NCCN Guidelines: Genetic/ Familial High-Risk Assessment

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I have no financial relationships to disclose.

NCCN Guidelines Version 1.2020
Genetic/Familial High-Risk Assessment: Colorectal

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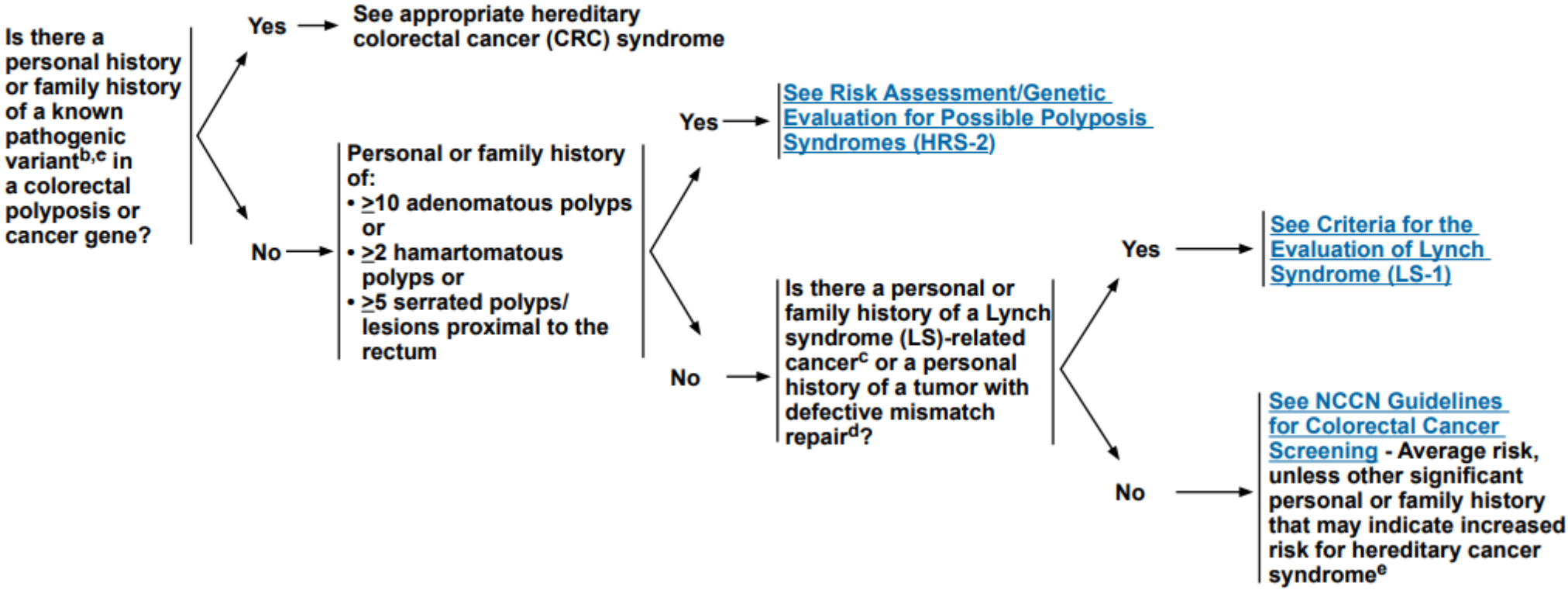
Discussion

ASSESSMENT FOR HEREDITARY CRC SYNDROME[a]



Lynch Syndrome

Changes to criteria for evaluation of Lynch Syndrome

Addition of “Personal history of a tumor with MMR deficiency determined by PCR, NGS or IHC diagnosed at any age”

Recommends tumor screening for all CRC and endometrial cancers regardless of age at diagnosis

> “Consider tumor screening for MMR deficiency for sebaceous neoplasms as well as the following adenocarcinomas: small bowel, gastric, pancreas, biliary tract, brain, bladder, urothelial, and adrenocortical cancers regardless of age at diagnosis”

