Practical Use of Genetic Testing in Clinical Practice

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Disclosures

None

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/index.php/protecting-families-saving-lives/page-3

Objectives

- Primer to genetic testing and counseling
- Universal tumor testing
- Criteria for referral to genetic testing

How common is Lynch syndrome in the general population?

A) 1:300

B) 1:1000

C) 1:5000

D) 1:10,000

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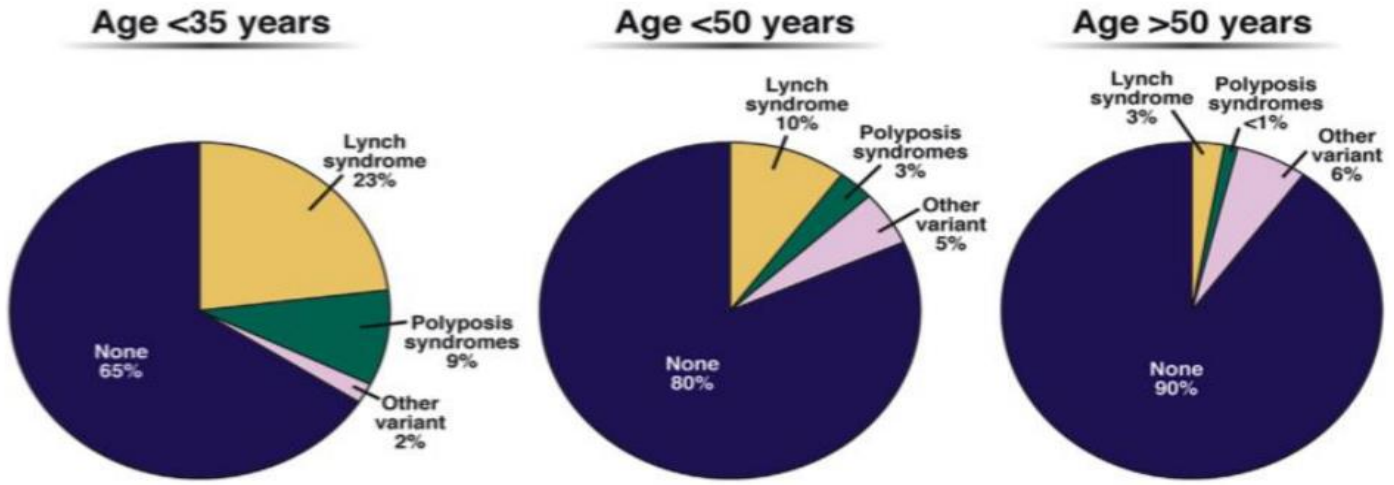
Genes associated with CRC



Lynch syndrome	Polyposis syndromes	Other pathogenic variants	
		High penetrance	Moderate/low penetrance
MLH1	*APC*	*BRCA1*	*CHEK2*
MSH2	*MUTYH*	*BRCA2*	*ATM*
MSH6	*SMAD4*	*TP53*	*NBN*
PMS2	*BMPR1A*	*PALB2*	*BARD1*
	PTEN	*CDKN2A*	*BRIP1*
	POLE		

Stoffel E, Murphy C. *Gastroenterol* 2020

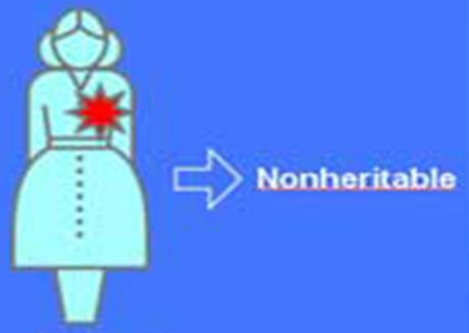
Lynch syndrome

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%		

Mutations: Somatic and Germline

Somatic mutations

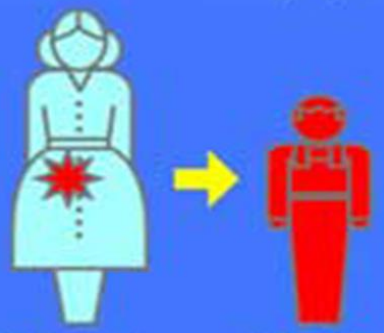
- Occur in nongermline tissues
- Are nonheritable



