



National Comprehensive
Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Genetic/Familial High-Risk Assessment: Colorectal

Version 1.2023 — May 30, 2023

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NCCN Guidelines Version 1.2023

Genetic/Familial High-Risk Assessment: Colorectal

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***Samir Gupta, MD/Chair** ✎
UC San Diego Moores Cancer Center

***Jennifer M. Weiss, MD, MS/Vice-chair** ✎
University of Wisconsin
Carbone Cancer Center

Lisen Axell, MS, CGC Δ
University of Colorado Cancer Center

Carol A. Burke, MD ✎
Case Comprehensive Cancer Center/
University Hospitals Seidman Cancer Center
and Cleveland Clinic Taussig Cancer Institute

Lee-May Chen, MD ¶
UCSF Helen Diller Family
Comprehensive Cancer Center

Daniel C. Chung, MD ✎ Δ
Massachusetts General Hospital
Cancer Center

Katherine M. Clayback, MS, CGC Δ
Roswell Park Comprehensive
Cancer Center

Susan Dallas ✎
Lynch Syndrome International

Seth Felder, MD ¶
Moffitt Cancer Center

Francis M. Giardiello, MD, MBA ✎
The Sidney Kimmel Comprehensive
Cancer Center at Johns Hopkins

William Grady, MD ✎
Fred Hutchinson Cancer Center

Andrea Hagemann, MD, MSCI ¶
Siteman Cancer Center at Barnes-
Jewish Hospital and Washington
University School of Medicine

Michael J. Hall, MD, MS † Δ
Fox Chase Cancer Center

Heather Hampel, MS, CGC Δ
City of Hope
National Medical Center

Rachel Hodan, MS, CGC Δ
Stanford Cancer Institute

Gregory Idos, MD, MS ✎
City of Hope
National Medical Center

Nawal Kassem, MD, MS †
Indiana University Melvin and Bren Simon
Comprehensive Cancer Center

Bryson Katona, MD, PhD ✎
Abramson Cancer Center at the
University of Pennsylvania

Laura Lamps, MD ≠
University of Michigan Rogel Cancer Center

Xavier Llor, MD, PhD ✎ †
Yale Cancer Center/
Smilow Cancer Hospital

Karen Lu, MD ¶
The University of Texas MD Anderson
Cancer Center

Arnold J. Markowitz, MD ✎
Memorial Sloan Kettering Cancer Center

Mariana Niell-Swiler, MS Δ
UCLA Jonsson Comprehensive
Cancer Center

Darryl Outlaw, MD † ‡
O'Neal Comprehensive
Cancer Center at UAB

Sara Pirzadeh-Miller, MS, CGC Δ
UT Southwestern Simmons
Comprehensive Cancer Center

Niloy Jewel Samadder, MD ✎
Mayo Clinic Cancer Center

David Shibata, MD ¶
St. Jude Children's Research Hospital/
The University of Tennessee Health Science
Center

Peter P. Stanich, MD ✎
The Ohio State University Comprehensive
Cancer Center - James Cancer Hospital
and Solove Research Institute

Benjamin J. Swanson, MD, PhD ≠
Fred & Pamela Buffett Cancer Center

Brittany M. Szymaniak, PhD, CGC Δ
Robert H. Lurie Comprehensive Cancer
Center of Northwestern University

Jeanna Welborn, MD †
UC Davis Comprehensive Cancer Center

Georgia L. Wiesner, MD † Δ
Vanderbilt-Ingram Cancer Center

Andrew Wolf, MD ✎
Duke Cancer Institute

Matthew B. Yurgelun, MD †
Dana-Farber/Brigham and Women's
Cancer Center

NCCN

Susan Darlow, PhD
Mary Dwyer, MS
Robin Isaac, PharmD

Continue

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Δ Cancer genetics	✎ Patient advocacy
✎ Gastroenterology	¶ Surgery/Surgical oncology
† Internal medicine	* Discussion Writing Committee Member
‡ Medical oncology	
‡ Hematology	
≠ Pathology	



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Genetic/Familial High-Risk Assessment: Colorectal

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[Abbreviations \(ABBR-1\)](#)

Clinical Trials: NCCN believes that the best management for any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise indicated.

See [NCCN Categories of Evidence and Consensus](#).

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NCCN Guidelines Version 1.2023

Genetic/Familial High-Risk Assessment: Colorectal

Updates in Version 1.2023 of the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal from Version 2.2022 include:

Global Changes

- Terminologies in all NCCN Guidelines are being actively modified to advance the goals of equity, inclusion, and representation.
- References updated throughout the Guideline
Genetic/Familial High-Risk Assessment: Colorectal

HRS-1

- Assessment for Hereditary CRC Syndrome
 - Footnote g revised: ...*cribriform-morular* variant of papillary thyroid cancer,...

Lynch Syndrome

HRS-3

- Criteria for Evaluation of Lynch syndrome...
 - Known MMR deficiency in tumor
 - ◇ Yes evaluation revised:... hereditary cancer syndromes *AND/OR* Additional tumor-based testing...
 - ◇ No revised by adding "or not tested" and evaluation option revised: *Utilize tumor and family history-based criteria for evaluation of LS (LS-1) and consider germline MGPT evaluation for LS and other hereditary cancer syndromes for all individuals with CRC aged ≥50 years at diagnosis*

HRS-A 2 of 2

- Test Selection modified: Germline MGPT should include at minimum the following CRC risk-associated genes: APC, MUTYH, MLH1, MSH2, MSH6, PMS2, EPCAM, BMPR1A, SMAD4, PTEN, STK11, *TP53*

Principles of Cancer Risk Assessment and Counseling

HRS-B 1 of 9

- Post-test counseling includes
 - Language modified from "Encouraging patient enrollment in a research study if a VUS is identified" to "Consider referral to research studies that aim to define the functional impact of VUSs such as variant reclassification programs through clinical labs or registries."

HRS-B 2 of 9

- Genetic Testing Considerations
 - 5th bullet modified: may benefit from ~~repeat~~ *additional* genetic testing using a larger MGPT.

HRS-B 5 of 9

- Heading added: Tumor Genomic Testing: Potential Implications for Germline Testing

HRS-B 6 of 9

- Detailed Medical and Surgical History
 - 1st bullet added: Sex assigned at birth
 - 6th bullet added: For patients with prior cancer: age at diagnosis, treatment history, results of any tumor-based genetic or molecular testing

HRS-B 7 of 9

- New page added: Common Pedigree Symbols



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Genetic/Familial High-Risk Assessment: Colorectal

Updates in Version 1.2023 of the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal from Version 2.2022 include:

Lynch Syndrome

LS-1

- Criteria for the Evaluation of Lynch Syndrome Based on Personal or Family History of Cancer
 - ▶ Known LS pathogenic variant in the family, heading modified: An individual with ~~colorectal or endometrial~~ a *LS-related* cancer and any of the following...

LS-A 1 of 9

- General, two bullets added:
 - ▶ For CRC, MSI has slightly greater sensitivity than IHC for identifying LS (92.9% vs. 88.9%–92.4%, respectively), but MSI is unable to be performed (due to small tumor size) more often than IHC (14% vs. 0.3%, respectively). Concordance between MSI and IHC is very high (99.1%).

LS-A 7 of 9

- Tumor Testing Results and Additional Testing Strategies
 - ▶ 2nd row added: Any abnormal IHC, MSS

Gene-Specific Lynch Syndrome Cancer Risks And Surveillance/Prevention Strategies

For all genes, the following changes were made:

- Cumulative Risk for Diagnosis Through Lifetime for General Population updated based date from via SEER*Explorer.
 - ▶ For biliary tract cancers, footnote added: Cumulative incidence for the general population specific to biliary tract cancer was not available through SEER*Explorer.
- Footnote added: Colonoscopy may not be able to prevent all CRC in individuals with LS (Moller P, et al. Hered Cancer Clin Pract 2022;20:36). It has been hypothesized that this may be because some cancers develop from dMMR crypts and do not form an intermediate adenoma (Ahadova A, et al. Int J Cancer 2018;143:139-150). However, available data have shown that exposure to colonoscopy can detect cancers at an early stage when they are more likely curable (Lindor NM, et al. JAMA 2006;296:1507-1517; Vasen HF, et al. 2010;138:2300-2306; Moller P, et al. Gut 2017;66:464-472; Jenkins MA, et al. J Clin Oncol 2015;33:326-331; Moller P, et al. Hered Cancer Clin Pract 2022;20:36).
- Footnote revised by adding: Longitudinal follow-up of the CAPP2 study, a randomized trial that included arms comparing supplementation of resistant starch for 2 to 4 years to no supplementation, showed that taking resistant starch had no effect on the risk for colon cancer. However, a 46% relative reduction in risk for extracolonic cancers (especially cancers of the upper GI tract, (stomach, duodenal, bile duct, and pancreas) was observed [Mathers JC, et al. Cancer Prev Res (Phila) 2022;15:623634]. The potential mechanisms by which resistant starch might reduce risk for extracolonic cancers has not been widely studied. These results are insufficient for recommending routine supplementation with resistant starch for reduction of extracolonic cancer risk in LS.
- Gastric and small bowel cancer modified: ...Push enteroscopy can be considered in place of EGD to enhance small bowel visualization, although *its incremental yield of push enteroscopy for detection of neoplasia* over EGD in LS remains uncertain.

[Continued](#)

UPDATES



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Genetic/Familial High-Risk Assessment: Colorectal

Updates in Version 1.2023 of the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal from Version 2.2022 include:

Adenomatous Polyposis

[POLYP-1](#)

- Testing Criteria

- ▶ 1st bullet added: Recommend testing if a personal history of ≥ 1 of the following criteria:
- ▶ 2nd bullet modified by adding: ≥ 1 of the following criteria:
 - ◊ 7th sub-bullet added: Family history of polyposis and family unwilling/unable to have testing

- Results

- ▶ Genetic testing for familial pathogenic variant, arm modified: ~~On familial MUTYH pathogenic variant found~~ *Positive for monoallelic (single copy) MUTYH pathogenic variant*

APC-Associated Polyposis

[FAP/AFAP-1](#)

- Phenotype, Classical FAP

- ▶ 5th bullet modified: Increased risk for *colorectal cancer, ...Pancreatic periampullary cancer...*

Familial Adenomatous Polyposis

[FAP-2](#)

- Footnote g modified: Colonoscopy is preferred due to the possibility of missing ~~transverse colon and~~ right-sided polyps when limiting to sigmoidoscopy...

[FAP-A 1 of 3](#)

- Pancreatic cancer site and risk and corresponding surveillance strategy removed.

[FAP-C 2 of 2](#)

- Basic Principles of Management of Duodenal and Ampullary Adenomas

- ▶ 4th sub-bullet modified from "Recommends referral to an expert center for multidisciplinary discussion of weight loss surgery options, taking into account the challenge of routine duodenal surveillance after a Roux-en-Y gastric bypass surgery" to "Recommends that individuals with FAP who are considering weight loss surgery be referred to an expert center for multidisciplinary discussion of bariatric interventions, taking into account the challenge of routine duodenal and gastric surveillance after Roux-en-Y gastric bypass surgery. See guidelines from the American Society for Gastrointestinal Endoscopy for specific recommendations about the approach to sampling/removal of polyps in the duodenum."

MUTYH-Associated Polyposis

[MAP-1](#)

- Phenotype

- ▶ 4th bullet modified: Fewer than 100 adenomas (~~range 0-100 and~~ uncommonly >100)

[Continued](#)

UPDATES



NCCN Guidelines Version 1.2023

Genetic/Familial High-Risk Assessment: Colorectal

Updates in Version 1.2023 of the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal from Version 2.2022 include:

Colonic Adenomatous Polyposis of Unknown Etiology

CPUE-1

- Management/Surveillance
- 2nd row, 2nd bullet modified: ~~Consider baseline upper endoscopy (including complete visualization of the ampulla of Vater) at time of next colonoscopy surveillance by age 20-25 y and repeat following duodenal surveillance guidelines on page FAP-C.~~
- 3rd row,
 - ▶ 1st sub-bullet modified: ~~At minimum, clearing of all polyps (≥2 mm) is recommended. Repeat at short interval if residual polyps are present based on residual polyp burden~~
 - ▶ 2nd sentence modified: ~~Consider baseline upper endoscopy (including complete visualization of the ampulla of Vater) at time of next colonoscopy surveillance by age 20-25 y and repeat following duodenal surveillance guidelines on page FAP-C.~~
- 4th row, 2nd bullet added: Consider baseline upper endoscopy at time of next colonoscopy surveillance by age 20–25 y and repeat following duodenal surveillance guidelines on page FAP-C.
- Footnote removed: Cap-assisted endoscopy may be adequate for visualization of the ampulla (Kallenberg F, et al. Endoscopy 2017;49:181-185).

Serrated Polyposis Syndrome

SPS-1

- 3rd bullet modified: ...Genetic testing may be favored based on patient preference, family history of CRC, or presence of features (such as adenomas, See POLYP-1).

Genetic/Familial High-Risk Assessment: Colorectal

GENE-1

- Overview, 1st bullet modified:...Tables on GENE-3 through GENE-14 provide a list of genes that may be found on commercially available multigene panels *and include colon cancer risk and management, colorectal phenotype, and other risks and management with the strength of evidence, risk level for CRC, and phenotypic association,* and Table 4 provides current recommendations for surveillance, based on gene pathogenic variant type.

GENE-3

- Header added: The inclusion of a gene in this table below does not imply the endorsement either for or against multi-gene testing for moderate-penetrance genes. (Also on GENE-4 through GENE-14)

GENE-4

- APC promotor 1B
 - ▶ Colon Cancer Risk and Management, sub-bullet modified: ~~Manage based on family history. See NCCN Guidelines for Colorectal Cancer Screening Colonoscopy at time of diagnosis to exclude colon polyposis, if not previously done~~
 - ▶ Other Risks and Management
 - ◊ Absolute risk modified: Stomach cancer - ~~43%~~ 12-25%
 - ◊ Management, 2nd sub-bullet modified: Consider risk-reducing total gastrectomy from third decade, annual gastroscopy from age 15, ~~and colonoscopy to exclude colon polyposis~~

GENE-5

- AXIN2, comment modified: Associated with oligodontia (absence of >6 adult non-wisdom teeth) and other features of cartilage hair hypoplasia. Polymorphisms in ~~AXIN2 in this gene~~ have also been associated with CRC and other cancers, but ~~this entry~~ *the information above* is referring to individuals with pathogenic/likely pathogenic variants in AXIN2.
- BMPR1A, Other Cancers modified: Stomach cancer - *up to 21%*



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Updates in Version 1.2023 of the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal from Version 2.2022 include:

[GENE-7](#)

- New gene/syndrome added: MBD4-associated neoplasia syndrome.

[GENE-9](#)

- MUTYH biallelic pathogenic variants/MUTYH-associated polyposis
 - ▶ Colon Cancer Risk and Management, Absolute Risk modified: 70%-90% *if polyposis left untreated*
 - ▶ Colorectal Phenotype modified: 0-→100 10-100
- MUTYH *monoallelic pathogenic variant*/ heterozygotes (*carrier*)
 - ▶ Absolute risk revised from "10%–13% with first-degree relative with colon cancer; 6%–7% irrespective of family history" to "No increased risk"
 - ▶ Colon Cancer Risk and Management
 - ◊ 2nd sub-bullet modified: "For probands with a personal history of CRC and a MUTYH pathogenic variant: See surveillance recommendations for post-CRC resection:..." to "For probands with a personal or first-degree family history of CRC or polyps: increased screening as per the relevant guideline:..."
 - ◊ Sub-bullet removed: For probands unaffected by CRC but with a family history of a first-degree relative with CRC: High-quality colonoscopy screening every 5 y, beginning at age 40 or 10 y prior to age of first-degree relative's age at CRC diagnosis.
 - ◊ Sub-bullet removed: For probands unaffected by CRC with NO family history of CRC: Data are unclear as to whether specialized screening is warranted for MUTYH heterozygous carriers unaffected by CRC with no family history of CRC or polyposis.
 - ▶ Comments section extensively revised.

[GENE-10](#)

- NTHL1 biallelic pathogenic variants/ NTHL1 tumor syndrome
 - ▶ Other Risks and Management, Management
 - ◊ 1st sub-bullet modified: Breast cancer: Risk may be elevated; however, there is not enough data yet to support increased breast cancer surveillance
~~Annual mammogram with consideration of tomosynthesis and consider breast MRI with contrast starting at age 40 y~~
 - ◊ Sub-bullet removed: Breast risk reduction: Evidence insufficient for risk-reducing mastectomy (RRM), manage based on family history
 - ◊ Sub-bullet added: Duodenal cancer: Baseline upper endoscopy (including complete visualization of the ampulla of Vater beginning at age 30–35 y [see FAP-C for follow-up of duodenoscopic findings])

[GENE-12](#)

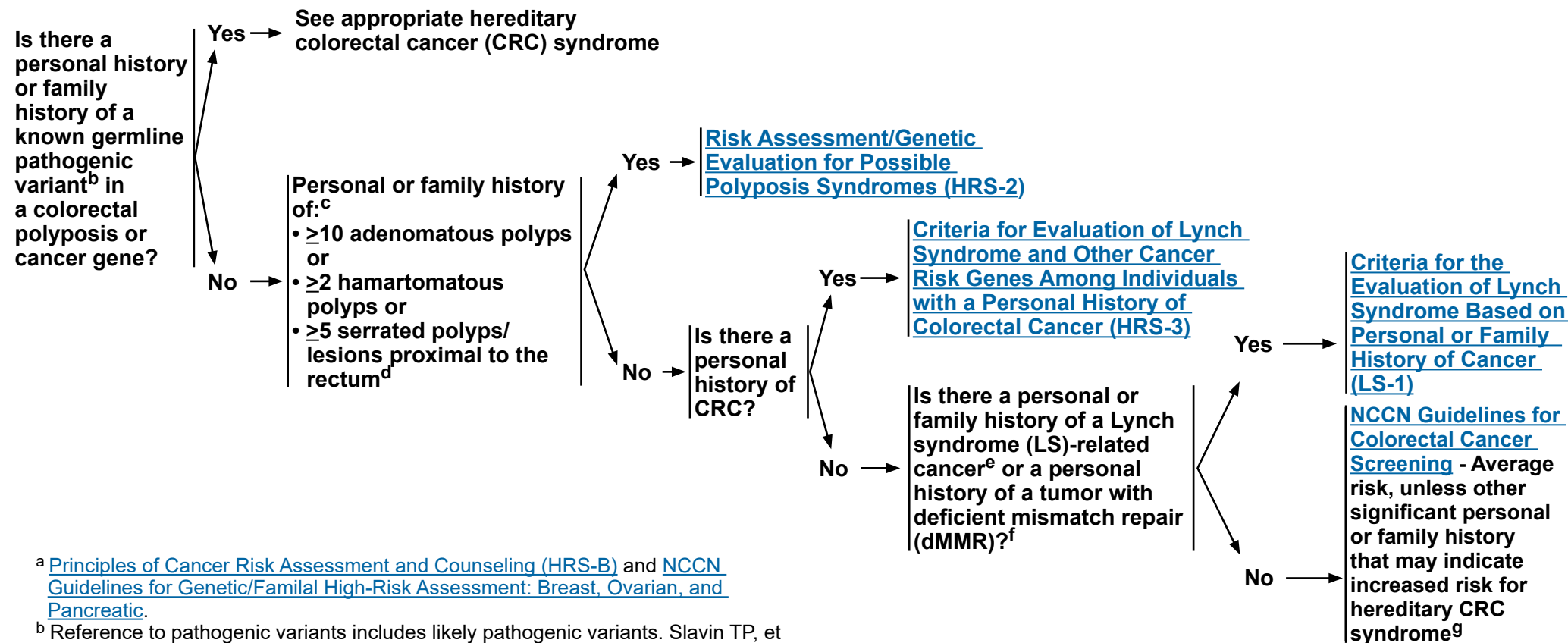
- PMS2/Lynch syndrome, Colon Cancer Risk and Management, risk modified: ~~Estimated~~ Absolute Risk: 8.7%-20%



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Genetic/Familial High-Risk Assessment: Colorectal

ASSESSMENT FOR HEREDITARY CRC SYNDROME^a



^a [Principles of Cancer Risk Assessment and Counseling \(HRS-B\)](#) and [NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic](#).

^b Reference to pathogenic variants includes likely pathogenic variants. Slavin TP, et al. J Natl Cancer Inst 2018;110:1059-1066.

^c Personal or family history of polyps is based on cumulative lifetime history of adenomas, hamartomas, and/or serrated polyps/lesions in the proband or a single family member.

^d In this case, serrated polyps/lesions refers to sessile serrated lesions (previously referred to as sessile serrated adenoma/polyps) with or without dysplasia, traditional serrated adenomas, and hyperplastic polyps ≥1 cm in size.

^e LS-related cancers include colorectal, endometrial, gastric, ovarian, pancreatic, urothelial, brain (usually glioblastoma), biliary tract, and small intestine, as well as sebaceous adenomas, sebaceous carcinomas, and keratoacanthomas as seen in Muir-Torre syndrome.

^f Any tumor that 1) is microsatellite instability-high (MSI-H) by polymerase chain reaction (PCR) or next-generation sequencing (NGS); or 2) has abnormal/deficient MMR protein expression (dMMR) on immunohistochemistry (IHC) without concurrent MLH1 promoter hypermethylation or *BRAF* V600E mutation.

^g Increased risk warranting genetic evaluation may be indicated by, but not restricted to personal or family history of congenital hypertrophy of the retinal pigment epithelium (CHRPE), osteomas, supernumerary teeth, desmoid tumor, cribriform-morular variant of papillary thyroid cancer, brain cancer (usually medulloblastoma), and hepatoblastoma, which may raise the potential for familial adenomatous polyposis (FAP), or personal or family history of other cancers, particularly multiple cancers or early age onset cancers.

Note: All recommendations are category 2A unless otherwise indicated.

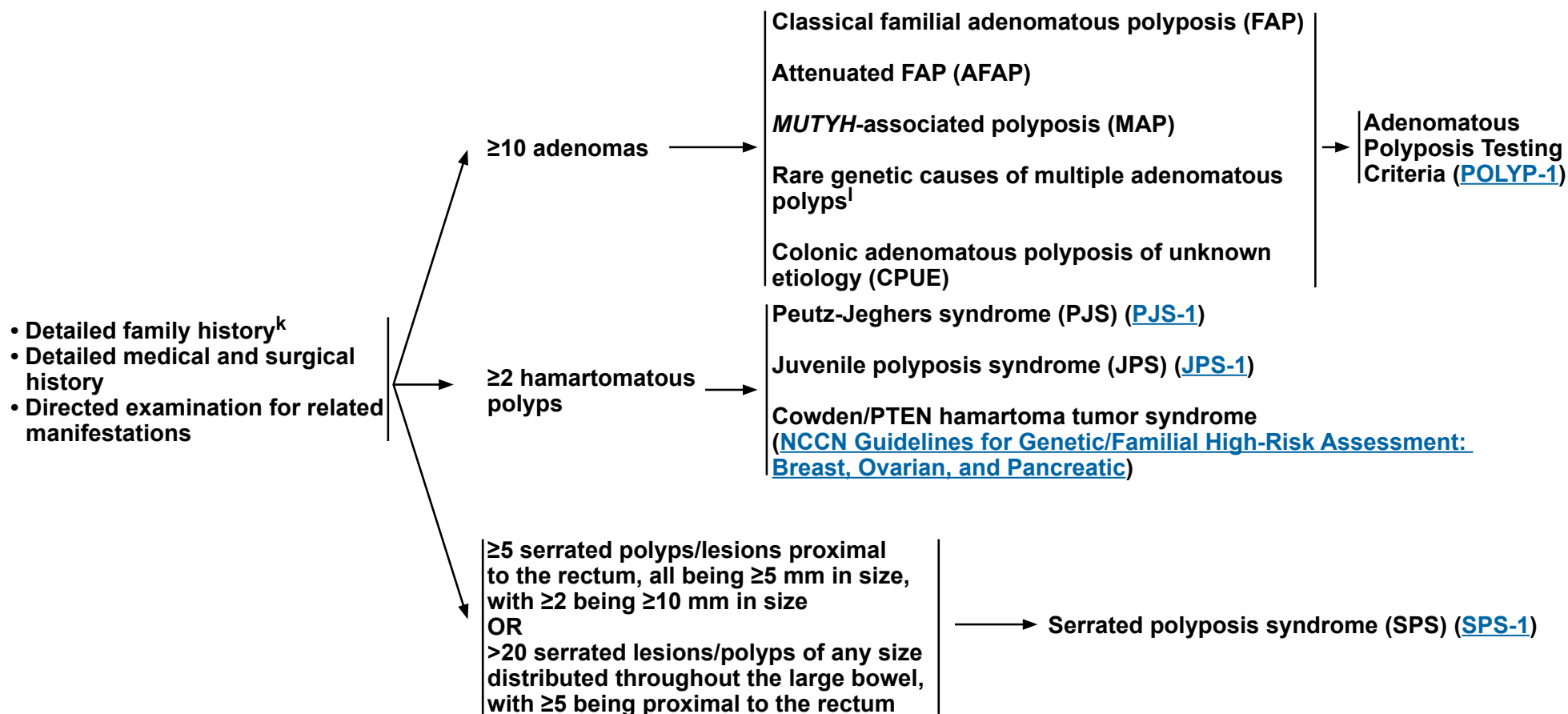
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



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High-Risk Colorectal Cancer Syndromes

RISK ASSESSMENT/GENETIC EVALUATION FOR POSSIBLE POLYPOSIS SYNDROMES^{h,i,j}



^h [Obtaining a Comprehensive Assessment for Hereditary Colorectal Cancer \(HRS-B 6 of 9\)](#).

ⁱ Genetic counseling/patient education is highly recommended when genetic testing is offered and after results are disclosed. A genetic counselor, medical geneticist, oncologist, gastroenterologist, surgeon, oncology nurse, or other health professional with expertise and experience in cancer genetics should be involved early in counseling patients who potentially meet criteria for an inherited syndrome.

^j If personal history of CRC and more than one syndrome might explain the presentation, consider multigene testing.

^k If evaluation is based on family history of ≥1 relative with polyposis, then type of polyps in the affected relative (if known) may guide testing.

^l Pathogenic variants associated with adenomatous polyposis include, but are not limited to monoallelic pathogenic variants in *GREM1*, *POLE*, *POLD1*, and *AXIN2*, and biallelic pathogenic variants in *NTHL1* and *MSH3*.

Note: All recommendations are category 2A unless otherwise indicated.

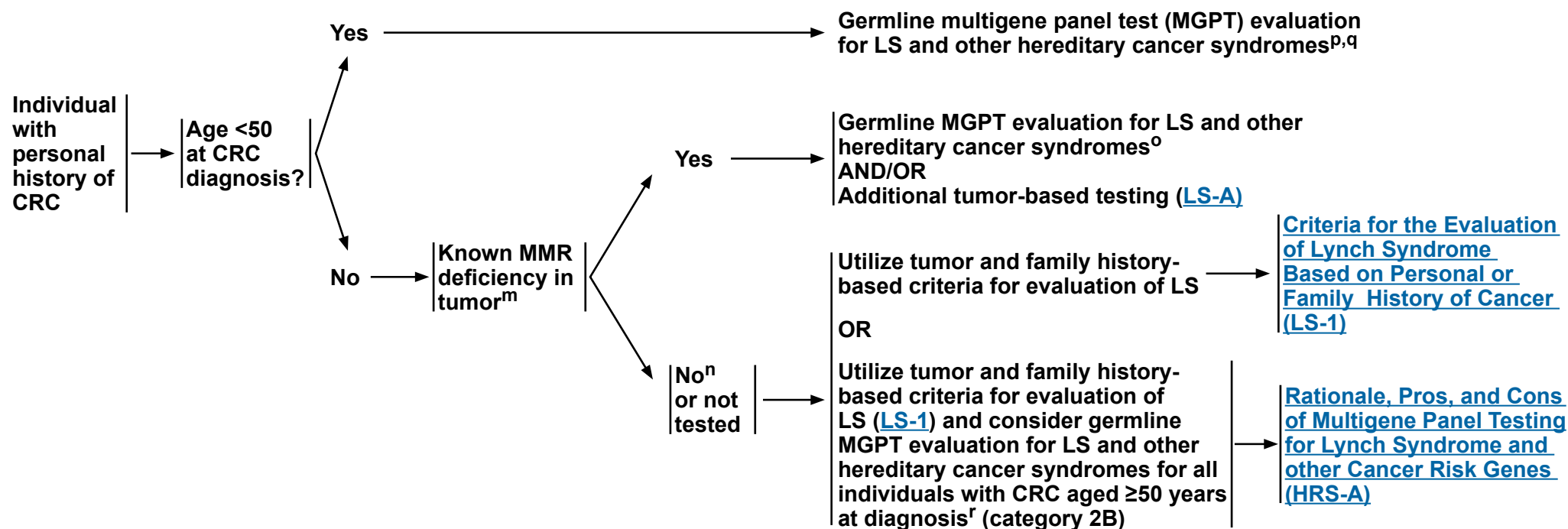
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Lynch Syndrome

CRITERIA FOR EVALUATION OF LYNCH SYNDROME AND OTHER CANCER RISK GENES AMONG INDIVIDUALS WITH A PERSONAL HISTORY OF COLORECTAL CANCER



^m Pursuing a strategy of screening for LS and other cancer risk genes may be favored when the family history of cancer includes both LS-associated and non-LS-associated cancers.

ⁿ A person without a known MMR deficiency may still warrant additional genetic evaluation based on personal and family history.

^o Biallelic *MUTYH* gene mutations have been shown to lead to dMMR tumors; therefore, *MUTYH* should be included in the testing at a minimum with consideration of other base-excision repair genes (*NTHL1*) and DNA polymerase genes (*POLE* and *POLD1*), which have the potential to also lead to biallelic somatic MMR gene inactivation (Morak M, et al. Eur J Hum Genet 2014;22:1334-1337).

^p Pearlman R, et al. JAMA Oncol 2017;3:464-471.

^q Yurgelun M, et al. J Clin Oncol 2017;35:1086-1095.

^r Pearlman R, et al. JCO Precis Oncol 2021;5:779-791; Jiang W, et al. J Med Genet 2022;59:370-376; Uson PLS, et al. Clin Gastroenterol Hepatol 2021;20:e508-e528; Samadder NJ, et al. JAMA Oncol 2021;7:230-237.

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Lynch Syndrome

RATIONALE, PROS, AND CONS OF MULTIGENE PANEL TESTING FOR LYNCH SYNDROME AND OTHER CANCER RISK GENES

Rationale:

The germline MGPT strategy is an alternative to tumor- and family history-driven selection of patients with CRC for genetic testing, because it is more sensitive for identifying individuals with LS and other cancer risk genes than a strategy of selecting for germline testing based on family history and tumor-based criteria.

Pros	Cons
- Compared to genetic evaluation based on family history or tumor testing for evidence of dMMR, MGPT has: - comparable or even higher yield for identifying individuals with LS.^{1,2,3,4} - higher yield for identifying individuals with a pathogenic variant in a cancer risk gene. MGPT identifies a pathogenic variant in 7.8% to 16.0% of patients with CRC.^{2,3,4,5} - Some of the pathogenic variants identified by MGPT are clinically actionable and inform screening and surveillance recommendations. - Identified pathogenic variants allow for subsequent family cascade testing and may allow for additional opportunities for early detection and prevention of cancer.^{3,5,6} - A majority of individuals with a personal history of CRC do not meet previous NCCN criteria for MGPT based on family history or tumor-based criteria.³ - MGPT may simplify referral and testing for genetic evaluation. - MGPT is augmented by, but not dependent on knowledge of family history or tumor characteristics. - Steps required for evaluating for a genetic syndrome are simplified.	- Based on current evidence and available therapies, a germline MGPT result alone does not inform CRC treatment decision-making. - Presence of a pathogenic variant in an LS-associated MMR gene, or in <i>POLE/D1</i> is not sufficient to initiate immune checkpoint blockade therapy, because tumor-based microsatellite instability (MSI) testing, immunohistochemistry (IHC) testing for expression of the MMR proteins, or a measure of tumor mutational burden are the gold standards for determining eligibility for immune checkpoint blockade therapy. - Pathogenic variants in cancer risk genes for which clinical management is uncertain or not informed by well-established evidence will be identified. - Many individuals will have variants of uncertain significance (VUS). 29% to 63% of individuals with CRC may have a VUS at time of MGPT depending on the size of the gene panel.^{2,3,4,5} - Proportion of patients with VUS may be higher among people from racial/ethnic groups, particularly with utilization of large multigene panels, potentially increasing burden of uncertain results on these populations.^{5,7,8,9} - Capacity to offer MGPT to all patients with CRC and CRC survivors is uncertain. - In the United States, 150,000 individuals are diagnosed with CRC annually, and there are currently 1.5 million CRC survivors. - It is unclear if there is sufficient capacity to deliver pre-test informed consent and appropriate counseling to all individuals with pathogenic variants and VUS, as well as negative results. Currently, <40% of patients with CRC receive indicated genetic services.^{10,11,12} - Results may not return in time to inform surgical decision-making.

Note: All recommendations are category 2A unless otherwise indicated.

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[Continued](#)

HRS-A
1 OF 2



RATIONALE, PROS, AND CONS OF MULTIGENE PANEL TESTING FOR LYNCH SYNDROME AND OTHER CANCER RISK GENES

Challenges and Evidence Gaps:

- Impact of MGPT on subsequent cascade testing and evaluation for family members is uncertain.
 - ▶ Currently available studies of evaluating MGPT for patients with CRC report cascade testing occurred in 16% to 65% of families.^{3,5}
- Cost effectiveness is uncertain. There is no recent U.S.-based study using current testing costs. A Swiss study suggested MGPT was cost-effective relative to tumor-based screening for LS.¹³
- Yield in individuals with CRC unselected based on other characteristics is uncertain.
- Most currently available studies have potential selection bias that might overestimate yield of MGPT across the spectrum of all patients with CRC.
- Spectrum of pathogenic variants occurring in cancer risk genes among people from racial and ethnic groups requires additional research.

Test Selection:

- Germline MGPT should include at minimum the following CRC risk-associated genes: *APC*, *MUTYH*, *MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*, *BMP1A*, *SMAD4*, *PTEN*, *STK11*, and *TP53*
 - ▶ Selection of a panel that includes additional genes beyond this minimal set should be based on personal and family history of cancer, as well as patient and provider preference. For a list of additional genes that may confer a risk for colon and other cancers and any associated recommendations, see tables in [Multigene Testing \(GENE-1\)](#) and in the [NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic](#).

¹ Pearlman R, et al. JAMA Oncol 2017;3:464-471.

² Yurgelun MB, et al. J Clin Oncol 2017;35:1086-1095.

³ Pearlman R, et al. JCO Precis Oncol 2021;5:779-791.

⁴ Jiang W, et al. J Med Genet 2022;59:370-376.

⁵ Uson PLS, et al. Clin Gastroenterol Hepatol 2021;20:e508-e528.

⁶ Samadder NJ, et al. JAMA Oncol 2021;7:230-237.

⁷ Ricker C, et al. Cancer Genet 2016;209:130-137.

⁸ Caswell-Jin JL, et al. Genet Med 2018;20:234-239.

⁹ Ndugga-Kabuye MK and Issaka RB. Fam Cancer 2019;18:465-469.

¹⁰ Irons RF, et al. Int J Colorectal Dis 2017;32:1345-1348.

¹¹ Wood ME, et al. J Clin Oncol 2014;32:824-829.

¹² Cross DS, et al. Genet Med 2013;15:933-940.

¹³ Salikhanov I, et al. J Med Genet 2022;59:924-930.

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NCCN Guidelines Version 1.2023

High-Risk Colorectal Cancer Syndromes

PRINCIPLES OF CANCER RISK ASSESSMENT AND COUNSELING

- Cancer risk assessment and genetic counseling are highly recommended when genetic testing is offered, including consideration of the most appropriate tests to order (ie, pre-test counseling), and after results are disclosed (ie, post-test counseling).¹⁻⁵ A genetic counselor, medical geneticist, oncologist, gastroenterologist, surgeon, oncology nurse, or other health professional with expertise and experience in cancer genetics should be involved early in the counseling of patients.
- Testing should be considered in appropriate individuals at high risk where it will impact the medical care of the tested individuals and/or their family members who are at risk. Testing should be performed in a setting in which it can be adequately interpreted.¹

Pre-test counseling includes	Post-test counseling includes
• Assessing the patient's needs, level of concern about cancer risk/ mutation status, and goals of the cancer risk assessment • Collecting at least a three-generation pedigree/family history ▶ Note that when assessing family history, close blood relatives include first-, second-, and third-degree relatives on each side of the family and should include types of cancer, subtype and pathology, laterality, age of diagnosis, known consanguinity, and the patient/family's ancestry/country of origin (HRS-B 7 of 9) • Generating a differential diagnosis and educating the patient on inheritance patterns, penetrance, variable expressivity, and the possibility of genetic heterogeneity • Preparing the patient for possible outcomes of testing including positive (pathogenic, likely pathogenic), negative, uncertain, or mosaic results and unexpected findings such as a pathogenic variant in a gene that does not currently explain the patient's personal or family history • Discussing possible management options if a pathogenic variant is identified (ie, enhanced surveillance, risk-reducing chemopreventive agents, risk-reducing surgery) • Obtaining informed consent and documenting in the patient's medical record • Discussing plan for results disclosure, including patient consent for possibility of releasing results to the patient's relative or other designated individual if necessary • Discussing the financial costs of genetic counseling and testing • Discussing current legislation regarding genetic discrimination and privacy of genetic information (eg, Genetic Information Nondiscrimination Act of 2008 [GINA])	• Discussing results along with their significance and impact and recommended medical management options • Interpreting results in the context of patient's personal and family history of cancer • Informing about the importance of notifying family members who are at risk and offering materials/resources (eg, family letter) for informing and testing those family members • Making resources available to patients, such as disease-specific support groups, individual counseling, and research studies • Reviewing risk assessment and management recommendations for patients with family/personal history of polyps or cancer, but no identified pathogenic variant • Considering referral to research studies that aim to define the functional impact of VUSs such as variant reclassification programs through clinical labs or registries.

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[References](#)
[Continued](#)

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High-Risk Colorectal Cancer Syndromes

PRINCIPLES OF CANCER RISK ASSESSMENT AND COUNSELING

Genetic Testing Considerations

- Choice of/discussion of multigene testing options
- The probability of pathogenic/likely pathogenic variant detection will vary based on family structure. Individuals with unknown or limited family history/structure may have an underestimated probability of familial pathogenic/likely pathogenic variant detection. It is also important to consider potential inaccuracy of patient family history reporting.^{6,7,8}
- Comprehensive genetic testing includes full sequencing and testing for large genomic rearrangements. It is encouraged that testing be done in commercial or academic labs that are clinically approved and validated. [HRS-B 4 of 9](#).
- Likely pathogenic variants are typically treated as pathogenic variants.
- Patients who had limited genetic testing in the past (eg, *MLH1* or *MSH2* or *APC* only testing) may benefit from additional genetic testing using a larger MGPT.
- In children <18 years, genetic testing is generally not recommended unless results would impact medical management, such as initiation of early colonoscopy surveillance.⁹ Clear exceptions include when FAP, JPS, PJS, or constitutional MMR deficiency (CMMRD) syndrome are suspected or known to be present in a family, in which case testing prior to age 18 is recommended to guide medical management.
- Patients who have received an allogeneic bone marrow transplant should not have molecular genetic testing via blood or saliva samples due to unreliable test results from contamination by donor DNA. In such cases, DNA of the individual being tested should be extracted from a fibroblast culture from a skin punch biopsy. If this is not possible, buccal cells may be considered as an alternative source of DNA. However, it has been reported that over time buccal epithelial cells can be replaced by donor-derived cells. Fibroblast culture is also indicated when testing individuals with active or recent hematologic malignancies.

¹ Robson ME, Bradbury AR, Arun B, et al. American Society of Clinical Oncology Policy Statement Update: Genetic and Genomic Testing for Cancer Susceptibility. *J Clin Oncol* 2015;33:3660-3667.

² Berliner JL, Fay AM, Cummings SA, et al. NSGC practice guideline: Risk assessment and genetic counseling for hereditary breast and ovarian cancer. *J Genet Couns* 2013;22:155-163.

³ American College of Obstetricians and Gynecologists; ACOG Committee on Practice Bulletins--Gynecology; ACOG Committee on Genetics; Society of Gynecologic Oncologists. ACOG Practice Bulletin No. 103: Hereditary breast and ovarian cancer syndrome. *Obstet Gynecol* 2009;113:957-966.

⁴ Lancaster JM, Powell CB, Chen LM, Richardson DL; SGO Clinical Practice Committee. Society of Gynecologic Oncology statement on risk assessment for inherited gynecologic cancer predispositions. *Gynecol Oncol* 2015;136:3-7.

⁵ Weitzel JN, Blazer KR, Macdonald DJ, et al. Genetics, genomics, and cancer risk assessment: State of the art and future directions in the era of personalized medicine. *CA Cancer J Clin* 2011;61:327-359.

⁶ Schneider K, DiGianni L, Patenaude A, et al. Accuracy of cancer family histories: comparison of two breast cancer syndromes. *Genet Test* 2004;8:222-228.

⁷ Mitchell R, Brewster D, Campbell H, et al. Accuracy of reporting of family history of colorectal cancer. *Gut* 2004;53:291-295.

⁸ Ozanne E, O'Connell A, Bouzan C, et al. Bias in the reporting of family history: implications for clinical care. *J Genet Couns* 2012;21:547-556.

⁹ Committee on Bioethics; Committee on Genetics, and; American College of Medical Genetics and; Genomic Social; Ethical; Legal Issues Committee. Ethical and policy issues in genetic testing and screening of children. *Pediatrics* 2013;131:620-622.

Note: All recommendations are category 2A unless otherwise indicated.

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[Continued](#)



NCCN Guidelines Version 1.2023

High-Risk Colorectal Cancer Syndromes

PRINCIPLES OF CANCER RISK ASSESSMENT AND COUNSELING

Genetic Testing Approach

- If more than one family member is affected with cancer highly associated with a particular inherited cancer susceptibility syndrome, consider testing first a family member with youngest age at diagnosis, multiple primary cancers, or other cancers associated with the syndrome, or most closely related to the proband/patient. If there are no living family members with cancer that is a cardinal feature of the syndrome in question, consider testing first- or second-degree family members affected with other cancers thought to be related to the gene in question (eg, colorectal, endometrial, or urothelial with LS pathogenic variants).
- Testing of unaffected family members when no affected member is available should be considered. Significant limitations of interpreting test results should be discussed.
- If no pathogenic/likely pathogenic variant is found, consider referral for expert genetics evaluation if not yet performed; testing for other hereditary cancer syndromes may be appropriate.
- Testing family members for a VUS should not be performed for clinical purposes. Consider referral to research studies that aim to define the functional impact of VUSs such as variant reclassification programs through clinical labs or registries.

Risk to Relatives

- Advise about possible inherited cancer risk to relatives, options for risk assessment, and management.
- Recommend genetic counseling and consideration of genetic testing for relatives who are at risk.

Reproductive Options

- For patients of reproductive age, advise about options for prenatal diagnosis and assisted reproduction, including pre-implantation genetic testing. Discussion should include known risks, limitations, and benefits of these technologies.
- Biallelic pathogenic/likely pathogenic variants in some genes, such as *MUTYH*, and certain other genes included in gene panels, may be associated with autosomal recessive conditions. Thus, for these types of genes, consideration would be given to carrier testing the partner for pathogenic/likely pathogenic variants in the same gene if it would inform reproductive decision-making and/or risk assessment and management.¹⁰

¹⁰ Offit K, Levran O, Mullaney B, et al. Shared genetic susceptibility to breast cancer, brain tumors, and Fanconi anemia. J Natl Cancer Inst 2003;95:1548-1551.

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High-Risk Colorectal Cancer Syndromes

PRINCIPLES OF CANCER RISK ASSESSMENT AND COUNSELING

Evaluating the Source of Genetic Testing Information

- Prior to using any germline findings for medical management, it is important to establish whether the reported findings were obtained from a laboratory that is certified by both the College of American Pathologists (CAP) and Clinical Laboratory Improvement Amendments (CLIA) to issue a report of germline findings directly to ordering health care providers. Some states (eg, New York) may have additional reporting requirements.
- Confirmatory germline testing through an appropriately certified laboratory is recommended when a potential pathogenic/likely pathogenic variant is identified through various data sources as noted below:
 - ▶ Commercial entities providing ancestry (and sometimes health) information typically do so through microarray-based single nucleotide polymorphism (SNP) testing that has not been validated for clinical use. Third-party software applications can be used by consumers to obtain an interpretation of the raw data provided by these companies. Raw data and third-party software are not able to provide information that is appropriate for medical management, as these services are not subject to quality-control processes and recent research suggests that the error rate is substantial.¹¹
 - ▶ Research: Patients may have participated in research studies that include germline genomic analysis, or had some type of genomic testing because of a suspected genetic condition in their self or a relative. Incidental germline findings relating to cancer risk may have been reported.¹² In such cases, it is recommended to review the patient's findings with a genetics professional and/or the reporting laboratory to establish whether the original report was generated by an appropriately certified laboratory, and whether confirmatory testing is recommended.

¹¹ Tandy-Connor S, Guiltinan J, Krempely K, et al. False-positive results released by direct-to-consumer genetic tests highlight the importance of clinical confirmation testing for appropriate patient care. *Genet Med* 2018;20:1515-1521.

¹² Green R, Berg J, Grody W, et al. ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. *Genet Med* 2013;15:565-574.

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[Continued](#)

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High-Risk Colorectal Cancer Syndromes

PRINCIPLES OF CANCER RISK ASSESSMENT AND COUNSELING

Tumor Genomic Testing: Potential Implications for Germline Testing

- Tumor testing can be complementary to germline testing and can assist in interpretation of results. However, the following points should be considered:
 - ▶ Pathogenic/likely pathogenic variants reported by laboratories providing tumor-only profiling may be of somatic or germline origin. Although germline origin can sometimes be inferred with a high degree of confidence, confirmatory germline testing is indicated for pathogenic/likely pathogenic variants with a reasonable clinical suspicion of being of germline origin (based on patient/family history or clinical characteristics, presence of founder mutation, and in some cases variant allele frequency).
 - ▶ Somatic pathogenic/likely pathogenic variants in several genes with germline implications are common (eg, *TP53*, *STK11*, *PTEN*, *APC*), and will rarely be indicative of a need for germline testing unless clinical/family history features suggest the possibility of a germline pathogenic/likely pathogenic variant.
 - ▶ It should be noted that the absence of reported pathogenic/likely pathogenic variants in a particular gene based on tumor testing does not rule out the possibility of a germline pathogenic/likely pathogenic variant in that gene. Clinically indicated germline testing is still appropriate for patients meeting testing guidelines regardless of tumor profiling results.

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High-Risk Colorectal Cancer Syndromes

PRINCIPLES OF CANCER RISK ASSESSMENT AND COUNSELING

Obtaining a Comprehensive Assessment for Hereditary Colorectal Cancer¹³

Family History of Cancer and Expanded Pedigree

- It is essential to obtain a detailed family history, including:
 - Parents
 - Children
 - Siblings/half-siblings
 - Aunts and uncles
 - Grandparents
 - First cousins
 - Nieces and nephews
- Recommended data on each affected relative:
 - Current age and age at diagnosis of cancer (medical record documentation of cancer is strongly encouraged)
 - Age and cause of death
 - Type of cancer (note multiple primaries)
 - Ethnicity/country of origin
 - Consanguinity
 - Concerns regarding non-paternity
 - Birth resulting from sperm or egg donor
 - Suspected colon cancer syndromes and additional syndrome-specific features (eg, Muir-Torre syndrome, Turcot syndrome, PJS, JPS)¹⁴
 - All other inherited conditions and birth defects
 - History of allogeneic (related or unrelated donor) bone marrow transplant
 - Genetic test results in family members

Detailed Medical and Surgical History

- Sex assigned at birth
- Pathology verification strongly encouraged
- Polyps, including number and histology
- Inflammatory bowel disease
- Inherited polyposis and cancer syndromes
- For patients with prior cancer:
 - age at diagnosis
 - treatment history
 - results of any tumor-based genetic or molecular testing

Directed Examination for Related Manifestations (if suspicion for a CRC syndrome)

- Colonoscopy
- Esophagogastroduodenoscopy (EGD)
- Indicated only if suspicion of a specific syndrome
 - Eye examination
 - Skin, soft tissue, and bone examination
 - Oral examination
 - Measurement of head circumference to evaluate for macrocephaly (≥97%; ≥58 cm in adult patients assigned female at birth and ≥60 cm in adult patients assigned male at birth)

Common Pedigree Symbols (HRS-B 7 of 9)

and

Pedigree: First-, Second-, and Third-Degree

Relatives of Proband (HRS-B 9 of 9)

¹³ Providers should be aware that multiple factors may limit the benefits of family history in helping to determine a patient's degree of cancer risk, including: small family size; unknown family history, eg, adoption or non-paternity; the potential for a new pathogenic variant arising in the patient (de novo pathogenic variant); variable penetrance of a pathogenic variant; autosomal recessive inheritance of risk; and mosaicism.

¹⁴ Burt R and Neklason DW. Genetic testing for inherited colon cancer. *Gastroenterology* 2005;128:1696-1716. Muir-Torre syndrome refers to individuals with LS who have LS-associated skin findings of sebaceous adenomas/carcinomas or keratoacanthomas. Turcot syndrome refers to individuals with LS or FAP and brain tumors, most commonly glioblastomas and medulloblastomas, respectively. Reference to Turcot syndrome is therefore imprecise and NCCN recommends against use of this eponym.

