

Hereditary Colorectal Cancer

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The UCSF logo is located in the bottom right corner of the slide. It consists of the letters "UCSF" in a white, sans-serif font, centered within a dark blue square background.

UCSF

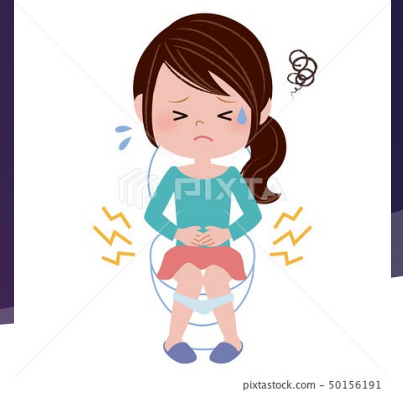
Disclosures

None

Objectives

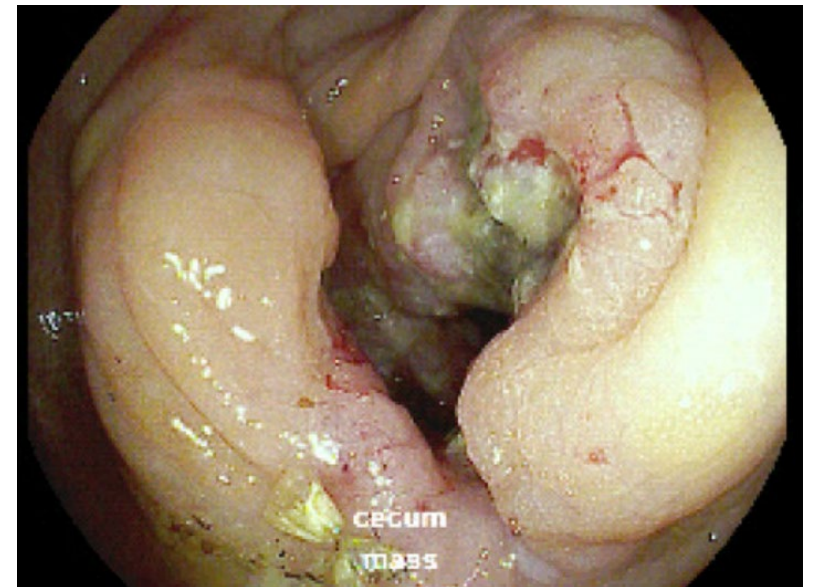
- ▶ Introduction to hereditary colorectal cancers
- ▶ Basics of genetic testing
- ▶ Criteria for referral for genetic testing

Ms J



pixtastock.com - 50156191

- ▶ 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?

