National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric

Version 1.2024 — August 8, 2024

NCCN.org

NCCN recognizes the importance of clinical trials and encourages participation when applicable and available. Trials should be designed to maximize inclusiveness and broad representative enrollment.

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NCCN Guidelines Panel Disclosures

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Find an NCCN Member Institution: https://www.nccn.org/home/memberinstitutions.

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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Terminologies in all NCCN Guidelines are being actively modified to advance the goals of equity, inclusion, and representation.

Updates in Version 1.2024 of the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric from Version 2.2023 include:

New

- Endometrial cancer recommendations included throughout.
- Hereditary Diffuse Gastric Cancer section added (see HGAST-1).

Global Changes

- References updated throughout the Guideline.

Principles of Cancer Risk Assessment and Counseling

EVAL-A 1 of 9

- Pre-test counseling column revised as follows:
  - 4th bullet modified: ...in a gene that does not currently explain the patient's personal or family history *of cancer*.

EVAL-A 2 of 9

- 5th bullet modified to include APC/*MUTYH* only testing.
- 6th bullet added: MGPT increases the likelihood of finding P/LP variants in genes; however, some genes do not have clear clinical significance actionability or result in a change in medical management.
- Footnote a added: Single-gene testing or testing that is not otherwise sufficient to address the personal and/or family history.

EVAL-A 5 of 9

- Page for "Tumor Genomic Testing: Potential Implications for Germline Testing" extensively revised.

EVAL-A 6 of 9

- Page for "Post-Germline Test Counseling" extensively revised.

EVAL-A 7 of 9

- Page for positive results added.

EVAL-A 8 of 9

- Page for negative results added.

EVAL-B 1 of 4

- Family History of Cancer and Expanded Pedigree, bullet 2
  - Sub-bullet 3 revised: *Cancer site and* type ~~of cancer~~
  - Sub-bullet 8 revised: Suspected colon cancer/*polyposis, endometrial cancer or gastric cancer* syndromes...(eg, Muir-Torre syndrome, Turcot syndrome, ~~PJS, JPS~~)
  - Sub-bullet 9 revised: All other inherited conditions and birth defects *(eg, cleft lip and/or palate)*
  - Sub-bullet 11: revised from "Genetic test results in family members" to "Documentation of prior germline test results for proband or family"
- Detailed Medical and Surgical History
  - Bullet 5 revised as follows:
    - ◊ *For patients with prior polyps:*
      - *Pathology verification strongly encouraged*
      - Polyp~~s, including~~ number, *location* and ~~histology~~ *histologic type*
    - ◊ For patients with prior cancer, sub-bullets added:
      - *Pathology verification strongly encouraged*
      - *Hormone or oral contraceptive use*
      - *History of risk-reducing surgeries*
- Directed Examination for Related Manifestations (if suspicion for a CRC/*polyposis, endometrial, or gastric cancer* syndrome)
  - Bullet 3, sub-bullet 1 revised: Eye (*including retinal)* examination

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UPDATES

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Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric

HRS-1

- Page significantly revised and title updated to "General Criteria for Testing and Genetic Evaluation for Hereditary Syndromes Associated with Colorectal, Endometrial, and Gastric Cancer" and includes two sections, "Testing is clinically indicated in the following scenarios" and "Genetic evaluation is clinically indicated in the following scenarios"

HRS-2

- Footnote l revised: *Rare* PVs associated with adenomatous polyposis include...and biallelic PVs in *MLH3,* MSH3, *MBD4*, and NTHL1.

HRS-3

- Header revised to add ... Colorectal *or Endometrial* Cancer and "or EC" added as appropriate.
- No or not tested pathway: Added "*and*/or"; removed "Utilize tumor and family history based criteria for evaluation of LS and."
- Footnote o added: For multidisciplinary treatment planning, many patients will require tumor-based testing; see the NCCN Treatment Guidelines.

Rational, Pros, and Cons of Multigene Panel Testing

HRS-A 1 of 3

- Pros column, 1st bullet, 2nd sub-bullet, 3rd sentence added: MGPT identified a PV in 9.2%–14% of patients with EC.
- Cons column:
  - 1st bullet revised: ...a germline MGPT result alone does not inform CRC *or EC* treatment...
    - Sub-bullet modified: ...in an LS-associated MMR gene~~, or in POLE/D1~~ is not sufficient to initiate immune checkpoint blockade therapy *based on MSI-H status*. ~~because~~ Tumor-based microsatellite instability (MSI) testing *or* immunohistochemistry (IHC) testing for expression of the MMR proteins~~, or a measure of tumor mutational burden are the gold standards for~~ *are required for* determining eligibility for immune checkpoint blockade therapy *based on presence of dMMR*.
  - 5th bullet, sub-bullet 1, last sentence added: *In the United States, 66,200 women are diagnosed with EC annually, and there are >600,000 EC survivors.*
  - 5th bullet, sub-bullet 2, last sentence added: *Tumor Registry data from 2013–2019 indicate that genetic testing rates among CRC and EC patients are 5%–6%.*

HRS-A 2 of 3

- Test Selection section extensively revised.

Lynch Syndrome

LS-1

- Header added: Evaluation is indicated in the following scenarios
- 1st row added: Personal history of CRC or EC at any age
- 3rd row added: Personal history of a P/LP variant identified on tumor genomic testing that has clinical implications if also identified in the germline

LS-1A

- Footnote c added: Tumor mutational burden (TMB) can be used as surrogate to some degree for MSI, but there are causes of increased TMB other than dMMR.
- Footnote d added: This should prompt a careful evaluation of personal and family history of the individual to determine the yield of germline sequencing.
- Footnote e added: Mandelker D, et al. Ann Oncol 2019;30:1221-1231.

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LS-A 2 of 10
- Bullet 2 revised: ...germline genetic testing (*PV detection)* or tumor testing...
- Bullet 3 added: Absence of MMR protein expression in both cancer and normal tissue may be suggestive of CMMRD.
- Footnote a added: Patients with constitutional MLH1 epimutation are a rare exception. Consider referral to individual with expertise in genetic testing for consideration of constitutional MLH1 methylation testing in patients with early-onset CRC (≤55 y), no BRAF V600E PV, loss of MLH1 on IHC, and no germline MLH1 P/ LP variant or >1 tumor with MLH1 promoter hypermethylation at any age. Hitchins MP, et al. J Natl Compr Canc Netw 2023;21:743-752.

LS-A 3 of 10
- Adenomas
  - Bullet 1 first sentence revised: IHC *for MMR protein expression* can also be performed...
  - Bullet 1, last sentence revised: If PMS2 and MLH1 *protein expression are absent* ~~are missing~~, further tumor testing should be considered...

LS-A 7 of 10
- Additional Testing, last row revised: None, unless young age of onset ~~or significant family history;~~ then consider constitutional MLH1 epimutation testing...

Gene Specific Lynch Syndrome Cancer Risks And Surveillance/Prevention Strategies

MLH1 Lynch Syndrome: Surveillance/Prevention

LS-B 3 of 5 (Also for LS-C 3 of 5, LS-D 3 of 5, and LS-E 3 of 5)
- Footnote t, 2nd sentence revised from, "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" to "Daily low-dose (81 mg/d) aspirin use in pregnancy is considered safe and is associated with a low likelihood of serious maternal or fetal complications related to use."

LS-B 4 of 5
- Endometrial cancer surveillance
  - Bullet 3 revised by adding: For patients requiring a colorectal surgery such as for CRC resection, coordination with hysterectomy should be considered. Given the higher risks of early EC in MLH1, hysterectomy with bilateral salpingectomy may be considered starting at age 40 y with delayed bilateral oophorectomy starting at age 50 y.
- Ovarian cancer surveillance
  - Bullet 2 revised: *For patients requiring a colorectal surgery such as for CRC resection, coordination with hysterectomy and oophorectomy should be considered. Given the higher risks of EC and ovarian cancer in MLH1, hysterectomy with bilateral salpingectomy may be considered starting at age 40 y, with delayed bilateral oophorectomy starting at age 50 y. As premature menopause due to oophorectomy can cause detriments to bone health, cardiovascular health, and generalized quality of life, estrogen replacement therapy should be considered.* ~~Estrogen replacement after premenopausal oophorectomy may be considered.~~
  - Bullet 3 revised: *Data do not support routine ovarian cancer screening for LS. CA-125 and pelvic ultrasound are recommended for preoperative planning.* ~~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.~~
  - Bullet 4 added: Salpingectomy has been shown to reduce the risk of ovarian cancer in the general population and is an option for premenopausal patients with hereditary cancer risk who are not yet ready for oophorectomy. (Also for LS-C 4 of 5, LS-D 4 of 5 and LS-E 4 of 5)
  - Bullet 5 revised: Consider risk-reduction agents for endometrial and ovarian cancers, including *oral contraceptive pills and progestin intrauterine systems* ~~discussing risks and benefits~~ (see Discussion for details). (Also for LS-C 4 of 5, LS-D 4 of 5 and LS-E 4 of 5)
  - Bullet removed: 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.
- Gastric and small bowel cancer surveillance: (Also for LS-C 4 of 5, LS-D 4 of 5 and LS-E 4 of 5)
  - Bullet 1 revised: Upper GI surveillance with *high-quality* EGD...

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MSH2 and EPCAM Lynch Syndrome: Surveillance/Prevention

LS-C 4 of 5

- Endometrial cancer surveillance
  - Bullet 3 revised by adding: For patients requiring a colorectal surgery such as for CRC resection, coordination with hysterectomy should be considered. Given the higher risks of early EC and ovarian cancer in MSH2, hysterectomy with BSO may be considered starting at age 40 y. As premature menopause due to oophorectomy can cause detriments to bone health, cardiovascular health, and generalized quality of life, estrogen replacement therapy should be considered.
- Ovarian cancer surveillance
  - Bullet 2 revised: *For patients requiring a colorectal surgery such as for CRC resection, coordination with hysterectomy and oophorectomy should be considered. For patients requiring a colorectal surgery such as for CRC resection, coordination with hysterectomy should be considered. Given the higher risks of EC and ovarian cancer in MSH2, hysterectomy with BSO may be considered starting at age 40 y. As premature menopause due to oophorectomy can cause detriments to bone health, cardiovascular health, and generalized quality of life, estrogen replacement therapy should be considered.* ~~Estrogen replacement after premenopausal oophorectomy may be considered.~~
  - Footnote u added: Evidence for gynecologic cancer surveillance recommendations for individuals with a P/LP EPCAM variant are lacking.