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High-Risk Colorectal Cancer Syndromes

PRINCIPLES OF CANCER RISK ASSESSMENT AND COUNSELING

COMMON PEDIGREE SYMBOLS¹⁵

Gender	Sex		
	Male	Female	Unassigned at Birth
Man/Boy		 AFAB (assigned female at birth)	 UAAB (unassigned at birth)
Woman/Girl	 AMAB (assigned male at birth)		 UAAB (unassigned at birth)
Non-binary/ Gender diverse	 AMAB (assigned male at birth)	 AFAB (assigned female at birth)	 UAAB (unassigned at birth)

[Pedigree: First-, Second-, and Third-Degree
Relatives of Proband \(HRS-B 9 of 9\)](#)

¹⁵ Bennett R, French K, Resta R, Austin J. Practice resource-focused revision: Standardized pedigree nomenclature update centered on sex and gender inclusivity: A practice resource of the National Society of Genetic Counselors. J Genet Couns 2022;31:1238-1248.

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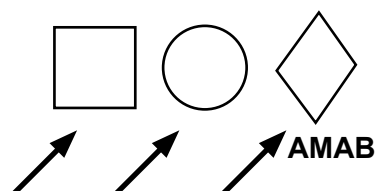


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High-Risk Colorectal Cancer Syndromes

PRINCIPLES OF CANCER RISK ASSESSMENT AND COUNSELING

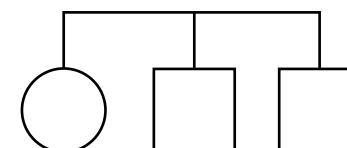
COMMON PEDIGREE SYMBOLS¹⁵



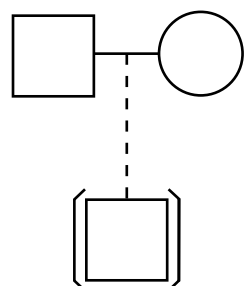
Consultand/
Proband
(initiating genetic
workup, shade if
affected)



Relationship
line



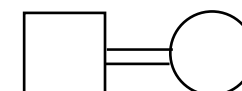
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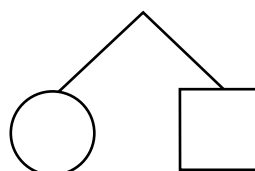
Adopted into
a family



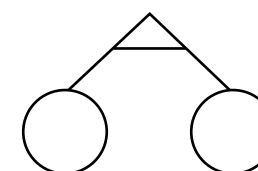
Deceased



Consanguinity



Dizygotic
twins



Monozygotic
twins

AMAB = assigned male at birth

[Pedigree: First-, Second-, and Third-Degree
Relatives of Proband \(HRS-B 9 of 9\)](#)

¹⁵ Bennett R, French K, Resta R, Austin J. Practice resource-focused revision: Standardized pedigree nomenclature update centered on sex and gender inclusivity: A practice resource of the National Society of Genetic Counselors. J Genet Couns 2022;31:1238-1248.

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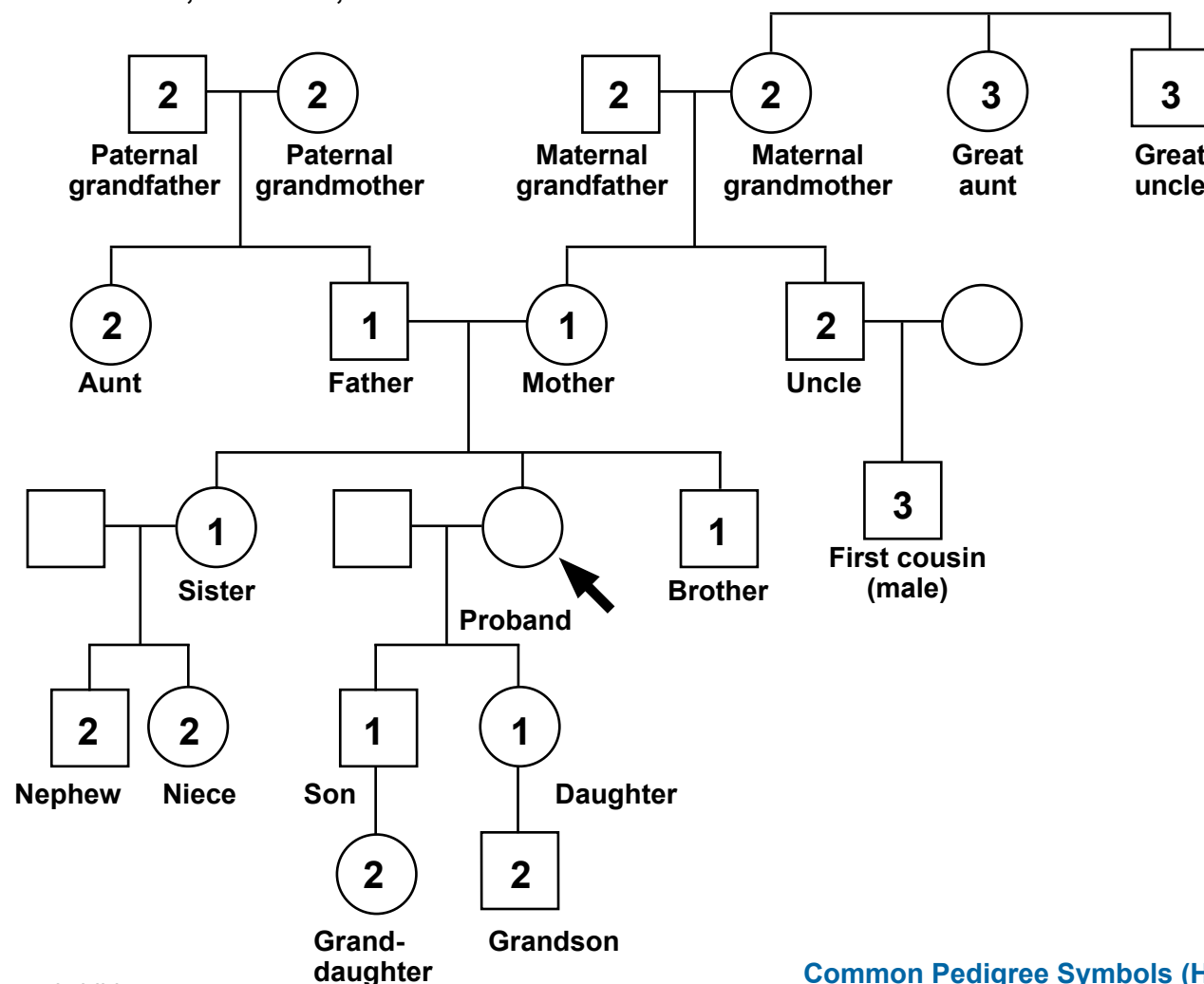


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High-Risk Colorectal Cancer Syndromes

PRINCIPLES OF CANCER RISK ASSESSMENT AND COUNSELING

PEDIGREE: FIRST-, SECOND-, AND THIRD-DEGREE RELATIVES OF PROBAND¹⁶



[Common Pedigree Symbols \(HRS-B 7 of 9\)](#)

¹⁶ First-degree relatives: parents, siblings, and children;

Second-degree relatives: grandparents, aunts, uncles, nieces, nephews, grandchildren, and half-siblings;

Third-degree relatives: great-grandparents, great-aunts, great-uncles, great-grandchildren, first cousins, and half aunts and half uncles.

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NCCN Guidelines Version 1.2023

Lynch Syndrome

CRITERIA FOR THE EVALUATION OF LYNCH SYNDROME BASED ON PERSONAL OR FAMILY HISTORY OF CANCER^a

• Known LS pathogenic variant in the family

• An individual with a LS-related cancer^b and any of the following:

- ▶ Diagnosed <50 y
- ▶ A synchronous or metachronous LS-related cancer^b regardless of age
- ▶ 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 regardless of age
- ▶ ≥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 LS

- ▶ An individual with a ≥5% risk of having an MMR gene pathogenic variant based on predictive models (ie, PREMM₅, MMRpro, MMRpredict)
 - ◊ Individuals with a personal history of CRC and/or endometrial cancer with a PREMM₅ score of ≥2.5% should be considered for MGPT.
 - ◊ For individuals without a personal history of CRC and/or endometrial cancer, some data have suggested using a PREMM₅ score threshold of ≥2.5% rather than ≥5% to select individuals for MMR genetic testing. Based on these data, it is reasonable for testing to be done based on the ≥2.5% score result and clinical judgment. Of note, with the lower threshold, there is an increase in sensitivity, but a decrease in specificity.

• Personal history of a tumor with MMR deficiency determined by PCR, NGS, or IHC diagnosed at any age^{b,d}

[Strategies for
Evaluating for
LS \(LS-2\)](#)

Germline MGPT
evaluation for LS
and other hereditary
cancer syndromes^e
OR
Additional tumor-
based testing ([LS-A](#))

^a This assumes criteria for evaluation for a polyposis syndrome on hereditary risk assessment has not been met.

^b LS-related cancers include colorectal, endometrial, gastric, ovarian, pancreatic, urothelial, brain (usually glioblastoma), biliary tract, and small intestine, as well as sebaceous adenomas, sebaceous carcinomas, and keratoacanthomas as seen in Muir-Torre syndrome.

^c Indicates family history on same side of family.

^d The panel recommends tumor screening for MMR deficiency for all CRC and endometrial cancers regardless of age at diagnosis. Tumor screening for CRCs for MMR deficiency for purposes of screening for LS is not required if MGPT is chosen as the strategy for screening for LS, but may still be required for CRC therapy selection. Consider tumor screening for MMR deficiency for sebaceous neoplasms as well as the following adenocarcinomas: small bowel, ovarian, gastric, pancreatic, biliary tract, brain, bladder/urothelial, and adrenocortical cancers regardless of age at diagnosis. Latham A, et al. J Clin Oncol 2019;37:286-295. [Tumor Testing Results and Additional Testing Strategies \(LS-A 7 of 9\)](#). Direct referral for germline testing to rule out LS may be preferred in patients with a strong family history or if diagnosed prior to age 50 y (Pearlman R, et al. JAMA Oncol 2017;3:464-471; Yurgelun M, et al. J Clin Oncol 2017;35:1086-1095), MSI-H, or loss of MMR protein expression. See [LS-A](#) for details on tumor screening for LS. For patients aged ≥50 at CRC diagnosis, the panel has also recommended to consider germline MGPT evaluation for LS and other hereditary cancer syndromes (category 2B, see [HRS-3](#)).

^e Biallelic *MUTYH* gene mutations have been shown to lead to dMMR tumors; therefore, *MUTYH* should be included in the testing at a minimum with consideration of other base-excision repair genes (*NTHL1*) and DNA polymerase genes (*POLE* and *POLD1*), which have the potential to also lead to biallelic somatic MMR gene inactivation (Morak M, et al. Eur J Hum Genet 2014;22:1334-1337).

Note: All recommendations are category 2A unless otherwise indicated.

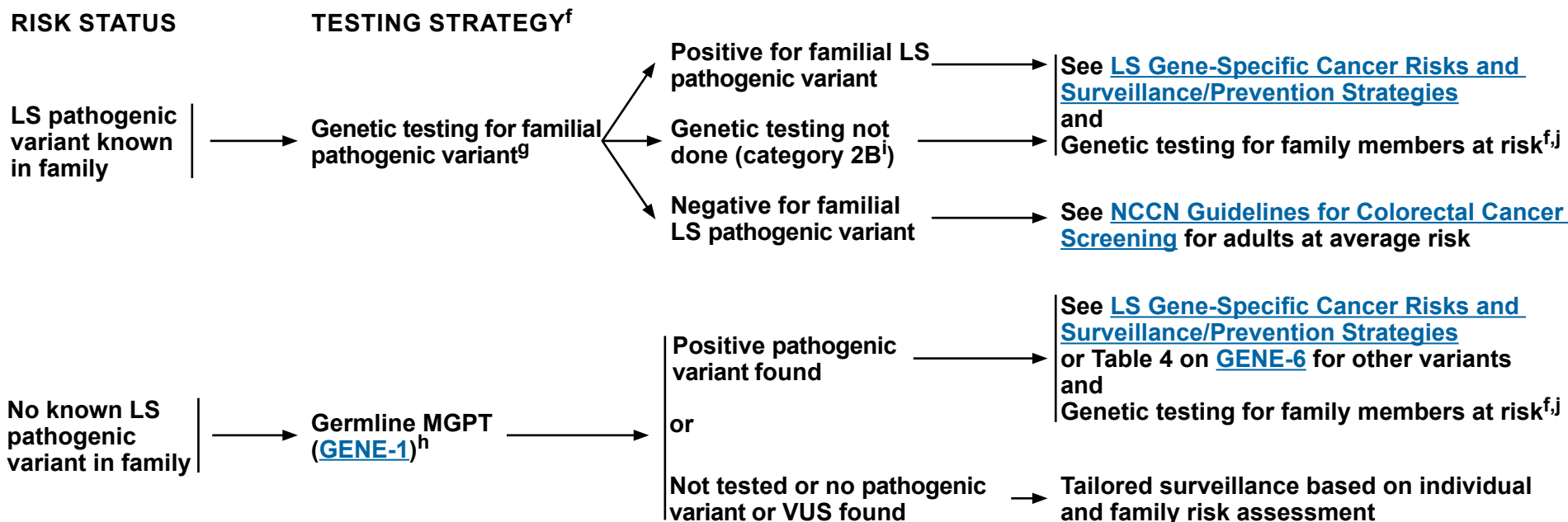
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Lynch Syndrome

STRATEGIES FOR EVALUATING FOR LS IN INDIVIDUALS MEETING CRITERIA FOR THE EVALUATION OF LS



^f An individual with expertise in genetics should be involved in the testing process. Minimum pretest counseling (in person or through written or video) materials with pros and cons of testing should be provided. See [Principles of Cancer Risk Assessment and Counseling \(HRS-B\)](#).

^g Additional testing may be indicated based on personal and family medical history.

^h If there is more than one affected family member, first consider testing the family member with: youngest age at diagnosis, multiple primaries, or colorectal or endometrial cancers. Testing of unaffected family members when no affected member is available should be considered. Limitations of interpreting test results should be discussed.

ⁱ The recommendation to provide care for patients in whom genetic testing was not done using LS management recommendations is category 2B.

^j If a first-degree relative is unavailable or unwilling to be tested, more distant relatives should be offered testing for the known pathogenic variant in the family.

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**PRINCIPLES OF dMMR TESTING FOR LYNCH SYNDROME**

- The panel recommends universal screening of all CRCs and endometrial cancers to maximize sensitivity for identifying individuals with LS and to simplify care processes. The panel also recommends considering tumor screening for MMR deficiency for sebaceous neoplasms as well as the following adenocarcinomas: small bowel, ovarian, gastric, pancreatic, biliary tract, brain, bladder/urothelial, and adrenocortical cancers regardless of age at diagnosis (Latham A, et al. J Clin Oncol 2019;37:286-295). Counseling by an individual with expertise in genetics is not required prior to routine tumor testing. An infrastructure needs to be in place to handle the screening results.

General

- IHC and MSI analyses are screening tests (either by themselves or in conjunction) that are typically performed on colorectal and endometrial cancer tissue to identify individuals at higher risk for having LS. Greater than 90% of LS tumors are MSI-high (MSI-H) and/or lack expression of at least one of the MMR proteins by IHC. Ten percent to 15% of sporadic colon cancers exhibit abnormal IHC and are MSI-H most often due to abnormal methylation of the *MLH1* gene promoter, rather than due to LS. Mutant *BRAF* V600E is found in many sporadic MSI-H CRCs and is rarely found in LS-related CRCs. There are some tumors that will have *MLH1* methylation but lack a *BRAF* pathogenic variant. Thus, the presence of an abnormal *MLH1* IHC test increases the possibility of LS but does not make a definitive diagnosis. Confirmed diagnosis of LS is based on germline testing, when tumor-based testing scenarios or other factors raise suspicion for the diagnosis ([LS-A 7 of 9](#)). Also, sporadic endometrial cancers may exhibit abnormal MSI/IHC due to abnormal methylation of the *MLH1* promoter. Somatic MMR genetic testing of the corresponding gene(s) (see “Plausible Etiologies” for possibilities on [LS-A 7 of 9](#)) could be performed on tumor DNA to assess for pathogenic variants that might explain the abnormal IHC and/or MSI-H results.
- For CRC, MSI has slightly greater sensitivity than IHC for identifying LS (92.9% vs. 88.9%–92.4%, respectively), but MSI is unable to be performed (due to small tumor size) more often than IHC (14% vs. 0.3%, respectively). Concordance between MSI and IHC is very high (99.1%).¹
- The panel recommends a universal screening strategy be the primary approach to identify patients with CRC and LS. However, in other lower resource settings, other historic criteria for selecting patients for testing may be relevant. The Bethesda criteria ([Discussion](#)) are intended to help identify patients with CRC whose tumors should be tested for MMR defects, by MSI and/or IHC analysis, thereby identifying patients with a greater chance of having LS.

¹ Pearlman R, Frankel W, Swanson B, et al. Prospective Statewide Study of Universal Screening for Hereditary Colorectal Cancer: The Ohio Colorectal Cancer Prevention Initiative. JCO Precis Oncol 2021 May 5.

Note: All recommendations are category 2A unless otherwise indicated.

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[Continued](#)

**PRINCIPLES OF dMMR TESTING FOR LYNCH SYNDROME****IHC**

- IHC refers to staining tumor tissue for protein expression of the 4 MMR genes known to be mutated in LS: *MLH1*, *MSH2*, *MSH6*, and *PMS2*. A normal IHC test implies all 4 MMR proteins are normally expressed, and thus it is unlikely that an underlying MMR gene pathogenic variant is present. An abnormal test means that at least one of the proteins is "not detected," and an inherited pathogenic variant may be present in the related gene. Loss of protein expression by IHC in any one of the MMR genes guides further genetic testing (pathogenic variant detection) to the gene(s) where protein expression is not observed or to the corresponding protein dimer. Absent expression of one or more of the 4 DNA MMR proteins is often reported as abnormal or "positive" IHC. When "positive" IHC is reported, caution should be taken in making sure that positive refers to absence of MMR protein expression, and not to presence of expression.
- Abnormal *MLH1* IHC should be followed by either germline genetic testing or tumor testing for *MLH1* methylation for CRC or endometrial cancers. Alternatively for CRCs with loss of *MLH1* on IHC, the tumor can be tested for a *BRAF* V600E pathogenic variant. Testing for *BRAF* pathogenic variants using IHC is not sufficiently sensitive in general but it may be an option for situations with insufficient tumor material for molecular testing since it only requires one slide. Presence of *MLH1* hypermethylation, *BRAF* V600E pathogenic variant, or abnormal *BRAF* V600E protein by IHC is consistent with sporadic cancer. If *MLH1* promoter methylation or *BRAF* testing is normal, or negative, germline genetic testing is indicated ([LS-A 7 of 9](#)). Those with a germline pathogenic variant are then identified as patients with LS. *BRAF* V600E pathogenic variants are found in 69% of methylated CRCs, so the absence of a *BRAF* V600E pathogenic variant does not rule out *MLH1* methylation. As a result, there may be a role for methylation testing to rule out LS in MSI-H tumors in which no *BRAF* pathogenic variant is found either prior to genetic testing or in the event genetic testing is negative. If abnormal IHC is followed by germline testing and no LS-causing pathogenic variants are identified, the panel strongly recommends proceeding with *MLH1* methylation analysis of the tumor. Patients who have normal germline testing and *MLH1* hypermethylation are likely to have sporadic cancer and should be treated as such taking into account their family history.
- If clinical suspicion for LS is high despite a normal IHC screening result, consider genetic evaluation and testing.
- There is a 5%–10% false-negative rate with IHC testing.^{1,2}

¹ Pearlman R, Frankel W, Swanson B, et al. Prospective Statewide Study of Universal Screening for Hereditary Colorectal Cancer: The Ohio Colorectal Cancer Prevention Initiative. JCO Precis Oncol 2021 May 5.

² Hampel H, Pearlman R, de la Chapelle A, et al. Double somatic mismatch repair gene pathogenic variants as common as Lynch syndrome among endometrial cancer patients. Gynecol Oncol 2021;160:161-168.

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[Continued](#)

**PRINCIPLES OF dMMR TESTING FOR LYNCH SYNDROME****IHC (continued)****• Adenomas:**

▶ IHC can also be performed on colorectal adenomas if cancer tissue is not available. An abnormal result, defined by loss of staining, can be identified in as many as 70%–79% of Lynch-associated adenomas. Adenoma size >10 mm and/or the presence of high-grade dysplasia within the polyp increases sensitivity of IHC for LS.^{3,4,5} The suboptimal sensitivity of IHC performed on polyps means this approach should not be used to exclude LS. An abnormal polyp IHC result should be referred for genetic evaluation and testing. If *PMS2* and *MLH1* are missing, further tumor testing should be considered before referring for genetic testing.

• Rectal cancers treated with neoadjuvant chemotherapy and radiation therapy (RT):⁶

▶ False abnormal IHC has been reported in rectal cancer resection specimens after neoadjuvant chemotherapy and RT. As a result, some NCCN Member Institutions avoid doing IHC on rectal cancers after neoadjuvant chemotherapy and RT. Others still perform IHC on rectal cancers after neoadjuvant chemotherapy and RT, but if expression is absent (particularly *MSH6*) the testing is repeated on the pretreatment biopsy.

• Sebaceous neoplasms:⁷⁻¹¹

▶ The sensitivity and specificity of MMR IHC on sebaceous neoplasms in LS is much lower than that of CRC (85% vs. 92%–94% and 48% vs. 88%–100%). The false-positive rate has been reported to be 56%. A scoring system taking into account age at diagnosis, number of sebaceous neoplasms, and personal or family history of LS-associated cancers can be used to determine which patients with sebaceous neoplasms need IHC.¹¹

• Metastatic CRC (liver, lymph node, and other metastases):¹²

▶ There are data showing that the MSI and IHC results in primary tumors match the MSI and IHC results in metastatic tissue from the same tumor; therefore, this should be an acceptable alternative if the primary tumor is not available.

³ Pino MS, Mino-Kenudson M, Wildemore BM, et al. Deficient DNA mismatch repair is common in Lynch syndrome-associated colorectal adenomas. *J Mol Diagn* 2009;11:238-247.

⁴ Walsh MD, Buchanan DD, Pearson S-A, et al. Immunohistochemical testing of conventional adenomas for loss of expression of mismatch repair proteins in Lynch syndrome mutation carriers: a case series from the Australasian site of the colon cancer family registry. *Mod Pathol* 2012;25:722-730.

⁵ Yurgelun MB, Goel A, Hornick JL, et al. Microsatellite instability and DNA mismatch repair protein deficiency in Lynch syndrome colorectal polyps. *Cancer Prev Res (Phila)* 2012;5:574-582.

⁶ Vilkin A, Halpern M, Morgenstern S, et al. How reliable is immunohistochemical staining for DNA mismatch repair proteins performed after neoadjuvant chemoradiation? *Hum Pathol* 2014;45:2029-2036.

⁷ Roberts ME, Riegert-Johnson DL, Thomas BC, et al. Screening for Muir-Torre syndrome using mismatch repair protein immunohistochemistry of sebaceous neoplasms. *J Genet Couns* 2013;22:393-405.

⁸ Hampel H, Frankel WL, Martin E, et al. Feasibility of screening for Lynch syndrome among patients with colorectal cancer. *J Clin Oncol* 2008;26:5783-5788.

⁹ Hampel H, Stephens JA, Pukkala E, et al. Cancer risk in hereditary nonpolyposis colorectal cancer syndrome: later age of onset. *Gastroenterology* 2005;129:415-421.

¹⁰ Lindor NM, Burgart LJ, Leontovich O, et al. Immunohistochemistry versus microsatellite instability testing in phenotyping colorectal tumors. *J Clin Oncol* 2002;20:1043-1048.

¹¹ Roberts ME, Riegert-Johnson DL, Thomas BC, et al. A clinical scoring system to identify patients with sebaceous neoplasms at risk for the Muir-Torre variant of Lynch syndrome. *Genet Med* 2014;16:711-716.

¹² Haraldsdottir S, Roth R, Pearlman R, et al. Mismatch repair deficiency concordance between primary colorectal cancer and corresponding metastasis. *Fam Cancer* 2016;15:253-260.

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[Continued](#)

**PRINCIPLES OF dMMR TESTING FOR LYNCH SYNDROME****MSI**

- **MSI-H in tumors refers to the tumor having a proportion of alterations in a predetermined panel of microsatellite repeat markers that indicates the loss of MMR activity. Its significance, use, and implications are similar to that of IHC, although the tests are slightly complementary.**
- **Laboratories vary in their approach in testing MSI. Dinucleotide markers may be less specific than mononucleotide markers of MSI.¹³**
- **There is a 5%–15% false-negative rate with MSI testing.**

General Principles of MSI Detection by PCR^{14,15}

- **In this method, MSI is identified by PCR amplification of microsatellite repeats, followed by either electrophoresis or liquid chromatography.**
- **Various panels exist that range from testing five (Bethesda/NCI) to seven (Promega) unique microsatellite loci.**
- **The Bethesda/NCI panel consists of two mononucleotide loci (BAT-25 and BAT-26) and three dinucleotide loci (D2S123, D5S346, and D17S250).**
- **The Promega panel consists of five mononucleotide loci (BAT-25, BAT-26, NR-21, NR-24, and MONO-27) as well as two pentanucleotide loci (used for specimen identification).**
- **MSI is identified when a microsatellite in the tumor has changed in size compared to the patient's normal control.**
- **Using the Bethesda/NCI method, tumors are classified as microsatellite stable (MSS) (zero loci show a change in size/are unstable), MSI-low (MSI-L) (one locus shows a change in size/are unstable), or MSI-H (two or greater loci show a change in size/are unstable)**
- **Using the Promega method, tumors are classified as MSS (zero or one loci show a change in size/are unstable) or MSI-H (two or greater loci show a change in size/are unstable).**
- **The estimated specificity of the detection of LS by PCR-based methods for MSI is 90.2% (95% CI, 87.7%–92.7%).**
- **The estimated sensitivity of the detection of LS by PCR-based methods for MSI is 85% (95% CI, 75%–92%).**

¹³ Xicola RM, Llor X, Pons E. Performance of different microsatellite marker panels for detection of mismatch repair-deficient colorectal tumors. J Natl Cancer Inst 2007;99:244-252.

¹⁴ Palomaki GE, McClain MR, Melillo S, et al. EGAPP supplementary evidence review: DNA testing strategies aimed at reducing morbidity and mortality from Lynch syndrome. Genet Med 2009;11:42-65.

¹⁵ Baudrin LG, Deleuze JF, How-Kit A. Molecular and computational methods for the detection of microsatellite instability in cancer. Front Oncol 2018;8:621.

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[Continued](#)



PRINCIPLES OF dMMR TESTING FOR LYNCH SYNDROME

General Principles of Next-Generation Sequencing (NGS) Testing for MSI¹⁵⁻²⁰

- MSI can be detected through bioinformatic analysis of NGS.
- Rather than 5–8 microsatellite foci analyzed (as performed in MSI by PCR), NGS can analyze anywhere from dozens to hundreds of microsatellites.
- MSI is determined by comparing the length distribution and variation of a selection of microsatellite loci within a tumor and determining a differential as compared to the read counts of all normal alleles within a distribution.
- The size of microsatellite loci can include pentamers, tetramers, trimers, dimers, and monomers.
- Various comparative methods exist to identify MSI: tumor vs. paired normal or tumor vs. baseline normal
- Sophisticated bioinformatics protocols are necessary to use NGS as a method for MSI.
- Depending on the bioinformatic program used, analysis may be of whole exome sequencing data, whole genome sequencing data, or targeted genomic sequencing data.
- Tumor mutational burden (TMB) can be used as a surrogate to some degree for MSI, but there are causes of increased TMB other than dMMR.
- Further studies are needed to determine the sensitivity and specificity compared to MMR IHC and MSI by PCR.
- Any patient with a tumor that demonstrates MSI-H by NGS should be referred to a cancer geneticist for germline MMR testing.
- MSI by NGS does not require confirmation by more traditional measurement of MSI by PCR or IHC if the laboratory has validated the assay for use in the cancer in which it is being used.

- ¹⁵ Baudrin LG, Deleuze JF, How-Kit A. Molecular and computational methods for the detection of microsatellite instability in cancer. *Front Oncol* 2018;8:621.
- ¹⁶ Bonneville R, Krook MA, Chen HZ, et al. Detection of microsatellite instability biomarkers via next-generation sequencing. *Methods Mol Biol* 2020;2055:119-132.
- ¹⁷ Kautto EA, Bonneville R, Miya J, et al. Performance evaluation for rapid detection of pan-cancer microsatellite instability with MANTIS. *Oncotarget* 2017;8:7452-7463.
- ¹⁸ Niu B, Ye K, Zhang Q, et al. MSIsensor: microsatellite instability detection using paired tumor-normal sequence data. *Bioinformatics* 2014;30:1015-1016.
- ¹⁹ Salipante SJ, Scroggins SM, Hampel HL, et al. Microsatellite instability detection by next generation sequencing. *Clin Chem* 2014;60:1192-1199.
- ²⁰ Latham A, Srinivasan P, Kemel Y, et al. Microsatellite instability is associated with the presence of Lynch syndrome pan-cancer. *J Clin Oncol* 2019;37:286-295.

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[Continued](#)

LS-A
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Lynch Syndrome

PRINCIPLES OF dMMR TESTING FOR LYNCH SYNDROME

Pros and Cons of Universal Tumor Screening with IHC and/or MSI for LS Using Colonoscopy-Based Biopsy Versus Surgical Resection Specimen^{21,22}

Pre-surgical Testing Considerations

- **Pros**
 - Informs surgical decision-making (subtotal vs. segmental resection)
 - For rectal tumors requiring neoadjuvant chemotherapy and RT, IHC is more reliable when done on pre-RT specimens^{23,24}
 - Allows for LS screening of patients with rectal cancer who elect for neoadjuvant therapy or nonoperative management
- **Cons**
 - Possibility of insufficient tissue for analysis
 - Screening could be done twice (once on biopsy and once on surgical resection), thereby decreasing cost-effectiveness

Post-surgical Testing Considerations

- **Pros**
 - Larger specimen allows for higher chance of informative dMMR testing
 - Ensures test is only done once
- **Cons**
 - Cannot inform surgical decision-making
 - In rectal tumors exposed to neoadjuvant chemotherapy and RT, IHC may be less reliable, with the potential for false-negative result (particularly *MSH6*)

Pros and Cons of Universal Tumor Screening with IHC and/or MSI for LS Using Endometrial Biopsy Versus Surgical Resection

Pre-surgical Testing Considerations

- **Pros**
 - Informs surgical decision-making (salpingo-oophorectomy vs. salpingectomy)
 - For endometrial tumors treated with progestin therapy, there may not be residual tumor at hysterectomy
 - Some patients may not undergo hysterectomy
- **Cons**
 - Possibility of insufficient tissue for analysis

Post-surgical Testing Considerations

- **Pros**
 - Larger specimen allows for higher chance of informative dMMR testing
- **Cons**
 - Possibility of insufficient tissue for diagnosis due to treatment response or complete resection at endometrial sampling. In these cases, the preoperative biopsy specimen may be tested for evidence of dMMR
 - Missed opportunity to counsel on and perform bilateral salpingo-oophorectomy at time of hysterectomy

²¹ Kumarasinghe AP, de Boer B, Bateman AC, Kumarasinghe MP. DNA mismatch repair enzyme immunohistochemistry in colorectal cancer: a comparison of biopsy and resection material. *Pathology* 2010;42:414-420.

²² Shia J, Stadler Z, Weiser MR, et al. Immunohistochemical staining for DNA mismatch repair proteins in intestinal tract carcinoma: How reliable are biopsy samples? *Am J Surg Pathol* 2011;35:447-454.

²³ Bao F, Panarelli NC, Rennert H, et al. Neoadjuvant therapy induces loss of MSH6 expression in colorectal carcinoma. *Am J Surg Pathol* 2010;34:1798-1804.

²⁴ Radu OM, Nikiforova MN, Farkas LM, Krasinskas AM. Challenging cases encountered in colorectal cancer screening for Lynch syndrome reveal novel findings: nucleolar MSH6 staining and impact of prior chemoradiation therapy. *Hum Pathol* 2011;42:1247-1258.

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[Continued](#)



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Lynch Syndrome

TUMOR TESTING RESULTS AND ADDITIONAL TESTING STRATEGIES^j

Tumor Testing ^a							Plausible Etiologies	NOTE: Regardless of LS test Additional Testing ^{e,f} results, consider genetic evaluation if <50 years
IHC				MSI ^b	BRAF V600E ^c	MLH1 Promoter Methylation		
MLH1	MSH2	MSH6	PMS2					
NL	NL	NL	NL	MSS	N/A	N/A	1) Sporadic cancer 2) Other (not LS hereditary CRC syndrome)	1) None ^d
Any AB				MSS	N/A	N/A	1) Sporadic cancer 2) Germline pathogenic variant in any of the LS genes	1) Germline MMR testing or paired germline MMR/somatic MMR tumor testing ^g 2) If germline testing negative and paired somatic MMR genetic testing not done, consider somatic MMR genetic testing ⁱ
NL	NL	NL	NL	MSI-H	N/A	N/A	1) Sporadic cancer 2) Germline pathogenic variant in any of the LS genes	1) Germline MMR testing or paired germline MMR/somatic MMR tumor testing; ^g 2) If germline testing negative and paired somatic MMR genetic testing not done, consider somatic MMR genetic testing ⁱ
N/A	N/A	N/A	N/A	MSI-H	N/A	N/A	1) Sporadic cancer 2) Germline pathogenic variant in any of the LS genes	1) Consider IHC analysis and additional testing depending on IHC results 2) If IHC not performed, consider germline MMR testing or paired germline MMR/somatic MMR tumor testing 3) If germline testing negative and paired somatic MMR genetic testing not done, consider somatic MMR genetic testing ⁱ
AB	NL	NL	AB	N/A	N/A	N/A	1) Sporadic cancer 2) Germline <i>MLH1</i> pathogenic variant or rarely <i>PMS2</i>	1) <i>BRAF</i> pathogenic variant testing ^c / <i>MLH1</i> promoter methylation testing first ^l 2) If <i>BRAF/MLH1</i> methylation testing normal, germline MMR testing or paired germline MMR/somatic MMR tumor testing; ^g 3) If germline testing negative and paired somatic MMR genetic testing not done, consider somatic MMR genetic testing ⁱ
AB	NL	NL	AB	N/A	Positive	N/A	1) Sporadic cancer 2) Rarely germline <i>MLH1</i> pathogenic variant or constitutional <i>MLH1</i> epimutation	1) None, unless young age of onset or significant family history; then consider constitutional <i>MLH1</i> epimutation testing ^h and/or germline MMR testing ^g
AB	NL	NL	AB	N/A	Negative	Positive	1) Sporadic cancer 2) Rarely germline <i>MLH1</i> pathogenic variant or constitutional <i>MLH1</i> epimutation	

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[Footnotes on LS-A 9 of 9](#)



NCCN Guidelines Version 1.2023

Lynch Syndrome

TUMOR TESTING RESULTS AND ADDITIONAL TESTING STRATEGIES^l

Tumor Testing ^a							Plausible Etiologies	Additional Testing ^{e,f} NOTE: Regardless of LS test results, consider genetic evaluation if <50 years
IHC				MSI	BRAF V600E ^c	MLH1 Promoter Methylation		
MLH1	MSH2	MSH6	PMS2					
AB	NL	NL	AB	N/A	Negative	Negative	1) Germline <i>MLH1</i> pathogenic variant or rarely <i>PMS2</i> 2) Sporadic cancer	1) Germline MMR testing or paired germline MMR/somatic MMR tumor testing; ⁹ 2) If germline testing negative and paired somatic MMR genetic testing not done, consider somatic MMR genetic testing ⁱ
NL	AB	AB	NL	N/A	N/A	N/A	1) Germline <i>MSH2/EPCAM</i> pathogenic variant; or rarely germline <i>MSH6</i> pathogenic variant 2) Sporadic cancer	
NL	NL	NL	AB	N/A	N/A	N/A	1) Germline <i>PMS2</i> pathogenic variant 2) Germline <i>MLH1</i> pathogenic variant 3) Sporadic cancer	
NL	AB	NL	NL	N/A	N/A	N/A	1) Germline <i>MSH2/EPCAM</i> pathogenic variant 2) Sporadic cancer	
NL	NL	AB	NL	N/A	N/A	N/A	1) Germline <i>MSH6</i> pathogenic variant 2) Germline <i>MSH2</i> pathogenic variant 3) Sporadic cancer/Treatment effect ^k	1) Germline MMR testing or paired germline MMR/somatic MMR tumor testing; ⁹ 2) If germline testing negative and paired somatic MMR genetic testing not done, consider somatic MMR genetic testing ⁱ 3) If applicable, consider MSI analysis or repeat IHC testing on nontreated tumor ^k
AB	NL	NL	NL	N/A	N/A	N/A	1) Sporadic cancer; 2) Germline <i>MLH1</i> pathogenic variant; 3) Germline <i>PMS2</i> pathogenic variant; 4) Somatic <i>MLH1</i> or <i>PMS2</i> pathogenic variant	1) <i>BRAF</i> pathogenic variant testing ^c / <i>MLH1</i> promoter methylation; ^j 2) If <i>BRAF/MLH1</i> methylation testing normal, germline MMR testing or paired germline MMR/somatic MMR tumor testing; ⁹ 3) If germline testing negative and paired somatic MMR genetic testing not done, consider somatic MMR genetic testing ⁱ
AB	AB	AB	AB	N/A	N/A	N/A	1) Germline pathogenic variant in any LS gene 2) Sporadic cancer	1) <i>BRAF</i> pathogenic variant testing ^c / <i>MLH1</i> promoter methylation AND Germline MMR testing or paired germline MMR/somatic MMR tumor testing (which often include <i>MLH1</i> methylation testing); ⁹ 2) If germline testing negative and paired somatic MMR genetic testing not done, consider somatic MMR genetic testing ⁱ

N/A = Either testing was not done or results may not influence testing strategy; NL = Normal presence of positive protein staining; AB = Abnormal/Absence (negative) protein staining

[Footnotes on LS-A 9 of 9](#)

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**TUMOR TESTING RESULTS AND ADDITIONAL TESTING STRATEGIES****Footnotes from [LS-A 7 of 9](#) and [LS-A 8 of 9](#)**

^a Tumor testing strategies apply to colorectal and endometrial cancers.

^b Some clinical labs report MSI-L or MSI-intermediate (MSI-I) results. These results should be managed in consultation with a genetics professional based on family history and clinical judgment.

^c Testing is not appropriate for tumors other than CRC.

^d If strong family history (ie, Amsterdam criteria) or additional features of hereditary cancer syndromes (multiple colon polyps) are present, additional testing may be warranted in the proband, or consider tumor testing in another affected family member due to the possibility of a phenocopy.

^e Studies have shown that 45%–68% of cases with unexplained defective MMR (MSI-H and/or abnormal IHC with no evidence of *MLH1* promoter hypermethylation when indicated) have biallelic somatic MMR gene inactivation (sometimes referred to as double somatic MMR mutations). Biallelic somatic MMR gene inactivation is defined by having either two pathogenic sequence variants or one pathogenic sequence variant and loss of heterozygosity [LOH] in the MMR genes. (Sourrouille I, et al. *Fam Cancer* 2013;12:27-33. Mensenkamp A, et al. *Gastroenterology* 2014;146:643-646. Geurts-Giele W, et al. *J Pathol* 2014;234:548-559. Haraldsdottir S, et al. *Gastroenterology* 2014;147:1308-1316.) In addition, the proportion of cases due to biallelic somatic MMR gene inactivation or LS vary based on the IHC findings, and this may help with decisions about whether to order germline testing alone first or paired tumor and germline testing first (Pearlman R, et al. *J Med Genet* 2019;56:462-470). As a result, tumor sequencing may be helpful for individuals with tumor testing showing dMMR and no germline pathogenic variant detected. If biallelic somatic MMR gene inactivation is identified, it is recommended that these patients and their close relatives be receive care based on their family history and NOT as if they have LS. If biallelic somatic MMR gene inactivation is identified, LS is ruled out but there may still be some increased familial risk. If only one somatic pathogenic variant is found, the unidentified pathogenic variant could either be germline or somatic. If no somatic pathogenic variants are found, it is possible that the IHC results were incorrect (especially if the tumor was found to be MSS on tumor sequencing) or that none of the pathogenic variants (germline or somatic) are identifiable. In any of these cases, the patient and their close relatives still need to receive care based on their personal and/or family history. If the family history meets Amsterdam II criteria, the family should be followed as if they have LS. Genetic consultation should be considered for interpretation of complex results.

^f Prior to germline genetic testing, proper pre-test counseling should be done by an individual with expertise in genetics.

^g Germline MMR testing may include testing of the gene(s) that are indicated (see “Plausible Etiologies” for possibilities on [LS-A 7 of 9](#) and [LS-A 8 of 9](#)) by the abnormal tumor test results; or instead, multigene testing that includes *MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM* concurrently may be performed. Biallelic *MUTYH* gene mutations have been shown to lead to dMMR tumors; therefore, *MUTYH* should be included in the testing at a minimum with consideration of other base-excision repair genes (*NTHL1*) and DNA polymerase genes (*POLE* and *POLD1*), which have the potential to also lead to biallelic somatic MMR gene inactivation (Morak M, et al. *Eur J Hum Genet* 2014;22:1334-1337).

^h Evaluation for constitutional *MLH1* epimutation involves *MLH1* promoter hypermethylation studies on blood or other sources of normal tissue.

ⁱ Somatic MMR genetic testing of the corresponding gene(s) (see “Plausible Etiologies” for possibilities on [LS-A 7 of 9](#) and [LS-A 8 of 9](#)) could be performed on tumor DNA to assess for somatic pathogenic variants that might explain the abnormal IHC and/or MSI results. Some labs will not do paired somatic MMR genetic testing on biopsy specimens and a surgical resection specimen may be required.

^j If *BRAF* pathogenic variant testing is done by itself and is normal, consider *MLH1* promoter methylation testing next prior to germline MMR testing or move straight to paired germline MMR/somatic tumor testing (which often includes *MLH1* methylation testing). This approach is informed by the fact that *BRAF* mutation testing has an excellent positive predictive value but poor negative predictive value in predicting *MLH1* promoter methylation (Adar T, et al. *Mod Pathol* 2017;30:440-447).

^k Absent *MSH6* in rectal tumor tissue may be due to treatment effect (neoadjuvant chemoradiotherapy).

^l These tumor testing results may also have implications for treatment in cases that are sporadic or hereditary. See the [NCCN Guidelines for Colon Cancer](#) for more information on pathologic review and the impact on management. Consult with an expert if the scenario is not covered by this table.

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GENE-SPECIFIC LYNCH SYNDROME CANCER RISKS AND SURVEILLANCE/PREVENTION STRATEGIES

[MLH1 \(LS-B\)](#)

[MSH2 and EPCAM \(LS-C\)](#)

[MSH6 \(LS-D\)](#)

[PMS2 \(LS-E\)](#)

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Lynch Syndrome

MLH1 LYNCH SYNDROME: CANCER RISKS^{a,b}

Site	Estimated Average Age of Presentation	Cumulative Risk for Diagnosis Through Age 80 y ^c	Cumulative Risk for Diagnosis Through Lifetime for General Population ^d	Comments and References
Colorectal	44 years	46%–61% ^e	4.1%	See footnote g References 1, 2, 3
Endometrial	49 years	34%–54%	3.1%	References 1, 4
Ovarian	46 years	4%–20%	1.1%	References 1, 5
Renal pelvis and/or ureter	59–60 years	0.2%–5%	— ^f	See footnote h References 1, 2, 5, 6, 7
Bladder	59 years	2%–7%	2.3%	References 2, 5, 6, 7
Gastric	52 years	5%–7%	0.8%	References 2, 5, 8
Small bowel	47 years	0.4%–11%	0.3%	References 1, 5
Pancreas	No data	6.2%	1.7%	Reference 2
Biliary tract	50 years	1.9%–3.7%	— ^l	References 1, 2
Prostate	63 years	4.4%–13.8%	12.6%	See footnote i Reference 6
Breast (female)	See footnote j			
Brain	No data	0.7%–1.7%	0.5%	References 6, 9
Skin	See footnote k, references 10, 11			

[Footnotes and References \(LS-B 2 of 5\)](#)

[Surveillance/Prevention Strategies for MLH1 Pathogenic Variant Carriers \(LS-B 3 of 5\)](#)

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

**MLH1 LYNCH SYNDROME: CANCER RISKS**

- ^a The panel cautions that new data may confirm or change prior findings suggesting no increased risk, as more studies are needed to clarify lifetime risks for cancer in LS by mutation type. Point estimates for cancer risk in many studies were associated with wide confidence intervals, and should be interpreted with caution.
- ^b There is evidence of important variability in cancer risk among different families, even within the same variant in a specific LS-causing gene. This variability may be due to shared biologic (eg, genetic risk modifiers) and/or social and behavioral exposures. Thus, when assessing individual cancer risks, it is important to consider specific family history of cancer and factors shown to be associated with CRC risk including key exposures (eg, tobacco, alcohol), diet (eg, processed and red meat consumption), and lifestyle factors (eg, physical exercise) (International Mismatch Repair Consortium. *Lancet Oncol* 2021;22:1014-1022).
- ^c Cumulative risk among LS pathogenic variant carriers represents cumulative incidence based on available cohort studies. In some studies the cumulative risks are through a younger age (eg, age 70 or 75). For some cancer sites, case series and other observational studies may have reported higher cumulative risks. Note that some studies included patients who were under active screening and surveillance, and therefore risk estimates may reflect the impact of possible risk reduction due to such exposures.
- ^d Cumulative risk for the general population represents cumulative incidence reported by the Surveillance, Epidemiology, and End Results 21 program data, 2017-2019. Accessed November 16, 2022 via [SEER*Explorer](#).
- ^e A meta-analysis has reported cumulative risk for CRC for *MLH1* carriers through age 70 for males to be 43.9% and for females to be 37.3% (Wang C, et al. *JNCI Cancer Spectr* 2020;4:pkaa027).
- ^f Cumulative incidence for the general population specific to ureter and renal pelvis cancer were not available through SEER*Explorer.
- ^g Non-cohort and/or lower quality studies have shown risk for CRC as high as 80%.
- ^h Moller P, et al 2018 study may have pooled bladder cancer with renal pelvis and ureter.
- ⁱ Studies specific to LS have not reported cumulative prostate cancer risk higher than 7% for *MLH1*. However, the panel did not interpret these data as suggesting risk for an LS carrier would be lower than for the general population.
- ^j While studies have found that 42%–51% of breast cancers in women with LS are dMMR with abnormal IHC corresponding to their germline pathogenic MMR gene variant (Walsh M, et al. *Clin Cancer Res* 2010;16:2214-2224 and Schwartz C, et al. *Clin Cancer Res* 2022;28:404-413), there are insufficient data supporting an increased risk for breast cancer for women with LS (Engel C, et al. *J Clin Oncol* 2012;30:4409-4415; Barrow E, et al. *Clin Genet* 2009;75:141-149; Dominguez-Valentin M, et al. *Genet Med* 2020;22:15-25; Harkness EF, et al. *J Med Genet* 2015;52:553-556; Hu C, et al. *N Engl J Med* 2021;384:440-451; Dorling L, et al. *N Engl J Med* 2021;384:428-439; Stoll J, et al. *J Clin Oncol* 2020;4:51-60). As a result, breast cancer is not included on the LS increased cancer risks table. Breast cancer risk management should be based on personal and family history (see [NCCN Guidelines for Breast Cancer Screening and Diagnosis](#)).
- ^k Frequency of malignant and benign skin tumors such as sebaceous adenocarcinomas, sebaceous adenomas, and keratoacanthomas has been reported to be increased among patients with LS. Cumulative lifetime risk specific to *MLH1* carriers is not available.
- ^l Cumulative incidence for the general population specific to biliary tract cancer was not available through SEER*Explorer.
- ¹ Bonadona V, Bonaiti B, Olschwang S, et al. Cancer risks associated with germline mutations in *MLH1*, *MSH2*, and *MSH6* genes in Lynch syndrome. *JAMA* 2011;305:2304-2310.
- ² Moller P, Seppala TT, Bernstein I, et al. Cancer risk and survival in path_MMR carriers by gene and gender up to 75 years of age: a report from the Prospective Lynch Syndrome Database. *Gut* 2018;67:1306-1316.
- ³ Ryan NAJ, Morris J, Green K, et al. Association of mismatch repair mutation with age at cancer onset in Lynch syndrome: Implications for stratified surveillance strategies. *JAMA Oncol* 2017;3:1702-1706.
- ⁴ Moller P, Seppala T, Bernstein I, 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;66:464-472.
- ⁵ Engel C, Loeffler M, Steinke V, et al. Risks of less common cancers in proven mutation carriers with lynch syndrome. *J Clin Oncol* 2012;30:4409-4415.
- ⁶ Dominguez-Valentin M, Joost P, Therkildsen C, et al. Frequent mismatch-repair defects link prostate cancer to Lynch syndrome. *BMC Urol* 2016;16:15.
- ⁷ Joost P, Therkildsen C, Dominguez-Valentin M, et al. Urinary tract cancer in Lynch syndrome; increased risk in carriers of *MSH2* mutations. *Urology* 2015;86:1212-1217.
- ⁸ Capelle L, van Grieken N, Lingsma H, et al. Risk and epidemiological time trends of gastric cancer in Lynch syndrome carriers in the Netherlands. *Gastroenterology* 2010;138:487-492.
- ⁹ Watson P, Vasen HFA, Mecklin JP, et al. The risk of extra-colonic, extra-endometrial cancer in the Lynch syndrome. *Int J Cancer* 2008;123:444-449.
- ¹⁰ South CD, Hampel H, Comeras I, et al. Frequency of Muir-Torre syndrome among Lynch syndrome families. - *J Natl Cancer Inst* 2008;100:277-281.
- ¹¹ Adan F, Crijns MB, Zandstra WSE, et al. Cumulative risk of skin tumors in patients with Lynch syndrome. *Br J Dermatol* 2018;179:522-523.

