ASCP 2020

VIRTUAL

SEPTEMBER 9-11, 2020

DMT129-20 GIPS: Sizzling Updates in the GI Tract: The New WHO and Beyond

The Rodger C. Haggitt GI Pathology Society

Dr. Wendy Frankel, OSU, Update on Hereditary Tumor Syndromes involving the Colorectum

Dr. Christopher Hartley, Mayo Clinic, Update on Pancreas

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Update on Hereditary Tumor Syndromes Involving the Colorectum

Wendy L. Frankel, MD

The Ohio State Wexner Medical Center

www.ascp.org/2020

Disclosures

Wendy L Frankel MD has nothing to disclose

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Objectives

1. To know select updates in Genetic Syndromes in the GI Tract, WHO 2019 and NCCN Guideline- Genetic/Familial High Risk Assessment: Colorectal, 2020
2. To be aware of new genetic, diagnostic and treatment information in Lynch syndrome and Serrated polyposis syndrome

Hereditary Tumor Syndromes Involving Colon WHO 2019

- Syndromes better defined not only by clinicopathological criteria but by new genetic information
- Adenomatous polyposis can be seen in newer polyposis defined by specific genetic aberrations
- Lynch syndrome risk stratified by gene & clinical features
- Lynch-like syndrome described
- New diagnostic criteria Serrated polyposis syndrome

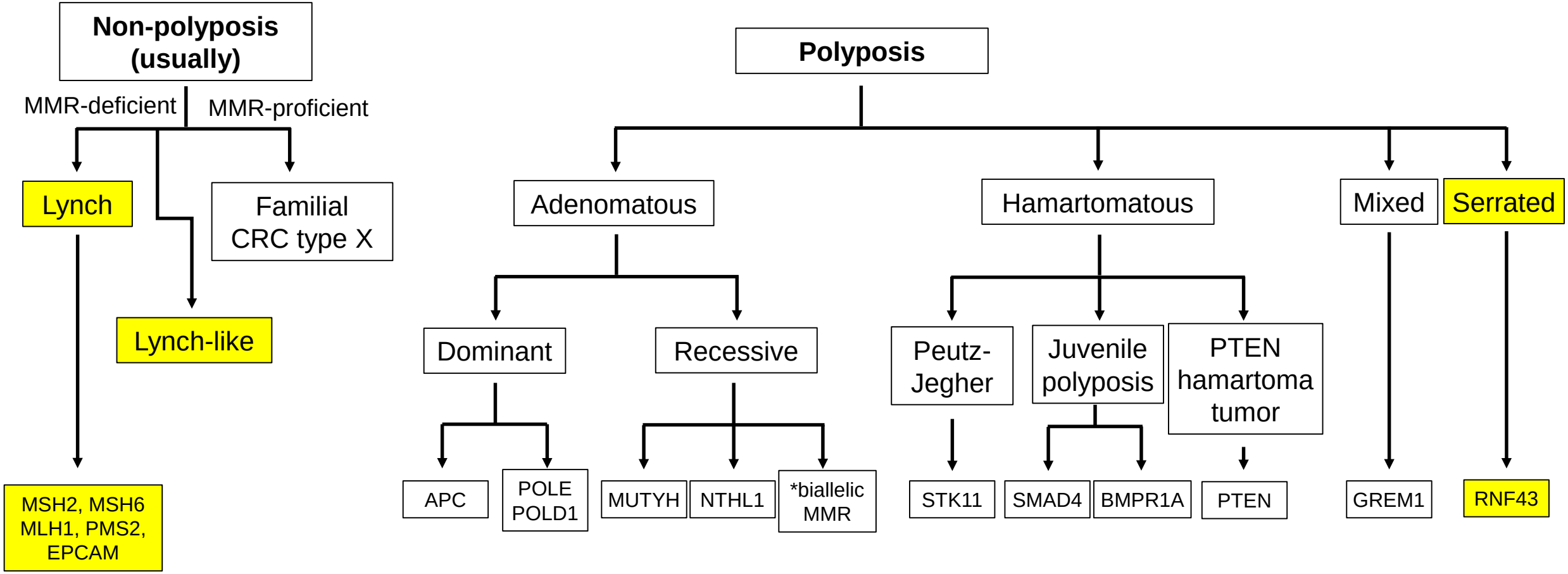
Genetic Tumor Syndromes of the GI Tract, World Health Organization, 2019

Hereditary Tumor Syndromes Involving Colon NCCN Guidelines, July 2020

- Recommendation- all with personal history of tumor with MMRd diagnosed any age, regardless of site, have evaluation to exclude Lynch syndrome
- Recommendation- consider tumor screening for MMRd for patients with variety of tumors (in addition to CRC and endometrial); small bowel, gastric, pancreas, biliary tract, brain, bladder, urothelial, and adrenocortical cancers, and sebaceous neoplasms, regardless of age at diagnosis
- To aid in risk and management, lifetime cancer risks and surveillance recommendation are presented by specific Lynch syndrome associated gene impacted (e.g. *MLH1*)

NCCN Guidelines Version 1.2020 Genetic/Familial High Risk Assessment: Colorectum, July 2020

Hereditary CRC and Polyposis Syndromes

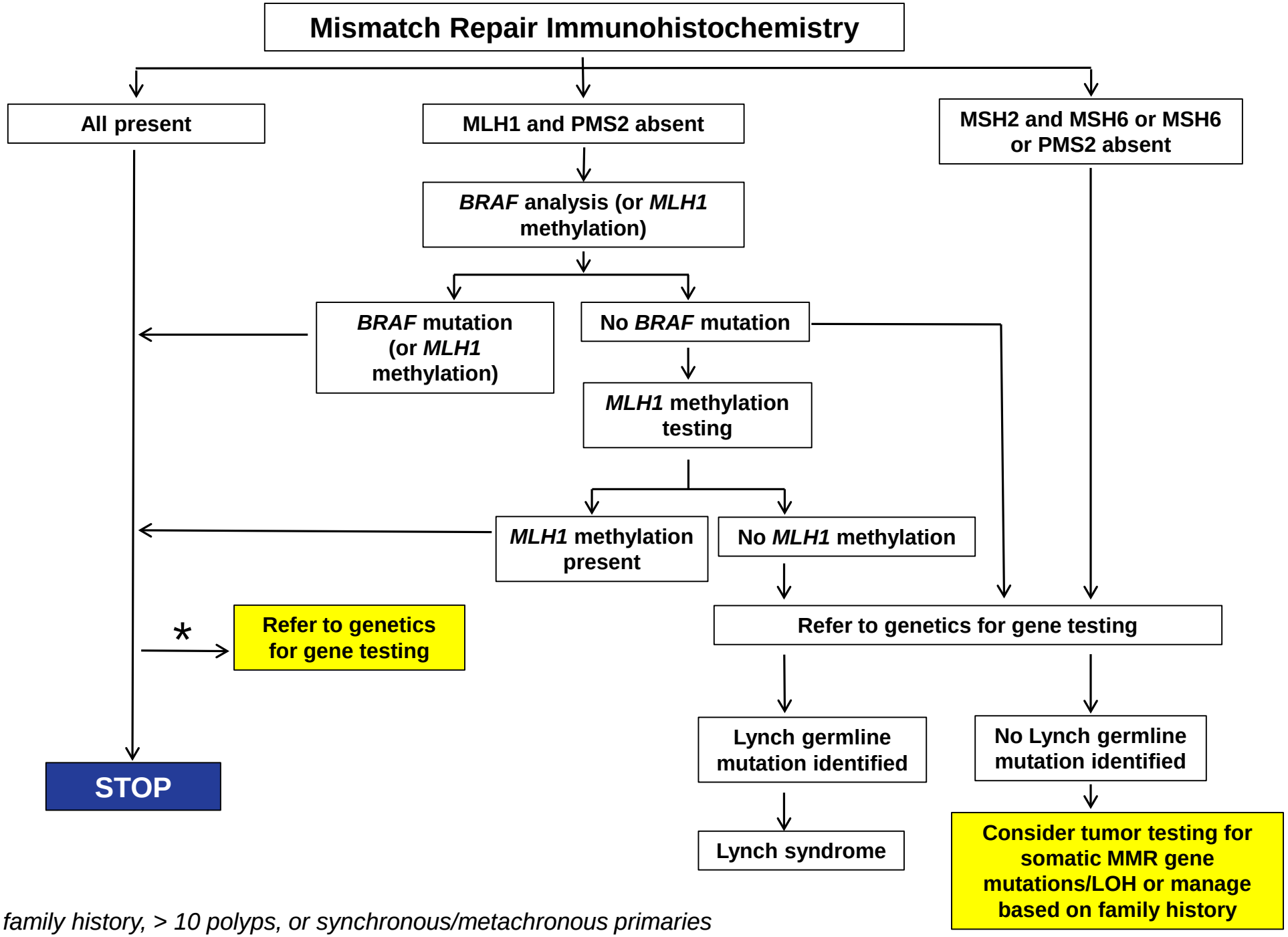


Valle, L. Clin Gastroenterol and Hepatol, 2017

Lynch Syndrome

- Most common hereditary CRC syndrome
- 3-4% of CRCs, 1 in 25 unselected CRC patients
- Autosomal dominant, penetrance up to 80%
- Early, variable age at CRC diagnosis
- Susceptibility to CRC & extracolonic cancers
- Germline mutation in genes belonging to DNA MMR family- *MLH1, MSH2, MSH6, PMS2, EPCAM*
- Mutations lead to defective DNA repair & MSI

