Lynch syndrome

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6.11.2018

THE OHIO STATE UNIVERSITY
WEXNER MEDICAL CENTER

Disclosures

- No relevant disclosures
- No relevant conflicts of interest

Objectives

- Identify the spectrum of cancers associated with Lynch syndrome
- Understand the importance of regular colonoscopy and other surveillance testing in Lynch syndrome
- Recognize patients that should be referred for genetic testing for Lynch syndrome

Outline

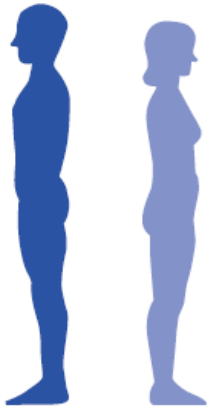
- Lynch syndrome
  - Background
  - Diagnosis
  - Clinical manifestations and surveillance
- Overview of a Cancer Genetics appointment
- Which patients should be referred to Cancer Genetics?

Why is colon cancer important?

Figure 3. Leading Sites of New Cancer Cases and Deaths – 2018 Estimates

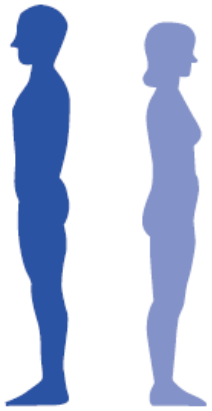
Estimated New Cases

Male			Female		
Prostate	164,690	19%	Breast	266,120	30%
Lung & bronchus	121,680	14%	Lung & bronchus	112,350	13%
Colon & rectum	75,610	9%	Colon & rectum	64,640	7%
Urinary bladder	62,380	7%	Uterine corpus	63,230	7%
Melanoma of the skin	55,150	6%	Thyroid	40,900	5%
Kidney & renal pelvis	42,680	5%	Melanoma of the skin	36,120	4%
Non-Hodgkin lymphoma	41,730	5%	Non-Hodgkin lymphoma	32,950	4%
Oral cavity & pharynx	37,160	4%	Pancreas	26,240	3%
Leukemia	35,030	4%	Leukemia	25,270	3%
Liver & intrahepatic bile duct	30,610	4%	Kidney & renal pelvis	22,660	3%
All sites	**856,370**	**100%**	**All sites**	**878,980**	**100%**



Estimated Deaths

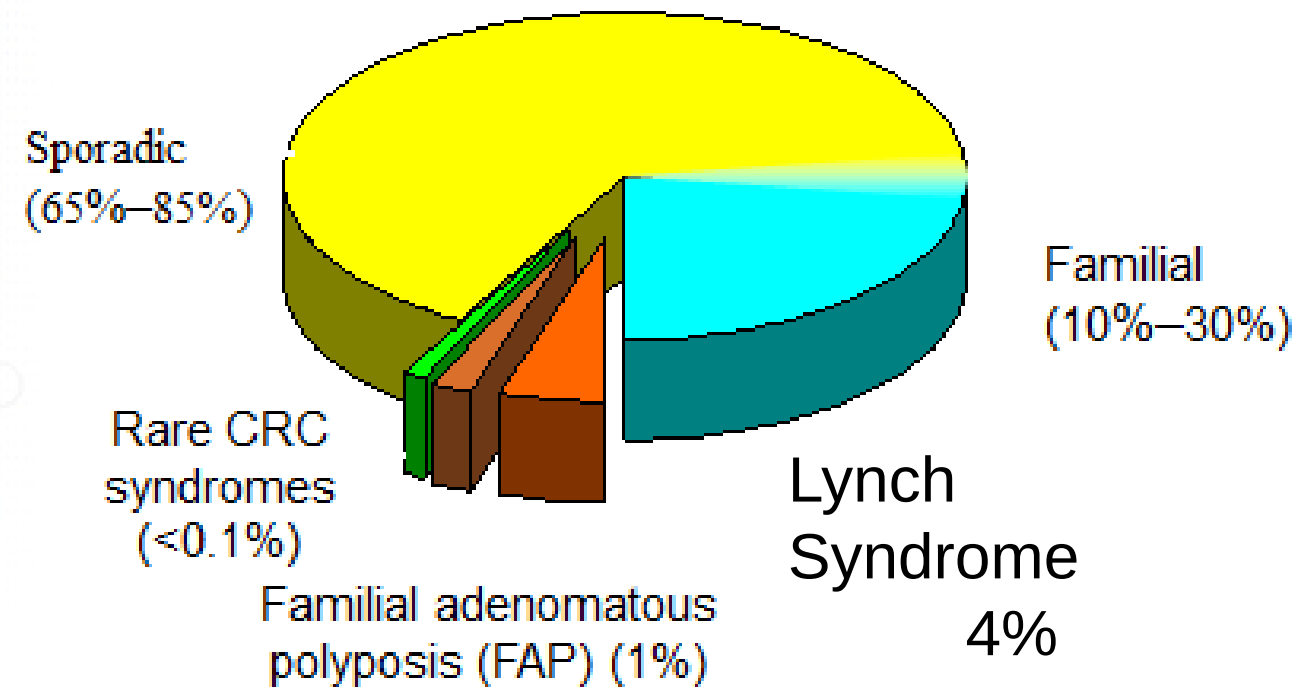
Male			Female		
Lung & bronchus	83,550	26%	Lung & bronchus	70,500	25%
Prostate	29,430	9%	Breast	40,920	14%
Colon & rectum	27,390	8%	Colon & rectum	23,240	8%
Pancreas	23,020	7%	Pancreas	21,310	7%
Liver & intrahepatic bile duct	20,540	6%	Ovary	14,070	5%
Leukemia	14,270	4%	Uterine corpus	11,350	4%
Esophagus	12,850	4%	Leukemia	10,100	4%
Urinary bladder	12,520	4%	Liver & intrahepatic bile duct	9,660	3%
Non-Hodgkin lymphoma	11,510	4%	Non-Hodgkin lymphoma	8,400	3%
Kidney & renal pelvis	10,010	3%	Brain & other nervous system	7,340	3%
All sites	**323,630**	**100%**	**All sites**	**286,010**	**100%**



***Overall lifetime risk is 4.5%**

American Cancer Society

Why are hereditary colorectal cancer syndromes important?



Adapted from Burt RW et al. *Prevention and Early Detection of CRC*, 1996

Lynch syndrome

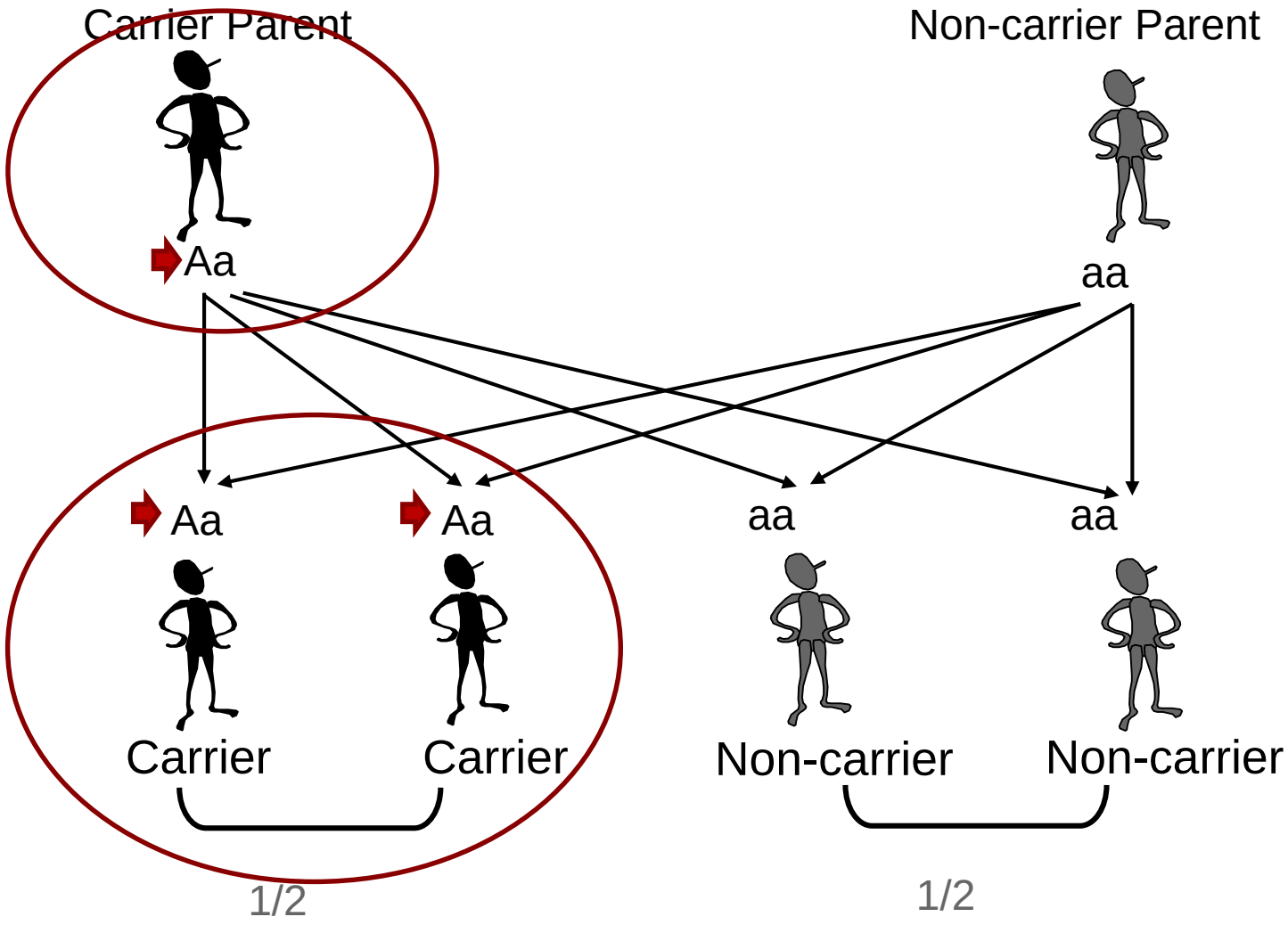
- Germline (ie, inherited) inactivation of the DNA mismatch repair gene results in Lynch syndrome
- Mismatch repair system monitors and correct errors by DNA polymerase during DNA replication
- Autosomal dominant (ie, 50% chance of receiving causative gene)
- De novo mutations rare (2.3%), or less likely than paternal discrepancy (3.7%)
    - [Win, J Med Genet. 2011 and Bellis, J Epidemiol Community Health 2005]

Lynch syndrome

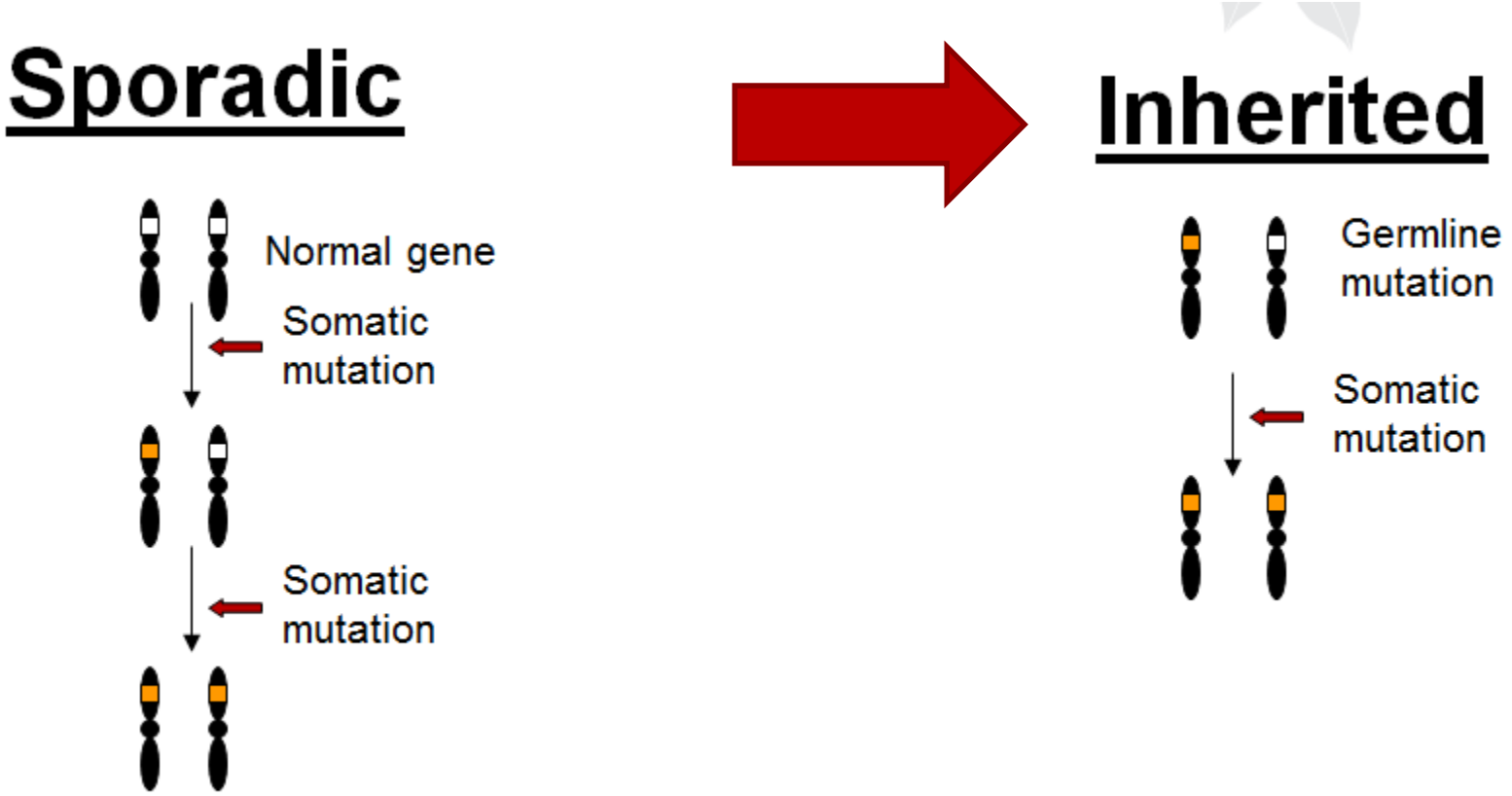
- First described clinically in 1966, genetic mutations identified in the 1990s

- Also labeled “hereditary non-polyposis colorectal cancer” in past, but this is vague and potentially misleading

Autosomal Dominant Inheritance



Genetics of Lynch syndrome



Mismatch repair genes

- 5 known genes:
  - *MSH2*
  - *MLH1*
  - *MSH6*
  - *PMS2*
  - *EPCAM* (affects *MSH2*)