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**MLH1 LYNCH SYNDROME: SURVEILLANCE/PREVENTION STRATEGIES^{m,n}****Site**

Colorectal cancer	- High-quality colonoscopy^o at age 20–25 years or 2–5 years prior to the earliest CRC if it is diagnosed before age 25 years^p and repeat every 1–2 years.^{q,r} Follow-up of Surveillance Findings (LS-F) - The panel recommends that all individuals with LS who have a risk for future CRC (ie, excluding those with prior total proctocolectomy [TPC]) consider using daily aspirin to reduce their future risk of CRC.^s The decision to use aspirin for reduction of CRC risk in LS and the dose chosen should be made on an individual basis, including discussion of individual risks, benefits, adverse effects, and childbearing plans.^t In determining whether an individual with LS should take aspirin and in deciding on the appropriate dosing, the panel recommends that providers carefully review patient-specific factors that may increase the risk of aspirin therapy—including but not limited to increased age, prior allergy, concurrent use of antiplatelets/anticoagulants, and untreated <i>H. pylori</i> or unconfirmed <i>H. pylori</i> eradication—as well as patient-specific factors that indicate a comparably low future cumulative risk of CRC (ie, increased age, <i>PMS2</i>-associated LS, history of prior colectomy) and who may thus be less likely to experience significant benefit.
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^m Other than colorectal and endometrial cancer, surveillance recommendations are expert opinion rather than evidence-based.

ⁿ The panel recognizes that there are limited population-based studies on the lifetime risk for most of the cancers related to each of these genes. Although there are some pathogenic variant-specific data available, a generalized screening approach is suggested. Screening and the option of risk-reducing surgeries should be individualized after risk assessment and counseling.

^o Colonoscopy may not be able to prevent all CRC in individuals with LS (Moller P, et al. *Hered Cancer Clin Pract* 2022;20:36). It has been hypothesized that this may be because some cancers develop from dMMR crypts and do not form an intermediate adenoma (Ahadova A, et al. *Int J Cancer* 2018;143:139-150). However, available data have shown that exposure to colonoscopy can detect cancers at an early stage when they are more likely curable (Lindor NM, et al. *JAMA* 2006;296:1507-1517; Vasen HF, et al. 2010;138:2300-2306; Moller P, et al. *Gut* 2017;66:464-472; Jenkins MA, et al. *J Clin Oncol* 2015;33:326-331; Moller P, et al. *Hered Cancer Clin Pract* 2022;20:36).

^p There is little evidence to guide the timing of initiating screening relative to the youngest age of diagnosis in a relative and the timing should be individualized.

^q Patients who may benefit from a shorter 1- versus longer 2-year interval include those with risk factors such as history of CRC, male sex assigned at birth, *MLH1/MSH2* pathogenic variant, age >40 years, and history of adenoma. See [Discussion](#).

^r One study has modeled the cost-effectiveness of various strategies for age of initiation and frequency of colonoscopy for reducing incidence and mortality among individuals with LS. They reported that the optimal age to initiate and follow-up screening was age 25, repeating every 1 year for *MLH1* LS, age 25 repeating every 2 years for *MSH2* LS, age 35 repeating every 3 years for *MSH6* LS, and age 40 repeating every 3 years for *PMS2* LS. Notably, selection of optimal strategies was based on the combination of quality-adjusted life-years gained and cost (Kastrinos F, et al. *Gastroenterology* 2021;161:453-462).

^s In a large, prospective, placebo-controlled, multinational CAPP2 study of individuals with *MLH1*-, *MSH2*-, and *MSH6*-associated LS, daily aspirin 600 mg/day for at least 2 years was found to significantly decrease the likelihood of incident CRC (per-protocol HR, 0.56; 95% CI, 0.34–0.91; intention-to-treat HR, 0.65; 95% CI, 0.43–0.97) with no significant increased likelihood of adverse events (Burn J, et al. *Lancet* 2020;395:1855-1863). These data demonstrate that 1 CRC is prevented for every 24 LS carriers treated with aspirin. The CAPP2 study showed no significant difference in the incidence of cancers other than CRC in those treated with aspirin versus placebo. The panel emphasizes that other doses and durations of aspirin therapy have not been studied, though the ongoing CAPP3 study is examining different dosing strategies. Longitudinal follow-up of the CAPP2 study, a randomized trial that included arms comparing supplementation of resistant starch for 2 to 4 years to no supplementation, showed that taking resistant starch had no effect on the risk for colon cancer. However, a 46% relative reduction in risk for extracolonic cancers (especially cancers of the upper GI tract, (stomach, duodenal, bile duct, and pancreas) was observed [Mathers JC, et al. *Cancer Prev Res (Phila)* 2022;15:623-634]. The potential mechanisms by which resistant starch might reduce risk for extracolonic cancers has not been widely studied. These results are insufficient for recommending routine supplementation with resistant starch for reduction of extracolonic cancer risk in LS.

^t Aspirin is currently considered Pregnancy Category D: There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant patients despite potential risks. During the first trimester, high-dose aspirin may increase the risk of pregnancy loss and congenital defects. Taking higher doses of aspirin during the third trimester increases the risk of premature closure of the ductus arteriosus and also increases the risk of fetal intracranial hemorrhage.

Note: All recommendations are category 2A unless otherwise indicated.

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NCCN Guidelines Version 1.2023

Lynch Syndrome

MLH1 LYNCH SYNDROME: SURVEILLANCE/PREVENTION STRATEGIES^{m,n}

Site	
Endometrial cancer	- Because endometrial cancer can often be detected early based on symptoms, patients 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. - Total 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 can be considered. - Timing of total hysterectomy can be individualized based on whether childbearing is complete, comorbidities, family history, and LS gene, as risks for endometrial cancer vary by pathogenic variant. - Endometrial cancer screening does not have proven benefit in patients with LS. However, endometrial biopsy is both highly sensitive and highly specific as a diagnostic procedure. Screening via endometrial biopsy every 1–2 years starting at age 30–35 years can be considered. - Transvaginal ultrasound to screen for endometrial cancer in postmenopausal patients 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 patients 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 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 pathogenic variant. Estrogen replacement after premenopausal oophorectomy may be considered. - Since there is no effective screening for ovarian cancer, patients 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 patient's baseline should prompt evaluation by their physician. - 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 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).
Urothelial cancer (renal pelvis, ureter, and/or bladder)	There is no clear evidence to support surveillance for urothelial cancers in LS. Surveillance may be considered in selected individuals such as those with a family history of urothelial cancer. Surveillance options may include annual urinalysis starting at age 30–35 y. However, there is insufficient evidence to recommend a particular surveillance strategy.
Gastric and small bowel cancer	- Upper GI surveillance with EGD starting at age 30–40 years and repeat every 2–4 years, preferably performed in conjunction with colonoscopy (Ladigan-Badura S, et al. Int J Cancer 2021;148:106-114; Farha N, et al. Gastrointest Endosc 2022;95:105-114; Kumar S, et al. Can Prev Res [Phila] 2020;13:1047-1054). Age of initiation prior to 30 years and/or surveillance interval less than 2 years may be considered based on family history of upper GI cancers or high-risk endoscopic findings (such as incomplete or extensive gastric intestinal metaplasia [GIM], gastric or duodenal adenomas, or Barrett esophagus with dysplasia). Random biopsy of the proximal and distal stomach should at minimum be performed on the initial procedure to assess for <i>H. pylori</i> (with treatment indicated if <i>H. pylori</i> is detected), autoimmune gastritis, and intestinal metaplasia. Push enteroscopy can be considered in place of EGD to enhance small bowel visualization, although its incremental yield for detection of neoplasia over EGD remains uncertain. - Individuals not undergoing upper endoscopic surveillance should have one-time noninvasive testing for <i>H. pylori</i> at the time of LS diagnosis, with treatment indicated if <i>H. pylori</i> is detected. The value of eradication for the prevention of gastric cancer in LS is unknown.

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

[Footnotes on
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4 OF 5**



NCCN Guidelines Version 1.2023

Lynch Syndrome

MLH1 LYNCH SYNDROME: SURVEILLANCE/PREVENTION STRATEGIES^{m,n}

Site	
Pancreatic cancer	- Consider pancreatic cancer screening beginning at age 50 years (or 10 years younger than the earliest exocrine pancreatic cancer diagnosis in the family, whichever is earlier) for individuals with exocrine pancreatic cancer in ≥1 first- or second-degree relatives from the same side of (or presumed to be from the same side of) the family as the identified pathogenic/likely pathogenic germline variant (Abe T, et al. J Clin Oncol 2019;37:1070-1080). - For individuals considering pancreatic cancer screening, the panel recommends that screening be performed in experienced high-volume centers. The panel recommends that such screening only take place after an in-depth discussion about the potential limitations to screening, including cost, the high incidence of benign or indeterminate pancreatic abnormalities, and uncertainties about the potential benefits of pancreatic cancer screening. - The panel recommends that screening be considered using annual contrast-enhanced MRI/magnetic resonance cholangiopancreatography (MRCP) and/or endoscopic ultrasound (EUS), with consideration of shorter screening intervals for individuals found to have potentially concerning abnormalities on screening. The panel emphasizes that most small cystic lesions found on screening will not warrant biopsy, surgical resection, or any other intervention. See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic for additional details on pancreatic cancer screening.
Prostate cancer	Patients with LS should consider their risk based on the LS gene and family history of prostate cancer. The NCCN Guidelines for Prostate Cancer Early Detection recommend that it is reasonable for patients with LS to consider beginning shared decision-making about prostate cancer screening at age 40 years and to consider screening at annual intervals rather than every other year.
Breast cancer	There have been suggestions that there is an increased risk for breast cancer in patients with LS; however, there is not enough evidence to support increased screening above average-risk breast cancer screening recommendations or those based on personal/family history of breast cancer. See NCCN Guidelines for Breast Cancer Screening and Diagnosis.
Brain cancer	Patients should be educated regarding signs and symptoms of neurologic cancer and the importance of prompt reporting of abnormal symptoms to their physicians.
Skin manifestations	- Frequency of malignant and benign skin tumors such as sebaceous adenocarcinomas, sebaceous adenomas, and keratoacanthomas has been reported to be increased among patients with LS, but cumulative lifetime risk and median age of presentation are uncertain. - Consider skin exam every 1–2 years with a health care provider skilled in identifying LS-associated skin manifestations. Age to start surveillance is uncertain and can be individualized.
Reproductive options	- For patients of reproductive age, advise about options for prenatal diagnosis and assisted reproduction including pre-implantation genetic testing. Discussion should include known risks, limitations, and benefits of these technologies. - For patients of reproductive age, advise about the risk of a rare recessive syndrome called CMMRD syndrome (Wimmer K, et al. J Med Genet 2014;51:355-365). If both partners are a carrier of a pathogenic variant(s) in the same MMR gene, then their future offspring will be at risk of having CMMRD syndrome.
Risk to relatives	- Advise patients to tell their relatives about possible inherited cancer risk, options for risk assessment, and management. - Recommend genetic counseling and consideration of genetic testing for relatives who are at risk.

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[Footnotes on
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NCCN Guidelines Version 1.2023

Lynch Syndrome

MSH2 AND EPCAM LYNCH SYNDROME: CANCER RISKS^{a,b}

Site	Estimated Average Age of Presentation	Cumulative Risk for Diagnosis Through Age 80 y ^c	Cumulative Risk for Diagnosis Through Lifetime for General Population ^d	Comments and References
Colorectal	44 years	33%–52% ^e	4.1%	See footnote g References 1, 2, 3, 4
Endometrial	47–48 years	21%–57%	3.1%	References 1, 2, 3, 5
Ovarian	43 years	8%–38%	1.1%	References 1, 2, 3, 5, 6
Renal pelvis and/or ureter	54–61 years	2.2%–28%	— ^f	See footnote h References 1, 2, 5, 6, 7, 8
Bladder	59 years	4.4%–12.8%	2.3%	References 2, 5, 6, 7
Gastric	52 years	0.2%–9.0%	0.8%	References 1, 2, 6, 8, 9
Small bowel	48 years	1.1%–10%	0.3%	References 1, 2, 6, 8
Pancreas	No data	0.5%–1.6%	1.7%	See footnote i Reference 2
Biliary tract	57 years	0.02%–1.7%	— ^l	References 1, 2
Prostate	59–63 years	3.9%–23.8%	12.6%	References 5, 6, 10
Breast (female)	See footnote j			
Brain	No data	2.5%–7.7%	0.5%	References 2, 5, 8
Skin	See footnote k, references 11, 12			

[Footnotes and References \(LS-C 2 of 5\)](#)

[Surveillance/Prevention Strategies for MSH2 Pathogenic Variant Carriers \(LS-C 3 of 5\)](#)

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**MSH2 AND EPCAM LYNCH SYNDROME: CANCER RISKS**

^a The panel cautions that new data may confirm or change prior findings suggesting no increased risk, as more studies are needed to clarify lifetime risks for cancer in LS by mutation type. Point estimates for cancer risk in many studies were associated with wide confidence intervals, and should be interpreted with caution.

^b There is evidence of important variability in cancer risk among different families, even within the same variant in a specific LS-causing gene. This variability may be due to shared biologic (eg, genetic risk modifiers) and/or social and behavioral exposures. Thus, when assessing individual cancer risks, it is important to consider specific family history of cancer and factors shown to be associated with CRC risk including key exposures (eg, tobacco, alcohol), diet (eg, processed and red meat consumption), and lifestyle factors (eg, physical exercise). (International Mismatch Repair Consortium. *Lancet Oncol* 2021;22:1014-1022).

^c Cumulative risk among LS pathogenic variant carriers represents cumulative incidence based on available cohort studies. In some studies the cumulative risks are through a younger age (eg, age 70 or 75). For some cancer sites, case series and other observational studies may have reported higher cumulative risks. Note that some studies included patients who were under active screening and surveillance, and therefore risk estimates may reflect the impact of possible risk reduction due to such exposures.

^d Cumulative risk for the general population represents cumulative incidence reported by the Surveillance, Epidemiology, and End Results 21 program data, 2017-2019. Accessed November 16, 2022 via [SEER*Explorer](#).

^e A meta-analysis has reported cumulative risk for CRC for MSH2 carriers through age 70 for males to be 53.9% and for females to be 38.6% (Wang C, et al. *JNCI Cancer Spectr* 2020;4:pkaa027).

¹ Bonadona V, Bonaiti B, Olschwang S, et al. Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome. *JAMA* 2011;305:2304-2310.

² Moller P, Seppala TT, Bernstein I, et al. Cancer risk and survival in path_MMR carriers by gene and gender up to 75 years of age: a report from the Prospective Lynch Syndrome Database. *Gut* 2018;67:1306-1316.

³ Moller P, Seppala T, Bernstein I, 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;66:464-472.

⁴ Ryan NAJ, Morris J, Green K, et al. Association of mismatch repair mutation with age at cancer onset in Lynch syndrome: Implications for stratified surveillance strategies. *JAMA Oncol* 2017;3:1702-1706.

⁵ Dominguez-Valentin M, Sampson J, Seppälä T, et al. Cancer risks by gene, age, and gender in 6350 carriers of pathogenic mismatch repair variants: findings from the Prospective Lynch Syndrome Database. *Genet Med* 2020;22:15-25.

^f Cumulative incidence for the general population specific to ureter and renal pelvis cancer were not available through SEER*Explorer.

^g Non-cohort and/or lower-quality studies have shown risk for CRC as high as 80%.

^h Moller P, et al 2018 study may have pooled bladder cancer with renal pelvis and ureter.

ⁱ Studies specific to LS have not reported cumulative pancreatic cancer risk higher than 0.5% for MSH2. However, the panel did not interpret these data as suggesting risk for an LS carrier would be lower than for the general population.

^j While studies have found that 42%–51% of breast cancers in women with LS are dMMR with abnormal IHC corresponding to their germline pathogenic MMR gene variant (Walsh M, et al. *Clin Cancer Res* 2010;16:2214-2224 and Schwartz C, et al. *Clin Cancer Res* 2022;28:404-413), there are insufficient data supporting an increased risk for breast cancer for women with LS (Engel C, et al. *J Clin Oncol* 2012;30:4409-4415; Barrow E, et al. *Clin Genet* 2009;75:141-149; Dominguez-Valentin M, et al. *Genet Med* 2020;22:15-25; Harkness EF, et al. *J Med Genet* 2015;52:553-556; Hu C, et al. *N Engl J Med* 2021;384:440-451; Dorling L, et al. *N Engl J Med* 2021;384:428-439; Stoll J, et al. *J Clin Oncol* 2020;4:51-60). As a result, breast cancer is not included on the LS increased cancer risks table. Breast cancer risk management should be based on personal and family history (see [NCCN Guidelines for Breast Cancer Screening and Diagnosis](#)).

^k Frequency of malignant and benign skin tumors such as sebaceous adenocarcinomas, sebaceous adenomas, and keratoacanthomas has been reported to be increased among patients with LS. Cumulative lifetime risk specific to MSH2 carriers is not available. History of sebaceous adenocarcinomas, sebaceous adenomas, or keratoacanthoma has been reported to be higher among MSH2 c.942+3A>T variant carriers.

^l Cumulative incidence for the general population specific to biliary tract cancer was not available through SEER*Explorer.

⁶ Engel C, Loeffler M, Steinke V, et al. Risks of less common cancers in proven mutation carriers with lynch syndrome. *J Clin Oncol* 2012;30:4409-4415.

⁷ Joost P, Therkildsen C, Dominguez-Valentin M, et al. Urinary tract cancer in lynch syndrome; increased risk in carriers of MSH2 mutations. *Urology* 2015;86:1212-1217.

⁸ Watson P, Vasen HFA, Mecklin JP, et al. The risk of extra-colonic, extra-endometrial cancer in the Lynch syndrome. *Int J Cancer* 2008;123:444-449.

⁹ Capelle L, van Grieken N, Lingsma H, et al. Risk and epidemiological time trends of gastric cancer in Lynch syndrome carriers in the Netherlands. *Gastroenterology* 2010;138:487-492.

¹⁰ Dominguez-Valentin M, Joost P, Therkildsen C, et al. Frequent mismatch-repair defects link prostate cancer to Lynch syndrome. *BMC Urol* 2016;16:15.

¹¹ South CD, Hampel H, Comeras I, et al. Frequency of Muir-Torre syndrome among Lynch syndrome Families. *J Natl Cancer Inst* 2008;100:277-281.

¹² Adan F, Crijns MB, Zandstra WSE, et al. Cumulative risk of skin tumors in patients with Lynch syndrome. *Br J Dermatol* 2018;179:522-523.

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**MSH2 AND EPCAM LYNCH SYNDROME: SURVEILLANCE/PREVENTION STRATEGIES^{m,n}****Site****Colorectal cancer**

- High-quality colonoscopy^o at age 20–25 years or 2–5 years prior to the earliest CRC if it is diagnosed before age 25 years^p and repeat every 1–2 y.^{q,r}
[Follow-up of Surveillance Findings \(LS-F\)](#)
- The panel recommends that all individuals with LS who have a risk for future CRC (ie, excluding those with prior TPC) consider using daily aspirin to reduce their future risk of CRC.^s The decision to use aspirin for reduction of CRC risk in LS and the dose chosen should be made on an individual basis, including discussion of individual risks, benefits, adverse effects, and childbearing plans.^t In determining whether an individual with LS should take aspirin and in deciding on the appropriate dosing, the panel recommends that providers carefully review patient-specific factors that may increase the risk of aspirin therapy—including but not limited to increased age, prior allergy, concurrent use of antiplatelets/anticoagulants, and untreated *H. pylori* or unconfirmed *H. pylori* eradication—as well as patient-specific factors that indicate a comparably low future cumulative risk of CRC (ie, increased age, *PMS2*-associated LS, history of prior colectomy) and who may thus be less likely to experience significant benefit.

^m Other than colorectal and endometrial cancer, surveillance recommendations are expert opinion rather than evidence-based.

ⁿ The panel recognizes that there are limited population-based studies on the lifetime risk for most of the cancers related to each of these genes. Although there are some pathogenic variant-specific data available, a generalized screening approach is suggested. Screening and the option of risk-reducing surgeries should be individualized after risk assessment and counseling.

^o Colonoscopy may not be able to prevent all CRC in individuals with LS (Moller P, et al. *Hered Cancer Clin Pract* 2022;20:36). It has been hypothesized that this may be because some cancers develop from dMMR crypts and do not form an intermediate adenoma (Ahadova A, et al. *Int J Cancer* 2018;143:139-150). However, available data have shown that exposure to colonoscopy can detect cancers at an early stage when they are more likely curable (Lindor NM, et al. *JAMA* 2006;296:1507-1517; Vasen HF, et al. 2010;138:2300-2306; Moller P, et al. *Gut* 2017;66:464-472; Jenkins MA, et al. *J Clin Oncol* 2015;33:326-331; Moller P, et al. *Hered Cancer Clin Pract* 2022;20:36).

^p There is little evidence to guide the timing of initiating screening relative to the youngest age of diagnosis in a relative and the timing should be individualized.

^q Patients who may benefit from a shorter 1- versus longer 2-year interval include those with risk factors such as history of CRC, male sex assigned at birth, *MLH1/MSH2* pathogenic variant, age >40 years, and history of adenoma. See [Discussion](#).

^r One study has modeled the cost-effectiveness of various strategies for age of initiation and frequency of colonoscopy for reducing incidence and mortality among individuals with LS. They reported that the optimal age to initiate and follow-up screening was age 25, repeating every 1 year for *MLH1* LS, age 25 repeating every 2 years for *MSH2* LS, age 35 repeating every 3 years for *MSH6* LS, and age 40 repeating every 3 years for *PMS2* LS. Notably, selection of optimal strategies was based on the combination of quality-adjusted life-years gained and cost (Kastrinos F, et al. *Gastroenterology* 2021;161:453-462).

^s In a large, prospective, placebo-controlled, multinational CAPP2 study of individuals with *MLH1*-, *MSH2*-, and *MSH6*-associated LS, daily aspirin 600 mg/day for at least 2 years was found to significantly decrease the likelihood of incident CRC (per-protocol HR, 0.56; 95% CI, 0.34–0.91; intention-to-treat HR, 0.65; 95% CI, 0.43–0.97) with no significant increased likelihood of adverse events (Burn J, et al. *Lancet* 2020;395:1855-1863). These data demonstrate that 1 CRC is prevented for every 24 LS carriers treated with aspirin. The CAPP2 study showed no significant difference in the incidence of cancers other than CRC in those treated with aspirin versus placebo. The panel emphasizes that other doses and durations of aspirin therapy have not been studied, though the ongoing CAPP3 study is examining different dosing strategies. Longitudinal follow-up of the CAPP2 study, a randomized trial that included arms comparing supplementation of resistant starch for 2 to 4 years to no supplementation, showed that taking resistant starch had no effect on the risk for colon cancer. However, a 46% relative reduction in risk for extracolonic cancers (especially cancers of the upper GI tract, (stomach, duodenal, bile duct, and pancreas) was observed [Mathers J, et al. *Cancer Prev Res (Phila)* 2022;15:623-634]. The potential mechanisms by which resistant starch might reduce risk for extracolonic cancers has not been widely studied. These results are insufficient for recommending routine supplementation with resistant starch for reduction of extracolonic cancer risk in LS.

^t Aspirin is currently considered Pregnancy Category D: There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant patients despite potential risks. During the first trimester, high-dose aspirin may increase the risk of pregnancy loss and congenital defects. Taking higher doses of aspirin during the third trimester increases the risk of premature closure of the ductus arteriosus and also increases the risk of fetal intracranial hemorrhage.

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Lynch Syndrome

MSH2 AND EPCAM LYNCH SYNDROME: SURVEILLANCE/PREVENTION STRATEGIES^{m,n}

Site	
Endometrial cancer	• Because endometrial cancer can often be detected early based on symptoms, patients 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. • Total 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 can be considered. • Timing of total hysterectomy can be individualized based on whether childbearing is complete, comorbidities, family history, and LS gene, as risks for endometrial cancer vary by pathogenic variant. • Endometrial cancer screening does not have proven benefit in patients with LS. However, endometrial biopsy is both highly sensitive and highly specific as a diagnostic procedure. Screening via endometrial biopsy every 1–2 years starting at age 30–35 years can be considered. • Transvaginal ultrasound to screen for endometrial cancer in postmenopausal patients 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 patients due to the wide range of endometrial stripe thickness throughout the normal menstrual cycle.
Ovarian cancer	• BSO may reduce the incidence of ovarian cancer. The decision to have a BSO as a risk-reducing option 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 pathogenic variant. Estrogen replacement after premenopausal oophorectomy may be considered. • Since there is no effective screening for ovarian cancer, patients 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 patient's baseline should prompt evaluation by their physician. • 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 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).
Urothelial cancer (renal pelvis, ureter, and/or bladder)	• There is no clear evidence to support surveillance for urothelial cancers in LS. Surveillance may be considered in selected individuals such as those with a family history of urothelial cancer. Individuals with <i>MSH2</i> pathogenic variants (especially males) appear to be at higher risk. Surveillance options may include annual urinalysis starting at age 30–35 years. However, there is insufficient evidence to recommend a particular surveillance strategy.
Gastric and small bowel cancer	• Upper GI surveillance with EGD starting at age 30–40 years and repeat every 2–4 years, preferably performed in conjunction with colonoscopy (Ladigan-Badura S, et al. Int J Cancer 2021;148:106-114; Farha N, et al. Gastrointest Endosc 2022;95:105-114; Kumar S, et al. Can Prev Res [Phila] 2020;13:1047-1054). Age of initiation prior to 30 years and/or surveillance interval less than 2 years may be considered based on family history of upper GI cancers or high-risk endoscopic findings (such as incomplete or extensive GIM, gastric or duodenal adenomas, or Barrett esophagus with dysplasia). Random biopsy of the proximal and distal stomach should at minimum be performed on the initial procedure to assess for <i>H. pylori</i> (with treatment indicated if <i>H. pylori</i> is detected), autoimmune gastritis, and intestinal metaplasia. Push enteroscopy can be considered in place of EGD to enhance small bowel visualization, although its incremental yield for detection of neoplasia over EGD remains uncertain. • Individuals not undergoing upper endoscopic surveillance should have one-time noninvasive testing for <i>H. pylori</i> at the time of LS diagnosis, with treatment indicated if <i>H. pylori</i> is detected. The value of eradication for the prevention of gastric cancer in LS is unknown.

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NCCN Guidelines Version 1.2023

Lynch Syndrome

MSH2 AND EPCAM LYNCH SYNDROME: SURVEILLANCE/PREVENTION STRATEGIES^{m,n}

Site	
Pancreatic cancer	- There are limited data on pancreatic cancer risk among <i>MSH2</i> pathogenic variant carriers. Consider pancreatic cancer screening beginning at age 50 years (or 10 years younger than the earliest exocrine pancreatic cancer diagnosis in the family, whichever is earlier) for individuals with exocrine pancreatic cancer in ≥1 first- or second-degree relatives from the same side of (or presumed to be from the same side of) the family as the identified pathogenic/likely pathogenic germline variant (Abe T, et al. J Clin Oncol 2019;37:1070-1080). - For individuals considering pancreatic cancer screening, the panel recommends that screening be performed in experienced high-volume centers. The panel recommends that such screening only take place after an in-depth discussion about the potential limitations to screening, including cost, the high incidence of benign or indeterminate pancreatic abnormalities, and uncertainties about the potential benefits of pancreatic cancer screening. - The panel recommends that screening be considered using annual contrast-enhanced MRI/MRCP and/or EUS, with consideration of shorter screening intervals for individuals found to have potentially concerning abnormalities on screening. The panel emphasizes that most small cystic lesions found on screening will not warrant biopsy, surgical resection, or any other intervention. See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic for additional details on pancreatic cancer screening.
Prostate cancer	Patients with LS should consider their risk based on the LS gene and family history of prostate cancer. The NCCN Guidelines for Prostate Cancer Early Detection recommend that it is reasonable for patients with LS to consider beginning shared decision-making about prostate cancer screening at age 40 years and to consider screening at annual intervals rather than every other year.
Breast cancer	There have been suggestions that there is an increased risk for breast cancer in patients with LS; however, there is not enough evidence to support increased screening above average-risk breast cancer screening recommendations or those based on personal/family history of breast cancer. See NCCN Guidelines for Breast Cancer Screening and Diagnosis.
Brain cancer	Patients should be educated regarding signs and symptoms of neurologic cancer and the importance of prompt reporting of abnormal symptoms to their physicians.
Skin manifestations	- Frequency of malignant and benign skin tumors such as sebaceous adenocarcinomas, sebaceous adenomas, and keratoacanthomas has been reported to be increased among patients with LS, but cumulative lifetime risk and median age of presentation are uncertain. - Consider skin exam every 1–2 years with a health care provider skilled in identifying LS-associated skin manifestations. Age to start surveillance is uncertain and can be individualized.
Reproductive options	- For patients of reproductive age, advise about options for prenatal diagnosis and assisted reproduction including pre-implantation genetic testing. Discussion should include known risks, limitations, and benefits of these technologies. - For patients of reproductive age, advise about the risk of a rare recessive syndrome called CMMRD syndrome (Wimmer K, et al. J Med Genet 2014;51:355-365). If both partners are a carrier of a pathogenic variant(s) in the same MMR gene, then their future offspring will be at risk of having CMMRD syndrome.
Risk to relatives	- Advise patients to tell their relatives about possible inherited cancer risk, options for risk assessment, and management. - Recommend genetic counseling and consideration of genetic testing for relatives who are at risk.

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Lynch Syndrome

MSH6 LYNCH SYNDROME: CANCER RISKS^{a,b}

Site	Estimated Average Age of Presentation	Cumulative Risk for Diagnosis Through Age 80 y ^{c,d}	Cumulative Risk for Diagnosis Through Lifetime for General Population ^e	Comments and References
Colorectal	42–69 years	10%–44% ^f	4.1%	See footnote h References 1, 2, 3, 4, 5
Endometrial	53–55 years	16%–49%	3.1%	References 1, 2, 3
Ovarian	46 years	≤1%–13%	1.1%	References 1, 2
Renal pelvis and/or ureter	65–69 years	0.7%–5.5%	— ^g	See footnote i References 1, 2, 6, 7, 8
Bladder	71 years	1.0%–8.2%	2.3%	References 2, 6, 7, 8
Gastric	2 cases reported at age 45 and 81	≤1%–7.9%	0.8%	References 1, 6
Small bowel	54 years	≤1%–4%	0.3%	References 1, 7
Pancreas	No data	1.4%–1.6%	1.7%	See footnote j Reference 2
Biliary tract	No data	0.2%–≤1%	— ^o	References 1, 2
Prostate	63 years	2.5%–11.6%	12.6%	See footnote k Reference 6
Breast (female)	See footnote l			
Brain	43–54 years	0.8%–1.8%	0.5%	See footnote m References 3, 6, 9
Skin	See footnote n; references 10, 11			

[Footnotes and References \(LS-D 2 of 5\)](#)

[Surveillance/Prevention Strategies for MSH6 Pathogenic Variant Carriers \(LS-D 3 of 5\)](#)

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Lynch Syndrome

MSH6 LYNCH SYNDROME: CANCER RISKS

- ^a The panel cautions that new data may confirm or change prior findings suggesting no increased risk, as more studies are needed to clarify lifetime risks for cancer in LS by mutation type. Point estimates for cancer risk in many studies were associated with wide confidence intervals, and should be interpreted with caution.
- ^b There is evidence of important variability in cancer risk among different families, even within the same variant in a specific LS-causing gene. This variability may be due to shared biologic (eg, genetic risk modifiers) and/or social and behavioral exposures. Thus, when assessing individual cancer risks, it is important to consider specific family history of cancer and factors shown to be associated with CRC risk including key exposures (eg, tobacco, alcohol), diet (eg, processed and red meat consumption), and lifestyle factors (eg, physical exercise). (International Mismatch Repair Consortium. *Lancet Oncol* 2021;22:1014-1022).
- ^c Cumulative risk among LS pathogenic variant carriers represents cumulative incidence based on available cohort studies. In some studies the cumulative risks are through a younger age (eg, age 70 or 75). For some cancer sites, case series and other observational studies may have reported higher cumulative risks. Note that some studies included patients who were under active screening and surveillance, and therefore risk estimates may reflect the impact of possible risk reduction due to such exposures.
- ^d In studies where no cases were identified, the panel has represented the data as ≤1%.
- ^e Cumulative risk for the general population represents cumulative incidence reported by the Surveillance, Epidemiology, and End Results 21 program data, 2017-2019. Accessed November 16, 2022 via [SEER*Explorer](#).
- ^f A meta-analysis has reported cumulative risk for CRC for MSH6 carriers through age 70 for males to be 12.0% and for females to be 12.3% (Wang C, et al. *JNCI Cancer Spectr* 2020;4:pkaa027).
- ^g Cumulative incidence for the general population specific to ureter and renal pelvis cancer were not available through SEER*Explorer.
- ^h Non-cohort and/or lower quality studies have shown risk for CRC as high as 80%.
- ⁱ Moller P, et al 2018 study may have pooled bladder cancer with renal pelvis and ureter.
- ^j Studies specific to LS have not reported cumulative pancreatic cancer risk >1.4% for MSH6. However, the panel did not interpret these data as suggesting risk for an LS carrier would be lower than for the general population.
- ^k Studies specific to LS have not reported cumulative prostate cancer risk >4.8% for MSH6. However, the panel did not interpret these data as suggesting risk for an LS carrier would be lower than for the general population.
- ^l While studies have found that 42%–51% of breast cancers in women with LS are dMMR with abnormal IHC corresponding to their germline pathogenic MMR gene variant (Walsh M, et al. *Clin Cancer Res* 2010;16:2214-2224 and Schwartz C, et al. *Clin Cancer Res* 2022;28:404-413), there are insufficient data supporting an increased risk for breast cancer for women with LS (Engel C, et al. *J Clin Oncol* 2012;30:4409-4415; Barrow E, et al. *Clin Genet* 2009;75:141-149; Dominguez-Valentin M, et al. *Genet Med* 2020;22:15-25; Harkness EF, et al. *J Med Genet* 2015;52:553-556; Hu C, et al. *N Engl J Med* 2021;384:440-451; Dorling L, et al. *N Engl J Med* 2021;384:428-439; Stoll J, et al. *J Clin Oncol* 2020;4:51-60). As a result, breast cancer is not included on the LS increased cancer risks table. Breast cancer risk management should be based on personal and family history (see [NCCN Guidelines for Breast Cancer Screening and Diagnosis](#)).
- ^m One report estimated cumulative 13.4% risk specific to the p.Leu585Pro allele.
- ⁿ Frequency of malignant and benign skin tumors such as sebaceous adenocarcinomas, sebaceous adenomas, and keratoacanthomas has been reported to be increased among patients with LS. Cumulative lifetime risk specific to MSH6 carriers is not available.
- ^o Cumulative incidence for the general population specific to biliary tract cancer was not available through SEER*Explorer.
- ¹ Bonadona V, Bonaiti B, Olschwang S, et al. Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome. *JAMA* 2011;305:2304-2310.
- ² Moller P, Seppala TT, Bernstein I, et al. Cancer risk and survival in path_MMR carriers by gene and gender up to 75 years of age: a report from the Prospective Lynch Syndrome Database. *Gut* 2018;67:1306-1316.
- ³ Baglietto L, Lindor NM, Dowty JG, et al. Risks of Lynch syndrome cancers for MSH6 mutation carriers. *J Natl Cancer Inst* 2010;102:193-201.
- ⁴ Suerink M, Rodriguez-Gironde M, van der Klift HM, et al. An alternative approach to establishing unbiased colorectal cancer risk estimation in Lynch syndrome. *Genet Med* 2019;21:2706-2712.
- ⁵ Ryan N, Morris J, Green K, et al. Association of mismatch repair mutation with age at cancer onset in Lynch syndrome: Implications for Stratified Surveillance Strategies. *JAMA Oncol* 2017;3:1702-1706.
- ⁶ Dominguez-Valentin M, Joost P, Therkildsen C, et al. Frequent mismatch-repair defects link prostate cancer to Lynch syndrome. *BMC Urol* 2016;16:15.
- ⁷ Engel C, Loeffler M, Steinke V, et al. Risks of less common cancers in proven mutation carriers with lynch syndrome. *J Clin Oncol* 2012;30:4409-4415.
- ⁸ Joost P, Therkildsen C, Dominguez-Valentin M, et al. Urinary tract cancer in lynch syndrome; increased risk in carriers of MSH2 mutations. *Urology* 2015;86:1212-1217.
- ⁹ Haraldsdottir S, Rafnar T, Frankel WL, et al. Comprehensive population-wide analysis of Lynch syndrome in Iceland reveals founder mutations in MSH6 and PMS2. *Nature Comm* 2017;8:14755.
- ¹⁰ South CD, Hampel H, Comeras I, et al. Frequency of Muir-Torre syndrome among Lynch syndrome families. *J Natl Cancer Inst* 2008;100:277-281.
- ¹¹ Adan F, Crijns MB, Zandstra WSE, et al. Cumulative risk of skin tumors in patients with Lynch syndrome. *Br J Dermatol* 2018;179:522-523.

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NCCN Guidelines Version 1.2023

Lynch Syndrome

MSH6 LYNCH SYNDROME: SURVEILLANCE/PREVENTION STRATEGIES^{p,q}

Site	
Colorectal cancer	- High-quality colonoscopy^r at age 30–35 years or 2–5 years prior to the earliest CRC if it is diagnosed before age 30 years^s and repeat every 1–3 years.^{t,u} See Follow-up of Surveillance Findings (LS-F) - The panel recommends that all individuals with LS who have a risk for future CRC (ie, excluding those with prior TPC) consider using daily aspirin to reduce their future risk of CRC.^v The decision to use aspirin for reduction of CRC risk in LS and the dose chosen should be made on an individual basis, including discussion of individual risks, benefits, adverse effects, and childbearing plans.^w In determining whether an individual with LS should take aspirin and in deciding on the appropriate dosing, the panel recommends that providers carefully review patient-specific factors that may increase the risk of aspirin therapy—including but not limited to increased age, prior allergy, concurrent use of antiplatelets/anticoagulants, and untreated <i>H. pylori</i> or unconfirmed <i>H. pylori</i> eradication—as well as patient-specific factors that indicate a comparably low future cumulative risk of CRC (ie, increased age, <i>PMS2</i>-associated LS, history of prior colectomy) and who may thus be less likely to experience significant benefit.

^p Other than colorectal and endometrial cancer, surveillance recommendations are expert opinion rather than evidence-based.

^q The panel recognizes that there are limited population-based studies on the lifetime risk for most of the cancers related to each of these genes. Although there are some pathogenic variant-specific data available, a generalized screening approach is suggested. Screening and the option of risk-reducing surgeries should be individualized after risk assessment and counseling.

^r Colonoscopy may not be able to prevent all CRC in individuals with LS (Moller P, et al. *Hered Cancer Clin Pract* 2022;20:36). It has been hypothesized that this may be because some cancers develop from dMMR crypts and do not form an intermediate adenoma (Ahadova A, et al. *Int J Cancer* 2018;143:139-150). However, available data have shown that exposure to colonoscopy can detect cancers at an early stage when they are more likely curable (Lindor NM, et al. *JAMA* 2006;296:1507-1517; Vasen HF, et al. 2010;138:2300-2306; Moller P, et al. *Gut* 2017;66:464-472; Jenkins MA, et al. *J Clin Oncol* 2015;33:326-331; Moller P, et al. *Hered Cancer Clin Pract* 2022;20:36).

^s There is little evidence to guide the timing of initiating screening relative to the youngest age of diagnosis in a relative and the timing should be individualized.

^t Patients who may benefit from a shorter 1- versus longer 2-year interval include those with risk factors such as history of CRC, male sex assigned at birth, *MLH1/MSH2* pathogenic variant, age >40 years, and history of adenoma. See [Discussion](#).

^u One study has modeled the cost-effectiveness of various strategies for age of initiation and frequency of colonoscopy for reducing incidence and mortality among individuals with LS. They reported that the optimal age to initiate and follow-up screening was age 25, repeating every 1 year for *MLH1* LS, age 25 repeating every 2 years for *MSH2* LS, age 35 repeating every 3 years for *MSH6* LS, and age 40 repeating every 3 years for *PMS2* LS. Notably, selection of optimal strategies was based on the combination of quality-adjusted life-years gained and cost (Kastrinos F, et al. *Gastroenterology* 2021;161:453-462).

^v In a large, prospective, placebo-controlled, multinational CAPP2 study of individuals with *MLH1*-, *MSH2*-, and *MSH6*-associated LS, daily aspirin 600 mg/day for at least 2 years was found to significantly decrease the likelihood of incident CRC (per-protocol HR, 0.56; 95% CI, 0.34–0.91; intention-to-treat HR, 0.65; 95% CI, 0.43–0.97) with no significant increased likelihood of adverse events (Burn J, et al. *Lancet* 2020;395:1855-63). These data demonstrate that 1 CRC is prevented for every 24 LS carriers treated with aspirin. The CAPP2 study showed no significant difference in the incidence of cancers other than CRC in those treated with aspirin versus placebo. The panel emphasizes that other doses and durations of aspirin therapy have not been studied, though the ongoing CAPP3 study is examining different dosing strategies. Longitudinal follow-up of the CAPP2 study, a randomized trial that included arms comparing supplementation of resistant starch for 2 to 4 years to no supplementation, showed that taking resistant starch had no effect on the risk for colon cancer. However, a 46% relative reduction in risk for extracolonic cancers (especially cancers of the upper GI tract, (stomach, duodenal, bile duct, and pancreas) was observed [Mathers J, et al. *Cancer Prev Res (Phila)* 2022;15:623-634]. The potential mechanisms by which resistant starch might reduce risk for extracolonic cancers has not been widely studied. These results are insufficient for recommending routine supplementation with resistant starch for reduction of extracolonic cancer risk in LS.

^w Aspirin is currently considered Pregnancy Category D: There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant patients despite potential risks. During the first trimester, high-dose aspirin may increase the risk of pregnancy loss and congenital defects. Taking higher doses of aspirin during the third trimester increases the risk of premature closure of the ductus arteriosus and also increases the risk of fetal intracranial hemorrhage.

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Lynch Syndrome

MSH6 LYNCH SYNDROME: SURVEILLANCE/PREVENTION STRATEGIES^{P,9}

Site	
Endometrial cancer	- Because endometrial cancer can often be detected early based on symptoms, patients 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. - Total 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 can be considered. - Timing of total hysterectomy can be individualized based on whether childbearing is complete, comorbidities, family history, and LS gene, as risks for endometrial cancer vary by pathogenic variant. - Endometrial cancer screening does not have proven benefit in patients with LS. However, endometrial biopsy is both highly sensitive and highly specific as a diagnostic procedure. Screening via endometrial biopsy every 1–2 years starting at age 30–35 years can be considered. - Transvaginal ultrasound to screen for endometrial cancer in postmenopausal patients 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 patients due to the wide range of endometrial stripe thickness throughout the normal menstrual cycle.
Ovarian cancer	- Insufficient evidence exists to make a specific recommendation for risk-reducing salpingo-oophorectomy (RRSO) in <i>MSH6</i> pathogenic variant carriers. BSO may reduce the incidence of ovarian cancer. The decision to have a BSO as a risk-reducing option 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 pathogenic variant. Estrogen replacement after premenopausal oophorectomy may be considered. - Since there is no effective screening for ovarian cancer, patients 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 patient's baseline should prompt evaluation by their physician. - 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 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).
Urothelial cancer (renal pelvis, ureter, and/or bladder)	There is no clear evidence to support surveillance for urothelial cancers in LS. Surveillance may be considered in selected individuals such as those with a family history of urothelial cancer. Surveillance options may include annual urinalysis starting at age 30–35 y. However, there is insufficient evidence to recommend a particular surveillance strategy.
Gastric and small bowel cancer	- Upper GI surveillance with EGD starting at age 30–40 years and repeat every 2–4 years, preferably performed in conjunction with colonoscopy (Ladigan-Badura S, et al. <i>Int J Cancer</i> 2021;148:106-114; Farha N, et al. <i>Gastrointest Endosc</i> 2022;95:105-114; Kumar S, et al. <i>Can Prev Res [Phila]</i> 2020;13:1047-1054). Age of initiation prior to 30 years and/or surveillance interval less than 2 years may be considered based on family history of upper GI cancers or high-risk endoscopic findings (such as incomplete or extensive GIM, gastric or duodenal adenomas, or Barrett esophagus with dysplasia). Random biopsy of the proximal and distal stomach should at minimum be performed on the initial procedure to assess for <i>H. pylori</i> (with treatment indicated if <i>H. pylori</i> is detected), autoimmune gastritis, and intestinal metaplasia. Push enteroscopy can be considered in place of EGD to enhance small bowel visualization, although its incremental yield for detection of neoplasia over EGD remains uncertain. - Individuals not undergoing upper endoscopic surveillance should have one-time noninvasive testing for <i>H. pylori</i> at the time of LS diagnosis, with treatment indicated if <i>H. pylori</i> is detected. The value of eradication for the prevention of gastric cancer in LS is unknown.

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NCCN Guidelines Version 1.2023

Lynch Syndrome

MSH6 LYNCH SYNDROME: SURVEILLANCE/PREVENTION STRATEGIES^{P,9}

Site	
Pancreatic cancer	- There are limited data on pancreatic cancer risk among <i>MSH6</i> pathogenic variant carriers. Consider pancreatic cancer screening beginning at age 50 years (or 10 years younger than the earliest exocrine pancreatic cancer diagnosis in the family, whichever is earlier) for individuals with exocrine pancreatic cancer in ≥1 first-or second-degree relatives from the same side of (or presumed to be from the same side of) the family as the identified pathogenic/likely pathogenic germline variant (Abe T, et al. J Clin Oncol 2019;37:1070-1080). - For individuals considering pancreatic cancer screening, the panel recommends that screening be performed in experienced high-volume centers. The panel recommends that such screening only take place after an in-depth discussion about the potential limitations to screening, including cost, the high incidence of benign or indeterminate pancreatic abnormalities, and uncertainties about the potential benefits of pancreatic cancer screening. - The panel recommends that screening be considered using annual contrast-enhanced MRI/MRCP and/or EUS, with consideration of shorter screening intervals for individuals found to have potentially concerning abnormalities on screening. The panel emphasizes that most small cystic lesions found on screening will not warrant biopsy, surgical resection, or any other intervention. See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic for additional details on pancreatic cancer screening.
Prostate cancer	Patients with LS should consider their risk based on the LS gene and family history of prostate cancer. The NCCN Guidelines for Prostate Cancer Early Detection recommend that it is reasonable for patients with LS to consider beginning shared decision-making about prostate cancer screening at age 40 years and to consider screening at annual intervals rather than every other year.
Breast cancer	There have been suggestions that there is an increased risk for breast cancer in patients with LS; however, there is not enough evidence to support increased screening above average-risk breast cancer screening recommendations or those based on personal/family history of breast cancer. See NCCN Guidelines for Breast Cancer Screening and Diagnosis.
Brain cancer	Patients should be educated regarding signs and symptoms of neurologic cancer and the importance of prompt reporting of abnormal symptoms to their physicians.
Skin manifestations	- Frequency of malignant and benign skin tumors such as sebaceous adenocarcinomas, sebaceous adenomas, and keratoacanthomas has been reported to be increased among patients with LS, but cumulative lifetime risk and median age of presentation are uncertain. - Consider skin exam every 1–2 years with a health care provider skilled in identifying LS-associated skin manifestations. Age to start surveillance is uncertain and can be individualized.
Reproductive options	- For patients of reproductive age, advise about options for prenatal diagnosis and assisted reproduction including pre-implantation genetic testing. Discussion should include known risks, limitations, and benefits of these technologies. - For patients of reproductive age, advise about the risk of a rare recessive syndrome called CMMRD syndrome (Wimmer K, et al. J Med Genet 2014;51:55-365). If both partners are a carrier of a pathogenic variant(s) in the same MMR gene, then their future offspring will be at risk of having CMMRD syndrome.
Risk to relatives	- Advise patients to tell their relatives about possible inherited cancer risk, options for risk assessment, and management. - Recommend genetic counseling and consideration of genetic testing for relatives who are at risk.

[Footnotes on
LS-D 3 of 5](#)

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



NCCN Guidelines Version 1.2023

Lynch Syndrome

PMS2 LYNCH SYNDROME: CANCER RISKS^{a,b}

Site	Estimated Average Age of Presentation	Cumulative Risk for Diagnosis Through Age 80 y ^{c,d}	Cumulative Risk for Diagnosis Through Lifetime for General Population ^e	Comments and References
Colorectal	61–66 years	8.7%–20%	4.1%	References 1, 2, 3
Endometrial	49–50 years	13%–26%	3.1%	References 1, 2, 4, 5, 6
Ovarian	51–59 years	1.3–3% ^f	1.1%	Reference 6
Renal pelvis and/or ureter	No data	≤1%–3.7%	— ^g	Reference 6
Bladder	71 years	≤1%–2.4%	2.3%	See footnote h, i References 2, 4, 6
Gastric	Inadequate data	Inadequate data	0.8%	
Small bowel	Single case - 59 years	0.1%–0.3%	0.3%	See footnote j Reference 2
Pancreas	No data	≤1%–1.6%	1.7%	See footnote k Reference 4
Biliary tract	No data	0.2%– ≤1%	— ^p	Reference 4
Prostate	No data	4.6%–11.6%	12.6%	See footnote l Reference 6
Breast (female)	See footnote m			
Brain	40 years	0.6%–≤1%	0.5%	See footnote n Reference 2
Skin	See footnote o; references 7, 8			

[Footnotes and References \(LS-E 2 of 5\)](#)

[Surveillance/Prevention Strategies for PMS2 Pathogenic Variant Carriers \(LS-E 3 of 5\)](#)

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**PMS2 LYNCH SYNDROME: CANCER RISKS**

- ^a The panel cautions that new data may confirm or change prior findings suggesting no increased risk, as more studies are needed to clarify lifetime risks for cancer in LS by mutation type. Point estimates for cancer risk in many studies were associated with wide confidence intervals, and should be interpreted with caution.
- ^b There is evidence of important variability in cancer risk among different families, even within the same variant in a specific LS-causing gene. This variability may be due to shared biologic (eg, genetic risk modifiers) and/or social and behavioral exposures. Thus, when assessing individual cancer risks, it is important to consider specific family history of cancer and factors shown to be associated with CRC risk including key exposures (eg, tobacco, alcohol), diet (eg, processed and red meat consumption), and lifestyle factors (eg, physical exercise) (International Mismatch Repair Consortium. *Lancet Oncol* 2021;22:1014-1022).
- ^c Cumulative risk among LS pathogenic variant carriers represents cumulative incidence based on available cohort studies. In some studies the cumulative risks are through a younger age (eg, age 70 or 75). For some cancer sites, case series and other observational studies may have reported higher cumulative risks. Note that some studies included patients who were under active screening and surveillance, and therefore risk estimates may reflect the impact of possible risk reduction due to such exposures.
- ^d In studies where no cases were identified, the panel has represented the data as ≤1%.
- ^e Cumulative risk for the general population represents cumulative incidence reported by the Surveillance, Epidemiology, and End Results 21 program data, 2017-2019. Accessed November 16, 2022 via [SEER*Explorer](#).
- ^f Although studies have suggested a 3% lifetime risk for ovarian cancer that is higher than the observed risk in the general population, studies that specifically examine risks among PMS2 carriers have not been able to demonstrate a statistically significant relative increased risk for ovarian cancer.
- ^g Cumulative incidence for the general population specific to ureter and renal pelvis cancer were not available through SEER*Explorer.
- ^h Moller P, et al 2018 study may have pooled bladder cancer with renal pelvis and ureter.