Hampel, NEJM 2005; Lynch, Nature Reviews 2015; Pai, Am J Surg Pathol 2016



*If < 50y, strong family history, > 10 polyps, or synchronous/metachronous primaries

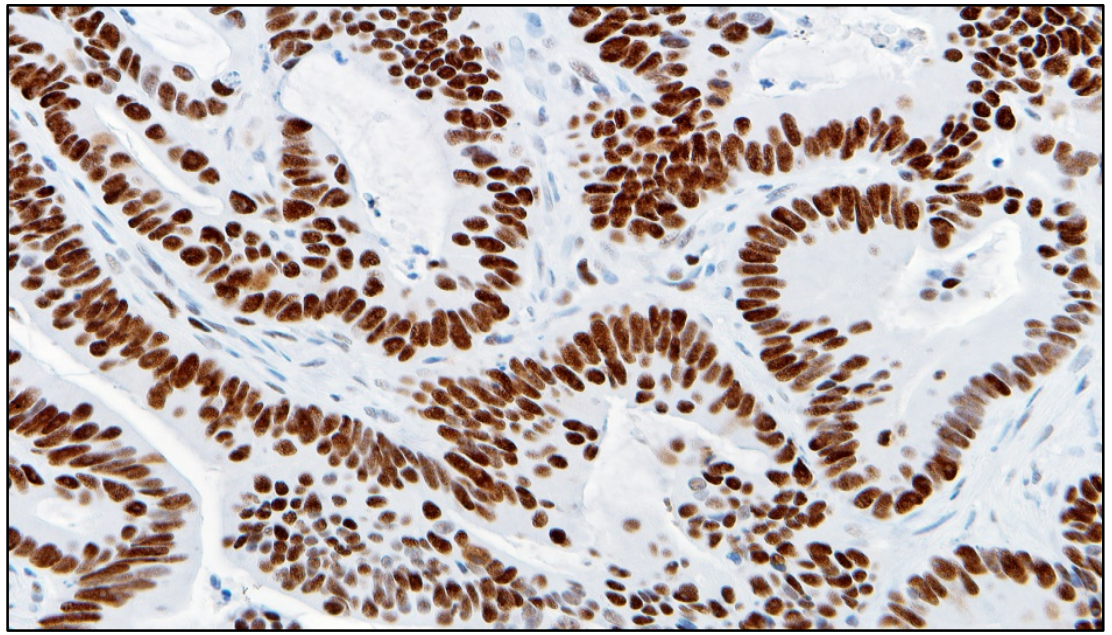
IHC MMRP- Interpretation and Reporting

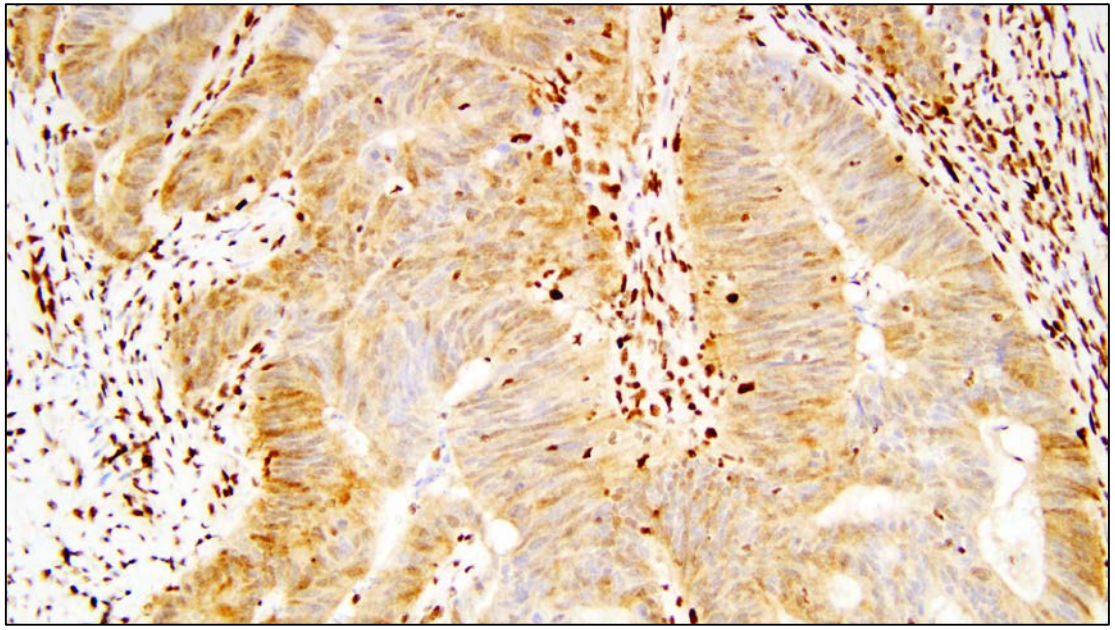
- Report as present/intact or absent/lost not + or -
- Cutoff- any convincing nuclear staining
  - 1%
  - 5% (we use this)
  - 10%
  - Must be as strong as control

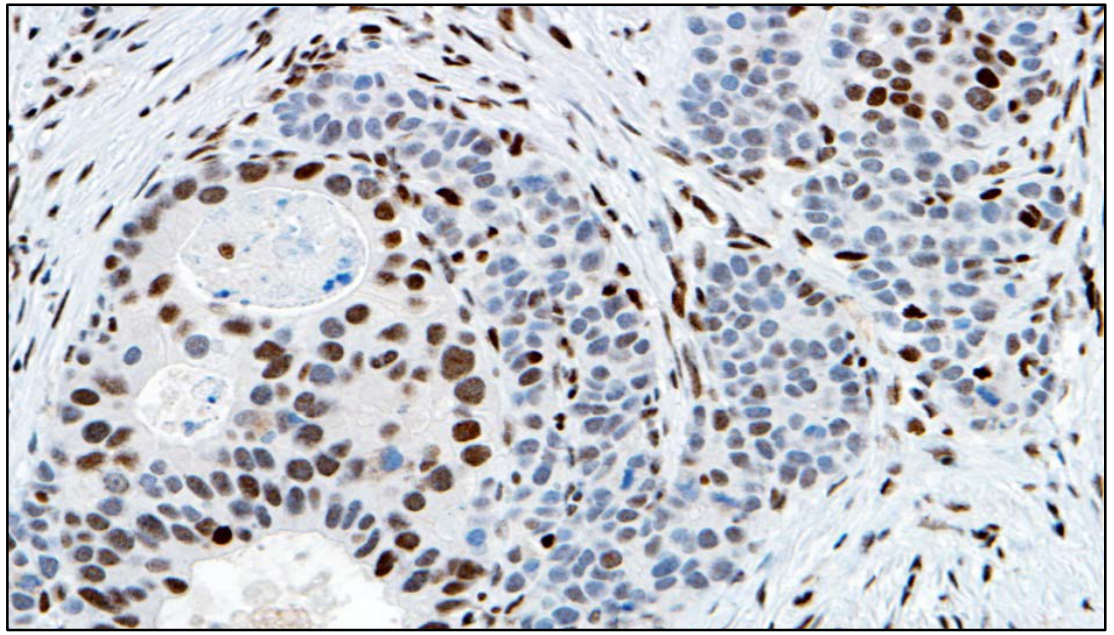
Shia, Am J Surg Pathol 2011; Bartley, CAP Colon Rectum Biomarker Protocol, Arch Pathol Lab Med 2014; Pai, Am J Surg Pathol 2016; Chen, Mod Pathol 2018

IHC MMRP Interpretation

- Strong, diffuse nuclear
- Variability
- Cytoplasmic staining
- Tissue and fixation

