Hereditary Aspects of Colorectal Cancer

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2017 JADPRO Live at APSHO

Learning Objectives

1. Describe Lynch syndrome and identify patients at risk for having Lynch syndrome
2. Recognize other hereditary colorectal cancer syndromes, particularly polyposis conditions
3. Interpret immunohistochemical staining results for the four mismatch repair proteins and other tumor screening test results for Lynch syndrome
4. Understand the difference in cancer surveillance for individuals with Lynch syndrome compared to those in the general population
5. Describe the role of biomarkers (e.g., *BRAF, KRAS, NRAS*) and MSI-H in predicting response to targeted therapies used for the treatment of CRC

CRC = colorectal cancer; MSI-H = microsatellite instability high.

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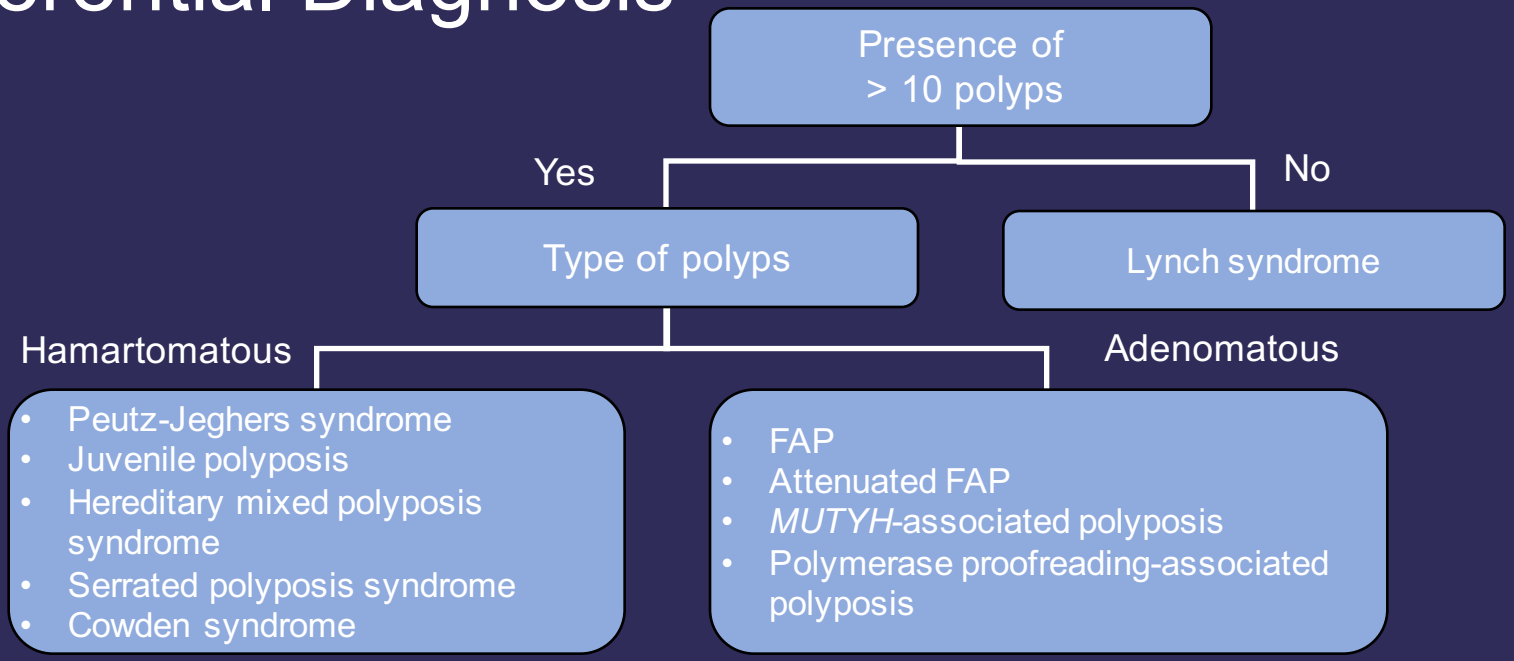
- Ms. Hampel is the PI of a grant that receives free genetic testing from Myriad Genetics Laboratories, Inc., is on the scientific advisory board for InVitae Genetics and Genome Medical, and has stock in Genome Medical.
- Dr. Hall has nothing to disclose.

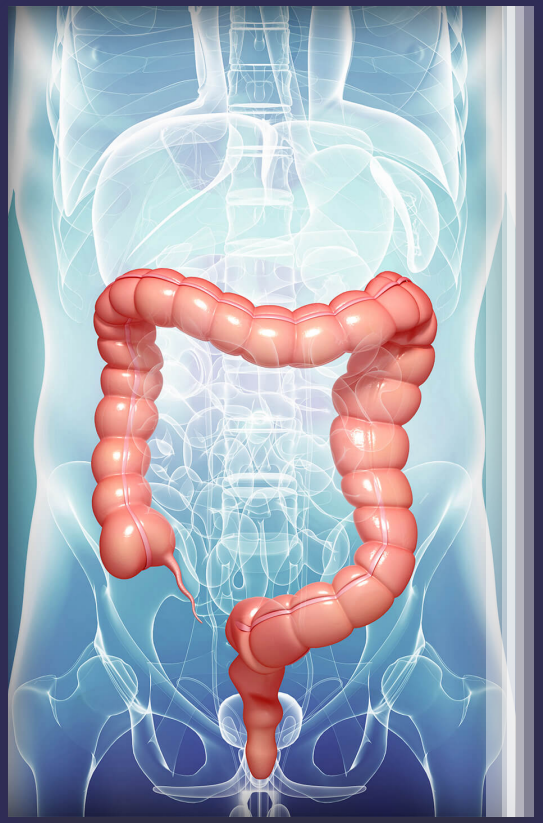
Flowchart for Hereditary Colon Cancer Differential Diagnosis



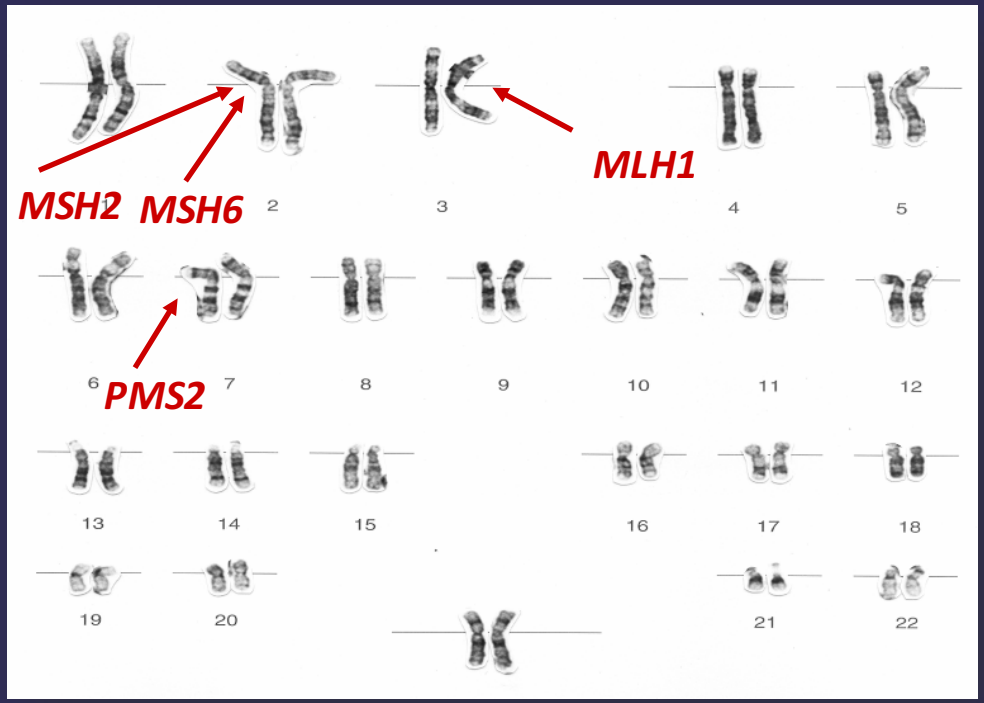
FAP = familial adenomatous polyposis.