MSH6 Lynch Syndrome: Surveillance/Prevention

LS-D 4 of 5

- Endometrial cancer surveillance
  - Bullet 3 revised by adding: For patients requiring a colorectal surgery such as for CRC resection, coordination with hysterectomy should be considered. Given the higher risks of EC in MSH6, hysterectomy with bilateral salpingectomy may be considered starting at age 40 y, with delayed bilateral oophorectomy starting at age 50 y
- Ovarian cancer surveillance
  - Bullet 2 revised: *For patients requiring a colorectal surgery such as for CRC resection, coordination with hysterectomy and oophorectomy should be considered. Given the higher risks of EC and ovarian cancer in MSH6, hysterectomy with BSO may be considered starting at age 40 y, with delayed bilateral oophorectomy starting at age 50 y. As premature menopause due to oophorectomy can cause detriments to bone health, cardiovascular health, and generalized quality of life, estrogen replacement therapy should be considered.* ~~Estrogen replacement after premenopausal oophorectomy may be considered.~~

PMS2 Lynch Syndrome: Surveillance/Prevention

LS-E 4 of 5

- Endometrial cancer surveillance
  - Bullet 4 revised by adding: Given the higher risks of EC in PMS2, hysterectomy with BSO may be considered starting at age 50 y.
- Ovarian cancer surveillance
  - Bullet 3 revised: *Hysterectomy with BSO may be considered starting at age 50 y. As premature menopause due to oophorectomy can cause detriments to bone health, cardiovascular health, and generalized quality of life, estrogen replacement therapy should be considered.* ~~Estrogen replacement after premenopausal oophorectomy may be considered.~~

LS-F

- Adenomas
  - Bullet revised: Complete endoscopic polypectomy with follow-up colonoscopy every 1–2 y *for MSH2/MLH1 and every 1–3 y for PMS2/MSH6.*

LS-G

- New table added: Surgical Options for Treating the Colon in Patients with LS

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Adenomatous Polyposis

POLYP-1

- Testing Criteria
  - Sub-bullets moved from Consider testing to Recommend testing: Family history of polyposis and family unwilling/unable to have testing and Cribriform-morular variant of papillary thyroid cancer
  - Bullet 3 added: In individuals with any cancer with a P/LP APC variant identified on tumor-only genomic testing, germline testing should be considered for:
    - ◊ Those meeting one or more of the other adenomatous testing criterion above after reevaluation of personal and family history
    - ◊ Those diagnosed age <30 y with any cancer.
- Results
  - PV not identified, branch added: *If individual has <10 adenomas*

POLYP-1A

- Footnotes
  - Footnote a added: Also known as retinal pigment epithelium (RPE) hamartomas associated with FAP (RPEH-FAP).
  - Footnote c added: This should prompt a careful evaluation of personal and family history of the individual to determine the yield of germline sequencing. Somatic APC P/LP variants are common in many tumor types in absence of a germline P/LP variant.
  - Footnote d added: Mandelker D, et al. Ann Oncol 2019;30:1221-1231.

APC-Associated Polyposis

FAP/AFAP-1

- Classical FAP
  - Bullet 5 revised: ...hepatoblastoma, ~~periampullary cancer,~~ gastric cancer, duodenal/*periampullary* cancer
- Attenuated FAP
  - Bullet 5 revised: Upper GI findings, thyroid and duodenal/*periampullary* cancer risks are similar to classical FAP
- Footnote b revised: ~~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.~~ *MGPT is recommended to differentiate APC from MAP and other adenomatous polyposis syndromes and CPUE. See HRS-A for CRC/polyposis gene list and GENE-1 for surveillance recommendations.*
- Footnote c revised: Individuals with ~~>~~ ≥*100* polyps...

Familial Adenomatous Polyposis

FAP-2

- Surveillance
  - APC negative pathway revised: NCCN Guidelines for Colorectal Cancer Screening~~- Average risk~~ (Also for AFAP-2)
  - Not tested, bullet 2: If genetic testing not completed, high-quality colonoscopy ~~(preferred) or flexible sigmoidoscopy~~ every 12 mo beginning at age 10–15 y.

FAP-A 1 of 3

- Sites updated:
  - Colo*rectal* cancer (without colectomy)
  - ~~Colon~~ *Rectal/Pouch* cancer (post-colectomy)
- Footnote a added: There is one report showing increased pancreas cancer risk, but this study had significant limitations (Karstensen J, et al. Gastro 2023;165:573-581; see Discussion); whether pancreatic cancer risk is increased remains uncertain.

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FAP-B
- Gastric cancer: Recommendations removed and bullet added: See FAP-D for follow-up of gastric findings.
- CNS cancer: *There is currently no support for routine surveillance imaging. However,* 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: ~~If personal history of symptomatic desmoids, consider imaging with abdominal CT or MRI with and without contrast no less frequently than annually.~~ Suggestive abdominal symptoms should prompt ~~immediate~~ abdominal imaging. *Patients should be educated regarding signs and symptoms of intra-abdominal desmoids and the importance of prompt reporting of abdominal symptoms to their physicians.* See NCCN Guidelines for Soft Tissue Sarcoma.
- 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 *or CT/MRI enterography*), especially if advanced duodenal polyposis.

FAP-C 1 of 2
- Spigelman Score 9-12, surveillance revised: Expert surveillance every 3–6 mo *and surgical consultation for consideration of duodenectomy*.

FAP-D
- New section added: Gastric Findings and Management.

FAP-E
- Surgical Options for Treating the Colon and Rectum: Proctocolectomy with end ileostomy (PC/EI), Possible advantages, bullet 1 revised: Removes ~~risk of CRC~~ *rectal cancer risk*

MUTYH-Associated Polyposis

MAP-3
- Surveillance, No MUTYH PVs found pathway revised: NCCN Guidelines for Colorectal Cancer Screening~~- Average risk~~
- Footnote removed: There are no specific data available to determine screening recommendations for a patient with heterozygous MUTYH PV and a second-degree relative affected with CRC.

Colonic Adenomatous Polyposis of Unknown Etiology

CPUE-1
- Management/Surveillance, "including complete visualization of the ampulla of Vater" added to baseline upper endoscopy.
- Footnote b, 2nd sentence revised: and biallelic PVs in NTHL1, MUTYH, *MBD4, MLH3*, and MSH3 and 3rd sentence added. *See HRS-A for CRC/polyposis gene list and GENE-1 for surveillance recommendations*. (Also for CPUE-2)
- Footnote d added: Cap-assisted endoscopy may be adequate for visualization of the ampulla (Kallenberg F, et al. Endoscopy 2017;49:181-185).

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Peutz-Jeghers Syndrome

PJS-1

- Indications for Genetic Testing for PJS
  - Bullet 2 added: STK11 P/LP variant detected by tumor genomic testing on any tumor type in the absence of germline analysis.
  - Bullet 2, sub-bullet added: This should prompt a careful evaluation of personal and family history of the individual to determine the yield of germline sequencing. Somatic STK11 P/LP variants are common in many tumor types in absence of germline P/LP variant.

PJS-3

- Breast (female), Screening Procedure and Interval
  - Bullet 2 revised: Clinical breast exam every 6–*12* mo

Juvenile Polyposis Syndrome

JPS-1

- Indications for Genetic Testing for PJS
  - Bullet 2 added: BMPR1A or SMAD4 P/LP variants detected by tumor genomic testing on any tumor type in the absence of germline analysis.
  - Bullet 2, sub-bullet added: This should prompt a careful evaluation of personal and family history of the individual to determine the yield of germline sequencing.

JPS-2

- Footnote e revised: *For consensus guidelines for the management and prevention of HHT-related symptoms and complications*, see Faughnan M, et al. Ann Intern Med 2020;173:989-1001.

JPS-3

- Stomach
  - Patients column: separated SMAD4 and BMPR1A.
  - % Lifetime risk of BMPR1A changed to "Rare"
- Footnote f added: In a meta-analysis of 204 patients (Singh A, et al. Gastrointest Endosc 2023;97:407-414) with BMPR1A, only one patient with gastric cancer was identified.

Multigene Testing

GENE-3

- APC I1307K variant
  - Comments revised: In the Ashkenazi Jewish population in the United States, the APC c.3920T>A (p.I1307K) variant is reported in ~~6%–7%~~ 1*1.5% of those diagnosed with CRC and 7.2% of those not diagnosed with CRC*. (~~Abrahamson J, et al. Cancer Res 1998;58:2919-2922~~ *Valle L, et al. J Med Genet 2023;60:1035-1043*).

GENE-4

- APC promoter 1B/Gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS)
  - Colon Cancer, Management revised: *Baseline* colonoscopy at time of ~~diagnosis~~ *first EGD* to exclude colon polyposis, if not previously done.
  - Other Cancers, Management, bullet 2 revised: Consider risk-reducing total gastrectomy from third decade, annual ~~gastroscopy~~ *EGD* from age 15.

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UPDATES

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Multigene Testing

GENE-5

- BMPR1A
  - Other Cancers, Absolute Risk updated: Stomach cancer - ~~up to 21%~~ *see comment*
  - Comments, 2nd sentence added: In a meta-analysis of 204 patients (Singh A, et al. Gastrointest Endosc 2023;97:407-414.e1) with BMPR1A, only one patient with gastric cancer was identified. For management, see JPS-3.