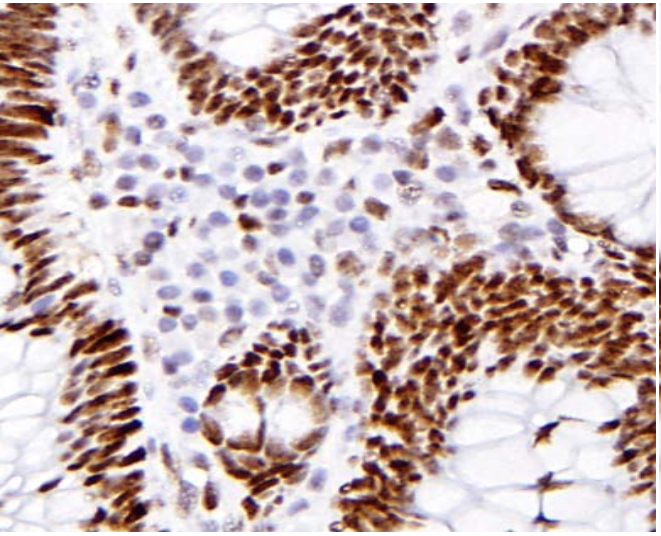
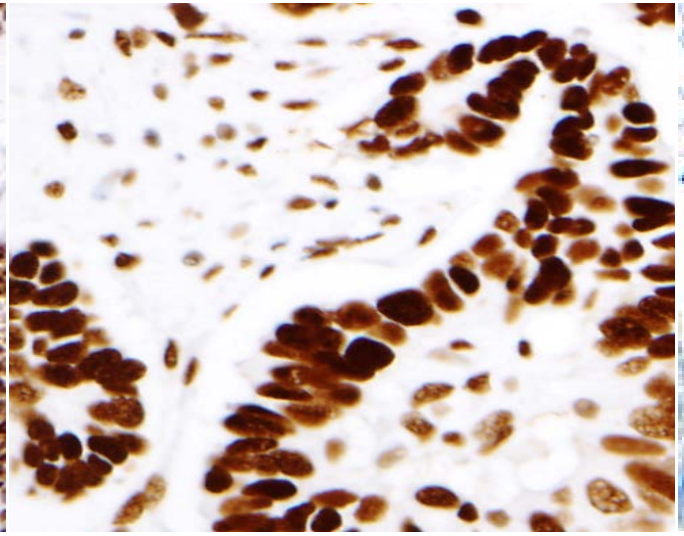
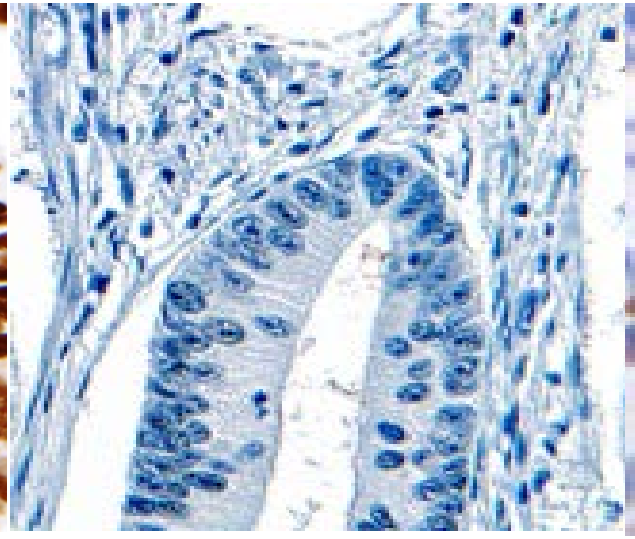
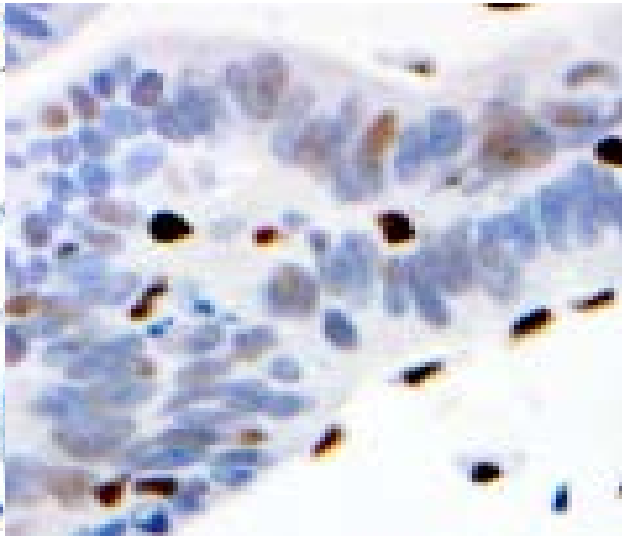






Control is the Key

- Tumor should stain as strong or stronger than control
- If control is negative, cannot call tumor absent
- If tumor staining is weaker than control, caution

Problems in Interpretation

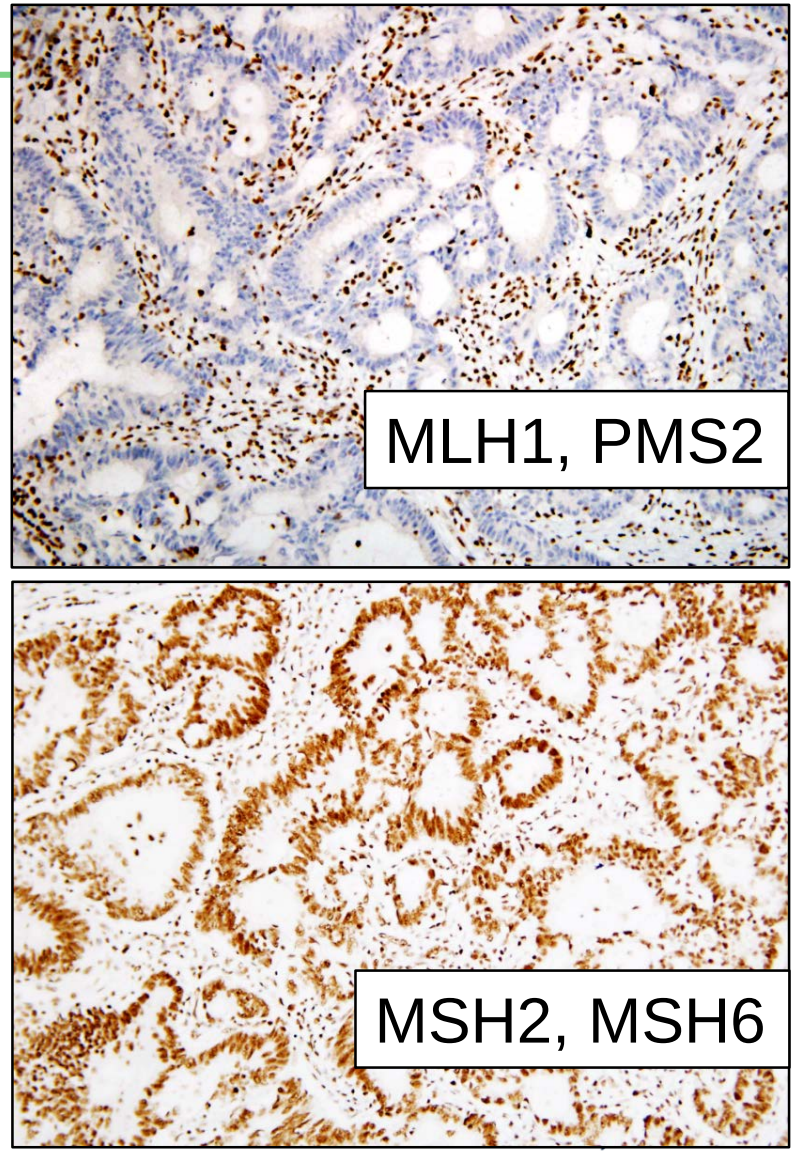
- MMRP present but 40y, family hx, suspicious features
  - If MSI+ and MMR gene mutation found
    - Possibly protein present but not functional (missense)

- MMRP lost, MMR gene mutation or methylation not found
  - “Lynch-like”

Haroldsdottir, Gastroenterol 2014; Hechtman, Mod Pathol 2020; Chen, Hum Pathol, In press