**PMS2* mutations can be difficult to isolate and prevalence low in older series due to this

Genetics of Lynch syndrome

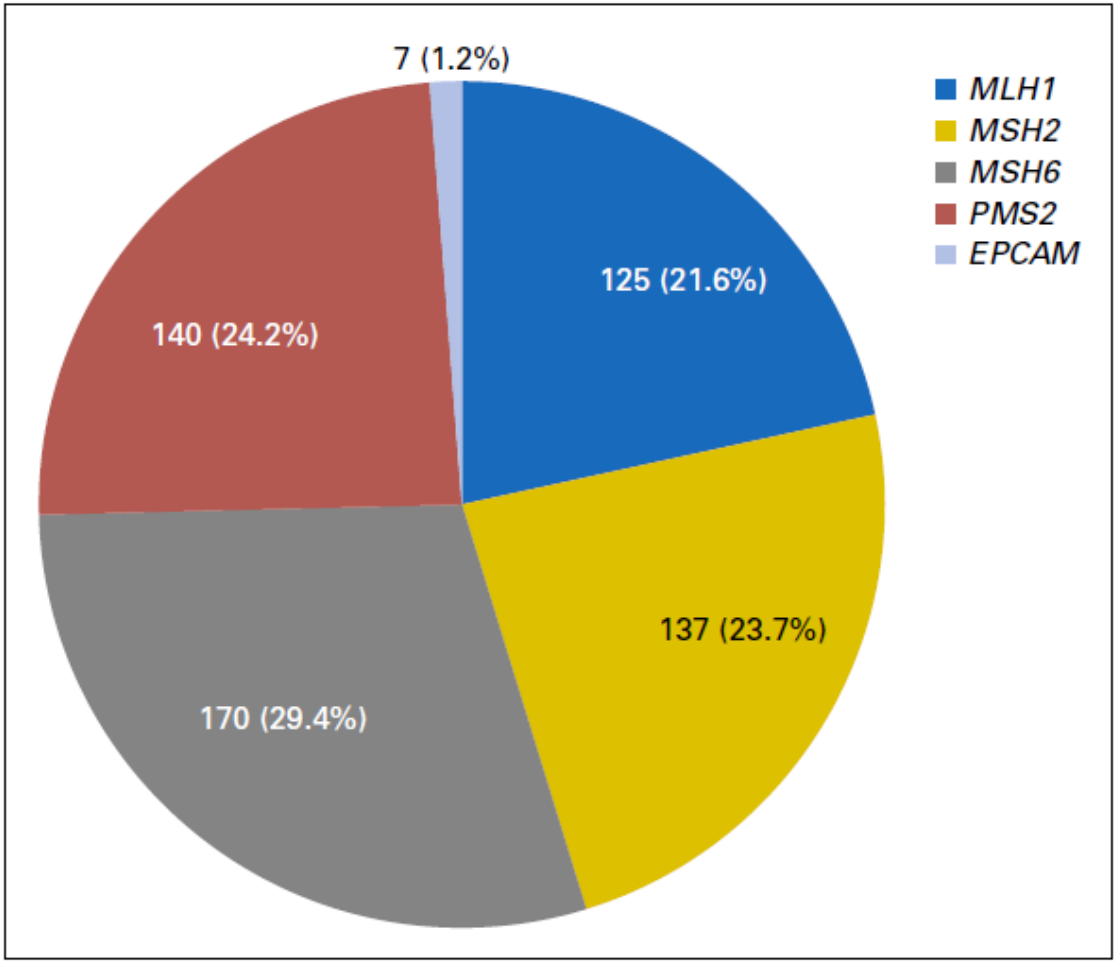


Fig 1. Overall mismatch repair gene and *EPCAM* mutation distribution (n = 579).

Espenschied et al. JCO 2017.

Diagnosis of Lynch syndrome

- Clinical criteria
- Tumor testing
- Genetic testing (confirmatory)

Genetic testing

- Consists of single blood draw or mouthwash kit
- Labs have guaranteed maximum out of pocket costs and often as little as $250 independent of insurance coverage
  - As little as $50 if familial mutation is previously identified
- Best done after genetic counseling
  - More to come later in talk

Clinical criteria

- Amsterdam II Criteria: meant to be diagnostic of HNPCC (expanded tumors from Ams. I criteria)
- **The 3-2-1 rule**

1. Three or more relatives with histologically verified HNPCC-associated cancer (colorectal cancer, cancer of the endometrium, small bowel, ureter, or renal pelvis), 1 of which is a first-degree relative of the other 2. Familial adenomatous polyposis should be excluded.
2. Cancer involving at least 2 generations.
3. One or more cancer cases diagnosed before the age of 50 years.

*Many would also include **ovary, stomach,** HB and brain

Clinical criteria

- Revised Bethesda Criteria: meant to identify candidates for tumor testing (more on this later)

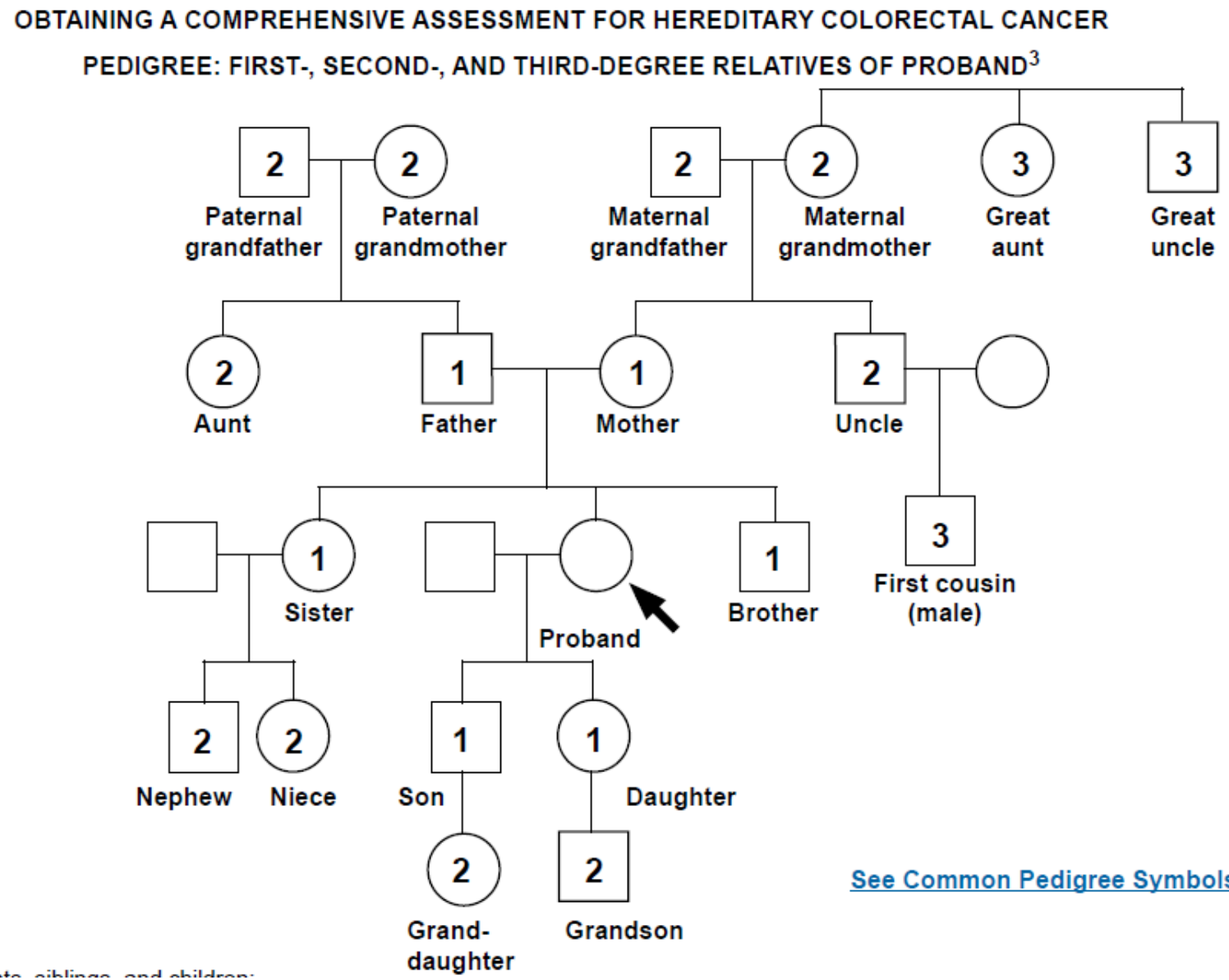
1.	CRC diagnosed at younger than 50 years.
2.	Presence of synchronous or metachronous CRC or other LS-associated tumors.[a]
3.	CRC with MSI-high pathologic-associated features (Crohn-like lymphocytic reaction, mucinous/signet cell differentiation, or medullary growth pattern) diagnosed in an individual younger than 60 years old.
4.	Patient with CRC and CRC or LS-associated tumor[a] diagnosed in at least 1 first-degree relative younger than 50 years old.
5.	Patient with CRC and CRC or LS-associated tumor[a] at any age in 2 first-degree or second-degree relatives.

[a]LS-associated tumors include tumor of the colorectum, endometrium, stomach, ovary, pancreas, ureter, renal pelvis, biliary tract, brain, small bowel, sebaceous glands, and kerotoacanthomas.

Clinical criteria

- Why this is often inadequate…
- Family size shrinking
- Success of CRC screening in decreasing cancer incidence
- Difficulty obtaining full family history in busy clinical setting

Physicians and family history



Physicians and family history

- Analysis of patients with CRC seen at an Onc clinic

Table 2. Family History Among Individuals With a First- or Second-Degree Relative With Cancer

Family history	Total (%)
Oncologist notes with a comprehensive family cancer history	184 (59)
Concordance between questionnaire and physician's note	141 (77)
Additional information in physician's note	30 (16)
Information only recorded in physician's note	13 (7)
Oncologist notes without a comprehensive family cancer history	127 (41)
No history recorded or negative history	37 (29)
History incomplete with additional information in questionnaire	69 (54)
Discordant information in physician's note and questionnaire	21 (17)
Total	311

Table 4. Multivariate Analysis Assessing the Relative Importance of Factors Predicting a Comprehensive Family History Assessment

Variable	Odds ratio (95% confidence interval)	*P* value
First-degree relative with colon cancer	1.68 (0.99–2.87)	0.06
Young age (<45 yr)	0.87 (0.45–1.70)	0.68
Number of family cancers	0.63 (0.53–0.74)	<0.0001

NOTE. Increasing number of family cancers was associated with a less comprehensive family history assessment.

*75 of 387 (19%) CRC patients met Bethesda guidelines for genetics assessment, however, only 13 of 75 (17%) were referred.

Grover et al. Physician assessment of family cancer history and referral for genetic evaluation in colorectal cancer patients. Clin Gastroenterol Hepatol, 2 (2004), pp. 813–819.

Clinical criteria

- There are clinical predictive models available

PREMM5 MODEL | LYNCH SYNDROME

Lynch syndrome prediction model

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

The $PREMM_5$ 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
- Types of cancer and ages at diagnosis of first-degree relatives from the affected side of the family (parents, siblings, children)

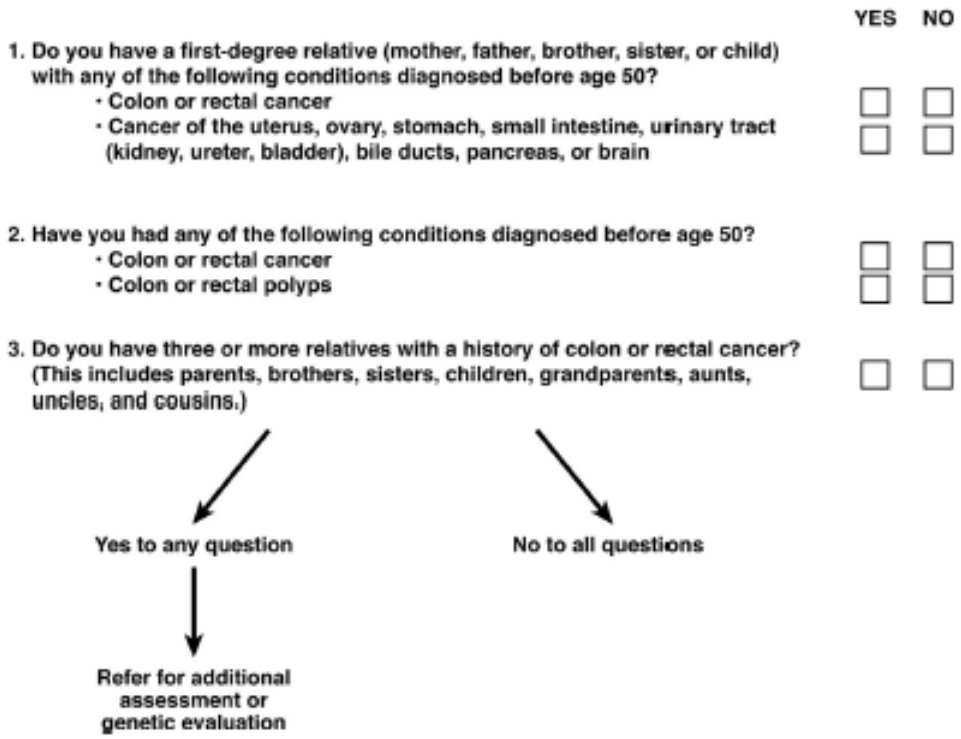
http://premm.dfci.harvard.edu/

***If concerned, recommend Genetics referral for providers with expertise and most importantly time!**

Future steps

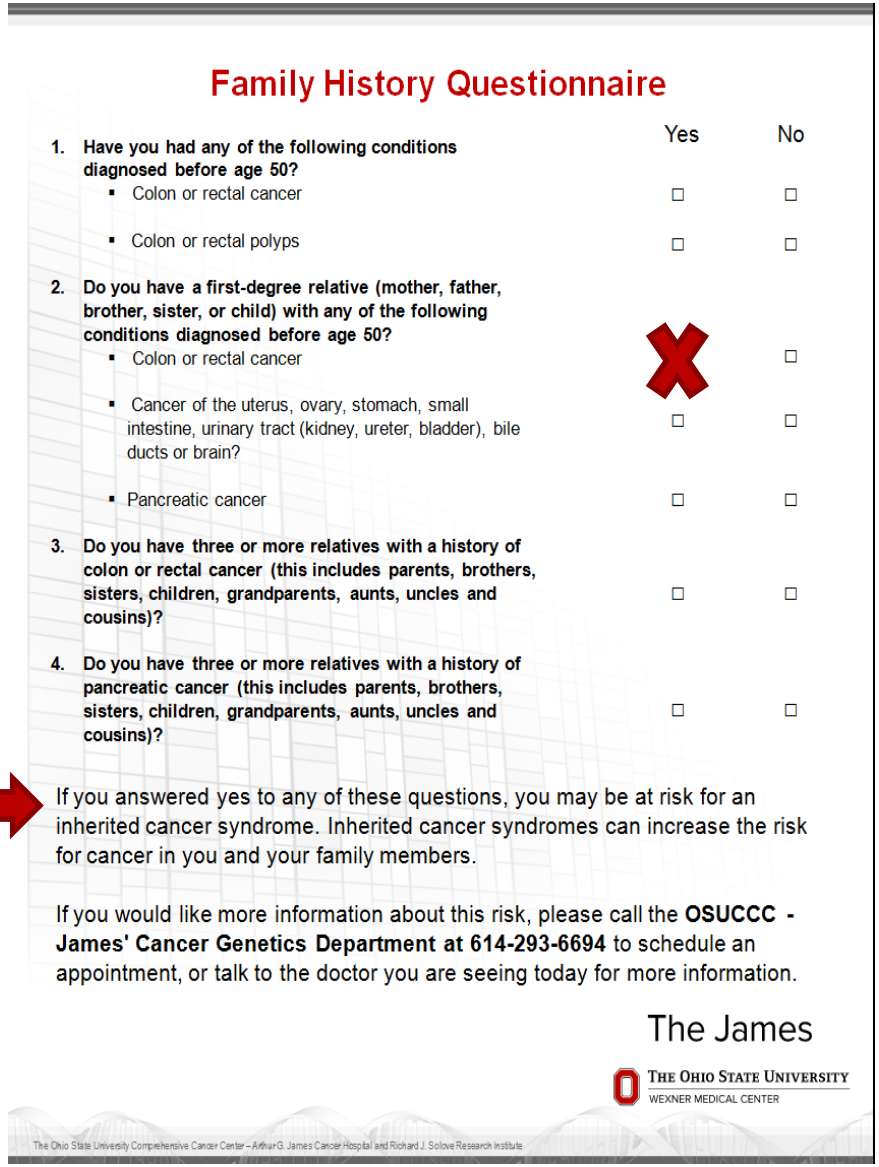
- Universal screening (perhaps pre-colonoscopy)

- Recent data shows this can be reasonably incorporated into GI practice, either with PREMM score or simple questionnaire



Kastrinos et al. Development and Validation of a Colon Cancer Risk Assessment Tool for Patients Undergoing. *The American Journal of Gastroenterology* **104**, 1508-1518 .