Revision of MSI false negative rate from 5-10% to 5-15%

CRITERIA FOR THE EVALUATION OF LYNCH SYNDROME

- Known LS pathogenic variant in the family
- Personal history of a tumor with MMR deficiency determined by PCR, NGS, or IHC diagnosed at any age[a] (See LS-A)
- An individual with colorectal or endometrial cancer and any of the following:
  - Diagnosed <50 y
  - A synchronous or metachronous LS-related cancer[b]
  - 1 first-degree or second-degree relative with an LS-related cancer[b] diagnosed <50 y
  - ≥2 first-degree or second-degree relatives with an LS-related cancer[b] regardless of age
- Family history[c] of any of the following:
  - ≥1 first-degree relative with a colorectal or endometrial cancer diagnosed <50 y
  - ≥1 first-degree relative with a colorectal or endometrial cancer and a synchronous or metachronous LS-related cancer[b]
  - ≥2 first-degree or second-degree relatives with LS-related cancers,[b] including ≥1 diagnosed <50 y
  - ≥3 first-degree or second-degree relatives with LS-related cancers,[b] regardless of age
- Increased model-predicted risk for Lynch syndrome
  - An individual with a ≥5% risk[d] of having an MMR gene pathogenic variant based on predictive models (ie, PREMM5, MMRpro, MMRpredict)

→ See Strategies For Evaluating LS (LS-2)

Cancer Risks in Lynch Syndrome

	What was revised?	Details
Risks in LS v. General Population	Each gene now has its own section	See next slide
Colon	Dosage/Duration of aspirin use	From “uncertain” to 600mg/daily for 2y
Endometrial	Starting age of biopsy	Starting at 30-35y can be considered
Ovarian	BSO consideration	Removed “by women who have completed childbearing”; addition of *should* be individualized (rather than *can)*
Urothelial	Who should have screening	Removal of emphasis on male MSH2 carriers- surveillance may be considered in selected individuals such as those with a family history of urothelial cancer

Summary of Screening by Gene

	MLH1	MSH2/EPCAM	MSH6	PMS2
Colonoscopy	20-25y or or 2-5y prior to earliest dx if <25, repeat every 1-2y		30-35y or 2-5y prior to earliest dx if <30, repeat every 1-2y	
Aspirin use	600 mg/daily			Not shown to decrease CRC risk
Hysterectomy	Consider to reduce endometrial cancer incidence, does not reduce mortality			Modestly increased risk, can consider
Endometrial biopsy	30-35y, repeat every 1-2y can be considered			
Oophorectomy	Timing of BSO should be individualized based on childbearing, menopause status, comorbidities, FHx ovarian ca		Insufficient evidence to make rec., consider factors listed for MLH1/MSH2	Not at increased risk, can be considered
Transvaginal US/ CA- 125	Not sufficiently sensitive or specific to be a routine recommendation			
Urinalysis	Insufficient evidence to recommend a strategy, may consider annual starting at 30-35. May select for individuals with FHx of urothelial ca or males w/ MSH2 pathogenic variant			
EGD	No clear data to support surveillance- consider baseline EGD w/ random bx of proximal & distal stomach for H. pylori, autoimmune gastritis, intestinal metaplasia beginning at 40y, repeat every 3-5y			
MRCP and/or EUS	Consider annual surveillance for individuals with pancreatic cancer in >1 FDR or SDR on the same or presumed side of the family with the PV/LPV, starting at age 50 or 10y younger than earliest dx, whichever is earlier			
Neurological exam	Annual physical/neurological exam starting at 25-30			

Lynch syndrome, continued

Insufficient evidence to support increased screening above general population for