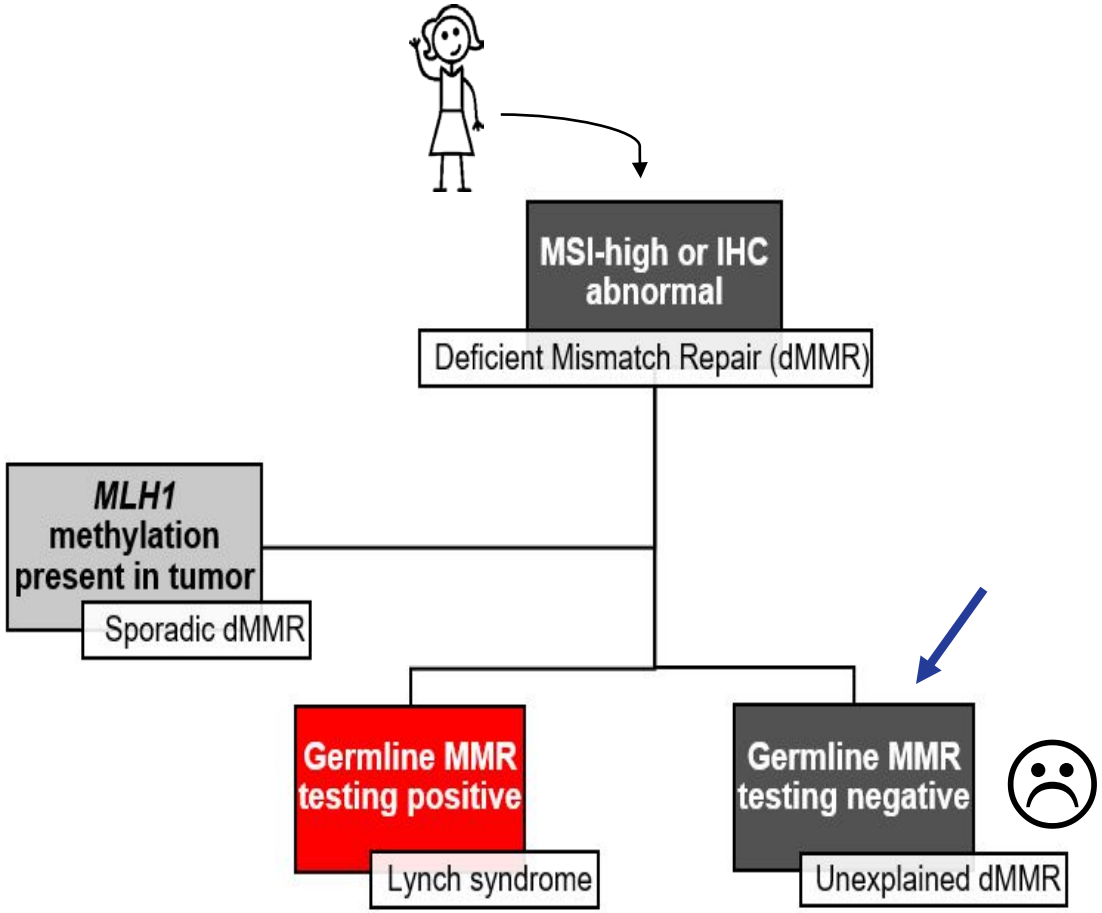
“Lynch-Like”- Unexplained MMRd

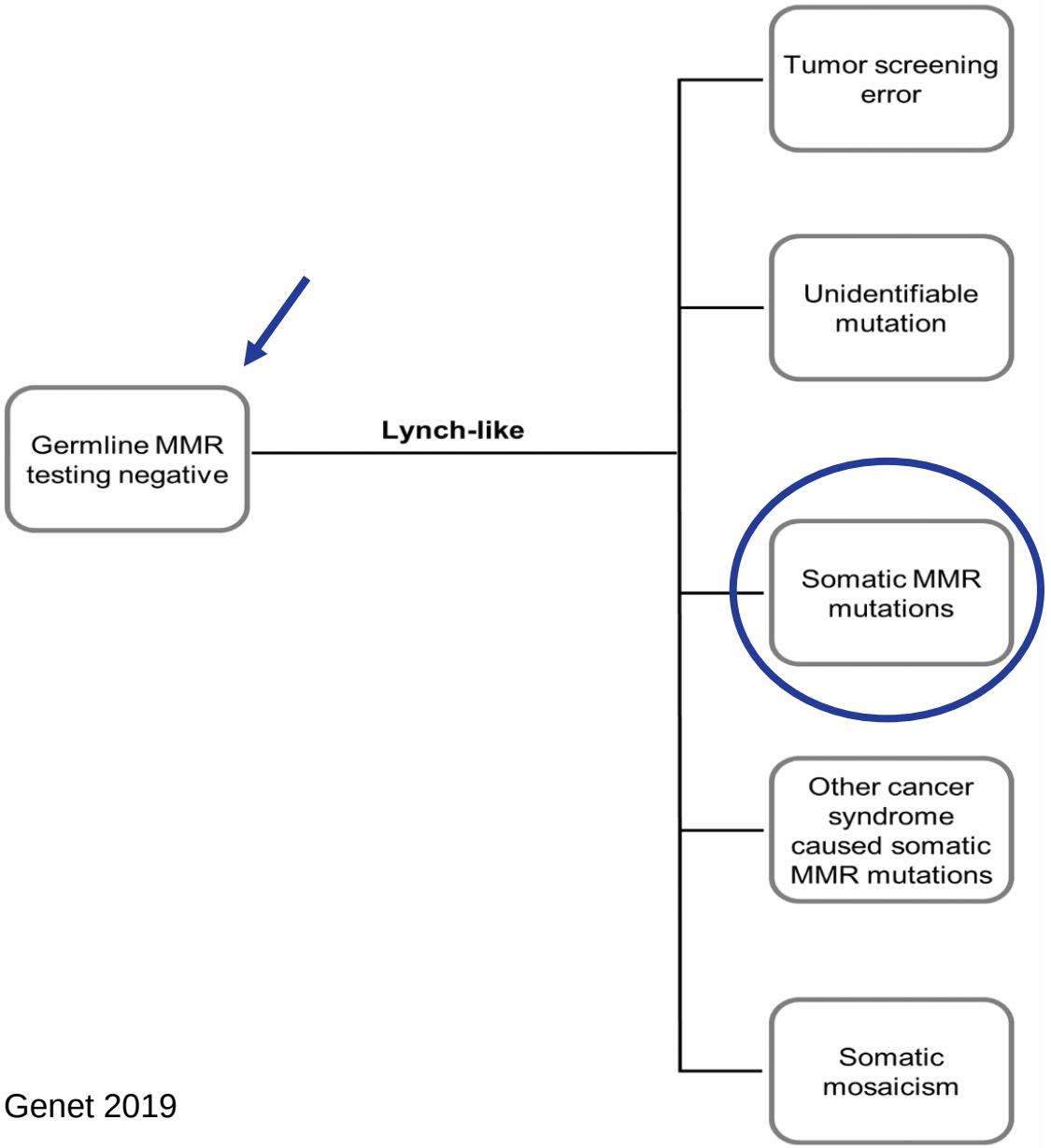
- IHC suggests MMRd
- No *BRAF*, *MLH1* methylation or germline mutation
- “Lynch-like”- waste basket term
- Must test tumor
- Double somatic most common
  - DS & LS patients similar age & histology
  - LS patients more often other LS-associated tumors



Haroldsdottir, Gastroenterol 2014; Hemminger, Hum Pathol 2018; Pearlman, J Med Genet 2019

Lynch-Like Syndrome





Haroldsdottir, Gastroenterol 2014; Hemminger, Hum Pathol 2018; Pearlman, J Med Genet 2019