- ⁱ Studies specific to LS have not reported increased cumulative bladder cancer risk. However, the panel did not interpret these data as suggesting risk for an LS carrier would be lower than for the general population.
- ^j Studies specific to LS have not reported cumulative small bowel cancer risk higher than 0.1% for PMS2. However, the panel did not interpret these data as suggesting risk for an LS carrier would be lower than for the general population.
- ^k Studies specific to LS have not reported cumulative pancreatic cancer risk higher than 1% for PMS2. However, the panel did not interpret these data as suggesting risk for an LS carrier would be lower than for the general population.
- ^l Studies specific to LS have not reported cumulative prostate cancer risk higher than 4.6% for PMS2. However, the panel did not interpret these data as suggesting risk for an LS carrier would be lower than for the general population.
- ^m While studies have found that 42%–51% of breast cancers in patients with LS are dMMR with abnormal IHC corresponding to their germline pathogenic MMR gene variant (Walsh M, et al. *Clin Cancer Res* 2010;16:2214-2224 and Schwartz C, et al. *Clin Cancer Res* 2022;28:404-413), there are insufficient data supporting an increased risk for breast cancer for patients with LS (Engel C, et al. *J Clin Oncol* 2012;30:4409-4415; Barrow E, et al. *Clin Genet* 2009;75:141-149; Dominguez-Valentin M, et al. *Genet Med* 2020;22:15-25; Harkness EF, et al. *J Med Genet* 2015;52:553-556; Hu C, et al. *N Engl J Med* 2021;384:440-451; Dorling L, et al. *N Engl J Med* 2021;384:428-439; Stoll J, et al. *J Clin Oncol* 2020;4:51-60). As a result, breast cancer is not included on the LS increased cancer risks table. Breast cancer risk management should be based on personal and family history (see [NCCN Guidelines for Breast Cancer Screening and Diagnosis](#)).
- ⁿ Studies specific to LS have not reported cumulative brain cancer risk higher than 0.57% for PMS2. However, the panel did not interpret these data as suggesting risk for an LS carrier would be lower than for the general population.
- ^o Frequency of malignant and benign skin tumors such as sebaceous adenocarcinomas, sebaceous adenomas, and keratoacanthomas has been reported to be increased among patients with LS. Cumulative lifetime risk specific to PMS2 carriers is not available.
- ^p Cumulative incidence for the general population specific to biliary tract cancer was not available through SEER*Explorer.

- ¹ Senter L, Clendenning M, Sotamaa K, et al. The clinical phenotype of Lynch syndrome due to germ-line PMS2 mutations. *Gastroenterology* 2008;135:419-428.
- ² Ten Broeke SW, van der Klift HM, Tops CMJ, et al. Cancer risks for PMS2-associated Lynch syndrome. *J Clin Oncol* 2018;36:2961-2968.
- ³ Suerink M, et al. An alternative approach to establishing unbiased colorectal cancer risk estimation in Lynch syndrome. *Genet Med* 2019; 21:2706-2712.
- ⁴ Moller P, Seppala TT, Bernstein I, et al. Cancer risk and survival in path MMR carriers by gene and gender up to 75 years of age: a report from the Prospective Lynch Syndrome Database. *Gut* 2018;67:1306-1316.

- ⁵ Moller P, Seppala T, Bernstein I, 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;66:464-472.
- ⁶ Dominguez-Valentin M, Sampson J, Seppälä T, et al. Cancer risks by gene, age, and gender in 6350 carriers of pathogenic mismatch repair variants: findings from the Prospective Lynch Syndrome Database. *Genet Med* 2020;22:15-25.
- ⁷ South CD, Hampel H, Comeras I, et al. Frequency of Muir-Torre syndrome among Lynch syndrome families. *J Natl Cancer Inst* 2008;100:277-281.
- ⁸ Adan F, Crijs MB, Zandstra WSE, et al. Cumulative risk of skin tumors in patients with Lynch syndrome. *Br J Dermatol* 2018;179:522-523.

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NCCN Guidelines Version 1.2023

Lynch Syndrome

PMS2 LYNCH SYNDROME: SURVEILLANCE/PREVENTION STRATEGIES^{q,r}

Site	
Colorectal cancer	- High-quality colonoscopy^s at age 30–35 years or 2–5 years prior to the earliest CRC if it is diagnosed before age 30 years^t and repeat every 1–3 y.^{u,v} See Follow-up of Surveillance Findings (LS-F). - The panel recommends that all individuals with LS who have a risk for future CRC (ie, excluding those with prior TPC) consider using daily aspirin to reduce their future risk of CRC.^w The decision to use aspirin for reduction of CRC risk in LS and the dose chosen should be made on an individual basis, including discussion of individual risks, benefits, adverse effects, and childbearing plans.^x In determining whether an individual with LS should take aspirin and in deciding on the appropriate dosing, the panel recommends that providers carefully review patient-specific factors that may increase the risk of aspirin therapy—including but not limited to increased age, prior allergy, concurrent use of antiplatelets/anticoagulants, and untreated <i>H. pylori</i> or unconfirmed <i>H. pylori</i> eradication—as well as patient-specific factors that indicate a comparably low future cumulative risk of CRC (ie, increased age, PMS2-associated LS, history of prior colectomy) and who may thus be less likely to experience significant benefit.

^q Other than colorectal and endometrial cancer, surveillance recommendations are expert opinion rather than evidence-based.

^r The panel recognizes that there are limited population-based studies on the lifetime risk for most of the cancers related to each of these genes. Although there are some pathogenic variant-specific data available, a generalized screening approach is suggested. Screening and the option of risk-reducing surgeries should be individualized after risk assessment and counseling.

^s Colonoscopy may not be able to prevent all CRC in individuals with LS (Moller P, et al. *Hered Cancer Clin Pract* 2022;20:36). It has been hypothesized that this may be because some cancers develop from dMMR crypts and do not form an intermediate adenoma (Ahadova A, et al. *Int J Cancer* 2018;143:139-150). However, available data have shown that exposure to colonoscopy can detect cancers at an early stage when they are more likely curable (Lindor NM, et al. *JAMA* 2006;296:1507-1517; Vasen HF, et al. 2010;138:2300-2306; Moller P, et al. *Gut* 2017;66:464-472; Jenkins MA, et al. *J Clin Oncol* 2015;33:326-331; Moller P, et al. *Hered Cancer Clin Pract* 2022;20:36).

^t There is little evidence to guide the timing of initiating screening relative to the youngest age of diagnosis in a relative and the timing should be individualized.

^u Patients who may benefit from a shorter 1- versus longer 2-year interval include those with risk factors such as history of CRC, male sex assigned at birth, *MLH1*/*MSH2* pathogenic variant, age >40 years, and history of adenoma. See [Discussion](#).

^v One study has modeled the cost-effectiveness of various strategies for age of initiation and frequency of colonoscopy for reducing incidence and mortality among individuals with LS. They reported that the optimal age to initiate and follow-up screening was age 25, repeating every 1 year for *MLH1* LS, age 25 repeating every 2 years for *MSH2* LS, age 35 repeating every 3 years for *MSH6* LS, and age 40 repeating every 3 years for *PMS2* LS. Notably, selection of optimal strategies was based on the combination of quality-adjusted life-years gained and cost (Kastrinos F, et al. *Gastroenterology* 2021;161:453-462).

^w In a large, prospective, placebo-controlled, multinational CAPP2 study of individuals with *MLH1*-, *MSH2*-, and *MSH6*-associated LS, daily aspirin 600 mg/day for at least 2 years was found to significantly decrease the likelihood of incident CRC (per-protocol HR, 0.56; 95% CI, 0.34–0.91; intention-to-treat HR, 0.65; 95% CI, 0.43–0.97) with no significant increased likelihood of adverse events (Burn J, et al. *Lancet* 2020;395:1855-63). These data demonstrate that 1 CRC is prevented for every 24 LS carriers treated with aspirin. The CAPP2 study showed no significant difference in the incidence of cancers other than CRC in those treated with aspirin versus placebo. The panel emphasizes that other doses and durations of aspirin therapy have not been studied, though the ongoing CAPP3 study is examining different dosing strategies. Longitudinal follow-up of the CAPP2 study, a randomized trial that included arms comparing supplementation of resistant starch for 2 to 4 years to no supplementation, showed that taking resistant starch had no effect on the risk for colon cancer. However, a 46% relative reduction in risk for extracolonic cancers (especially cancers of the upper GI tract, (stomach, duodenal, bile duct, and pancreas) was observed [Mathers J, et al. *Cancer Prev Res (Phila)* 2022;15:623-634]. The potential mechanisms by which resistant starch might reduce risk for extracolonic cancers has not been widely studied. These results are insufficient for recommending routine supplementation with resistant starch for reduction of extracolonic cancer risk in LS.

^x Aspirin is currently considered Pregnancy Category D: There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant patients despite potential risks. During the first trimester, high-dose aspirin may increase the risk of pregnancy loss and congenital defects. Taking higher doses of aspirin during the third trimester increases the risk of premature closure of the ductus arteriosus and also increases the risk of fetal intracranial hemorrhage.

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NCCN Guidelines Version 1.2023

Lynch Syndrome

PMS2 LYNCH SYNDROME: SURVEILLANCE/PREVENTION STRATEGIES^{q,r}

Site	
Endometrial cancer	• <i>PMS2</i> carriers appear to be at only a modestly increased risk of endometrial cancer in contrast to <i>MLH1</i>, <i>MSH2</i>, and <i>MSH6</i>. • Because endometrial cancer can often be detected early based on symptoms, patients 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. • Total 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 can be considered. • Timing of total hysterectomy can be individualized based on whether childbearing is complete, comorbidities, family history, and LS gene, as risks for endometrial cancer vary by pathogenic variant. • Endometrial cancer screening does not have proven benefit in patients with LS. However, endometrial biopsy is both highly sensitive and highly specific as a diagnostic procedure. Screening via endometrial biopsy every 1–2 years starting at age 30–35 years can be considered. • Transvaginal ultrasound to screen for endometrial cancer in postmenopausal patients 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 patients due to the wide range of endometrial stripe thickness throughout the normal menstrual cycle.
Ovarian cancer	• Insufficient evidence exists to make a specific recommendation for RRSO for <i>PMS2</i> pathogenic variant carriers. <i>PMS2</i> pathogenic variant carriers appear to be at no greater than average risk for ovarian cancer, and may consider deferring surveillance and may reasonably elect not to have oophorectomy. • BSO may reduce the incidence of ovarian cancer. The decision to have a BSO as a risk-reducing option by patients who have completed childbearing should be individualized and done with consultation with a gynecologist with expertise in LS. • 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 pathogenic variant. Estrogen replacement after premenopausal oophorectomy may be considered. • Since there is no effective screening for ovarian cancer, patients 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 patient's baseline should prompt evaluation by their physician. • 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).
Urothelial cancer (renal pelvis, ureter, and/or bladder)	• There is no clear evidence to support surveillance for urothelial cancers in LS. Surveillance may be considered in selected individuals such as those with a family history of urothelial cancer. Surveillance options may include annual urinalysis starting at age 30–35 years. However, there is insufficient evidence to recommend a particular surveillance strategy.

[Footnotes on
LS-E 3 of 5](#)

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Lynch Syndrome

PMS2 LYNCH SYNDROME: SURVEILLANCE/PREVENTION STRATEGIES^{q,r}

Site	
Gastric and small bowel cancer	- Consider upper GI surveillance with EGD starting at age 30–40 years and repeat every 2–4 years, preferably performed in conjunction with colonoscopy (Ladigan-Badura S, et al. Int J Cancer 2021;148:106-114; Farha N, et al. Gastrointest Endosc 2022;95:105-114; Kumar S, et al. Can Prev Res [Phila] 2020;13:1047-1054). Age of initiation prior to age 30 and/or surveillance interval less than 2 years may be considered based on family history of upper GI cancers or high-risk endoscopic findings (such as incomplete or extensive GIM, gastric or duodenal adenomas, or Barrett esophagus with dysplasia). Random biopsy of the proximal and distal stomach should at minimum be performed on the initial procedure to assess for <i>H. pylori</i> (with treatment indicated if <i>H. pylori</i> is detected), autoimmune gastritis, and intestinal metaplasia. Push enteroscopy can be considered in place of EGD to enhance small bowel visualization, although its incremental yield for detection of neoplasia over EGD remains uncertain. There are limited available data on upper GI cancer risk in PMS2 LS, and new evidence is likely to inform changes to these recommendations in the future. - Individuals not undergoing upper endoscopic surveillance should have one-time noninvasive testing for <i>H. pylori</i> at the time of LS diagnosis, with treatment indicated if <i>H. pylori</i> is detected. The value of eradication for the prevention of gastric cancer in LS is unknown.
Pancreatic cancer	- PMS2 carriers have not been shown to be at increased risk for pancreatic cancer. - Patients with a family history of pancreatic cancer should receive care based on careful assessment and clinical judgment. - See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic for additional details on pancreatic cancer screening.
Prostate cancer	Patients with LS should consider their risk based on the LS gene and family history of prostate cancer. The NCCN Guidelines for Prostate Cancer Early Detection recommend that it is reasonable for patients with LS to consider beginning shared decision-making about prostate cancer screening at age 40 years and to consider screening at annual intervals rather than every other year.
Breast cancer	There have been suggestions that there is an increased risk for breast cancer in patients with LS; however, there is not enough evidence to support increased screening above average-risk breast cancer screening recommendations or those based on personal/family history of breast cancer. See NCCN Guidelines for Breast Cancer Screening and Diagnosis.
Brain cancer	Patients should be educated regarding signs and symptoms of neurologic cancer and the importance of prompt reporting of abnormal symptoms to their physicians.
Skin manifestations	- Frequency of malignant and benign skin tumors such as sebaceous adenocarcinomas, sebaceous adenomas, and keratoacanthomas has been reported to be increased among patients with LS, but cumulative lifetime risk and median age of presentation are uncertain. Further, an elevated risk of sebaceous tumors and keratoacanthoma has not been documented for PMS2 carriers. - Consider skin exam every 1–2 years with a health care provider skilled in identifying LS-associated skin manifestations. Age to start surveillance is uncertain and can be individualized.
Reproductive options	- For patients of reproductive age, advise about options for prenatal diagnosis and assisted reproduction including pre-implantation genetic testing. Discussion should include known risks, limitations, and benefits of these technologies. - For patients of reproductive age, advise about the risk of a rare recessive syndrome called CMMRD syndrome (Wimmer K, et al. J Med Genet 2014;51:355-365). If both partners are a carrier of a pathogenic variant(s) in the same MMR gene, then their future offspring will be at risk of having CMMRD syndrome.
Risk to relatives	- Advise patients to tell their relatives about possible inherited cancer risk, options for risk assessment, and management. - Recommend genetic counseling and consideration of genetic testing for relatives who are at risk.

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[Footnotes on
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NCCN Guidelines Version 1.2023

Lynch Syndrome

SURVEILLANCE COLONOSCOPY FINDINGS	FOLLOW-UP ^a
No pathologic findings	Continued surveillance every 1–3 years^{b,c}
Adenocarcinoma	- See appropriate NCCN Guidelines for Treatment by Cancer Type - For patients with colon adenocarcinoma, either a segmental or extended colectomy is indicated depending on clinical scenario and factors such as age and pathogenic variant.^{d,e} After surgery, if colon or rectum remain, colonoscopy surveillance should be performed every 1–2 years.^b - For patients with rectal adenocarcinoma, proctectomy or TPC is indicated depending on the clinical scenario and factors such as age, pathogenic variant, relationship to the anal sphincter, and anticipated need for pelvic radiation.
Adenomas	Complete endoscopic polypectomy with follow-up colonoscopy every 1–2 years^b
Adenomas not amenable to endoscopic resection	- Referral to center of expertise for endoscopic resection (preferred) or for segmental or extended colectomy depending on clinical scenario.^d Surgery is not required if adenoma is successfully resected. - Examine all remaining colonic mucosa every 1–2 years^b

^a For patients being sent for colon surgery, consider pre-colectomy gynecologic consultation to discuss risk-reducing options.

^b Patients who may benefit from a shorter 1- versus longer 2-year interval include those with risk factors such as history of CRC, male sex assigned at birth, *MLH1*/*MSH2* pathogenic variant, age >40 years, and history of adenoma. See [Discussion](#).

^c May consider subtotal colectomy if patient is not a candidate for optimal surveillance.

^d The type of surgical procedure chosen should be based on individual considerations and discussion of risk.

^e LS gene pathogenic variant should be considered as risk for metachronous tumors varies by pathogenic variant and age. Risk for metachronous CRC is higher with segmental versus extended colectomy. For *MLH1* and *MSH2* carriers who have segmental resection, there is up to a 43% cumulative lifetime risk of metachronous CRC. Risk may be lower for *MSH6*. There are limited data on *PMS2* but no marked increase in risk for metachronous CRC in available literature. For *PMS2*, based on lack of evidence for a significant increased risk for metachronous CRC and lower total CRC risk compared to *MLH1*, *MSH2*, and *MSH6*, consider segmental colectomy.

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Adenomatous Polyposis Testing Criteria

ADENOMATOUS POLYPOSIS TESTING CRITERIA

- Recommend testing if a personal history of ≥ 1 of the following 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 ≥ 1 of the following criteria:
 - ▶ between 10–19 cumulative adenomas,^a
 - ▶ desmoid tumor,
 - ▶ hepatoblastoma,
 - ▶ cribriform-morular variant of papillary thyroid cancer,
 - ▶ unilateral CHRPE, or
 - ▶ individual meets criteria for SPS ([SPS-1](#)) with at least some adenomas
 - ▶ Family history of polyposis and family unwilling/unable to have testing

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 ([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

Positive for monoallelic (single copy) *MUTYH* pathogenic variant^e

Pathogenic variant identified

Pathogenic variant not identified

TREATMENT/SURVEILLANCE

To determine classical FAP vs. AFAP, see [FAP/AFAP-1](#)

[MAP-1](#)

[GENE-3](#)

Manage as if positive for the known familial pathogenic variant

Personal history of ≥ 10 adenomas

[CPUE-1](#)

<10 adenomas

[NCCN Guidelines for Colorectal Cancer Screening](#)

[GENE-9](#)

See appropriate hereditary CRC syndrome

If individual has >10 adenomas, see [CPUE-1](#)

^a Age of onset, family history, personal history of CRC, and/or presence of other features may influence whether genetic testing is offered in these situations.

^b There are clinically relevant yet rarer genes that can cause a polyposis syndrome that may be phenotypically indistinguishable from *APC/MUTYH* polyposis.

^c Additional testing may be indicated based on personal and family medical history.

^d Multigene panel should include all polyposis and CRC genes (Stanich P, et al. Clin Gastroenterol Hepatol 2019;17:2008-2015).

^e Siblings of a patient with MAP are recommended to have site-specific testing for the familial pathogenic variants. Full sequencing of *MUTYH* may be considered in an unaffected parent when the other parent has MAP. If the unaffected parent is found to have one *MUTYH* pathogenic variant, testing the adult offspring for the familial *MUTYH* pathogenic variants is indicated. If the unaffected parent is not tested, comprehensive testing of *MUTYH* should be considered in the adult offspring. Testing of adult offspring of *MUTYH* heterozygotes should be offered if the other parent is also a heterozygote or could still be offered if the other parent is not a heterozygote and management would change (if they have a first-degree relative affected with CRC) or inform reproductive risks (since their future children could be at risk for MAP).

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APC-Associated Polyposis

PHENOTYPE

Classical FAP:^a

- Germline *APC* pathogenic variant
- Presence of ≥ 100 cumulative adenomas^b (sufficient for clinical suspicion of FAP) or fewer polyps at younger ages, especially in a family known to have FAP
- Autosomal dominant inheritance^c
- Possible associated additional findings
 - ▶ CHRPE
 - ▶ Osteomas, supernumerary teeth, odontomas
 - ▶ Desmoids, epidermoid cysts
 - ▶ Duodenal and other small bowel adenomas
 - ▶ Gastric fundic gland polyps
- Increased risk for CRC, medulloblastoma, papillary carcinoma of the thyroid, hepatoblastoma, periampullary cancer, gastric cancer, duodenal cancer

[Cancer Risks \(FAP-A\)](#)

RISK STATUS

Personal history of classical FAP

[Treatment and Surveillance \(FAP-1\)](#)

Family history of classical FAP, family member at risk, family pathogenic variant known

[Genetic Testing and Surveillance \(FAP-2\)](#)

Attenuated FAP:^d

- Germline *APC* pathogenic variant
- Presence of 10–<100 cumulative adenomas (average of 30 polyps)
- Frequent right-sided distribution of polyps
- Adenomas and cancers at age older than classical FAP (mean age of cancer diagnosis >50 y)
- Upper GI findings, thyroid and duodenal cancer risks are similar to classical FAP
- Other extraintestinal manifestations such as CHRPE are unusual
- Desmoid tumors are associated with 3' mutations in the *APC* gene

Personal history of AFAP

[Treatment and Surveillance \(AFAP-1\)](#)

Family history of AFAP, family member at risk, family pathogenic variant known

[Genetic Testing and Surveillance \(AFAP-2\)](#)

^a A clinical diagnosis of classical FAP is suspected when >100 polyps are present at a young age; however, genetic testing with MGPT is recommended to differentiate FAP, MAP, polyposis due to a mutation in a rare gene for which testing is available, and colonic polyposis of unknown etiology. Identification of a germline *APC* pathogenic variant confirms the diagnosis of FAP.

^b Individuals with >100 polyps occurring at older ages (≥ 35 –40 years) may be found to have AFAP.

^c There is a 30% spontaneous new pathogenic variant rate; thus, family history may be negative. This is especially noteworthy if onset age <50 y.

^d There is currently no consensus on what constitutes a clinical diagnosis of AFAP. AFAP is considered when >10–<100 adenomas are present and is confirmed when an *APC* pathogenic variant is identified. Genetic testing with MGPT is recommended to differentiate FAP/AFAP, MAP, polyposis due to a mutation in a rare gene for which testing is available, and colonic polyposis of unknown etiology.

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**FAP/
AFAP-1**



PERSONAL HISTORY OF CLASSICAL FAP

TREATMENT



^a [Cancer Risks \(FAP-A\)](#).

^b *APC* genetic testing is recommended in a proband to confirm a diagnosis of FAP and allow for pathogenic variant-specific testing in other family members. Additionally, knowing the location of the pathogenic variant in the *APC* gene can be helpful for predicting severity of polyposis, rectal involvement, and desmoid tumors.

^c [Surgical Options for Treating the Colon and Rectum in Patients with FAP \(FAP-D\)](#).

^d Timing of proctocolectomy in patients <18 y of age is not established since colon cancer is rare before age 18. In patients <18 y without severe polyposis and without family history of early cancer or severe genotype, the timing of proctocolectomy can be individualized. An annual colonoscopy is recommended if surgery is delayed.

Note: All recommendations are category 2A unless otherwise indicated.

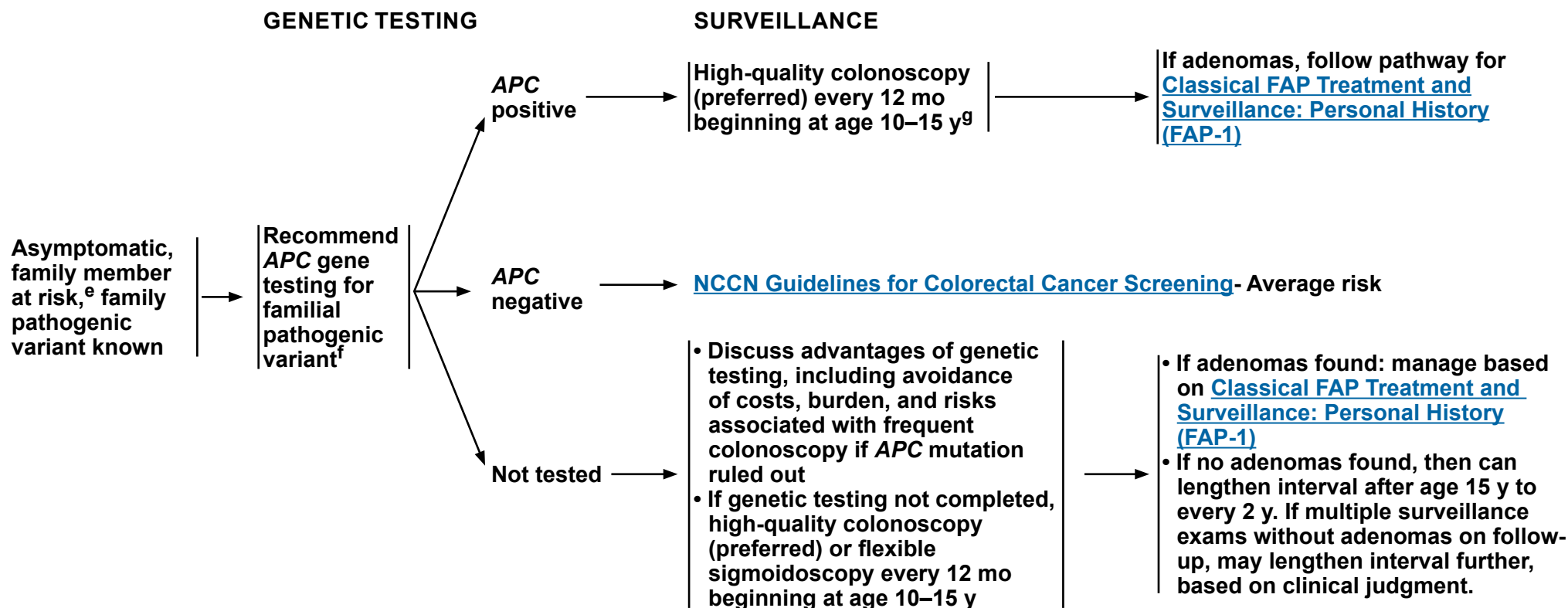
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



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Familial Adenomatous Polyposis

FAMILY HISTORY OF CLASSICAL FAP - PATHOGENIC VARIANT KNOWN: GENETIC TESTING AND SURVEILLANCE



^e If a first-degree relative is unavailable or unwilling to be tested, more distant relatives should be offered testing for the known pathogenic variant in the family.

^f FAP genetic testing in children should be done by age 10–15 y when colon screening would be initiated. If there is intent to do hepatoblastoma screening, FAP genetic testing should be considered in infancy.

^g Colonoscopy is preferred due to the possibility of missing right-sided polyps when limiting to sigmoidoscopy. However, based on patient and family preference or clinical judgment, sigmoidoscopy may also be considered. Earlier initiation of screening can be considered based on family history. In addition, individuals with active symptoms (eg, bleeding, anemia, persistent diarrhea) should undergo appropriate endoscopic workup regardless of age.

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Familial Adenomatous Polyposis

FAP: CANCER RISKS

Site	Estimated Average Age of Presentation	Cumulative Risk for Diagnosis Through Age 80 y ^a	Cumulative Risk for Diagnosis Through Lifetime for General Population ^f	References
Colon cancer (without colectomy)	39 years (median)	Approaches 100%	4.1%	Reference: 1
Colon cancer (post-colectomy)	Rectal (s/p IRA): 46–48 years Pouch and ATZ/rectal cuff (s/p IPAA): Not available	Rectal (s/p IRA): 10%–30% ^b Pouch and ATZ/rectal cuff (s/p IPAA): <1%–3%	4.1%	References: 2–10
Duodenal or periampullary cancer	50–52 years	<1%–10%	— ^g	References: 11–19
Gastric cancer	52–57 years	0.1%–7.1% ^c	0.8%	References: 19–27
Small bowel cancer (distal to duodenum)	43 years	<1%	0.3%	Reference: 19
Intra-abdominal desmoid tumors	31–33 years	10%–24% ^d Mutations in the 3' end of the APC gene have a higher risk ^e	— ^g	References: 28–33
Thyroid cancer (predominantly papillary thyroid carcinoma)	26–44 years	1.2%–12%	1.2%	References: 34–43
Hepatoblastoma	18–33 months	0.4%–2.5%	— ^g	References: 44–48
CNS cancer (predominantly medulloblastoma)	18 years	1%	0.6%	References: 49–50

ATZ = anal transition zone

Footnotes on [FAP-A 2 of 3](#)
References on [FAP-A 2 of 3](#) and [FAP-A 3 of 3](#)

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**FOOTNOTES**

- ^a Cumulative risk among patients with FAP represents cumulative incidence based on available cohort studies. In some studies, the cumulative risks are through a younger age (eg, age 70 or 75). For some cancer sites, case series and other observational studies may have reported higher cumulative risks. Note that some studies included patients who were under active screening and surveillance, and therefore risk estimates may reflect the impact of possible risk reduction due to such exposures.
- ^b These estimates are based on older studies that were performed prior to newer practices for case selection of ileorectal anastomosis (IRA) candidates.
- ^c The cumulative risks at the higher end of the range have been reported in Asian populations in Japan and Korea.
- ^d Studies have shown that the median time to development of desmoid tumors after abdominal surgery is 28.8–36 months (range 1–474 months) and that approximately 25% developed in individuals with no prior history of surgery or no local association to previous surgical procedures (Niewenhuis MH, et al. *Dis Colon Rectum* 2011;54:1229-1234; Schiessling S et al. *Br J Surg* 2013;100:694-703).
- ^e Genotype-phenotype correlation shows that higher risk (up to 37%) is associated with mutations in the 3' end (Church J, et al. *Dis Colon Rectum* 2015;58:444-448).
- ^f Cumulative risk for the general population represents cumulative incidence reported by the Surveillance, Epidemiology, and End Results 21 program data, 2016-2018, accessed November 16, 2021 at [SEER*Explorer](#).
- ^g Cumulative incidence for the general population specific to cancer site was not available through SEER*Explorer.

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[Continued](#)**Note: All recommendations are category 2A unless otherwise indicated.****Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**



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Familial Adenomatous Polyposis

CLASSICAL FAP: PERSONAL HISTORY - SURVEILLANCE STRATEGIES^{a,b}

Site		
Colon cancer (post-colectomy) (FAP-D)	- If patient had colectomy with ileorectal anastomosis (IRA), then endoscopic evaluation of the rectum every 6–12 mo depending on polyp burden. - If patient had TPC with ileal pouch-anal anastomosis (IPAA), then endoscopic evaluations of the ileal pouch and rectal cuff annually depending on polyp burden. Surveillance frequency should be shortened to every 6 mo for large, flat polyps with villous histology and/or high-grade dysplasia identified. - If patient had an ileostomy, consider careful visualization and stoma inspection by ileoscopy to evaluate for polyps or malignancy annually; evidence to support this recommendation is limited. - Chemoprevention may be considered to facilitate management of the remaining rectum or pouch post-surgery in select patients with progressive polyp burden (eg, based on size, number, and pathology). There are no FDA-approved medications for this indication at present. While there are data to suggest that sulindac is the most potent polyp regression medication, it is not known if the decrease in polyp burden decreases cancer risk. Patients interested in chemoprevention may consider referral to an expert center and enrollment in a clinical trial.	- In retained rectosigmoid, completion proctocolectomy if dense polyposis or high-grade dysplasia that cannot be managed endoscopically - If cancer found, see appropriate NCCN Guidelines for Treatment by Cancer Type
Duodenal or periampullary cancer	Upper endoscopy^c (including complete visualization of the ampulla of Vater) starting at around age 20–25 y. Consider baseline upper endoscopy earlier, if family history of aggressive duodenal adenoma burden or cancer. See FAP-C for follow-up of duodenoscopic findings.	
Gastric cancer	- Fundic gland polyps occur in a majority of patients with FAP, and focal low-grade dysplasia can occur but is typically non-progressive. The risk of gastric cancer in patients with FAP appears to be increased in patients from geographic areas with high gastric cancer risk and may be elevated in the setting of certain endoscopic findings, including carpeting of fundic gland polyps, solitary polyps larger than 20 mm, and mounds of polyps. High-risk histologic features include tubular adenomas, polyps with high-grade dysplasia, and pyloric gland adenomas. Need for specialized surveillance or surgery should be considered in presence of high-risk histologic features, preferably at a center of expertise. Presence of fundic gland polyps with low-grade dysplasia alone in the absence of high-risk features does not require specialized surveillance. ► Patients with high-risk lesions that cannot be removed endoscopically should be referred to a specialized center for consideration of gastrectomy.	
Thyroid cancer	Ultrasound at baseline starting in late teenage years. If normal, consider repeating ultrasound every 2–5 y and if abnormal, consider referral to a thyroid specialist. Shorter intervals may be considered for individuals with a family history of thyroid cancer.	

^a It is recommended that patients receive care by physicians or centers with expertise in FAP and that care be individualized to account for genotype, phenotype, and personal considerations.

^b Other than colon cancer, screening recommendations are expert opinion rather than evidence-based.

^c Cap-assisted endoscopy may be adequate for visualization of the ampulla (Kallenberg F, et al. Endoscopy 2017;49:181-185).

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[Continued](#)



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Familial Adenomatous Polyposis

CLASSICAL FAP: PERSONAL HISTORY - SURVEILLANCE STRATEGIES^{a,b}

Site	
CNS cancer	Patients should be educated regarding signs and symptoms of neurologic cancer and the importance of prompt reporting of abnormal symptoms to their physicians.
Intra-abdominal desmoids	Suggestive abdominal symptoms should prompt immediate abdominal imaging. If personal history of symptomatic desmoids, consider imaging with abdominal CT or MRI with and without contrast no less frequently than annually.
Small bowel polyps and cancer	High-level evidence to support routine small bowel screening distal to the duodenum is lacking. However, may consider small bowel visualization (eg, capsule endoscopy), especially if advanced duodenal polyposis.
Hepatoblastoma	High-level evidence to support routine hepatoblastoma screening is lacking. However, may consider liver palpation, abdominal ultrasound, and measurement of alpha-fetoprotein (AFP) every 3–6 mo during the first 5 y of life.

^a It is recommended that patients be receive care by physicians or centers with expertise in FAP and that care be individualized to account for genotype, phenotype, and personal considerations.

^b Other than colon cancer, screening recommendations are expert opinion rather than evidence-based.

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Familial Adenomatous Polyposis

DUODENAL FINDINGS AND MANAGEMENT^a

- The starting point for management of duodenal findings is the calculation of the modified Spigelman score.^{b,c} To calculate the overall Spigelman score, add up the scores for each factor.

	SCORE			
Factors	0 Points	1 Point	2 Points	3 Points
Number of polyps	0	1–4	5–20	>20
Polyp size, mm	No polyps	1–4	5–10	>10
Histology	No adenomas	Tubular adenomas	Tubulovillous adenoma	Villous adenoma
Dysplasia	No dysplasia	Low grade	—	High grade

- Endoscopic duodenal surveillance based on modified Spigelman score and stage:

SPIGELMAN SCORE	SPIGELMAN STAGE	SURVEILLANCE ^{d,e,f}
0	0	Repeat endoscopy every 3–5 y
1–4	I	Repeat endoscopy every 2–3 y
5–6	II	Repeat endoscopy every 1–2 y
7–8	III	Repeat endoscopy every 6–12 mo
9–12	IV	Expert surveillance every 3–6 mo

Additional considerations

- After downgrading of Spigelman stage by endoscopic/surgical management, individuals continue to require close surveillance. Surveillance intervals should be based on prior Spigelman stage, family history, and careful clinical judgment with shared decision-making.
- Individuals who have undergone duodenectomy for advanced duodenal polyposis or duodenal/ampullary cancer should continue annual surveillance.
- Small bowel evaluation with capsule endoscopy or CT/MRI enterography may be considered prior to surgical management of duodenal findings to identify large lesions that might modify the surgical approach.
- Utility of routine small bowel surveillance (such as with capsule endoscopy or enterography) has not been proven, but may be considered in patients at high risk (eg, history of advanced duodenal polyps, history of duodenal/ampullary cancer).

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[Footnotes](#)
[Continued](#)

FAP-C
1 OF 2



DUODENAL FINDINGS AND MANAGEMENT^a

Basic Principles for Management of Duodenal and Ampullary Adenomas:^{f,g,h}

- For patients with advanced duodenal polyposis consider referral to an expert center for management by endoscopists with expertise in FAP.
- Biopsy ampullary lesions that are suspicious for neoplasia before attempted endoscopic resection.
- The Panel
 - ▶ Recommends EUS for large ampullary lesions or large duodenal polyps with features concerning for malignancy before endoscopic or surgical resection.
 - ▶ Suggests endoscopic retrograde cholangiopancreatograph (ERCP) at the time of endoscopic papillectomy to assess for evidence of extension into either the biliary or pancreatic ducts.
 - ▶ Recommends prophylactic pancreatic duct stent placement and rectal indomethacin during papillectomy to reduce the risk of post-procedural pancreatitis.
 - ▶ Recommends that individuals with FAP who are considering weight loss surgery be referred to an expert center for multidisciplinary discussion of bariatric interventions, taking into account the challenge of routine duodenal and gastric surveillance after Roux-en-Y gastric bypass surgery. See [guidelines from the American Society for Gastrointestinal Endoscopy](#) for specific recommendations about the approach to sampling/removal of polyps in the duodenum.

Chemoprevention:

- There are no FDA-approved medications for the prevention or regression of duodenal adenomas at present. Data are insufficient regarding definitive endpoints such as prevention of duodenal/ampullary cancer or need for surgical management. Patients with duodenal polyposis who are interested in chemoprevention should be referred to expert centers for consideration of enrollment in a clinical trial.

^a Intervals for upper endoscopy surveillance can be determined based on gastric and/or duodenal findings; whichever requires the closest surveillance intervals should be applied.

^b Spigelman AD, Williams CB, Talbot IC, et al. Upper gastrointestinal cancer in patients with familial adenomatous polyposis. *Lancet* 1989;2:783-785.

^c Saurin JC, Gutknecht C, Napoleon B, et al. Surveillance of duodenal adenomas in familial adenomatous polyposis reveals high cumulative risk of advanced disease. *J Clin Oncol* 2004;22:493-498.

^d Recommend examination with side-viewing endoscope or cap-assisted endoscopy (Kallenberg F, et al. *Endoscopy* 2017;49:181-185).

^e Shorter intervals for endoscopic surveillance, regardless of Spigelman stage, may be considered based on personal or family history of massive gastric polyposis, multiple gastric adenomas, large ampullary adenoma (>10 mm), family or personal history of gastric/duodenal cancer, or advancing age.

^f Chathadi KV, Khashab MA, Acosta RD, et al. The role of endoscopy in ampullary and duodenal adenomas. *Gastrointest Endosc* 2015;82:773-781.

^g Campbell DR, Lee JH. A comprehensive approach to the management of benign and malignant ampullary lesions in hereditary and sporadic settings. *Curr Gastroenterol Report* 2020;22:46.

^h Hirota WK, Zuckerman MJ, Adler DG, et al. ASGE guideline: the role of endoscopy in the surveillance of premalignant conditions of the upper GI tract. *Gastrointest Endosc* 2006;63:570-580.

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Familial Adenomatous Polyposis

SURGICAL OPTIONS FOR TREATING THE COLON AND RECTUM IN PATIENTS WITH FAP^a

	TOTAL ABDOMINAL COLECTOMY WITH ILEORECTAL ANASTOMOSIS (TAC/IRA)	PROCTOCOLECTOMY WITH END ILEOSTOMY (PC/EI)	PROCTOCOLECTOMY WITH ILEAL POUCH-ANAL ANASTOMOSIS (PC/IPAA)
Indications	The decision to remove the rectum is dependent on whether the polyps are amenable to endoscopic surveillance and resection.	- Very low, advanced rectal cancer - Inability to perform IPAA - Patient with IPAA with unacceptable function - Patient with a contraindication to IPAA - Concern regarding ability to participate in close endoscopic surveillance after surgery - Patient choice	- Severe disease in colon and/or rectum - After TAC/IRA with endoscopically unmanageable disease in the rectum - Curable rectal cancer
Possible contra-indications	- Severe rectal disease (size or number of polyps) - Patient not reliable for follow-up surveillance of retained rectum		- Intra-abdominal desmoid that would interfere with completion of surgery - Patient is not a candidate for IPAA (eg, concomitant Crohn's disease, anal sphincter dysfunction) - Concern regarding ability to participate in close endoscopic surveillance after surgery
Advantages	- Technically straightforward - Relatively low complication rate - Good functional outcome - No permanent or temporary stoma - Avoids the risks of infertility or infecundity,^b and sexual or bladder dysfunction that can occur following proctectomy	- Removes risk of CRC - One operation	- Reduced rectal cancer risk - No permanent stoma - Reasonable bowel function
Disadvantages	Risk of metachronous cancer in the remaining rectum	- Risks of infertility or infecundity,^b and sexual or bladder dysfunction - Permanent stoma - May discourage family members from seeking evaluation for fear of permanent stoma	- Complex operation - Usually involves temporary stoma - Risks of infertility or infecundity,^b and sexual or bladder dysfunction - Risk of fecal incontinence and increased risk of anal sphincter injury with vaginal delivery - Functional results are variable

^a It is recommended that patients receive care by physicians or centers with expertise in FAP and that care be individualized to account for genotype, phenotype, and personal considerations.

^b Infertility is the inability to conceive 1 year after unprotected intercourse. Infecundity is the inability to bear children.

Note: All recommendations are category 2A unless otherwise indicated.

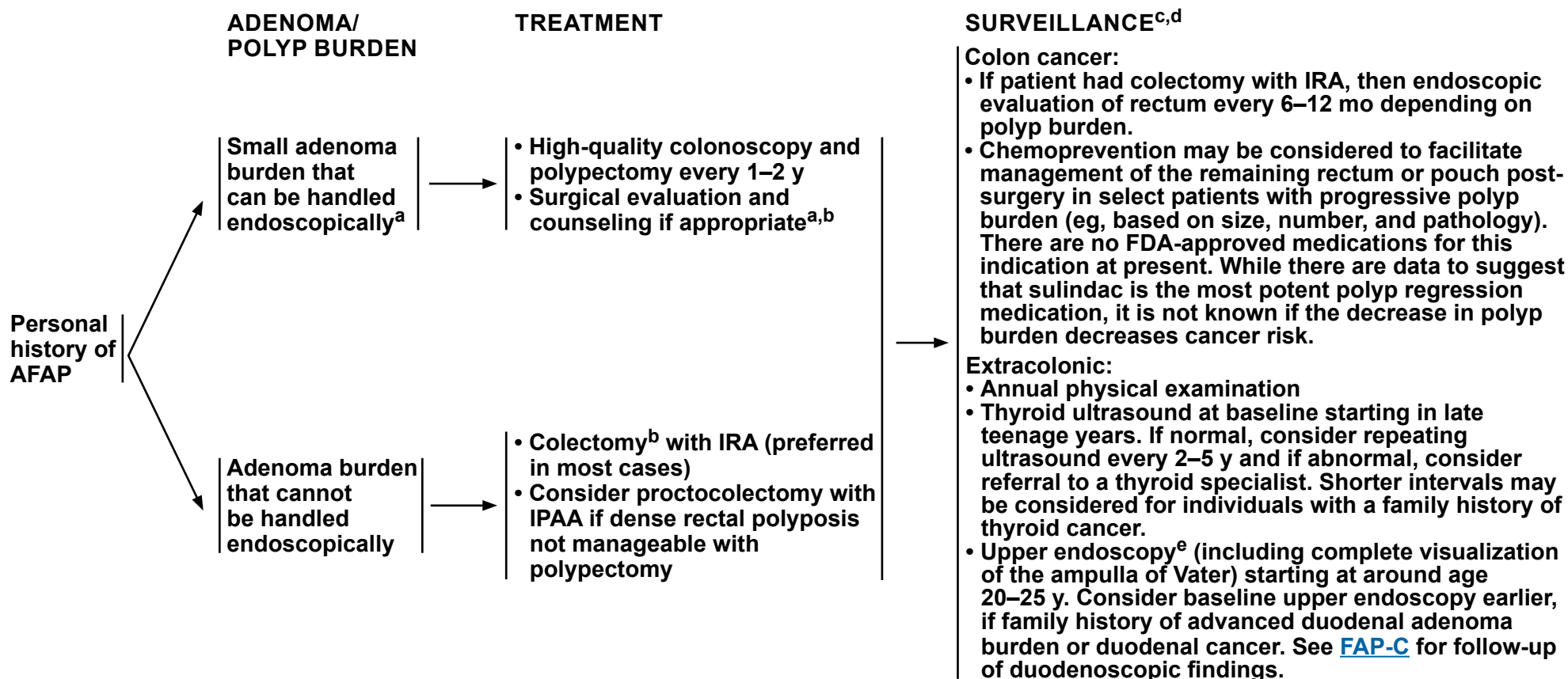
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Attenuated Familial Adenomatous Polyposis

ATTENUATED FAP TREATMENT AND SURVEILLANCE: PERSONAL HISTORY



^a Small adenoma burden is defined (somewhat arbitrarily) as fewer than 20 adenomas, all <1 cm in diameter, and none with advanced histology, so that colonoscopy with polypectomy can be used to effectively eliminate the polyps. Colectomy may be indicated before this level of polyp burden, especially if colonoscopy is difficult and polyp control is uncertain. Surgery could be considered when polyp burden is >20 at any individual examination, when polyps have been previously ablated, when some polyps have reached a size >1 cm, or when advanced histology is encountered in any polyp.

^b [Surgical Options for Treating the Colon and Rectum in Patients with FAP \(FAP-D\)](#).

^c It is recommended that patients receive care by physicians or centers with expertise in FAP/AFAP and that care be individualized to account for genotype, phenotype, and personal considerations.

^d Surveillance for upper GI findings for AFAP is similar to classical FAP.

^e Cap-assisted endoscopy may be adequate for visualization of the ampulla (Kallenberg F, et al. Endoscopy 2017;49:181-185).

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



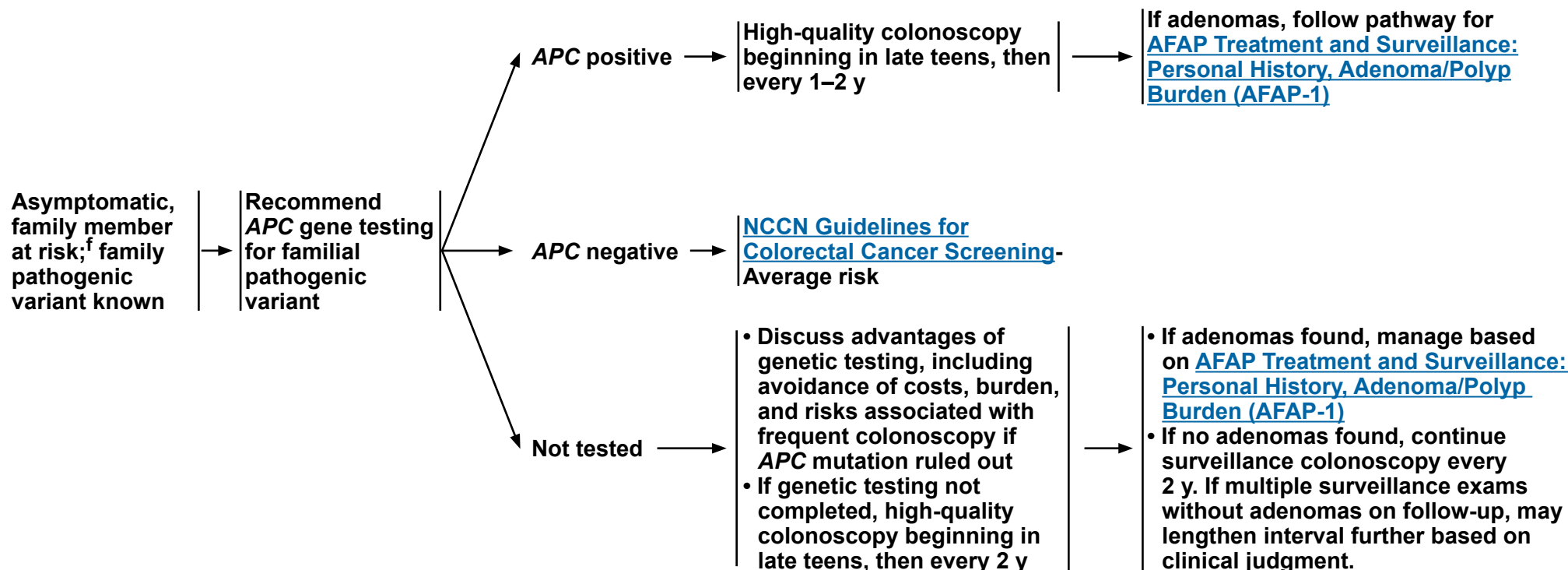
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Attenuated Familial Adenomatous Polyposis

ATTENUATED FAP GENETIC TESTING AND SURVEILLANCE: FAMILY HISTORY OF ATTENUATED FAP PATHOGENIC VARIANT KNOWN

GENETIC TESTING

SURVEILLANCE



^f If a first-degree relative is unavailable or unwilling to be tested, more distant relatives should be offered testing for the known pathogenic variant in the family.