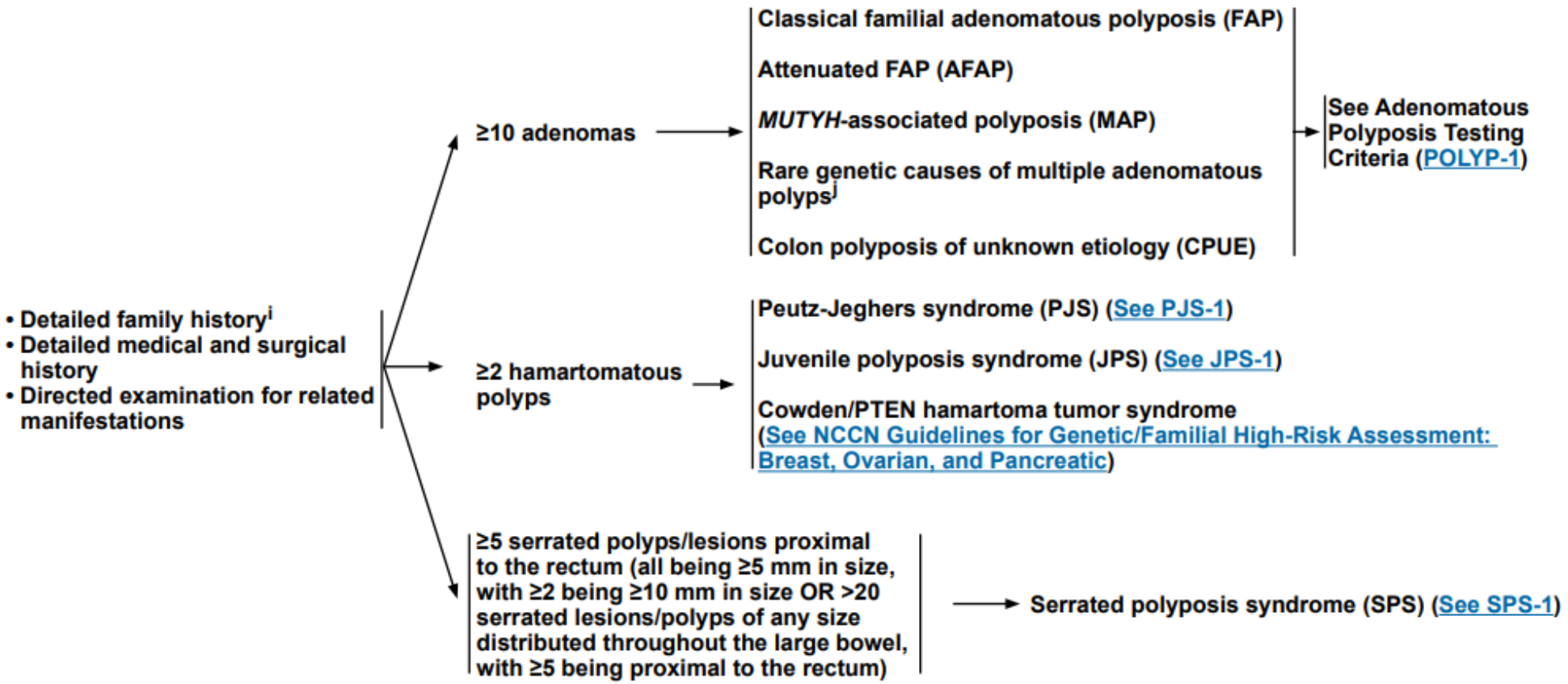
- Prostate cancer
- Breast cancer

After surgery for colorectal cancer, repeat colonoscopy every 1-2 years if colon or rectum remain

Polyposis Syndromes

FAP, AFAP, MAP

RISK ASSESSMENT/GENETIC EVALUATION FOR POSSIBLE POLYPOSIS SYNDROMES[f,g,h]