OSU pre-endoscopy history questionnaire



Family History Questionnaire

	Yes	No
1. Have you had any of the following conditions diagnosed before age 50?		
▪ Colon or rectal cancer	☐	☐
▪ Colon or rectal polyps	☐	☐
2. Do you have a first-degree relative (mother, father, brother, sister, or child) with any of the following conditions diagnosed before age 50?		
▪ Colon or rectal cancer	X	☐
▪ Cancer of the uterus, ovary, stomach, small intestine, urinary tract (kidney, ureter, bladder), bile ducts or brain?	☐	☐
▪ Pancreatic cancer	☐	☐
3. Do you have three or more relatives with a history of colon or rectal cancer (this includes parents, brothers, sisters, children, grandparents, aunts, uncles and cousins)?	☐	☐
4. Do you have three or more relatives with a history of pancreatic cancer (this includes parents, brothers, sisters, children, grandparents, aunts, uncles and cousins)?	☐	☐

If you answered yes to any of these questions, you may be at risk for an inherited cancer syndrome. Inherited cancer syndromes can increase the risk for cancer in you and your family members.

If you would like more information about this risk, please call the **OSUCCC - James' Cancer Genetics Department at 614-293-6694** to schedule an appointment, or talk to the doctor you are seeing today for more information.

The James

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The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute

Colorectal (and Endometrial) tumor testing

- A way to overcome limitations of family history and identify de novo mutations
- OSU, USMSTF and NCCN favor universal tumor testing:

1. Greater sensitivity for the identification of Lynch syndrome compared with multiple alternative strategies

2. Cost-effectiveness ratio comparable to other accepted preventive services

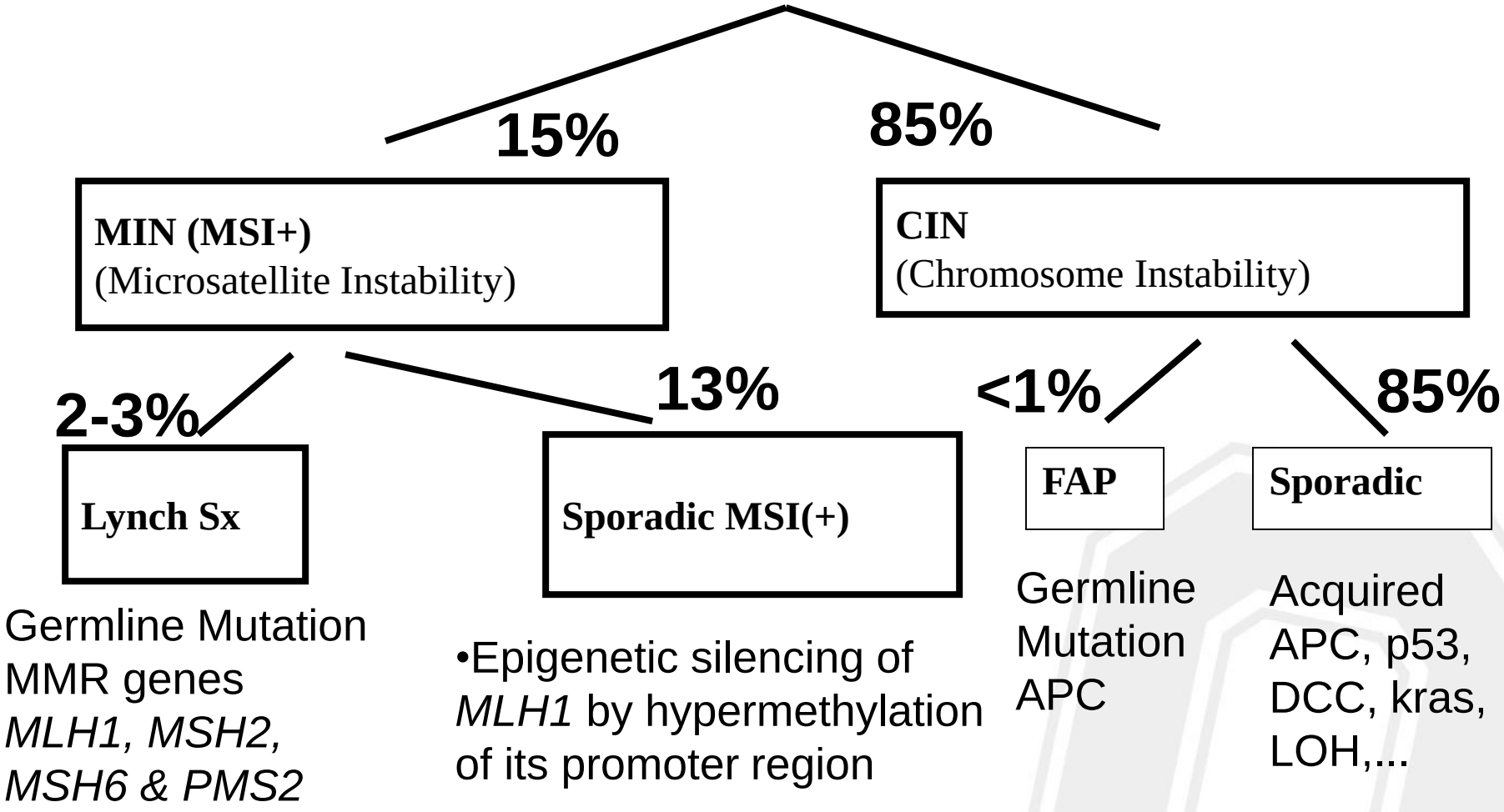
Hampel H. Point: justification for Lynch syndrome screening among all patients with newly diagnosed colorectal cancer. J Natl Compr Canc Netw. 2010 May;8(5):597-601.

Moreira L. Identification of Lynch syndrome among patients with colorectal cancer. JAMA. 2012 Oct 17;308(15):1555-65.

Microsatellite instability

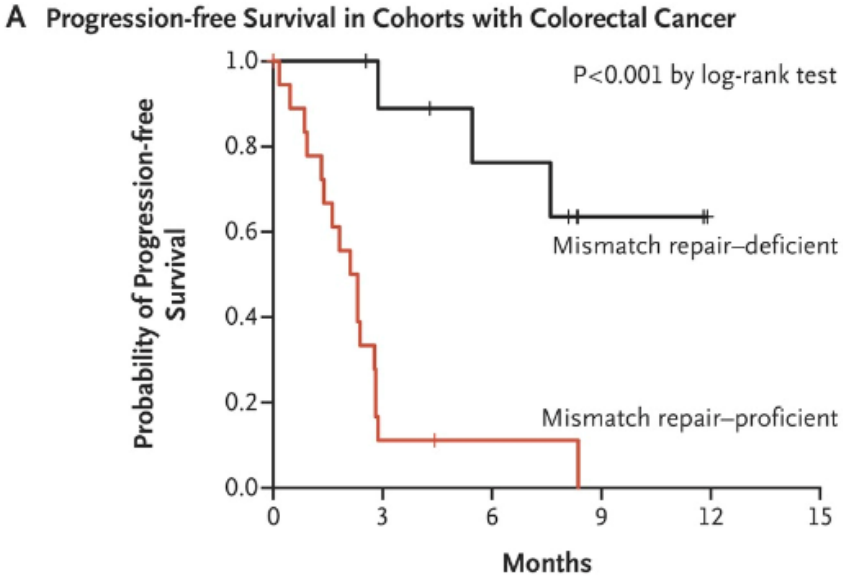
- Microsatellites are simple repetitive sequences normally found throughout the genome
- Microsatellite instability (MSI) is abnormal expansion/contraction of these repeats in tumor DNA
- MSI graded as MSI-high, MSI-low or MSS (stable)
- Lynch syndrome cancers are usually MSI-high, but sporadic cancers can be as well

Colorectal cancer tumor testing



Why else is MSI important?

- MSI colon cancer patients have a better prognosis
- MSI colon cancer does not respond to standard 5-FU based chemotherapy
- MSI predictive of response to immunotherapy (anti-PD1 and anti-PDL1 treatments) – even patients with treatment-refractory progressive metastatic cancer



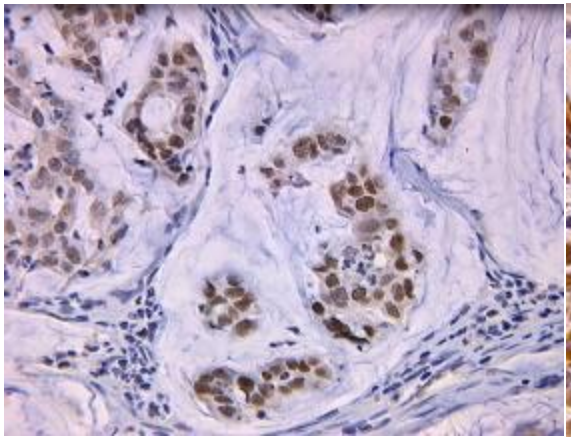
Le et al. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency NEJM 2015.

Tumor testing

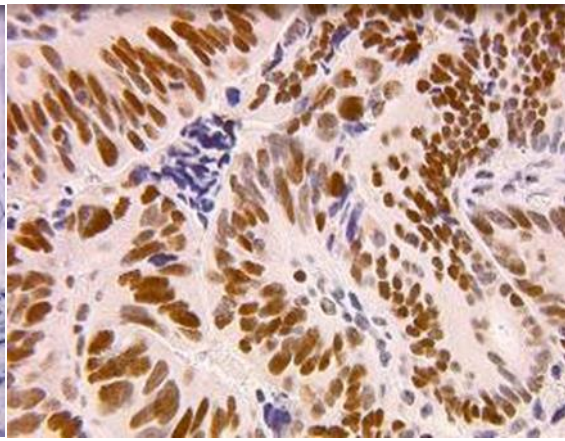
- Immunohistochemistry (IHC) is another option for tumor testing
- More commonly performed in US centers
- Utilizes antibodies to the Lynch genes
- Absence of staining is abnormal

Mismatch Repair Immunohistochemistry

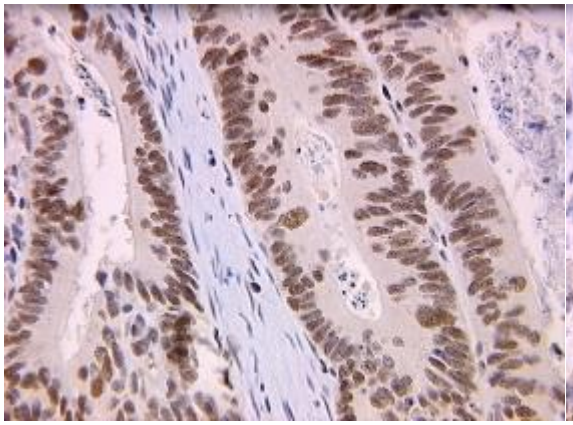
- Normally present
- If protein absent, gene not being expressed (mutation/methylation)
- Benefit over MSI testing is this can direct gene testing by predicting likely involved gene



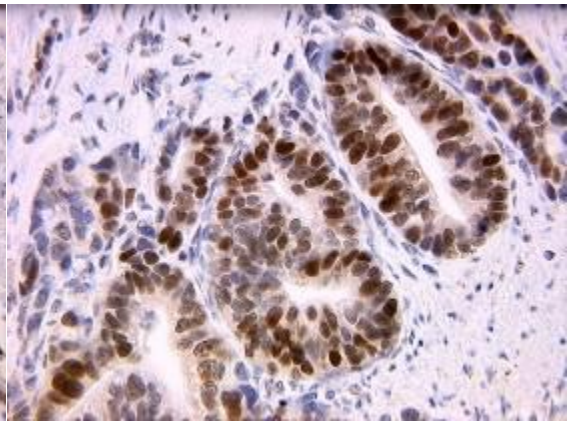
MLH1



MSH2



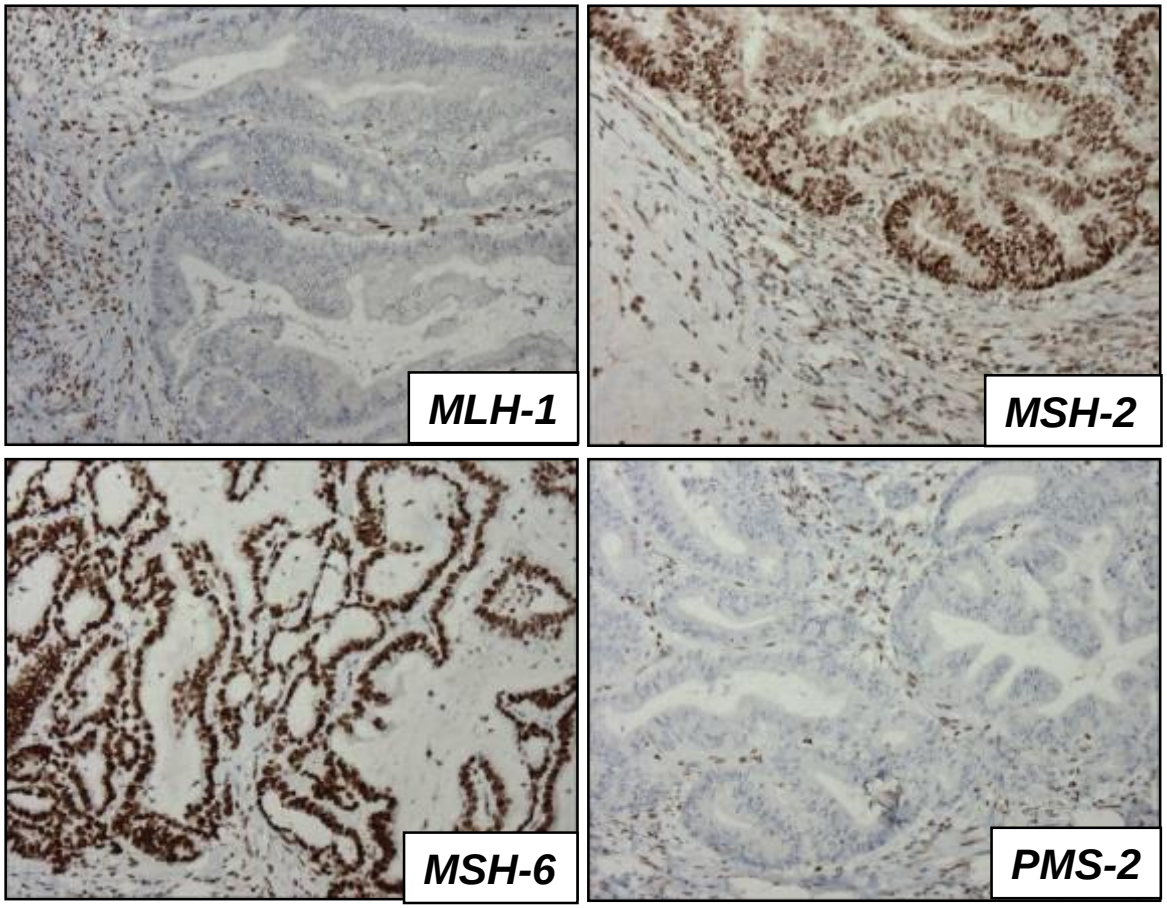
PMS2



MSH6

MLH1 & PMS2 Absent

- 15% of the time
- CRC is MSI
- 80% acquired methylation of *MLH1*
- 20% will be LS
- **Reflex to test for *BRAF or MLH1* hypermethylation to clarify**