GENE-6

- CHEK2
  - Colon Cancer
    - ◊ Estimated Absolute Risk revised from "5%–10%" to "No increased risk"
    - ◊ Management revised from "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'CRC diagnosis when indicated." to "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 guidelines: NCCN Guidelines for Colon Cancer, NCCN Guidelines for Rectal Cancer, and NCCN Guidelines for Colorectal Cancer Screening."
    - ◊ Strength of Evidence revised from "Limited" to "Strong"
    - ◊ Comment removed: Heterogeneity in CRC risk may exist based on type of pathogenic CHEK2 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 decisionmaking. One model has 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 persons at average risk initiating screening at age 50 (Katona B, et al. Genet Med 2018;20:1324-1327).

GENE-9

- MUTYH/monoallelic pathogenic variant/heterozygote (carrier)
  - Colon Cancer, Management, bullet 2 revised: For probands with a personal or first-degree family history of CRC or polyps (*not explained by MAP):* increased screening as per the relevant guideline...

GENE-10

- NTHL1 biallelic pathogenic variants
  - Comments, added: Beck SH, et al. Fam Cancer 2022;21:453-462.

GENE-11

- POLD1/Polymerase proofreading-associated polyposis and POLE/Polymerase proofreading-associated polyposis
  - Colon Cancer
    - ◊ Management revised: Begin high-quality colonoscopy at age 25–30 y *or 2–5 y prior to the earliest CRC in the family if it is diagnosed before age 25 y and* repeat every 2–3 y if negative.
    - ◊ Strength of Evidence revised from "Limited" to "Strong"
  - Other cancers revised from "Unknown or insufficient evidence" to "See comment"
  - Comments extensively revised

GENE-12

- PTEN/PTEN hamartoma tumor syndrome
  - Estimated Absolute Risk revised from 11%–20% to 9%–20%.

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NCCN Guidelines Version 1.2024 Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric

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Discussion

Updates in Version 1.2024 of the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric from Version 2.2023 include:

Multigene Testing

GENE-13

- RPS20
  - Colon cancer, Management revised from "Evidence insufficient to provide specialized CRC screening recommendations; manage based on family history" to "Colonoscopy every 5 y beginning at age 20. If the patient had a hematopoietic cell transplant prior to age 20, colonoscopy is recommended to begin one year after transplant."
  - Comments extensively revised.

GENE-15

- Footnote k revised by adding: Breen KE, Katona BW, Catchings A, et al. An updated counseling framework for moderate-penetrance colorectal cancer susceptibility genes. Genet Med 2022;24:2587-2590.
- Footnote removed and added to HRS-A: 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.
- Footnote removed: 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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Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric

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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

- **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 (EVAL-B)**
- **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 [P/LP]), negative, uncertain, or mosaic results and unexpected findings such as a pathogenic variant (PV) in a gene that does not currently explain the patient's personal or family history of cancer**
- **Discussing possible management options if a P/LP 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])**

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

References Continued

PRINCIPLES OF CANCER RISK ASSESSMENT AND COUNSELING

Genetic Testing Considerations

- **Choice of/discussion of multigene testing options**
- **The probability of P/LP variant detection will vary based on family structure. Individuals with unknown or limited family history/structure may have an underestimated probability of familial P/LP 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 (EVAL-A 4 of 9).**
- **Likely PVs are typically treated as PVs.**
- **Patients who had limited genetic testing[a] in the past (eg, *MLH1* or *MSH2* or *APC/MUTYH* only testing) may benefit from additional genetic testing using a larger multigene panel test (MGPT).**
- **MGPT increases the likelihood of finding P/LP variants in genes; however, some genes do not have clear clinical significance actionability or result in a change in medical management.**
- **In children <18 y, genetic testing is generally not recommended unless results would impact medical management, such as initiation of early colonoscopy surveillance.[9] Clear exceptions include when familial adenomatous polyposis (FAP), juvenile polyposis syndrome (JPS), Peutz-Jeghers syndrome (PJS), or constitutional mismatch repair 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.**

References
Continued

[a] Single-gene testing or testing that is not otherwise sufficient to address the personal and/or family history.

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

PRINCIPLES OF CANCER RISK ASSESSMENT AND COUNSELING

Genetic Testing Approach

- If more than one family member is affected with a cancer highly associated with a particular inherited cancer susceptibility syndrome, consider testing first a family member with the 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 a 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 Lynch syndrome [LS] PVs).
- 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 P/LP 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 VUS 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 P/LP 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 P/LP variants in the same gene if it would inform reproductive decision-making and/or risk assessment and management.[10]

References Continued

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

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 P/LP 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.**

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

References Continued

PRINCIPLES OF CANCER RISK ASSESSMENT AND COUNSELING

Tumor Genomic Testing: Potential Implications for Germline Testing

- Testing may provide information suggesting a potential germline finding. P/LP variants reported in the tumor may be of somatic or germline origin.
  - Because tumor genomic testing is designed to address treatment actionability, not germline status, a variant that may be considered as P/LP in the germline may not be reported at all, or reported as normal in the tumor if it lacks clinical implications.
  - The filtering of raw sequencing data may differ between tumor and germline testing labs so that variants reported out with one analysis may not be reported with the other.
  - Somatic P/LP variants seen in tumor specimens are common in some genes with germline implications (eg, ***TP53, STK11, PTEN, APC***) and may not indicate the need for germline testing unless the clinical/family history is consistent with a P/LP variant in the germline.
  - Tumor-only sequencing may not detect about 10% of clinically actionable P/LP germline variants (eg, deletion, duplication, and splicing variants).[13]
  - The fraction of PVs in cancer susceptibility genes identified through tumor-only testing, and also present in the germline, is highly variable between genes.[14,15]
- Regardless of findings in the tumor, when germline testing is clinically indicated, it should be performed in a CLIA-approved lab with established experience in germline testing because:
  - The germline panel performed by some labs offering paired tumor and germline testing may have incomplete coverage and analyze only a subset of those genes of interest to the clinician.
  - The sensitivity of most tumor genomic testing is lower (particularly for intermediate-sized deletions and duplications) than germline testing.
  - Similarly, circulating tumor DNA (ctDNA) has the potential to identify both somatic and germline variants with germline treatment implications. Some ctDNA assays, but not all, will alert providers that the particular gene variant identified has a high enough variant allele frequency (VAF) that it is suspicious for germline origin. However, most commercially available assays specializing in somatic ctDNA detection are neither intended nor validated for the reporting or interpretation of germline variants. Thus, variants detected by ctDNA that are suspected to be present in the germline should be evaluated via a CLIA-approved assay specializing in detection and interpretation of germline variants.
  - ctDNA, detected by mutation profile, copy number changes, altered methylation patterns, fragmentation, size alterations, or other approaches, has application for disease monitoring as well as early detection. For individuals at increased hereditary risk for cancer, use of pre-symptomatic ctDNA cancer detection assays should only be offered based on specific FDA-approved indications, or in the setting of prospective clinical trials, because the sensitivity, false-positive rates, and positive predictive value of ctDNA tests for early-stage disease, which are needed to derive clinical utility and determine clinical validity, are not fully defined.[16-19] ctDNA tests intended for cancer detection have not been validated in patients with hereditary cancer syndromes.

References Continued

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PRINCIPLES OF CANCER RISK ASSESSMENT AND COUNSELING

Post-Test Counseling (after germline testing)

- **When the testing provider/facility does not include pre-test counseling or have all of the resources or expertise for facilitating follow-up testing, management, or family testing, referral to a genetics provider is recommended. In particular, referral to a genetics provider is recommended for the following test results:**
  - **P/LP variant identified**
  - **Negative results but tumor profiling, personal history, or family history remain suggestive of inherited condition**
  - **Any VUS result that warrants further evaluation or for which a patient or provider considers using to guide management**
  - **A mosaic/possibly mosaic result or clonal hematopoiesis**
  - **Discrepant interpretation of variants, including discordant results across laboratories**
  - **Interpretation of polygenic risk scores (PRS), if they are being considered for use in clinical management, recognizing that the clinical value of PRS has not yet been established**
  - **Interpretation of P/LP variants for patients tested through direct-to-consumer (DTC) or consumer-initiated models**

- **Post-test counseling includes the following elements:**
  - **Discussion of results and associated medical risks**
  - **Interpretation of results in context of personal and family history of cancer**
  - **Discussion of recommended medical management options including discussion of therapeutic implications by a qualified health care provider if positive**
  - **Discussion of the importance of notifying family members and offering materials/resources for informing and testing family members who also have increased risk**
  - **Discussion of available resources such as high-risk clinics, disease-specific support groups, and research studies**