Somatic mutation
(e.g., breast)

Germline mutations

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



Mutation in egg or sperm

All cells affected in offspring

NATIONAL CANCER INSTITUTE

Universal Tumor Testing for CRC

- Microsatellite instability (MSI)/ Immunohistochemistry (IHC) tumor testing to all CRC

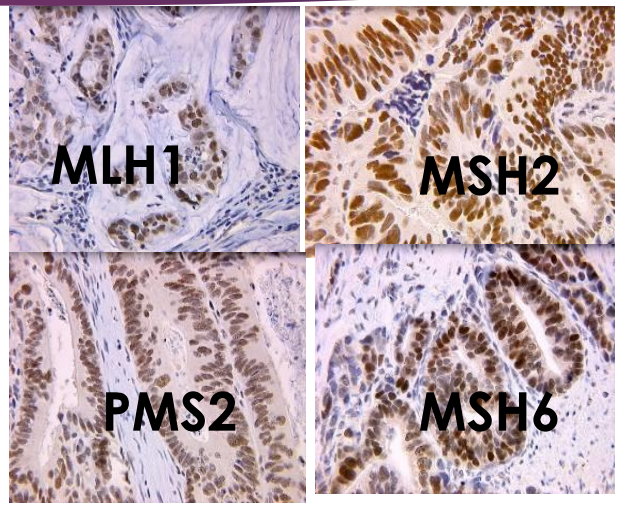
- Does not require written consent

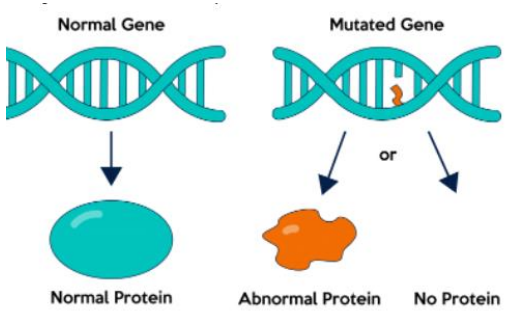
Microsatellite Instability Testing (MSI)

- Microsatellite
  - Stretches of DNA with repetitive sequences of nucleotide
    - (eg. AAAAA or CGCGCGCG)
- Susceptible to errors when MMR genes are mutated

Immunohistochemistry (IHC)