Somatic MMR Mutation

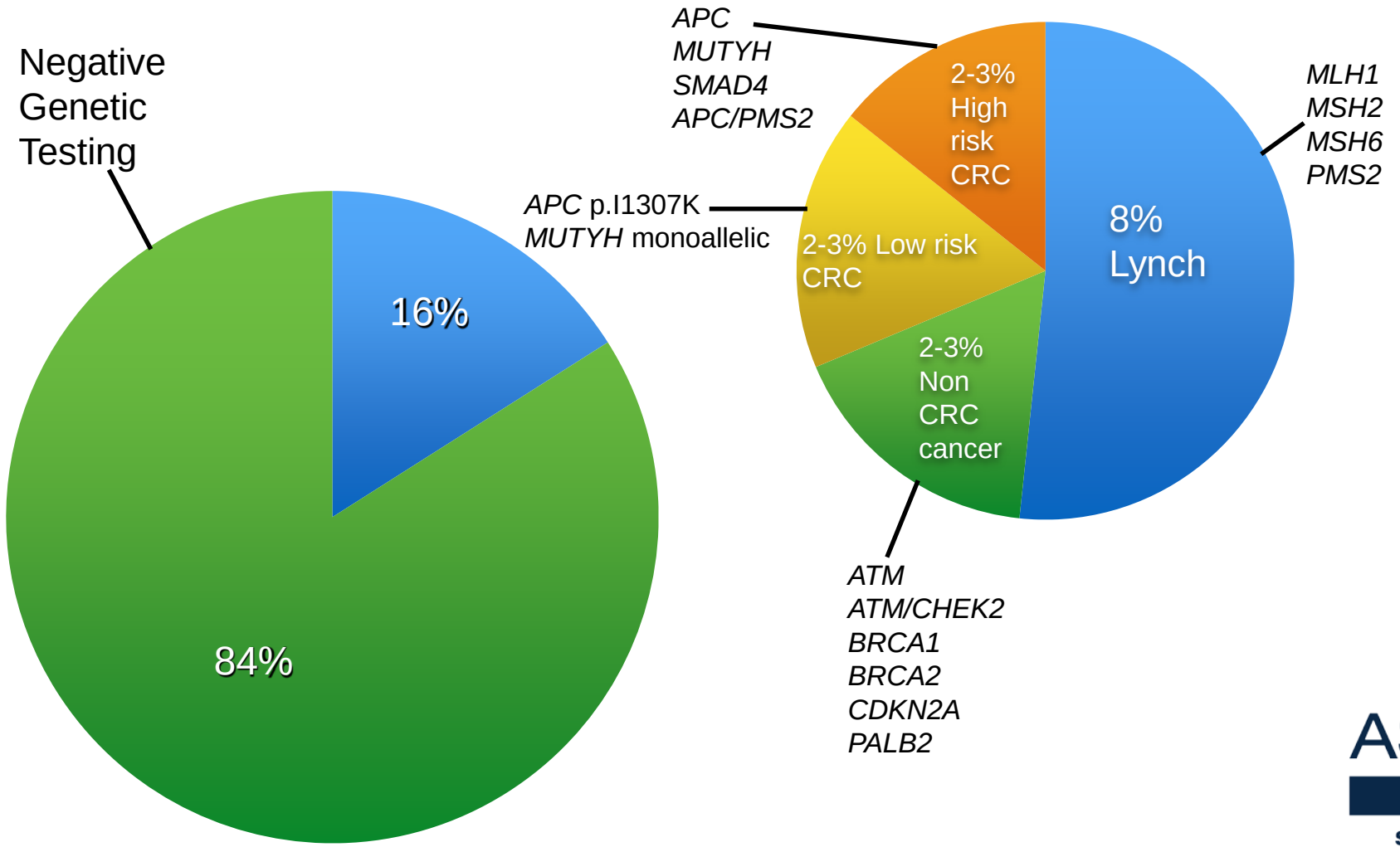
- The cancer is considered sporadic rather than hereditary
- Likely not Lynch and not increased risk for additional cancers
- Recommend standard treatment and follow-up (colonoscopy at 1y, then if unremarkable 3y, then every 5y)
- Risk CRC in family estimated by age diagnosis; if early, then
  - First-degree relatives 3.3x risk of CRC or 16.5% lifetime risk
  - Colonoscopy every 5y beginning at 17y (or 10y before earliest diagnosis in immediate family)

Lynch Syndrome in Young Patients

- 450 Ohio Colorectal Cancer Prevention Initiative < 50y with CRC
- 72 (16%) had at least 1 clinically actionable mutation
  - 8% Lynch syndrome
  - 7.6% other syndrome (including 6 with BRCA1/2!)
  - 0.4% 2 syndromes (PMS2 and APC mutation)
- If only targeted-testing done, 17 (31%) missed
- All early-onset CRC patients should be referred for genetic testing with a comprehensive hereditary cancer gene panel

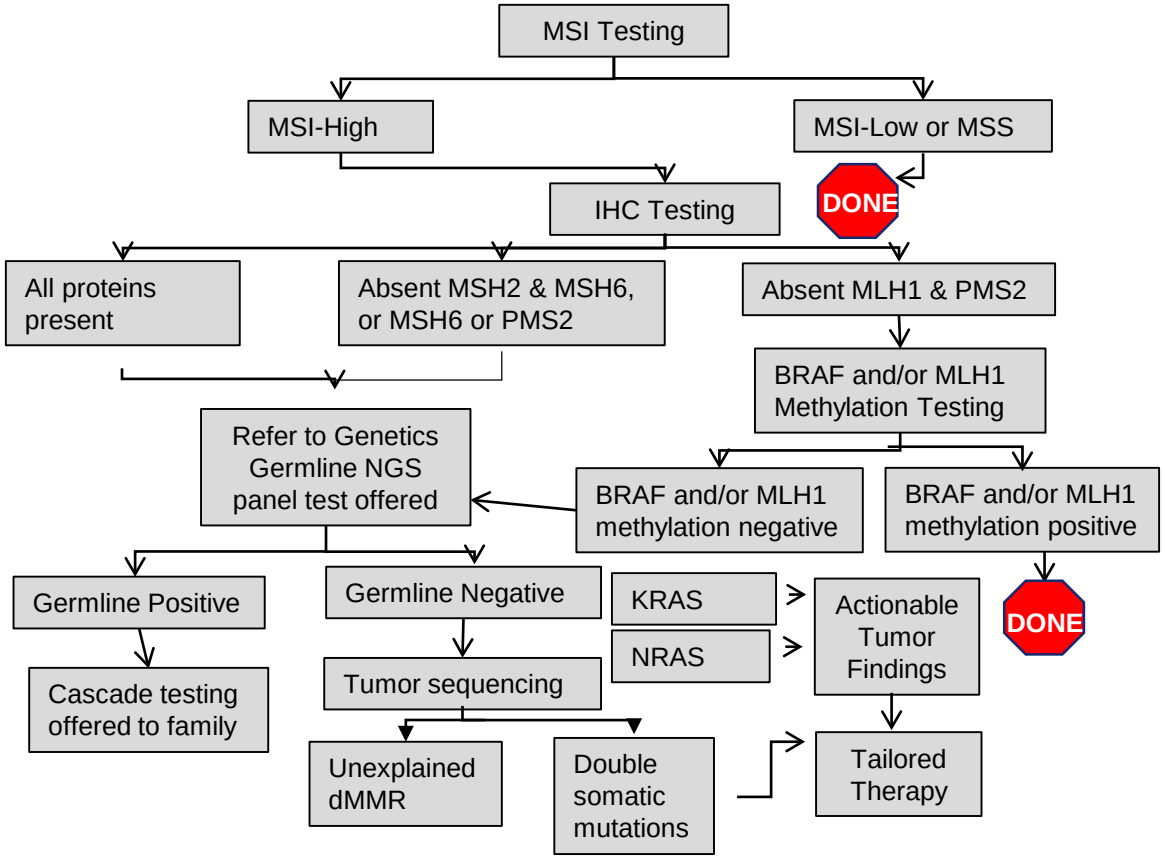
Pearlman, JAMA Oncol 2016

Early Onset Colorectal Cancer and Likelihood of Positive Genetic Testing

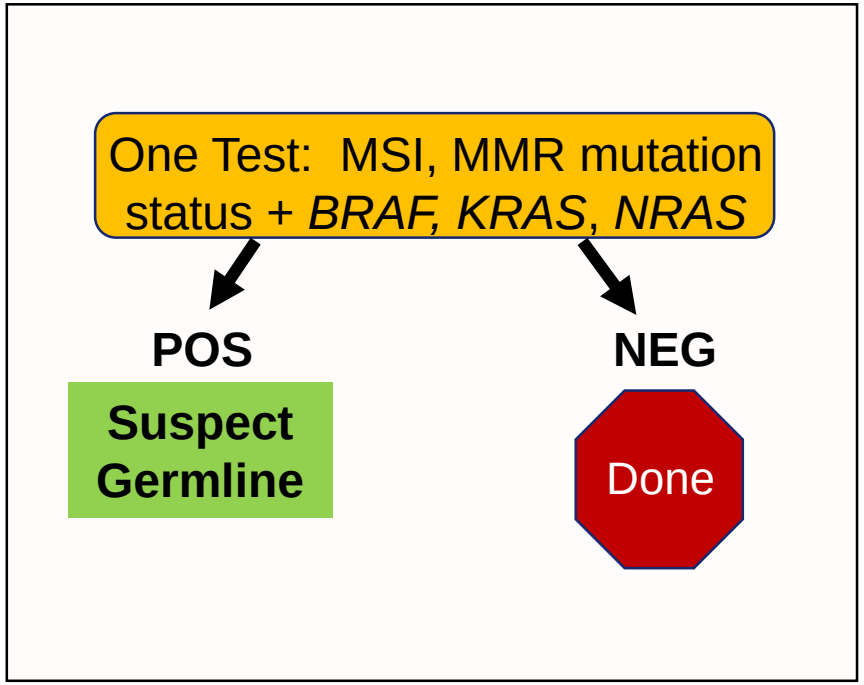


Tumor Sequencing as First-Line Lynch Screening Simplifies Testing

TRADITIONAL SCREENING



TUMOR NGS SCREENING



Hampel, JAMA Oncol 2018

Tumor Sequencing Upfront

- Targeted tumor sequencing first
  - Detect *KRAS*, *NRAS*, *BRAF* mutations used to treat stage IV CRC
  - Can detect MSI status by NGS profiling of multiple microsatellites
  - Test 4 MMR genes
- Allele fraction of mutations can tell if likely germline or somatic
  - Germline mutations have an allele fraction of ~50%
  - Somatic mutations may have allele fraction significantly less than 50% (depending on tumor %)
- Would only need to order single mutation analysis to rule out or suspect a germline mutation