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

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PRINCIPLES OF CANCER RISK ASSESSMENT AND COUNSELING

- **Positive results:**
  - Some medical centers include services that are specialized in cancer screening, risk reduction, and treatment for individuals with a P/LP variant associated with increased risk for cancer. Where available, consider referring patients to these services, either on a consultative basis or for coordination of ongoing care.
  - In patients being treated for cancer, identification of a P/LP variant may affect options and recommendations for treatment of their disease. A P/LP variant in certain genes is also a component of eligibility for some clinical trials. Specific circumstances are addressed in the NCCN Treatment Guidelines.
  - Many patients who have been diagnosed with cancer and have a P/LP variant are at increased risk for additional primary cancers in the future. Management of those risks may be appropriate after treatment of the current cancer or may be combined with treatment for a current cancer.
  - Multiple sources, including these NCCN Guidelines, provide estimated lifetime risks of cancer associated with specific P/LP variants. A discussion of risk should include:
    - ◊ Presenting risk estimates as a range rather than a single number (ie, 30%–40%)
    - ◊ Presenting absolute risk and minimizing use of relative risk terminology (ie, odds ratios or hazard ratios)
    - ◊ Acknowledging that risk estimates always have a margin of error[b]
    - ◊ Identifying that these risk estimates change over time (ie, older patients will have lower remaining lifetime risk)
  - Individuals with a P/LP variant should be informed of the importance of this information for their blood relatives. Knowledge of the P/LP variant may affect risk assessment and recommendations for genetic testing, early detection, and/or cancer risk reduction in those relatives. Where relationships allow, individuals should be encouraged to communicate this information to their blood relatives. A medical provider can assist by providing patients with information for relatives written in simple language and a copy of their genetic test results.
  - Over time, patients with a P/LP variant benefit from re-consultation with a medical provider who is familiar with inherited risk for cancer. This re-consultation is important for:
    - ◊ Increasing adherence with screening guidelines, which is known to decrease over time
    - ◊ Re-evaluating personal choices about risk-reducing surgeries, based on changing life stage and circumstances
    - ◊ Ensuring patients are following up-to-date guidelines
    - ◊ Discussing additional genetic testing options
    - ◊ Reviewing improved risk models as appropriate
  - The frequency of follow-up depends on many factors, such as age, reproductive planning, comorbidities, risk-reducing surgeries, and other risk factors.
  - For patients of reproductive age, advise about options for prenatal diagnosis and assisted reproduction, including pre-implantation genetic testing and donor gametes. Discussion should include known risks, limitations, and benefits of these technologies. See Discussion for details.
  - Biallelic P/LP variants in some genes, included on gene panels, may be associated with rare autosomal recessive conditions, such as Fanconi anemia (FA) or CMMRD. Thus, for these genes, consideration should be given to carrier testing the partner for P/LP variants in the same gene if it would inform reproductive decision-making and/or risk assessment and management.[f0]
  - Some P/LP variants found in blood, saliva, or buccal samples, most notably in *TP53*, warrant consideration of testing of non-blood samples to try to distinguish between germline, constitutional mosaicism, and somatic findings.

[b] Risk estimates are influenced by the numbers of individuals with these mutations: the more individuals, the more precise the estimates are (ie, the confidence interval is narrower).

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PRINCIPLES OF CANCER RISK ASSESSMENT AND COUNSELING

- **Negative results:**
  - These results reduce concern for cancer risk. However, the individual may still have increased cancer risk based on personal and family history. Also, other family members may have a P/LP variant that the tested individual did not inherit.
  - Although negative results of genetic testing are generally reassuring, other reasons that a patient can test negative include:
    1) A gene P/LP variant may exist in the gene that was not recognized due to limitations in technology.
    2) P/LP variants exist in genes that were not evaluated by this testing.
    3) Family members may harbor a P/LP variant that the patient may not have inherited.
  - Other family members may be appropriate candidates for testing, both to assess their own cancer risk as well as to clarify the overall contribution of known P/LP variants to the family history. If another family member tests positive for a P/LP variant, this might lower concern for the individuals who tested negative. The determination of a "true negative" result depends on the specific family history of cancer, the specific P/LP variant found, and the relationship to the family member(s) who tested positive.
  - When an individual has tested negative, it may still be appropriate to consider increased screening and risk reduction measures for cancer based on family history. See appropriate screening based on family history in the guidelines as outlined in Summary of Genes and/or Syndromes Included/Mentioned in Other NCCN Guidelines in NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic. Some medical centers include specialized high-risk clinics to offer this type of family history-based screening.
  - Over time an individual who tested negative may be a candidate for additional genetic testing due to additional family history, as new genes are identified to be associated with cancer risk or technology advances.
- **Variants of uncertain significance (VUS)**
  - VUS are alterations in the genetic code for which the impact on protein function is uncertain.
  - VUS are common, particularly with the use of large multigene panels. The more genes that are included on a genetic testing panel, the more likely a VUS will be identified.[20]
  - VUS are more commonly found during genetic testing of racial and ethnic minorities compared with non-Hispanic white individuals.[20]
  - In VUS that are reclassified, approximately 80%–90% are reclassified as likely benign or benign and 10%–20% as P/LP.[21,22]
  - There are discordant variant interpretations across labs,[23] requiring careful counseling and skilled interpretation. Resources are available to review the available data supporting pathogenic consequences of specific variants and identify discrepant results (eg, https://www.ncbi.nlm.nih.gov/clinvar; https://brcaexchange.org/about/app; cangene-canvaruk.org/canvig-uk).
  - VUS should not be used to alter medical management. In the event additional discussion is needed for classification and management, additional genetic expertise is recommended. Screening and risk reduction strategies should be recommended on the basis of personal and family history.
  - RNA studies (when appropriate) may be a consideration to further define functional impact of variants. Testing family members for a VUS should not be done for clinical purposes, unless there are data to support discrepancy in interpretation of results. Consider a referral to research studies that aim to define the functional impact of variants such as variant reclassification programs through clinical labs or registries.

References

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

PRINCIPLES OF CANCER RISK ASSESSMENT AND COUNSELING – REFERENCES

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

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PRINCIPLES OF CANCER RISK ASSESSMENT AND COUNSELING

Obtaining a Comprehensive Assessment for Hereditary Colorectal/Endometrial/Gastric Cancers[a]

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
  - Cancer site and type (note multiple primaries)
  - Ethnicity/country of origin
  - Consanguinity
  - Concerns regarding non-paternity
  - Birth resulting from sperm or egg donor
  - Suspected colon cancer/polyposis, endometrial cancer (EC), or gastric cancer syndromes and additional syndrome-specific features (eg, Muir-Torre syndrome, Turcot syndrome)[b]
  - All other inherited conditions and birth defects (eg, cleft lip and/or palate)
  - History of allogeneic (related or unrelated donor) bone marrow transplant
  - Documentation of prior germline test results for proband or family

Common Pedigree Symbols (EVAL-B 2 of 4) and
Pedigree: First-, Second-, and Third-Degree Relatives of Proband (EVAL-B 4 of 4)

Detailed Medical and Surgical History

- Sex assigned at birth
- Inflammatory bowel disease
- Inherited polyposis and cancer syndromes
- Pathology verification strongly encouraged
- For patients with prior polyps:
  - Pathology verification strongly encouraged
  - Polyp number, location and histologic type
- For patients with prior cancer:
  - Pathology verification strongly encouraged
  - Cancer site and type
  - Age at diagnosis
  - Treatment history
  - Results of any tumor-based genetic or molecular testing
  - Hormone or oral contraceptive use
  - History of risk-reducing surgeries

Directed Examination for Related Manifestations (if suspicion for a CRC/polyposis, endometrial, or gastric cancer syndrome)

- Colonoscopy
- Esophagogastroduodenoscopy (EGD)
- Indicated only if suspicion of a specific syndrome
  - Eye (including retinal) 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 [AFAB] and ≥60 cm in adult patients assigned male at birth [AMAB])

[a] 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 PV arising in the patient (de novo PV); variable penetrance of a PV; autosomal recessive inheritance of risk; and mosaicism.

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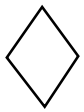
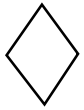
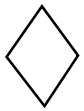
Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF CANCER RISK ASSESSMENT AND COUNSELING

COMMON PEDIGREE SYMBOLS[c]

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 (EVAL-B 4 of 4)

[c] 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.

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

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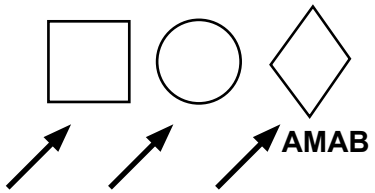
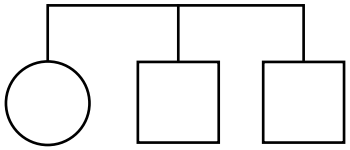
PRINCIPLES OF CANCER RISK ASSESSMENT AND COUNSELING

COMMON PEDIGREE SYMBOLS[c]

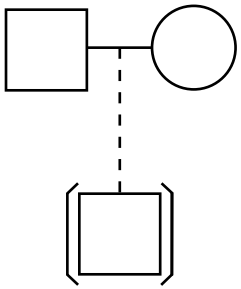


Consultand/ Proband (initiating genetic workup, shade if affected)

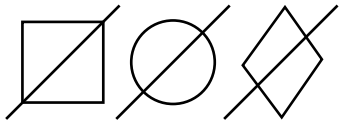
Relationship line



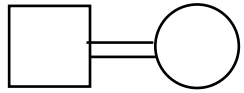
Sibship line



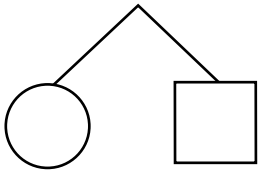
Adopted into a family



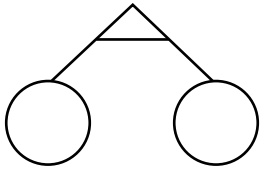
Deceased



Consanguinity



Dizygotic twins



Monozygotic twins

AMAB = assigned male at birth

Pedigree: First-, Second-, and Third-Degree Relatives of Proband (EVAL-B 4 of 4)