Lynch Syndrome

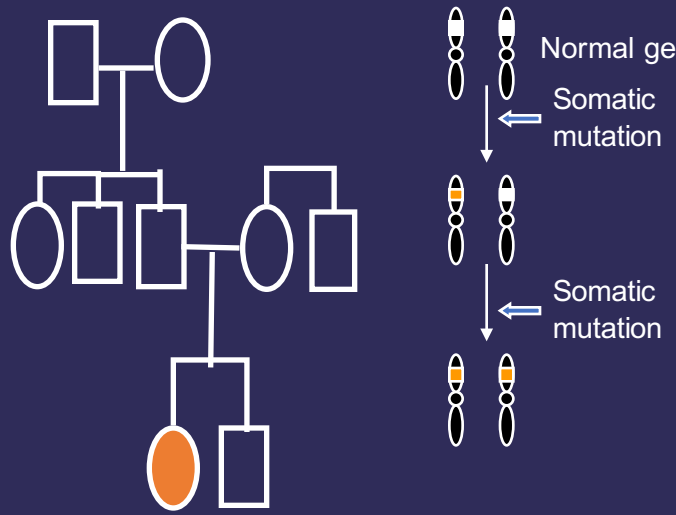
- Over 1.2 million individuals in the United States have Lynch syndrome
- Inherited condition that causes high risks for colorectal cancer, endometrial cancer, and other cancers
- Preventable cancers with early and more frequent screening
- 95% of affected individuals do not know they have Lynch syndrome



Lynch Syndrome Genes

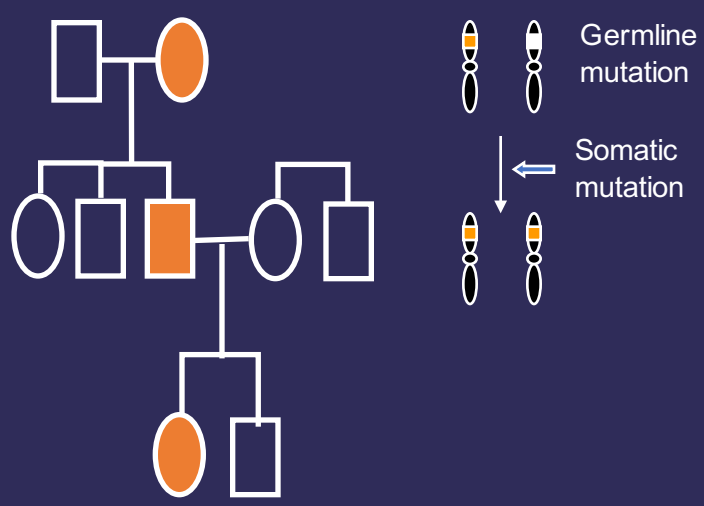


Sporadic



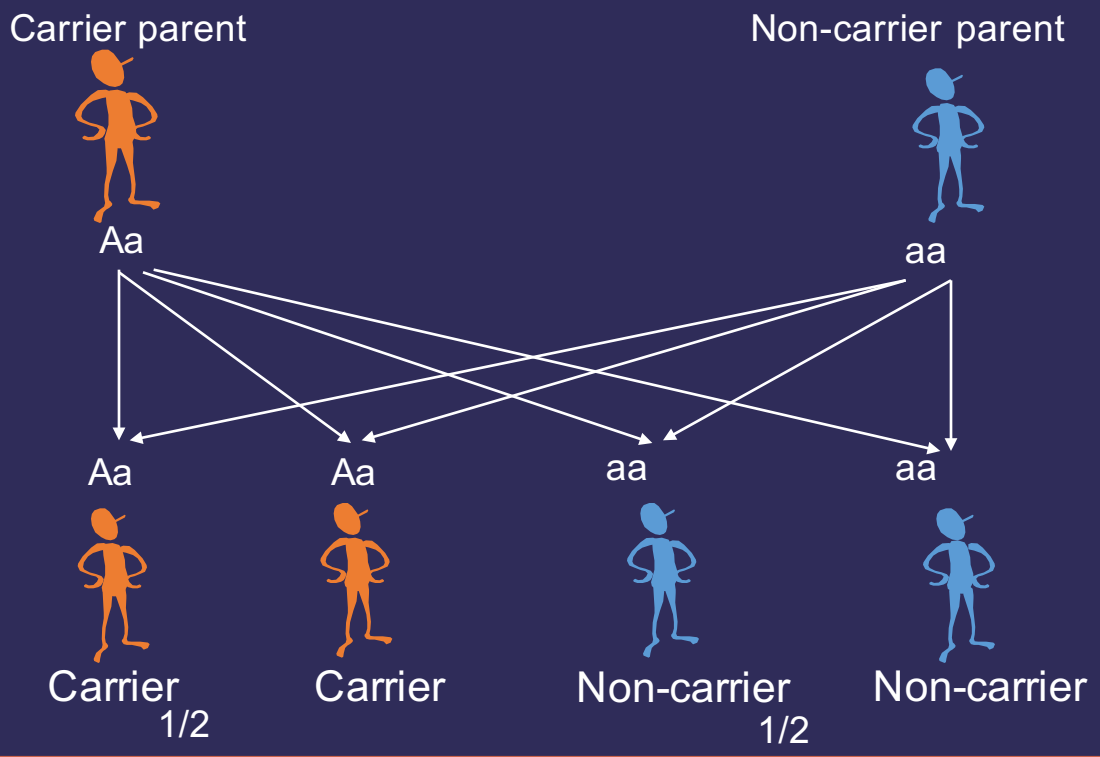
- Later age at onset (60s or 70s)
- Little or no family history of cancer
- Single or unilateral tumors

Inherited



- Early age at onset (< 50)
- Multiple generations with cancer
- Multiple primary cancers (e.g., colon/endometrial)