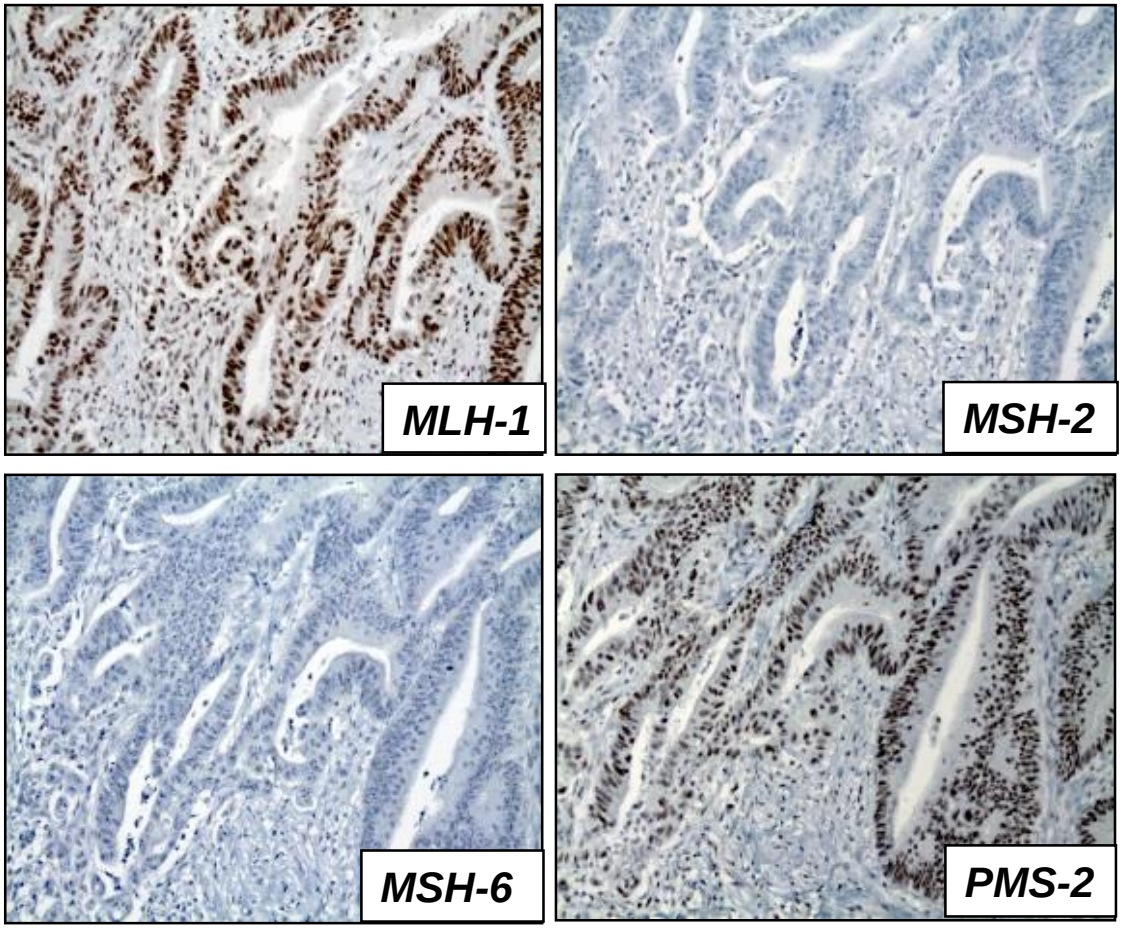
MLH1 absence on IHC

- Somatic events can cause loss of *MLH1* and are more common than Lynch syndrome (especially in people older than age 70)
- These include changes in *BRAF* gene and *MLH1* promoter hypermethylation (just the latter for Endometrial cancer)
- Tumor testing is available for these abnormalities to guide need for further genetic testing.

- If *BRAF* mutation or *MLH1* hypermethylation positive, tumor is sporadic and no further testing needed.

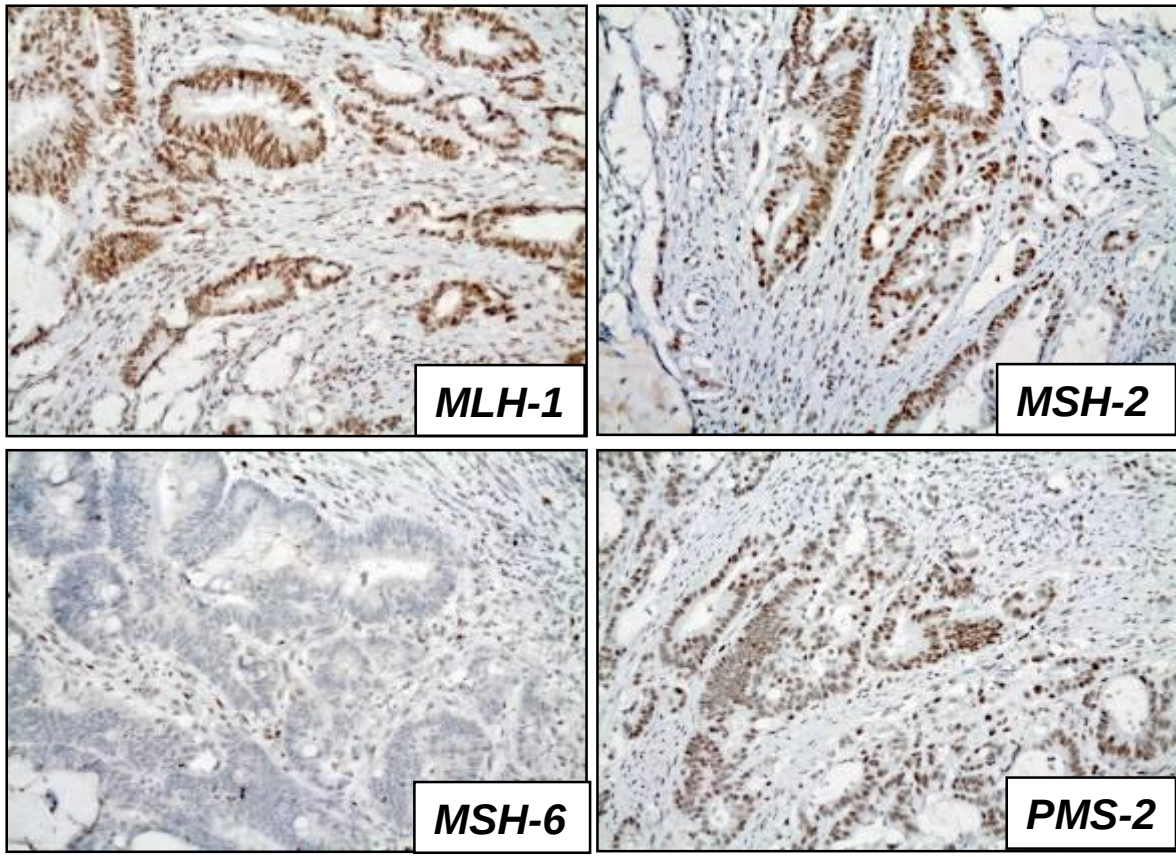
MSH2 & MSH6 Absent

- 3% of the time
- CRC is MSI
- Most likely LS due to *MSH2* (*MSH6* or *EPCAM* less likely) gene mutation



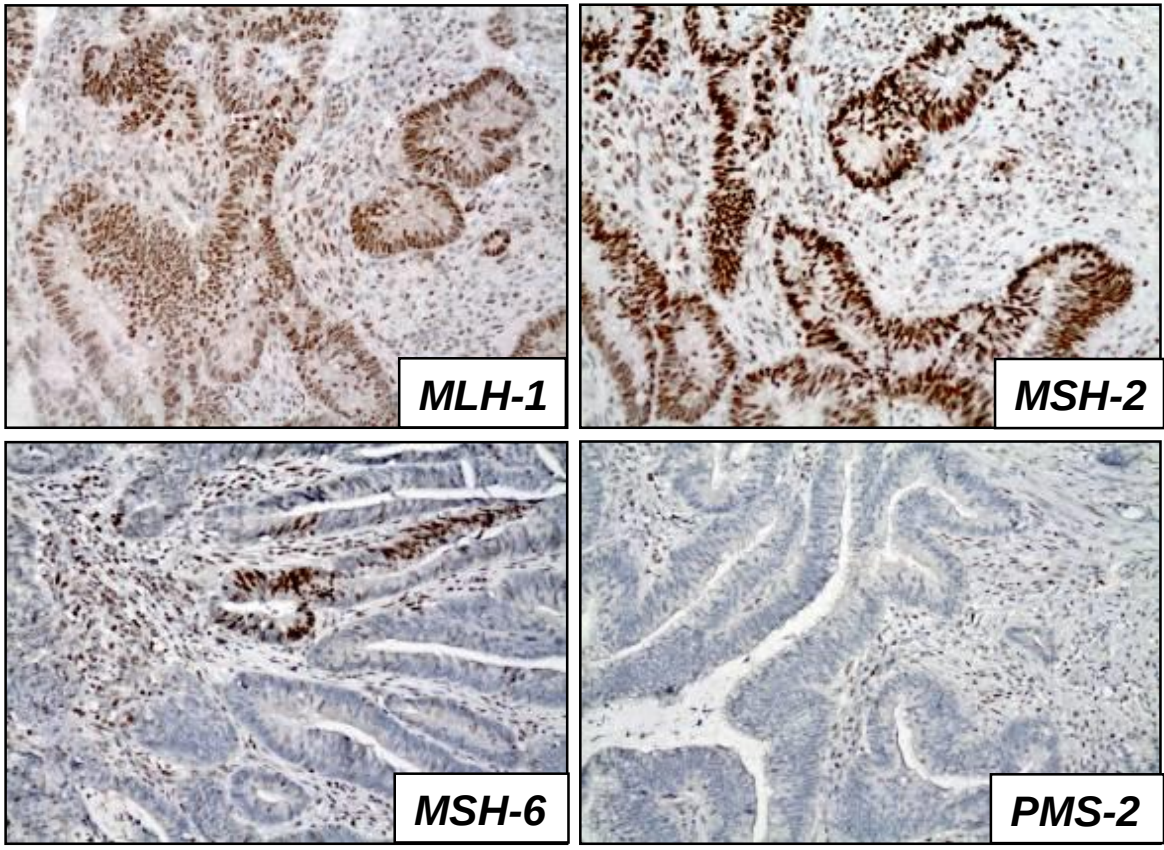
MSH6 Absent

- 1% of the time
- CRC is MSI
- Most likely LS due to an *MSH6* gene mutation



PMS2 Absent

- 1% of the time
- CRC is MSI
- Most likely LS due to a *PMS2* gene mutation



Tumor testing

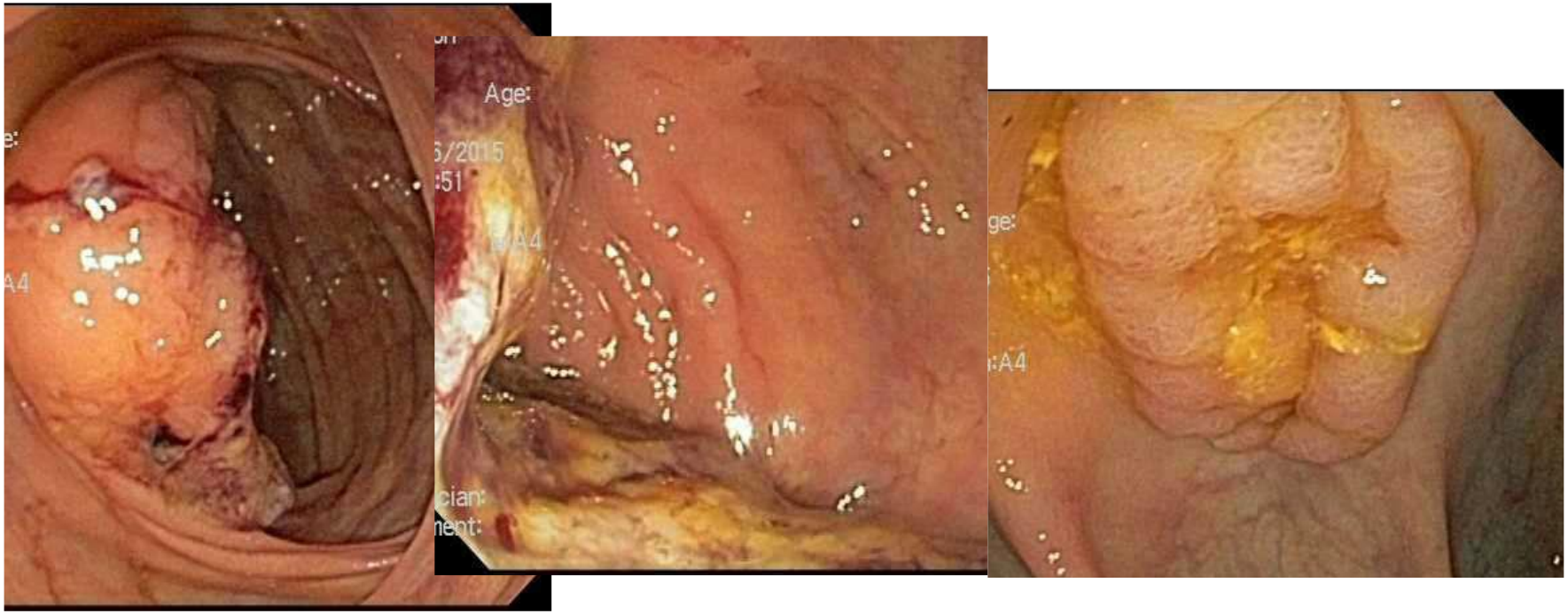
- Don’t need to memorize, but remember where to look for this (NCCN or USMSTF guidelines)
- If any question, refer to Genetics

TUMOR TESTING RESULTS AND ADDITIONAL TESTING STRATEGIES

Tumor Testing[a]							Plausible Etiologies	Additional Testing[d,e]
IHC				MSI	*BRAF* V600E[b]	MLH1 Promoter Methylation		
MLH1	*MSH2*	*MSH6*	*PMS2*					
+	+	+	+	MSS/MSI-Low	N/A	N/A	1) Sporadic cancer	1) None[c]
+	+	+	+	MSI- High	N/A	N/A	1) Germline mutation in any one of the known mismatch repair genes	1) Consider germline testing of *MLH1* and *MSH2* followed by *MSH6* and possibly *PMS2*
N/A	N/A	N/A	N/A	MSI- High	N/A	N/A	1) Sporadic cancer or germline mutation in any one of the known mismatch repair genes	1) Consider IHC testing to guide genetic testing 2) If IHC not done, *MLH1* and *MSH2* genetic testing followed by *MSH6* and possibly *PMS2*
--	+	+	--	N/A	N/A	N/A	1) Sporadic cancer 2) Germline mutation *MLH1*	1) Consider *BRAF*[b]/methylation studies 2) *MLH1* genetic testing if no *BRAF* mutation and/or hypermethylation, or testing not done
--	+	+	--	N/A	Positive	N/A	1) Sporadic cancer	1) None[c]
--	+	+	--	N/A	Negative	Positive	1) Sporadic cancer 2) Rarely germline mutation *MLH1* or constitutional *MLH1* epimutation	1) None, unless young age of onset or significant family history; then consider *MLH1* genetic testing or if young onset consider evaluation for constitutional *MLH1* epimutation
--	+	+	--	N/A	Negative	Negative	1) Germline mutation *MLH1*	1) *MLH1* genetic testing
+	--	--	+	N/A	N/A	N/A	1) Germline mutation *MSH2* (testing for *MSH2* should include *EPCAM* deletion testing); rarely germline mutation in *MSH6*	1) Consider *MSH6* genetic testing, if *MSH2* and *EPCAM* are negative
+	+	+	--	N/A	N/A	N/A	1) Germline mutation *PMS2* 2) Rarely germline mutation *MLH1*	1) *PMS2* genetic testing 2) *MLH1* genetic testing, if negative *PMS2*
+	--	+	+	N/A	N/A	N/A	1) Germline mutation *MSH2*	1) *MSH2* genetic testing
+	+	--	+	N/A	N/A	N/A	1) Germline mutation *MSH6* 2) Germline mutation *MSH2*	1) MSH6 genetic testing 2) Consider *MSH2* genetic testing, if negative *MSH6*
–	+	+	+	N/A	N/A	N/A	1) Sporadic cancer 2) Germline mutation *MLH1*	1) Consider *BRAF*[b]/methylation studies 2) *MLH1* genetic testing if no *BRAF* mutation and/or hypermethylation, or testing not done
–	–	–	–	N/A	N/A	N/A	1) Germline mutation in *MLH1*, *MSH2*, *MSH6*, *PMS2*, or *EPCAM* 2) Sporadic cancer	1) Genetic testing of *MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM* 2) If no *MLH1* germline mutation detected, consider *BRAF*[b]/methylation studies

Case

- 70 year old female with IC valve mass and hepatic flexure large 2.5 cm polyp
- Mother had CRC at 65 and maternal Aunt with CRC at 55



What to do next with path?

