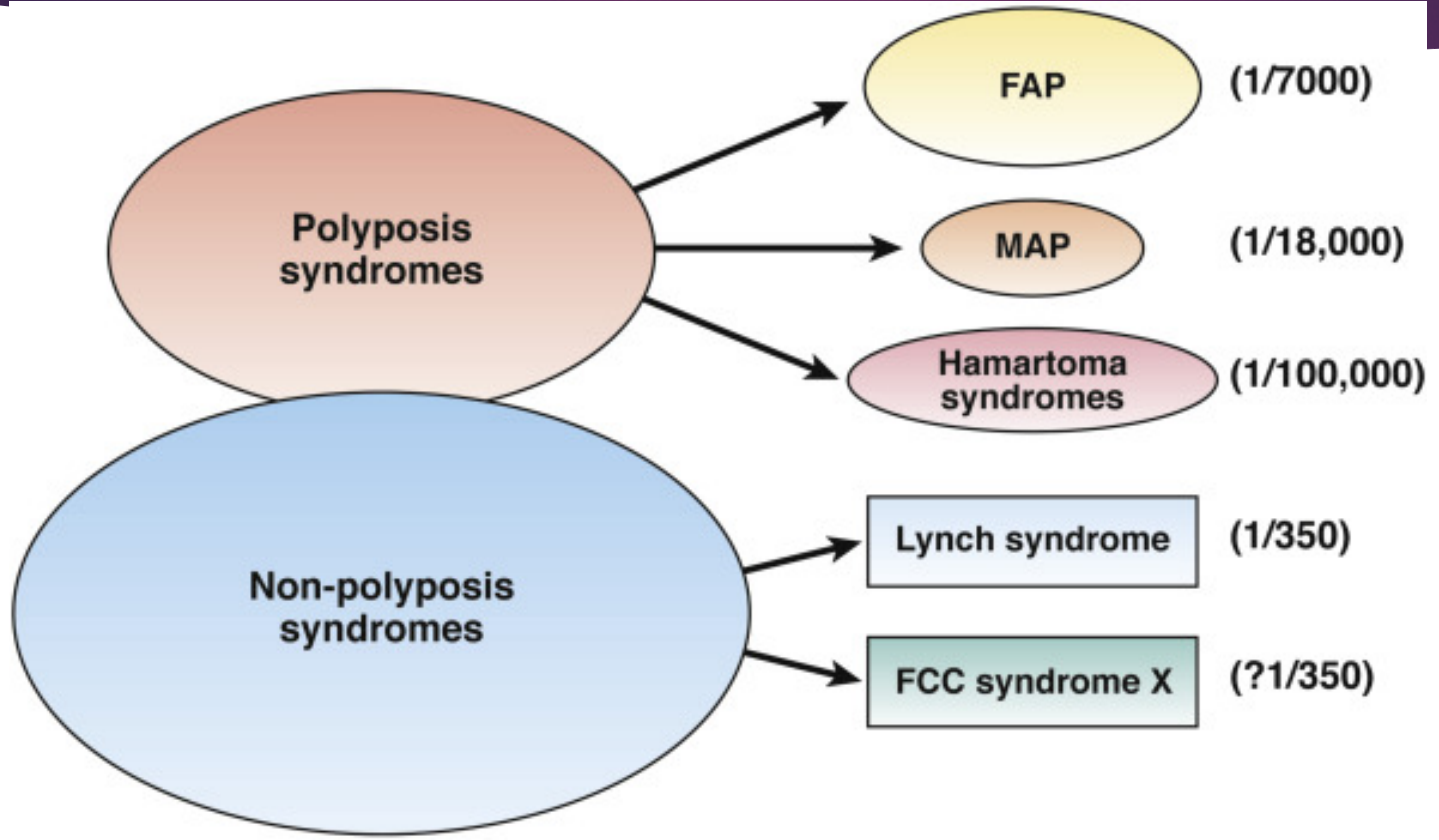
Patient's story…

- "Until my diagnosis, there were no less than **thirteen doctors** who could have taken detailed family history from the members of my family and referred them for genetic testing.