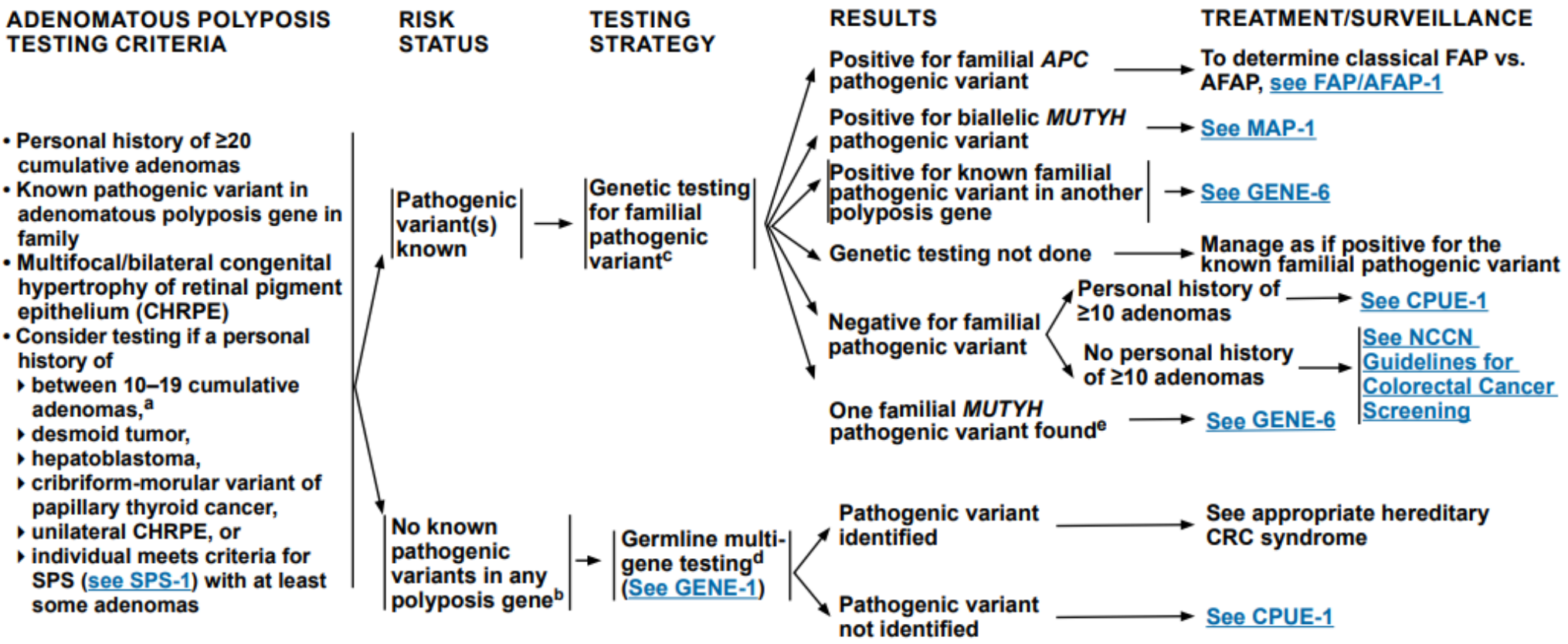


Testing Criteria changes for polyposis

Addition of “Multifocal/bilateral congenital hypertrophy of retinal pigment epithelium (CHRPE)”

Consider testing if:

- Change number of polyps from “11-20” to “10-19”
- Addition of unilateral CHRPE


ADENOMATOUS POLYPOSIS TESTING CRITERIA
• Personal history of ≥20 cumulative adenomas
• Known pathogenic variant in adenomatous polyposis gene in family
• Multifocal/bilateral congenital hypertrophy of retinal pigment epithelium (CHRPE)
• Consider testing if a personal history of
▸ between 10–19 cumulative adenomas,[a]
▸ desmoid tumor,
▸ hepatoblastoma,
▸ cribriform-morular variant of papillary thyroid cancer,
▸ unilateral CHRPE, or
▸ individual meets criteria for SPS (see SPS-1) with at least some adenomas
RISK STATUS
Pathogenic variant(s) known
No known pathogenic variants in any polyposis gene[b]
TESTING STRATEGY
Genetic testing for familial pathogenic variant[c]
Germline multi-gene testing[d] (See GENE-1)
RESULTS
Positive for familial APC pathogenic variant
Positive for biallelic MUTYH pathogenic variant
Positive for known familial pathogenic variant in another polyposis gene
Genetic testing not done
Negative for familial pathogenic variant
Personal history of ≥10 adenomas
No personal history of ≥10 adenomas
One familial MUTYH pathogenic variant found[e]
Pathogenic variant identified
Pathogenic variant not identified
TREATMENT/SURVEILLANCE
To determine classical FAP vs. AFAP, see FAP/AFAP-1
See MAP-1
See GENE-6
Manage as if positive for the known familial pathogenic variant
See CPUE-1
See NCCN Guidelines for Colorectal Cancer Screening
See GENE-6
See appropriate hereditary CRC syndrome
See CPUE-1

FAP Management Changes

Recommend multi-gene panel testing to differentiate FAP, MAP, polyposis in a rare gene, or polyposis of unknown etiology

Genetic testing in children should be done by age 10-12

Baseline thyroid US in late teenage years
- If negative, repeat every 2-5y
- If abnormal, refer to thyroid specialist
- Consider shorter intervals for individuals with FHx thyroid

Consider small bowel visualization with capsule endoscopy, especially with advanced duodenal polyposis

Consider liver palpation, abdominal US and AFP measurement every 3-6mo for first 5 years of life for hepatoblastoma

Pancreatic cancer screening may be individualized based on family history

AFAP Management Changes

Changed “annual thyroid exam” to US at baseline starting in late teenage years
- If normal, repeat every 2-5y
- If abnormal, referral to thyroid specialist
- Can consider shorter interval if there’s a FHx of thyroid cancer