Note: All recommendations are category 2A unless otherwise indicated.

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MUTYH-Associated Polyposis

PHENOTYPE

RISK STATUS

- Biallelic *MUTYH* pathogenic variants
- Polyposis or colon cancers consistent with autosomal recessive inheritance (ie, parents unaffected, siblings affected)
- Possibility of consanguinity
- Fewer than 100 adenomas^a (uncommonly >100)
- Adenomas and CRC at age older than classical FAP (median CRC age >50 y)
- Duodenal cancer (5%)
- Duodenal adenomas

Personal history of MAP

[Treatment and Surveillance \(MAP-2\)](#)

Asymptomatic family member at risk; family pathogenic variant known

[Genetic Testing and Surveillance \(MAP-3\)](#)

^a Multiple serrated polyps (hyperplastic polyps, sessile serrated polyps, and traditional serrated adenomas) may also be seen in patients with MAP polyposis. Patient with MAP may also meet criteria for SPS.

Note: All recommendations are category 2A unless otherwise indicated.

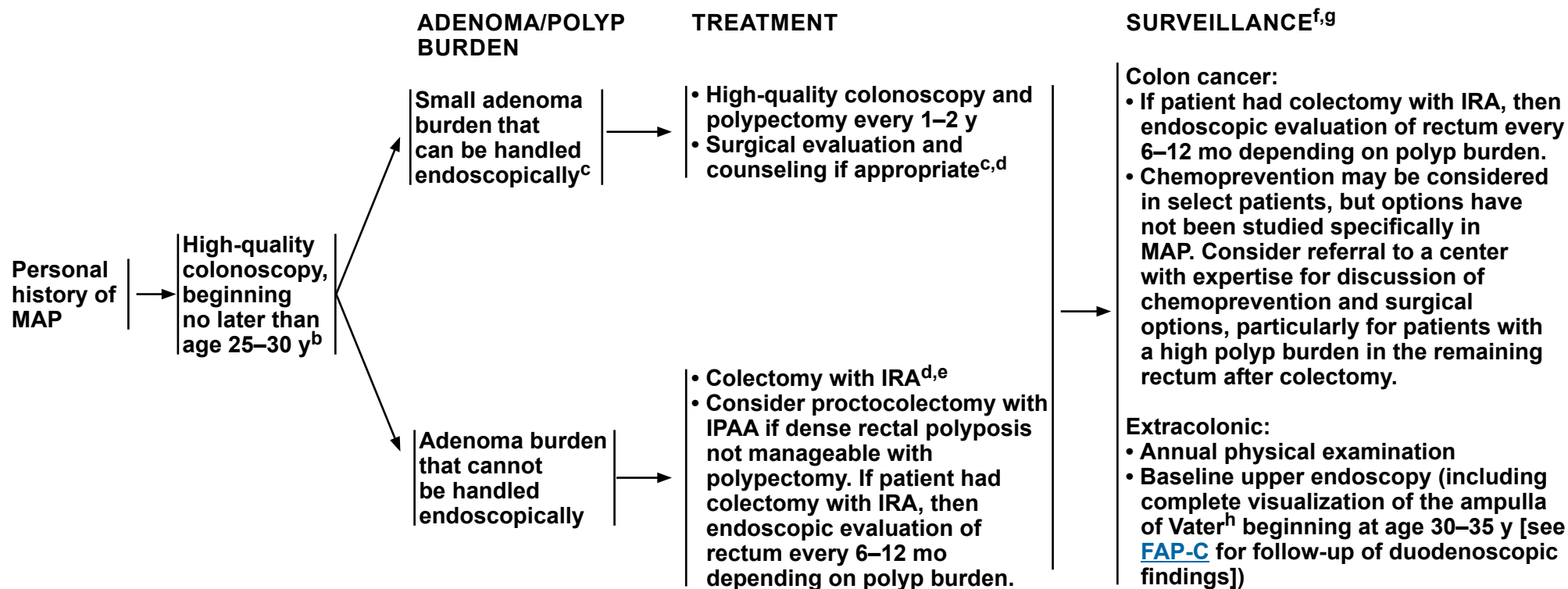
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



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MUTYH-Associated Polyposis

MAP TREATMENT AND SURVEILLANCE: PERSONAL HISTORY



^b Earlier colonoscopy may be indicated based on family history.

^c Small adenoma burden is defined (somewhat arbitrarily) as fewer than 20 adenomas, all <1 cm in diameter, and none with advanced histology, so that colonoscopy with polypectomy can be used to effectively eliminate the polyps. Colectomy may be indicated before this level of polyp burden, especially if colonoscopy is difficult and polyp control is uncertain. Surgery could be considered when polyp burden is >20 at any individual examination, when polyps have been previously ablated, when some polyps have reached a size >1 cm, or when advanced histology is encountered in any polyp. Extent of colectomy may be modified based on the burden and distribution of adenomas.

^d [Surgical Options for Treating the Colon and Rectum in Patients with FAP \(FAP-D\)](#).

^e Earlier surgical intervention should be considered in patients who are nonadherent.

^f It is recommended that patients receive care by physicians or centers with expertise in MAP and that care be individualized to account for genotype, phenotype, and personal considerations.

^g Surveillance for upper GI findings for MAP is similar to classical FAP.

^h Cap-assisted endoscopy may be adequate for visualization of the ampulla (Kallenberg F, et al. Endoscopy 2017;49:181-185).

Note: All recommendations are category 2A unless otherwise indicated.

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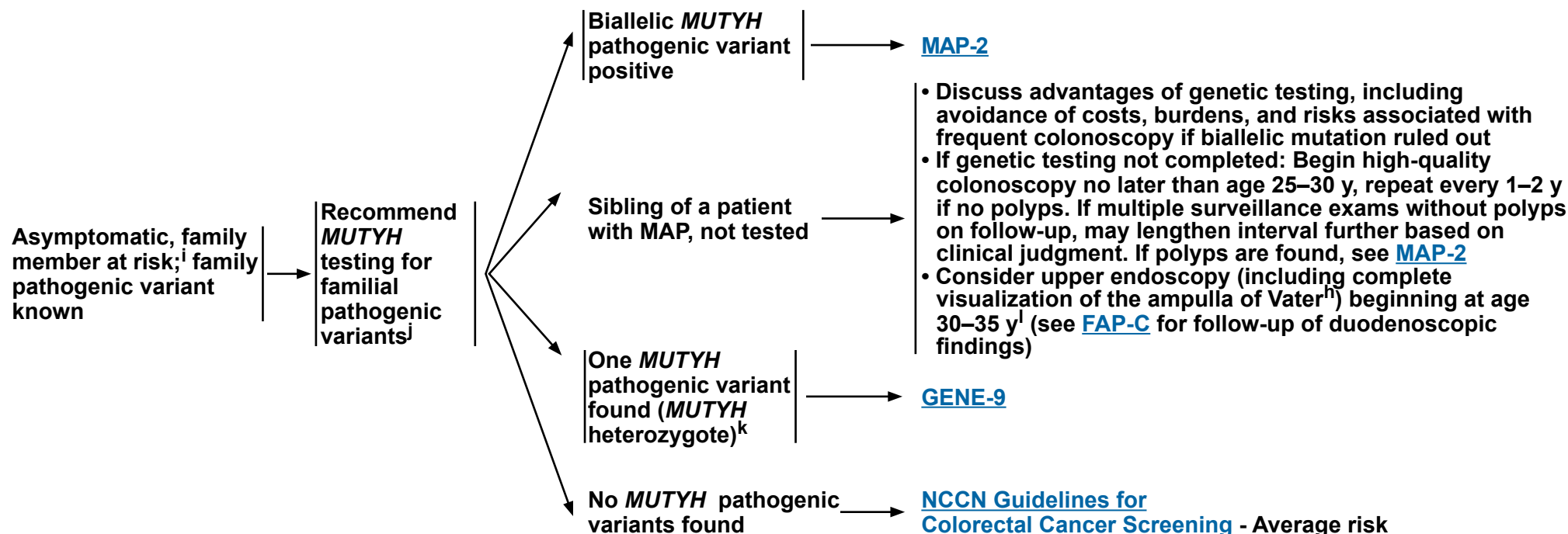
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MUTYH-Associated Polyposis

MAP TREATMENT AND SURVEILLANCE: FAMILY HISTORY OF MAP PATHOGENIC VARIANT KNOWN

GENETIC TESTING

SURVEILLANCE



^h Cap-assisted endoscopy may be adequate for visualization of the ampulla (Kallenberg F, et al. Endoscopy 2017;49:181-185).

ⁱ A family member at risk can be defined as a sibling of an affected individual and/or proband. Other individuals in a family may also be at risk of having MAP or a monoallelic *MUTYH* pathogenic variant.

^j Siblings of a patient with MAP are recommended to have site-specific testing for the familial pathogenic variants. Full sequencing of *MUTYH* may be considered in an unaffected parent when the other parent has MAP. If the unaffected parent is found to not have a *MUTYH* pathogenic variant, genetic testing in the children is not necessary to determine MAP status. If the unaffected parent is not tested, comprehensive testing of *MUTYH* should be considered in the adult children. If the unaffected parent is found to have one *MUTYH* pathogenic variant, testing the adult children for the familial *MUTYH* pathogenic variants is indicated.

^k There are no specific data available to determine screening recommendations for a patient with a heterozygous *MUTYH* pathogenic variant and a second-degree relative affected with CRC. See the [NCCN Guidelines for Colorectal Cancer Screening](#).

^l Hurley J, et al. Gastrointest Endosc 2018;88:665-673; Vogt S, et al. Gastroenterology 2009;137:1976-1985; Walton SJ, et al. Clin Gastroenterol Hepatol 2016;14:986-992.

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Colonic Adenomatous Polyposis of Unknown Etiology

COLONIC ADENOMATOUS POLYPOSIS OF UNKNOWN ETIOLOGY (CPUE)

(CPUE is defined as an individual with cumulative lifetime ≥ 10 –20 adenomas without a pathogenic variant identified in a polyposis gene)^a

The following are surveillance/management recommendations for CPUE:^b

Phenotype (based on cumulative lifetime adenomas)	Management/Surveillance
Personal history of ≥ 100 adenomas	Manage as FAP (FAP-1)
Personal history of 20–<100 adenomas: Adenoma burden that cannot be managed endoscopically	- Surgical evaluation and counseling if appropriate - Baseline upper endoscopy at time of next colonoscopy surveillance by age 20–25 y and repeat following duodenal surveillance guidelines on page FAP-C.
Personal history of 20–<100 adenomas: Adenoma burden manageable by colonoscopy and polypectomy	- High-quality colonoscopy and polypectomy every 1–2 years - Repeat at short interval based on residual polyp burden^c - Baseline upper endoscopy at time of next colonoscopy surveillance by age 20–25 y and repeat following duodenal surveillance guidelines on page FAP-C. - Surgical evaluation may be considered if polyps not manageable or based on patient preference
Personal history of 10–19 adenomas	- Manage based on clinical judgment. Frequency of surveillance may be modified based on factors such as age at which patient met cumulative adenoma threshold or total number of adenomas at most recent colonoscopy, with more frequent surveillance favored for younger age at meeting threshold or higher adenoma burden at last colonoscopy. See NCCN Guidelines for Colorectal Cancer Screening - Consider baseline upper endoscopy at time of next colonoscopy surveillance by age 20–25 y and repeat following duodenal surveillance guidelines on page FAP-C.

[Family history on CPUE-2](#)

^a Prior to assigning diagnosis of CPUE, therapy-associated polyposis attributable to treatment for childhood and young adult cancer should be considered as a potential explanation for otherwise unexplained polyposis [Yurgelun M, et al. Clin Gastroenterol Hepatol 2014;12:1046-1050 and Biller L, et al. Cancer Prev Res (Phila) 2020;13:291-298].

^b Prior to managing as CPUE, multigene testing including all polyposis and CRC genes should be strongly considered (Stanich P, et al. Clin Gastroenterol Hepatol 2019;17:2008-2015). Pathogenic variants associated with adenomatous polyposis include, but are not limited to monoallelic pathogenic variants in *APC*, *GREM1*, *POLE*, *POLD1*, and *AXIN2*, and biallelic pathogenic variants in *MUTYH*, *NTHL1*, and *MSH3*. Updated genetic testing may be considered in patients who have previously had limited genetic testing as clinically indicated.

^c Based on findings at multiple surveillance exams, interval between colonoscopies may be lengthened based on clinical judgment.

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NCCN Guidelines Version 1.2023

Colonic Adenomatous Polyposis of Unknown Etiology

COLONIC ADENOMATOUS POLYPOSIS OF UNKNOWN ETIOLOGY (CPUE)

(CPUE is defined as an individual with cumulative lifetime ≥ 10 –20 adenomas without a pathogenic variant identified in a polyposis gene)^a

The following are surveillance/management recommendations for CPUE:^b

Phenotype (based on cumulative lifetime adenomas)	Management/Surveillance
Family history of ≥ 100 adenomas in a first-degree relative^{d,e} AND meets one of the following criteria: 1) Family member tested, with no pathogenic variant identified; OR 2) Family member not tested and the unaffected individual with family history has been tested, with no pathogenic variant identified	- High-quality colonoscopy every 12 mo beginning at age 10–15 y. In some families, based on clinical judgment, initiating colonoscopy beginning in late teens, then every 2 y may be appropriate. - If no adenomas, then can lengthen interval to every 2 y. If multiple surveillance exams without adenomas on follow-up, may lengthen interval further based on clinical judgment. - If ≥ 100 adenomas found, manage based on Classical FAP Treatment and Surveillance: Personal History (FAP-1) or - If < 100 adenomas found, manage based on AFAP Treatment and Surveillance: Personal History, Adenoma/Polyp Burden (AFAP-1)
Family history of 20–< 100 adenomas in a first-degree relative^{d,e} AND meets one of the following criteria: 1) Family member tested, with no pathogenic variant identified; OR 2) Family member not tested and the unaffected individual with family history has been tested, with no pathogenic variant identified	- Initiation age and frequency of colonoscopy should be modified based on clinical judgment taking account into first-degree relative's history with respect to age and cumulative adenoma burden. Consider high-quality colonoscopy beginning in late teens, then every 2 y. Initiation age should be modified if cumulative family history of 20–< 100 adenomas was reached later in life in the affected relative. If multiple surveillance exams without adenomas on follow-up, may lengthen interval further based on clinical judgment. - If adenomas found, manage based on AFAP Treatment and Surveillance: Personal History, Adenoma/Polyp Burden (AFAP-1)
Family history of 10–19 adenomas in a first-degree relative AND meets one of the following criteria: 1) Family member tested, with no pathogenic variant identified; OR 2) Family member not tested and the unaffected individual with family history has been tested, with no pathogenic variant identified	Manage based on clinical judgment. Frequency of surveillance may be modified based on personal, cumulative history of adenomas, taking into account current polyp surveillance guidelines (NCCN Guidelines for Colorectal Cancer Screening) and the family history

^a Prior to assigning diagnosis of CPUE, therapy-associated polyposis attributable to treatment for childhood and young adult cancer should be considered as a potential explanation for otherwise unexplained polyposis.

^b Prior to managing as CPUE, multigene testing including all polyposis and CRC genes should be strongly considered (Stanich P, et al. Clin Gastroenterol Hepatol 2019;17:2008-2015). Pathogenic variants associated with adenomatous polyposis include, but are not limited to monoallelic pathogenic variants in *APC*, *GREM1*, *POLE*, *POLD1*, and *AXIN2*, and biallelic pathogenic variants in *MUTYH*, *NTHL1*, and *MSH3*. Updated genetic testing may be considered in patients who have previously had limited genetic testing as clinically indicated.

^d Recommend genetic testing ([POLYP-1](#)) in family member affected with polyposis.

^e There are limited data to suggest definitive recommendations for when to initiate screening or the interval of screening.

Note: All recommendations are category 2A unless otherwise indicated.

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NCCN Guidelines Version 1.2023

Peutz-Jeghers Syndrome

PJS Diagnosis:^{a,b}

- A clinical diagnosis of PJS can be made when an individual has two or more of the following features:
 - ▶ Two or more Peutz-Jeghers-type hamartomatous polyps of the GI tract
 - ▶ Mucocutaneous hyperpigmentation of the mouth, lips, nose, eyes, genitalia, or fingers
 - ▶ Family history of PJS
- Clinical genetic testing is recommended for any patient meeting the above criteria or with a family history of PJS. The majority of cases occur due to pathogenic variants in the *STK11 (LKB1)* gene.

General Treatment and Surveillance Considerations:^c

- Patients who meet clinical criteria for PJS or with a pathogenic variant in *STK11* – recommend referral to a specialized team and encourage participation in any available clinical trials.
- Surveillance should begin at the approximate ages on [PJS-2](#) and [PJS-3](#) or earlier if symptoms occur.
- Small bowel polypectomy should be performed for all polyps causing symptoms and polyps >10 mm in size, to prevent polyp-related complications. Balloon-assisted enteroscopy and if needed, surgery-assisted enteroscopy, is recommended based upon available expertise.
- The surveillance guidelines listed on [PJS-2](#) and [PJS-3](#) for the multiple organs at risk for cancer may be considered, but limited data exist regarding the efficacy of the various screening modalities in PJS.
- Patients with PJS are at increased risk for iron deficiency anemia, bowel obstruction/intussusception from polyps, GI bleeding, and cancer. Therefore, regardless of the surveillance interval, any new signs/symptoms of GI disease should receive timely workup in both the pediatric and adult populations.

[Pediatric Surveillance Guidelines \(PJS-2\)](#)

[Adult Surveillance Guidelines \(PJS-3\)](#)

^a Tomlinson IP, et al. J Med Genet 1997;34:1007-1011.

^b Due to the rarity of the syndrome and complexities of diagnosing and managing individuals with PJS, referral to a specialized team or centers with expertise is recommended.

^c Li B, et al. Eur J Pediatr 2020;179:611-617; Wang Y, et al. J Dig Dis 2019;20:415-420; Blanco-Velasco G, et al. Rev Gastroenterol Mex 2018;83:234-237; Belsha D, et al. J Pediatr Gastroenterol Nutr 2017;65:500-502; Oncel M, et al. Colorectal Dis 2004;6:332-335.

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NCCN Guidelines Version 1.2023

Peutz-Jeghers Syndrome

Peutz-Jeghers Syndrome: Pediatric Surveillance

Site	Risk Reduction Targets	Screening/Intervention and Interval	Initiation Age (y)
Colon Stomach	- Bleeding - Iron deficiency anemia	Upper endoscopy and high-quality colonoscopy with polypectomy: If polyps are found, repeat every 2–3 y. Shorter intervals may be indicated based on polyp size, number, and pathology. If no polyps, then resume at age 18 y.	8–10 y - Endoscopy should be initiated at an earlier age or repeated more frequently if signs/symptoms of GI blood loss or intussusception/obstruction
Small intestine	- Bleeding - Iron deficiency anemia - Intussusception	Small bowel visualization (video capsule endoscopy or CT/MRI enterography) at baseline with follow-up interval based on findings, but at least by age 18 y, then every 2–3 y. Shorter intervals may be indicated based on polyp size, number, and pathology.	8–10 y - Start at an earlier age or repeat more frequently if signs/symptoms of GI blood loss or intussusception/obstruction
Ovary	Sex cord tumor with annular tubules (SCTAT) – estimated lifetime risk at least 20%	Annual physical examination for observation of precocious puberty	~ 8 y
Testes	Sertoli cell tumors – estimated lifetime risk 9%	Annual testicular exam and observation for feminizing changes	~ 10 y

[Adult Surveillance Guidelines \(PJS-3\)](#)

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NCCN Guidelines Version 1.2023

Peutz-Jeghers Syndrome

Peutz-Jeghers Syndrome: Adult Surveillance

Cancer Site	% Lifetime Risk ^d	Screening Procedure and Interval	Initiation Age (y)
Breast (female)	32%–54%	- Mammogram and breast MRI annually^f - Clinical breast exam every 6 mo	~ 30 y
Colon	39%	High-quality colonoscopy every 2–3 y. Shorter intervals may be indicated based on polyp size, number, and pathology.	~ 18 y
Stomach	29%	Upper endoscopy every 2–3 y. Shorter intervals may be indicated based on polyp size, number, and pathology.	~ 18 y
Small intestine	13%	Small bowel visualization (video capsule endoscopy or CT/MR enterography) every 2–3 y. Shorter intervals may be indicated based on polyp size, number, and pathology.	~ 18 y
Pancreas	11%–36%	Annual imaging of the pancreas with either EUS or MRI/MRCP (both ideally performed at center of expertise). Also see NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic.	~ 30–35 y ^g
Cervix (typically minimal deviation adenocarcinoma^e)	At least 10%	- Annual pelvic examination and Pap smear - Consider total hysterectomy (including uterus and cervix) once completed with childbearing	~ 18–20 y
Uterus	9%	Annual pelvic examination with endometrial biopsy if abnormal bleeding	~ 18–20 y
Ovary (SCTAT)	At least 20%	Annual pelvic examination with annual pelvic ultrasound	~ 18–20 y
Lung	7%–17%	Provide education about symptoms and smoking cessation. See NCCN Guidelines for Smoking Cessation. No other specific recommendations have been made.	
Testes (Sertoli cell tumors)	9%	Annual testicular exam and observation for feminizing changes	Continued from pediatric screening

^d Hearle N, et al. Clin Cancer Res 2006;12:3209-3215; Giardiello FM, et al. Gastroenterology 2000;119:1447-1453; Ishida H, et al. Surg Today 2016;46:1231-1242.

^e Formerly known as cervical adenoma malignum.

^f See [NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic \(BRCA-A\)](#) for further breast screening recommendations regarding mammogram and breast MRI screening. High-quality breast MRI limitations include

having: a need for a dedicated breast coil, the ability to perform biopsy under MRI guidance, experienced radiologists in breast MRI, and regional availability. Breast MRI is performed preferably days 7–15 of menstrual cycle for premenopausal patients. The appropriateness of imaging modalities and scheduling is still under study. Lowry KP, et al. Cancer 2012;118:2021-2030.

^g Based on clinical judgment, early initiation age may be considered, such as 10 y younger than the earliest age of onset in the family.

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NCCN Guidelines Version 1.2023

Juvenile Polyposis Syndrome

JPS Definition:^{a,b}

- A clinical diagnosis of JPS is considered in an individual who meets at least one of the following criteria:
 - ▶ ≥5 juvenile polyps of the colon
 - ▶ Multiple juvenile polyps found throughout the GI tract
 - ▶ Any number of juvenile polyps in an individual with a family history of JPS
- Clinical genetic testing is recommended for any patient meeting the above criteria or with a family history of JPS. Approximately 50% of patients meeting clinical criteria for JPS will have pathogenic variants detected in the *BMPR1A* or *SMAD4*^c genes.
- In families with a known *BMPR1A* pathogenic variant, genetic testing should be performed by age 12–15 when surveillance would begin (or sooner if symptoms warrant evaluation).
- If there is a known *SMAD4* pathogenic variant in the family, genetic testing should be performed within the first 6 months of life due to the coexistence of *SMAD4*-related JPS-hereditary hemorrhagic telangiectasia (HHT) overlap, which requires specialized surveillance.

General Treatment and Surveillance Considerations:

- For patients who meet clinical criteria for JPS or with a pathogenic variant in *BMPR1A* or *SMAD4*, we recommend referral to a specialized team and encourage participation in any available clinical trials.
- Surveillance should begin at the approximate ages listed on [JPS-2](#) and [JPS-3](#) or earlier if symptoms occur.
- The surveillance guidelines listed on [JPS-2](#) and [JPS-3](#) for the multiple organs at risk for cancer may be considered. Limited data exist regarding the efficacy of various screening modalities in JPS.
- Patients with JPS are at increased risk for iron deficiency anemia, GI bleeding, and cancer. Therefore, regardless of the surveillance interval, any new signs/symptoms of GI disease should receive timely workup in both the pediatric and adult populations.

[Pediatric Surveillance Guidelines \(JPS-2\)](#)

[Adult Surveillance Guidelines \(JPS-3\)](#)

^a Due to the rarity of the syndrome and complexities of diagnosing and providing care for individuals with JPS, referral to a specialized team is recommended.

^b Syngal S, et al. Am J Gastroenterol 2015;110:223-262.

^c Faughnan M, et al. Ann Intern Med 2020;173:989-1001.

Note: All recommendations are category 2A unless otherwise indicated.

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NCCN Guidelines Version 1.2023

Juvenile Polyposis Syndrome

Juvenile Polyposis Syndrome: Pediatric Surveillance^{a,b}

Site	Risk Reduction Targets	Screening/Surveillance Procedure and Interval	Initiation Age (y)
Stomach	- Bleeding - Iron deficiency anemia	Upper endoscopy with polypectomy: If polyps are found, repeat every 2–3 y. Shorter intervals may be indicated based on polyp size, number, and pathology.^d If no polyps, then resume at 18 y.	12–15 y - Endoscopy should be initiated at an earlier age or repeated more frequently if signs/symptoms of GI blood loss
Colon	- Bleeding - Iron deficiency anemia	High-quality colonoscopy with polypectomy: If polyps are found, repeat every 2–3 y. Shorter intervals may be indicated based on polyp size, number, and pathology.^d If no polyps, then resume at 18 y.	12–15 y - Endoscopy should be initiated at an earlier age or repeated more frequently if signs/symptoms of GI blood loss
HHT	- Epistaxis - Bleeding - Iron deficiency anemia	In individuals with a <i>SMAD4</i> pathogenic variant, screen for signs, symptoms, and vascular lesions associated with HHT.^{a,c}	Within first 6 mo of life or at time of diagnosis

^a Due to the rarity of the syndrome and complexities of diagnosing and providing care for individuals with JPS, referral to a specialized team is recommended.

^b Syngal S, et al. Am J Gastroenterol 2015;110:223-262.

^c Faughnan M, et al. Ann Intern Med 2020;173:989-1001.

^d If polyp burden or polyp-related symptoms (ie, anemia) cannot be controlled endoscopically or prevent optimal surveillance for cancer, consideration should be given to gastrectomy and/or colectomy.

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NCCN Guidelines Version 1.2023

Juvenile Polyposis Syndrome

Juvenile Polyposis Syndrome: Adult Surveillance^{a,b}

Site	Patients	% Lifetime Risk	Screening/Surveillance Procedure and Interval	Initiation Age (y)
Colon	SMAD4/ BMPR1A	Up to 50%	• High-quality colonoscopy every 1–3 years. Intervals should be based on polyp size, number, and pathology. ^d	~18 y
	No pathogenic variant identified	Undefined	• High-quality colonoscopy every 1–3 years. Intervals should be based on polyp size, number, and pathology. ^d If no polyps, consider increasing interval to every 5 years. ^e	
Stomach	SMAD4/ BMPR1A	Up to 21% especially if multiple gastric polyps present	• Upper endoscopy every 1–3 years. Intervals should be based on polyp size, number, and pathology. ^{d,f}	~18 y
	No pathogenic variant identified	Undefined	• Upper endoscopy every 1–3 years. Intervals should be based on polyp size, number, and pathology. ^d If no polyps, consider increasing interval to every 5 years. ^e	
Small intestine	All patients with JPS	Rare, undefined	• No recommendations have been made.	
HHT	SMAD4	22% ^g	• Screen for signs, symptoms, and vascular lesions associated with HHT	At time of diagnosis

^a Due to the rarity of the syndrome and complexities of diagnosing and providing care for individuals with JPS, referral to a specialized team is recommended.

^b Syngal S, et al. Am J Gastroenterol 2015;110:223-262.

^d If polyp burden or polyp-related symptoms (ie, anemia) cannot be controlled endoscopically or prevent optimal surveillance for cancer, consideration should be given to gastrectomy and/or colectomy.

^e MacFarland SP, et al. Cancer Prev Res (Phila) 2021;14:215-222.

^f While *SMAD4* pathogenic variant carriers often have severe upper gastrointestinal tract involvement, *BMPR1A* pathogenic variant carriers may have a less severe upper gastrointestinal tract phenotype and may merit lengthened surveillance intervals in the absence of polyps. Gastric cancer risk for *BMPR1A* pathogenic variant carriers may be lower than for *SMAD4* pathogenic variant carriers. Latchford A, et al. Dis Colon Rectum 2012;55:1038-1043. Aytac E, et al. Br J Surg 2015;102:114-118.

^g O'Malley M, LaGuardia L, Kalady M, et al. Hered Cancer Clin Pract 2011;9(Suppl 1):O5.

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Serrated Polyposis Syndrome

Serrated polyposis syndrome (previously known as hyperplastic polyposis) definition:^{a,b,c}

- A clinical diagnosis of serrated polyposis is considered in an individual who meets at least one of the following empiric criteria:^{d,e}
 - 1) ≥5 serrated lesions/polyps proximal to the rectum, all being ≥5 mm in size, with ≥2 being ≥10 mm in size
 - 2) >20 serrated lesions/polyps of any size distributed throughout the large bowel, with ≥5 being proximal to the rectum
- Any histologic subtype of serrated lesion/polyp (hyperplastic polyp, sessile serrated lesion without or with dysplasia, traditional serrated adenoma, and unclassified serrated adenoma) is included in the final polyp count. The polyp count is cumulative over multiple colonoscopies.
- For the majority of patients with SPS, no cause is identifiable. Pathogenic variants in *RNF43* have been identified as a rare cause, as have biallelic pathogenic variants in *MUTYH*. Several studies have observed SPS occurring in patients who were previously treated for Hodgkin lymphoma and other childhood or young adulthood cancers [Rigter LS, et al. *Cancer* 2019;125:990-999 and Biller LH, et al. *Cancer Prev Res (Phila)* 2020;13:291-298]. Genetic testing may be favored based on patient preference, family history of CRC, or presence of features (such as adenomas, see [POLYP-1](#).) that could overlap with other hereditary CRC syndromes.
- Adenomas may frequently be found in patients with SPS.
- The risk for colon cancer in this syndrome is elevated, although the precise risk remains to be defined.
- Extracolonic manifestations of SPS have not been consistently identified to date but literature in this area may evolve.
- Occasionally, more than one affected case of serrated polyposis is seen in a family.^e

Surveillance recommendations for individuals with serrated polyposis:

- High-quality colonoscopy with polypectomy until all polyps ≥5 mm are removed, then colonoscopy every 1 to 3 years depending on number and size of polyps. Clearing of all polyps is preferable but not always possible.
- Consider surgical referral if colonoscopic treatment and/or surveillance is inadequate.

Surveillance recommendations for individuals with a family history of serrated polyposis:

- The risk of CRC in first-degree relatives of individuals with serrated polyposis is elevated.
- First-degree relatives are encouraged to have colonoscopy at the earliest of the following:
 - ▶ Age 40 years
 - ▶ Same age as youngest diagnosis of serrated polyposis if uncomplicated by cancer
 - ▶ Ten years earlier than earliest diagnosis in family with CRC secondary to serrated polyposis
- Following baseline exam, repeat every 5 years if no polyps are found. If proximal serrated polyps or multiple adenomas are found, consider colonoscopy every 1–3 years.

^a The Serrated Polyposis Syndrome Guidelines are based on expert opinion on the current data available.

^b Rosty C, Brosens L, Dekker E, Nagtegaal ID. Serrated polyposis. In: Lokuhetty D, White VA, Watanabe R, Cree IA, editor. *WHO Classification of Tumours: Digestive System Tumours*. Lyon, France: IARC, 2019:532-534 and Dekker E, et al. *Gastroenterology* 2020;158:1520-1523.

^c The final classification of SPS awaits more definitive genetic/epigenetic molecular characterization. These lesions are considered premalignant. Until more data are available, it is recommended that they be managed similarly to adenomas.

^d There may be other clinical scenarios (eg, patient has between 5–10 serrated polyps, <1 cm) that increase colon cancer risk and may require additional evaluation per clinical judgment (Egoavil C, Juárez M, Guarinos C, et al. Increased risk of colorectal cancer in patients with multiple serrated polyps and their first-degree relatives. *Gastroenterology* 2017;153:106-112).

^e Boparai KS, Reitsma JB, Lemmens V, et al. Increased colorectal cancer risk in first-degree relatives of patients with hyperplastic polyposis syndrome. *Gut* 2010;59:1222-1225.

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NCCN Guidelines Version 1.2023

Genetic/Familial High-Risk Assessment: Colorectal

MULTIGENE TESTING

Overview

- The introduction of multigene testing for hereditary forms of cancer has rapidly altered the clinical approach to testing affected patients at risk and their families. Based on NGS technology, these tests simultaneously analyze a set of genes that are associated with a specific family cancer phenotype or multiple phenotypes. Given the relative novelty of multigene testing, terminology and associated definitions used in this section of the guidelines are outlined in [Table 1](#). Pros and cons of multigene testing are outlined in [Table 2](#). Tables on GENE-3 through GENE-14 provide a list of genes that may be found on commercially available multigene panels and include colon cancer risk and management, colorectal phenotype, and other risks and management.
- When more than one gene can explain an inherited cancer syndrome, multigene testing is more efficient than single-gene testing, or sequential single syndrome testing.
- There is also a role for multigene testing in individuals who have tested negative (indeterminate) for a single syndrome, but whose personal or family history remains strongly suggestive of an inherited susceptibility.
- Chances of finding a VUS or pathogenic variant with uncertain clinical management increase as the number of genes included in the multigene panel increase.
 - Reclassification of VUS is commonplace.^{a,b} Historically, >91% of VUS in hereditary cancer testing have been downgraded to benign or likely benign categories.^{a,b} Nonetheless, clinical phenotypic correlation is warranted with further discussion with the testing laboratory if there is evidence supporting variant pathogenicity. Patient and provider guidelines and policies for follow-up of VUS have been developed.^{c,d}
- As commercially available tests differ in the specific genes analyzed (as well as classification of variants, reclassification procedures, and many other factors), choosing the specific laboratory and test panel is important.
- Multigene testing can include “intermediate” penetrant (moderate-risk) genes. For many of these genes, there are limited data on the degree of cancer risk and there are no clear guidelines on risk management for carriers of pathogenic variants. Not all genes included on available multigene tests are necessarily clinically actionable.
- As is the case with high-risk genes, it is possible that the risks associated with moderate-risk genes may not be entirely due to that gene alone, but may be influenced by gene/gene or gene/environment interactions. In addition, certain pathogenic variants in a gene may pose higher or lower risk than other pathogenic variants in that same gene. Therefore, it may be difficult to use a known pathogenic variant alone to assign risk for relatives.
- In many cases, diagnosing mutations in moderate-penetrance genes does not change management compared to management based on family history alone.
- It is for these and other reasons that multigene testing is ideally offered in the context of professional genetic expertise for pre- and post-test counseling. Individuals with the recommended expertise include certified genetic counselors, as well as clinicians who have had extensive training and/or experience in identification and management of hereditary syndromes.

^a Mersch J, Brown N, Pirzadeh-Miller S, et al. Prevalence of variant reclassification following hereditary cancer genetic testing. JAMA 2018;320:1266-1274.

^b Slavin T, Van Tongeren L, Behrendt C, et al. Prospective study of cancer genetic variants: Variation in rate of reclassification by ancestry. J Natl Cancer Inst 2018;110:1059-1066.

^c Slavin T, Manjarrez S, Pritchard C, et al. The effects of genomic germline variant reclassification on clinical cancer care. Oncotarget 2019;10:417-423.

^d David K, Best R, Brenman L, et al. Patient re-contact after revision of genomic test results: points to consider—a statement of the American College of Medical Genetics and Genomics (ACMG). Genet Med 2019;21:769-771.

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[Continued](#)



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Genetic/Familial High-Risk Assessment: Colorectal

MULTIGENE TESTING

Table 1: Multigene Testing Definitions

TERM	DEFINITION
Multigene panel	Laboratory test that includes testing for pathogenic variants of more than one gene.
Syndrome-specific panel	Panel that only tests for one syndrome (eg, LS, adenomatous polyposis).
Cancer-specific panel	Panel that tests for more than one gene associated with a specific type of cancer.
“Comprehensive” cancer panel	Panel that tests for more than one gene associated with multiple cancers or multiple cancer syndromes.
Actionable pathogenic variant	Pathogenic variant that results in a recommendation for a change in clinical management.
Variant of uncertain significance	Genetic test result indicating a sequence variant in a gene that is of uncertain significance. Variants are generally not clinically actionable, and most (but not all) are ultimately reclassified as benign. ^{a,b}

Table 2: Pros and Cons of Multigene Testing for Hereditary Colorectal Syndromes^e

PROS	CONS
• More efficient testing when more than one gene may explain presentation and family history. • Higher chance of providing proband with possible explanation for cause of cancer. • Competitive cost relative to sequentially testing single genes. • Chance of identifying pathogenic variants in multiple actionable genes that could impact screening and care for the individual and family members that may be missed using cancer syndrome-specific panels.^{f,g,h}	• Higher chance of identifying pathogenic variants for which clinical management is uncertain. Estimates suggest that 3%–4%^{f,i} of pathogenic variants identified are not clearly clinically actionable, such as finding a pathogenic variant in a moderate-risk gene for which management is unclear. • Higher chance of identifying VUS that are not actionable; reported rates of finding VUS range from 17%–38%. • Higher chance that patient will mistakenly receive overtreatment and overscreening if VUS or pathogenic variants for which clinical management is uncertain are incorrectly interpreted.

^a Mersch J, Brown N, Pirzadeh-Miller S, et al. Prevalence of variant reclassification following hereditary cancer genetic testing. JAMA 2018;320:1266-1274.

^b Slavin T, Van Tongeren L, Behrendt C, et al. Prospective study of cancer genetic variants: Variation in rate of reclassification by ancestry. J Natl Cancer Inst 2018;110:1059-1066.

^e Hall M, Forman A, Pilarski R, et al. Gene panel testing for inherited cancer risk. J Natl Compr Canc Netw 2014;12:1339-1346.

^f Yurgelun M, Allen B, Kaldete R et al. Identification of a variety of mutations in cancer predisposition genes in Patients with suspected Lynch syndrome. Gastroenterology 2015;149:604-613.

^g Idos G, Kurian A, Ricker C, et al. Multicenter prospective cohort study of the diagnostic yield and patient experience of multiplex gene panel testing for hereditary cancer risk. JCO Precis Oncol 2019;3:PO.18.00217.

^h Uson P, et al. Germline cancer susceptibility gene testing in unselected patients with colorectal adenocarcinoma: A multicenter prospective study. Clin Gastroenterol Hepatol 2022;20:e508–e528.

ⁱ Cragun D, Radford C, Dolinsky J, et al. Panel-based testing for inherited colorectal cancer: a descriptive study of clinical testing performed by a US laboratory Clin Genet 2014;86:510-520.

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Continued



NCCN Guidelines Version 1.2023

Genetic/Familial High-Risk Assessment: Colorectal

MULTIGENE TESTING^j

The inclusion of a gene in this table below does not imply the endorsement either for or against multigene testing for moderate-penetrance genes.

<u>Gene/Syndrome</u>	<u>Colon Cancer Risk and Management</u>	<u>Colorectal Phenotype</u> (polyposis defined as ≥10 polyps)	<u>Other Risks and Management</u>
APC/Familial adenomatous polyposis	• Absolute Risk: Approaches 100% if polyposis is left untreated • Management: Familial Adenomatous Polyposis (FAP-1) • Strength of Evidence: Strong	• ≥100 adenomas	Other Cancers • Familial Adenomatous Polyposis - Risk table (FAP-A) • Management: Familial Adenomatous Polyposis (FAP-B)
Comments: About half of patients with FAP develop adenomas by 15 years of age and 95% by age 35 years. FAP may also present with gastric fundic gland polyps/adenomas, duodenal adenomas, CHRPE, osteomas, supernumerary teeth, odontomas, desmoids, and epidermoid cysts.			
APC/Attenuated familial adenomatous polyposis	• Absolute Risk: Approaches 70% if polyposis left untreated • Management: Attenuated Familial Adenomatous Polyposis (AFAP-1) • Strength of Evidence: Strong	• 10–<100 adenomas	Other Cancers • Attenuated Familial Adenomatous Polyposis (AFAP-1) • Management: Attenuated Familial Adenomatous Polyposis (AFAP-1)
APC I1307K variant^{k,l}	• Estimated Absolute Risk: 5%–10% • Management: ▸ For probands with CRC and this pathogenic variant: See surveillance recommendations for post-CRC resection: NCCN Guidelines for Colon Cancer and NCCN Guidelines for Rectal Cancer ▸ For probands without a personal history of CRC: High-quality colonoscopy screening every 5 y, beginning at age 40 or 10 y prior to age of first-degree relative's CRC diagnosis. • Strength of Evidence: Strong	• No polyposis	Other Cancers • Unknown or insufficient evidence
Comments: The APC c.3920T>A (p.I1307K) variant is reported in 6%–7% of the Ashkenazi Jewish population in the United States (Abrahamson J, et al. Cancer Res 1998;58:2919-2922). The incidence of CRC in probands and family members is similar for both Ashkenazi Jewish APC I1307K heterozygotes and non-Jewish APC I1307K heterozygotes. Similar screening recommendations apply to all APC I1307K variant heterozygotes.			

[Continued](#)
[Footnotes on GENE-15](#)
[References on GENE-16](#)

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Genetic/Familial High-Risk Assessment: Colorectal

MULTIGENE TESTING

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<u>Gene/Syndrome</u>	<u>Colon Cancer Risk and Management</u>	<u>Colorectal Phenotype</u> (polyposis defined as ≥ 10 polyps)	<u>Other Risks and Management</u>
APC promoter 1B/ Gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS)	• Estimated Absolute Risk: Insufficient data to define • Management: Colonoscopy at time of diagnosis to exclude colon polyposis, if not previously done • Strength of Evidence: Limited	• No polyposis	Other Cancers • Polyposis of stomach ▶ Gastric polyps restricted to body and fundus with no evidence of colorectal or duodenal polyposis ▶ >100 polyps carpeting proximal stomach in index case or >30 polyps in a first-degree relative and family history of gastric cancer or dysplastic fundic gland polyposis ▶ Predominantly fundic gland polyps, some having regions of dysplasia • Absolute Risk: Stomach cancer - 12%–25% • Management: ▶ No current guidelines ▶ Consider risk-reducing total gastrectomy from third decade, annual gastroscopy from age 15
ATM	• Estimated Absolute Risk: 5%–10% • Management: Evidence insufficient to provide specialized CRC screening recommendations, manage based on family history. See NCCN Guidelines for Colorectal Cancer Screening • Strength of Evidence: Limited	• Not described	Other Cancers • Strong evidence for increased lifetime risk of cancers of breast (15%–40%), ovaries (<3%), and pancreas (5%–10%) • Management: See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic
Comment: Counsel for risk of autosomal recessive condition, ataxia-telangiectasia, in offspring.			

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Genetic/Familial High-Risk Assessment: Colorectal

MULTIGENE TESTING

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<u>Gene/Syndrome</u>	<u>Colon Cancer Risk and Management</u>	<u>Colorectal Phenotype</u> (polyposis defined as ≥ 10 polyps)	<u>Other Risks and Management</u>
AXIN2	• Estimated Absolute Risk: Insufficient data to define • Management: ▶ Begin high-quality colonoscopy at age 25–30 y and repeat every 2–3 y if negative. If polyps are found, high-quality colonoscopy every 1–2 y with consideration of surgery if the polyp burden becomes unmanageable by colonoscopy. ▶ Surgical evaluation if appropriate. • Strength of Evidence: Limited	• 0 – >100 • Mainly adenomas	Other Cancers • Unknown or insufficient evidence
Comment: Associated with oligodontia (absence of >6 adult non-wisdom teeth) and other features of cartilage hair hypoplasia. Polymorphisms in AXIN2 have also been associated with CRC and other cancers, but the information above is referring to individuals with pathogenic/likely pathogenic variants in AXIN2.			
BLM heterozygotes	• Estimated Absolute Risk: 5%–10% • Management: Evidence insufficient to provide specialized CRC screening recommendations; manage based on family history. See NCCN Guidelines for Colorectal Cancer Screening • Strength of Evidence: Limited	• No polyposis	Other Cancers • Unknown or insufficient evidence
Comment: Counsel for risk of autosomal recessive condition, Bloom syndrome, in offspring. Cuniff C, Djavid AR, Carrubba S, et al. Health supervision for people with Bloom syndrome. Am J Med Genet A 2018;176:1872-1881.			
BMPR1A	• Absolute Risk: 40%–50% • Management: See Juvenile Polyposis Syndrome (JPS-2) • Strength of Evidence: Strong	• ≥ 5 • Hamartomatous polyps, sometimes referred to as juvenile polyps or juvenile type hamartomas	Other Cancers • Absolute Risk: Stomach cancer - up to 21% • Management: See Juvenile Polyposis Syndrome (JPS-2) • Strength of Evidence: Strong
Comment: Not associated with features of HHT.			

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Genetic/Familial High-Risk Assessment: Colorectal

MULTIGENE TESTING

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Gene/Syndrome	Colon Cancer Risk and Management	Colorectal Phenotype (polyposis defined as ≥10 polyps)	Other Risks and Management
CHEK2^{k,l,m}	• Estimated Absolute Risk: 5%–10% • Management: ▶ For probands with a personal history of CRC and one of these pathogenic variants: See surveillance recommendations for post-CRC resection: NCCN Guidelines for Colon Cancer and NCCN Guidelines for Rectal Cancer ▶ For probands without a personal history of CRC, high-quality colonoscopy screening every 5 y, beginning at age 40 or 10 y prior to age of first-degree relative's CRC diagnosis when indicated. • Strength of Evidence: Limited Comments: Heterogeneity in CRC risk may exist based on type of pathogenic <i>CHEK2</i> variant (Han FF, et al. DNA Cell Biol 2013;32:329-335; Liu C, et al. Asian Pac J Cancer Prev 2012;13:2051-2055); some patients may elect for less aggressive screening based on shared decision-making. One model has suggested that earlier screening than the average-risk initiation may be justified for <i>CHEK2</i> 1100delC and I157T carriers based on reaching the same risk for CRC at an earlier age than observed among persons at average risk initiating screening at age 50 (Katona B, et al. Genet Med 2018;20:1324-1327).	• No polyposis	Other Cancers • Absolute Risk: Breast cancer - 15%–40% • Management: NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic
EPCAM/ Lynch syndrome	• Absolute Risk: 33%–52% • Management: See Lynch Syndrome (LS-C) • Strength of Evidence: Very strong Comment: Counsel for risk of rare autosomal recessive condition, CMMRD syndrome, in offspring. CMMRD can occur if both parents are a carrier of a pathogenic variant in the same DNA MMR gene. Only large deletions including 3' untranslated regions of EPCAM cause LS. Single loss of function (LOF) pathogenic variants do not cause LS but are carriers of an autosomal recessive condition called congenital tufting enteropathy.	• No polyposis • Polyp spectrum can include adenomas and sessile serrated lesions	Other Cancers • Lynch Syndrome (LS-C)
GALNT12	• Estimated Absolute Risk: 5%–10% • Management: Evidence insufficient to provide specialized CRC screening recommendations; manage based on family history. See NCCN Guidelines for Colorectal Cancer Screening • Strength of Evidence: Limited	• No polyposis	Other Cancers • Unknown or insufficient evidence

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Genetic/Familial High-Risk Assessment: Colorectal

MULTIGENE TESTING

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Gene/Syndrome	Colon Cancer Risk and Management	Colorectal Phenotype (polyposis defined as ≥10 polyps)	Other Risks and Management
<i>GREM1</i>^{k1} Hereditary mixed polyposis syndrome	• Estimated Absolute Risk: 11%–20% • Management: ▶ Begin high-quality colonoscopy at age 25–30 y and repeat every 2–3 y if negative. If polyps are found, high-quality colonoscopy every 1–2 y with consideration of surgery if the polyp burden becomes unmanageable. ▶ Surgical evaluation if appropriate. • Strength of Evidence: Limited	• Mixed polyposis • Adenomas and a unique polyp composed of a mixture of hyperplastic polyp and inflammatory polyp–type changes are the most frequent (serrated, hamartomatous, hyperplastic, and juvenile polyps have also been reported).	Other Cancers • Unknown or insufficient evidence
<i>MBD4</i> biallelic pathogenic variants/ <i>MBD4</i> -associated neoplasia syndrome	• Estimated Absolute Risk: Insufficient data to define • Management: Begin high-quality colonoscopy at age 18–20 y or date of diagnosis and repeat every 2–3 y if negative • Strength of Evidence: Limited	• 15–100+ • Adenomas	Other Cancers (biallelic) • Acute myeloid leukemia (AML): Complete blood count (CBC) at diagnosis Other cancers (biallelic and heterozygotes) • Uveal melanoma: Annual ophthalmologic exam starting at diagnosis
<i>MLH1</i> / Lynch syndrome	• Absolute Risk: 46%–61% • Management: Lynch Syndrome (LS-B) • Strength of Evidence: Very strong	• No polyposis • Polyp spectrum can include adenomas and sessile serrated lesions	Other Cancers • Lynch Syndrome (LS-B)
<i>MSH2</i> / Lynch syndrome	• Absolute Risk: 33%–52% • Management: Lynch Syndrome (LS-C) • Strength of Evidence: Very strong	• No polyposis • Polyp spectrum can include adenomas and sessile serrated lesions	Other Cancers • Lynch Syndrome (LS-C)

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Genetic/Familial High-Risk Assessment: Colorectal

MULTIGENE TESTING

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<u>Gene/Syndrome</u>	<u>Colon Cancer Risk and Management</u>	<u>Colorectal Phenotype</u> (polyposis defined as ≥10 polyps)	<u>Other Risks and Management</u>
MSH6/ Lynch syndrome	• Absolute Risk: 10%–44% • Management: See Lynch Syndrome (LS-D). • Strength of Evidence: Very strong	• No polyposis • Polyp spectrum can include adenomas and sessile serrated lesions	Other Cancers • Lynch Syndrome (LS-D)
Comment: Counsel for risk of rare autosomal recessive condition, CMMRD syndrome, in offspring. CMMRD can occur if both parents are a carrier of a pathogenic variant in the same DNA MMR gene.			
MSH3 biallelic pathogenic variants^{k/} MSH3-associated polyposis syndrome	• Estimated Absolute Risk: Insufficient data to define • Management: ▶ Begin high-quality colonoscopy at age 25–30 y and repeat every 2–3 y if negative. If polyps are found, high-quality colonoscopy every 1–2 y with consideration of surgery if the polyp burden becomes unmanageable. ▶ Surgical evaluation if appropriate • Strength of Evidence: Limited	• 30 – >100 • Adenomas	Other Cancers • Unknown or insufficient evidence
Comment: Duodenal polyposis, gastric cancer, and astrocytoma were also reported in 4 affected individuals from 2 families. <i>MSH3</i> heterozygote cancer risks are unclear.			
MLH3 biallelic pathogenic variants^{k/} MLH3-associated polyposis syndrome	• Estimate Absolute Risk: Insufficient data to define • Management: ▶ Begin high-quality colonoscopy at age 25–30 y and repeat every 2–3 y if negative. If polyps are found, high-quality colonoscopy every 1–2 y with consideration of surgery if the polyp burden becomes unmanageable. ▶ Surgical evaluation if appropriate. • Strength of Evidence: Limited	• 30 – >100 • Adenomas	Other Cancers • Unknown or insufficient evidence
Comment: Breast and brain tumors were noted in the 5 families reported. <i>MLH3</i> heterozygote cancer risks are unclear.			