1:300

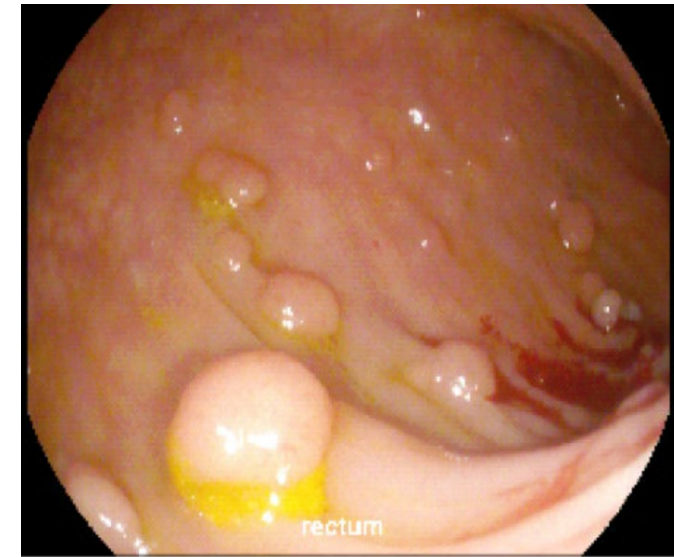
Mr Y

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



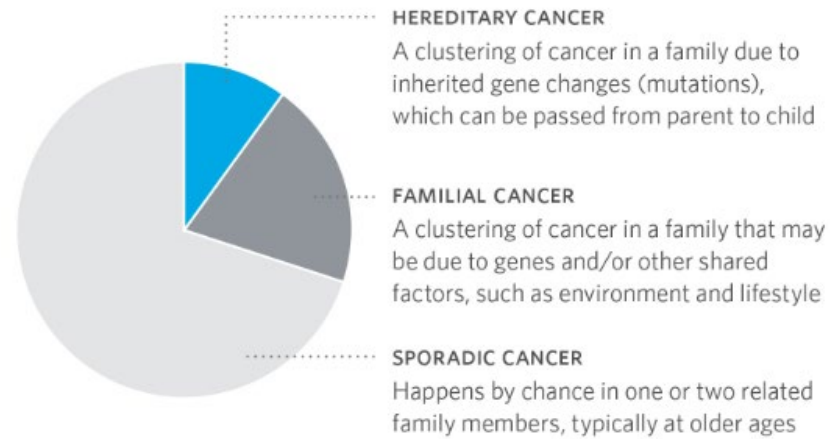
Mr Y: Diagnosis FAP

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

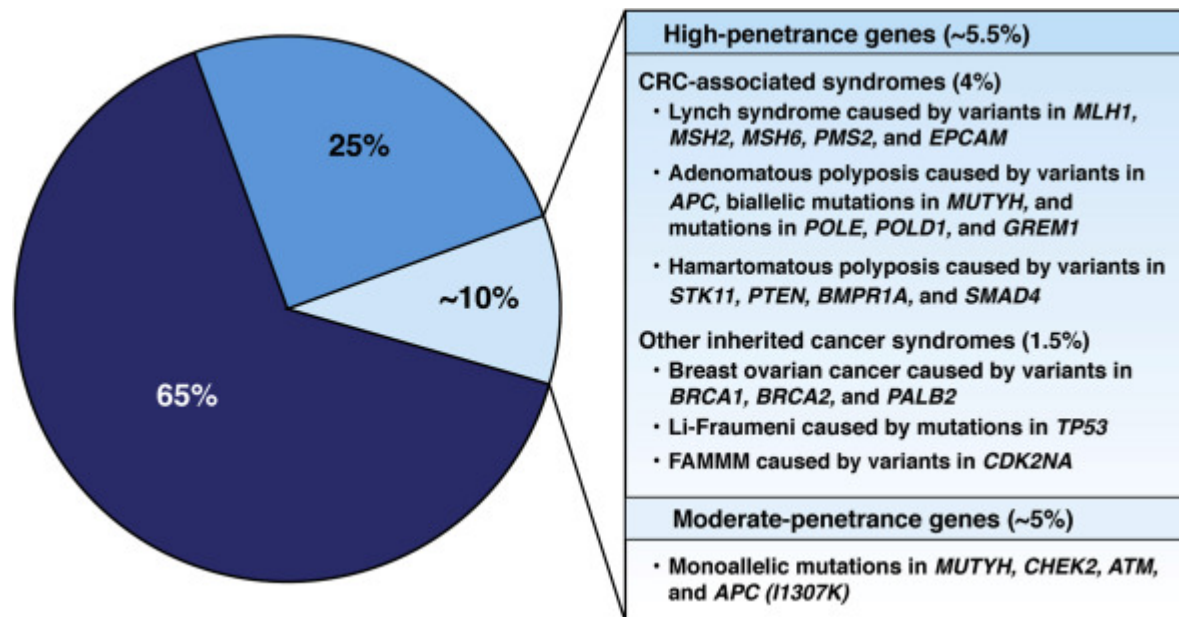


Sporadic Vs Hereditary Cancers