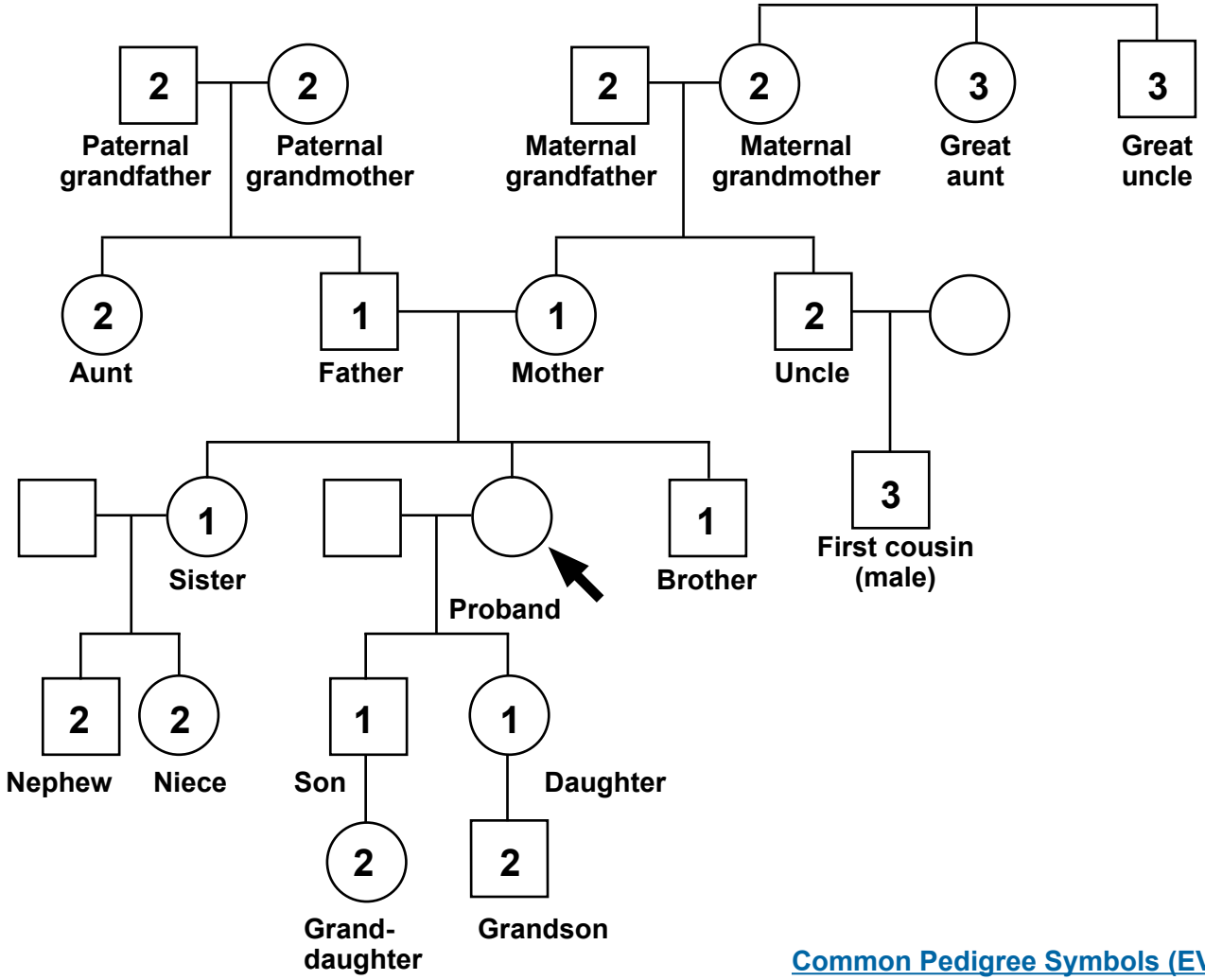
[c] Bennett R, French K, Resta R, Austin J. Practice resource-focused revision: Standardized pedigree nomenclature update centered on sex and gender inclusivity: A practice resource of the National Society of Genetic Counselors. J Genet Couns 2022;31:1238-1248.

Continued

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

PRINCIPLES OF CANCER RISK ASSESSMENT AND COUNSELING

PEDIGREE: FIRST-, SECOND-, AND THIRD-DEGREE RELATIVES OF PROBAND[d]



Common Pedigree Symbols (EVAL-B 2 of 4)

[d] 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.

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

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2024 Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric

NCCN Guidelines Index
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Discussion

GENERAL CRITERIA FOR TESTING AND GENETIC EVALUATION FOR HEREDITARY SYNDROMES ASSOCIATED WITH COLORECTAL, ENDOMETRIAL, AND GASTRIC CANCER

Testing is clinically indicated in the following scenarios:[a]

- **Individuals with any blood relative with a known P/LP variant in a cancer susceptibility gene**
- **Individuals meeting the criteria below but who tested negative with previous limited testing (eg, single gene and/or absent deletion duplication analysis) and are interested in pursuing multigene testing**
- **A P/LP variant identified on tumor genomic testing that has clinical implications if also identified in the germline[b]**
- **Individual who meets LS testing criteria (LS-1)**
- **Individual who meets adenomatous polyposis testing criteria (POLYP-1)**
- **Individual who meets clinical criteria for:**
  - **JPS (JPS-1)**
  - **PJS (PJS-1)**
- **Individual who meets hereditary diffuse gastric cancer (HDGC) testing criteria (HGAST-1)**
- **Individual who meets Li-Fraumeni syndrome (LFS) testing criteria or Cowden syndrome (CS)/*PTEN* hamartoma tumor syndrome (PHTS) testing criteria (see NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic)**

Genetic evaluation is clinically indicated in the following scenarios:[a]

- **For personal or family history of[c]**
  - **Colorectal cancer (CRC) (HRS-3)**
  - **Endometrial cancer (EC) (HRS-3)**
  - **Gastric cancer (HGAST-1)**
  - **≥10 adenomatous polyps (HRS-2)**
  - **≥2 hamartomatous polyps (HRS-2)**
  - **≥5 serrated polyps/lesions proximal to the rectum[d] (HRS-2)**
- **Individual who meets clinical criteria for serrated polyposis syndrome (SPS) (SPS-1)**
- **Personal or family history of an LS-related cancer[e] or a personal history of a tumor that is mismatch repair deficient (dMMR)[f] (LS-1)**
- **To aid in surgical decision-making[g]**

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

[b] Somatic P/LP 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 P/LP variant.

[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/dMMR protein expression on immunohistochemistry (IHC) without concurrent *MLH1* promoter hypermethylation or *BRAF* V600E mutation.

[g] Eg, planning extent of colon resection and type and timing of risk-reducing surgeries. See the relevant NCCN Treatment Guidelines for further details.

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

RISK ASSESSMENT/GENETIC EVALUATION FOR POSSIBLE POLYPOSIS SYNDROMES[h,i,j]

- Detailed family history[k]
- Detailed medical and surgical history
- Directed examination for related manifestations

→ **≥10 adenomas** →
- Classical FAP
- Attenuated FAP (AFAP)
- *MUTYH*-associated polyposis (MAP)
- Rare genetic causes of multiple adenomatous polyps[l]
- Colonic adenomatous polyposis of unknown etiology (CPUE)

→ Adenomatous Polyposis Testing Criteria (POLYP-1)

→ **≥2 hamartomatous polyps** →
- PJS (PJS-1)
- JPS (JPS-1)
- CS/PHTS (NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic)

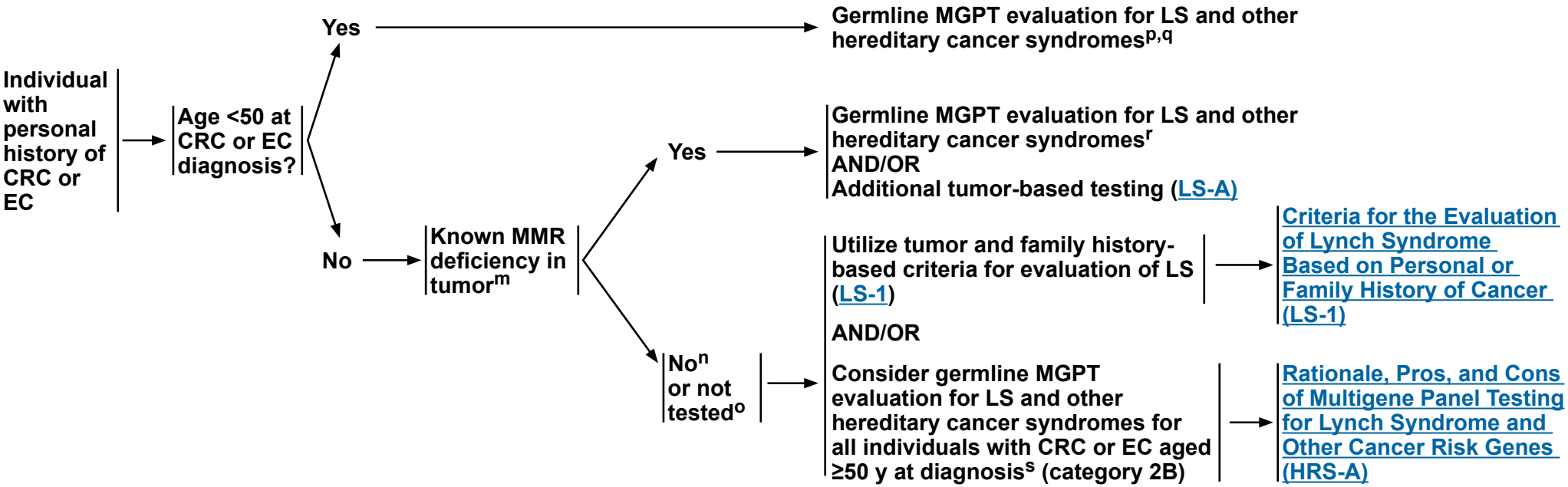
→ **≥5 serrated polyps/lesions proximal to the rectum, all being ≥5 mm in size, with ≥2 being ≥10 mm in size**
OR
>20 serrated polyps/lesions of any size distributed throughout the large bowel, with ≥5 being proximal to the rectum

→ SPS (SPS-1)

[h] Obtaining a Comprehensive Assessment for Hereditary Colorectal/Endometrial/Gastric Cancers (EVAL-B).
[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] Rare PVs associated with adenomatous polyposis include, but are not limited to monoallelic PVs in *AXIN2, GREM1, POLE, and POLD1*, and biallelic PVs in *MLH3, MSH3, MBD4, and NTHL1*.

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

CRITERIA FOR EVALUATION OF LYNCH SYNDROME AND OTHER CANCER RISK GENES AMONG INDIVIDUALS WITH A PERSONAL HISTORY OF COLORECTAL OR ENDOMETRIAL 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] For multidisciplinary treatment planning, many patients will require tumor-based testing; see the appropriate NCCN Treatment Guidelines.
[p] Pearlman R, et al. JAMA Oncol 2017;3:464-471.
[q] Yurgelun M, et al. J Clin Oncol 2017;35:1086-1095.
[r] 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).
[s] 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.