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Genetic/Familial High-Risk Assessment: Colorectal

MULTIGENE TESTING

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Gene/Syndrome	Colon Cancer Risk and Management	Colorectal Phenotype (polyposis defined as ≥10 polyps)	Other Risks and Management
MUTYH biallelic pathogenic variants/ MUTYH -associated polyposis	• Absolute Risk: 70%–90% if polyposis left untreated • Management: See MUTYH-Associated Polyposis (MAP-2) • Strength of Evidence: Strong	• 10–100 • Adenomas and hyperplastic polyps most frequent; serrated, sessile serrated, mixed polyps less frequent; 18% meet criteria for SPS	Other Cancers • Absolute Risk: ▶ Duodenal polyposis - 17%–34% ▶ Duodenal cancer - 4% ▶ Gastric fundic gland polyps - 11% • Management: See MUTYH-Associated Polyposis (MAP-2)
	Comment: Limited evidence of increased risk for endometrial cancer 3%–9% (Sutcliffe EG, et al. Fam Cancer 2019;18:203-209) and gastric cancer (Vogt S, et al. Gastroenterology 2009;137:1976-1985) but no changes in management have been made. Ovarian, bladder, breast, and thyroid cancers have been reported.		
MUTYH monoallelic pathogenic variant/ heterozygote (carrier)	• Absolute Risk: No increased risk • Management: ▶ General population screening is appropriate for these individuals ▶ For probands with a personal or first-degree family history of CRC or polyps: increased screening as per the relevant guideline: NCCN Guidelines for Colon Cancer and NCCN Guidelines for Rectal Cancer and NCCN Guidelines for Colorectal Cancer Screening • Strength of Evidence: Limited	• No polyposis	Other Cancers • Unknown or insufficient evidence
	Comment: • Approximately 1%–2% of the general population are monoallelic <i>MUTYH</i> carriers (Yurgelun MB, et al. J Clin Oncol 2017;35:1086-1095; Thompson AB, et al. Fam Cancer 2022;231:415-422) • A study comparing the prevalence of <i>MUTYH</i> heterozygotes in 4,636 colorectal, 2,556 endometrial, or 20,043 patients with breast cancer undergoing genetic testing at a commercial testing laboratory compared to 51,375 (22,150 female) controls of European (non-Finnish) descent from GnomAD with cancer cohorts removed found no difference in the prevalence, suggesting there is no association between colorectal, endometrial, or breast cancer and <i>MUTYH</i> heterozygosity in individuals of European ancestry (Thompson AB, et al. Fam Cancer 2022;231:415-422). A large metanalysis (Ma X, et al. Gut 2014;63:326-336) of monoallelic <i>MUTYH</i> carriers (25,981 cases vs. 18,811 controls) found only a slight increase in CRC risk (OR, 1.17; 95% CI, 1.01–1.34). • A study including 125 <i>MUTYH</i> heterozygotes who underwent at least one surveillance colonoscopy did not identify any colorectal cancers and the adenoma rate was not high supporting guidance to provide care for these patients in the same way as the general population (Patel R, et al. Int J Colorectal Dis 2021;36:2199-2204). • Some reports suggest monoallelic <i>MUTYH</i> may be associated with an increased risk of gastric, liver, breast, and endometrial cancer (Win AK, et al. Int J Cancer 2016;139:1557-63), whereas other reports demonstrate no association with breast or endometrial cancer (Thompson AB, et al. Fam Cancer 2022;231:415-422; Fulk K, et al. Fam Cancer 2019;18:197-201).		

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Genetic/Familial High-Risk Assessment: Colorectal

MULTIGENE TESTING

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Gene/Syndrome	Colon Cancer Risk and Management	Colorectal Phenotype (polyposis defined as ≥10 polyps)	Other Risks and Management
<i>NTHL1</i> biallelic pathogenic variants^k/ <i>NTHL1</i> tumor syndrome	• Estimated Absolute Risk: >20% • Management: ▶ Begin high-quality colonoscopy at age 25–30 y and repeat every 2–3 y if negative. If polyps are found, high-quality colonoscopy every 1–2 y with consideration of surgery if the polyp burden becomes unmanageable. ▶ Surgical evaluation if appropriate. • Strength of Evidence: Limited	• 1–100 • Adenomas most frequent; serrated, sessile serrated, and hyperplastic polyps less frequent	Other Cancers • Absolute Risk: 6%–56% for extracolonic tumor by age 60 y ▶ Breast cancer most common, endometrial (pre) malignancies, urothelial carcinomas, brain tumors, hematologic malignancies, basal cell carcinomas, head and neck squamous cell carcinomas, and cervical cancers in multiple individuals. • Management: ▶ Breast cancer: Risk may be elevated; however, there is not enough data yet to support increased breast cancer surveillance ▶ Endometrial: Because endometrial cancer can often be detected early based on symptoms, patients 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. Transvaginal ultrasound to screen for endometrial cancer in postmenopausal patients 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 patients due to the wide range of endometrial stripe thickness throughout the normal menstrual cycle. ▶ Duodenal cancer: Baseline upper endoscopy (including complete visualization of the ampulla of Vater beginning at age 30–35 y [see FAP-C for follow-up of duodenoscopic findings])
Comment: <i>NTHL1</i> heterozygotes do not appear to be at increased risk for polyposis and/or CRC (Elsayed FA, et al. Gastroenterology 2020;159:2241-2243).			

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Gene/Syndrome	Colon Cancer Risk and Management	Colorectal Phenotype (polyposis defined as ≥10 polyps)	Other Risks and Management
<i>POLD1</i>^K/ Polymerase proofreading- associated polyposis	• Estimated Absolute Risk: >20% • Management: ▶ Begin high-quality colonoscopy at age 25–30 y and repeat every 2–3 y if negative. If polyps are found, high-quality colonoscopy every 1–2 y with consideration of surgery if the polyp burden becomes unmanageable. ▶ Surgical evaluation if appropriate. • Strength of Evidence: Limited Comment: Limited evidence of increased risk for endometrial cancer and brain cancers (Buchanan DD, et al. Genet Med 2018;20:890-895; Valle L, et al. Hum Mol Genet 2014;23:3506-3512; Palles C, et al. Nat Genet 2013;45:136-144) have been reported. NCCN has not made recommendations for extracolonic surveillance based on currently available evidence. Other cancers have been reported in 1–3 individuals with <i>POLD1</i> pathogenic variant including breast cancers, gastrointestinal stromal tumor (GIST), gastric cancer, bladder cancer, and “intestinal” cancer (Bellido F, et al. Genet Med 2016;18:325-332; Buchanan DD, et al. Genet Med 2018;20:890-895; Valle L, et al. Hum Mol Genet 2014;23:3506-3512).	• 30–100 • Adenomas	Other Cancers • Unknown or insufficient evidence
<i>POLE</i>^K/ Polymerase proofreading- associated polyposis	• Estimated Absolute Risk: >20% • Management: ▶ Begin high-quality colonoscopy at age 25–30 y and repeat every 2–3 y if negative. If polyps are found, high-quality colonoscopy every 1–2 y with consideration of surgery if the polyp burden becomes unmanageable. ▶ Surgical evaluation if appropriate. • Strength of Evidence: Limited Comments: Limited evidence of increased risk for endometrial cancer, ovarian cancer, brain cancers, pancreatic cancer, breast cancer, and melanoma (Aoude LG, et al. Fam Cancer 2015;14:621-628; Elsayed FA, et al. Eur J Hum Genet 2015;23:1080-1084; Buchanan DD, et al. Genet Med 2018;20:890-895; Hansen MF, et al. Fam Cancer 2015;14:437-448; Rohlin A, et al. Int J Oncol 2014;45:77-81; Spier I, et al. Int J Cancer 2015;137:320-331; Mur P, et al. Genet Med 2020;22:2089-2100) have been reported. NCCN has not made recommendations for extracolonic surveillance based on currently available evidence. Multiple other cancers have been reported in 1–3 individuals with <i>POLE</i> pathogenic variants (Rohlin A, et al. Int J Oncol 2014;45:77-81; Spier I, et al. Int J Cancer 2015;137:320-331; Chubb D, B et al. J Clin Oncol 2015;33:426-432; Mur P, et al. Genet Med 2020;22:2089-2100; Buchanan DD, et al. Genet Med 2018;20:890-895).	• 30–100 • Adenomas	Other Cancers • Unknown or insufficient evidence

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Genetic/Familial High-Risk Assessment: Colorectal

MULTIGENE TESTING

The inclusion of a gene in this table below does not imply the endorsement either for or against multigene testing for moderate-penetrance genes.

Gene/Syndrome	Colon Cancer Risk and Management	Colorectal Phenotype (polyposis defined as ≥ 10 polyps)	Other Risks and Management
PMS2/ Lynch syndrome	• Absolute Risk: 8.7%–20% • Management: ▶ Lynch Syndrome (LS-E) • Strength of Evidence: Strong	• No polyposis • Polyp spectrum can include adenomas and sessile serrated lesions	Other Cancers • Lynch Syndrome (LS-E)
Comment: Counsel for risk of rare autosomal recessive condition, CMMRD syndrome, in offspring. CMMRD can occur if both parents are a carrier of a pathogenic variant in the same DNA MMR gene.			
PTEN/ PTEN hamartoma tumor syndrome	• Estimated Absolute Risk: 11%–20% • Management: NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic • Strength of Evidence: Strong	• 0 – >100 • Mixed polyposis: hamartomas, hyperplastic, adenomas, inflammatory, ganglioneuromas	Other Cancers • Strong evidence for increased lifetime risk of cancers of breast (40%–60% [historical cohort data], >60% [projected estimates]), thyroid (35%), endometrium (28%), kidney (34%), and melanoma (6%) • Management: NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic
Comment: Published studies have shown a CRC risk range from 9%–18% (Tan MH, et al. Clin Cancer Res 2012;18:400-407; Riegert-Johnson DL, et al. Hered Cancer Clin Pract 2010;8:6; Nieuwenhuis MH, et al. Colorectal Dis 2012;14:e562-e566). Multiple non-cancer features, which are included in major/minor criteria. (NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian and Pancreatic - COWD-A 1 of 3)			
RNF43/ Serrated polyposis syndrome	• Absolute Risk: Insufficient data to define • Management: Serrated Polyposis Syndrome (SPS-1) if features of SPS are present • Strength of Evidence: Limited	• 5 – >100 • Any histologic subtype of serrated lesions/polyps (hyperplastic polyp, sessile serrated lesion without or with dysplasia, traditional serrated adenoma, and unclassified serrated adenoma)	Other Cancers • Unknown or insufficient evidence
Comments: Pathogenic variants in <i>RNF43</i> have been identified as a rare cause of SPS.			

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Genetic/Familial High-Risk Assessment: Colorectal

MULTIGENE TESTING

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<u>Gene/Syndrome</u>	<u>Colon Cancer Risk and Management</u>	<u>Colorectal Phenotype</u> (polyposis defined as ≥10 polyps)	<u>Other Risks and Management</u>
RPS20	• Absolute Risk: Insufficient data to define • Management: Evidence insufficient to provide specialized CRC screening recommendations; manage based on family history. See NCCN Guidelines for Colorectal Cancer Screening • Strength of Evidence: Limited	• Unknown	Other Cancers • Unknown or insufficient evidence
	Comment: Three families have been reported to meet all meet Amsterdam criteria, including one where all the CRCs were MSS (familial CRC type X) and one individual had metachronous CRC primaries at age 39. Multiple family members have been reported to have colon polyps of mixed histology, including two individuals with >10 polyps in one of these families. Two unrelated children with Diamond-Blackfan anemia (DBA), lacking variants in known DBA genes, were found by exome sequencing to have de novo novel missense variants in RPS20. The variants affect the same amino acid but result in different substitutions and reduce the RPS20 protein level (Bhar S, et al. Hum Mutat 2020;41:1918-1930).		
SMAD4/ Juvenile polyposis syndrome	• Absolute Risk: Up to 50% • Management: Juvenile Polyposis Syndrome (JPS-1) • Strength of Evidence: Strong	• ≥5 hamartomatous polyps, sometimes referred to as juvenile polyps or juvenile type hamartomas	Other Cancers • Absolute Risk: Stomach cancer - Up to 21% • Management: Juvenile Polyposis Syndrome (JPS-1)
	Comment: Possible increased risk for small intestine cancer but no management recommendations have been made. SMAD4 carriers are at increased risk for HHT, for which screening should begin ideally within the first 6 months of life. See Juvenile Polyposis Syndrome (JPS-1) for additional information.		

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MULTIGENE TESTING

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<u>Gene/Syndrome</u>	<u>Colon Cancer Risk and Management</u>	<u>Colorectal Phenotype</u> (polyposis defined as ≥10 polyps)	<u>Other Risks and Management</u>
STK11/ Peutz-Jeghers syndrome	• Absolute Risk: 39% lifetime risk for CRC • Management: Peutz-Jeghers Syndrome • Strength of Evidence: Strong	• ≥2 Peutz-Jeghers-type hamartomatous polyps (colon and small intestine)	Other Cancers • Well-established increased risk for breast, pancreatic, stomach, small intestine, lung, testicular, and gynecologic cancers. • See Peutz-Jeghers Syndrome for details regarding lifetime risk estimates and management.
	Comment: <i>STK11</i> is associated with characteristic mucocutaneous pigmentation, and starting as children, patients are at increased risk for bleeding, iron deficiency anemia, small bowel obstruction and intussusception, and young age onset ovarian and testicular tumors. See Peutz-Jeghers Syndrome for additional details regarding clinical features and management.		
TP53/ Li-Fraumeni syndrome	• Absolute Risk: >20% • Management: NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic for details on evaluation and management • Strength of Evidence: Strong	• No polyposis	Other Cancers • Well-established increased risk for sarcoma, breast, brain, leukemia, lung, adrenocortical, and other cancers. • NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic for details on evaluation and management.
	Comment: <i>TP53</i> carriers require evaluation and management of cancer risk at an early age. See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic for details on evaluation and management.		

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Genetic/Familial High-Risk Assessment: Colorectal

Strength of Evidence:

- **Very Strong:** prospective cohort studies in a population-based setting have demonstrated risk.
- **Strong:** traditional case-control studies or more than three case-control studies including those with cases ascertained by commercial laboratories or those without controls from the same population. Traditional case control study: a retrospective study that compares patients with a disease or specific outcome (cases) with patients without the disease or outcome (controls).
- **Limited:** small sample size or case series
- **None**

FOOTNOTES

^j The following genes and others are found on some genetic testing panels, but at present there is insufficient evidence to make any recommendations for specialized CRC screening for *MBD4* and *FOCAD*.

^k The panel recognizes that data to support the surveillance recommendations for these particular genes are evolving at this time. Caution should be used when implementing final colonoscopy surveillance regimens in context of patient preferences and new knowledge that may emerge.

^l Katona BW, Yurgelun MB, Garber JE, et al. A counseling framework for moderate-penetrance colorectal cancer susceptibility genes. *Genet Med* 2018;20:1324-1327.

^m Heterogeneity in CRC risk may exist based on type of pathogenic *CHEK2* variant (Han F, Guo C, Liu L. The effect of *CHEK2* variant I157T on cancer susceptibility: evidence from a meta-analysis. *DNA Cell Biol* 2013;32:329-335; Liu C, Wang Q, Wang Y. The *CHEK2* I157T variant and colorectal cancer susceptibility: a systematic review and meta-analysis. *Asian Pac J Cancer Prev* 2012;13:2051-2055; Xiang H, Geng X, Ge W, Li H. Meta-analysis of *CHEK2* 1100delC variant and colorectal cancer susceptibility. *Eur J Cancer* 2011;47:2546-2551); some patients may elect for less aggressive screening based on shared decision-making. One model has suggested that earlier start of screening than average-risk initiation may be justified for *CHEK2* 1100delC and I157T carriers based on reaching the same risk for CRC at an earlier age than observed among persons at average risk initiating screening at age 50 (Katona BW, Yurgelun MB, Garber JE, et al. A counseling framework for moderate-penetrance colorectal cancer susceptibility genes. *Genet Med* 2018;20:1324-1327).

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Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



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ABBREVIATIONS

AFAB	assigned female at birth	FAP	familial adenomatous polyposis	NGS	next-generation sequencing
AFAP	attenuated familial adenomatous polyposis	GI	gastrointestinal	PC	proctocolectomy
AMAB	assigned male at birth	GIM	gastric intestinal metaplasia	PCR	polymerase chain reaction
BSO	bilateral salpingo-oophorectomy	HHT	hereditary hemorrhagic telangiectasia	PJS	Peutz-Jeghers syndrome
CHRPE	congenital hypertrophy of retinal pigment epithelium	IHC	immunohistochemistry	RRSO	risk-reducing salpingo-oophorectomy
CMMRD	constitutional mismatch repair deficiency	IPAA	ileal pouch-anal anastomosis	SCTAT	sex cord tumor with annular tubules
CNS	central nervous system	IRA	ileorectal anastomosis	SPS	serrated polyposis syndrome
CPUE	colonic adenomatous polyposis of unknown etiology	JPS	juvenile polyposis syndrome	TAC	total abdominal colectomy
CRC	colorectal cancer	LS	Lynch syndrome	TMB	tumor mutational burden
DBA	Diamond-Blackfan anemia	MAP	MUTYH-associated polyposis	TPC	total proctocolectomy
dMMR	mismatch repair deficient	MGPT	multigene panel test	UAAB	unassigned at birth
EGD	esophagogastroduodenoscopy	MMR	mismatch repair	VUS	variant of uncertain significance
EUS	endoscopic ultrasound	MRCP	magnetic resonance cholangiopancreatography		
		MSI	microsatellite instability		
		MSI-H	microsatellite instability-high		
		MSI-L	microsatellite instability-low		
		MSS	microsatellite stable		



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NCCN Categories of Evidence and Consensus

Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

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Discussion

This discussion corresponds to the NCCN Guidelines for NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal. Last updated: December 7, 2022.

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Overview

Colorectal cancer (CRC) is the fourth most frequently diagnosed cancer and the second leading cause of cancer death in the United States. In 2022, an estimated 106,180 new cases of colon cancer and 44,850 new cases of rectal cancer will occur in the United States. During the same year, it is estimated that 52,580 people will die from CRC.¹ Importantly, the incidence of CRC per 100,000 decreased from 60.5 in 1976 to 46.4 in 2005.² The incidence rate for CRC reported by the Centers for Disease Control and Prevention (CDC) for 2011 is 40.0 per 100,000 persons.³ In addition, mortality from CRC decreased by almost 35% from 1990 to 2007,⁴ and by 53% from 1970 to 2016.⁵ These improvements in incidence of and mortality from CRC are thought in part to be a result of cancer prevention and earlier diagnosis through screening and better treatment modalities.

Despite the observed improvements in the overall CRC incidence rate, a retrospective cohort study of the SEER CRC registry found that the incidence of CRC in patients <50 years has been increasing.⁶ The authors estimate that the incidence rates for colon and rectal cancers will increase by 90.0% and 124.2%, respectively, for patients 20 to 34 years of age by 2030. The cause of this trend is currently unknown.

Approximately 5% to 10% of all CRCs are attributed to well-defined hereditary colon cancer syndromes. These well-defined inherited syndromes include Lynch syndrome, adenomatous polyposis syndromes (eg, familial adenomatous polyposis [FAP], attenuated familial adenomatous polyposis [AFAP], *MUTYH*-associated polyposis [MAP]), and hamartomatous polyposis syndromes (eg, juvenile polyposis syndrome [JPS], Peutz-Jeghers syndrome [PJS], *PTEN* hamartoma tumor syndrome [PHTS]).^{7,8} These NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal provide recommendations for the care of patients with high-risk syndromes, including Lynch syndrome, FAP, MAP,

PJS, JPS, serrated polyposis syndrome (SPS), and other high-risk syndromes associated with CRC risk (Li-Fraumeni syndrome [LFS] and Cowden syndrome/PHTS).

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines® for Genetic/Familial High-Risk Assessment: Colorectal, an electronic search of the PubMed database was performed to obtain key literature in the field of high-risk CRC published since the previous Guidelines update, using the following search terms: (lynch syndrome) or (hereditary nonpolyposis colorectal cancer) or (familial adenomatous polyposis) or (*MUTYH* polyposis) or (Peutz-Jeghers syndrome) or (polyposis syndrome) or (familial colon cancer) or (familial rectal cancer) or (familial colorectal cancer) or (hereditary colon cancer) or (hereditary rectal cancer) or (hereditary colorectal cancer) or (multigene testing). The PubMed database was chosen because it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.⁹

NCCN recommendations have been developed to be inclusive of individuals of all sexual and gender identities to the greatest extent possible. When citing published studies and recommendations from other organizations, the terms used (eg, male, female) reflect the cited sources.

Assessment for Hereditary CRC Syndrome (HRS-1)

Genetic susceptibility to CRC includes well-defined inherited syndromes such as Lynch syndrome, FAP, MAP, and other less common syndromes. Many approaches have been proposed for identifying individuals with hereditary CRC syndromes. NCCN recommends a stepwise approach. First, if an individual has a personal or family history of a known germline pathogenic variant in a colorectal polyposis or cancer gene, further evaluation and management appropriate for established hereditary CRC



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syndromes is warranted. A pathogenic variant in this case includes likely pathogenic variants.¹⁰ Second, if there is no known personal or family history of a known pathogenic variant in a colorectal polyposis or cancer gene, the patient's personal history of any of the following should be determined:

- ≥10 adenomatous polyps, or
- ≥2 hamartomatous polyps, or
- ≥5 serrated polyps proximal to the rectum

NCCN recommends that individuals meeting any of the above criteria have detailed risk assessment and potential genetic evaluation to rule out polyposis syndromes (HRS-2). The presence of ≥10 adenomas may be linked to FAP, AFAP, MAP, and rare genetic causes of multiple adenomatous polyps including pathogenic/likely pathogenic (P/LP) variants in *AXIN2*, *GREM1*, *NTHL1*, *POLE*, *POLD1*, or *MSH3*. Greater than or equal to 2 hamartomatous polyps may be associated with PJS, JPS, or Cowden syndrome/PHTS (see the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic at www.NCCN.org), or be characterized as colonic adenomatous polyposis of unknown etiology (CPUE). Greater than or equal to 5 serrated polyps/lesions proximal to the rectum with two ≥10 mm (or >20 serrated lesions/polyps of any size distributed throughout the large bowel, with ≥5 being proximal to the rectum) is consistent with a diagnosis of SPS.

Third, if the patient has been diagnosed with CRC but personal history is not suspicious for a polyposis syndrome, then the patient should be considered for the evaluation of Lynch syndrome and other cancer risk genes (HRS-3; see *Lynch Syndrome: Criteria for the Evaluation of Lynch Syndrome and Other Cancer Risk Genes Among Individuals with a History of CRC* in this Discussion, below).

Next, personal or family history of other Lynch syndrome-associated cancers beyond CRC should be elicited. Lynch syndrome-associated cancers beyond CRC include: endometrial, gastric, ovarian, pancreatic, ureter and renal pelvis, brain (usually glioblastoma), biliary tract, and small intestine, as well as sebaceous adenomas, sebaceous carcinomas, and keratoacanthomas as seen in Muir-Torre syndrome. Personal history of a tumor with defective mismatch repair (MMR) should also be evaluated at this time to exclude Lynch syndrome as an etiology. This refers to any tumor that is microsatellite instability-high (MSI-H) by polymerase chain reaction (PCR) or next-generation sequencing (NGS), or absent ≥1 DNA MMR protein by immunohistochemistry (IHC) without *MLH1* methylation or *BRAF* V600E mutations. Those with a personal or family history of Lynch syndrome-related cancers or MMR deficiency should undergo further evaluation (See HRS-5 and *Lynch Syndrome: Criteria for the Evaluation of Lynch Syndrome and Other Cancer Risk Genes Among Individuals with a History of CRC* in this Discussion, below).

Individuals not meeting any of the above criteria may be considered average risk for CRC, and follow the NCCN Guidelines for Colorectal Cancer Screening (available at www.NCCN.org), unless other significant personal or family history indicate increased risk for a hereditary cancer syndrome or more frequent CRC screening/surveillance. Increased risk warranting genetic evaluation may be indicated by, but not restricted to personal or family history of congenital hypertrophy of the retinal pigment epithelium (CHRPE), osteomas, supernumerary teeth, desmoid tumor, cribriform variant of papillary thyroid cancer, brain cancer (typically medulloblastoma), and hepatoblastoma.

Management After Diagnosis with a Genetic Syndrome

Following evaluation, those with Lynch syndrome, FAP, MAP, and other syndromes are managed as described in the following sections.



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Lynch Syndrome

Lynch syndrome is the most common form of genetically determined colon cancer predisposition, accounting for 2% to 4% of all CRC cases.¹¹⁻¹⁴

Lynch syndrome results from a germline P/LP variant in 1 of 4 DNA MMR genes (*MLH1*, *MSH2*, *MSH6*, or *PMS2*).¹⁵ Additionally, deletions in the *EPCAM* gene, which lead to hypermethylation of the *MSH2* promoter and subsequent *MSH2* silencing, cause Lynch syndrome.^{16,17} Identification of Lynch syndrome is important both for individuals with cancer, because of high personal risk for metachronous Lynch syndrome cancers (ie, endometrial cancer after CRC or vice versa; second CRC), and for their families because of autosomal dominant inheritance and potentially high penetrance. After identification of Lynch syndrome, surveillance (particularly for first or metachronous CRC) offers an opportunity for early detection and perhaps even prevention of cancer among P/LP variant carriers. Further, cancer site-specific evaluation and heightened attention to symptoms is also advised for other cancers that occur with increased frequency in affected persons, including colorectal, endometrial, gastric, ovarian, pancreatic, ureter and renal pelvis, biliary tract, brain (glioblastoma), and small intestinal cancers, as well as sebaceous adenomas, sebaceous carcinomas, and keratoacanthomas.

Criteria for the Evaluation of Lynch Syndrome and Other Cancer Risk Genes Among Individuals with a History of CRC (HRS-3)

Strategies for identifying individuals with Lynch syndrome, as well as other cancer risk genes, are evolving. Previously, the NCCN panel has endorsed the following strategies for identifying individuals with Lynch syndrome, and continues to endorse these strategies:

- Germline multigene panel testing for patients diagnosed with CRC at age <50 years
- Germline multigene panel testing for individuals at increased risk of a hereditary CRC syndrome based on personal or family history

- Germline multigene panel testing based on increased model-based risk

Emerging evidence demonstrates that 3.0% to 12.5% of patients with CRC may have a P/LP variant in a cancer risk gene other than those associated with Lynch syndrome, when individuals with CRC undergo multigene panel testing.¹⁸⁻²¹ While a significant proportion of patients with CRC meet NCCN criteria for multi-gene testing based on the aforementioned criteria, a considerable number do not, allowing for expanded opportunity for genetic evaluation. Also, “up front” multigene panel testing for individuals with CRC may have additional advantages. The panel carefully reviewed available evidence to support upfront multigene panel testing and now recommends consideration of germline multigene panel testing for patients whose personal history is not suspicious for a polyposis syndrome and who were diagnosed with CRC age ≥50 years (category 2B).

Challenges and evidence gaps surrounding upfront multigene panel testing remain. Currently, less than 40% of patients with CRC receive recommended genetic services.²²⁻²⁴ It is unclear if there is sufficient capacity to deliver pretest informed consent and appropriate genetic counseling to all individuals with a P/LP variant and/or variant of uncertain significance (VUS), as well as negative results. Therefore, the capacity to offer multi-gene panel testing to all patients with and survivors of CRC is uncertain. In addition, currently available studies evaluating multi-gene panel testing for patients with CRC report that cascade testing occurred in 16% to 65% of families.^{18,20} Therefore, the impact of multi-gene panel testing on subsequent cascade testing and evaluation of family members is also uncertain. Finally, most currently available studies have potential selection bias that might overestimate yield of multi-gene panel testing across the spectrum of all patients with CRC.

The optimal approach for multi-gene testing remains uncertain. The panel currently does not assert that multi-gene testing is a logistically simpler



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approach to genetic evaluation, compared to selection based on personal and family history and tumor-based screening. In addition, there is currently a lack of evidence regarding the impact of multi-gene testing on CRC incidence and mortality, and on inequities in genetic evaluation and follow-up by race, ethnicity, and other social determinants of health.

For a full discussion of multi-gene panel testing, including the advantages and disadvantages, see HRS-4, GENE-1, and the section on *Multi-Gene Testing*, below in this Discussion.

Criteria for the Evaluation of Lynch Syndrome Based on Personal or Family History of Cancer (HRS-5)

If an individual has a personal or family history of a Lynch syndrome-related cancer and does not meet criteria as described above for a polyposis syndrome on hereditary risk assessment, the panel has summarized criteria that can be used to select patients for the evaluation of Lynch syndrome:

- Personal history of a tumor with MMR deficiency determined by PCR, NGS, or IHC at any age
- Known P/LP variant associated with Lynch syndrome in the family
- An individual with CRC or endometrial cancer and any of the following:
 - Diagnosed <50 years
 - A synchronous or metachronous LS-related cancer regardless of age
 - 1 first-degree or second-degree relative with an LS-related cancer diagnosed <50 years
 - ≥2 first-degree or second-degree relatives with Lynch syndrome-related cancers regardless of age
- Family history of any of the following:

- ≥1 first-degree relative with a CRC or endometrial cancer diagnosed <50 years
- ≥1 first-degree relative with a CRC or endometrial cancer and another synchronous or metachronous Lynch syndrome-related cancer regardless of age
- ≥2 first-degree or second-degree relatives with Lynch syndrome-related cancer; including ≥1 diagnosed <50 years
- ≥3 first-degree or second-degree relatives with Lynch syndrome-related cancers, regardless of age
- Increased model-predicted risk for Lynch syndrome:
 - An individual with a ≥5% risk of having an MMR gene pathogenic variant based on predictive models (PREMM5,²⁵ MMRpro, MMRpredict)
 - Individuals with a personal history of CRC and/or endometrial cancer with a PREMM5 score of ≥2.5% should be considered for multi-gene testing.
 - For individuals without a personal history of CRC and/or endometrial cancer, some data have suggested using a PREMM5 score threshold of ≥2.5% rather than ≥5% to select individuals for MMR genetic testing. Based on these data, it is reasonable for testing to be done based on the ≥2.5% score result and clinical judgment.

The panel recommends tumor screening for MMR deficiency for all CRC and endometrial cancers regardless of age at diagnosis. Tumor screening for CRC for MMR deficiency for purposes of screening for Lynch syndrome is not required if multi-gene testing is chosen as the strategy for screening for Lynch syndrome, but may still be required for CRC therapy selection. Consider tumor screening for MMR deficiency for sebaceous neoplasms, as well as the following adenocarcinomas: small bowel,



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ovarian, gastric, pancreatic, biliary tract, brain, bladder, urothelial, and adrenocortical cancers regardless of age at diagnosis.²⁶

Strategies for Evaluating for Lynch Syndrome in Individuals Meeting Criteria for the Evaluation of Lynch Syndrome (LS-1)

Deleterious Lynch syndrome pathogenic variant in family is known:

When a known Lynch syndrome pathogenic variant exists in the family, the individual should be tested for the familial pathogenic variant. If the test is positive or if testing is not performed for any reason, the individual should follow surveillance or prevention strategies for Lynch syndrome outlined below (See *Lynch Syndrome Management*). In addition, genetic testing should be offered to at-risk family members. However, the recommendation to treat patients in whom genetic testing was not done is category 2B. Individuals who test negative for the familial Lynch syndrome pathogenic variant are considered to be at average risk for CRC and should follow the NCCN Guidelines for Colorectal Cancer Screening (available at www.NCCN.org). Additional testing may be indicated based on personal, family, and medical history.

No known Lynch syndrome pathogenic variant in family: The traditional approach to identifying individuals at risk for Lynch syndrome has generally employed a 2-step screening process. With a 2-step process, patients are first assessed for clinical criteria based on family history, personal history of cancer, and/or identified pathologic characteristics, and then are recommended germline multi-gene testing if any of these clinical testing criteria are met.

The Amsterdam II Criteria outline increased risk for Lynch syndrome in a family with a proband affected by CRC or any other Lynch syndrome-associated cancer (ie, endometrial, small bowel, ureter, or renal-pelvic cancers), and two relatives with a Lynch syndrome-associated cancer provided the following family criteria are met:

- One relative should be a first-degree relative of the other two
- At least two successive generations should be affected
- At least one Lynch syndrome-associated cancer should have been diagnosed before age 50 years

Additionally, the Amsterdam II Criteria stipulate that FAP should be excluded, and tumors should be verified through pathologic examination.²⁷ Approximately 50% of families meeting the Amsterdam II Criteria have a P/LP variant in an MMR gene.²⁸ These criteria are very stringent, however, and miss as many as 68% of patients with Lynch syndrome.²⁹

The Bethesda Guidelines were later developed and updated to provide broader clinical criteria for Lynch syndrome screening.³⁰ Updated Bethesda criteria are as follows:³¹

- CRC diagnosed in a patient <50 years
- Synchronous, metachronous, colorectal, or other tumor associated with Lynch syndrome
- CRC with MSI-H histology (ie, presence of tumor-infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet-ring differentiation, medullary growth pattern) in a patient <60 years
- CRC in a patient with a family history of cancer diagnosed <50 years and associated with Lynch syndrome. If more than one relative was diagnosed with a Lynch syndrome-associated cancer, then the age criterion is not needed.

One study reported that *MLH1* and *MSH2* P/LP variants were detected in 65% of patients with MSI of colon cancer tissue who met the Bethesda criteria.³² Another study reported on the accuracy of the revised Bethesda criteria, concluding that the guidelines were useful for identifying patients who should undergo further testing.³³ Patients fulfilling the revised



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Bethesda criteria had an odds ratio (OR) for carrying a germline P/LP variant in *MLH1* or *MSH2* of 33.3 (95% confidence interval [CI], 4.3–250; *P* = .001). Still, a considerable number of patients with Lynch syndrome fail to meet even the revised Bethesda Guidelines.¹³

Statistical models that predict risk for carrying a P/LP variant in a DNA MMR gene are an additional commonly applied clinical approach to identifying individuals at risk for Lynch syndrome.^{29,34–36} These models give probabilities of P/LP variants and/or of the development of future cancers based on family and personal history. The PREMM5 model can be used online (<https://premm.dfci.harvard.edu/>) and the MMRpredict model is available for online use at <http://hnpccpredict.hgu.mrc.ac.uk>. Using a cut-off of 5%, one study suggests that both PREMM5 and MMRpredict are effective at predicting an individual's risk of carrying MMR P/LP variants, but they may be less effective at identifying individuals with *PMS2* P/LP variants.³⁷

Overall, for individuals without a previously known Lynch syndrome-associated pathogenic variant, the panel recommends additional evaluation for Lynch syndrome based on clinical criteria (see *Criteria for the Evaluation of Lynch Syndrome Based on Personal or Family History of Cancer*), including for individuals with no known Lynch syndrome pathogenic variant who meet the Amsterdam II Criteria or Bethesda Guidelines, have a CRC diagnosis at <50 years of age, or have a predicted risk for Lynch syndrome greater than 5% on one of the following prediction models: MMRpro, PREMM5,²⁵ or MMRpredict.

A problem with nearly all clinically based criteria for identifying individuals with Lynch syndrome is suboptimal sensitivity. This has led several groups to study an alternative strategy, referred to as “universal screening,” in which all individuals newly diagnosed with CRC have either MSI or IHC testing for absence of 1 of the 4 DNA MMR proteins. This approach provides a sensitivity of 100% (95% CI, 99.3%–100%) and a specificity of

93.0% (95% CI, 92.0%–93.7%) for identifying individuals with Lynch syndrome.³⁸ An alternative approach is to test all patients with CRC diagnosed at <70 years of age plus patients diagnosed at older ages who meet the Bethesda Guidelines.³⁸ This approach gave a sensitivity of 95.1% (95% CI, 89.8%–99.0%) and a specificity of 95.5% (95% CI, 94.7%–96.1%). This alternative approach had improved sensitivity compared to the revised Bethesda criteria, and improved specificity compared to universal screening regardless of age, but requires a more complex implementation strategy.

Cost-effectiveness of universal screening has been established and has been endorsed by the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group at the CDC, the U.S. Multi-Society Task Force on Colorectal Cancer, and the European Society for Medical Oncology (ESMO).^{39–43}

The panel recommends universal screening of all CRCs and endometrial cancers in order to maximize sensitivity for Lynch syndrome detection and simplify care processes.^{38,44,45} The panel also recommends considering tumor screening for MMR deficiency for sebaceous neoplasms as well as the following adenocarcinomas: small bowel, ovarian, gastric, pancreatic, biliary tract, brain, bladder, urothelial, and adrenocortical cancers regardless of age at diagnosis.²⁶ The panel also suggests that counseling by an individual with expertise in genetics is not required prior to routine tumor testing, but strongly recommends follow-up with a provider with expertise in genetics following a positive screen (see below).

Tumor Testing Methodologies

Screening for Lynch syndrome currently requires performance of 1 of 2 molecular tests (see *Principles of dMMR Testing for Lynch Syndrome* in algorithm), either after the aforementioned clinical criteria are met, or as part of a universal screening strategy with: 1) IHC for abnormal absence of MMR protein expression; or 2) MSI analysis to evaluate for MSI-H on a



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tumor specimen.⁴⁶ Greater than 90% of Lynch syndrome tumors are MSI-H and/or lack expression of at least one of the MMR proteins by IHC.

IHC analysis has the advantage of predicting which gene is most likely to be mutated (the gene for the affected protein or its corresponding dimer partner) and thus the first candidate(s) for germline sequencing.⁴⁶ Interpretation of IHC test reports can sometimes be confusing; when “positive” IHC is reported, care should be taken to ensure that “positive” means abnormal absence of MMR protein expression, as opposed to normal presence of expression.

MSI testing panels may consist of mononucleotide and dinucleotide markers.⁴⁷ In a study including 1058 patients with CRC, detection of MMR deficiency by a panel including both mononucleotide and dinucleotide markers (BAT26, BAT25, D5S346, D2S123, and D17S250) was compared to that of a panel including only mononucleotide markers (BAT26, BAT25, NR21, NR22, and NR24).⁴⁸ Sensitivity and positive predictive value of the panel including only mononucleotide markers (95.8% and 88.5%, respectively) were better, compared to the panel including both mononucleotide and dinucleotide markers (76.5% and 65.0%, respectively).

Some studies have shown that both IHC and MSI are cost-effective and useful for selecting high-risk patients who may have *MLH1*, *MSH2*, and *MSH6* germline P/LP variants.^{41,49,50} However, conclusive data are not yet available that establish which strategy is optimal.^{15,33,51-54} A review showed that the sensitivities of MSI and IHC testing are 77% to 89% and 83%, respectively; specificities are 90% and 89%, respectively⁴¹; as mentioned previously, even higher sensitivity has been reported for screening with MSI and IHC in context of “universal screening.” An analysis of 5591 unrelated CRC probands undergoing both MSI and IHC testing showed a concordance rate of 97.5%.³⁸ Some experts advocate for using both methods when possible.⁵⁵ However, the panel recommends using only

one test initially. If normal results are found and Lynch syndrome is strongly suspected, then the other test may be carried out. Alternatively, emerging studies suggest a role for NGS panels in Lynch syndrome tumor testing.^{26,56,57}

Where genetic testing is recommended, the panel recommends consultation with an individual with expertise in genetics, and germline testing to exclude presence of Lynch-associated P/LP variants. The approach to P/LP variant testing is evolving. Previously, a sequential approach in which 1 or 2 genes were sequenced guided by either disease prevalence or IHC results, followed by additional testing of other genes was followed. Recognition of scenarios in which IHC results were not available also allowed for syndrome-specific testing of the panel of genes that cause Lynch syndrome (*MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM*) simultaneously. Reductions in cost of sequencing, and recognition that some patients meeting Lynch syndrome testing criteria may have germline P/LP variants not associated with Lynch syndrome have led to growing use of so called “multi-gene” panels in clinical practice. These panels test not only for Lynch syndrome-associated genes, but also for additional P/LP variants. The panel recommends that for patients or families where colorectal or endometrial tumor is available, one of three options should be considered for workup: 1) tumor testing with IHC or MSI; 2) comprehensive tumor NGS panel (that includes, at minimum, the four MMR genes and *EPCAM*, *BRAF*, MSI, and other known familial cancer genes); or 3) germline multi-gene testing that includes the four MMR genes and *EPCAM*. The panel recommends tumor testing with IHC and/or MSI be used as the primary approach for pathology-lab–based universal screening. If no tumor is available, tumor material is insufficient, or the affected relative is unavailable, germline multi-gene testing may be considered that includes the four MMR genes and *EPCAM*. Multi-gene testing may be preferred, particularly for patients with a strong family history or if the age of CRC diagnosis is <50 years.^{19,58}



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Follow-up Testing of Individuals with Increased Risk Based on Screening

If abnormal MSI or IHC for one of the DNA MMR proteins is identified within a CRC or endometrial cancer, then a differential diagnosis must be considered. For example, 10% to 15% of CRCs have MSI or abnormal IHC (particularly in the case of absent *MLH1* expression) due to sporadic development of cancer, rather than an underlying inherited (germline) genetic P/LP variant. *Tumor Testing Results and Additional Testing Strategies* in the algorithm identifies a range of test result scenarios, the differential diagnosis, and recommended follow-up. In some scenarios, such as with absent *MSH2* expression by IHC, follow-up germline testing for indicated genes is directly recommended. In other scenarios, additional testing of tumor tissue is recommended. For example, for the common scenario of absent *MLH1* expression by IHC, the panel recommends additional tumor testing for presence of *MLH1* hypermethylation and/or *BRAF* V600E P/LP variant, either of which would be consistent with sporadic, rather than Lynch syndrome-associated, cancer.^{43,46,59,60}

Follow-up of Genetic Test Results

If a pathogenic variant for familial Lynch syndrome is found, the panel recommends that Lynch syndrome management guidelines be followed (See *Lynch Syndrome Management*).

If no pathogenic variant for familial Lynch syndrome is found, clinicians are advised to confirm that testing for large rearrangements and deletions of MMR genes were performed by the lab test provider. If still no pathogenic variant or a VUS is identified, the panel recommends tailored surveillance based on individual and family risk assessment. Notably, some individuals with abnormal MSI and/or IHC tumor results and no germline P/LP variant detected in the corresponding gene(s) may still have undetected Lynch syndrome. At this time, no consensus has been reached as to whether these patients (sometimes referred to as having “Lynch-like syndrome”) should be treated as having Lynch syndrome or treated based on

personal/family history. Although the efficacy of the approach has not yet been proven, genetic testing of the corresponding gene(s) could be performed on tumor DNA to assess for somatic P/LP variants. One study has reported that 88.4% of patients with abnormal MSI or IHC who have negative multigene testing results carry double somatic variants.¹⁸ Individuals found to have double somatic P/LP variants/changes in the MMR genes are unlikely to have Lynch syndrome, though double somatic P/LP variants might also be due to non-Lynch germline P/LP variants. Thus, care should be based on personal/family history until further research on Lynch-like syndrome emerges. Additionally, germline testing may be normal despite a strong family history (ie, Amsterdam criteria) or additional features of hereditary cancer syndromes (multiple colon polyps) being present. In these cases, additional testing may be warranted in the proband (such as expanded multi-gene testing), or tumor testing in an affected family member could be considered due to the possibility of a phenocopy.

Newly Identified Lynch Syndrome

When a Lynch syndrome P/LP variant is found in the family, it offers an opportunity to provide predictive testing for at-risk family members. If a first-degree relative is unavailable or unwilling to be tested, more distant relatives should be offered testing for the known family P/LP variant.

There are many other issues involved in the genetic counseling process of individuals for pre-symptomatic testing for cancer susceptibility. Some individuals elect not to undergo testing, and it is important to counsel these individuals so they continue with increased surveillance.

Lynch Syndrome Management (LS-B, LS-C, LS-D, LS-E)

The NCCN Panel carefully considered surveillance schemes for individuals with Lynch syndrome. Compared to the general population, these patients are at increased lifetime risk for CRC (46%–61% vs. 4.2%),



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endometrial cancer (34%–54% vs. 3.1%), and other cancers including of the stomach and ovary.^{61–64} Within Lynch syndrome carriers, risk may vary by specific type of DNA MMR P/LP variant. For example, individuals with *PMS2* P/LP variants have an 8.7% to 20% risk for colon cancer, while those with *MLH1* P/LP variants have a 46% to 61% risk. The panel currently provides P/LP variant-specific recommendations for cancer surveillance and prevention, recognizing that data to support variant-specific strategies are still emerging. When assessing individual cancer risks, it is important to consider specific family history of cancer and factors shown to be associated with CRC risk, including key exposures (eg, tobacco, alcohol), diet (eg, processed and red meat consumption), and lifestyle factors (eg, physical exercise).⁶⁵

Existing data on screening refer primarily to colon and endometrial cancers. More data are needed to evaluate the risks and benefits of extracolonic and extra-endometrial cancer screening, and recommendations are based mainly on expert opinion. The panel has provided P/LP variant specific lifetime risk estimates for LS-associated cancers based on a comprehensive literature review, and recognizes that emerging data are likely to result in updated estimates. Screening and the option of risk-reducing surgeries should be individualized after risk assessment and counseling.

Colon Cancer Surveillance

If Lynch syndrome is confirmed, a high-quality colonoscopy is advised. The age to start CRC screening will depend on the P/LP variant. For *MLH1* and *MSH2/EPCAM* variant carriers, a high-quality colonoscopy should start between the ages of 20 to 25 or 2 to 5 years younger than the youngest diagnosis age in the family, whichever comes first, and should be repeated every 1 to 2 years.^{42,43,59,60,66,67} For *MSH6* and *PMS2* P/LP variant carriers, consider a later age of onset for colonoscopy initiation, such as at age 30 to 35 years or 2 to 5 years younger than age of any

relative with CRC if diagnosed before age 30, repeating every 1 to 3 years.^{64,68}

Features of high-quality colonoscopy include exam complete to the cecum, bowel preparation adequate for detection of polyps greater than 5 mm in size, with careful attention to adenoma detection.⁶⁹ Some patients may benefit from a shorter 1-year versus a longer 2-year screening interval.⁷⁰ Factors that may favor a 1-year interval may include: being male, age >40 years, having *MLH1/MSH2* pathogenic variants, or having a history of CRC or adenomas.^{70,71}

There is some uncertainty regarding best age to initiate colonoscopic surveillance, and regarding frequency of surveillance. For example, the results of a meta-analysis in which CRC risk in 1114 Lynch syndrome families (*MLH1* and *MSH2* P/LP variant carriers) was examined showed that 5-year CRC risk for those aged 20 to 29 years is about 1%, with the risk for those aged 30 to 39 years being 3% to 5%, with greater risk in men.⁷² The investigators argued that annual colonoscopy in patients aged 25 to 29 years may be an overly aggressive recommendation that is not cost-effective (ie, 155 men and 217 women in this age group would need to be screened to prevent one CRC death). However, the panel concluded that more evidence was needed in order to understand best age of initiation of screening. One study modeled the cost-effectiveness of various strategies for age of initiation and frequency of colonoscopy for reducing incidence and mortality among individuals with Lynch syndrome.⁷³ It was reported that the optimal age to initiate and follow-up screening was age 25, repeating every 1 year for *MLH1* Lynch syndrome, age 25 repeating every 2 years for *MSH2* Lynch syndrome, age 35 repeating every 3 years for *MSH6* Lynch syndrome, and age 40 repeating every 3 years for *PMS2* Lynch syndrome. Notably, selection of optimal strategies was based on the combination of quality-adjusted life-years gained and cost.



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Chromoendoscopy may also be used during colonoscopy in which dye spray is used to enhance visualization. A systematic review of four studies indicated that chromoendoscopy is a promising technique for improving detection of lesions and flat adenomas in patients with Lynch syndrome.⁷⁴ Only one of these studies was a prospective randomized trial, however, and this trial was limited by a small sample of patients who had already undergone colonoscopy and inadequate statistical power to detect clinically meaningful effects.⁷⁵ A more recent meta-analysis including four randomized studies showed that adenoma detection rate in patients with Lynch syndrome was not significantly improved with chromoendoscopy compared to white light endoscopy (OR, 1.17; 95% CI, 0.81–1.70), though quality of evidence was low.⁷⁶ Chromoendoscopy may be considered in patients with Lynch syndrome, but larger prospective randomized trials are needed to better understand its role in Lynch syndrome.