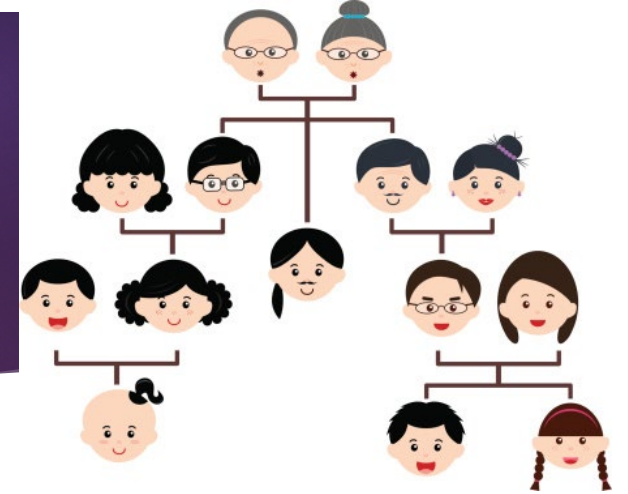
Types of Cancer



10% of CRC patients have hereditary syndromes



Family history matters



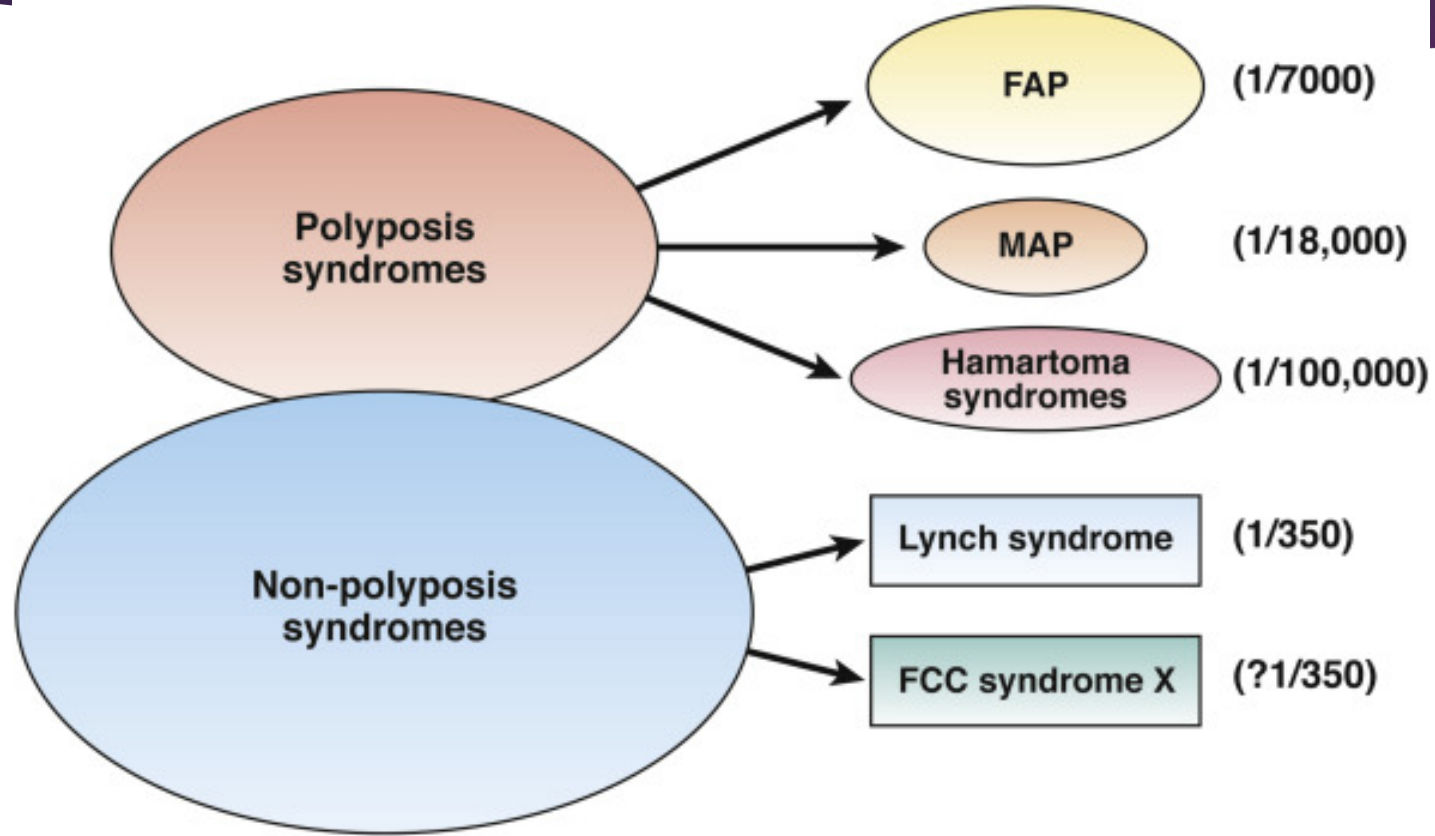
Family History	Absolute Risk (%) of CRC by Age 79 y
No family history	4
1 FDR with CRC	9
>1 FDR with CRC	16
1 FDR with CRC <45 y	15
One FDR with colorectal adenoma	8