- Easily available tumor test
- Antibodies used to stain for MMR proteins





Mismatch repair gene mutated → Abnormal Protein → Lack of staining on IHC

Immunohistochemistry tumor tissue

IHC Normal
MMR Proficient

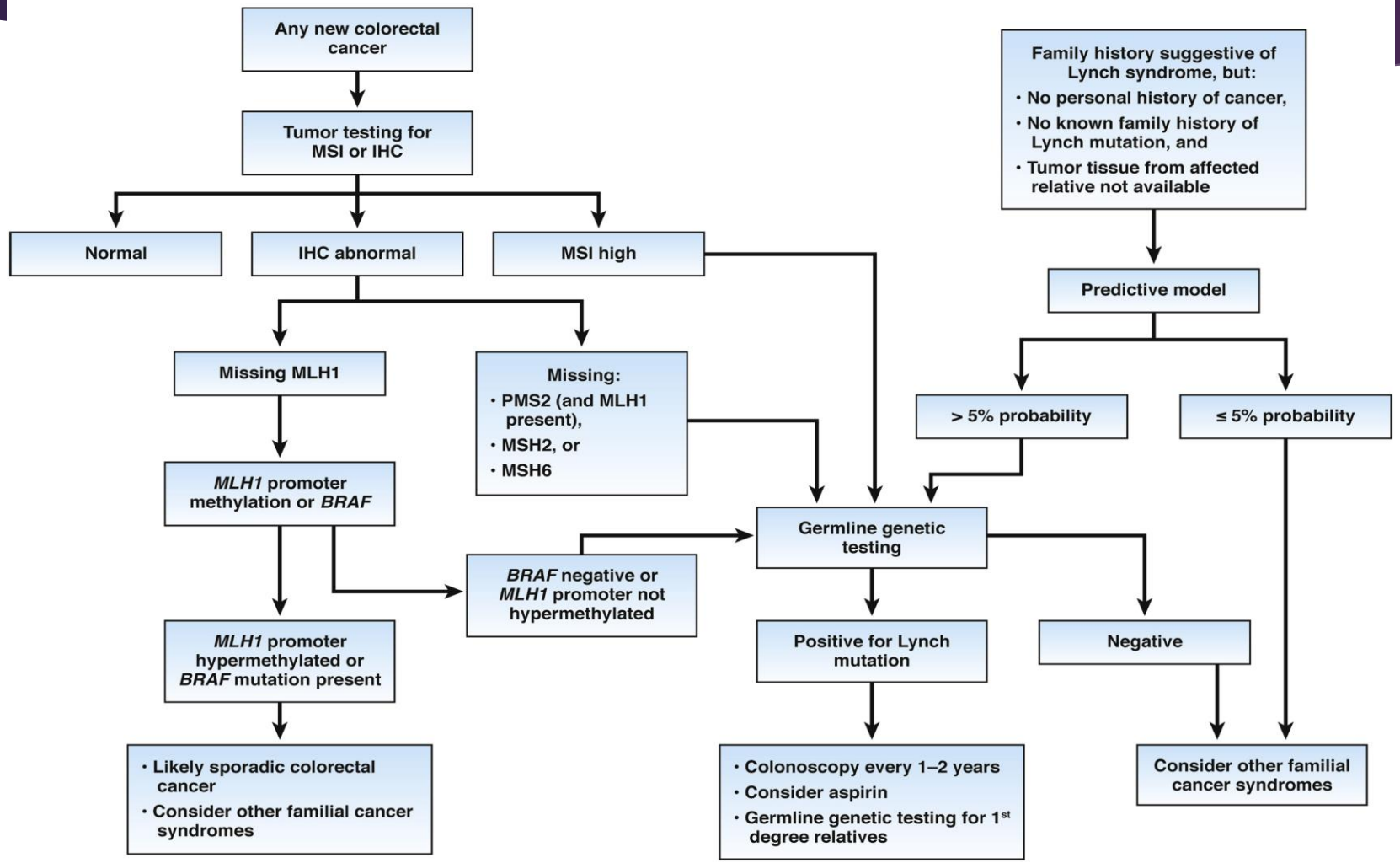
MLH1 expression: **Present**
PMS2 expression: **Present**
MSH2 expression: **Present**
MSH6 expression: **Present**

IHC Abnormal
dMMR
MMR Deficient

MLH1 expression: **Absent**
PMS2 expression: **Absent**
MSH2 expression: Present
MSH6 expression: Present