- It never occurred prior to the time, **I was diagnosed with a cancer**."

http://www.lynchcancers.com

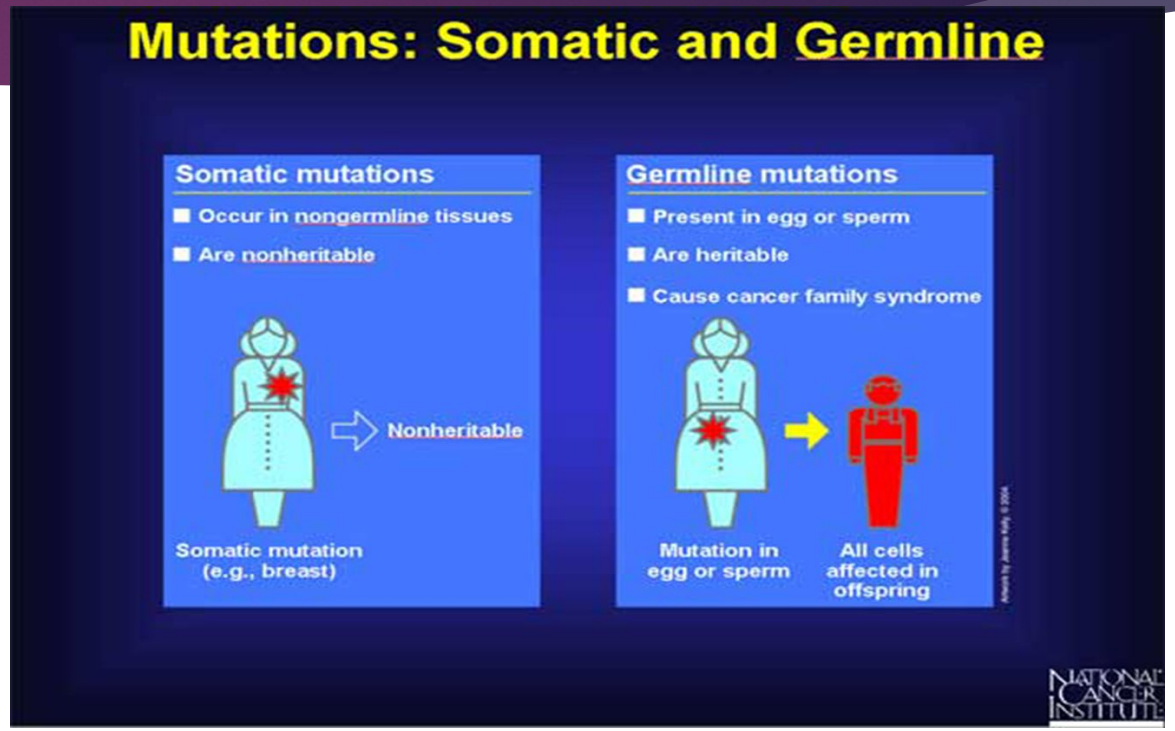
Hereditary Colorectal Cancer Syndromes



Stoffel et al, Gastroenterology,2015

What is a hereditary cancer

- Due to germline mutations
  - Person was born with the mutation
    - (they do not develop over time)
  - Present every cell