Autosomal Dominant Inheritance



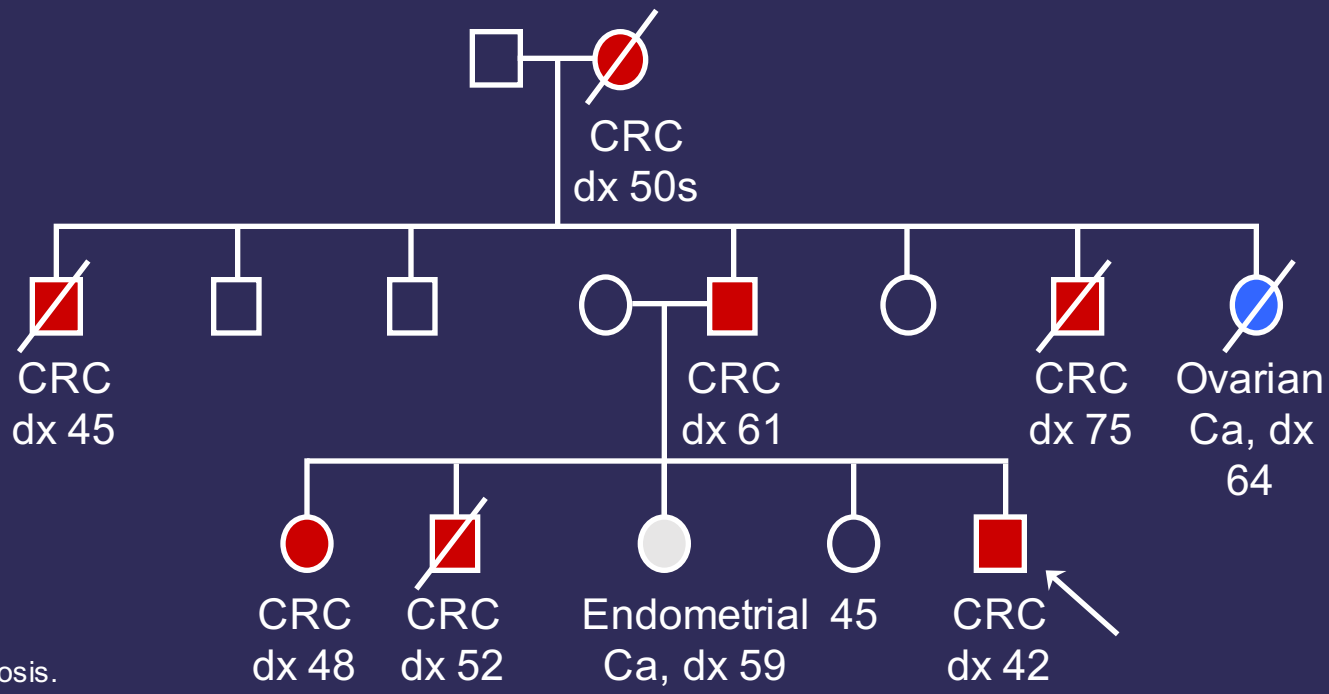
Lynch Syndrome Cancer Risks (to 70)

Cancer Type	*MLH1* and *MSH2*	*MSH6*	*PMS2*	General Public
Colon cancer (men)	40%-80%	10%-22%	15%-20%	5.5%
Endometrial cancer	25%-60%	16%-26%	15%	2.7%
Stomach	1%-13%	≤ 3%	< 6%	< 1%
Ovarian	4%-24%	1%-11%	< 6%	1.6 %

NCCN = National Comprehensive Cancer Network.

NCCN Guidelines for Colorectal Cancer Screening and Prevention v2.2017; Bonadona V, et al. *JAMA* 2011;305:2304-10; Senter L, et al. *Gastroenterology* 2008;135:419-48.

Family History Is Key to Diagnosing Lynch Syndrome…or Is It?



Ca = cancer; dx = diagnosis.

Amsterdam II Criteria

- Three or more relatives with verified HNPCC-associated cancer in family
- Two or more generations
- One case a first-degree relative of the other two
- One CRC diagnosis < 50
- FAP excluded
- Does not include ovarian, gastric, brain, biliary tract, or pancreatic cancer

HNPCC = hereditary nonpolyposis colorectal cancer.

Vasen HFA, et al. *Gastroenterology*. 1999;116:1453-6.

Bethesda Guidelines

- CRC diagnosis < 50
- Synchronous or metachronous CRC, or other HNPCC-associated tumors regardless of age
- CRC with MSI-H histology diagnosis < 60
- CRC with ≥ 1 FDR with an HNPCC-associated tumor, with one cancer diagnosis < 50
- CRC with ≥ 2 FDRs or SDRs with an HNPCC-associated tumor, regardless of age

FDR = first-degree relative; SDR = second-degree relative.

Umar A, et al. *J Natl Cancer Inst* 2004;96:261-8.

$PREMM_5$

- Probability of Lynch syndrome gene mutation
- Proband
  - Number of CRCs and youngest age at diagnosis
  - Y/N adenomas and youngest age at diagnosis
  - Y/N EC and youngest age at diagnosis
- FDRs and SDRs
  - Number with CRC and youngest age at diagnosis
  - Number with EC and youngest age at diagnosis
  - Y/N any with another HNPCC cancer
- Balmana et al. says refer anyone with > 2.5% mutation likelihood; NCCN still says > 5%

EC = endometrial cancer; Y/N = yes/no.

$PREMM_5$, http://premm.dfci.harvard.edu; Balmana J, et al. *JAMA* 2006;296:1469-78.

Warning: Family Histories Can Be Deceiving

- Family size is getting smaller
- Wider use of colonoscopy likely to prevent many colon cancers
- *MSH6* and *PMS2* have lower cancer risks

Tumor Tests to Screen for Lynch Syndrome

- MSI testing
  - Performed on DNA extracted from tumor and normal tissue; requires laboratory
  - Test is positive in 15% of CRC cases
  - Test is positive in 77%-89% of LS cases
- IHC staining
  - Performed on thin slide of tumor; can be done in pathology department
  - 1-2 proteins are absent in 15%-20% of CRC cases
  - 1-2 proteins are absent in 83% of LS cases
- Methylation testing/*BRAF* V600E testing
  - Tumors MSI positive and/or absent *MLH1* and *PMS2* on IHC will be studied for methylation
  - 80% will have acquired methylation (sporadic colon cancer)
  - 20% will have Lynch syndrome
  - 69% of methylated CRCs have the *BRAF* V600E mutation; this is an easier test, so many hospitals do *BRAF* testing when *MLH1* and *PMS2* are absent on IHC

IHC = immunohistochemistry; LS = Lynch syndrome; MSI = microsatellite instability.

Palomaki G et al. *Genetics in Medicine*. 2009:11(1):42-65.