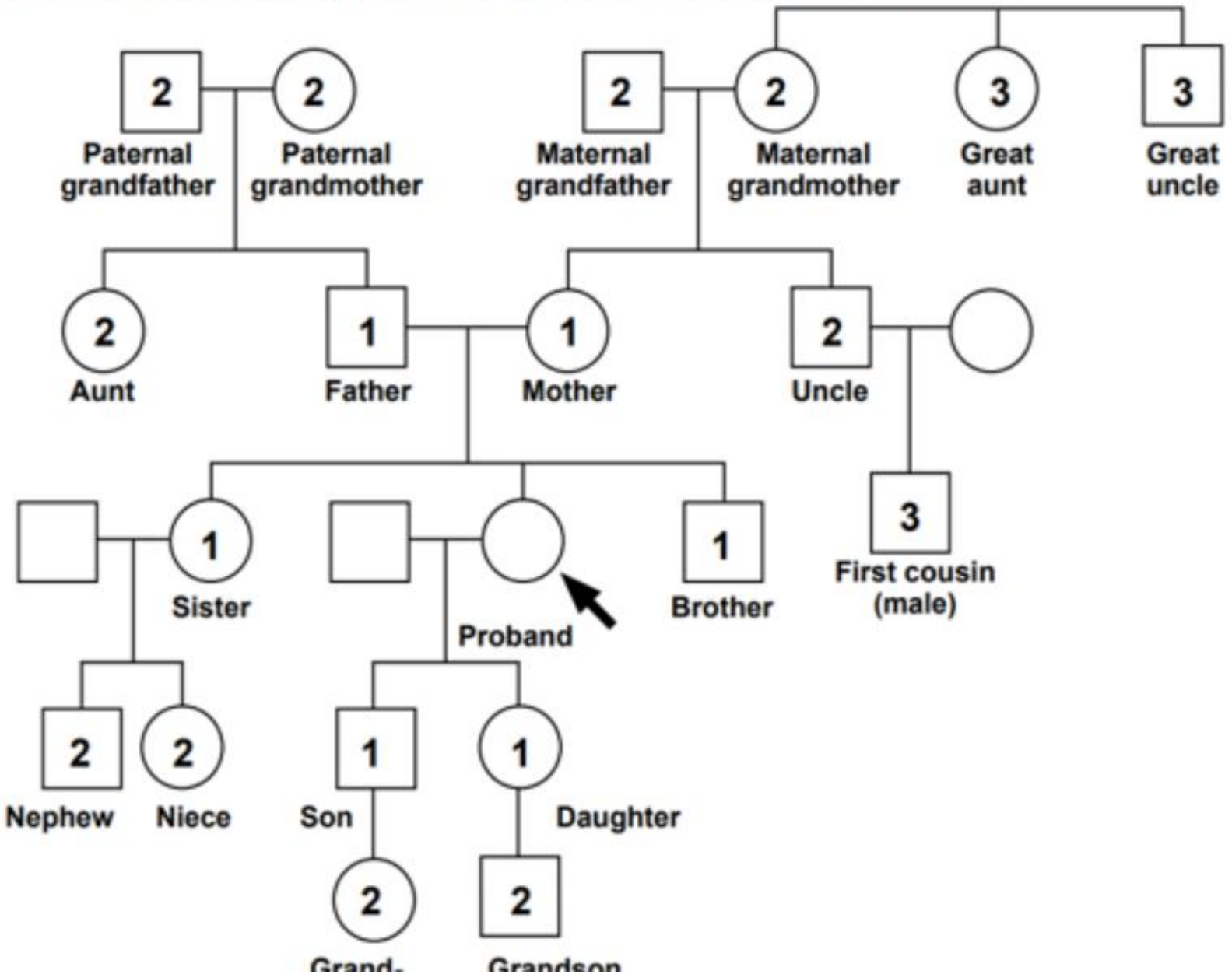
Diagnosis and Management of Lynch Syndrome

Clinical Decision Support Tool



Rubenstein et al. Gastroenterology,2015

PEDIGREE: FIRST-, SECOND-, AND THIRD-DEGREE RELATIVES OF PROBAND[16]



When to refer for genetic testing

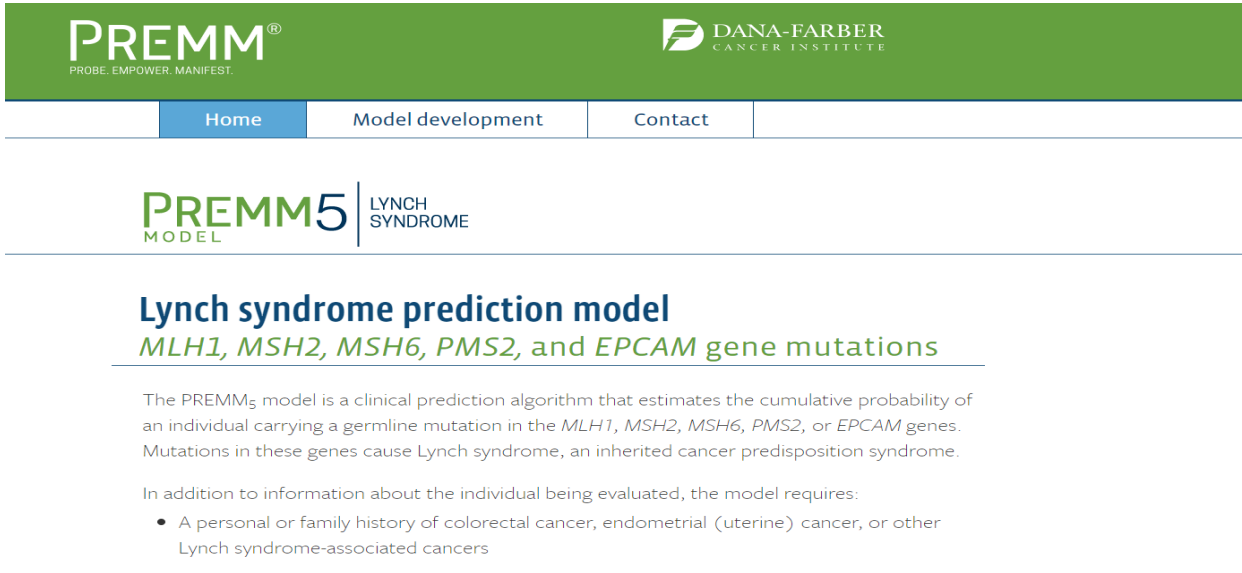
- ≥10 adenomatous polyps
- ≥ 2 hamartomatous polyps