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

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 or EC 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 PV in a cancer risk gene. MGPT identifies a PV in 7.8%–16.0% of patients with CRC.[2,3,4,5] MGPT identified a PV in 9.2%–14% of patients with EC.[6,7,8,9,10,11] • Some of the PVs identified by MGPT are clinically actionable and inform screening and surveillance recommendations. • Identified PVs allow for subsequent family cascade testing and may allow for additional opportunities for early detection and prevention of cancer.[3,5,12] • A majority of individuals with a personal history of CRC or EC 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 or EC treatment decision-making. ▸ Presence of a PV in an LS-associated MMR gene is not sufficient to initiate immune checkpoint blockade therapy based on MSI-H status. Tumor-based microsatellite instability (MSI) testing or immunohistochemistry (IHC) testing for expression of the MMR proteins are required for determining eligibility for immune checkpoint blockade therapy based on presence of dMMR.[13] • PVs in cancer risk genes for which clinical management is uncertain or not informed by well-established evidence will be identified. • Many individuals will have VUS. ▸ 29%–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.[5,14,15,16] • Capacity to offer MGPT to all patients with CRC or EC and CRC or EC survivors is uncertain. ▸ In the United States, 150,000 individuals are diagnosed with CRC annually, and there are currently 1.5 million CRC survivors; 66,200 women are diagnosed with EC annually, and there are >600,000 EC survivors. ▸ It is unclear if there is sufficient capacity to deliver pre-test informed consent and appropriate counseling to all individuals with PVs and VUS, as well as negative results. Tumor registry data from 2013–2019 indicate that genetic testing rates among CRC and EC patients are 5%–6%.[17] • Results may not return in time to inform surgical decision-making.

Continued
References

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

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.[18]
- 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 PVs occurring in cancer risk genes among people from racial and ethnic groups requires additional research.

Test Selection:

- For patients with CRC:
  - Germline MGPT should include at minimum the following CRC and/or polyposis risk-associated genes: *APC*, *BMPR1A, EPCAM, MUTYH*, *MLH1*, *MSH2*, *MSH6*, *PMS2*, *PTEN, SMAD4*, *STK11*, and *TP53.* Management recommendations for individuals with a PV in these genes are described in GENE-1.
  - Germline MGPT with the following genes that have also been associated with increased risk for polyposis and/or CRC may also be considered: monoallelic PVs in *AXIN2, GREM1, POLE,* and *POLD1*, and biallelic PVs in *MSH3, MLH3, MBD4,* and *NTHL1*. Management recommendations for individuals with a PV in these genes are described in GENE-1.
  - The following additional genes are found on some genetic testing panels: *ATM, BLM, CHEK2, FOCAD, GALNT12, RNF43,* and *RPS20*. Management recommendations for some of these genes are listed in GENE-1.
- For patients with EC:
  - Germline MGPT should include at minimum the following EC risk-associated genes: *MLH1, MSH2, MSH6, PMS2, EPCAM, PTEN, POLD1, POLE,* and *BRCA1/2.* Management recommendations for individuals with a PV in these genes are described in GENE-1.
- Selection of a panel and decision to retest that includes additional genes beyond these minimal sets should be based on considerations such as age at presentation, polyp phenotype, and 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 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.

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

References

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

[1] Pearlman R, Frankel WL, Swanson B, et al. Prevalence and spectrum of germline cancer susceptibility gene mutations among patients with early-onset colorectal cancer. JAMA Oncol 2017;3:464-471.
[2] Yurgelun MB, Kulke MH, Fuchs CS, et al. Cancer susceptibility gene mutations in individuals with colorectal cancer. J Clin Oncol 2017;35:1086-1095.
[3] Pearlman R, Frankel WL, Swanson BJ, et al. Prospective statewide study of universal screening for hereditary colorectal cancer: The Ohio Colorectal Cancer Prevention Initiative. JCO Precis Oncol 2021;5:PO.20.00525.
[4] Jiang W, Li L, Ke CF, et al. Universal germline testing among patients with colorectal cancer: clinical actionability and optimised panel. J Med Genet 2022;59:370-376.
[5] Uson PLS Jr, Riegert-Johnson D, Boardman L, et al. Germline cancer susceptibility gene testing in unselected patients with colorectal adenocarcinoma: A multicenter prospective study. Clin Gastroenterol Hepatol 2022;20:e508-e528.
[6] Gordhandas S, Rios-Doria E, Cadoo KA, et al. Comprehensive analysis of germline drivers in endometrial cancer. J Natl Cancer Inst 2023;11:560-569.
[7] Karpel HC, Chern JY, Smith J M, Smith A J, Pothuri B. Utility of germline multi-gene panel testing in patients with endometrial cancer. Gynecol Oncol 2022;165:546-551.
[8] Heald B, Mokhtary S, Nielsen SM, et al. Unexpected actionable genetic variants revealed by multigene panel testing of patients with uterine cancer. Gynecol Oncol 2022;166:344-350.
[9] Levine MD, Pearlman R, Hampel H, et al. Up-front multigene panel testing for cancer susceptibility in patients with newly diagnosed endometrial cancer: A multicenter prospective study. JCO Precis Oncol 2021;5:1588-1602.
[10] Cadoo KA, Mandelker DL, Mukherjee S, et al. Understanding inherited risk in unselected newly diagnosed patients with endometrial cancer. JCO Precis Oncol 2019;3:PO.18.00338.
[11] Ring KL, Bruegl AS, Allen BA, et al. Germline multi-gene hereditary cancer panel testing in an unselected endometrial cancer cohort. Mod Pathol 2016;29:1381-1389.
[12] Samadder NJ, Riegert-Johnson D, Boardman L, et al. Comparison of universal genetic testing vs guideline-directed targeted testing for patients with hereditary cancer syndrome. JAMA Oncol 2021;7:230-237. Erratum in JAMA Oncol 2021;7:312.
[13] Ranganathan M, Sacca RE, Trottier M, et al. Prevalence and clinical implications of mismatch repair-proficient colorectal cancer in patients with lynch syndrome. JCO Precis Oncol 2023;7:e2200675.
[14] Ricker C, Culver JO, Lowstuter K, et al. Increased yield of actionable mutations using multi-gene panels to assess hereditary cancer susceptibility in an ethnically diverse clinical cohort. Cancer Genet 2016;209:130-137.
[15] Caswell-Jin JL, Gupta T, Hall E, et al. Racial/ethnic differences in multiple-gene sequencing results for hereditary cancer risk. Genet Med 2018;20:234-239.
[16] Ndugga-Kabuye MK, Issaka RB. Inequities in multi-gene hereditary cancer testing: lower diagnostic yield and higher VUS rate in individuals who identify as Hispanic, African or Asian and Pacific Islander as compared to European. Fam Cancer 2019;18:465-469.
[17] Kurian AW, Abrahamse P, Furgal A, et al. Germline genetic testing after cancer diagnosis. JAMA 2023;330:43-51.
[18] Salikhanov I, Heinimann K, Chappuis P, et al. Swiss cost-effectiveness analysis of universal screening for Lynch syndrome of patients with colorectal cancer followed by cascade genetic testing of relatives. J Med Genet 2022;59:924-930.

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

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

Evaluation is indicated in the following scenarios:	
• Personal history of CRC or EC at any age	Criteria for Evaluation of Lynch Syndrome and Other Cancer Risk Genes Among Individuals with a Personal History of Colorectal or Endometrial Cancer (HRS-3)
• Personal history of a tumor with MMR deficiency determined by polymerase chain reaction (PCR), next-generation sequencing (NGS), or IHC diagnosed at any age[b,c]	Germline MGPT evaluation for LS and other hereditary cancer syndromes[h] OR Additional tumor-based testing (LS-A)
• Personal history of a P/LP variant identified on tumor genomic testing that has clinical implications if also identified in the germline[d,e]	
• Known LS PV in the family	Strategies for Evaluating for LS (LS-2)
• Personal history of a LS-related cancer[f] and any of the following: ▸ Diagnosed <50 y ▸ A synchronous or metachronous LS-related cancer[f] regardless of age ▸ 1 first-degree or second-degree relative with an LS-related cancer[f] diagnosed <50 y ▸ ≥2 first-degree or second-degree relatives with an LS-related cancer[f] regardless of age	
• Family history[g] of any of the following: ▸ ≥1 first-degree relative with a CRC or EC diagnosed <50 y ▸ ≥1 first-degree relative with a CRC or EC and a synchronous or metachronous LS-related cancer[f] regardless of age ▸ ≥2 first-degree or second-degree relatives with LS-related cancers,[f] including ≥1 diagnosed <50 y ▸ ≥3 first-degree or second-degree relatives with LS-related cancers[f] regardless of age	Strategies for Evaluating for LS (LS-2)
• Increased model-predicted risk for LS ▸ An individual with a ≥5% risk of having an MMR gene PV based on predictive models (ie, $PREMM_5$, MMRpro, MMRpredict) ◊ Individuals with a personal history of CRC and/or EC with a $PREMM_5$ score of ≥2.5% should be considered for MGPT. ◊ For individuals without a personal history of CRC and/or EC, some data have suggested using a $PREMM_5$ 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.	

Footnotes on LS-1A

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

CRITERIA FOR THE EVALUATION OF LYNCH SYNDROME BASED ON PERSONAL OR FAMILY HISTORY OF CANCER - FOOTNOTES

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

[b] The Panel recommends tumor screening for MMR deficiency for all CRCs and ECs 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. See 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).

[c] 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.

[d] This should prompt a careful evaluation of personal and family history of the individual to determine the yield of germline sequencing.

[e] Mandelker D, et al. Ann Oncol 2019;30:1221-1231.