When to refer for genetic testing

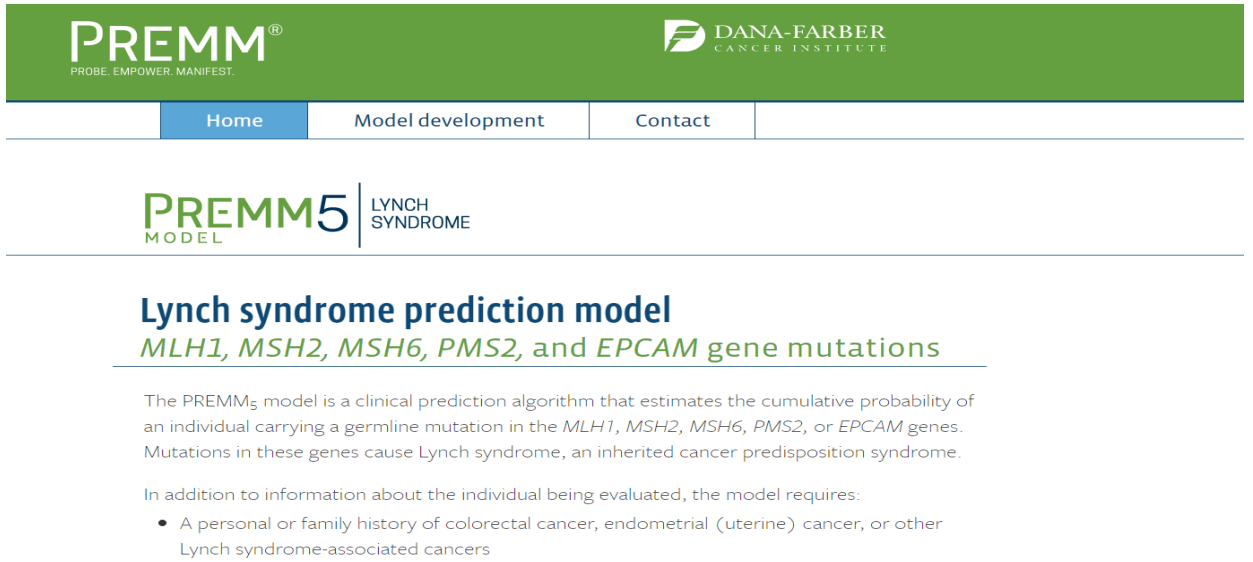
- ≥10 adenomatous polyps
- ≥ 2 hamartomatous polyps

- Tumor testing with MMR deficiency
- Family history of known genetic syndrome

- Meets NCCN criteria for Lynch testing
- Meets PREMM5 model cutoff (>2.5%)

Lynch Syndrome Prediction Model

- **PREMM 5** (https://premm.dfci.harvard.edu/)



NCCN Criteria for Lynch syndrome

- ≥1 FDR with a CRC or endometrial cancer <50 y
- ≥1 FDR with a CRC or endometrial cancer and a synchronous or metachronous **LS-related cancer*** regardless of age
- ≥2 FDR or SDR with **LS-related cancers**, including ≥1 diagnosed <50 y
- ≥3 FDR or SDR with **LS-related cancers** regardless of age

*glioblastoma, small bowel, stomach, pancreas, bile duct, gallbladder, kidney, ureter, bladder, prostate, sebaceous skin tumors

Genetic Testing sample

- **Saliva sample/ Buccal swab**
- Blood test
- Skin biopsy fibroblast culture

  (bone marrow transplant recipient, active/recent hematologic malignancy)

- Turnaround time: 2-3 weeks
- Covered by most insurance plans
- Out of pocket cost- $250

www.businessinsider.com

GINA

President George W. Bush signs H.R. 493, the Genetic Information Nondiscrimination Act of 2008, Wednesday, May 21, 2008, in the Oval Office. White House photo by Eric Draper.

- GINA (Genetic Information Non-discrimination Act)-2008
  - Excluded- Life insurance, disability, long term care insurance

Timely genetic testing is critical

- Timely genetic testing can alter:
  - Type of surgery
    - Hysterectomy/oophorectomy at the time of colectomy
    - Extended colectomy
  - Therapeutics -
    - Genomic instability may lead to neo-antigen expression and susceptibility to immunotherapy and better outcome
  - Lynch syndrome vaccine trials underway

Resources

GI Cancer Genetics

- www.findageneticcounselor.org (Find a genetic counselor)
- www.cgaigc.com/find-a-gi-genetics-clinic(GI cancer genetics clinic)
- www.plsd.eu (Prospective Lynch Syndrome Database (PLSD) - gene, organ specific cancer risk)
- www.nccn.org
- www.Ask2me.org (Calculate the risk of cancers associated with genes)

Patient information resources

- www.Kintalk.org
- www.facingourrisk.org
- www.alivenkickn.org
- www.nostomachforcancer.org

Take Home

- 10% of CRC can be hereditary
- Know your family history of CRC and polyps and discuss genetic testing, earlier colonoscopy with your provider
- Consider colonoscopy (not stool based test) for those with high risk of CRC

Thank you!

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Colorectal cancer

- Third most commonly diagnosed cancer in both men and women
- Annual estimate in the US
  - new colorectal cancer diagnosis 150,000
  - Death: 52,000