Tumor Sequencing as First-Line Lynch Screening Performs Better Than Traditional Screening

465 Patients

	Tumor NGS	MSI + BRAF	IHC + BRAF
Sensitivity	100% (94-100)	91% (81-97)	90% (79-96)
Specificity	95% (93-97)	95% (92-97)	95% (92-97)
PPV	40% (30-51)	34% (25-45)	33% (24-44)
NPV	>99% (99-100)	>99% (98-100)	>99% (98-100)
Lynch Cases Missed	**0 missed**	**5 missed**	**6 missed**

PPV= positive predictive value; NPV= negative predictive value (95% confidence intervals)

Hampel, JAMA Onc, 2018

Past Concerns for Testing

- Is IHC genetic testing- do we need consent/can we reflex?
- Are biopsies as good as resections?
- Should primary or metastatic tumors be tested?
- Should multiple tumors be tested?
- How can we save money?
  - IHC for MLH1/MSH2; most common mutations
  - IHC for MSH6/PMS2; taking advantage heterodimer partners
- What is better IHC or MSI by PCR; what about NGS?

What We Learned

- IHC is not genetic test (protein), many abnormals are somatic
- Reflex to *BRAF* or Methylation can save costs and anxiety
  - Methylation picks up more cases (68% methylated are *BRAF* mutated)
- Biopsies work as well as resections
  - May impact operation performed
  - Education essential for follow-up
- Metastases work as well as primaries
- If greater than 1 tumor, screen all if initial is MSS

Shia, Am J Surg Pathol 2011; Jin, Am J Clin Pathol 2013; Haroldsdottir Fam Cancer 2016; Roth, Am J Clin Pathol 2016

What We Learned

- 2 stain rather than 4 is not worthwhile
  - We will miss cases
- IHC and MSI by PCR similar rates of detection LS
- Double somatic is common cause of Lynch-like
  - Tumor testing essential if unexplained MMRd
- NGS of tumors can be used to screen for Lynch, should it?

Haroldsdottir, Gastroenterol 2014; Pearlman, JAMA Oncol 2016; Pearlman, Mod Pathol 2018; Hampel, JAMA Oncol 2018

Lynch Syndrome Surveillance Guidelines (Varies by Gene)

- **Colon:** Colonoscopy every 1-2y starting at 20-25y (30-35 with *MSH6/PMS2*), consider aspirin regimen
- **Endometrium/Ovary:** Consider prophylactic TAH/BSO after childbearing. Consider yearly endometrial biopsy, transvaginal ultrasound, CA-125 (*PMS2* risk lower)
- **Gastric/small bowel:** If +FHx or Asian ancestry, EGD with duodenscopy every 3-5y starting at 40y
- **Urothelial:** If FHx or *MSH2* yearly urinalysis starting at 30-35y

Lindor, JAMA 2006; Vasen, J Med Genet 2007; NCCN Guidelines Version 1.2020 Genetic/Familial High Risk Assessment: Colorectum, July 2020

LS: Take Home Message

1. Tumor screening should be considered for MMRd in several cancers (in addition to CRC and endometrial)
2. Patients with MMRd tumors (any site or age) should be worked up for Lynch; cancer risk differs by gene
3. Tumor somatic testing helpful for unexplained MMRd
4. Broad NGS panel should be used for all early onset CRC

Serrated Polyposis (SPS)

- First described 1977
- Old term hyperplastic polyposis syndrome
- Age range 50 to 60y but wide range; men = women
- Increased risk CRC; no extracolonic manifestations
- Individuals develop CRC on background of multiple colon polyps, most serrated polyps; adenomas can be found
- Environmental factors- cigarettes & high body mass index

Spjut and Estrada, Pathol Annu, 1977; Rosty, Genetic Tumor Syndromes of the GI Tract, World Health Organization, 2019

Serrated Polyposis Pathogenesis and Molecular Pathology

- Pathogenesis largely unknown
- Germline variants *RNF43* and biallelic variants of *MUTYH* identified in rare patients
- Serrated polyposis can be component of *MUTYH*-associated polyposis or hereditary mixed polyposis (*GREM1*)
- Half CRC arise via serrated pathway others likely through conventional adenoma-carcinoma pathway

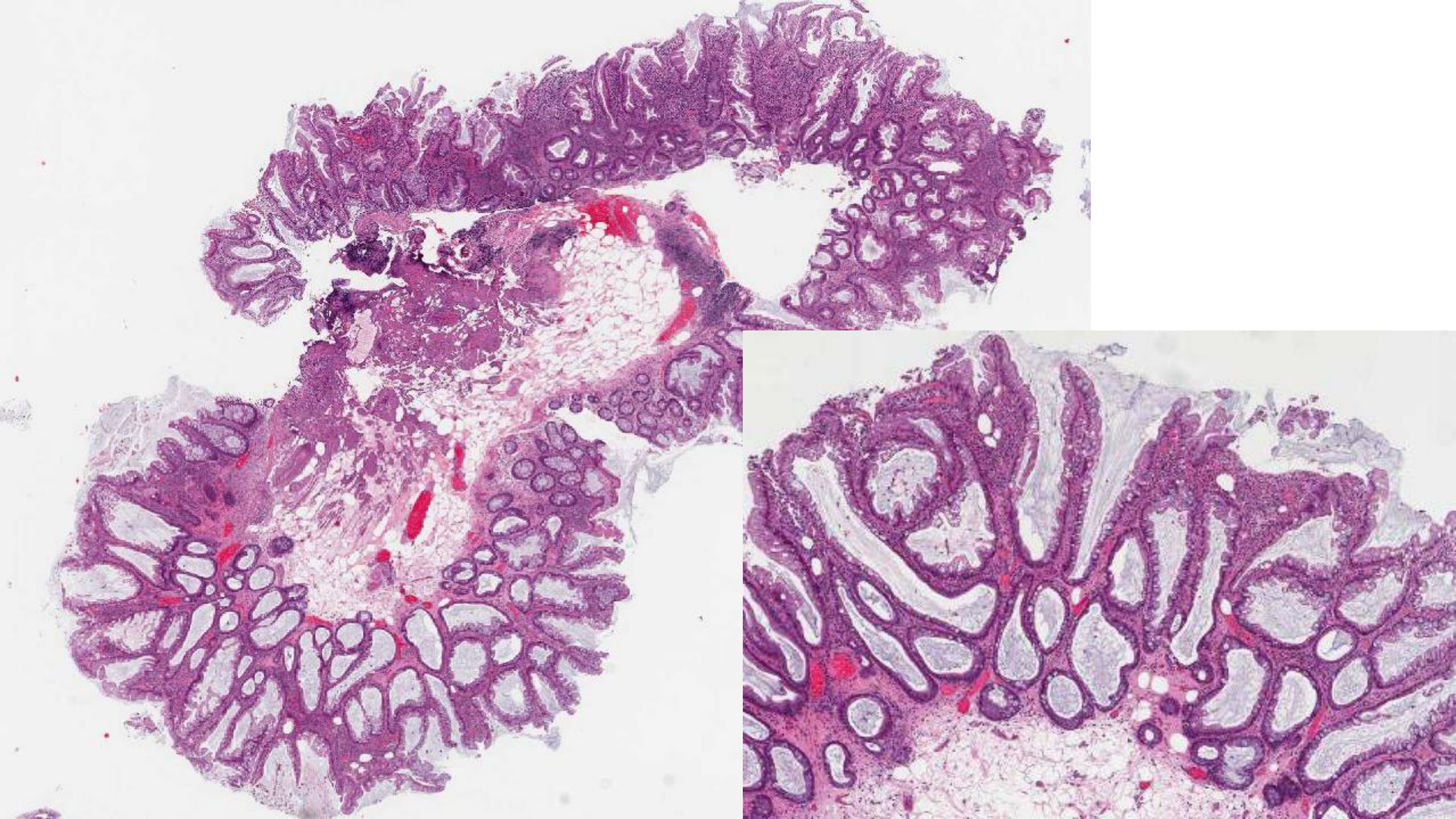
Rosty, Genetic Tumor Syndromes of the GI Tract, World Health Organization, 2019; NCCN 2020