MSI Testing on Genotype

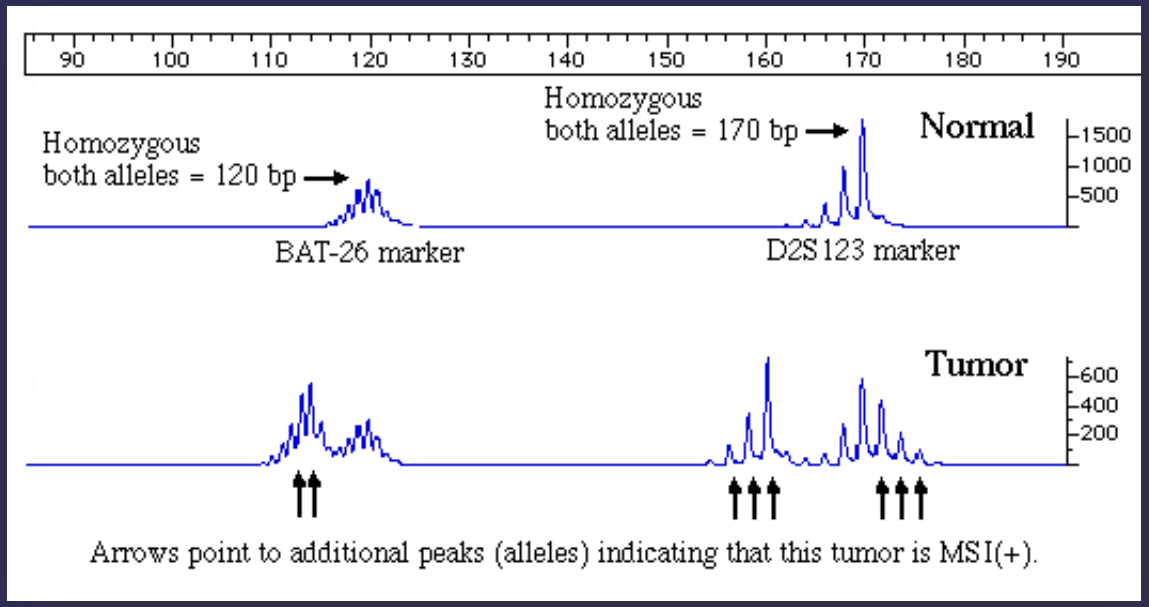


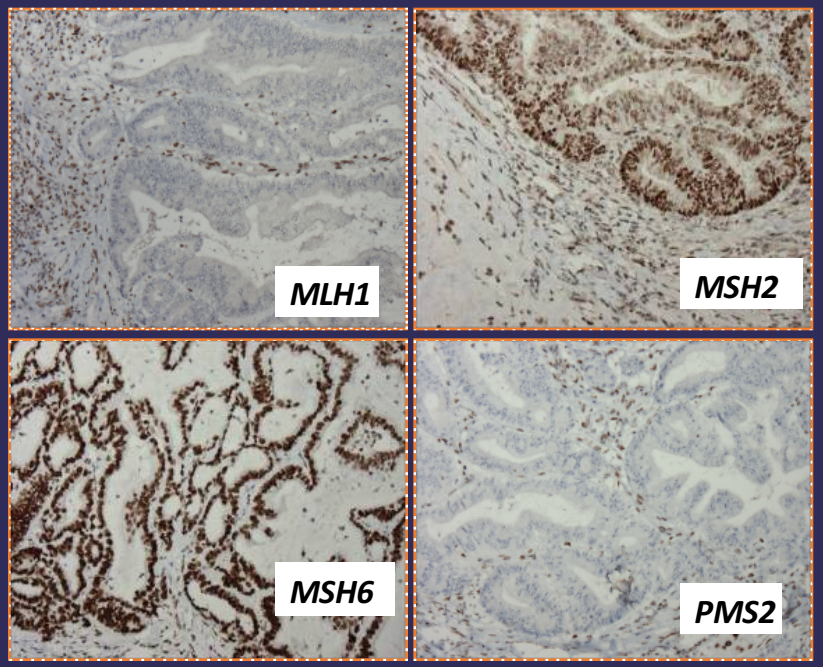
Image courtesy of The Ohio State University Comprehensive Cancer Center

IHC Normal: All Four Stains Present

- 80% of the time you will get this result
- CRC is probably not MSI+
- Prognosis worse than if MSI+
- Refer to Genetics **only** if
  - You suspect polyposis
  - Patient diagnosed over age 45
  - Patient has had multiple CRC primaries, or
  - Patient has a FDR with CRC at any age

IHC Abnormal: *MLH1* and *PMS2* Absent

- 15% of the time
- CRC is MSI+
- Better prognosis
- 80% acquired methylation of *MLH1*
- 20% will be LS
- *BRAF* test is done to help sort this out



Example Taken From Recent Pathology Report

Mismatch repair protein expression:
MLH1: Absent.
PMS2: Absent.
MSH2: Present.
MSH6: Present.

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

Interpretation: Mismatch Repair Protein Panel Abnormal
These results indicate defective DNA mismatch repair (MMR) function within the tumor due to defective MLH1 and PMS2. The absence of MLH1 and PMS2 may be due to the presence of a germline (heritable) mutation in this/these gene(s). Thus, this individual and other family members may be at increased risk for having an inherited colon cancer syndrome due to defective DNA mismatch repair. It is important to note that these results do not distinguish between germline and somatic (not heritable) alterations. Additional testing is required to distinguish between these two possibilities and to provide predictive testing for at risk family members. A genetic consultation may be of benefit for this individual and/or family to further discuss the implications of these findings.

Image courtesy of The Ohio State University Comprehensive Cancer Center

Follow-up *BRAF* Testing

SOMATIC BRAF GENE MUTATION ANALYSIS BY
POLYMERASE CHAIN REACTION (PCR) AND SNPlex ASSAY

RESULT:
NEGATIVE for BRAF V600E mutation.

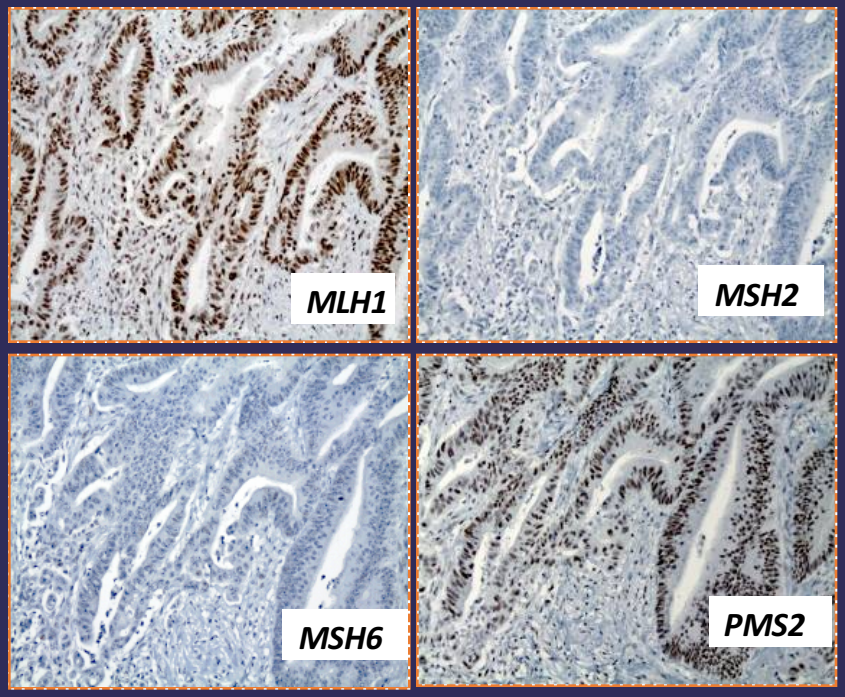
INTERPRETATION:
BRAF V600E Mutation is NOT detected in this specimen (S10-3599-B7).

BRAF encodes a protein belonging to the raf/mil family of serine/threonine protein kinases and plays a role in regulating the MAP kinase/ERKs signaling pathway, which affects cell division, differentiation, and secretion (1). The most common B-RAF mutation, a Thymidine to Adenosine transversion, converting Valine to Glutamate (V600E) in Exon 15, has been identified in malignant melanoma (27%-70%), papillary thyroid cancer (36%-53%), colorectal cancer (5%-22%) and serous ovarian and endometrium cancer (
30%). The association of the BRAF V600E mutation with prognosis in these tumors has been associated with a significantly poorer survival in microsatellite-stable colon cancers (2) and poor prognosis of papillary thyroid carcinomas when additional other gene alterations are present (3) . In addition, due to its absence in Lynch syndrome (LS), it has also been used as a guide regarding further work-up for LS (4, 5). If a BRAF V600E mutation is found (positive) in a microsatellite unstable tumor then the tumor is probably sporadic and further work-up for LS may not be warranted. If such mutation is not found (negative), then the tumor may be either sporadic or inherited, and further work-up for LS may be justified.