Cap-assisted endoscopy may be adequate for visualization of ampulla

For individuals not tested, colonoscopy every 2y starting in late teens
- May lengthen interval based on clinical judgment

Colonic Adenomatous Polyposis of Unknown Etiology

Defined as an individual with >10-20 adenomas without a pathogenic variant identified in a polyposis gene

Phenotype	Management
PHx >100 adenomas	Manage as FAP
PHx 20-100 adenomas	Colonoscopy and polypectomy every 1-2y, if not manageable by polypectomy, have surgical evaluation
PHx/FHx 10-19 adenomas	Manage based on clinical judgment
FHx >100 adenomas, no PV identified	Annual colonoscopy beginning at 10-15y, manage based on findings
FHx 20-100 adenomas, no PV identified	Colonoscopy beginning in late teens, repeat every 2y, manage based on findings

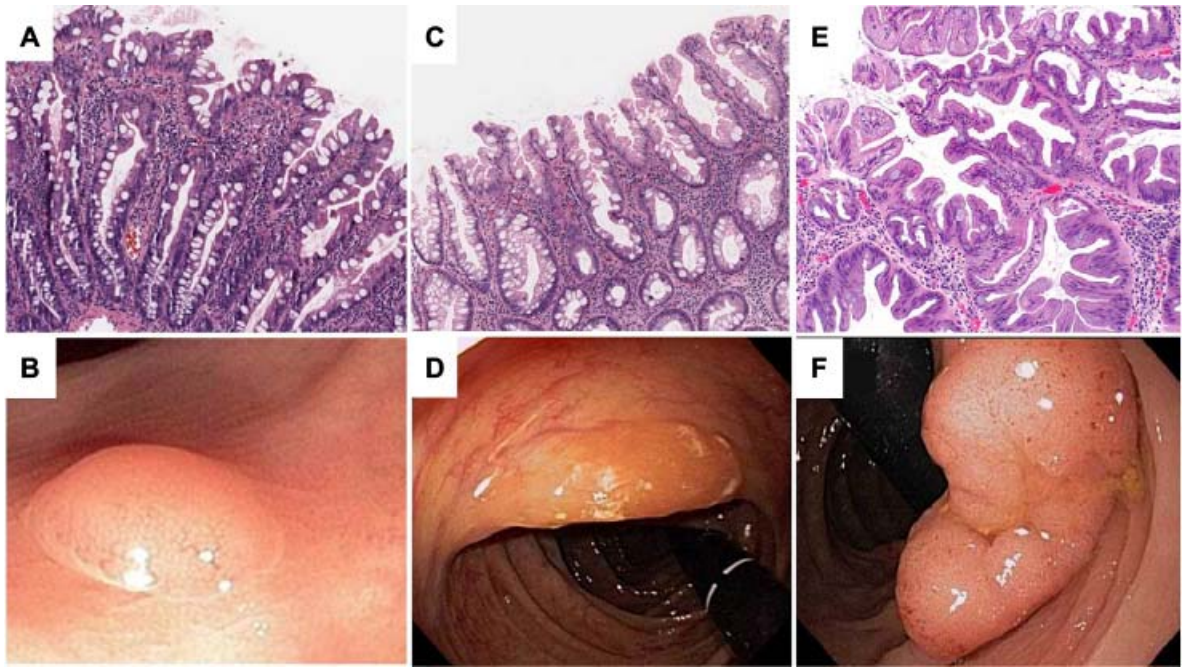


Image: O'Connell BM, Crockett SD. The clinical impact of serrated colorectal polyps. *Clin Epidemiol*. 2017;9:113-125 https://doi.org/10.2147/CLEP.S106257