Diagnostic Criteria WHO 2019

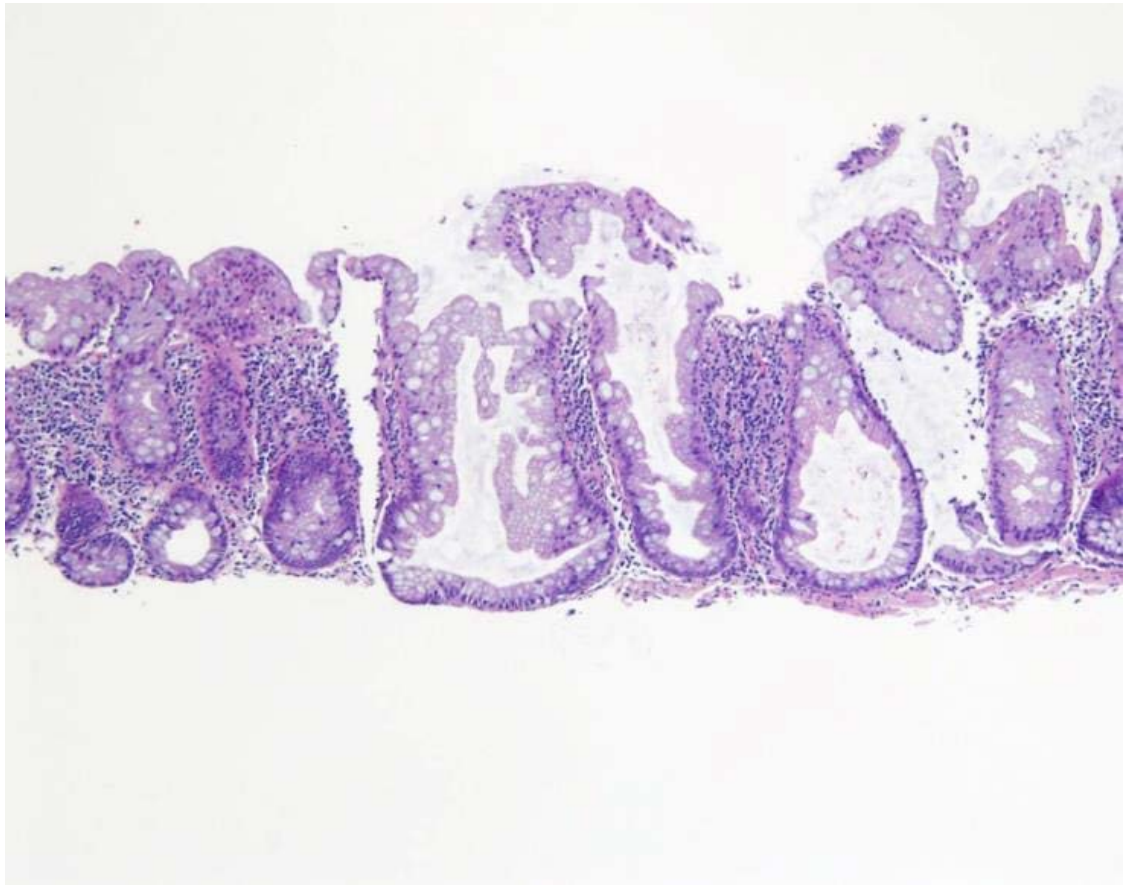
- ≥ 5 serrated lesion/polyp proximal to the rectum
  - All ≥ 5 mm in size
  - With ≥ 2 polyps, ≥ 10 mm in size
- > 20 serrated lesion/polyp of any size distributed throughout the colon
  - With ≥ 5 polyps proximal to the rectum

Serrated lesion/polyp: Hyperplastic, SSL/A/P (with or without dysplasia), TSA, serrated unclassifiable; number is cumulative over multiple colonoscopies

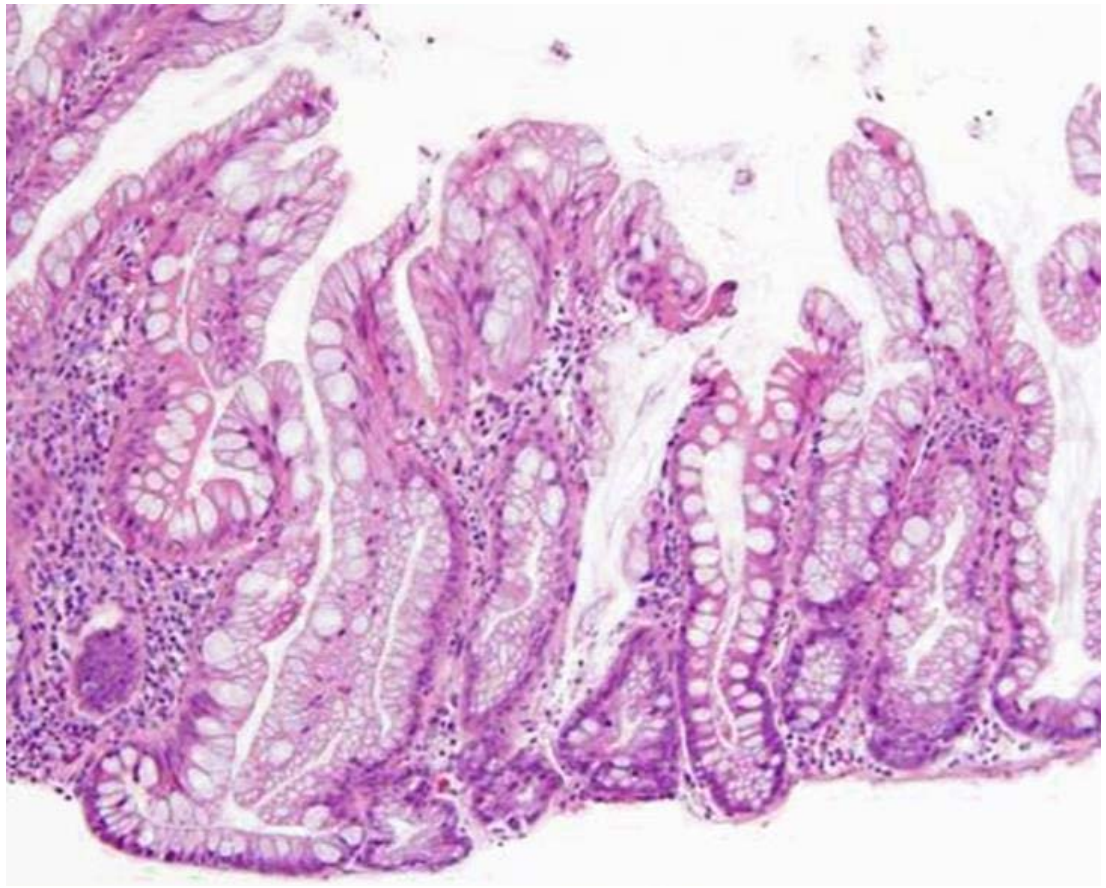
Rosty, Genetic Tumor Syndromes of the GI Tract, World Health Organization, 2019