- 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/)
  - Sex /Age
  - History of colorectal cancer and other Lynch related cancer
  - Number of first and second degree relatives with CRC/ Endometrial cancer



NCCN Criteria for Lynch syndrome

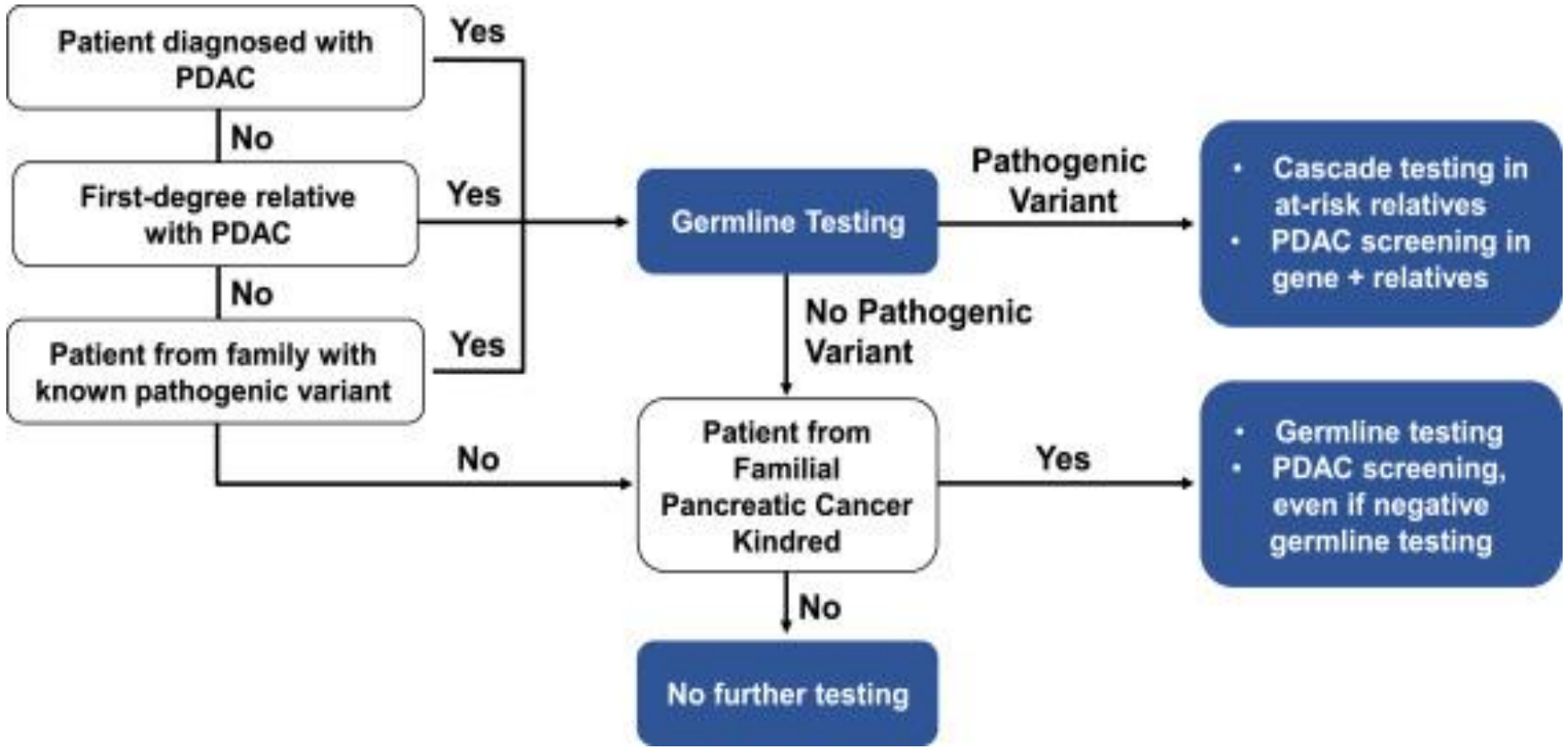
- ≥1 FDR with a CRC or endometrial cancer <50 y
- ≥1 FDR with a CRC or endometrial cancer and a synchronous or metachronous **LS-related cancer*** regardless of age
- ≥2 FDR or SDR with **LS-related cancers**, including ≥1 diagnosed <50 y
- ≥3 FDR or SDR with **LS-related cancers** regardless of age