Serrated Polyposis Syndrome

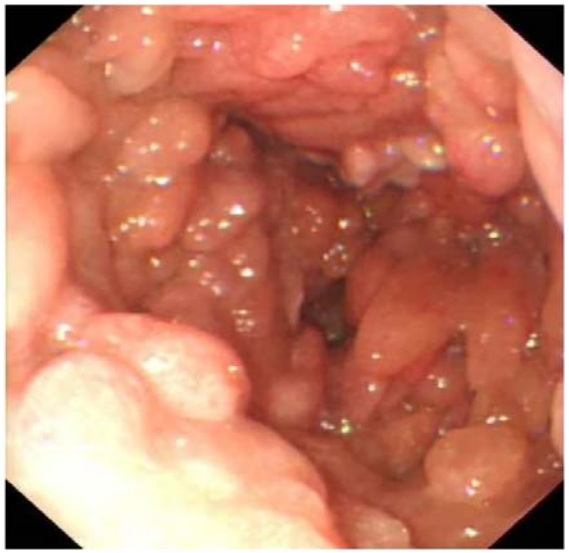
Changed "≥ 5 serrated polyps proximal to sigmoid" to "≥ 5 serrated polyps/lesions proximal to rectum"

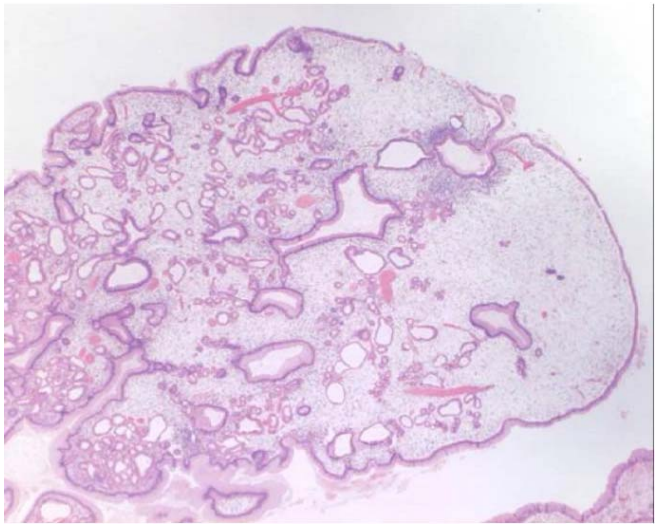
- All being ≥ 5mm in size, with ≥ 2 being ≥10mm in size OR
- ≥ 20 serrated lesions/polyps of any size distributed throughout large bowl, with ≥ 5 being proximal to the rectum

Cumulative polyp count includes hyperplastic polyps, sessile serrated lesions, traditional serrated adenoma, and unclassified serrated adenomas

Hamartomatous Polyposis Syndromes

(Cowden syndrome and other PTEN mutation syndromes not discussed)





Juvenile Polyposis

5 or more juvenile polyps of the colon

Multiple juvenile polyps throughout GI tract

Any number of juvenile polyps in an individual with a family history of JPS

Pathogenic variants in BMPR1A or SMAD4 genes

Suspect if patient also has

- intestinal malrotation
- Cleft palate
- Heart/brain abnormalities
- Polydactyly
- Genital or urinary tract abnormalities

Images: Kelly, S., Dwerryhouse, S., Safranek, P. *et al.* Juvenile polyposis syndrome affecting the stomach: A case report. *J Med Case Reports* **2,** 314 (2008). https://doi.org/10.1186/1752-1947-2-314

Juvenile Polyposis - Updates

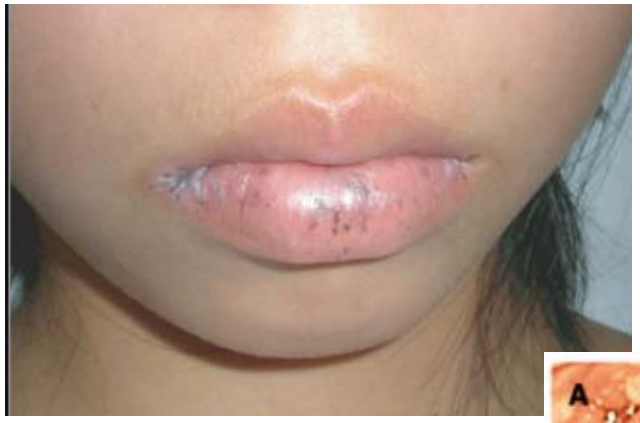
Colonoscopy- repeat every 2-3y, at shorter interval based on polyp size, number and pathology

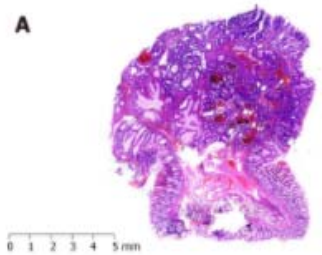
Upper endoscopy every 2-3y, at shorter interval based on polyp size, number and pathology