---Final Pathologic Diagnosis---

A. Ileocecal valve, mass, biopsy:
- Adenocarcinoma; see comment.

B. Colon, descending, polyp, polypectomy:
- Tubular adenoma.

COMMENT
The patient's history of large ileocecal valve mass is noted. Biopsy (A) shows fragments of adenocarcinoma with desmoplastic reaction consistent with invasion. Evaluation for the depth of invasion is limited due to the fragmented superficial biopsy material. Correlation with endoscopic and radiologic findings is recommended.

Addendum Status: Signed Out

Immunohistochemical stains on the colonic adenocarcinoma (A1) demonstrate the absence of MLH1 and PMS2 protein expression and the presence of MSH2 and MSH6 protein expression.

SOMATIC BRAF GENE MUTATION ANALYSIS BY
SNPlex ASSAY AND DIRECT DNA SEQUENCING

RESULT:
POSITIVE for BRAF V600E mutation.

INTERPRETATION:
BRAF V600E Mutation is detected in this specimen (S15-2935-A1).

Final diagnosis

- Sporadic CRC

Tumor Testing[a]							Plausible Etiologies	Additional Testing[d,e]
IHC				MSI	*BRAF* V600E[b]	MLH1 Promoter Methylation		
MLH1	*MSH2*	*MSH6*	*PMS2*					
--	+	+	--	N/A	Positive	N/A		

National Comprehensive Cancer Network

- Non-profit alliance of 27 leading cancer centers dedicated to improving cancer care
  - The OSU Comprehensive Cancer Center is a member
- Issues frequently updated guidelines in all facets of cancer care.
- Lynch syndrome is included in the "Genetic/Familial High-Risk Assessment: Colorectal guidelines"

Overview of risks

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2017
Lynch Syndrome

NCCN Guidelines Index
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Discussion

Cancer Risk Up to Age 70 Years in Individuals with Lynch Syndrome Compared to the General Population

Cancer	General Population Risk[1]	*MLH1* or *MSH2*[1,2]		*MSH6*[2,3]		*PMS2*[4]	
		Risk	Mean Age of Onset	Risk	Mean Age of Onset	Risk	Mean Age of Onset
Colon	4.5%	52%–82%	44–61 years	10%–22%	54 years	15%–20%	61–66 years
Endometrium	2.7%	25%–60%	48–62 years	16%–26%	55 years	15%	49 years
Stomach	<1%	6%–13%	56 years	≤3%	63 years	+	70–78 years
Ovary	1.6%	See LS-B 2 of 2					
Hepatobiliary tract	<1%	1%–4%	50–57 years	Not reported	Not reported	+	Not reported
Urinary tract	<1%	1%–7%[6]	54–60 years	<1%	65 years	+	Not reported
Small bowel	<1%	3%–6%	47–49 years	Not reported	54 years	+	59 years
Brain/CNS	<1%	1%–3%	~50 years	Not reported	Not reported	+	45 years
Sebaceous neoplasms	<1%	1%–9%	Not reported	Not reported	Not reported	Not reported	Not reported
Pancreas[5]	<1%	1%–6%	Not reported	Not reported	Not reported	Not reported	Not reported

Overview of Screening

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2017
Lynch Syndrome

NCCN Guidelines Index
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Discussion

LYNCH SYNDROME MANAGEMENT

Surveillance for *MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM* Mutation Carriers[l,m,n]

- Colon cancer:
  - Colonoscopy at age 20–25 y[o] or 2–5 y prior to the earliest colon cancer if it is diagnosed before age 25 y and repeat every 1–2 y.
  - There are data to suggest that aspirin may decrease the risk of colon cancer in LS but optimal dose and duration of aspirin therapy are uncertain

→ See Follow-up of Surveillance Findings (LS-5)

Other Extracolonic Cancers

- Gastric and small bowel cancer:
  - There are no clear data to support surveillance for gastric, duodenal, and small bowel cancer for LS. Selected individuals with a family history of gastric, duodenal, or small bowel cancer or those of Asian descent (Vasen HF, et al. Gut 2013;62:812-823) have an increased risk and may benefit from surveillance. If surveillance is performed, may consider upper endoscopy with visualization of the duodenum at the time of colonoscopy every 3–5 y beginning at age 30–35 y. Consider testing and treating H. pylori.
- Urothelial cancer:
  - Selected individuals such as with a family history of urothelial cancer or individuals with MSH2 mutations (especially males) may want to consider screening. Surveillance options may include annual urinalysis starting at 30–35 y. However, there is insufficient evidence to recommend a particular surveillance strategy.
- Central nervous system (CNS) cancer:
  - Consider annual physical/neurologic examination starting at 25–30 y; no additional screening recommendations have been made.
- Pancreatic cancer:
  - Despite data indicating an increased risk for pancreatic cancer, no effective screening techniques have been identified; therefore, no screening recommendation is possible at this time.
- Breast cancer:
  - There have been suggestions that there is an increased risk for breast cancer in LS patients; however, there is not enough evidence to support increased screening above average-risk breast cancer screening recommendations.

Overview of Screening

LYNCH SYNDROME MANAGEMENT

Surveillance for *MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM* Mutation Carriers[l,m,n]

Other Extracolonic Cancers

- **Endometrial cancer:**
  - **Because endometrial cancer can often be detected early based on symptoms, women should be educated regarding the importance of prompt reporting and evaluation of any abnormal uterine bleeding or postmenopausal bleeding. The evaluation of these symptoms should include endometrial biopsy.**
  - **Hysterectomy has not been shown to reduce endometrial cancer mortality, but can reduce the incidence of endometrial cancer. Therefore, hysterectomy is a risk-reducing option that should be considered.**
  - **Timing of hysterectomy should be individualized based on whether childbearing is complete, comorbidities, family history, and LS gene, as risks for endometrial cancer vary by mutated gene.**
  - **Endometrial cancer screening does not have proven benefit in women with LS. However, endometrial biopsy is both highly sensitive and highly specific as a diagnostic procedure. Screening via endometrial biopsy every 1 to 2 years can be considered.**
  - **Transvaginal ultrasound to screen for endometrial cancer in postmenopausal women has not been shown to be sufficiently sensitive or specific as to support a positive recommendation, but may be considered at the clinician's discretion. Transvaginal ultrasound is not recommended as a screening tool in premenopausal women due to the wide range of endometrial stripe thickness throughout the normal menstrual cycle.**
- **Ovarian cancer:**
  - **Bilateral salpingo-oophorectomy (BSO) may reduce the incidence of ovarian cancer. The decision to have a BSO as a risk-reducing option by women who have completed childbearing should be individualized. Timing of BSO should be individualized based on whether childbearing is complete, menopause status, comorbidities, family history, and LS gene, as risks for ovarian cancer vary by mutated gene.**
  - **Since there is no effective screening for ovarian cancer, women should be educated on the symptoms that might be associated with the development of ovarian cancer, such as pelvic or abdominal pain, bloating, increased abdominal girth, difficulty eating, early satiety, or urinary frequency or urgency. Symptoms that persist for several weeks and are a change from a woman's baseline should prompt her to seek evaluation by her physician.**
  - **While there may be circumstances where clinicians find screening helpful, data do not support routine ovarian cancer screening for LS. Transvaginal ultrasound for ovarian cancer screening has not been shown to be sufficiently sensitive or specific as to support a routine recommendation, but may be considered at the clinician's discretion. Serum CA-125 is an additional ovarian screening test with caveats similar to transvaginal ultrasound.**
- **Consider risk reduction agents for endometrial and ovarian cancers, including discussing risks and benefits (See Discussion for details).**

NCCN

Cancer incidence

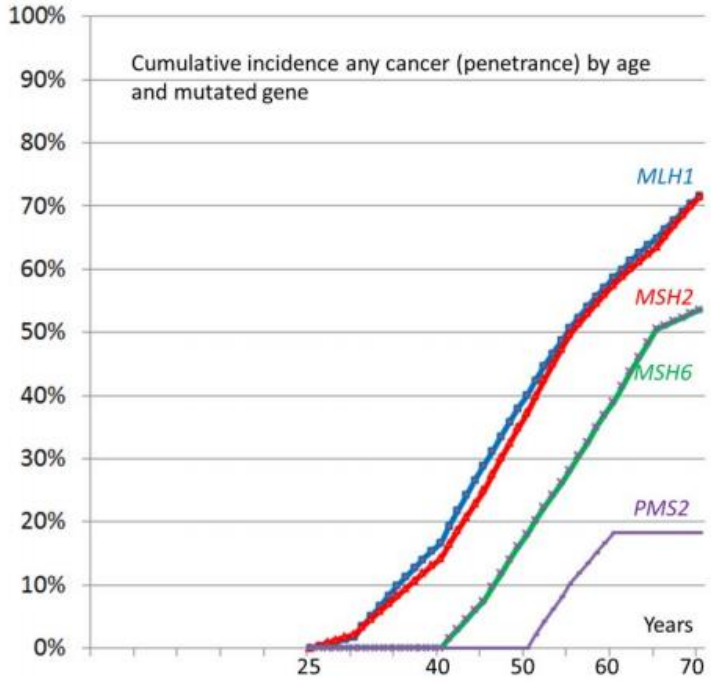


Figure 1 Calculated cumulative incidences by age and mutated gene for any cancer.

Table 7 5-year and 10-year crude survival after first cancer diagnosed by cancer type in Lynch syndrome (LS) patients without prior or prevalent cancer at first colonoscopy

Group	Number cases	5-year survival (95% CI)	10-year survival (95% CI)
Any cancer	301	90% (86 to 93)	87% (83 to 91)
Colorectal cancer	140	94% (90 to 98)	91% (84 to 95)
Endometrial cancer	71	98% (88 to 99.8)	98% (88 to 99.8)
Ovarian cancer	19	88% (60 to 97)	89% (60 to 97)
Upper GI cancer	24	58% (36 to 75)	53% (31 to 71)
Urinary tract cancer	17	82% (51 to 93)	73% (42 to 89)

Moller et al. Cancer incidence and survival in Lynch syndrome patients receiving colonoscopic and gynaecological surveillance: first report from the prospective Lynch syndrome database. Gut 2017.

Colorectal cancer

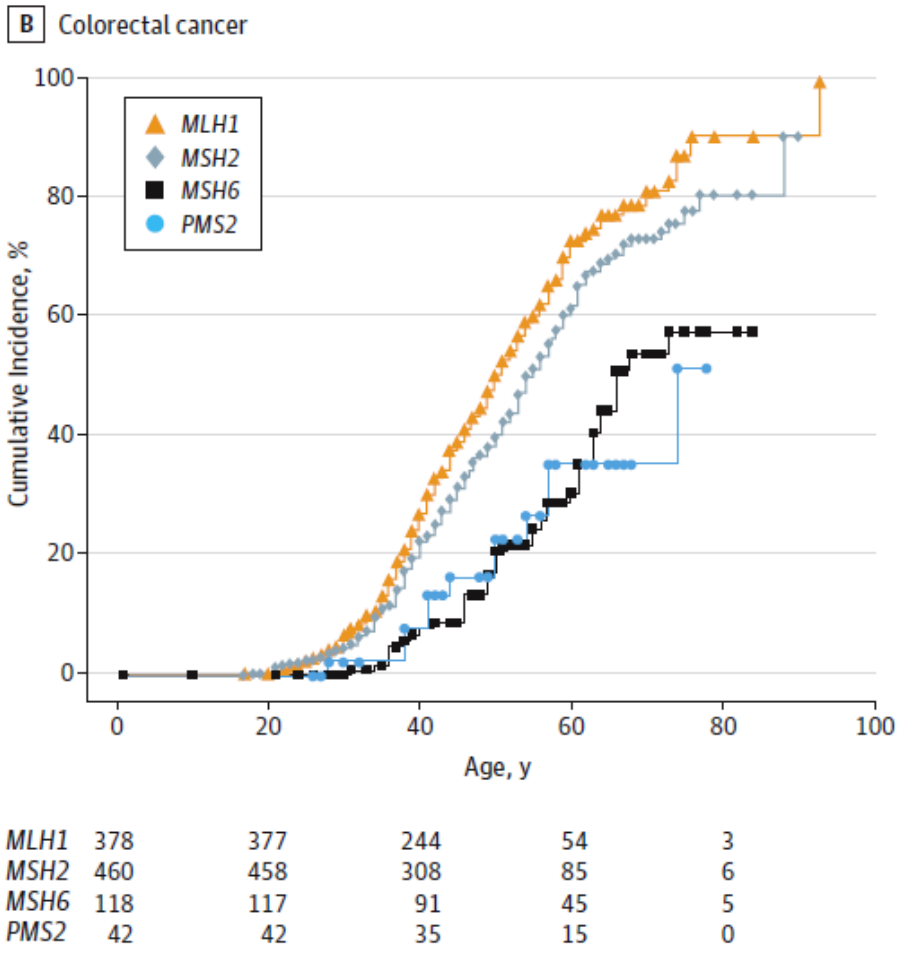
Cancer	General Population Risk[1]	*MLH1* or *MSH2*[1,2]		*MSH6*[2,3]		*PMS2*[4]	
		Risk	Mean Age of Onset	Risk	Mean Age of Onset	Risk	Mean Age of Onset
Colon	4.5%	52%–82%	44–61 years	10%–22%	54 years	15%–20%	61–66 years

Surveillance for *MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM* Mutation Carriers[l,m,n]

- Colon cancer:
  - Colonoscopy at age 20–25 y[o] or 2–5 y prior to the earliest colon cancer if it is diagnosed before age 25 y and repeat every 1–2 y.
  - There are data to suggest that aspirin may decrease the risk of colon cancer in LS but optimal dose and duration of aspirin therapy are uncertain

NCCN

Colorectal cancer



Ryan et al. Association of Mismatch Repair Mutation With Age at Cancer Onset in Lynch Syndrome. JAMA Oncology 2017.

Clinical care of Lynch patients

Large-scale surveillance programs have achieved a 62 % reduction in incidence of CRC and a **65–70 % decrease in mortality**. (Fam Cancer. 2013 Jun;12(2):261-5.)

Benefit of Colonoscopy: Controlled 15-year Trial

	Screened	Not screened	
	N=133	N=119	
CRC	8 (18%)*	19 (41%)	*P*=.02
Death from CRC	0 (0%)	9 (7%)	*P*<.001

*All CRCs in the screened group were local

- CRC rate reduced by 62%
- 65% fewer CRC deaths
- Can identify early-stage CRC

Järvinen HJ et al. *Gastroenterology*. 2000;118(5):829-834.
De Jong AE et al. *Gastroenterology*. 2006;130(3):665-671.