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

Pancreatic Cancer

- 10% of pancreatic cancers are due to genetic causes
  - (ATM, BRCA1/2, CDKN2A, Lynch Genes, PALB2, STK11, TP53)

How to approach a patient with family history of pancreas cancer

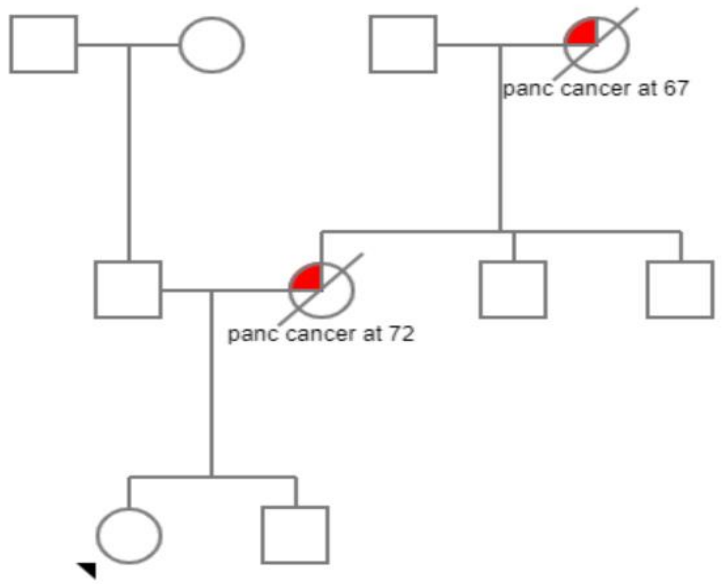


Hilfrank et al, Seminars in Oncology, 2021

Familial Pancreatic Cancer (FPC) Kindred

- A family with two or more individuals with pancreatic cancer and two of these have a first degree relationship to each other (parent, child, sibling)

- Absence of known hereditary syndrome



Genetic counseling

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.

- Limitation of testing review
  - Not all genes are known
  - Finding on VUS, genes with not well defined penetrance or management plan

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

Genetic Testing sample

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

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

www.businessinsider.com

- Turnaround time: 2-3 weeks
- Out of pocket cost- $250

Genetic Testing Results

Positive Mutation Pathogenic/Likely Pathogenic Deleterious/ Suspected Deleterious	• Positive Results
Negative	• Mange according to family history • Family testing not needed
VUS (Variant of Unknown Significance)	• Manage according to family history • Family testing not needed

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

Conclusion

- Technological advances have made genetic testing more affordable
- Timely diagnosis of genetic cancer syndromes can alter therapeutics and outcomes for the patients and their families
- Family history and referral to genetic testing should be a routine practice for all

Thank you!

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