Endometrial Cancer Surveillance

Women with Lynch syndrome are at heightened risk for endometrial cancer.^{61,66,77,78} With a lifetime risk of up to 60%, endometrial cancer is the second most common cancer in women with Lynch syndrome.⁷⁷ The estimated age of presentation and cumulative risk for diagnosis through age 80 years depends on the P/LP variant, ranging from average age of 49 to 50 years and cumulative risk of 13% to 26% for *PMS2* to average age of 49 years and cumulative risk of 34% to 54% for *MLH1* P/LP variant.^{61,63,64,71,79-82} See *Gene-Specific Lynch Syndrome Cancer Risks and Surveillance/Prevention Strategies* in the algorithm for the complete list of average age of presentation and cumulative risk for diagnosis through age 80 years for endometrial cancer in carriers of an MMR P/LP variant.

Endometrial cancer risk management should be individualized based on several considerations. Education that enhances recognition and prompt reporting of relevant symptoms (ie, dysfunctional uterine bleeding or postmenopausal bleeding) is advised in order to promote early

endometrial cancer detection. The evaluation of these symptoms should include an endometrial biopsy. Endometrial cancer screening does not have proven benefit in women with Lynch syndrome. However, endometrial biopsy is highly sensitive and specific as a diagnostic procedure. Screening through endometrial biopsy every 1 to 2 years starting at age 30 to 35 years may be considered.⁸³⁻⁸⁸

Routine transvaginal ultrasound to screen for endometrial cancer in postmenopausal women has not been shown to be sufficiently sensitive or specific to warrant a positive recommendation,⁸⁴⁻⁸⁹ but may be considered at the clinician's discretion. However, 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.

Total abdominal hysterectomy has not been shown to reduce endometrial cancer mortality, but is an option that may be considered for risk reduction.^{59,67,83,85,90,91} The timing of a hysterectomy can be individualized based on whether childbearing is complete, comorbidities, family history, and Lynch syndrome P/LP variant, as risks for endometrial cancer vary by mutated gene.

An observational study showed that hormonal contraceptive use is associated with lower risk for endometrial cancer in carriers of MMR P/LP variants (HR, 0.39; 95% CI, 0.23–0.64; $P < .001$).⁹² However, prospective data are needed before hormonal contraceptives are recommended for prevention of gynecologic cancers in patients with Lynch syndrome. In general, risk reduction agents should be considered, with detailed discussion between the physician and patient outlining the associated risks and benefits.



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Ovarian Cancer Surveillance

Women with Lynch syndrome are also at a heightened risk for ovarian cancer, which varies based on affected MMR gene and age (see *Gene-Specific Lynch Syndrome Cancer Risks and Surveillance/Prevention Strategies* in the algorithm for the complete list of average age of presentation and cumulative risk for diagnosis through age 80 years for ovarian cancer in carriers of an MMR P/LP variant).^{61,66,71,77,78,81} There are circumstances where clinicians may find screening helpful; however, the data do not support routine ovarian cancer screening for Lynch syndrome. Transvaginal ultrasound and serum CA-125 testing to screen for ovarian cancer in postmenopausal women has not been shown to be sufficiently sensitive or specific to warrant a routine recommendation,⁸⁴⁻⁸⁹ but may be considered at the clinician's discretion. Since there is no effective screening for ovarian cancer, women should be educated on the symptoms that may be associated with the development of ovarian cancer, such as pelvic or abdominal pain, bloating, increased abdominal girth, difficulty eating, early satiety, or increased urinary frequency or urgency. Symptoms that persist for several weeks and are a change from a woman's baseline should prompt evaluation by her physician. Bilateral salpingo-oophorectomy (BSO) may reduce the incidence of ovarian cancer.^{59,67,83,85,90,91} The decision and timing of BSO as an option should be individualized based on whether childbearing is complete, menopausal status, comorbidities, family history, and Lynch syndrome gene, as risks for ovarian cancer vary by mutated gene. Estrogen replacement after premenopausal oophorectomy may be considered. There is insufficient evidence to recommend risk-reducing salpingo-oophorectomy (RRSO) in *MSH6* and *PMS2* P/LP variant carriers. Similar to endometrial cancer management, risk reduction agents should be considered, with detailed discussion between the physician and patient outlining the associated risks and benefits.

Surveillance for Other Cancers

Lynch syndrome is associated with increased risk for upper gastrointestinal (GI) cancers, particularly gastric cancer and cancer of small bowel, though incidence rates vary by the specific Lynch-related P/LP variant carried. Risk factors for gastric cancer in Lynch syndrome include male sex, older age, *MLH1* (cumulative lifetime risk of diagnosis through age 80 is 5%–7%) or *MSH2* (cumulative lifetime risk of diagnosis through age 80 is up to 9%) pathogenic variants, a first-degree relative with gastric cancer, Asian ethnicity, or residing in, or immigrant from countries with high background incidence of gastric cancer, chronic autoimmune gastritis, gastric intestinal metaplasia (GIM), and gastric adenomas.^{61,63,78,93-95} Cumulative lifetime risk of diagnosis of small bowel adenocarcinoma through age 80 is elevated for carriers of *MLH1* and *MSH2/EPCAM* P/LP variants (0.4%–11%) and slightly elevated for carriers of an *MSH6* P/LP variant (<1%–4%).^{61,63,78,94} Studies specific to Lynch syndrome have not reported cumulative small bowel cancer risk higher than 0.1% for *PMS2*.⁸² However, the panel did not interpret these data as suggesting risk for a Lynch syndrome carrier would be lower than for the general population. There are data demonstrating that upper GI surveillance in Lynch syndrome detects upper GI cancers at early stages.⁹⁶⁻⁹⁸ Upper GI surveillance also identifies pre-neoplastic lesions of the upper GI tract in Lynch syndrome.^{97,98} At this time, it remains uncertain whether upper GI surveillance reduces upper GI cancer mortality in Lynch syndrome. For individuals with *MLH1*, *MSH2*, *MSH6*, or *EPCAM* P/LP variants, upper GI surveillance with esophagogastroduodenoscopy (EGD) starting at age 30–40 years and repeated every 2–4 years, preferably performed in conjunction with colonoscopy, is recommended.⁹⁶⁻⁹⁸ Age of initiation prior to 30 years and/or surveillance interval less than 2 years may be considered based on family history of upper GI cancers or high-risk endoscopic findings (such as incomplete or extensive GIM, gastric or duodenal adenomas, or Barrett esophagus with dysplasia). Random biopsy of the proximal and distal stomach should at minimum be



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performed on the initial procedure to assess for *H. pylori* (with treatment indicated if *H. pylori* is detected), autoimmune gastritis, and intestinal metaplasia. A 2022 retrospective analysis of 172 enteroscopies in 129 patients with Lynch syndrome showed that push enteroscopy identified distal duodenal or jejunal adenomatous polyps that would not have been identified by standard EGD screening in 1.2% of procedures.⁹⁹ Push enteroscopy can be considered in place of EGD to enhance small bowel visualization, although the yield of push enteroscopy over EGD in LS remains uncertain. Individuals not undergoing upper endoscopic surveillance should have one-time noninvasive testing for *H. pylori* at the time of LS diagnosis, with treatment indicated if *H. pylori* is detected. The value of eradication for the prevention of gastric cancer in LS is unknown. There are limited available data on upper GI cancer risk in *PMS2*-associated Lynch syndrome, and upper GI surveillance described above for *MLH1*, *MSH2*, *MSH6*, and *EPCAM* P/LP variants may be considered at the physician's discretion in individuals carrying a *PMS2* P/LP variant.

Risk for urothelial cancer in patients with Lynch syndrome varies and ranges from less than 1% to 18%, with greater risk among carriers of *MSH2* P/LP variants (ranging from 2%–18%), relative to *MLH1* (ranging from 0.2%–5%) and *MSH6* (ranging from 0.7%–7%) P/LP variant carriers.^{61,63,94,100} There is insufficient evidence to recommend a particular surveillance strategy, but surveillance may be considered in selected individuals—including those with a family history of urothelial cancer or individuals with *MSH2* pathogenic variants (especially males), as they appear to be at higher risk. These groups may benefit from annual urinalysis starting at age 30 to 35 years.

Risk for pancreatic cancer and brain cancer is also elevated in Lynch syndrome.^{77,78,101,102} Although there are limited data on pancreatic risk in *MSH2* and *MSH6* carriers, the panel recommends that patients with Lynch

syndrome with a P/LP variant in *MLH1*, *MSH2*, or *MSH6* begin screening for pancreatic cancer at age 50, or 10 years younger than the earliest familial exocrine pancreatic cancer diagnosis, whichever is earlier, for individuals with exocrine pancreatic cancer in ≥1 first- or second-degree relatives from the same family side as the identified pathogenic germline variant.¹⁰³ The International Cancer of the Pancreas Screening (CAPS) Consortium recommends that patients with Lynch syndrome due to a P/LP variant in *MLH1*, *MSH2*, and *MSH6* and one first-degree relative with pancreatic cancer should be considered for screening.¹⁰⁴ *PMS2* carriers have not been shown to be at increased risk for pancreatic cancer.⁶³ If screening is performed for pancreatic cancer, the panel recommends that it should be considered at high-volume centers with multidisciplinary teams, and only following in-depth discussions surrounding screening limitations including cost, incidence of abnormalities, and uncertainties about potential benefits of screening. Patients should be educated regarding signs and symptoms of neurologic cancer and the importance of prompt reporting of abnormal symptoms to their physicians.

The panel has concluded that there is not an increased risk for prostate cancer in individuals with Lynch syndrome, though prostate cancer risk in individuals with Lynch syndrome is not expected to be lower than that for the general population.^{79,94,105} Though the panel found insufficient evidence to conclude increased risk for prostate cancer in Lynch syndrome, they did recognize some studies have shown increased risk, such as one study showing a cumulative lifetime risk estimate as high as 23.8% for carriers of a *MSH2* P/LP variant.⁷⁹ Patients with Lynch syndrome should consider their risk based on the Lynch syndrome gene and family history of prostate cancer. The NCCN Guidelines for Prostate Cancer Early Detection (available at www.NCCN.org) recommend that patients with Lynch syndrome may consider beginning shared decision-making about prostate cancer screening at age 40 years and screening at annual intervals rather than every other year.



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While studies have found that 42% to 51% of breast cancers in patients with Lynch syndrome are dMMR with abnormal IHC corresponding to their germline pathogenic MMR gene variant,^{106,107} there are insufficient data supporting an increased risk for breast cancer for patients with Lynch syndrome.^{79,94,108-112} Breast cancer risk management should be based on personal and family history (see NCCN Guidelines for Breast Cancer Screening and Diagnosis, available at www.NCCN.org).

Skin Manifestations

The frequency of benign skin tumors such as sebaceous adenocarcinomas, sebaceous adenomas, and keratoacanthomas, has been reported to be increased among patients with Lynch syndrome;^{113,114} however, cumulative lifetime risk and median age of presentation are uncertain. History of these tumors has been reported to be higher among *MSH2* c.942+3A>T variant carriers. An elevated risk of sebaceous tumors and keratoacanthoma has not been documented for *PMS2* carriers.^{113,114} The panel recommends consideration of a skin exam every 1 to 2 years with a health care provider skilled in identifying Lynch syndrome-associated skin manifestations. The age at which to begin surveillance cannot be recommended with certainty, and therefore can be individualized.

Reproductive Options

Patients of reproductive age should be advised regarding their options for prenatal diagnosis and assisted reproduction, including pre-implantation genetic diagnosis. This discussion should include known risks, limitations, and benefits of these technologies. If both partners are a carrier of a P/LP variant(s) in the same MMR gene or *EPCAM* P/LP variant, then they should also be advised about the risk for constitutional MMR deficiency (CMMRD) syndrome, a rare recessive syndrome.¹¹⁵

Lynch Syndrome Colonoscopy Surveillance Findings and Follow-up (LS-F)

If there are no pathologic findings, continued surveillance every 1 to 3 years is recommended. Some patients may benefit from a shorter 1-year versus a longer 2-year screening interval.⁷⁰ Factors that may favor a 1-year interval may include: being male, age >40 years, harboring *MLH1/MSH2* P/LP variants, or having a history of CRC or adenomas.^{70,71} If the patient is not a candidate for routine surveillance, subtotal colectomy may be considered, though generally extended surgery is limited to patients following CRC diagnosis. After subtotal colectomy, endoscopic surveillance of the rectum is required, at similar intervals as described above.

Patients with confirmed adenocarcinoma should be treated following the appropriate NCCN Guidelines for Treatment by Cancer Type (available at www.NCCN.org). For patients with colorectal adenocarcinoma, either a segmental or extended colectomy is indicated depending on the clinical scenario, and factors such as age and pathogenic variant should be considered. LS P/LP variant should be considered as risk for metachronous tumors varies by pathogenic variant and age. Risk for metachronous CRC is higher with segmental versus extended colectomy. For *MLH1* and *MSH2* carriers who have segmental resection, there is up to a 43% cumulative lifetime risk of metachronous CRC. Risk may be lower for *MSH6*. There are limited data on *PMS2*, but no marked increase in risk for metachronous CRC has been reported. For *PMS2*, based on lack of evidence for a significant increased risk for metachronous CRC and lower total CRC risk compared to *MLH1*, *MSH2*, and *MSH6*, consider segmental colectomy. Colonoscopy surveillance every 1 to 2 years should be performed if rectum or colon remain following surgery. For patients with rectal adenocarcinoma, proctectomy or total proctocolectomy (TPC) is recommended depending on the relationship to the anal sphincter and



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anticipated need for pelvic radiation, in addition to the above-mentioned factors.

For patients with adenomatous polyps, recommendations include endoscopic polypectomy with a follow-up colonoscopy every 1 to 2 years. If an adenomatous polyp cannot be completely resected endoscopically, referral to a center of expertise for endoscopic resection is preferred, or for segmental or extended colectomy, depending on clinical scenario. Surgery is not required if adenoma is successfully resected. Post-colectomy patients should be followed with lower endoscopic exams every 1 to 2 years.

The option of segmental or extended segmental colectomy for patients with confirmed adenocarcinoma and/or adenomatous polyps is based on individual considerations and discussion of risks. For example, the U.S. Multi-Society Task Force on Colorectal Cancer recommends that surgery in those >60 to 65 years and those with underlying anal sphincter dysfunction should potentially be less extensive.⁴³ Surgical principles for polyps are similarly controversial. A patient who is unable or unlikely to comply with frequent colonoscopy should be considered for more extensive colectomy, especially if young. Post-colectomy patients should be followed with examination of all remaining colonic mucosa every 1 to 2 years.

Chemoprevention in Lynch Syndrome

In the randomized CAPP2 trial, 861 participants with Lynch syndrome took either daily aspirin (600 mg) or placebo for at least 2, and up to 4 years. The primary endpoint was the development of CRC.¹¹⁶ After a mean 10 year follow-up, participants taking daily aspirin for at least 2 years had a relative 35% reduction in the incidence of CRC (HR, 0.65; 95% CI, 0.43–0.97; $P = .035$).¹¹⁷ Adverse events in both groups were similar. In an observational study including 1858 patients from the Colon Cancer Family Registry who have Lynch syndrome, aspirin use was associated with

reduced risk for CRC, both for patients who took aspirin for 5 or more years (HR, 0.25; 95% CI, 0.10–0.62; $P = .003$) and patients who took aspirin between 1 month and 4.9 years (HR, 0.49; 95% CI, 0.27–0.90; $P = .02$), compared to those who took aspirin for less than 1 month.¹¹⁸

At this time, the panel suggests that aspirin may be used to reduce the future risk of CRC in patients with Lynch syndrome, but it is emphasized that the optimal dose and duration of therapy should be determined on an individual basis.¹¹⁷ The CAPP2 trial used a dose of 600 mg per day,¹¹⁶ though many clinicians who prescribe daily aspirin as chemoprevention in patients with Lynch syndrome utilize a lower dose. The CAPP3 randomized double-blind trial is currently examining the effects of low, moderate, and high doses of daily aspirin on Lynch syndrome-associated cancer incidence (NCT02497820), but results are not yet available. The panel's recommendation to consider aspirin for chemoprevention is consistent with the stance of the American Gastroenterological Association.⁶⁰ Due to limited mature data,^{116,119} the American College of Gastroenterology does not recommend standard use of aspirin for chemoprevention.⁶⁷ Discussion of individual risks, benefits, adverse effects, and childbearing plans should also be included. The panel also recommends that providers carefully review patient-specific factors that may increase the risk of aspirin therapy, as well as factors that indicate a low future cumulative risk of CRC, as some individuals may be less likely to experience significant benefit. Aspirin is pregnancy category D; as such, women with LS should avoid use if sexually active and not using contraception or if pregnant.

Adenomatous Polyposis Testing Criteria (POLYP-1)

Genetic testing for adenomatous polyposis is recommended when an individual has a personal history of ≥ 20 cumulative adenomas. Some have suggested genetic testing with a threshold of ≥ 10 cumulative



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adenomas.^{75,120} Genetic testing is also recommended when an individual has a family history of a known P/LP variant in polyposis genes.

Testing may also be considered if: 1) there is a personal history of a desmoid tumor, hepatoblastoma,¹²¹ cribriform-morular variant of papillary thyroid cancer,^{122,123} or multifocal/bilateral CHRPE;⁶⁷ 2) the individual meets one of the criteria for SPS and has at least some adenomas; or 3) the individual has a personal history of between 10 and 19 cumulative adenomas. Age of onset, family history, and/or presence of other features may influence whether genetic testing is offered in these situations.

A cross-sectional study of more than 7000 individuals found that the prevalence of *APC* P/LP variants was 80%, 56%, 10%, and 5% for those with ≥1000 adenomas, 100 to 999 adenomas, 20 to 99 adenomas, and 10 to 19 adenomas, respectively.¹²⁴ For the same groups, the prevalence of biallelic *MUTYH* P/LP variants was 2%, 7%, 7%, and 4%. Notably, these prevalence estimates may be overestimates since data from this study were taken from a convenience sample of individuals referred for genetic testing to a testing provider, and not from consecutive patients with multiple adenomas. In a cross-sectional study of 3789 individuals with at least 10 colorectal polyps who underwent multi-gene panel testing, the prevalence of P/LP variants in adenomatous polyposis genes decreased with increasing age in all polyp count groups ($P < .001$ for 10–19, 20–99, and ≥100 polyps).¹²⁰ Notably, prevalence of P/LP variants in all genes of interest remained above 5% in all age and polyp cohorts.¹²⁰ These data provide the rationale for recommending genetic testing for individuals with ≥20 cumulative lifetime adenomas, and considering genetic testing for those with ≥10 cumulative lifetime adenomas.

When colonic polyposis is present only in the proband and/or in siblings, consider recessive inheritance or *de novo APC* gene mutations. For example, MAP follows a recessive pattern of inheritance, so *MUTYH* testing should be considered if a recessive pattern is apparent in the

pedigree (eg, when family history is positive only for a sibling). If, on the other hand, a clear autosomal dominant inheritance pattern is observed, *MUTYH* testing is unlikely to be informative. In addition, *MUTYH* testing is not indicated based solely on a personal history of a desmoid tumor, hepatoblastoma, or cribriform-morular variant of papillary thyroid cancer. Overall, the decision to order *APC*, *MUTYH*, or germline multi-gene testing including these genes should be at the discretion of the clinician.

If P/LP variant(s) in the family is known, genetic testing for familial P/LP variant is recommended. If there is no known P/LP variant in any polyposis gene in the family, germline multi-gene testing is preferred, and the panel should include all polyposis and CRC genes.¹²⁰ Alternatively, when colonic polyposis is present in a single person with a negative family history, the panel recommends multigene testing including all polyposis and CRC genes.¹²⁰ P/LP variants associated with adenomatous polyposis include, but are not limited to monoallelic P/LP variants in *APC*, *GREM1*, *POLE*, *POLD1*, and *AXIN2*, and biallelic P/LP variants in *MUTYH*, *NTHL1*, and *MSH3*.

When a familial P/LP variant is known (ie, deleterious *APC* pathogenic variant, monoallelic or biallelic *MUTYH* pathogenic variant, or other known pathogenic variant in another polyposis gene), genetic testing can be considered for at-risk family members. An at-risk family member can be defined as a sibling of an affected individual and/or proband. Siblings of a patient with MAP are recommended to have site-specific testing for the familial P/LP variants. Other individuals in a family may also be at risk of having MAP or a monoallelic *MUTYH* pathogenic variant. Full sequencing of *MUTYH* may be considered in an unaffected parent when the other parent has MAP. If the unaffected parent is not tested, then comprehensive testing of *MUTYH* should be considered in the children. If the unaffected parent is found to have one *MUTYH* pathogenic variant, then testing the children for the familial *MUTYH* P/LP variants is clinically



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indicated. Testing of children of *MUTYH* heterozygotes should be offered if the other parent is also a heterozygote or could still be offered if the other parent is not a heterozygote and management would change, if they have a first-degree relative affected with CRC, or to inform reproductive risks, since their future children could be at risk for MAP.

Among patients with concern for a polyposis syndrome and a known familial P/LP variant, if the familial P/LP variant is not detected, further germline multi-gene testing is recommended. If a P/LP variant is identified in another polyposis gene, management should be based on the specific gene, as well as family and personal history of CRC and polyps. Patients negative for the familial P/LP variant and no personal history of adenomas may follow the NCCN Guidelines for Colorectal Cancer Screening (available at www.NCCN.org); however, individuals with higher cumulative polyp burden (eg, ≥10 adenomas) may require additional testing based on personal, family, and medical history, and specialized management, such as described in a subsequent section, *Colonic Adenomatous Polyposis of Unknown Etiology*. If genetic testing is not done, the individuals should be surveilled and treated as if positive for the known familial P/LP variant.

Counseling should be provided for at-risk individuals so that they are able to make informed decisions about the implications involved in genetic testing, as well as the implications for their own care. Genetic testing in these individuals should be considered before or at the age of screening. The age for beginning screening should be based on the patient's symptoms, family phenotype, and other individual considerations. Fatal CRC is rare before the age of 18 years. If an individual at risk is found not to carry the P/LP variant responsible for familial polyposis in the family, screening as an average-risk individual is recommended.

Surveillance and treatment recommendations depend on the performance and findings of genetic testing, as outlined below.

Familial Adenomatous Polyposis (FAP/AFAP-1)

Classical FAP and AFAP are autosomal dominant conditions characterized by germline P/LP variants in the *APC* gene, located on chromosome 5q21.^{125,126} Truncating P/LP variant of the *APC* gene is detectable in about 80% of patients with FAP using protein-truncating tests.^{127,128} Approximately 20% to 30% of cases are due to *de novo APC* germline P/LP variants, with some cases attributable to mosaicism.¹²⁹⁻¹³¹

Diagnosis: Classical vs. Attenuated FAP

A clinical diagnosis of classical FAP is suspected with the early onset of at least 100 cumulative adenomas in the large bowel. Individuals with classical FAP can start to develop adenomas in early adolescence and progress to hundreds to thousands of colonic adenomas at older ages, if no endoscopic or surgical interventions are performed. If risk-reducing surgery (ie, total abdominal colectomy with ileorectal anastomosis [TAC/IRA], proctocolectomy with ileal pouch-anal anastomosis (PC/IPAA), or PC with end-ileostomy) is not performed, the lifetime risk for CRC in individuals with classical FAP approaches 100% with a median age of presentation at 39 years.¹³² Even following IRA, cumulative lifetime risk of colon cancer is 10% to 30%, compared to <1% to 3% following IPAA, though these estimates are based on older studies that were performed prior to newer practices for case selection of candidates for IRA.¹³³⁻¹³⁸

Individuals with FAP also have an increased lifetime risk for other cancers, including duodenal/periampullary cancer (<1%–10%),¹³⁹⁻¹⁴⁶ thyroid cancer (1.2%–12%),¹⁴⁷⁻¹⁵⁷ gastric cancer (0.1%–7.1%),^{146,158-164} and hepatoblastoma (0.4%–2.5%, usually by age 5 years).^{121,165-168} The majority of thyroid cancers seen in FAP are papillary thyroid carcinomas, with the rare cribriform-morular variant considered almost pathognomonic.¹²² Cumulative risks for gastric cancer at the higher end of the range have been reported in Asian populations in Japan and



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Korea.^{158,161-163,169} Intra-abdominal desmoid tumors are also associated with FAP, and these occur more frequently in patients with P/LP variants in the 3 prime end of the APC gene (after codon 1444).¹⁷⁰⁻¹⁷⁴ Median time to development of desmoid tumors after abdominal surgery is 28.8 to 36 months, and approximately 25% developed in individuals with no prior history of surgery or no local association to previous surgical procedures.^{172,173} Other malignancies found in patients with FAP at a slightly higher rate than that in the general population include small bowel cancer (distal to the duodenum; <1%),¹⁴⁶ pancreatic cancer (1% to 2%),¹⁵⁰ and CNS cancer (mainly medulloblastoma; 1%).^{175,176} Increasingly, individuals are being diagnosed in the second decade of life through genetic testing for their specific familial P/LP variant or through endoscopic screening of at-risk family members.¹⁶⁶

AFAP is a recognized variant of FAP characterized by a later onset of disease and fewer cumulative lifetime adenomas than observed with classical FAP, typically ranging from 10 to less than 100.^{125,126} AFAP is due to APC P/LP variants in the 5 prime end of the gene, in exon 9, or in the 3 prime end of the gene.¹⁷⁷ Adenomas associated with AFAP are more prone to occur in the right colon. Phenotypic expression of classical versus AFAP is often variable within families. The onset of CRC is typically delayed by 10 to 20 years compared to patients with FAP,¹⁷⁷ but the incidence of cancer rises sharply after the age of 40 years and approaches 70% by age 80 years in absence of endoscopic or surgical intervention. Upper GI findings, including gastric and duodenal/ampullary cancer risks, as well as thyroid cancer risks are similar to those observed for classical FAP.

To confirm the diagnosis of FAP or AFAP, germline testing to evaluate for a P/LP variant in the APC gene is recommended. Single-site testing can be pursued if there is a known familial P/LP variant. Multi-gene panel testing for hereditary polyposis syndromes is recommended in the

absence of a known P/LP variant. Germline testing is important to differentiate between other etiologies of adenomatous polyposis (eg, MAP, POLE and POLD1 associated polyposis, and others) for the consideration of extra-colonic screening, as well as counseling, risk assessment, and testing of family members.

If there is suspicion for FAP/AFAP, genetic counseling and testing should be performed. Identifying a P/LP variant allows for screening and testing of at-risk family members. When the familial P/LP variant is known, genetic counseling and testing of asymptomatic, at-risk family members is indicated. If the clinically affected family member is not available for testing, testing of other at-risk family members can be considered. Genetic testing for FAP in at-risk children is recommended to be done no later than age 10 to 15 years, the age at which polyp surveillance would be initiated. If there is intent to perform hepatoblastoma screening, genetic testing may be considered in infancy. Genetic testing for AFAP in at-risk individuals may be done by the late teens, the age range during which endoscopic surveillance would be initiated.

Preoperative Surveillance for Individuals with a Family History of Classical FAP (FAP-2)

Surveillance for at-risk individuals with a family history of FAP depends on genetic testing results, as described below.

Negative genetic testing: If an individual at risk is found not to carry the APC P/LP variant responsible for familial polyposis in the family, screening as an average-risk individual is recommended.

Positive genetic testing: If an APC P/LP variant is found, high-quality colonoscopy every 12 months, beginning at 10 to 15 years of age, is recommended. Colonoscopy is preferred over flexible sigmoidoscopy due to the possibility of missing transverse colon and right-sided polyps when limiting to sigmoidoscopy. However, based on patient and family



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preference or clinical judgment, sigmoidoscopy may also be considered. Earlier initiation of screening can be considered based on family history. In addition, individuals with active symptoms (eg, bleeding, anemia, persistent diarrhea) should undergo appropriate endoscopic workup regardless of age. If adenomas develop, surgical options should be reviewed (see below).

No genetic testing: Some people who undergo genetic counseling are determined to have a high risk for FAP, but decide, for a variety of reasons, not to undergo genetic testing, which influences how their screening is managed. If an *APC* P/LP variant is ruled out, the advantages of genetic testing, including avoidance of costs, burden, and risks associated with frequent colonoscopy should be discussed. If genetic testing is not done, these individuals are considered to be potentially at risk and should be offered annual high-quality colonoscopy (preferred option) or flexible sigmoidoscopy every 12 months beginning at 10 to 15 years of age. If results continue to be negative, the surveillance intervals are recommended to extend to every 2 years after 15 years of age. If there are multiple surveillance exams without adenomas on follow-up, the interval may be lengthened further, based on clinical judgment.

There are several reasons why surveillance is recommended so often for these individuals. First, adenomas may begin to develop in adolescence. Most people with classic FAP present with adenomas before the age of 25 years, so annual surveillance with sigmoidoscopy will detect the majority of patients with FAP. Less often, people with FAP will not develop adenomas until a later age. The probability of FAP in a person without any adenomas on annual surveillance begins to decrease with age around this time, so that surveillance does not need to be as frequent between the ages of 24 and 34 years, and can be even less frequent between the ages of 34 and 44 years. This recommended schedule is more rigorous than screening guidelines for the general population, because serial negative

examinations up to age 35 years do not exclude the diagnosis of FAP. It is important to recognize that individuals with attenuated polyposis may not present until a later age and may have fewer adenomas than those with classic FAP, yet enhanced surveillance is still warranted in these individuals. Notably, the lack of data to support precise intervals for surveillance in individuals from families with FAP is one key reason to pursue genetic testing of an affected individual within the family, since identification of a P/LP variant can allow for surveillance to rule in and rule out disease in unaffected relatives.

No familial P/LP variant found: Evaluating asymptomatic individuals at risk in families for whom P/LP variants cannot be found with available testing technology presents a difficult problem. By far the best approach in this situation is additional attempts to identify the *APC* or *MUTYH* pathogenic variants in an affected family member, even if the available person is not a first-degree relative. If a P/LP variant is found, then the at-risk individual should be treated similarly to those with known familial P/LP variants. FAP can be excluded in a person at risk whose genetic testing results indicate no P/LP variant is found when a P/LP variant has been previously identified in an affected family member (a “true negative” test result).

If, however, a familial P/LP variant is still not identified, genetic testing of at-risk individuals can be considered. A positive test in an asymptomatic person is informative even when the familial P/LP variant has not been previously identified. However, interpreting a test in which “no P/LP variant is found” in an asymptomatic person is not the same as a “negative test.” This particular issue is often a source of confusion and misinterpretation. Thus, it is critical that patients receive appropriate genetic counseling to avoid false-negative interpretations of test results.¹⁷⁸ Surveillance for these at-risk individuals for whom no P/LP variant is found is identical to that for untested individuals with a known familial P/LP variant (see section



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above). If polyposis is detected, patients should be treated in the same way as those with a personal history of classical FAP.

Preoperative Surveillance for Individuals with a Personal History of AFAP (AFAP-1)

Treating patients with a personal history consistent with AFAP varies depending on the patient's age and adenoma burden. For patients with a small adenoma burden (defined somewhat arbitrarily as <20 adenomas, all <1 cm in diameter and none with advanced histology) that can be handled endoscopically, high-quality colonoscopy and polypectomy are recommended every 1 to 2 years with surgical evaluation and counseling if appropriate.

If adenoma burden is endoscopically unmanageable, colectomy with IRA is preferred in most cases. When rectal polyposis becomes too significant to be managed by polypectomy (ie, when polyps number >20 at any individual examination or when a polyp ≥1 cm in diameter or with advanced histology is identified), PC/IPAA may be considered (see *Surgical Options in FAP and AFAP* below for further description).

Preoperative Surveillance for Individuals with a Family History of AFAP (AFAP-2)

Similar genetic counseling, testing, and surveillance considerations discussed previously for patients with a classical FAP family history apply to patients with a family history of AFAP, except for the endoscopy approach. It is important to recognize that individuals with attenuated polyposis may not present until a later age and may have fewer adenomas than those with classical FAP. However, enhanced surveillance is still warranted for these patients.

Negative genetic testing: If an individual at risk is found not to carry the APC P/LP variant responsible for polyposis in the family, screening as an

average-risk individual is recommended, with modification based on their personal history of polyps and cancer.

Positive genetic testing, no genetic testing, or no familial pathogenic variant found: In an individual at risk who is found to carry the APC P/LP variant, colonoscopy surveillance should begin in the late teens, with repeat examinations every 1 to 2 years. If adenomas are detected, surveillance recommendations are as described for individuals with a personal history of AFAP. In the absence of a true negative genetic test result or if the individual has not undergone genetic testing, an individual with a family history of AFAP should begin colonoscopy surveillance in the late teens, with repeat examinations every 2 years. Thus, the late onset and right colon involvement is accommodated in contrast to classical FAP. If no adenomas are found, individuals should continue with surveillance every 2 years. Multiple surveillance exams without adenomas at follow-up may warrant a lengthened interval, based on clinical judgment.

Surgical Options in FAP and AFAP (FAP-D)

Three different surgical options are available for individuals with classical FAP and AFAP: PC/IPAA (recommended for FAP), TAC/IRA (recommended for AFAP), and PC with permanent end ileostomy (PC/EI).¹⁷⁹ The prime factors to consider when choosing an operation for FAP and AFAP are the personal and familial phenotype, including the rectal polyp burden (ie, distribution and number) and whether colon or rectal cancer is present at diagnosis. In patients presenting with the classical FAP phenotype, PC/IPAA is generally recommended because it prevents both colon and rectal cancers. For patients with AFAP, TAC/IRA is generally recommended; PC/IPAA can also be considered in cases of dense rectal polyposis not manageable with polypectomy. Surgery is performed either at the onset of polyposis or later, depending on the severity of the familial phenotype and genotype, the extent of polyposis at diagnosis, individual considerations, and local practices and expertise.



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Proper post-surgical surveillance should be followed as outlined in the sections below. In patients who are <18 years without severe polyposis and without a family history of early cancers or severe genotype, the timing of PC can be individualized. If surgery is delayed, then annual colonoscopy is recommended. Patients should be treated by physicians or centers with expertise in FAP, and treatment should be individualized to account for genotype, phenotype, and personal considerations.

Proctocolectomy with Ileal Pouch Anal Anastomosis: PC/IPAA, usually with a temporary loop ileostomy, is offered to patients with classical FAP, patients with AFAP with severe phenotypes resulting in carpeting of the rectum, patients with curable rectal cancer complicating the polyposis, and patients who underwent IRA and now have endoscopically unmanageable disease in the rectum. The operation is generally not offered to patients with incurable cancer, those with an intra-abdominal desmoid that may interfere with the completion of surgery, patients who have an anatomic, physiologic, or pathologic contraindication to an IPAA, or if there is cause for concern in the ability of patients to participate in close endoscopic surveillance following surgery. The advantages of this operation are that the risks of developing rectal cancer are reduced, and a permanent stoma is not needed. The disadvantages are that it is a complex operation, a temporary stoma is usually needed, and it carries a small risk of bladder dysfunction, sexual dysfunction, infertility (ie, inability to conceive 1 year after unprotected intercourse) and infecundity (ie, inability to bear children), and anal sphincter injury after proctectomy. IPAA is associated with increased risk of infertility in females, though data for FAP are largely extrapolated from studies of patients with ulcerative colitis.¹⁸⁰⁻¹⁸² Two meta-analyses including studies of infertility risk after IPAA for ulcerative colitis (one of the meta-analyses included a study of patients with FAP) showed average infertility rates of 48% to 63%.^{180,181} Decreased fertility from IPAA is more common from open surgery, compared to laparoscopy.¹⁸³ Functional results are variable with

IPAA. Bowel function, although usually reasonable, is also somewhat unpredictable. The ileal pouch requires surveillance, and the area of the IPAA should still be examined due to the imperfect nature of mucosectomy.

Total Abdominal Colectomy with Ileorectal Anastomosis: A TAC/IRA has an overall low morbidity rate. It generally results in good bowel function. Most patients have three to four bowel movements per day, and the risk of urgency or fecal incontinence is low. Without proctectomy, there should be no risk of bladder or sexual dysfunction, or infertility or infecundity, and even a temporary stoma is obviated. The main disadvantages of TAC/IRA are increased risk for developing metachronous rectal cancer, associated morbidity and mortality, and the potential need to undergo subsequent proctectomy due to severe rectal polyposis.^{134,184,185} A review of 659 patients in the Dutch-Scandinavian collaborative national polyposis registries who underwent colectomy with IRA found a high rate of advanced and fatal rectal cancers even though 88% of the patients underwent a diagnostic proctoscopy within 18 months of presentation. It was estimated that 12.5% of patients undergoing this procedure would die of rectal cancer by age 65 even if compliant with endoscopic screening.¹⁸⁵ The authors concluded that PC is the preferred procedure for most patients with the classical FAP phenotype, though some controversy remains regarding this choice. They and others also observed that patients could not reliably be selected for colectomy based on genotype alone. However, subsequent studies have reported that the risk for rectal cancer associated with TAC/IRA has declined since the 1980s when IPAA first became available for high-risk patients with severe polyposis.^{133,186}

The choice of TAC/IRA versus PC/IPAA centers on the issues of the relative quality of life.¹⁸⁷⁻¹⁹² A modest reduction in life expectancy is expected in patients with classical FAP with rectal preservation.^{134,193} The



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decision to remove the rectum is dependent on whether the polyps are amenable to endoscopic surveillance and resection. Proctoscopic examination of a retained rectum is indicated annually. IRA is the surgery of choice for the majority of patients with AFAP who either have rectal sparing or endoscopically manageable rectal polyposis. In certain cases, such as AFAP with mainly proximal polyps, the extent of colectomy may be modified based on the burden of adenoma distribution and number. It is not recommended for patients with extensive rectal polyposis. Patients and families must be absolutely reliable for follow-up endoscopic examinations. The risk to the rectal stump rises considerably after age 50 years. If an individual develops endoscopically unmanageable disease in the rectum, a proctectomy with either an IPAA or EI is recommended.¹⁹⁴

Proctocolectomy with End Ileostomy: A PC/EI is rarely indicated as a prophylactic procedure because good options are available that do not involve a permanent stoma, which has implications for the patient and the family. Fear of a permanent stoma may make family members reluctant to undergo screening. The operation removes all risk for colon and rectal cancer, but is associated with the risk of bladder or sexual dysfunction, including infertility and infecundity. This operation may be offered to patients with a low, locally advanced rectal cancer, patients who cannot have an ileal pouch due to a desmoid tumor, patients with a poorly functioning ileal pouch, patients who have a contraindication to an IPAA (eg, concomitant Crohn's disease, poor sphincter function), and patients where there is a concern for participation in close endoscopic surveillance after surgery.

PC with continent ileostomy is offered to patients who are motivated to avoid EI because they are either not suitable for PC/IPAA or they have a poorly functioning IPAA. This is a complex operation with a significant risk for reoperation.

Surveillance Following Surgery for FAP (FAP-B)

Colorectal Cancer

FAP patients with a retained rectum following TAC/IRA should undergo endoscopic rectal examination every 6 to 12 months, with the frequency of exams guided by polyp burden. After a PC/IPAA, the ileal pouch and rectal cuff should be evaluated endoscopically annually, with consideration for shorter interval follow-up based on polyp burden, large flat polyps with villous histology, or high-grade dysplasia. If the patient had a PC with end-ileostomy, consider careful visualization and stoma inspection by ileoscopy annually to evaluate for polyps or malignancy, although the panel notes that evidence to support this recommendation is limited. Chemoprevention should only be considered in select patients as an adjunct to standard endoscopic or surgical treatment with a full discussion of the risks, benefits, and alternatives. Optimally, it should be supervised by experts in chemoprevention and FAP, and enrollment in a clinical trial should be encouraged.

Duodenal or Periapillary Cancer

A major component of surveillance in patients with FAP or AFAP relates to the upper GI tract. Duodenal adenomatous polyposis develops in more than 90% of patients with FAP, and duodenal cancer occurs in up to 10%^{140,141,143-146,193,195,196} of patients and usually patients who are >40 years. Duodenal adenomas may be classified as Spigelman stage 0 to IV, based on endoscopic and histologic criteria.¹⁹⁷ The cumulative lifetime risk of developing severe duodenal polyposis (stage IV) has been estimated to be approximately 35%,¹⁹⁸ and the risk for duodenal cancer increases dramatically with Spigelman stage IV disease; however, stage IV polyposis does not always precede a diagnosis of duodenal cancer.¹⁴¹

Upper GI tract surveillance should be performed with upper endoscopy that includes complete visualization of the ampulla of Vater. A side-viewing duodenoscope or distal cap attachment to a standard upper endoscope (cap-assisted endoscopy) improves complete visualization of the



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ampulla.¹⁹⁹ The panel recommends that surveillance begin at approximately 20 to 25 years of age, or younger if there is a family history of significant duodenal polyposis burden or duodenal cancer. At time of endoscopy, the number, size, and appearance of polyps found in the duodenum and stomach should be documented. When neoplasia at the ampulla of Vater is suspected, biopsy of the suspicious-appearing area should be performed prior to attempted endoscopic resection.

The appropriate period for follow-up upper endoscopy relates to the burden of polyps, varying from every 3 to 5 years if no polyps are found to every 3 to 6 months for Spigelman stage IV polyposis. Surgical evaluation and counseling are recommended for invasive carcinoma, high-grade dysplasia, or dense polyposis that cannot be managed endoscopically. If surgery is deferred, surveillance endoscopy every 3 to 6 months is recommended. Endoscopic treatment options, when feasible, include endoscopic ampullectomy in addition to excision or ablation of resectable large or villous adenomatous polyps to potentially avert surgery. Potentially higher risk adenomas involving the ampulla of Vater, including adenomas ≥ 1 cm in size or adenomas extending into the ampulla of Vater, should be referred to an expert center for evaluation and management. A pilot trial reported that a combination of sulindac and low-dose erlotinib may reduce duodenal polyp burden in patients with FAP, and a larger clinical trial is ongoing.²⁰⁰ Patients with advanced duodenal polyp burden should be referred to expert centers for evaluation and treatment, and consideration for any clinical trials that are available. The panel recommends that individuals considered for surgical management of duodenal findings may have their small bowel evaluated with capsule endoscopy or CT/MRI enterography prior to surgery to identify large lesions that might modify the surgical approach. Although individuals may be considered for complete small bowel imaging surveillance, the panel notes that evidence of its utility is limited. Shorter intervals for endoscopic surveillance, regardless of Spigelman stage, may be considered based on

personal or family history of massive gastric polyposis, multiple gastric adenomas, large ampullary adenoma (>10 mm), family or personal history of gastric/duodenal cancer, or advancing age.

Other Cancers

Fundic gland polyps (FGPs) of the stomach also occur in the majority of patients with FAP and AFAP and often are too numerous to count. In FAP/AFAP, FGPs usually have biallelic inactivation of the *APC* gene, and often display foci of low-grade dysplasia or microadenomatous changes of the foveolar epithelium.²⁰¹ However, high-grade dysplasia or malignant progression in FGPs is uncommon. Lifetime risk for gastric cancer in patients with FAP/AFAP is reported to be in the range of 0.1% to 7.1%.^{146,158-164,169} The risk of gastric cancer in patients with FAP/AFAP may be increased in patients from geographic areas with a high prevalence of gastric cancer. Additionally, recent data suggest that gastric cancer risk may be elevated in the setting of certain endoscopic findings, including carpeting of FGPs, solitary polyps >10 mm to 20 mm, mounds of polyps, and proximal gastric white mucosal patches.²⁰²⁻²⁰⁴ High-risk histologic features include tubular adenomas, polyps with high-grade dysplasia, and pyloric gland adenomas.²⁰⁵ In light of this, the panel recommends that the need for specialized surveillance or surgery may be considered in the presence of described high-risk histologic features or high-risk lesions that cannot be removed endoscopically,⁶⁷ preferably at a center of expertise. Note that the presence of FGPs with low-grade dysplasia alone in the absence of high-risk features does not require specialized surveillance.

Patients with FAP/AFAP also have elevated risk for developing other extracolonic cancers that may warrant surveillance.²⁰⁶ Several studies suggest that there is an increased lifetime risk of developing thyroid cancer in patients with FAP and AFAP when compared to the general population, with incidence ranging from approximately 1% to 12%.^{147,150,151,154,156} The mean age of diagnosis of thyroid cancer in these patients ranges from 29 to 33 years.^{151,156} Thyroid cancers in patients with



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FAP/AFAP are most commonly papillary (cribriform-morular variant) and occur predominantly in women.^{149,151,154,206}

A retrospective analysis of 51 patients with a proven diagnosis of FAP demonstrated that out of 28 patients who had at least one screening ultrasound, 2 (7%) had papillary thyroid carcinoma.¹⁵¹ Another study performed thyroid ultrasounds on patients with FAP during their annual colonoscopy and found that out of 205 patients screened, 38% had thyroid cancer.¹⁴⁹ A concern regarding thyroid surveillance is potential for high rates of benign thyroid nodule detection. In the aforementioned series, rates of thyroid nodule detection ranged from 51.7% to 79%.^{149,151} Thus, the benefit of regular surveillance for thyroid cancer is uncertain and more studies may be necessary to develop optimal management.^{149,152} Currently the panel recommends thyroid ultrasound starting in the late teenage years, and considers repeating every 2 to 5 years if no nodules are identified. Shorter intervals may be considered in individuals with a family history of thyroid cancer or with concerning features on prior thyroid ultrasound exams.²⁰⁷

Classical FAP/AFAP is also associated with an increased risk for intra-abdominal desmoid tumors, the majority of which present within 5 years of colectomy or other intra-abdominal surgery. Given the relationship between surgery and development of desmoid tumors, it is important to know the location of the *APC* P/LP variant when determining timing of surgery, especially in individuals at higher risk, such as those with P/LP variants in codons 1444–1580.²⁰⁸ Since significant morbidity and mortality may be associated with advanced desmoid tumors, early diagnosis may be of benefit.²⁰⁹ If family history of symptomatic desmoids is present, the panel recommends consideration of abdominal CT with contrast or MRI with and without contrast no less frequently than annually. Abdominal imaging is warranted if suggestive abdominal symptoms are present such as new, unexplained abdominal pain. For small bowel polyps and cancer,

adding small bowel visualization to CT or MRI for desmoids as outlined above can be considered, especially if the patient has a personal history of advanced duodenal polyposis.

The risk for hepatoblastoma is increased in young children with FAP compared to children without FAP.¹²¹ Although the absolute risk is about 1.5%, given the potential lethality of the disease (25% mortality), surveillance by liver palpation, abdominal ultrasound, and serum alpha-fetoprotein (AFP) every 3 to 6 months during the first 5 years of life may be considered.

Medulloblastoma accounts for most of the brain tumors found in patients with FAP, predominantly in females <20 years.¹⁷⁵ Patients should be educated regarding signs and symptoms of neurologic cancer and the importance of prompt reporting of abnormal symptoms to their providers. The incidence of pancreatic cancer in FAP is not well-defined and is likely very low. Giardiello and colleagues reported 4 cases in a retrospective analysis of 1391 FAP-related subjects.¹⁵⁰ More studies are needed to elucidate the potential risk and benefit of surveillance for brain and pancreatic cancers, and should be individualized based on family history.

Surveillance After Surgery for AFAP (AFAP-1)

After surgery for AFAP, annual physical and thyroid examinations are recommended as for FAP. Surveillance of a retained rectum and the upper GI tract is similar to that for classical FAP.

Chemoprevention in FAP and AFAP

Cyclooxygenase-2 (COX-2) has been shown to be overexpressed in colorectal adenomatous polyps and cancers, and expression may be reduced with exposure to nonsteroidal anti-inflammatory drugs (NSAIDs). NSAIDs have been studied for their role in chemoprevention in patients with FAP and AFAP. In a randomized, double-blind, placebo-controlled study, the NSAID sulindac did not prevent the development of colorectal



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adenomatous polyps in persons with FAP prior to surgical intervention.²¹⁰ In addition, a randomized controlled trial failed to show a strong benefit of chemoprevention with aspirin in young patients with FAP prior to surgical intervention, despite non-significant trends in reduced colorectal polyp size and number.²¹¹ Some evidence suggests utility for NSAIDs when used in combination with other agents. Preclinical studies have demonstrated an association between COX-2 and the epidermal growth factor receptor (EGFR) signaling pathways and the development of intestinal tumorigenesis.²¹²⁻²¹⁴ A double-blind, randomized, placebo-controlled trial examined the effect of sulindac and erlotinib, an EGFR inhibitor, on duodenal adenomas in patients with FAP.²⁰⁰ Participants with FAP were randomized to receive placebo (n = 46) or 150 mg of sulindac twice a day and 75 mg of erlotinib once a day (n = 46) for 6 months.²⁰⁰ Over the course of 6 months, the median duodenal polyp burden increased in the placebo group and decreased in the sulindac/erlotinib group, with a net difference of -19.0 mm between the groups (95% CI, -32.0 to -10.9; $P < .001$).²⁰⁰

Chemoprevention with NSAIDs has also been studied following initial prophylactic surgery for both classical FAP and AFAP as an adjunct to endoscopic surveillance and to reduce the rectal polyp burden. Long-term use of sulindac may be effective in polyp regression and preventing recurrence of higher-grade adenomatous polyps in the retained rectal segment of patients with FAP.²¹⁵ In a randomized, double-blind, placebo-controlled study of 77 patients with FAP who had not had their entire colon and rectum removed, patients treated twice daily with 400 mg of celecoxib for 6 months had a 28% reduction in polyp number ($P = .003$) and a 31% decrease in sum of polyp diameters ($P = .001$), whereas patients receiving placebo had 4.5% and 4.9% reductions in those parameters, respectively.²¹⁶ It should be noted, however, that the FDA indication for use of celecoxib in FAP was removed in 2011 due to the lack of phase IV (follow-up) data.

A pilot study looked at a possible similar postoperative chemopreventive role in FAP and AFAP for the omega-3 polyunsaturated fatty acid, eicosapentaenoic acid (EPA).²¹⁷ Patients receiving EPA demonstrated a significant 22.4% decrease in polyp number and a significant 29.8% decrease in sum polyp diameter after 6 months of treatment, while patients in the placebo arm saw a worsening of global polyp burden during this time. However, the evidence is insufficient to recommend routine use, and a meta-analysis of N-3 polyunsaturated fatty acids intake and risk of CRC—not limited to FAP patients—did not show a clear protective association.