Colorectal cancer

Study of Lynch patients without previous cancer undergoing surveillance utilizing 2 year interval for colonoscopy (European standard)

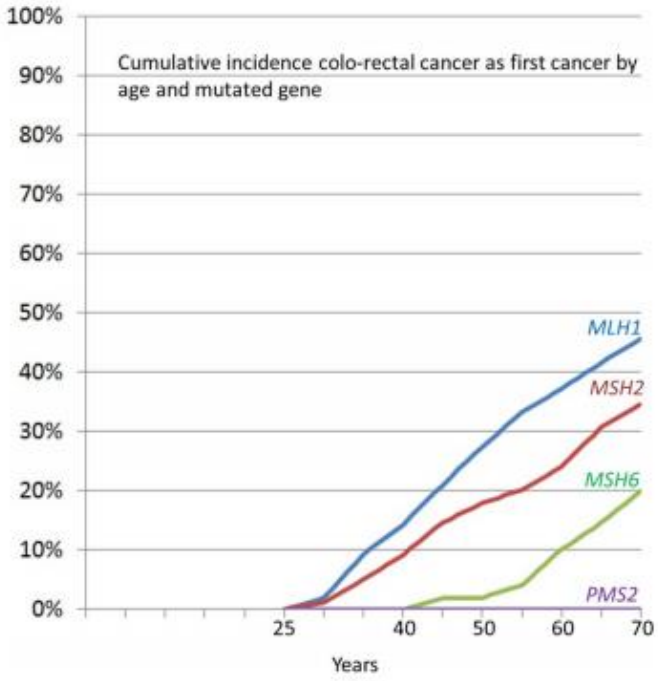


Figure 2 Calculated cumulative incidences by age and mutated gene for colorectal cancer (CRC) as the first cancer.

Moller et al. Cancer incidence and survival in Lynch syndrome patients receiving colonoscopic and gynaecological surveillance: first report from the prospective Lynch syndrome database. Gut 2017.

Lynch syndrome

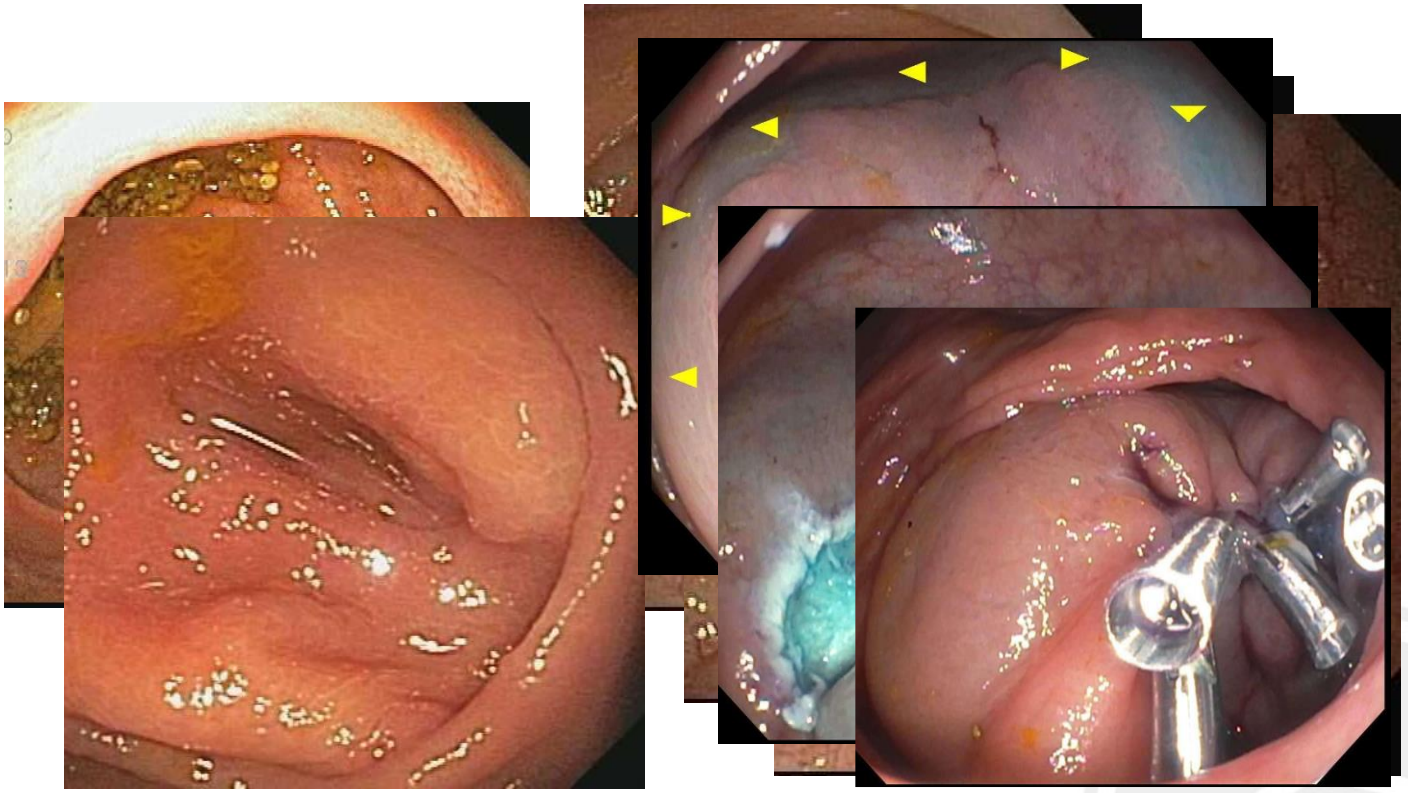
There is **rapid progression** from adenoma to CRC in comparison to accepted 10-15 year interval for sporadic polyps

Table 5. Dwell Time of Advanced Adenoma and Colorectal Cancer

	Advanced adenoma (*mo*)	Colorectal cancer (*mo*)
Mean ± standard deviation (range)	33.0 ± 16.2 (12–56)	35.2 ± 22.3 (7–96)

Edelstein et al. Rapid development of colorectal neoplasia in patients with Lynch syndrome. Clin Gastroenterol Hepatol. 2011 Apr;9(4):340-3.

Lynch syndrome



Index colonoscopy

50 weeks later

Lynch syndrome

- **DO NOT** have a great number of polyps

- Mean numbers of polyps are:
  - 1.3 for age 20–29 years
  - 1.8 for 30–39 years
  - 2.2 for 40–49 years
  - 3.5 for 50–59 years
  - 5.3 for 60–69 years
  - 7.6 for ages 70–79 years.

Edelstein et al. Rapid development of colorectal neoplasia in patients with Lynch syndrome. Clin Gastroenterol Hepatol. 2011 Apr;9(4):340-3.

Colorectal cancer

OSU GI Genetics recommendations:

- Colonoscopy every 1-2 years - favor yearly
- Starting at age 20-25 (favor 20)

Endometrial cancer

Cancer	General Population Risk[1]	*MLH1* or *MSH2*[1,2]		*MSH6*[2,3]		*PMS2*[4]	
		Risk	Mean Age of Onset	Risk	Mean Age of Onset	Risk	Mean Age of Onset
Endometrium	2.7%	25%–60%	48–62 years	16%–26%	55 years	15%	49 years

Other Extracolonic Cancers

- Endometrial cancer:
  - Because endometrial cancer can often be detected early based on symptoms, women should be educated regarding the importance of prompt reporting and evaluation of any abnormal uterine bleeding or postmenopausal bleeding. The evaluation of these symptoms should include endometrial biopsy.
  - Hysterectomy has not been shown to reduce endometrial cancer mortality, but can reduce the incidence of endometrial cancer. Therefore, hysterectomy is a risk-reducing option that should be considered.
  - Timing of hysterectomy should be individualized based on whether childbearing is complete, comorbidities, family history, and LS gene, as risks for endometrial cancer vary by mutated gene.
  - Endometrial cancer screening does not have proven benefit in women with LS. However, endometrial biopsy is both highly sensitive and highly specific as a diagnostic procedure. Screening via endometrial biopsy every 1 to 2 years can be considered.
  - Transvaginal ultrasound to screen for endometrial cancer in postmenopausal women has not been shown to be sufficiently sensitive or specific as to support a positive recommendation, but may be considered at the clinician's discretion. Transvaginal ultrasound is not recommended as a screening tool in premenopausal women due to the wide range of endometrial stripe thickness throughout the normal menstrual cycle.

Ovarian cancer

Cancer	General Population Risk	Ref.[7]	*MLH1*					Ref.[7]	*MSH2*				
			Cumulative Risk by Age in Years, % (95% confidence interval)				Mean Age of Onset		Cumulative Risk by Age in Years, % (95% confidence interval)				Mean Age of Onset
Ovary	1.6%		40	50	60	70			40	50	60	70	
		Ref. 1	0 (0-2)	4 (0-11)	15 (1-45)	20 (1-65)	45 years	Ref. 1	1 (0-3)	4 (1-9)	11 (2-28)	24 (3-52)	43 years
		Ref. 2	1 (0-3.6)	7 (2.2-11.2)	9 (2.9-12.2)	11 (3.2.19.8)		Ref. 2	4 (0.0-8.9)	12 (4.2-20.2)	15 (5.5-24.4)	15 (5.5-24.4)	
			MSH6[8]						*PMS2*[8]				
			Cumulative Risk by Age in Years, % (95% confidence interval)				Mean Age of Onset		Cumulative Risk by Age in Years, % (95% confidence interval)				Mean Age of Onset
			40	50	60	70			40	50	60	70	
		Ref. 1	0	0 (0-1)	1 (0-2)	1 (0-3)	46 years	Ref. 3	+	+	+	+	42 years
		Ref. 2	0 (-)	0 (-)	0 (-)	0 (-)		Ref. 2	0 (-)	0 (-)	0 (-)	0 (-)	

- Ovarian cancer:
  - Bilateral salpingo-oophorectomy (BSO) may reduce the incidence of ovarian cancer. The decision to have a BSO as a risk-reducing option by women who have completed childbearing should be individualized. Timing of BSO should be individualized based on whether childbearing is complete, menopause status, comorbidities, family history, and LS gene, as risks for ovarian cancer vary by mutated gene
  - Since there is no effective screening for ovarian cancer, women should be educated on the symptoms that might be associated with the development of ovarian cancer, such as pelvic or abdominal pain, bloating, increased abdominal girth, difficulty eating, early satiety, or urinary frequency or urgency. Symptoms that persist for several weeks and are a change from a woman's baseline should prompt her to seek evaluation by her physician.
  - While there may be circumstances where clinicians find screening helpful, data do not support routine ovarian cancer screening for LS. Transvaginal ultrasound for ovarian cancer screening has not been shown to be sufficiently sensitive or specific as to support a routine recommendation, but may be considered at the clinician's discretion. Serum CA-125 is an additional ovarian screening test with caveats similar to transvaginal ultrasound.
- Consider risk reduction agents for endometrial and ovarian cancers, including discussing risks and benefits (See Discussion for details).

Endometrial and ovarian cancer

OSU GI Genetics recommendations:

- Women should discuss options with their gynecologist
- Women should be aware that any abnormal uterine bleeding needs to be investigated
- Endometrial and ovarian cancer screening can be considered but does not have a proven benefit (and can be uncomfortable)
- Strongly consider TAHBSO at the completion of childbearing or around age 40
- Hormone replacement therapy is acceptable

Urinary tract cancer

Cancer	General Population Risk[1]	*MLH1* or *MSH2*[1,2]		*MSH6*[2,3]		*PMS2*[4]	
		Risk	Mean Age of Onset	Risk	Mean Age of Onset	Risk	Mean Age of Onset
Urinary tract	<1%	1%–7%[6]	54–60 years	<1%	65 years	+	Not reported

- Urothelial cancer:
  - Selected individuals such as with a family history of urothelial cancer or individuals with MSH2 mutations (especially males) may want to consider screening. Surveillance options may include annual urinalysis starting at 30–35 y. However, there is insufficient evidence to recommend a particular surveillance strategy.

NCCN

Urinary tract cancer

No proven effective screening exists

Urine cytology study of 1,868 screens (Myrhoj et al 2008)

- 2 cancers found
- 22 test were false positive with multiple tests needed
- 10 cancers found by symptoms outside of screening

CT scan and cystoscopy and cytology on 20 patients (Zachau et al 2012)

- 2 cancers found in 26 CTs and 48 cystoscopies

Urinary tract cancer

OSU GI Genetics recommendations:

- Consider annual urinalysis at age 30-40, especially if MSH2 mutation
- Must consider high likelihood of false positives with subsequent unnecessary testing
  - Urology consultation followed by CT or MRI urogram and cystoscopy

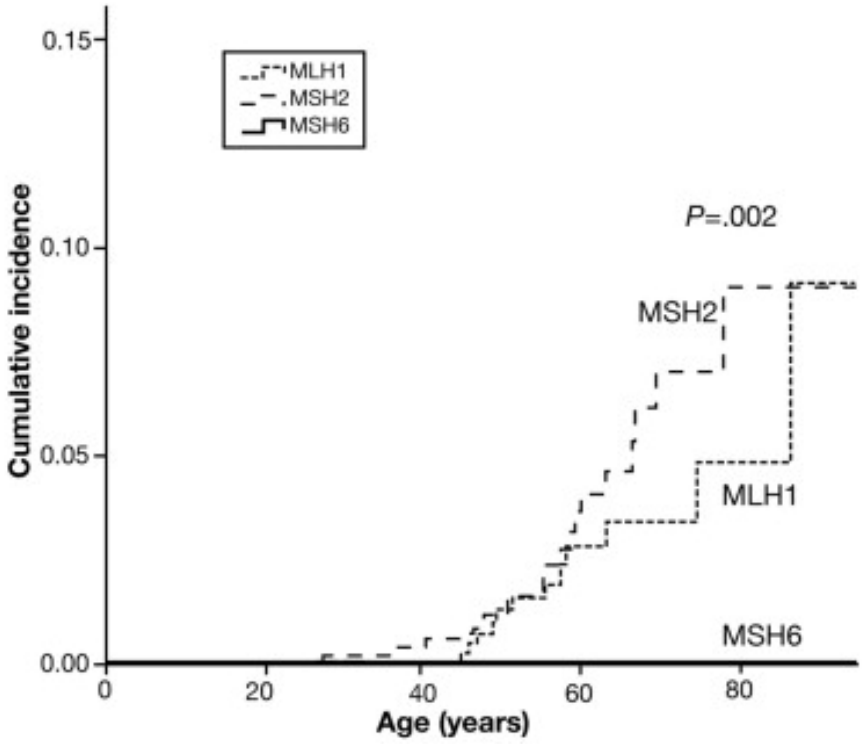
Gastric cancer and small bowel cancer

Cancer	General Population Risk[1]	*MLH1* or *MSH2*[1,2]		*MSH6*[2,3]		*PMS2*[4]	
		Risk	Mean Age of Onset	Risk	Mean Age of Onset	Risk	Mean Age of Onset
Stomach	<1%	6%–13%	56 years	≤3%	63 years	+	70–78 years
Small bowel	<1%	3%–6%	47–49 years	Not reported	54 years	+	59 years

- Gastric and small bowel cancer:
  - There are no clear data to support surveillance for gastric, duodenal, and small bowel cancer for LS. Selected individuals with a family history of gastric, duodenal, or small bowel cancer or those of Asian descent (Vasen HF, et al. Gut 2013;62:812-823) have an increased risk and may benefit from surveillance. If surveillance is performed, may consider upper endoscopy with visualization of the duodenum at the time of colonoscopy every 3–5 y beginning at age 30–35 y. Consider testing and treating H. pylori.