Image courtesy of The Ohio State University Comprehensive Cancer Center

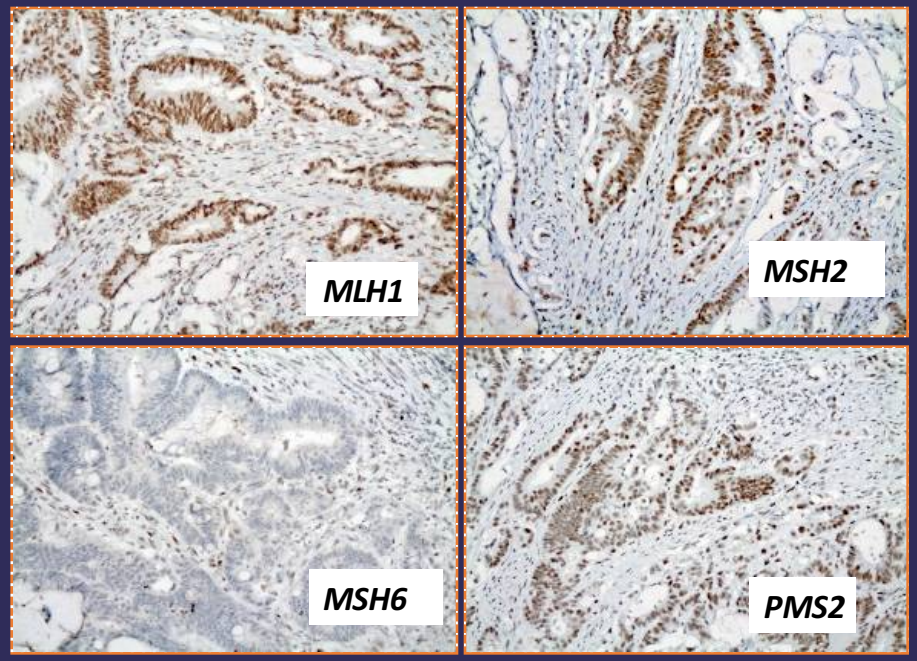
IHC Abnormal: *MSH2* and *MSH6* Absent

- 3% of the time
- CRC is MSI+
- Better prognosis
- Most likely LS due to either *MSH2* or *MSH6* gene mutation
- Always refer to Genetics

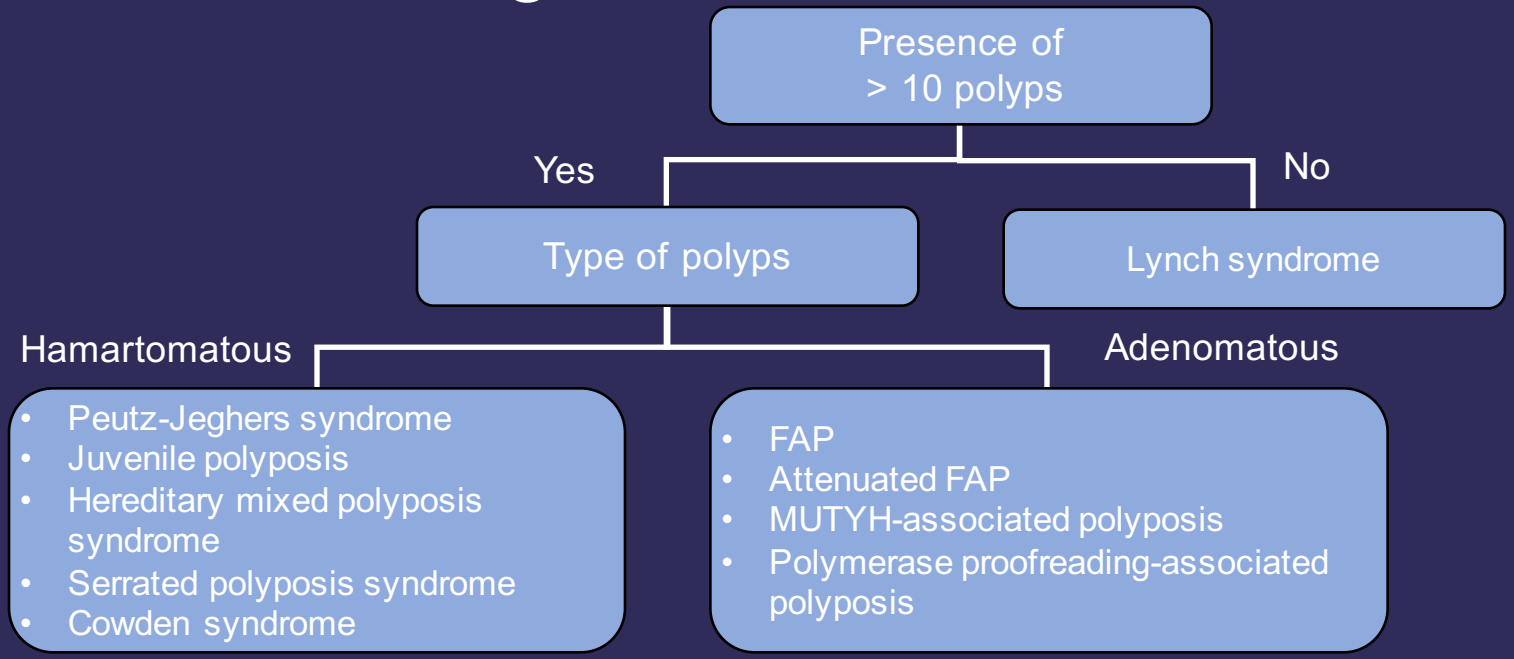


IHC Abnormal: *MSH6* or *PMS2* Absent

- 2% of the time
- CRC is MSI+
- Better prognosis
- Most likely LS due to an *MSH6* or *PMS2* gene mutation
- Always refer to Genetics



Flowchart for Hereditary Colon Cancer Differential Diagnosis



Adenomatous Polyposis Syndromes

- FAP
  - > 100 adenomatous polyps throughout colon
  - Increased risks for colorectal, duodenal, thyroid cancers, medulloblastoma, and hepatoblastoma
  - Gene: *APC* (30% of mutations are de novo)
- AFAP
  - 20-100 adenomas
  - Gene: *APC* (mutations in specific locations lead to milder phenotype)
- MAP
  - 20-100s of adenomatous polyps
  - Overlap with FAP and Lynch syndrome
  - Gene: *MUTYH* (recessive with 1/50 carrier frequency)
- Polymerase proofreading-associated polyposis
  - Increased risk of adenomatous colon polyps, colon cancer, uterine cancer, and possibly other cancers
  - Newer syndrome, still being defined
  - Genes: *POLD1, POLE*

AFAP = attenuated FAP; MAP = MUTYH-associated polyposis.

Hamartomatous Polyposis Syndromes

- Peutz-Jeghers syndrome
  - Peutz-Jeghers polyps primarily in the small intestine but can be throughout GI tract
  - Increased risk for GI cancers and multiple other cancers (breast, SCTAT of the ovaries and testicles, pancreatic)
  - Gene: *STK11*
- Juvenile polyposis syndrome
  - Juvenile polyps throughout GI tract, increased risk for GI cancers
  - > 5 JP is diagnostic criteria
  - Genes: *BMPR1A, SMAD4*
- Serrated polyposis syndrome
  - > 20 serrated/hyperplastic polyps throughout the colon
  - Increased risk for colon cancer
  - Gene: Not known

GI = gastrointestinal; JP = juvenile polyposis; SCTAT = sex cord tumor with annular tubules.

Mixed Polyposis Syndromes

- Hereditary mixed polyposis syndrome
  - Syndrome mostly seen in individuals of Ashkenazi Jewish ancestry
  - Adenomatous, hyperplastic, other type of polyps through GI tract
  - Gene: *SCG5/GREM1*
- Cowden syndrome
  - Multiple different types of polyps – ganglioneuromas especially suspicious
  - Increased risk for breast, thyroid, endometrial, and colon cancers
  - Gene: *PTEN*

Who to Test for Lynch Syndrome (the Right Person)?

- Clinical testing criteria
  - Patients who meet Revised Bethesda criteria or Amsterdam II criteria
  - Patients with endometrial cancer diagnosis < 50
  - Individuals with MMR mutation likelihood > 2.5%-5% on $PREMM_5$ model
  - Individuals with known diagnosis of LS in family
- Routine tumor testing criteria
  - All CRC patients, **OR**
  - CRC patients diagnosed < 70 and CRC patients diagnosed ≥ 70 who meet Revised Bethesda guidelines
  - All EC patients, **OR**
  - EC patients diagnosed < 60; **OR** EC patients who meet Modified Bethesda guidelines

MMR = mismatched repair.