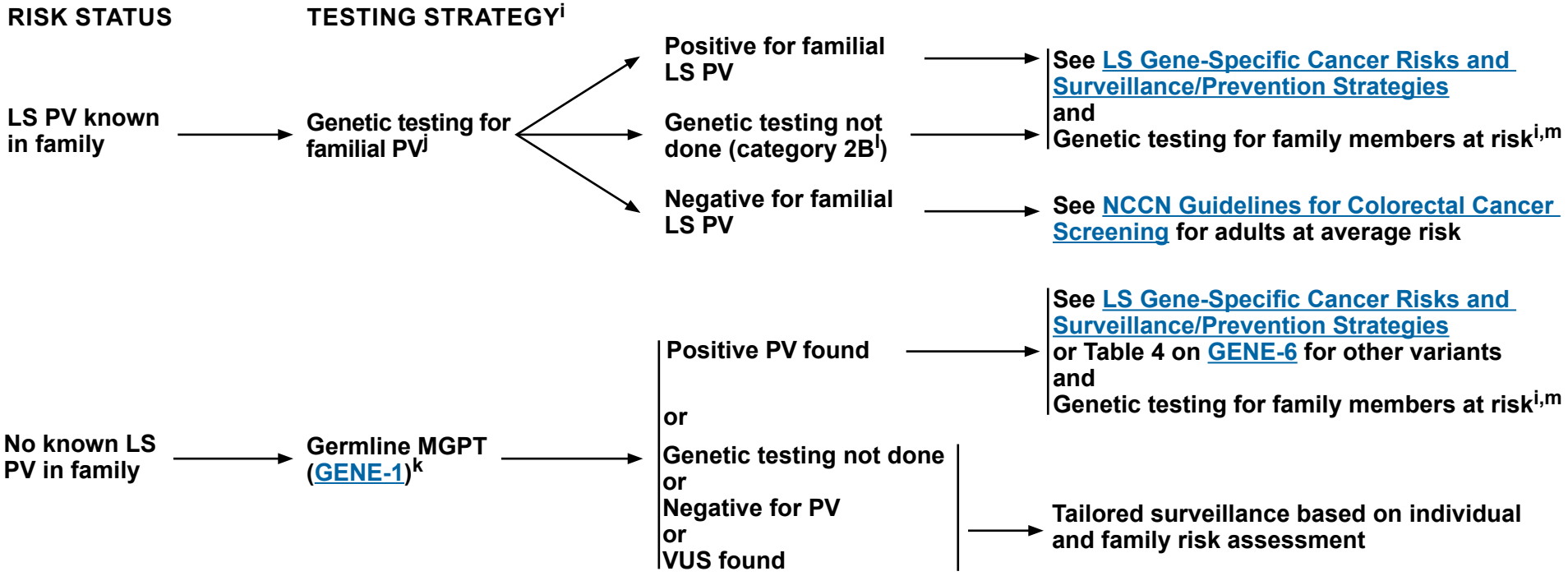
[f] LS-related cancers include colorectal, endometrial, gastric, ovarian, pancreatic, urothelial, brain (usually glioblastoma), biliary tract, and small intestine, as well as sebaceous adenomas, sebaceous carcinomas, and keratoacanthomas as seen in Muir-Torre syndrome.

[g] Indicates family history on same side of family.

[h] 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.

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



[i] 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 (EVAL-A).
[j] Additional testing may be indicated based on personal and family medical history.
[k] If there is more than one affected family member, first consider testing the family member with: youngest age at diagnosis, multiple primaries, or CRC or EC. Testing of unaffected family members when no affected member is available should be considered. Limitations of interpreting test results should be discussed.
[l] The recommendation to provide care for patients in whom genetic testing was not done using LS management recommendations is category 2B.
[m] If a first-degree relative is unavailable or unwilling to be tested, more distant relatives should be offered testing for the known PV in the family.

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

PRINCIPLES OF dMMR TESTING FOR LYNCH SYNDROME

- **The Panel recommends universal screening of all CRCs and ECs 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 CRC and EC 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* PV. 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 10). Also, sporadic ECs 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 10) could be performed on tumor DNA to assess for PVs 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.**

Continued
References

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

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 PV is present. An abnormal test means that at least one of the proteins is "not detected," and an inherited PV may be present in the related gene. Loss of protein expression by IHC in any one of the MMR genes guides further genetic testing (PV 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 (PV detection) or tumor testing for *MLH1* methylation for CRCs or ECs. Alternatively for CRCs with loss of *MLH1* on IHC, the tumor can be tested for a *BRAF* V600E PV. Testing for *BRAF* PVs 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 PV, 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 10). Those with a germline PV are then identified as patients with LS. *BRAF* V600E PVs are found in 69% of methylated CRCs, so the absence of a *BRAF* V600E PV 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* PV 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 PVs 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.[a]**
- **Absence of MMR protein expression in both cancer and normal tissue may be suggestive of CMMRD.**
- **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]**

[a] Patients with constitutional *MLH1* epimutation are a rare exception. Consider referral to individual with expertise in genetic testing for consideration of constitutional *MLH1* methylation testing in patients with early-onset CRC (≤55 y), no *BRAF* V600E PV, loss of *MLH1* on IHC, and no germline *MLH1* P/LP variant or >1 tumor with *MLH1* promoter hypermethylation at any age. Hitchins MP, et al. J Natl Compr Canc Netw 2023;21:743-752.

Continued
References

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

PRINCIPLES OF dMMR TESTING FOR LYNCH SYNDROME

IHC (continued)

- **Adenomas:**
  - **IHC for MMR protein expression 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* protein expression are absent, 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.**

Continued
References

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

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%).**

Continued
References

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

PRINCIPLES OF dMMR TESTING FOR LYNCH SYNDROME

General Principles of Next-Generation Sequencing (NGS) Testing for MSI[15-20]

- **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.**

Continued
References

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

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

Continued
References

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

TUMOR TESTING RESULTS AND ADDITIONAL TESTING STRATEGIES[b]

Tumor Testing[c]							Plausible Etiologies	Additional Testing[f,g]	NOTE: Regardless of LS test results, consider genetic evaluation if <50 y
IHC				MSI[d]	*BRAF* V600E[e]	*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[h]	
Any AB				MSS	N/A	N/A	1) Sporadic cancer 2) Germline PV in any of the LS genes	1) Germline MMR testing or paired germline MMR/somatic MMR tumor testing[i] 2) If germline testing negative and paired somatic MMR genetic testing not done, consider somatic MMR genetic testing[j]	
NL	NL	NL	NL	MSI-H	N/A	N/A	1) Sporadic cancer 2) Germline PV in any of the LS genes	1) Germline MMR testing or paired germline MMR/somatic MMR tumor testing[i] 2) If germline testing negative and paired somatic MMR genetic testing not done, consider somatic MMR genetic testing[j]	
N/A	N/A	N/A	N/A	MSI-H	N/A	N/A	1) Sporadic cancer 2) Germline PV 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[j]	
AB	NL	NL	AB	N/A	N/A	N/A	1) Sporadic cancer 2) Germline *MLH1* PV or rarely *PMS2*	1) *BRAF* PV testing[e]/*MLH1* promoter methylation testing first[k] 2) If *BRAF/MLH1* methylation testing normal, germline MMR testing or paired germline MMR/somatic MMR tumor testing[i] 3) If germline testing negative and paired somatic MMR genetic testing not done, consider somatic MMR genetic testing[j]	
AB	NL	NL	AB	N/A	Positive	N/A	1) Sporadic cancer 2) Rarely germline *MLH1* PV or constitutional *MLH1* epimutation	1) None, unless young age of onset then consider constitutional *MLH1* epimutation testing[k] and/or germline MMR testing[i]	
AB	NL	NL	AB	N/A	Negative	Positive	1) Sporadic cancer 2) Rarely germline *MLH1* PV or constitutional *MLH1* epimutation		

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

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

Continued on LS-A 8 of 10
Footnotes on LS-A 9 of 10

TUMOR TESTING RESULTS AND ADDITIONAL TESTING STRATEGIES[b]

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

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 10

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

TUMOR TESTING RESULTS AND ADDITIONAL TESTING STRATEGIES

Footnotes from LS-A 7 of 10 and LS-A 8 of 10

[b] 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.
[c] Tumor testing strategies apply to CRCs and ECs.
[d] 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.
[e] Testing is not appropriate for tumors other than CRC.
[f] 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 PV detected. If biallelic somatic MMR gene inactivation is identified, it is recommended that these patients and their close relatives 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 PV is found, the unidentified PV could either be germline or somatic. If no somatic PVs 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 PVs (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.
[g] Prior to germline genetic testing, proper pre-test counseling should be done by an individual with expertise in genetics.
[h] 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.
[i] Germline MMR testing may include testing of the gene(s) that are indicated (see “Plausible Etiologies” for possibilities on LS-A 7 of 10 and LS-A 8 of 10) 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. Er J Hum Genet 2014;22:1334-1337).
[j] Somatic MMR genetic testing of the corresponding gene(s) (see “Plausible Etiologies” for possibilities on LS-A 7 of 10 and LS-A 8 of 10) could be performed on tumor DNA to assess for somatic PVs 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.
[k] Evaluation for constitutional *MLH1* epimutation involves *MLH1* promoter hypermethylation studies on blood or other sources of normal tissue.
[l] Absent *MSH6* in rectal tumor tissue may be due to treatment effect (neoadjuvant chemoradiotherapy).
[m] If *BRAF* PV 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).

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

LS-A REFERENCES

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

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

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

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			

Surveillance/Prevention Strategies for *MLH1* Pathogenic Variant Carriers (LS-B 3 of 5)

Footnotes and References (LS-B 2 of 5)

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

MLH1 LYNCH SYNDROME: CANCER RISKS - FOOTNOTES AND REFERENCES

[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 PV 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 >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.