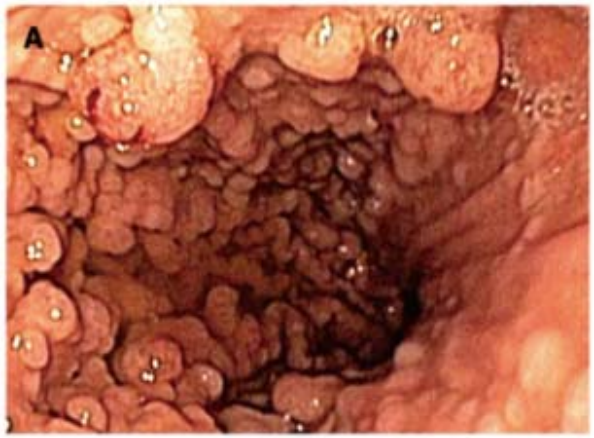
In individuals with SMAD4 PV, screen for signs, symptoms and vascular lesions of HHT

- Genetic testing should be performed in first 6 months of life

In a family in which a PV has not been identified, consider extending colonoscopy/upper endoscopy intervals in at-risk individuals w/ no polyps from 2-3y to 5y beginning at 20, and then every 10 years beginning at 40y







Peutz-Jegher Syndrome

Pathogenic variants in the STK11 gene

Clinical diagnosis: 2 or more of the following

- 2 or more PJ-type hamartomatous polyps of the GI tract
- Mucocutaneous hyperpigmentation of the mouth, lips, nose, eyes, genitalia, or fingers
- Family history of PJS

Screening recommendations for breast, colon, stomach, small intestine, pancreas, gynecologic, testicular, and lung cancer

Images: Chae, Hyun-Dong and C. Jeon. “Peutz-Jeghers syndrome with germline mutation of STK11.” *Annals of Surgical Treatment and Research* 86 (2014): 325 – 330; Kopacova M, Tacheci I, Rejchrt S, Bures J. Peutz-Jeghers syndrome: diagnostic and therapeutic approach. World J Gastroenterol. 2009 Nov 21;15(43):5397-408. doi: 10.3748/wjg.15.5397. PMID: 19916169; PMCID: PMC2778095.; Zheng Z, Xu R, Yin J, et al. Malignant tumors associated with Peutz-Jeghers syndrome: Five cases from a single surgical unit. *World J Clin Cases*. 2020;8(2):264-275. doi:10.12998/wjcc.v8.i2.264

Peutz-Jegher Syndrome – Updates

Revision of breast screening initiation changed from 25y to 30y

Consider MRCP w/ contrast or EUS annually at a center of expertise for pancreatic cancer risk

Annual physical exam for observation of precocious puberty starting at age 8

Genetic Counseling Revisions

Addition of “pretest counseling includes uncertain, and unexpected findings such as a pathogenic variant in a gene that does not necessarily explain the patient’s personal or family history”

Likely pathogenic variants are typically treated as pathogenic variants (used to say often treated similarly)

Testing minors- added caveat about FAP, in which testing children can guide management in childhood

When taking pedigree- discuss concerns of possible nonpaternity, genetic testing results of family members, and patient’s number/histology of polyps

Benefits of Genetic Counseling

Iowa genetic counselors are licensed by the Iowa Board of Medicine

Panel selection, family follow-up

Informed consent

Identification of services tailored to family history

Help improve access to genetic counseling and genetic testing:

Dear Colleagues,

We are writing to request your support in nominating **"Lynch Syndrome-Related Cancers: Risk Assessment, Genetic Counseling, and Genetic Testing"** as a New Topic to be reviewed by the United States Preventative Services Task Force (USPSTF). Any **individual** or **organization** can enter a request for a topic review.

As you are aware, Grade A and Grade B USPSTF recommendations are covered without cost sharing under the Affordable Care Act. These designations have the potential significantly improve access to genetic counseling and genetic testing.

How to enter a topic request:

1. Go to the USPSTF New Topic Page
2. Enter your name, affiliation
3. Use this document as a template to help fill out the fields
4. Feel free to forward these instructions to colleagues who support improving access to hereditary cancer risk assessment

Thank you for supporting this important issue!

CGA-IGC Council

Email lwinter@mercydesmoines.org to be forwarded this link!

Thank you!