Who to Test for Polyposis (the Right Person)?

- Adenomatous polyposis syndromes
  - Personal history of > 10 adenomas
  - Personal history of a desmoid tumor, CHRPE, hepatoblastoma
  - Known *APC/MUTYH/POLE/POLD1* mutation in family
- Hamartomatous polyposis syndromes
  - Two Peutz-Jeghers polyps
  - Five juvenile polyps
  - Ashkenazi Jewish or macrocephaly plus multiple mixed polyps

- Start testing with affected relative if possible
- If affected relative is deceased, can test at-risk relative but negative result is uninformative
- Can test minors for polyposis syndromes because cancer screening starts in childhood

CHRPE = congenital hypertrophy of the retinal pigment epithelium.

NCCN Guidelines for Colorectal Cancer Screening and Prevention 2014.

What Test Should Be Ordered (the Right Test)?

- Tumor screening tests cost ~$500 each
  - Check pathology reports because this may have already been performed
- Next-generation testing panels now available
  - Include many genes
    - Colon specific gene panels (14-25 genes)
    - Common hereditary gene panels (27-42+ genes)
  - Lower cost due to new technology ($249-$4000)
  - Due to overlap in polyposis syndromes and Lynch syndrome and the need to test more than one gene, this is the best approach to colorectal cancer genetic testing

Early-Onset Colorectal Cancer

- 16% of CRC patients diagnosed < 50 have a cancer susceptibility gene mutation
- 8% have Lynch syndrome
- 5% have other moderate to high-risk CRC genes
- 3% have mutations in genes not traditionally associated with CRC
  - *BRCA1, BRCA2, PALB2, ATM, CHEK2*
- Suggest testing all early-onset CRC patients with a broad cancer gene panel

Pearlman R, et al. *JAMA Oncology* 2017;3(4):464-71.

Cancer Prevention and Treatment in Lynch Syndrome

Important considerations when treating cancers associated with Lynch syndrome and when planning cancer surveillance, surgical prophylaxis, and chemoprevention

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Outline

- Screening, prophylaxis, and chemoprevention in Lynch syndrome
  - Comparison to average risk individuals
  - Controversy and variability
- Important biomarkers in the management of Lynch syndrome and mismatch repair deficient colorectal cancer
  - RAS family of markers
  - Mismatch repair deficiency

Useful Terms

- **Penetrance:** the likelihood of developing cancer if one carries a particular genetic mutation
- **Predictive biomarker:** a genetic marker (e.g., mutation) that predicts response to a particular therapy
- **Prognostic biomarker:** a genetic marker that predicts poorer prognosis/survival from a disease

Managing Colorectal Cancer Risk in LS

- Colonoscopy: start age 20-25, repeat every 1-2 years
  - For families with very early CRC; start 2-5 years before earliest
  - CRC risk is reduced by intensive screening, but not eliminated
- Colectomy is a consideration for select patients with LS
  - Preference not to screen or for definitive risk reduction
  - Multiple (synchronous or metachronous) CRCs
  - Colorectal polyps not amenable to routine polypectomy
  - High-grade dysplasia in multiple, diffuse, or very small polyps
- Contrast: average risk start colonoscopy screening at 50*
  - Those with family history, African American start earlier
  - Every 10 years is the recommended screening interval

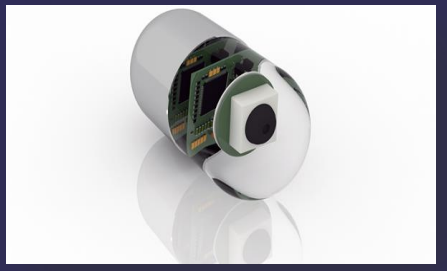
Gene	CA Risk	Age Onset	Screen Start
MLH1	52%-82%	44-61	20-25
MSH2	52%-82%	44-61	20-25
MSH6	10%-22%	54	20-25*
PMS2	15%-20%	61-66	20-25*

Risk Factor	Start (Interval)
African American race	45 (every 5-10 years)
>1 FDR any age	40 (every 5-10 years)
>1 SDR < 50 years	50 (every 5-10 years)
FDR advanced adenoma	40 (every 5-10 years)

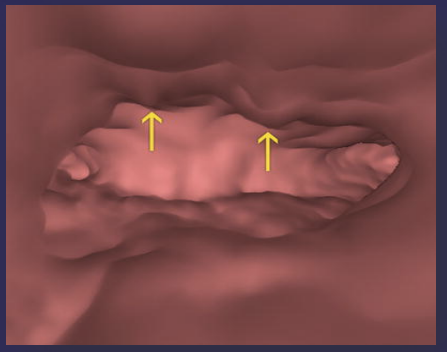
NCCN Guidelines for Colorectal Cancer Screening and Prevention v2.2017; American College of Gastroenterology, Colorectal Cancer Screening, https://gi.org/guideline/colorectal-cancer-screening.

Other Approaches to Colorectal Cancer Screening: Do They Make Sense for LS Patients?

- Modalities for CRC screening
  - Fecal immunochemical testing
  - Virtual endoscopy
  - Capsule endoscopy
  - Stool molecular/DNA testing
- Pros and cons in LS patients
  - Pros: convenience, less invasive, no anesthesia
  - Cons: poorer sensitivity for polyps, especially small polyps; virtual/capsule still need to do a prep; abnormalities still need to be assessed by colonoscopy



Example capsule



Virtual colon

Aspirin as Chemoprevention for CRC

- Numerous studies have demonstrated benefit of aspirin and COX-2 inhibition in adenoma and CRC prevention
  - USPSTF recommends ASA 81 mg for adults age 50-59 for primary CRC prevention (and CV disease prevention)
- CaPP2 study
  - Patients with Lynch syndrome randomized 2x2 factorial to ASA 600 mg/day and resistant starch (or placebo)
  - Early adenoma outcomes = no difference
  - At > 4 year follow-up, those who took ASA for at least 2 years experienced reduction in CRC (IRR 0.37) and non-CRC LS cancers (IRR 0.49)
- Expert groups have awaited follow-up confirmatory studies before endorsing these data (CaPP3)
  - Also concern for toxicities associated with this dose of ASA

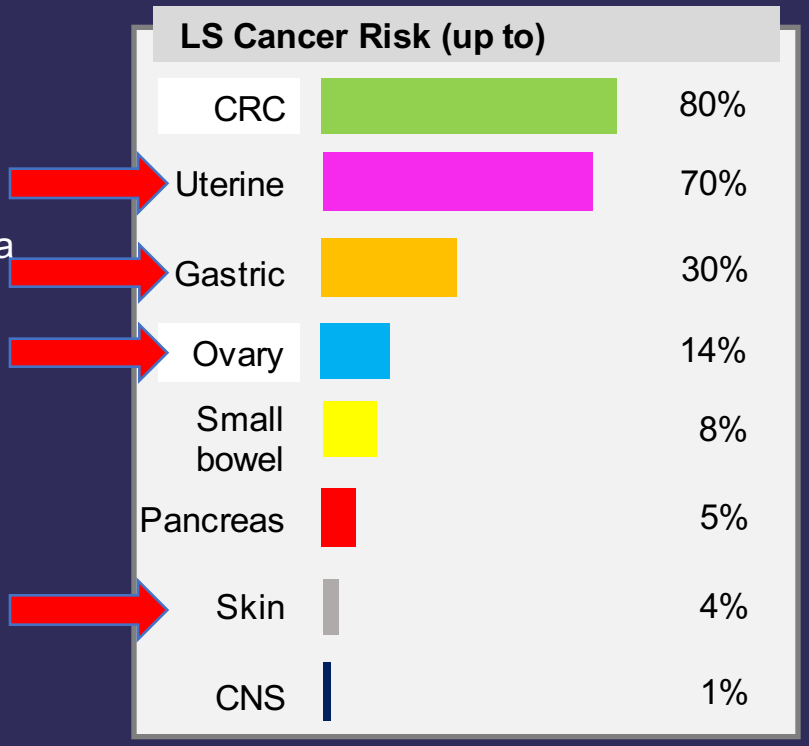
CaPP3
Cancer Prevention Programme

ASA = acetylsalicylic acid; CaPP3 = Colorectal Adenoma/Carcinoma Prevention Program; CV = cardiovascular; IRR = incidence rate ratio; USPSTF = US Preventive Services Task Force.