Small Sessile Serrated Lesion/Adenoma/Polyp



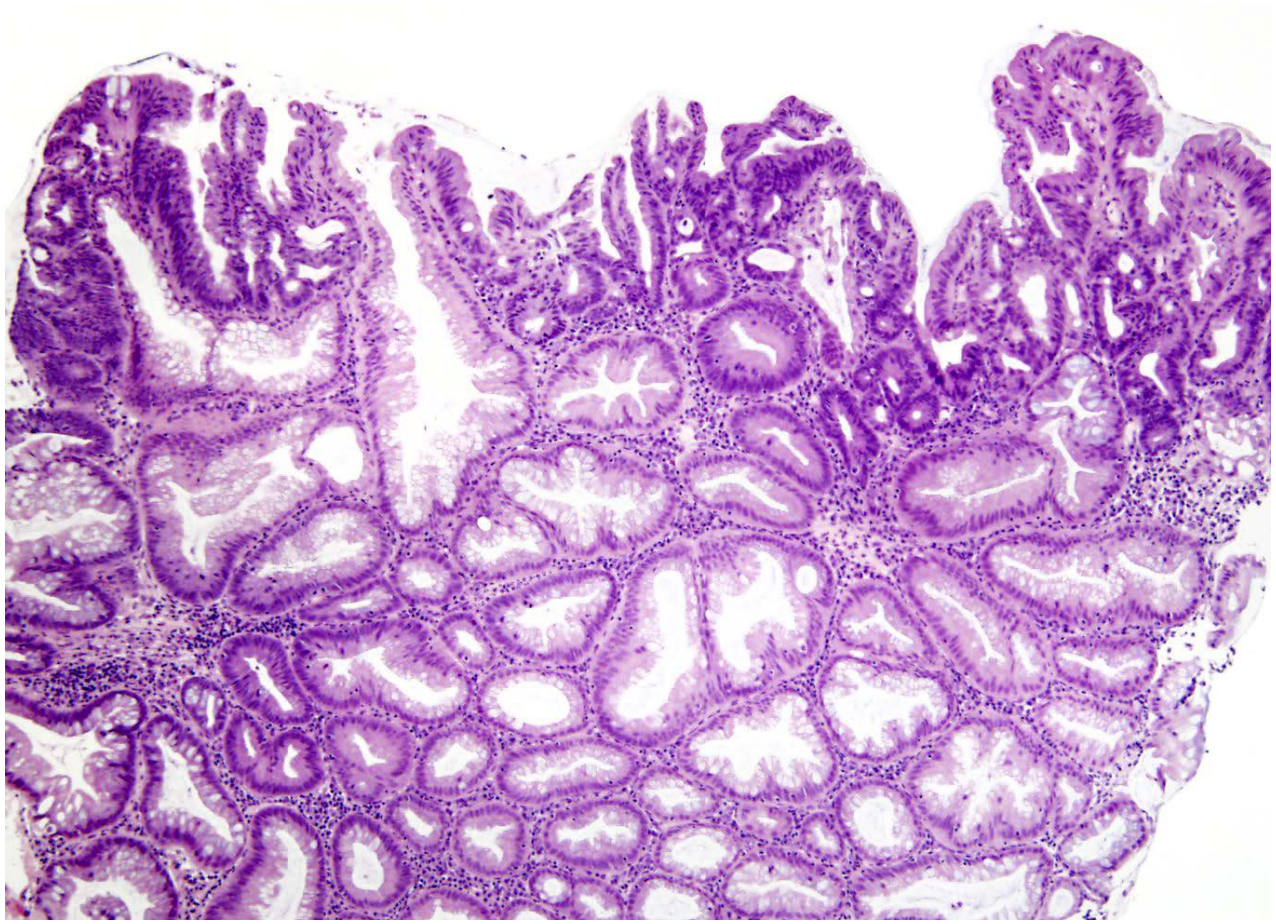
2010: 2-3 contiguous crypts

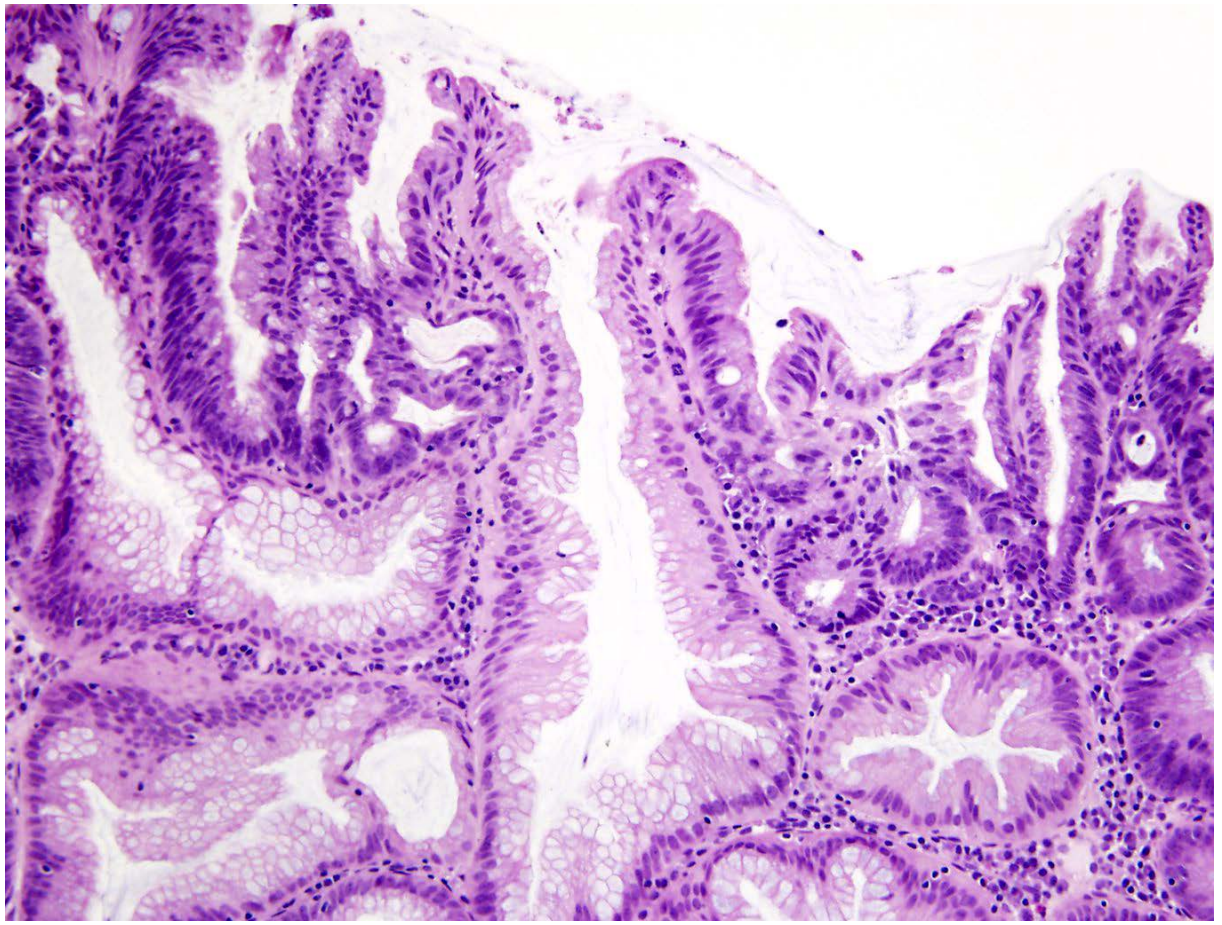


2012: 1 convincing

Aust, Virchows Arch, 2010; Rex, Am J Gastroenterol, 2012

Sessile Serrated Lesion/Polyp/Adenoma with Cytologic Dysplasia





SPS Management and Follow-up

- Colonoscopy with polypectomy if ≥ 5mm
- Colonoscopy every 1-3y depending on size and number
- Consider surgery if treatment/surveillance inadequate
- First degree relatives
  - Increased incidence of CRC vs. population
  - Screen youngest age SPS diagnosed, or 10y earlier than first CRC in family, or by 40y; whatever is earliest
  - Follow-up every 5y if no polyps or guided by findings

NCCN Guidelines Version 1.2020 Genetic/Familial High Risk Assessment: Colorectum, July 2020

SPS: Take Home Message

1. Serrated polyposis syndrome includes adenomas and serrated polyps
2. Increased risk colon cancer and can be hereditary, but exact risks and cause unclear
3. Serrated polyps can be seen in other hereditary syndromes

Newer Polyposis

- Hereditary mixed polyposis- *GREM1*
  - Inhibitor of TGFb signaling, autosomal dominant
- Polymerase proofreading associated polyposis- *POLE*, *POLD1*
  - DNA proofreading in replication, autosomal dominant
- *NTHL1* associated polyposis
  - DNA base excision, autosomal recessive
- *MSH3* associated polyposis
  - Mismatch repair gene, autosomal recessive
- *AXIN2* associated polyposis (oligodontia-CRC cancer syndrome)- regulator of B-catenin

Adenomas	Serrated polyps	Hamartomas
	Serrated polyposis syndrome	Juvenile polyposis
FAP Attenuated FAP *MUTYH*		Peutz-Jeghers
Polymerase proofreading associated polyposis		
Lynch syndrome (sometimes)		
	PTEN hamartoma tumor syndrome (Cowden)	
NTHL1, *MSH3*		
	Hereditary mixed polyposis (GREM1)	

The Pathologist Role in CRC and Polyposis

- Diagnosis polyp types
- Look up history, age
- Screen for MMRd and Lynch
- Communicate with Gastroenterologist if a syndrome is considered

Pearls

- Hereditary syndromes can present with colorectal cancer, adenomas, serrated polyps and/or hamartomas
- Patients (any age) with tumors at multiple sites in addition to colorectum, should be considered for screening for MMRd; MMRd tumors (any site or age) should be worked up for Lynch syndrome
- Gene panels should be considered for those under 50 years old at diagnosis of CRC

Wendy.Frankel@osumc.edu
@WendyFrankelMD

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