NCCN

Gastric cancer and small bowel cancer



Cappelle et al. Risk and Epidemiological Time Trends of Gastric Cancer in Lynch Syndrome Carriers in The Netherlands. Gastro 2010.

Gastric cancer and small bowel cancer

Upper endoscopy on 73 patients with Lynch compared to relatives (Sinisalao et al. 2002)

- 1 duodenal cancer found (already advanced)
- No difference in inflammation or intestinal metaplasia
- No difference in H pylori
- No gastric cancers during 4 years of follow-up

Video capsule endoscopy study of 200 patients (Haanstra et al. 2015)

- 2 patients with neoplasia detected (1 cancer, 1 polyp)
- 1 patient with cancer missed
- All lesions within range of endoscopy
- 155 repeated 2 years later and no neoplasms (but required 17 procedures for eval)

Gastric cancer and small bowel cancer

OSU GI Genetics recommendations:

- H. pylori testing and eradication if positive
- Plan enteroscopy at age 30-35 and repeat every 3-5 years if family history of gastric cancer or of Asian descent
- Consider baseline enteroscopy with gastric biopsies at age 30-35 or at time of diagnosis
- **Low threshold for aggressive testing of any symptoms**
  - **Abdominal pain, reflux, anemia, etc.**

Pancreas cancer

Cancer	General Population Risk[1]	*MLH1* or *MSH2*[1,2]		*MSH6*[2,3]		*PMS2*[4]	
		Risk	Mean Age of Onset	Risk	Mean Age of Onset	Risk	Mean Age of Onset
Pancreas[5]	<1%	1%–6%	Not reported	Not reported	Not reported	Not reported	Not reported

- Pancreatic cancer:
  - Despite data indicating an increased risk for pancreatic cancer, no effective screening techniques have been identified; therefore, no screening recommendation is possible at this time.

NCCN

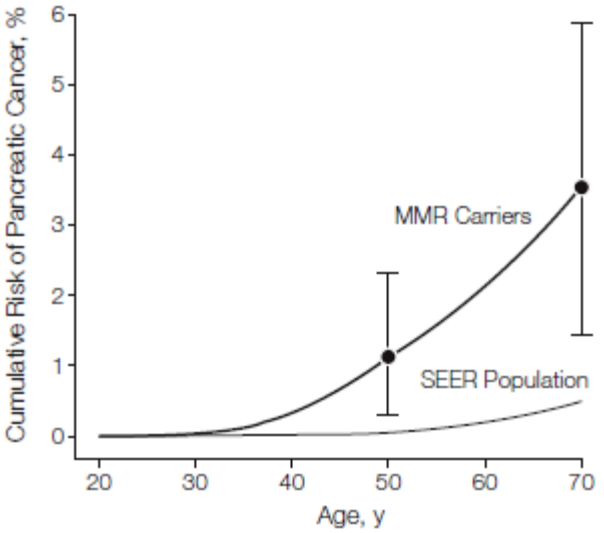
Pancreas cancer

Table 3. Age-Specific Cumulative Risk of Pancreatic Cancer[a]

Age, y	Cumulative Risk: Population, %[b]	Cumulative Risk: Families With MMR Gene Mutation, % (95% CI)	Hazard Ratio (95% CI)	
20	0	0		
30	0	0.03	30.5 (14.2-65.7)[c]	
40	0.01	0.23		8.6 (4.7-15.7)[e]
50	0.04	1.31 (0.31-2.32)		
60	0.18	1.98	5.1 (2.2-11.8)[d]	
70	0.52	3.68 (1.45-5.88)		

Abbreviations: CI, confidence interval; MMR, mismatch repair.
[a] Two age-specific hazard ratios in proportional hazards regression model (<50 y, ≥50 y), corrected for ascertainment by conditioning on genotype and phenotype of proband and phenotype of all colorectal cancer–affected first-degree relatives.
[b] 1992-2005 Surveillance, Epidemiology, and End Results (SEER) 13 (http://seer.cancer.gov).
[c] For age range, 20 to 49 years.
[d] For age range, 50 to 70 years.
[e] For age range, 20 to 70 years.

Figure. Age-Specific Cumulative Risk of Pancreatic Cancer in Families With Pathogenic Mutations in *MLH1*, *MSH2*, or *MSH6* Genes



Kastrinos et al. Risk of Pancreatic Cancer in Families With Lynch Syndrome. JAMA 2009.

Pancreas cancer

OSU GI Genetics recommendations:

- Refer to OSU Pancreas Clinic to discuss screening if a first or second degree relative with pancreatic cancer

- OSU Pancreas Clinic general recommendations (although should be personalized for all patients):
  - Annual fasting glucose and hemoglobin A1c
  - Annual MRI of pancreas and MRCP
  - Annual Endoscopic Ultrasound

  - At age 50 (or 10 years younger than earliest diagnosis), start a screening test every 6 months

Hepatobiliary tract cancer

No recommendations for screening

Cancer	General Population Risk[1]	*MLH1* or *MSH2*[1,2]		*MSH6*[2,3]		*PMS2*[4]	
		Risk	Mean Age of Onset	Risk	Mean Age of Onset	Risk	Mean Age of Onset
Hepatobiliary tract	<1%	1%–4%	50–57 years	Not reported	Not reported	+	Not reported

NCCN

Breast cancer

Risk not included in NCCN guidelines

- **Breast cancer:**
  - **There have been suggestions that there is an increased risk for breast cancer in LS patients; however, there is not enough evidence to support increased screening above average-risk breast cancer screening recommendations.**

NCCN

Breast cancer

2 new studies suggesting increased risk of breast cancer in Lynch syndrome

Based on examination of patient characteristics and testing results from 2 large commercial genetic testing labs

Espenschied at al. found that 22% of Lynch patients met BRCA testing criteria (more commonly MSH6 and PMS2)

Roberts et al. found that MSH6 and PMS2 associated with increased risk for breast cancer (2-3x increased)

Espenschied et al. Multigene Panel Testing Provides a New Perspective on Lynch Syndrome. JCO 2017.

Roberts et al. MSH6 and PMS2 germ-line pathogenic variants implicated in Lynch syndrome are associated with breast cancer. Genetics in Medicine 2018.

Breast cancer

OSU GI Genetics recommendations:

Follow average risk recommendations from American Cancer Society (Of note, more aggressive than other societies)

- Age 40 – 45: Discuss screening with your doctor (we favor starting mammogram)
- Age 45 – 55: Begin yearly mammograms
- Age 55+: Consider transition to every other year mammogram (we favor continuing yearly mammogram)

Stay tuned for potential future updates

Genetics clinics are under utilized

Especially in Colorectal Cancer!!!

Table 5. Referral of Patients With Breast or Colorectal Cancer for Genetic Counseling and/or Testing

Referral	Total (N = 10,466)	Breast Cancer (n = 6,569)	Colorectal Cancer (n = 3,897)	*P**
Referred for genetic counseling and/or testing, %	25.6	29.1	19.6	< .001
	n = 2,457	n = 1,556	n = 901	
Positive family history and referred, %	42.7	52.2	26.4	< .001

**P* value corresponds to differences between breast and colorectal cancers.

Wood et al. JCO 2014.

Genetic counseling

Cancer genetics appointments are about 90 min

They include:

1. Review of clinical history (personal and family)
2. Differential diagnosis
3. Discussion of pros/cons of genetic testing
4. Ordering, drawing and routing of genetic testing if indicated and patient provides informed consent **(along with knowledge of insurance and lab rules)**
5. Perhaps most importantly post-result counseling

Genetic counseling

Benefits of genetic counseling and testing:

Accurate counseling for patients of risks for cancers (both another colon cancer as well as other cancers)

Predictive testing of at risk family members

***If positive, prevent colon cancer through screening!**

***If negative, save patient from a lot of colonoscopies!**

Federal laws protecting against employment or health insurance discrimination

When to refer to Genetics?

Colorectal cancer

- Colorectal cancer dx at age <50
- Colorectal cancer dx at age ≥50 if there is a FDR with colorectal or endometrial cancer at any age
- Synchronous or metachronous colorectal or endometrial cancers in the same person
- Colorectal cancer showing mismatch repair deficiency on tumor screening
- Colorectal cancer and two additional cases of any LS-associated cancer (Table 6) in the same person or in close relatives
- Colorectal cancer and two additional Cowden syndrome criteria (Table 4) in the same person
- Colorectal cancer and one additional LFS tumor (Table 5) in the same person or in two relatives, one dx at age ≤45
- Colorectal cancer with ≥10 cumulative adenomatous colon polyps in the same person

Hampel et al. A practice guideline from the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors: referral indications for cancer predisposition assessment. *Genet Med*. 2014.

When to refer to Genetics?

Colorectal polypo… adenomatous	• ≥ 10 cumulative adenomatous colon polyps in the same person
Colorectal polyposis, hamartomatous	• 3–5 cumulative histologically proven juvenile polyps in the same person • Multiple juvenile polyps throughout the GI tract in the same person • Any number of juvenile polyps with a positive family history of JPS • ≥2 cumulative histologically proven PJ polyps in the same person • ≥1 PJ polyp and mucocutaneous hyperpigmentation in the same person • Any number of PJ polyps and a positive family history of PJS • GI hamartoma or ganglioneuroma and two additional Cowden syndrome criteria (Table 4) in the same person • Rectal hamartomatous polyps and one additional TSC criterion (Table 8) in the same person • Diffuse ganglioneuromatosis of the GI tract
Colorectal polyposis, serrated	• ≥5 SPs proximal to the sigmoid colon, two of which are >1 cm in diameter, in the same person • >20 SPs at any site in the large bowel in the same person • Any number of SPs proximal to the sigmoid colon and a positive family history of SPS
Colorectal polyposis, mixed	• ≥ 10 cumulative polyps with >1 histology in the same person

Hampel et al. A practice guideline from the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors: referral indications for cancer predisposition assessment. Genet Med. 2014.

JAMA Oncology April 2017 Volume 3, Number 4

OCCPI Ohio Colorectal Cancer Prevention Initiative

JAMA Oncology | Original Investigation

Prevalence and Spectrum of Germline Cancer Susceptibility Gene Mutations Among Patients With Early-Onset Colorectal Cancer

Rachel Pearlman, MS, CGC; Wendy L. Frankel, MD; Benjamin Swanson, MD; Weiqiang Zhao, MD, PhD; Ahmet Yilmaz, PhD; Kristin Miller, BS; Jason Bacher, BA; Christopher Bigley, MS; Lori Nelsen, BA; Paul J. Goodfellow, PhD; Richard M. Goldberg, MD; Electra Paskett, PhD; Peter G. Shields, MD; Jo L. Freudenheim, PhD; Peter P. Stanich, MD; Ilene Lattimer, BSN; Mark Arnold, MD; Sandya Liyanarachchi, MS, MAS; Matthew Kalady, MD; Brandie Heald, MS, CGC; Carla Greenwood, AA; Ian Paquette, MD; Marla Prues, RN; David J. Draper, MD; Carolyn Lindeman, MSN; J. Philip Kuebler, MD, PhD; Kelly Reynolds, BS; Joanna M. Brell, MD; Amy A. Shaper, MSW; Sameer Mahesh, MD; Nicole Buie, RN; Kisa Weeman, MD; Kristin Shine, BSN; Mitchell Haut, MD; Joan Edwards, RN; Shyamal Bastola, MD; Karen Wickham, RN; Karamjit S. Khanduja, MD; Rosemary Zacks, RN; Colin C. Pritchard, MD, PhD; Brian H. Shirts, MD, PhD; Angela Jacobson, MS, CGC; Brian Allen, MS, CGC; Albert de la Chapelle, MD, PhD; Heather Hampel, MS, CGC; for the Ohio Colorectal Cancer Prevention Initiative Study Group

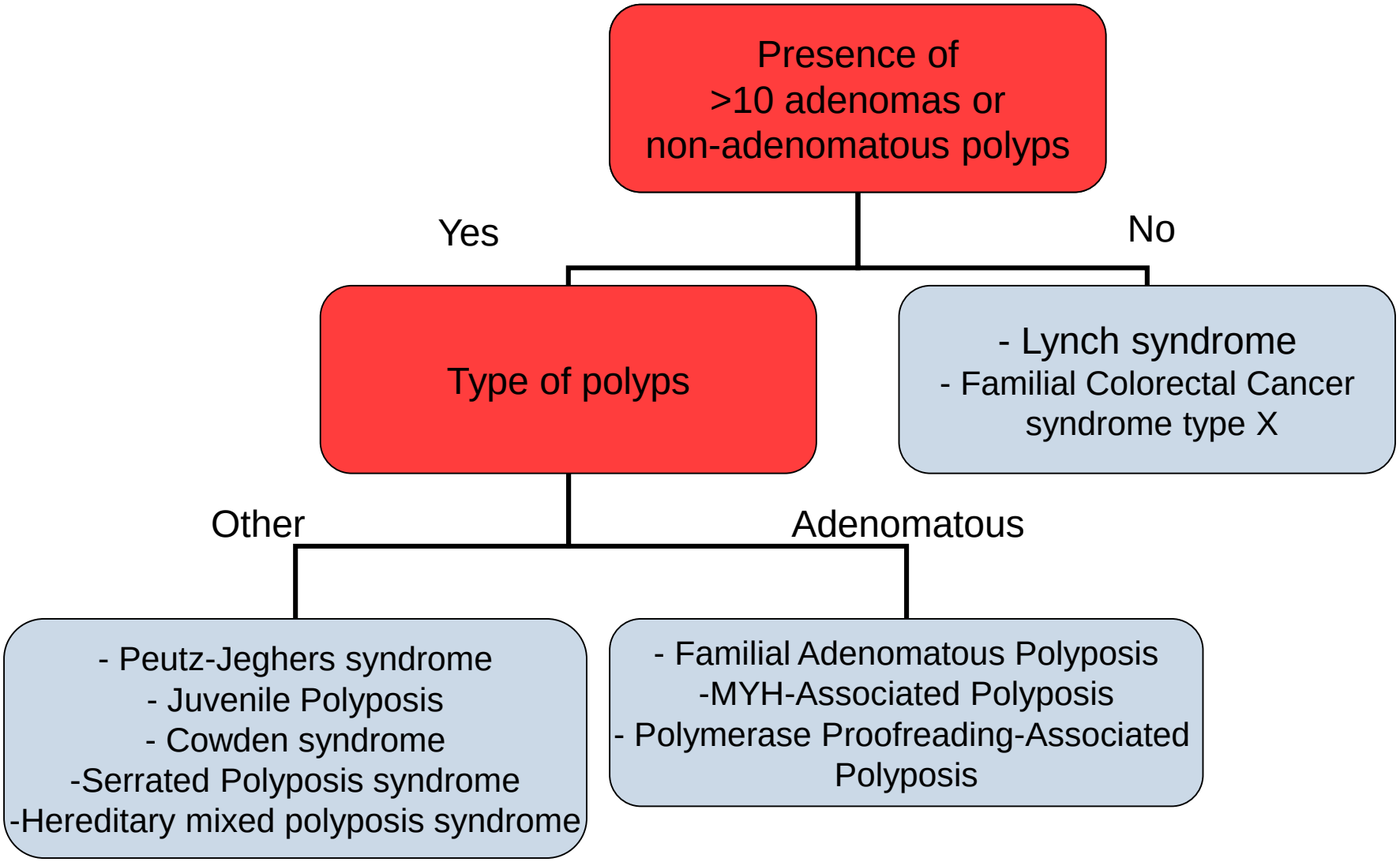
- **450** CRC patients diagnosed <50 years of age with completed testing as of June 2016
- All had tumor screening and broad multigene panel testing (MGPT)