Baron JA, et al. *N Engl J Med* 2003;348:891-9; Sandler RS, et al. *N Engl J Med* 2003;348:883-90; Cole BF, et al. *J Natl Cancer Inst* 2009;101:256-66; Arber N, et al. *N Engl J Med* 2006;355:885-95; Burn J, et al. *Lancet* 2011;378:2081-7.

Management of Other LS Risks

- Important caveats
  - Variations by expert group/society
  - Nearly all guidelines are based on expert recommendation and not randomized controlled trial data
  - Guidelines are evolving as we learn more about the syndrome and individual genes
- Guidelines are only guidelines—should be integrated with personal/family history and your best clinical judgment



CNS = central nervous system.

NCCN Guidelines for Colorectal Cancer Screening and Prevention v2.2017.

Endometrial and Ovarian Cancer Prevention

- Average risk women: none
  - Women with family history of OC can consider genetic testing and/or prophylactic oophorectomy
- Evolving recommendations in LS
  - NCCN 2017: TAH is a risk-reducing option to lower incidence of EC, but no mortality benefit
  - NCCN 2017: BSO *may reduce* incidence of OC, and new gene-specific risk estimates
- Moller et al. estimate EC and OC risks highest in *MSH2* (56.7% and 16.9% by age 70, respectively)

Endometrial Cancer

- No proven benefit to screening
- Endometrial biopsy every 1-2 years can be considered
- Trans-vaginal ultrasound can be considered in post-menopausal; not recommended in pre-meno; low sensitivity and specificity

Ovarian Cancer

- No effective screening, and data do not support routine LS screening (may be considered by doctor)
- Counsel patients on symptoms
- CA-125: neither sensitive nor specific

BSO = bilateral salpingo-oophorectomy; OC = ovarian cancer; TAH = total abdominal hysterectomy.

NCCN Guidelines Colorectal Cancer Screening and Prevention v2.2017; Moller P, et al. *Gut* 2017. Advance online publication.

Gastric Cancer Risk and Prevention

- Gastric cancer incidence has plummeted in United States
- Gastric cancer risk thought to be lower in US LS population vs. Asian population
  - More favorable gene-environment milieu (diet, *H. pylori*)
- *MLH1* and *MSH2* are the highest risk genes
  - Good prognosis (as gastric cancers go)
- Screening the stomach is complicated by proton pump inhibitor–induced fundic gland polyps
- Fox Chase anecdotes: *MLH1* carrier with a bizarre polypoid mass in gastric fundus; *MSH2* carrier with multiple tiny adenomas with high-grade dysplasia and invasion

Gastric CA screening

- Select individuals with a family history of gastric, duodenal, or small bowel or Asian ancestry
- Upper endoscopy with visualization of duodenum
- Every 3-5 years
- Begin age 30-35
- Test for a treat *H.pylori*

Gastric Cancer Histology in LS

- Lymphoid infiltrate/stroma
- Microsatellite instability
- Intestinal type (not diffuse)
- Older patients
- Lymph node negative
- More TILs = better prognosis

TILs = tumor-infiltrating lymphocytes.

Vasen HF, et al. *Gut* 2013;812-23; Moller P, et al. *Gut* 2017. Advance online publication; Hu B, et al. *J Gastrointest Oncol* 2012;3:251-61.

Skin Screening in Lynch Syndrome

- Around one-third of LS families are Muir-Torre variant LS
  - ~10% individual patients
  - Muir-Torre occurs with any gene; *MSH2* most common
- Sebaceous neoplasms are most common
  - Adenomas, epitheliomas, carcinomas
  - Also kerato-acanthomas
- Important to detect these early, as excision can lead to scars and large skin defects
  - Fox Chase Cancer Center anecdote: 37-year-old man with sebaceous adenomas on the forehead and in the groin area

Skin Screening

- In known Muir-Torre families, recommend skin screening yearly with a dermatologist
- New diagnoses of LS with a personal or family history of skin findings; dermatologic consult
- Recommend skin exams by PCP in all others

PCP = primary care physician.

South CD, et al. *J Natl Clin Inst* 2008;100:277-81.

The Impact of Lynch Syndrome and Mismatch Repair on the Treatment of Colorectal Cancer

The Treatment of CRC and the Growing Importance of MMR Deficiency

- Two primary molecular pathways in CRC
  - APC/WNT pathway (85%)
  - Mismatch repair pathway (15%)
- Mismatch repair pathway further divided into:
  - LS-associated MMR (germ-line risk)
  - Somatic MMR (non-hereditary)
- Several biomarkers (RAS family) are predictive and prognostic in the treatment of CRC
- Tumor sidedness (left vs. right) may also be important

CRC Biomarkers
- RAS FAMILY
- *KRAS* mutations
- *NRAS* mutations
- *BRAF* mutations

dMMR
- TILs
- Tumor mutational burden

dMMR = MMR deficiency.

Carethers JM, et al. *Gastroenterology* 2015;149:1177-90 Tejpar S, et al. *JAMA Oncol* 2016. Advanced online publication.

RAS Family of Predictive and Prognostic Biomarkers in CRC

- *KRAS* first marker driving clinical decisions
  - ~40% CRC have exon 2 mutations (codons 12 and 13)
- *NRAS* added to guidelines in 2015 (~2%-3% CRC)
  - Non-exon 2 *KRAS* and *NRAS* found in ~10% of exon 2 wild type
  - *EGFR* inhibitors in *KRAS/NRAS* mutant tumors = DETRIMENTAL
  - Prognosis of *KRAS/NRAS* mutations not established
- *BRAF* mutants
  - 5%-9% CRC have a *BRAF* V600E mutation
  - Strongly prognostic (poor, ~50% reduced overall survival)
  - NCCN guidelines 2017: evidence suggests this is also a negative predictive marker for *EGFR*-targeted therapy
  - Non-V600E *BRAF* tumors may have favorable prognosis

RAS FAMILY

Mutant gene	Prognostic	Predictive
KRAS		
Exon 2	+/-	++++
Exons 3 and 4	+/-	++
NRAS		
Exons 2-4	-	++
BRAF		
V600E	++++ (neg)	+/-
Non-V600E	+ (pos)	-

***EGFR*-Directed Therapy**

Cetuximab
- Mouse-derived antibody
- Weekly therapy

Panitumumab
- Humanized antibody
- Bimonthly therapy

EGFR = epidermal growth factor receptor.

NCCN Guidelines for Colorectal Cancer Screening and Prevention v2.2017 (MS 40-45); Jones JC, et al. *J Clin Oncol* 2017;35:2624-30; Cercek A, et al. *Clin Cancer Res* 2017;23:4753-60.