One recent study compared the efficacy of and safety of combination therapy with sulindac (an NSAID) and eflornithine (an inhibitor of ornithine decarboxylase) to either drug alone for preventing disease progression in patients with FAP.²¹⁸ Among 171 patients randomized, a non-statistically significant reduction in risk for disease progression was noted for the combination of both drugs compared with sulindac alone (HR, 0.71; 95% CI, 0.39–1.32), as well as the combination compared with eflornithine alone (HR, 0.66; 95% CI, 0.36–1.24). The combination of sulindac and eflornithine treatment for prevention of disease progression in FAP has not yet received FDA approval for this indication.

Although the panel notes that chemoprevention may be considered to facilitate post-surgical management of the rectum or pouch in select patients with poly burden, overall, there are no FDA-approved medications for this indication. While data suggest that sulindac, alone or combined with the EGFR inhibitor, erlotinib, may be a potent polyp-regression strategy,^{200,210,218} additional studies with longer follow-up are needed to determine if the decrease in polyp burden decreases cancer risk. Patients with polyposis who are interested in chemoprevention should be referred to expert centers for consideration of enrollment in a clinical trial.



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MUTYH-Associated Polyposis (MAP-1)

MAP is an autosomal recessive hereditary syndrome that predisposes individuals to attenuated adenomatous polyposis and CRC.²¹⁹⁻²²¹ It is caused by biallelic germline P/LP variants in the *MUTYH* gene. *MUTYH* encodes the A/G-specific adenine DNA glycosylase excision repair protein (also called hMYH), which is responsible for excising adenine nucleotides mismatched with 8-oxoguanine, a product of oxidative damage to DNA. Dysfunctional hMYH protein can thus result in G:C to T:A transversions during DNA replication. Adenomatous polyposis is thought to result from such transversions occurring within the *APC* gene. The lifetime risk for CRC for patients with MAP may be very high.²²² The median age of presentation is approximately 45 to 59 years. Individuals with MAP also have an increased risk for extracolonic tumors including duodenal cancer.²²³

While some studies have shown that monoallelic carriers of *MUTYH* P/LP variants may have a modest or slightly increased risk for CRC, the largest studies have shown no substantially increased risk except for patients with a family history of CRC.^{221,224-226} A study of 2332 relatives of patients with CRC with monoallelic *MUTYH* P/LP variants showed that carriers have an estimated 2.5-fold increased risk for CRC, relative to the general population.²²⁵ However, when monoallelic *MUTYH* P/LP carriers both with and without a family history of CRC were considered, estimated CRC risks up to 70 years of age were 7.2% (95% CI, 4.6%–11.3%) for male carriers of monoallelic *MUTYH* P/LP variants and 5.6% (95% CI, 3.6%–8.8%) for female carriers of monoallelic *MUTYH* P/LP variants.²²⁵ The risks for CRC were higher for carriers of monoallelic *MUTYH* P/LP variants with a first-degree relative with CRC.²²⁵ A study of 852 monoallelic *MUTYH* P/LP variant carriers who were relatives of patients with CRC showed an increase in risk for CRC, relative to the general population (standardized incidence ratio [SIR], 2.04; 95% CI, 1.56–2.70; $P < .001$).²²⁴ Another study evaluated the frequency of monoallelic *MUTYH* P/LP variants and

colorectal adenomas, and found that 13 of 72 individuals with CRC were monoallelic *MUTYH* P/LP variant carriers, and 11 of the 13 had a family history of cancer in first- or second-degree relatives.²²⁷ In contrast, a population-based analysis of 198 monoallelic *MUTYH* P/LP variant carriers showed that a monoallelic *MUTYH* P/LP variant does not significantly increase CRC risk (OR, 1.07; 95% CI, 0.87–1.31; $P = .55$).²²⁸ In addition, a meta-analysis of 945 articles investigating the associations between genetic variants and CRC risk determined that there is no substantial evidence supporting monoallelic *MUTYH* P/LP variants and increased CRC risk.²²⁹ The largest and most recent study, which evaluated over 25,000 individuals referred for genetic testing by a commercial laboratory with a personal history of CRC, endometrial cancer, or breast cancer, and compared risk to over 51,000 controls found no increased risk for CRC for monoallelic carriers (OR, 1.2; 95% CI, 0.99–1.50; $P = .064$).²³⁰

Given conflicting evidence regarding CRC risk associated with having a monoallelic *MUTYH* pathogenic variant,²²⁵ the NCCN Panel recommends specialized screening for CRC mainly based on family history (GENE-9). Specifically, the panel recommends that monoallelic *MUTYH* carriers unaffected by CRC with a first-degree relative with CRC receive colonoscopy screening every 5 years beginning at age 40 or 10 years prior to first-degree relative's age at CRC diagnosis. Notably, these are consistent with standard NCCN recommendations based on having a first-degree relative with CRC alone (see NCCN Guidelines for Colorectal Cancer Screening at www.NCCN.org). There are no specific data available to determine screening recommendations for a patient with one *MUTYH* pathogenic variant and a second-degree relative affected with CRC (see NCCN Guidelines for Colorectal Cancer Screening at www.NCCN.org). Data are unclear as to whether specialized screening is warranted for *MUTYH* monoallelic carriers unaffected by CRC with no family history of CRC.²³¹ For monoallelic *MUTYH* carriers with CRC, see



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recommendations in the NCCN Guidelines for Colon Cancer and the NCCN Guidelines for Rectal Cancer (available at www.NCCN.org).

Most individuals with MAP generally have fewer than 100 adenomas, although a minority can present with greater than 1000. Hyperplastic polyps, sessile serrated polyps (SSPs), and traditional serrated adenomas may also be seen in this setting. In fact, some patients with MAP may also meet the criteria for SPS. While duodenal polyposis is reported less frequently in MAP than in FAP, duodenal cancer occurs in about 5% of patients with MAP. In addition, individuals with MAP generally require colectomy at a later age than those with FAP.

Preoperative and Surgical Management of MAP (MAP-2/-3)

Genetic counseling and testing is recommended for individuals with a family history of MAP and known *MUTYH* pathogenic variants (see *Adenomatous Polyposis Testing Criteria*, above). With positive genetic testing (biallelic *MUTYH* pathogenic variants) or no testing in such individuals, high-quality surveillance colonoscopy should begin no later than age 25 to 30 years and should be repeated every 1 to 2 years if negative. If polyps are found, these patients should be treated as those with a personal history of MAP (see below). Upper endoscopy (including complete visualization of the ampulla of Vater) can also be considered beginning at age 30 to 35 years,^{205,223,232} with follow-up as described above for patients with a personal history of FAP. For individuals who have not elected for genetic testing to evaluate for a P/LP variant, advantages of genetic testing, including avoidance of costs, burdens, and risks associated with frequent colonoscopy if biallelic mutation is ruled out should be discussed.

Genetic counseling and testing is recommended for patients with multiple adenomatous polyps (see *Adenomatous Polyposis Testing Criteria*,

above). Such individuals who have a negative test for *MUTYH* pathogenic variant should be treated individually as patients with FAP.

Individuals <21 years of age with confirmed biallelic *MUTYH* pathogenic variants and small adenoma burden are followed with colonoscopy and complete polypectomy every 1 to 2 years, beginning no later than age 25 to 30; earlier colonoscopy may be indicated based on family history. Surgical evaluation and counseling are also recommended if appropriate. Colectomy and IRA may be considered as the patient gets older. Surgery in the form of colectomy with IRA is recommended in most cases of significant polyposis not manageable by polypectomy. PC/IPAA can be considered in cases of dense rectal polyposis not manageable by polypectomy. Extent of colectomy may be modified based on adenoma burden (distribution and number).

Postoperative Surveillance in MAP (MAP-2)

After colectomy with IRA, endoscopic evaluation of the rectum every 6 to 12 months is recommended, depending on polyp burden. The use of chemoprevention may be considered in select patients, but options have not been studied specifically in MAP. Consider referral to a center with expertise for discussion of chemoprevention and surgical options, particularly for patients with a high polyp burden in the remaining rectum after colectomy.

In addition to evaluation of the rectum, an annual physical exam is recommended, with baseline upper endoscopy (including complete visualization of the ampulla of Vater) beginning at age 30 to 35 years. Cap-assisted endoscopy may be adequate for visualization of the ampulla of Vater.¹⁹⁹ Follow-up of duodenoscopic findings is as described above for patients with FAP.



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Colonic Adenomatous Polyposis of Unknown Etiology (CPUE-1)

When genetic testing in an individual with colonic adenomatous polyposis does not diagnose a pathogenic variant in a polyposis gene, surveillance should be tailored based on individual and family risk assessment. P/LP variants associated with adenomatous polyposis include, but are not limited to monoallelic P/LP variants in *APC*, *GREM1*, *POLE*, *POLD1*, and *AXIN2*, and biallelic P/LP variants in *MUTYH*, *NTHL1*, and *MSH3*.

Therapy-associated polyposis attributed to treatment of cancer during childhood, adolescence, or young adulthood should be considered as a potential explanation for otherwise unexplained polyposis (see the NCCN Guidelines for Colorectal Cancer Screening; available at www.NCCN.org).^{233,234} If the patient has a history of ≥ 100 adenomas, the panel recommends that the patient be treated as described above for patients with a personal history of classical FAP.

If the patient has a history of 20 to <100 adenomas, and the adenoma burden is small and considered to be manageable by colonoscopy and polypectomy, the panel recommends high-quality colonoscopy and polypectomy every 1 to 2 years. At minimum, clearing of all polyps (≥ 2 mm) is recommended and can be repeated at short intervals if residual polyps are present; longer intervals between colonoscopies may be used depending on clinical judgment. An upper endoscopy (including complete visualization of the ampulla of Vater) at baseline may be considered,^{235,236} and repeated following duodenal surveillance guidelines as described above for patients with FAP (see FAP-C). Cap-assisted endoscopy may be adequate for visualization of the ampulla of Vater.¹⁹⁹ Surgical evaluation may be considered based on patient preference, or if polyps are unmanageable.

If the patient has a history of 20 to <100 adenomas, but the adenoma burden is dense and considered unmanageable by polypectomy, the panel recommends a surgical evaluation and consultation, if appropriate.

If the patient has a personal history of 10 to 19 adenomas, management should be based on clinical judgment. Frequency of surveillance may be modified based on factors such as age at which patient met cumulative adenoma threshold or total number of adenomas at most recent colonoscopy. For those with a family history of 10 to 19 adenomas in a first-degree relative with no P/LP variant identified in the relative or unaffected individual, surveillance may be done based on clinical judgment (ie, taking into account personal, cumulative history of adenomas, current polyp surveillance guidelines [see NCCN Guidelines for Colorectal Cancer Screening, available at www.NCCN.org], and family history).

In patients with a family history of ≥ 100 adenomas in a first-degree relative meeting either of the following criteria: family member tested with no pathogenic variant identified, or not tested and unaffected individual with family history has been tested with no pathogenic variant identified, the panel suggests consideration for high-quality colonoscopy screenings every 12 months beginning at age 10 to 15 years. The surveillance interval may be lengthened to every 2 years if no adenomas are found, with further lengthening based on clinical judgment. If ≥ 100 adenomas are detected, the panel recommends that patients be treated as described above for patients with a personal history of classical FAP. Patients with fewer than 100 adenomas found should be treated as described for patients with a personal history of AFAP (AFAP-1). In addition, the panel recommends genetic testing for family members affected with polyposis.

In patients with a family history of 20 to <100 adenomas in a first-degree relative meeting either of the following criteria: family member tested with no pathogenic variant identified, or not tested and unaffected individual



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with family history has been tested with no pathogenic variant identified, the panel suggests considering high-quality colonoscopy screenings every 2 years, beginning in the late teens. Initiation age and frequency of screening should be modified based on clinical judgment, taking into account the first-degree relative's history with respect to age and cumulative adenoma burden. If cumulative family history of 20 to <100 adenomas was reached later in life, then the screening initiation age should be modified accordingly. If adenomas are found, manage as described for patients with a personal history of AFAP (AFAP-1). As described above, the panel recommends genetic testing for family members affected with polyposis.

Peutz-Jeghers Syndrome (PJS-1)

PJS is an autosomal dominant condition mainly characterized by hamartomatous GI polyps.²³⁷ PJS polyps tend to be large and pedunculated, and have a characteristic histology showing broad bands of smooth muscle fibers (often in a tree-like configuration), chronic inflammation, edema, and fibrosis within the lamina propria and dilated glands.²³⁸ Medical treatment is often sought due to complications that arise from the polyps (eg, obstruction, bleeding). PJS polyps tend to be accompanied with freckling or hyperpigmentation on the lips, buccal mucosa, vulva, fingers, and toes, which appears early in life but tends to fade during adulthood.²³⁷ Besides being associated with an increased risk for CRC, PJS is also associated with increased risk for cancers of the breast, pancreas, and gallbladder.²³⁹⁻²⁴² A study of 33 patients with PJS in the United Kingdom showed that the risk of developing any cancer by age 65 years is 37% (95% CI, 21%–61%).²⁴³ In a study of 72 patients with PJS, 12.5% had a GI malignancy.²⁴² Risk of certain gynecologic cancers (ie, sex cord tumor with annular tubules, uterine cancer, minimal deviation adenocarcinoma of the uterine cervix) is also increased in patients with PJS.²⁴⁴⁻²⁴⁶ The majority of PJS cases occur due to P/LP variants in the *STK11* (*LKB1*) gene.^{247,248} However, other genetic P/LP variants may be

involved, as an estimated half of patients with PJS do not have detectable *STK11/LKB1* P/LP variants.²⁴³

A PJS clinical diagnosis is made when an individual has at least two of the following: two or more PJS-type polyps of the GI tract; mucocutaneous hyperpigmentation of the mouth, lips, nose, eyes, genitalia, or fingers; or family history of PJS. This is consistent with the statement from the U.S. Multi-Society Task Force on Colorectal Cancer regarding diagnosis and management of cancer risk in the GI hamartomatous polyposis syndromes.²⁴⁹ Genetic testing is recommended for any patient meeting the above criteria or with a family history of PJS.

Patients who meet clinical criteria for PJS or P/LP variant in *STK11* are recommended for referral to a specialized team and encouraged to participate in available clinical trials.

General treatment considerations should include small bowel polypectomy for all polyps causing symptoms and polyps >10 mm in size. Several studies have demonstrated the effectiveness of balloon-assisted enteroscopy in reducing polyp burden; therefore, it is recommended based upon available expertise.²⁵⁰⁻²⁵³ Due to the increased risk for iron deficiency anemia, bowel obstruction/intussusception from polyps, GI bleeding, and cancer, pediatric and adult populations should receive timely workup of any new signs or symptoms of GI disease.

Management of Peutz-Jeghers Syndrome (PJS-2/3)

As there are limited data regarding the efficacy of various screening modalities in PJS, panel recommendations were made while taking into consideration cancer risk in PJS and the known utility of the specific screening modalities. Individuals with PJS should receive a colonoscopy every 2 to 3 years, beginning at age 18 years.²⁵⁴ To screen for breast cancer, a mammogram and breast MRI should be done annually with a clinical breast exam conducted every 6 months, beginning at



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approximately age 30 years. For surveillance for gastric cancer, upper endoscopy should be done every 2 to 3 years beginning around age 18 years. Due to risks of bleeding and resultant iron deficiency anemia, children with PJS should receive an upper endoscopy and high-quality colonoscopy with polypectomy beginning between 8 to 10 years of age, with repeat intervals every 2 to 3 years if polyps are found. For small intestinal cancers, small bowel visualization should be performed with video capsule endoscopy or CT/MRI enterography every 2 to 3 years at age 18 years. In children, due to risk of bleeding with resultant iron deficiency anemia and risk of intussusception, small bowel visualization should be done at baseline at ages 8 to 10 years with follow-up interval based on findings but at least by age 18 years. Repeat imaging may then occur every 2 to 3 years (though this may be individualized). Screening for pediatric individuals should be initiated at an earlier age or repeated more frequently if signs or symptoms of GI obstruction or blood loss are present. To monitor for cancer of the pancreas, imaging of the pancreas with endoscopic ultrasound and/or MRI/magnetic resonance cholangiopancreatography (ideally performed at a center of expertise) should be considered annually beginning by age 30 to 35 years. Based on clinical judgment, an earlier age of initiation may be considered, such as 10 years younger than the earliest age of onset in the family. To monitor for gynecologic cancer, a pelvic exam and Pap smear should be done annually, beginning at around ages 18 to 20 years. Annual pelvic ultrasound may be considered. Endometrial biopsy may be done if abnormal bleeding is present, and total hysterectomy (including the uterus and cervix) may be considered when childbearing is complete. In pediatric individuals, an annual physical examination for observation of precocious puberty is recommended beginning at around age 8 years. For screening of the testes, an annual testicular exam and observation for feminizing changes should be done beginning at around age 10 years. For lung cancer, education should be provided about symptoms and smoking cessation, if necessary. No other specific recommendations have been

made for lung cancer. The panel's recommendations for screening of extracolonic cancers in patients with PJS reflect recommendations from the U.S. Multi-Society Task Force on Colorectal Cancer regarding diagnosis and management of cancer risk in the GI hamartomatous polyposis syndromes.²⁴⁹

Juvenile Polyposis Syndrome (JPS-1)

JPS is an autosomal dominant condition that is characterized by multiple hamartomatous polyps of the colon and rectum that usually manifests during childhood. Colonic polyps tend to be located in the rectosigmoid region,²⁵⁵⁻²⁵⁸ and 90% of patients present with bleeding and/or anemia.²⁵⁹ Histologically, polyps from patients with JPS are exophytic and eroded, and contain marked edema and inflammation within the lamina propria, cystic glands filled with thick mucin, and some degree of smooth muscle proliferation.²³⁸ Though patients with JPS are usually diagnosed during adolescence, it is a heterogeneous condition in that symptom intensity and age at diagnosis vary across patients.²⁶⁰ About 50% to 64% of JPS cases occur due to P/LP variants in the *BMPT1A* and *SMAD4* genes.^{67,254,258} If there is a known *SMAD4* P/LP variant in the family, genetic testing should be done within the first 6 months of life (or at time of diagnosis) due to risk of hereditary hemorrhagic telangiectasia (HHT).²⁶¹ In a retrospective review of 44 patients with JPS from a polyposis registry in the United Kingdom, 9% had telangiectasia or vascular abnormalities.²⁵⁸ Family history of juvenile polyposis is present in about half of patients with JPS.²⁵⁹ Though lifetime risk for CRC has been difficult to estimate, a review of a large JPS kindred (117 members) provided an estimate of a 50% risk of GI malignancy; 38% had colon cancer and 21% had upper GI cancers.²⁶² The large number of polyps often found in JPS increases the risk of malignancy.²⁵⁹ In a separate review of 218 patients with juvenile polyposis, GI malignancy developed in 17% of patients, and most malignancies were located in the distal colon and rectum, with one instance of gastric cancer and one of duodenal cancer.²⁵⁹ The mean age of cancer diagnosis in this



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sample was 33.5. Out of the 36 malignancies that developed, 4 were not resectable, 7 were poorly differentiated, and 4 were metastatic.

A clinical diagnosis is made if at least one of three criteria is met: 1) there are at least five juvenile polyps of the colon; 2) multiple juvenile polyps are found throughout the GI tract; and 3) at least one juvenile polyp has been found in an individual with a family history of JPS.^{67,263,264}

Management of Juvenile Polyposis Syndrome

Since JPS is rare, referral to a specialized team is recommended. Further, there are limited data regarding the efficacy of various screening modalities in JPS, so panel recommendations were made while taking into consideration cancer risk in JPS and the known utility of the specific screening modalities.

CRC screening via colonoscopy should begin around age 18 years, since the mean age of diagnosis for juvenile polyps is 18.6 years.^{259,265,266} High-quality colonoscopy should be repeated every 1 to 3 years for surveillance. Intervals should be based on polyp size, number, and pathology. In pediatric individuals with JPS, due to the risk of bleeding and anemia, high-quality colonoscopy with polypectomy is recommended beginning between 12 and 15 years of age, repeating every 2 to 3 years if polyps are found. If no polyps are found, screening may resume at age 18 years. Screening for stomach polyps and cancer should also begin around age 18 years. An upper endoscopy screening schedule should match that of the appropriate colonoscopy screening schedule for adult or pediatric individuals. *SMAD4* P/LP variant carriers often have more severe upper GI tract involvement, *BMPR1A* P/LP variant carriers typically have a less severe upper GI tract phenotype and may merit lengthened surveillance intervals in the absence of polyps.^{258,267} In families without an identified genetic P/LP variant, consider increasing colonoscopy/upper endoscopy surveillance intervals in at-risk individuals who have no polyps from 1 to 3

years beginning at age 18, to every 5 years.²⁶⁸ In patients with gastric polyps, management issues related to anemia from giant confluent polyps may occur. In severe cases, if anemia cannot be controlled endoscopically or prevents optimal surveillance, gastrectomy and/or colectomy should be considered. Both the panel and the U.S. Multi-Society Task Force on Colorectal Cancer²⁴⁹ have made no recommendations regarding surveillance of the small intestine, since small intestine cancer in patients with JPS is rare and/or undefined, though the American College of Gastroenterology recommends screening of the small intestine.⁶⁷

Serrated Polyposis Syndrome (SPS-1)

Serrated polyps include hyperplastic polyps, sessile serrated adenomas/polyp/lesions, and traditional serrated adenomas.²⁶⁹ SSPs are flat or slightly raised and usually occur on the right side, while traditional serrated adenomas are generally polypoid.²⁷⁰ Serrated polyps are more difficult to detect during colonoscopy and account for a disproportionate amount of interval cancers.²⁷¹ Serrated lesions such as SSPs may account for as many as a third of CRCs, and should be managed similarly to adenomas.²⁷¹

A clinical diagnosis of SPS (previously known as hyperplastic polyposis syndrome) is considered if at least one of the following criteria established by the WHO are met: 1) ≥5 serrated lesions/polyps proximal to the rectum, all being ≥5 mm in size, with ≥2 being ≥10 mm in size; or 2) >20 serrated lesions/polyps of any size distributed throughout the large bowel, with ≥5 being proximal to the rectum.²⁷² The polyp count is cumulative over multiple colonoscopies, and includes any histologic subtype of serrated lesion/polyp. There may be other clinical scenarios (eg, patient has between 5–10 serrated polyps or polyps are <1 cm) that increase CRC risk and may require additional evaluation per clinical judgment.²⁷³ Individuals with SPS have an increased risk for colon cancer.^{274,275} One retrospective study found that 35% of patients developed CRC during a



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mean follow-up period of 5.6 years (0.5–26.6 years).²⁷⁴ In a retrospective cohort study examining 52 individuals who met criteria for serrated polyposis, 82% had colorectal adenomas, 16% had a personal history of CRC, and 37% had a family history of CRC.²⁷⁶ Another retrospective analysis of 64 patients with serrated polyposis showed an SIR of 18.72 (95% CI, 6.87–40.74) for CRC.²⁷⁷ Several studies have also observed a link between patients previously treated for Hodgkin lymphoma and other childhood or young adult cancers and the development of SPS.^{233,278}

For the majority of patients with SPS, no causative gene is identifiable. A 2022 study including 173 patients diagnosed with SPS who underwent germline genetic testing with a hereditary CRC panel showed that a P/LP variant was detected in 9.6%.²⁷⁹ P/LP variants detected included *MUTYH* (n = 2), *SMAD4* (n = 1), *CHEK2* (n = 2), *POLD1* (n = 1), and *RNF43* (n = 1). Whole exome sequencing of 20 unrelated individuals with multiple sessile serrated adenomas (16 who fulfilled WHO criteria of SPS) led to the identification of nonsense variants in *RNF43* in two individuals.²⁸⁰ The *RNF43* variants were associated with multiple serrated polyps (OR, 3.0; 95% CI, 0.9–8.9; *P* = .04).²⁸⁰ One study identified a germline *RNF43* P/LP variant in 1 out of 4 families with serrated polyposis, but more research is needed to understand prevalence of *RNF43* P/LP variants in patients with SPS.²⁸¹ Notably, some patients with a diagnosis of *MYH*-associated polyposis may have a phenotype also meeting criteria for SPS.²⁸² As such, patients meeting criteria with SPS and some adenomas may benefit from genetic evaluation to exclude presence of biallelic *MYH* P/LP variants, though data on yield of genetic testing for patients with SPS are still emerging (see POLYP-1 in the algorithm).

Treatment of Serrated Polyposis (SPS-1)

High-quality colonoscopy with polypectomy is recommended for all polyps ≥5 mm, every 1 to 3 years depending on size and number of polyps, consistent with recommendations by the American College of

Gastroenterology.⁶⁷ It may not always be possible to remove all polyps. Colonoscopic surveillance with consideration of surgical referral is recommended if colonoscopic treatment and/or surveillance is inadequate or if high-grade dysplasia occurs.⁶⁷

Treatment of First-Degree Relatives (SPS-1)

The risk for CRC is elevated in first-degree relatives of individuals with SPS.²⁸³⁻²⁸⁵ One study that compared CRC incidence in 347 first-degree relatives of patients with SPS to that in the general population (Eindhoven Cancer Registry) found 27 cases compared to an expected 5 cases (rate ratio [RR], 5.4; 95% CI, 3.7–7.8; *P* < .001).²⁸³ In addition, this study found that four first-degree relatives satisfied the criteria for SPS (projected RR, 39; 95% CI, 13–121), suggesting a hereditary basis in some cases. Another multinational retrospective study found a similar increase in risk for CRC in both first- and second-degree relatives of patients with SPS.²⁸⁵ In addition, an increased risk for pancreatic cancer was observed. In a prospective study, 76% of first-degree relatives of patients with SPS were found to have SPS at colonoscopy.²⁸⁶

The panel considers it reasonable to screen first-degree relatives at the youngest age of onset of SPS diagnosis, 10 years earlier than earliest diagnosis with CRC in the family, or by age 40 years, whichever is earliest. Subsequent screening is per colonoscopic findings or every 5 years if no polyps are found.

Multi-Gene Testing (GENE-1)

NGS allows for the sequencing of multiple genes simultaneously. This is referred to as multi-gene testing. The introduction of multi-gene testing for hereditary forms of cancer has rapidly altered the clinical approach to testing at-risk patients and their families. Multi-gene testing simultaneously analyzes a set of genes that are associated with a specific family cancer phenotype or multiple phenotypes. Multi-gene testing may include



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syndrome-specific tests (ie, panels that test for only one syndrome like Lynch syndrome, adenomatous polyposis), cancer-specific tests (ie, panels that test for more than one gene associated with a specific type of cancer like CRC), and comprehensive cancer panels (ie, panels that test for more than one gene associated with multiple cancers or cancer syndromes).

Multi-gene testing can include only high-penetrance genes associated with a specific cancer, or both high- and moderate-penetrance genes. Comprehensive cancer risk panels, which include a large number of genes associated with a variety of cancer types, are also available.²⁸⁷ The decision to use multi-gene testing for patient care should be no different than the rationale for testing a single gene known to be associated with the development of a specific type of cancer. Testing is focused on identifying a P/LP variant known to be clinically actionable; that is, whether the treatment of an individual patient is altered based on the presence or absence of a P/LP variant. Multi-gene testing may be most useful when more than one gene can explain a patient's clinical and family history. In these cases where more than one P/LP variant could potentially influence a condition, multi-gene testing may be more efficient and/or cost-effective.²⁸⁷ Multi-gene testing with panels that include genes associated with Lynch syndrome, as well as other highly penetrant genes associated with CRC, may be cost-effective,²⁸⁸ and this approach may detect P/LP variants not found in single-gene testing.²⁸⁹ Multi-gene testing has comparable, or even higher, yield for Lynch syndrome, compared to tumor-based testing.^{18,19,21} Cost-effectiveness of this approach remains uncertain, as there are currently no recent studies in the United States evaluating current testing costs. Multi-gene testing may also be considered for those who tested negative (indeterminate) for one particular syndrome, but whose personal and family history is strongly suggestive of an inherited susceptibility.^{287,290} Multi-gene testing also provides the possibility of identifying pathogenic variants in multiple actionable genes

that would potentially impact screening and treatment for the individuals and family members who may otherwise be overlooked using cancer syndrome-specific panels.^{291,292}

A major dilemma regarding multi-gene testing is that there are limited data and a lack of clear guidelines regarding degree of cancer risk associated with some of the genes assessed in multi-gene testing, and how to communicate and manage risk for carriers of these genes.^{290,293,294} This issue is compounded by the low incidence rates of hereditary disease, leading to a difficulty in conducting adequately powered studies.²⁹³ Some multi-gene tests may include low- or moderate-penetrance genes, for which there are little available data regarding degree of cancer risk and guidelines for risk management.^{287,294-297} Further, it is possible that the risks associated with these genes may not be due entirely to that gene only, but may be influenced by gene/gene or gene/environment interactions. It is important to note that a germline multi-gene panel test result alone does not inform treatment decision-making for CRC. For example, presence of a P/LP variant in a Lynch-associated MMR gene, or in *POLE1* or *POLD1*, is not sufficient to initiate immune checkpoint inhibitor (ICI) therapy, since tumor-based MSI testing, IHC testing for expression of MMR proteins, or a measure of TMB-H are necessary for determination of eligibility of ICI treatment of CRC.

Multi-gene tests also increase the likelihood of detecting VUS,^{287,290,294,297-300} with likelihood rates ranging from 29% to 63% in patients with CRC.¹⁸⁻²¹ The proportion of patients with VUS may be higher among members of racial/ethnic minority groups, particularly with utilization of large multi-gene panels, potentially increasing burden of uncertain results on these populations.^{20,301-303} The considerable possibility of detecting a VUS adds to the complexity of counseling following multi-gene testing. However, as multi-gene testing is increasingly used, the frequency of a VUS being detected is expected to decrease. In addition, many VUS previously



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identified through hereditary cancer testing have been reclassified and downgraded to benign or likely benign categories.^{10,304} Nonetheless, clinical phenotypic correlation is warranted with further discussion with the testing laboratory if evidence supports potential pathogenicity of a VUS. Patient and provider guidelines for follow-up of VUS have been developed.^{305,306}

There are other issues to consider regarding multi-gene testing. First, commercially available tests may differ significantly on a number of factors, such as number of genes analyzed, turnaround time, and insurance coverage, among others. Tests requiring a longer turnaround time may not be suitable for patients who need rapid results. Results may not return in time to inform surgical decision-making. The specific laboratory and multi-gene test should be chosen carefully.²⁸⁷ Second, in some cases, NGS may miss some P/LP variants that would have been detected with traditional single-gene analysis.²⁸⁷ Third, P/LP variants identified for more than one gene add complexity that may lead to difficulty in making risk management recommendations.²⁹⁰ A management plan should only be developed for identified P/LP variants that are clinically actionable; care should be taken to ensure that overtreatment or over-screening does not occur due to findings for which clinical management is uncertain, or findings that are incorrectly interpreted due to lack of evidence.

Multi-gene testing is a new and rapidly growing field, but there is currently a lack of evidence regarding proper procedures and risk management strategies that should follow testing, especially when P/LP variants are found for moderate-penetrance genes and when a VUS is found. For this reason, the NCCN Panel recommends that multi-gene testing be ideally offered in the context of professional genetic expertise, with pre- and post-test counseling being offered. Panel recommendations are in agreement with recommendations by ASCO, which issued an updated statement

regarding genetic testing in 2015.³⁰⁷ Carriers of a genetic P/LP variant should be encouraged to participate in clinical trials or genetic registries.

Multi-gene testing is not recommended when: 1) there is an individual from a family with a known P/LP variant and there is no other reason for multi-gene testing; and 2) the patient's family history is strongly suggestive of a known hereditary syndrome. In these scenarios, syndrome-specific panels may be considered. For patients whose personal history is not suspicious for a polyposis syndrome and who were diagnosed with CRC ≥50 years with no known MMR deficiency in the tumor, multigene testing may be considered (category 2B). Otherwise, tumor and family history-based criteria for evaluation of Lynch syndrome is recommended for these patients.

Emerging evidence has identified additional genes that may be associated with increased risk for CRC, and the panel has evaluated the strength of the evidence based on published reports. Although research has demonstrated a potential risk for CRC associated with these P/LP variants, the value of including these genes for clinical testing (eg, as part of a multi-gene panel) remains uncertain. Nonetheless, the panel recognizes that many testing companies offer panels that include these genes, and that patients are being tested and may need guidance regarding subsequent screening and surveillance. Accordingly, while the panel recommends caution in recommending multi-gene testing, guidance on management of results is discussed below. At a minimum, a germline multigene panel should include the following genes associated with CRC risk: *APC*, *MUTYH*, *MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*, *BMPR1A*, *SMAD4*, *PTEN*, and *STK11*.

Evidence to support screening and surveillance is limited, but the panel has conditionally developed a framework of recommendations for genes commonly included in multi-gene panels, which are outlined after a brief discussion of relevant data.



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APC I1307K Pathogenic Variant

The adenomatous polyposis coli (*APC*) gene is a tumor-suppressor gene associated with CRC.³⁰⁸ There is well-established evidence that the I1307K polymorphism in the *APC* gene, which occurs in approximately 6% to 8% of individuals of Ashkenazi Jewish descent, predisposes carriers to CRC.³⁰⁹⁻³¹⁴ In an analysis of 3305 individuals from Israel who underwent colonoscopic examinations, 8% were identified as carriers of the I1307K polymorphism, and the overall adjusted OR for all colorectal neoplasia in carriers versus non-carriers was 1.51 (95% CI, 1.16–1.98).³⁰⁹ A subgroup analysis found that the prevalence of the I1307K polymorphism in individuals of Ashkenazi Jewish descent was 10.1%. The adjusted OR for all colorectal neoplasia in carriers of the variant versus non-carriers in average-risk individuals of Ashkenazi Jewish descent was 1.75 (95% CI, 1.26–2.45).³⁰⁹ A meta-analysis including 40 studies showed that compared to carriers of wild-type I1307K, individuals of Ashkenazi Jewish descent who carried the I1307K polymorphism had a significantly increased risk of colorectal neoplasia, with a pooled OR of 2.17 (95% CI, 1.64–2.86).³¹² Some studies have identified the I1307K polymorphism in the *APC* gene in individuals of non-Ashkenazi Jewish and Arabic descent, though the prevalence is higher in individuals of Ashkenazi Jewish descent.³¹⁵⁻³¹⁷ An analysis of 900 cases from a population-based case-controlled study in northern Israel found the I1307K polymorphism in the *APC* gene in 78 CRC cases, with a prevalence of 11.2%, 2.7%, or 3.1% among individuals of Ashkenazi Jewish, non-Ashkenazi Jewish, or Arabic descent, respectively.³¹⁶ Overall, however, there is insufficient evidence to determine whether risk for CRC associated with the *APC* I1307K polymorphism differs among individuals with versus without Ashkenazi Jewish descent, and the panel recognizes that some individuals may not be aware of Ashkenazi Jewish heritage.

For carriers of the *APC* I1307K pathogenic variant with CRC, the panel recommends high-quality colonoscopy surveillance based on the NCCN Guidelines for Colon Cancer and the NCCN Guidelines for Rectal Cancer (available at www.NCCN.org). For carriers of the *APC* I1307K pathogenic variant unaffected by CRC, the panel recommends colonoscopy surveillance every 5 years beginning at age 40 or 10 years prior to a first-degree relative's age at CRC diagnosis.

APC Promoter 1B

Gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS) is a rare familial gastric cancer syndrome and an autosomal trait caused by *APC* promoter 1B.³¹⁸ Criteria for GAPPS diagnosis are as follows: gastric polyps restricted to the body and fundus with no evidence of colorectal or duodenal polyposis; >100 polyps carpeting the proximal stomach of the proband or >30 polyps in a first-degree relative; predominantly FGPs, some with regions of dysplasia or a family member with dysplastic FGPs or gastric adenocarcinoma; autosomal dominant pattern of inheritance; and exclusion of other heritable gastric polyposis syndrome and use of proton pump inhibitors.³¹⁹ There is a 12% to 25% lifetime risk of developing gastric cancer in GAPPS.³²⁰ In individuals with GAPPS, gastric cancer risk management includes annual gastroscopy beginning at age 15 and consideration of risk-reducing total gastrectomy beginning no earlier than age 30.³²¹ Colonoscopy to exclude colon polyposis may be considered. There are insufficient data to define CRC risk associated with *APC* promoter 1B, so CRC risk management should be based on family history.

ATM P/LP Variants

P/LP variants in the *ATM* (ataxia-telangiectasia mutated) gene may increase risk for CRC (absolute lifetime risk 5%–10%),³²²⁻³²⁵ breast cancer (20%–40%),^{323,326-328} ovarian cancer (2%–3%),³²⁹⁻³³¹ and pancreatic cancer (5%–10%).³³²⁻³³⁸ There is currently insufficient evidence to provide specific CRC risk management recommendations for carriers of an *ATM* P/LP



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variant, so this should be based on family history. Given the association between *ATM* and development of the autosomal recessive condition ataxia telangiectasia, counseling for carriers of *ATM* P/LP variants should include a discussion of reproductive options. Information about risk management for breast, ovarian, and pancreatic cancers can be found in the NCCN Guidelines for Familial/High-Risk Assessment: Breast, Ovarian, and Pancreatic (available at www.NCCN.org).

***AXIN2* P/LP Variants**

P/LP variants in the Axin-related protein (*AXIN2*) gene are associated with polyposis and oligodontia (congenital absence of more than 6 teeth).³³⁹⁻³⁴³ In a study of a four-generation family from Finland, 11 family members had oligodontia and eight of them had either CRC or precancerous lesions, attributed to a nonsense P/LP variant in the *AXIN2* gene.³³⁹ Other studies support the association of *AXIN2* P/LP variants and oligodontia.^{341,343} A report described a family with an inherited *AXIN2* P/LP variant (c.1989G>A) segregating in an autosomal dominant pattern with oligodontia and other findings including colonic polyposis, gastric polyps, a mild ectodermal dysplasia phenotype, and early-onset colorectal and breast cancers.³⁴¹ A study of 23 families with FAP resulted in the identification of a novel *AXIN2* variant (c.1387C>T) in one family with attenuated polyposis.³⁴² Carriers of the variant had a variable number of polyps, but no oligodontia or ectodermal dysplasia.³⁴² For carriers of *AXIN2* P/LP variants, the panel recommends initiation of high-quality colonoscopic surveillance at ages 25 to 30 years and if no polyps are detected, to repeat colonoscopy every 2 to 3 years. If polyps are found, colonoscopic surveillance every 1 to 2 years is recommended, with consideration of surgical interventions if the polyp burden becomes unmanageable by colonoscopy.

***BLM* Heterozygotes**

Heterozygous P/LP variants in the DNA *RECQL*-helicase gene *BLM* may also be at increased risk for CRC (absolute lifetime risk 5%–10%).^{325,344,345} There is currently insufficient evidence to provide specific CRC risk management recommendations for carriers of a *BLM* P/LP heterozygote, so this should be based on family history. The autosomal recessive disorder Bloom syndrome is caused by mutations in a *BLM* P/LP variant; therefore, carriers of a heterozygous P/LP variant in *BLM* should be counseled accordingly.³⁴⁶

***CHEK2* P/LP Variants**

Germline P/LP variants in the cell cycle checkpoint kinase 2 (*CHEK2*) gene are associated with increased risk for breast cancer and CRC, though heterogeneity may exist based on type of *CHEK2* pathogenic variant.³⁴⁷⁻³⁵⁰ In a population-based study of 5953 patients with breast, prostate, and colon cancer (1934 patients had colon cancer), 533 were *CHEK2*-positive and 431 were affected relatives.³⁴⁷ After adjusting for P/LP variant type, the risk of colon cancer was higher among relatives of probands with colon cancer than among relatives of patients with prostate or breast cancer (HR, 4.2; 95% CI, 2.4–7.8; *P* = .0001).³⁴⁷ Significant associations between *CHEK2* P/LP variants and CRC risk have been identified in meta-analyses.^{349,350} A meta-analysis of seven studies, including 4029 cases and 13,844 controls based on search criteria, found a significant association between the *CHEK2* I157T variant and CRC risk.³⁴⁹ For carriers of *CHEK2* P/LP variants, the panel recommends high-quality colonoscopy surveillance based on the NCCN Guidelines for Colon Cancer and the NCCN Guidelines for Rectal Cancer (available at www.NCCN.org). For carriers of *CHEK2* P/LP variants unaffected by CRC, the panel recommends colonoscopy surveillance every 5 years beginning at age 40 or 10 years prior to a first-degree relative's age at CRC diagnosis. Some patients may elect for less aggressive screening based on shared decision-making. One model has



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suggested that earlier screening than the average-risk initiation may be justified for *CHEK2* 1100delC and I157T carriers based on reaching the same risk for CRC at an earlier age than observed among average-risk persons initiating screening at age 50 years.²³¹

GALNT12

P/LP variants in the protein-coding gene *GALNT12* are also believed to be associated with increased risk for CRC (absolute lifetime risk 5%–10%).^{351–354} There is currently insufficient evidence to provide specific CRC risk management recommendations for carriers of a *GALNT12* P/LP variant, so this should be based on family history.

***GREM1* Alterations**

Hereditary mixed polyposis syndrome (HMPS) is a rare, autosomal-dominant condition that occurs primarily in individuals of Ashkenazi Jewish descent and is characterized by multiple types of colorectal polyps, extracolonic tumors, onset of polyps in adolescence, and progression of some polyps to advanced adenomas.^{355,356} HMPS is due to a 40 kb duplication upstream of the gremlin 1 gene (*GREM1*), which increases ectopic *GREM1* expression in normal epithelium.³⁵⁵ Exome sequencing combined with linkage analyses and detection of copy-number variations identified a 16 kb duplication upstream of *GREM1* in a family of non-Ashkenazi Jewish descent with AFAP.³⁵⁷ For carriers of *GREM1* alterations, the panel recommends similar management strategies as described for carriers of *AXIN2* P/LP variants.

***MSH3* Biallelic Pathogenic Variants**

MutS homolog 3 (*MSH3*) is a DNA MMR gene implicated in tumorigenesis of colon cancer with MSI.³⁵⁸ Some data have linked biallelic *MSH3* germline P/LP variants as a recessive subtype of colorectal adenomatous polyposis.^{359,360} However, given available data, the panel agreed that the strength of evidence linking heterozygous P/LP *MSH3* carriers to increased CRC risk is not currently well established.

For carriers of two *MSH3* P/LP variants, the panel recommends similar management strategies as described for carriers of *AXIN2* P/LP variants.

***MLH3* Biallelic Pathogenic Variants**

Exome sequencing of 40 cases of FAP/AFAP from Finland and panel sequencing of 829 patients from Sweden who were referred to counseling for suspicion of a hereditary colon cancer syndrome showed that biallelic *MLH3* may be associated with polyposis, and also potentially breast and brain cancer.³⁶¹ For carriers of two *MLH3* P/LP variants, the panel recommends similar management strategies as described for carriers of *AXIN2* P/LP variants.

***NTHL1* Biallelic Pathogenic Variants**

The endonuclease III-like 1 (*NTHL1*) gene is involved in base excision repair and acts on oxidized pyrimidine residues.³⁶² There is some evidence that biallelic *NTHL1* P/LP variants are associated with increased risk of colorectal polyposis.^{363–365} Monoallelic *NTHL1* P/LP variants do not appear to be associated with increased risk of polyposis or CRC.³⁶⁶ In a pan-cancer sequencing study (N = 11,081), biallelic *NTHL1* P/LP variants were found in one patient who was diagnosed with early-onset breast cancer.³⁶⁰ Another study including 29 carriers of biallelic *NTHL1* P/LP variants showed that 60% of females were diagnosed with breast cancer.³⁶⁷ Whole-exome sequencing on 51 individuals from 48 families diagnosed with polyposis identified a homozygous germline nonsense P/LP variant in *NTHL1* in seven affected individuals from three unrelated families.³⁶³ Out of the three affected females, all were diagnosed with endometrial cancer.

For carriers of two *NTHL1* P/LP variants, the panel recommends similar CRC management strategies as described for carriers of *AXIN2* P/LP variants. Breast cancer risk management should include annual mammogram with consideration of tomosynthesis and consideration of breast MRI with contrast beginning at age 40. There is insufficient



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evidence to recommend risk-reducing mastectomy, though this may be considered depending on family history. Because endometrial cancer can often be detected early based on symptoms, individuals who have a uterus 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. Transvaginal ultrasound may be considered at the clinician's discretion, but is otherwise not recommended as a screening tool in patients who are premenopausal due to the wide range of endometrial stripe thickness throughout the normal menstrual cycle.

POLD1 and POLE P/LP Variants

DNA polymerases delta [δ]1 (*POLD1*) and epsilon [ϵ] (*POLE*) are involved in DNA proofreading and replication.³⁶⁸ P/LP variants in the *POLD1* and *POLE* genes may be associated with polyposis and increased risk for CRC.³⁶⁹⁻³⁷³ Using whole-genome sequencing in combination with linkage and association analysis, heterozygous *POLD1* and *POLE* germline variants were identified in multiple adenoma and/or CRC cases.³⁷¹ In an analysis of 858 Spanish patients with early-onset and/or familial CRC and/or colonic polyposis, one patient was found to have a *POLE* P/LP variant.³⁷² In an analysis of 266 unrelated probands with polyposis or who met the Amsterdam criteria, a *POLE* P/LP variant was found in 1.5% of patients.³⁷⁴ Limited evidence for increased risk of extracolonic cancers have been reported in carriers of *POLD1* and *POLE* P/LP variants; specifically, endometrial and brain cancers for *POLD1* P/LP variants, and endometrial cancer, ovarian cancer, brain cancers, pancreatic cancer, breast cancer, and melanoma for *POLE* P/LP variants.³⁷¹⁻³⁷⁹ Presently, for carriers of *POLD1* and *POLE* P/LP variants, the panel recommends similar management strategies as described for carriers of *AXIN2* P/LP variants. There is currently insufficient evidence to support risk management strategies for extracolonic cancers.

PTEN/PTEN Hamartoma Tumor Syndrome

The spectrum of disorders resulting from germline P/LP variants in *PTEN* are referred to as PHTS.³⁸⁰ In an analysis of 67 *PTEN* P/LP variant carriers undergoing colonoscopy, colorectal polyps were found in 92.5% of patients.³⁸¹ About half of the patients undergoing colonoscopy had hyperplastic polyps, and about 25% had polyps that were hamartomatous, ganglioneuromatous, or adenomatous.³⁸¹ Adenomatous or hyperplastic polyps were associated with development of CRC in this sample. Out of 39 carriers of a *PTEN* P/LP variant undergoing EGD, upper GI polyps were found in 67% of patients.³⁸¹ A systematic review of published case series (N = 102) regarding GI manifestations in Cowden syndrome/PHTS and component syndromes showed that 92.5% of these patients had polyps, with 64% having 50 or more.³⁸² Histologies were described as: hyperplastic (44%), adenomatous (40%), hamartomatous (38%), ganglioneuroma (33%), and inflammatory (24.5%). Early-onset (<50 years of age) CRC has been reported in 13% of patients with *PTEN* P/LP variant-associated Cowden syndrome/PHTS, suggesting that routine colonoscopy may be warranted in this population.³⁸¹ The lifetime risk for CRC has been estimated as 9% to 18%.³⁸³⁻³⁸⁵

Cowden syndrome is also associated with multiple hamartomatous and/or cancerous lesions in various organs and tissues, including the skin, mucous membranes, breast, thyroid, endometrium, and brain.^{386,387} The lifetime risk for breast cancer for women diagnosed with Cowden syndrome/PHTS has been estimated at 40% to 60%, with an average age of 38 to 50 years at diagnosis.^{386,388} Some studies have reported a higher cumulative lifetime risk for breast cancer (77%–85%) in individuals with Cowden syndrome/PHTS or *PTEN* P/LP variants.^{383,384,389} The lifetime risk for thyroid cancer (follicular or papillary) has been estimated at 3% to 10%.^{386,390} In addition, brain tumors are occasionally seen in individuals with Cowden syndrome/PHTS, although the risks for developing these conditions are not well defined.^{386,388} See the NCCN Guidelines for



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Familial/High-Risk Assessment: Breast, Ovarian, and Pancreatic (available at www.NCCN.org) for risk management recommendations for patients with Cowden syndrome/PHTS.

risk emerge, the panel expects that these surveillance recommendations will evolve.

TP53/Li-Fraumeni Syndrome

LFS is a rare hereditary cancer syndrome associated with germline *TP53* P/LP variants.³⁹¹ LFS is a highly penetrant cancer syndrome associated with a high lifetime risk for cancer. An analysis from the NCI Li-Fraumeni Syndrome Study (N = 286) showed a cumulative lifetime cancer incidence of nearly 100%.³⁹² LFS is characterized by a wide spectrum of neoplasms occurring at a young age. It is associated with soft tissue sarcomas, osteosarcomas (although Ewing sarcoma is less likely to be associated with LFS), premenopausal breast cancer, colon cancer, gastric cancer, adrenocortical carcinoma, bronchoalveolar carcinoma, and brain tumors.^{391,393-400} Sarcoma, breast cancer, adrenocortical tumors, and certain brain tumors have been referred to as the “core” cancers of LFS since they account for the majority of cancers observed in individuals with germline *TP53* P/LP variants, and, in one study, at least one of these cancers was found in one or more members of all families with a germline *TP53* P/LP variant.³⁹⁵ Hypodiploid acute lymphoblastic leukemia is also strongly associated with LFS.^{401,402} See the NCCN Guidelines for Familial/High-Risk Assessment: Breast, Ovarian, and Pancreatic (available at www.NCCN.org) for risk management recommendations for patients with LFS.

Emerging Data on Other P/LP Variants

There are emerging data that *RPS20* P/LP variants may be associated with increased risk for CRC, but more data are required to fully assess this association.^{365,403-406} *MBD4* and *FOCAD* are found on some genetic testing panels, but, at present, there is insufficient evidence for CRC risk management recommendations for carriers of these variants. Overall, as data regarding the clinical significance of genes associated with CRC



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update in
progress