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.**”



Hereditary Colorectal Cancer Syndromes



What is a hereditary cancer

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

Mutations: Somatic and Germline

Somatic mutations

- Occur in **nongermline** tissues
- Are **nonheritable**



Somatic mutation
(e.g., breast)

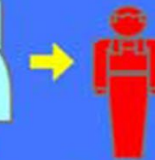
➔ Nonheritable

Germline mutations

- Present in egg or sperm
- Are **heritable**
- Cause cancer family syndrome



Mutation in
egg or sperm



All cells
affected in
offspring

Adapted by Jerome Kelly, © 2004

When to refer for genetic testing

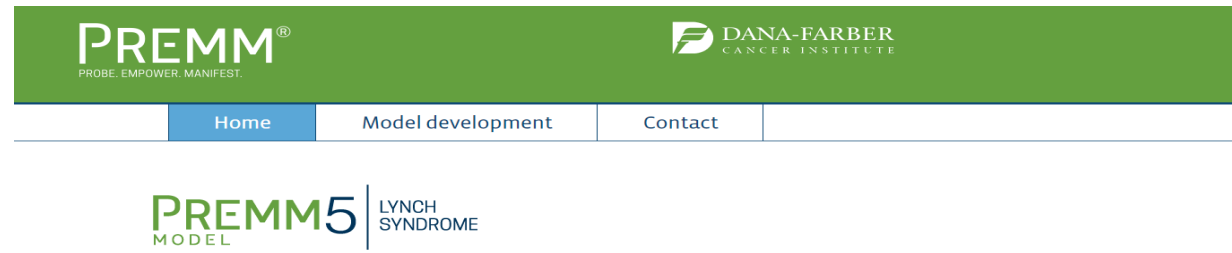
- ▶ ≥ 10 adenomatous polyps
- ▶ ≥ 2 hamartomatous polyps

- ▶ 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/>)



The screenshot shows the top portion of the PREMM5 website. At the top left is the PREMM logo with the tagline "PROBE. EMPOWER. MANIFEST." Below it is a navigation bar with three buttons: "Home" (highlighted in blue), "Model development", and "Contact". To the right of the navigation bar is the Dana-Farber Cancer Institute logo. Below the navigation bar is the "PREMM5 MODEL" logo, with "LYNCH SYNDROME" written vertically to its right.

Lynch syndrome prediction model

MLH1, MSH2, MSH6, PMS2, and EPCAM gene mutations

The PREMM₅ model is a clinical prediction algorithm that estimates the cumulative probability of an individual carrying a germline mutation in the *MLH1*, *MSH2*, *MSH6*, *PMS2*, or *EPCAM* genes. Mutations in these genes cause Lynch syndrome, an inherited cancer predisposition syndrome.

In addition to information about the individual being evaluated, the model requires:

- A personal or family history of colorectal cancer, endometrial (uterine) cancer, or other Lynch syndrome-associated cancers

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



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