Results from early-onset cohort

- **1 out of 6** (**16%**) had at least one hereditary cancer syndrome (75 mutations in 72 patients)
- **1 out of 12** (**8.4%**) had Lynch syndrome
- **1 out of 13** (**7.8%**) had another syndrome
- 24 mutation-positive patients (33%) did NOT meet established guidelines for the gene(s) in which they had a mutation

Pearlman et al. *JAMA Oncol.* 2017;3(4):464-471

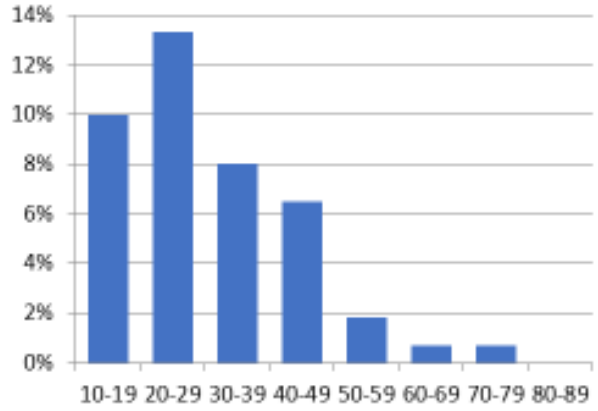
Hereditary Colon Cancer Differential Diagnosis



Patients with > 10 polyps receiving genetic testing

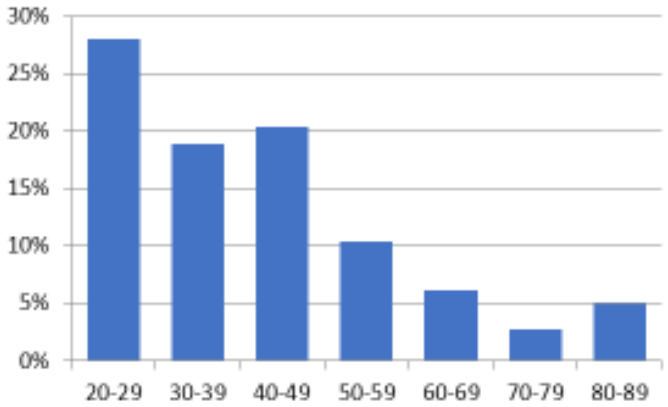
Mutation prevalence in polyposis genes decreased with age in all polyp count groups

10 – 19 polyps



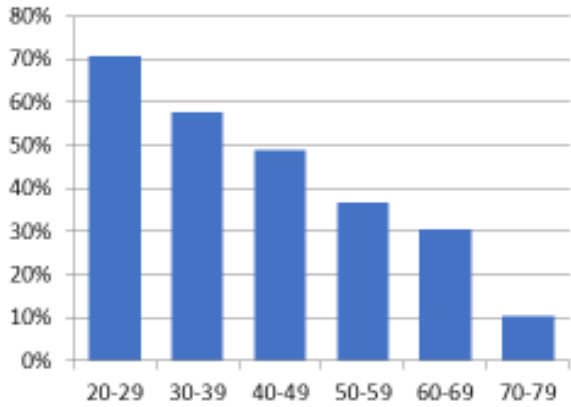
p < 0.001

20 – 99 polyps



p < 0.001

100+ polyps



p < 0.001

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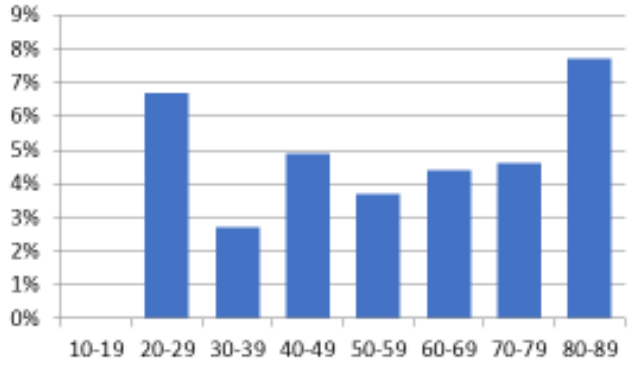
The Ohio State University
Wexner Medical Center

Patients with > 10 polyps receiving genetic testing

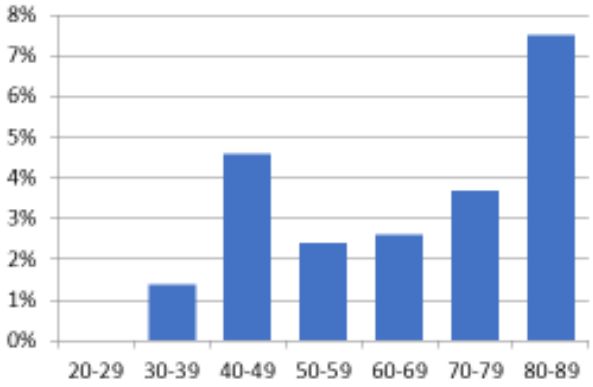
Mutation prevalence in non-polyposis genes was not associated with age for any group

10 – 19 polyps



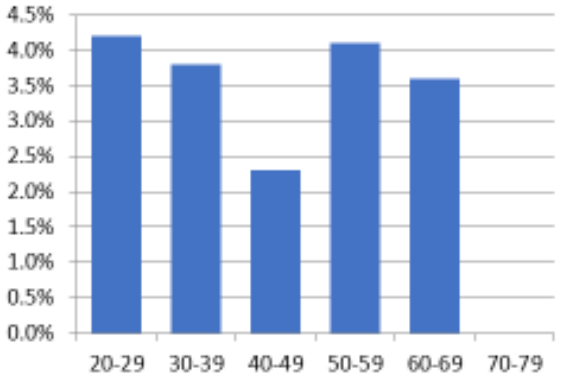
p = 0.9

20 – 99 polyps



p = 0.3

100+ polyps



p = 0.9

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Patients with > 10 polyps receiving genetic testing

Total mutation prevalence in genes of interest in study remained > 5% in all groups

	Total number of colorectal polyps		
Age at Testing	**10-19**	**20-99**	**100+**
10-19	10.0%	*	*
20-29	20.0%	28.0%	75.0%
30-39	10.7%	20.3%	61.5%
40-49	11.4%	25.0%	51.1%
50-59	5.5%	12.8%	40.8%
60-69	5.1%	8.7%	34.0%
70-79	5.3%	6.4%	10.5%
80-89	7.7%	12.5%	*

* indicates n <10

Summary

- Lynch syndrome is associated with colon, endometrial and ovarian cancer most commonly
- Tumor testing for Lynch syndrome needs to be monitored and referred for genetic testing if abnormal
- Colonoscopy saves lives in Lynch syndrome!
- You should have a low threshold to consider genetics consultation if history of colon cancer or multiple colon polyps

Thank You!

- Call Genetics at (614) 293-6694 or GI office at (614) 293-6255 for appointments
- Peter.Stanich@osumc.edu
- @DocStanich

Familial Colorectal Cancer Type X

- Same family history as with Lynch syndrome, but with **microsatellite stable** colorectal cancers
- Increased incidence **only** for colorectal cancer (SIR, 2.3; 95% confidence interval, 1.7-3.0) but less than Lynch (SIR, 6.1; 95% confidence interval, 5.2-7.2) (*P*.001).
- “It may be reasonable to offer colorectal cancer screening initiated 5 to 10 years prior to the age of earliest colorectal cancer diagnosis, with frequency determined by initial findings but no less often than every 5 years.”

Lindor et al. *JAMA. 2005;293:1979-1985*

Screening is working!

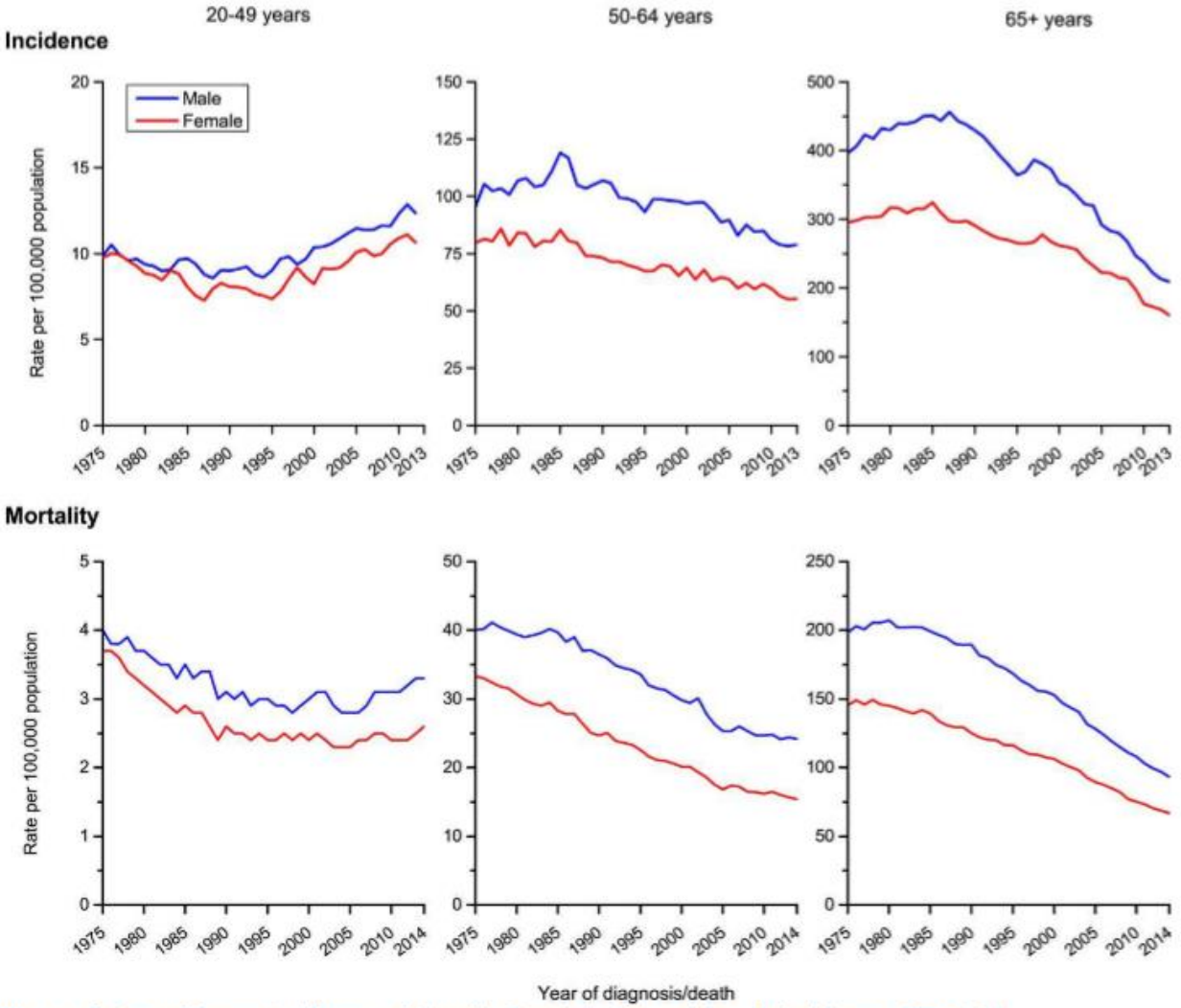


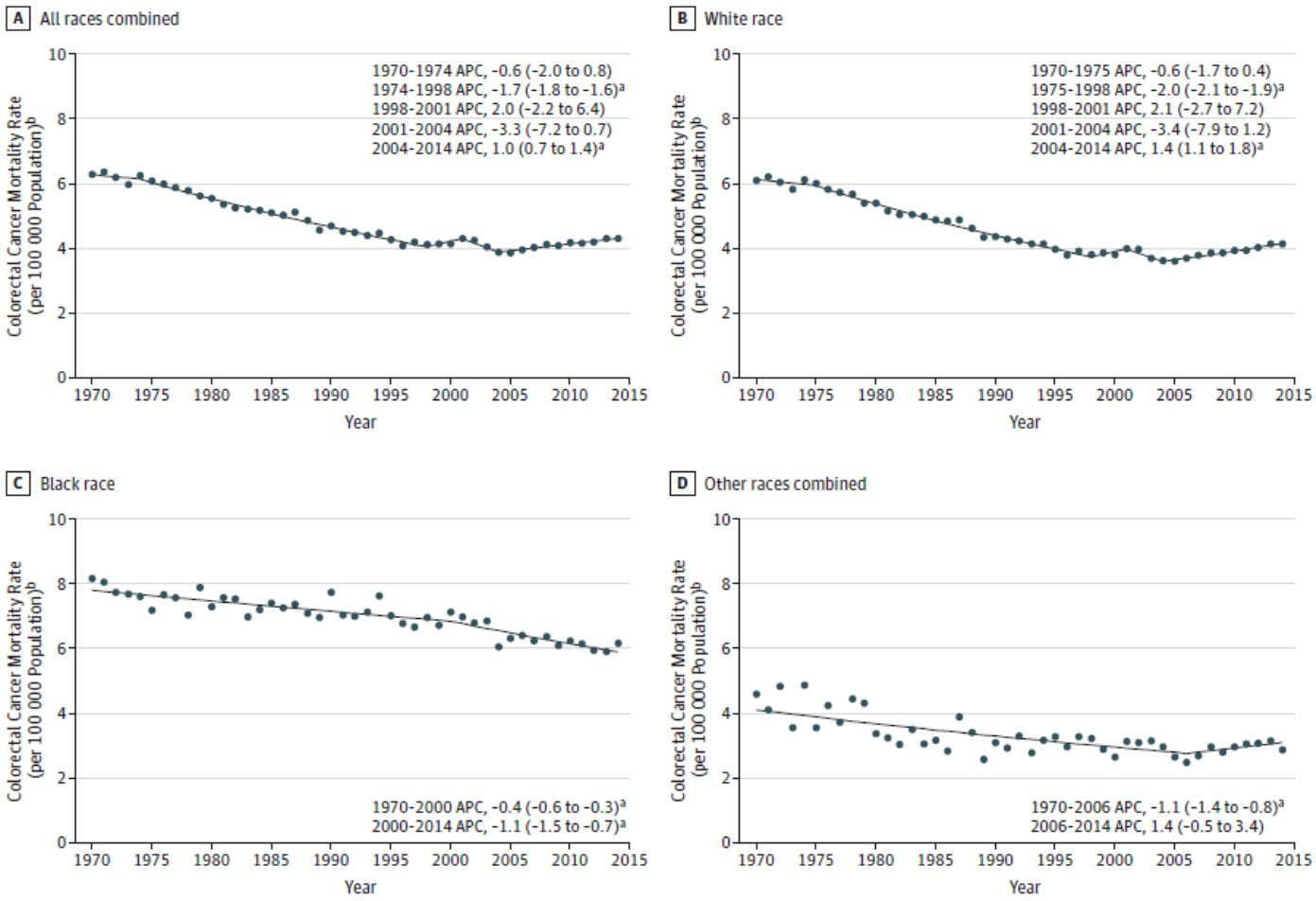
FIGURE 5. Colorectal Cancer Incidence and Mortality Trends by Age and Sex, United States, 1975-2014.

Siegel at al. CA: A Cancer Journal for Clinicians. Colorectal Cancer Statistics, 2017.

What about colon cancer in young people?

- This is a very hot topic

Figure. Annual Percent Change (APC) in Colorectal Cancer Mortality Rates Among Adults Aged 20 to 54 Years in the United States by Race, 1970-2014



What about colon cancer in young people?

- Remember – despite increasing percentage, the actual number of people affected is low
  - Mortality - 3.9 per 100k in 2004 to 4.3 in 2014
- Continue aggressive evaluation of bleeding symptoms (IDA, melena, rectal bleeding)
- Evidence for screening at age 45 is controversial and based on modelling
  - Maybe FIT for those 45 – 49?
  - Remember to check on insurance coverage

Thank You

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