RAS Mutations: Predictors of Benefit From Anti-*EGFR* Inhibitors

- Numerous studies have shown that the absence of mutations in *KRAS*, *NRAS*, and *BRAF* predicts response to cetuximab or panitumumab
  - Correlation is not 100%
  - Speculation that certain *KRAS* mutants *may* respond
  - Non-*BRAF* V600E *may* have better prognosis
- ASCO and NCCN recommend RAS testing of all metastatic CRC and recommend against treating RAS mutant cancers with *EGFR* inhibition
- Analyses suggest descending colorectal RAS wild-type tumors may be most responsive to *EGFR* inhibitors

CALGB 80405

- Left-sided tumors had longer survival than right-sided (33 vs. 19 months)

ACCENT Database

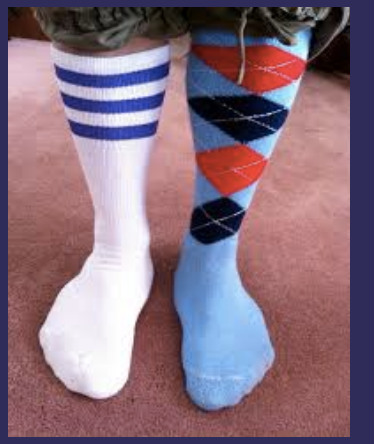
- Significant benefit of chemotherapy plus anti-*EGFR* for left-side tumors (HR 0.75 for survival) but not right-side tumors (HR 1.12)
- Same relationship seen with PFS and RR

ASCO = American Society of Clinical Oncology; HR = hazard ratio; PFS = progression-free survival; RR = response rate.

Bokeneyer C, et al. *Eur J Cancer* 2015;51:1243-52; Venook A, et al. *J Clin Oncol* 2016;32 (suppl; abstr LBA3); Arnold D, et al. *Ann Oncol* 2017;28:1713-29.

Mismatch Repair in Colorectal Tumors

- Two broad categories of deficient MMR
  - Germline + somatic MMR gene mutations (aka LS)
  - Somatic + somatic MMR gene mutations
    - *MLH1* promoter methylation, somatic mutation + LOH, double somatic mutants (and secondary somatic mutations from upstream non-MMR gene mutations such as *POLE, POLD1*, or *MUTYH*)
- All of these are targetable with anti-PD-1/anti-PD-L1 immunotherapies



Frequency of Cause of Tumor dMMR in CRC

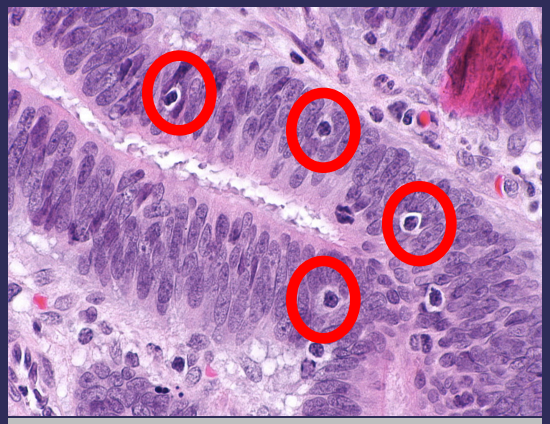
- Germline + somatic: ~3%
- *MLH1* methylation: ~8%-10%
- Somatic + LOH: ~2%
- Double somatic: ~2%
- Secondary somatic: < 1%

LOH = loss of heterozygosity; PD-1 = programmed death 1; PD-L1 = programmed death ligand 1.

Okugawa Y, et al. *Gastroenterology* 2015;149;1204-25; Carethers JM, et al. *World J Gastroenterol* 2015;21:9253-61.

Why Are MMR-Deficient Tumors Responsive to Immunotherapies?

- MMR-deficient tumors are more immunogenic than other CRCs
  - More TILs
  - Higher mutational burden
  - Greater production of protein products that are truncated or incorrectly coded; therefore seen as foreign to the body (frameshift proteins)
- Studies have shown association of mutational burden, MSI, and TILs to immunotherapy response



Tumor infiltrating lymphocytes

Okugawa Y, et al. *Gastroenterology* 2015;149;1204-25; Carethers JM, et al. *World J Gastroenterol* 2015;21:9253-61; Goyal G, et al. *Fam Cancer* 2016;15:359-66; Wesstdorp H, et al. *Cancer Immunol Immunother* 2016;65:1249-59

MMR Deficiency Predicts Response to Anti-PD-1 and PD-L1 Immunotherapy

- Le DT et al NEJM 2015
- Responses in non-CRC MMR-deficient GI cancers also reported (GI ASCO 2016)
  - Complete responses in gastric, ampullary, and cholangiocarcinoma
- FDA has recently approved pembrolizumab for MMR deficient solid tumors

Objective responses by RECIST Criteria

Response	MMR deficient CRC N=10	MMR proficient CRC N=18	MMR deficient non-CRC* N=7
CR	0	0	1 (14)
PR	4 (40)	0	4 (57)
SD	5 (50)	2 (11)	0
PD/NE	1 (10)	15 (89)	2 (29)
OR	40 (12-47)	0	71 (29-96)
DCR	90 (55-100)	11 (1-35)	71 (29-96)

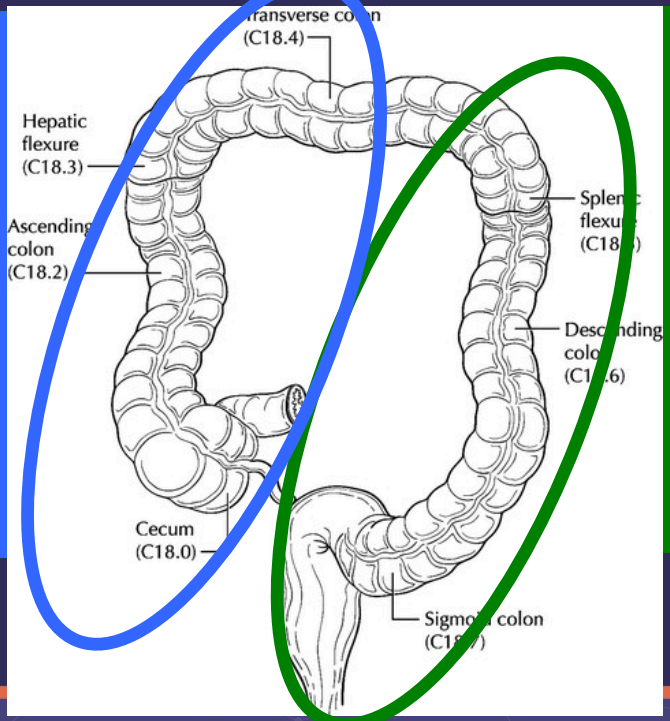
FDA = US Food and Drug Administration.

Le DT, et al. *N Engl J Med* 2015;372:2509-20; Le DT, et al. *J Clin Oncol* 34 (suppl; abstr 195).

CRC Is Like Real Estate: Location, Location, Location

Ascending Colon

- Cecum, right, transverse
- Present with anemia
- More often MMR deficient
- More often *BRAF* (10%-15%) and *KRAS* (50%-60%) mutant
- Less chemo responsive
- Poorer survival



Descending Colon

- Descending, sigmoid, rectum
- Present with obstruction/bleeding
- Increasing in young adults
- Chromosomal changes (18q, 20q, 22q)
- HER2 upregulation
- More often NRAS mutant (especially African Americans)
- More chemo responsive, in particular to anti-*EGFR* therapy

Carlson R. *Oncology Times* 2016;38:37.

Thank you for your attention and interest!

2017 JADPRO live AT APSHO