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

MLH1 LYNCH SYNDROME: SURVEILLANCE/PREVENTION STRATEGIES[m,n]

Site	Surveillance
Colorectal cancer	• High-quality colonoscopy[o] at age 20–25 y or 2–5 y prior to the earliest CRC if it is diagnosed before age 25 y[p] and repeat every 1–2 y.[q,r] See Follow-up of Surveillance Colonoscopy 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, 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 CRC and EC, 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 PV-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 PV, age >40 y, 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 y for MSH2 LS, age 35 repeating every 3 y for MSH6 LS, and age 40 repeating every 3 y 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 y 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 y 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 gastrointestinal [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. Daily low-dose (81 mg/d) aspirin use in pregnancy is considered safe and is associated with a low likelihood of serious maternal or fetal complications related to use. 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.

MLH1 LYNCH SYNDROME: SURVEILLANCE/PREVENTION STRATEGIES[m,n]

Site	Surveillance
Endometrial cancer	• Because EC 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 EC mortality, but can reduce the incidence of EC. 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 EC vary by LS gene. For patients requiring a colorectal surgery such as for CRC resection, coordination with hysterectomy should be considered. Given the higher risks of early EC in *MLH1*, hysterectomy with bilateral salpingectomy may be considered starting at age 40 y with delayed bilateral oophorectomy starting at age 50 y. • EC 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 y starting at age 30–35 y can be considered. • Transvaginal ultrasound to screen for EC 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 LS gene. For patients requiring a colorectal surgery such as for CRC resection, coordination with hysterectomy and oophorectomy should be considered. Given the higher risks of EC and ovarian cancer in *MLH1*, hysterectomy with bilateral salpingectomy may be considered starting at age 40 y, with delayed bilateral oophorectomy starting at age 50 y. As premature menopause due to oophorectomy can cause detriments to bone health, cardiovascular health, and generalized quality of life, estrogen replacement therapy should be considered. • Data do not support routine ovarian cancer screening for LS. CA-125 and pelvic ultrasound are recommended for preoperative planning. • Salpingectomy has been shown to reduce the risk of ovarian cancer in the general population and is an option for premenopausal patients with hereditary cancer risk who are not yet ready for oophorectomy. • Consider risk-reduction agents for endometrial and ovarian cancers, including oral contraceptive pills and progestin intrauterine systems (see Discussion for details).
Gastric and small bowel cancer	• Upper gastrointestinal (GI) surveillance with high-quality EGD starting at age 30–40 y and repeat every 2–4 y, 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 y and/or surveillance interval <2 y 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 *H. pylori* (with treatment indicated if *H. pylori* 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 *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.

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

Footnotes on LS-B 3 of 5

MLH1 LYNCH SYNDROME: SURVEILLANCE/PREVENTION STRATEGIES[m,n]

Site	Surveillance
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.
Pancreatic cancer	• Consider pancreatic cancer screening beginning at age 50 y (or 10 y 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 P/LP 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 y 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 y 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 PV(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.

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

Footnotes on LS-B 3 of 5

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			

Surveillance/Prevention Strategies for *MSH2* and *EPCAM* Pathogenic Variant Carriers (LS-C 3 of 5)

Footnotes and References (LS-C 2 of 5)

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

MSH2 AND EPCAM LYNCH SYNDROME: CANCER RISKS - FOOTNOTES AND REFERENCES

[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 PV 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).

[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 >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.

[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.

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[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.

[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.

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[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.

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[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	Surveillance
Colorectal cancer	• High-quality colonoscopy[o] at age 20–25 y or 2–5 y prior to the earliest CRC if it is diagnosed before age 25 y[p] and repeat every 1–2 y.[q,r] See Follow-up of Surveillance Colonoscopy 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 CRC and EC, 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 PV-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* PV, age >40 y, 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 y for *MSH2* LS, age 35 repeating every 3 y for *MSH6* LS, and age 40 repeating every 3 y 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 y 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 y 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. Daily low-dose (81 mg/d) aspirin use in pregnancy is considered safe and is associated with a low likelihood of serious maternal or fetal complications related to use. 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.

MSH2 AND EPCAM LYNCH SYNDROME: SURVEILLANCE/PREVENTION STRATEGIES[m,n]

Site	Surveillance
Endometrial cancer (*MSH2*)[u]	• Because EC 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 EC mortality, but can reduce the incidence of EC. 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 EC vary by LS gene. For patients requiring a colorectal surgery such as for CRC resection, coordination with hysterectomy should be considered. Given the higher risks of early EC and ovarian cancer in *MSH2,* hysterectomy with BSO may be considered starting at age 40 y. As premature menopause due to oophorectomy can cause detriments to bone health, cardiovascular health, and generalized quality of life, estrogen replacement therapy should be considered. • EC 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 y starting at age 30–35 y can be considered. • Transvaginal ultrasound to screen for EC 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 (*MSH2*)[u]	• 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 LS gene. For patients requiring a colorectal surgery such as for CRC resection, coordination with hysterectomy should be considered. Given the higher risks of EC and ovarian cancer in *MSH2*, hysterectomy with BSO may be considered starting at age 40 y. As premature menopause due to oophorectomy can cause detriments to bone health, cardiovascular health, and generalized quality of life, estrogen replacement therapy should be considered. • Data do not support routine ovarian cancer screening for LS. CA-125 and pelvic ultrasound are recommended for preoperative planning. • Salpingectomy has been shown to reduce the risk of ovarian cancer in the general population and is an option for premenopausal patients with hereditary cancer risk who are not yet ready for oophorectomy. • Consider risk-reduction agents for endometrial and ovarian cancers, including oral contraceptive pills and progestin intrauterine systems (see Discussion for details).
Gastric and small bowel cancer	• Upper GI surveillance with high-quality EGD starting at age 30–40 y and repeat every 2–4 y, 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 y and/or surveillance interval <2 y 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 *H. pylori* (with treatment indicated if *H. pylori* 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 *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.

[u] Evidence for gynecologic cancer surveillance recommendations for individuals with a P/LP *EPCAM* variant are lacking.

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

MSH2 AND EPCAM LYNCH SYNDROME: SURVEILLANCE/PREVENTION STRATEGIES[m,n]

Site	Surveillance
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 *MSH2* PVs (especially males) appear to be at higher risk. Surveillance options may include annual urinalysis starting at age 30–35 y. However, there is insufficient evidence to recommend a particular surveillance strategy.
Pancreatic cancer	• There are limited data on pancreatic cancer risk among *MSH2* PV carriers. Consider pancreatic cancer screening beginning at age 50 y (or 10 y 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 P/LP 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 y 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 y 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 PV(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-C 3 of 5

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

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			

Surveillance/Prevention Strategies for *MSH6* Pathogenic Variant Carriers (LS-D 3 of 5)

Footnotes and References (LS-D 2 of 5)

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

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 PV 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 where 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-Girondo 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.

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

MSH6 LYNCH SYNDROME: SURVEILLANCE/PREVENTION STRATEGIES[p,q]

Site	Surveillance
Colorectal cancer	• High-quality colonoscopy[r] at age 30–35 y or 2–5 y prior to the earliest CRC if it is diagnosed before age 30 y[s] and repeat every 1–3 y.[t,u] See Follow-up of Surveillance Colonoscopy 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 *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.

[p] Other than CRC and EC, 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 PV-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 PV, age >40 y, 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 y for MSH2 LS, age 35 repeating every 3 y for MSH6 LS, and age 40 repeating every 3 y 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 y 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 y 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. Daily low-dose (81 mg/d) aspirin use in pregnancy is considered safe and is associated with a low likelihood of serious maternal or fetal complications related to use. 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.

MSH6 LYNCH SYNDROME: SURVEILLANCE/PREVENTION STRATEGIES[p,q]

Site	Surveillance
Endometrial cancer	• Because EC 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 EC mortality, but can reduce the incidence of EC. 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 EC vary by LS gene. For patients requiring a colorectal surgery such as for CRC resection, coordination with hysterectomy should be considered. Given the higher risks of EC in *MSH6,* hysterectomy with bilateral salpingectomy may be considered starting at age 40 y, with delayed bilateral oophorectomy starting at age 50 y. • EC 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 y starting at age 30–35 y can be considered. • Transvaginal ultrasound to screen for EC 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 *MSH6* PV 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 LS gene. For patients requiring a colorectal surgery such as for CRC resection, coordination with hysterectomy and oophorectomy should be considered. Given the higher risks of EC and ovarian cancer in *MSH6,* hysterectomy with BSO may be considered starting at age 40 y, with delayed bilateral oophorectomy starting at age 50 y. As premature menopause due to oophorectomy can cause detriments to bone health, cardiovascular health, and generalized quality of life, estrogen replacement therapy should be considered. • Data do not support routine ovarian cancer screening for LS. CA-125 and pelvic ultrasound are recommended for preoperative planning. • Salpingectomy has been shown to reduce the risk of ovarian cancer in the general population and is an option for premenopausal patients with hereditary cancer risk who are not yet ready for oophorectomy. • Consider risk-reduction agents for endometrial and ovarian cancers, including oral contraceptive pills and progestin intrauterine systems (see Discussion for details).
Gastric and small bowel cancer	• Upper GI surveillance with high-quality EGD starting at age 30–40 y and repeat every 2–4 y, 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 y and/or surveillance interval <2 y 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 *H. pylori* (with treatment indicated if *H. pylori* 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 *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.

Footnotes on LS-D 3 of 5

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

MSH6 LYNCH SYNDROME: SURVEILLANCE/PREVENTION STRATEGIES[p,q]

Site	Surveillance
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.
Pancreatic cancer	• There are limited data on pancreatic cancer risk among *MSH6* PV carriers. Consider pancreatic cancer screening beginning at age 50 y (or 10 y 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 P/LP 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 y 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 y 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;5155-365). If both partners are a carrier of a PV(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.

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 footnotes 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			

Surveillance/Prevention Strategies for *PMS2* Pathogenic Variant Carriers (LS-E 3 of 5)

Footnotes and References (LS-E 2 of 5)

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

PMS2 LYNCH SYNDROME: CANCER RISKS - FOOTNOTES AND REFERENCES

[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 PV 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 where 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 >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 >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 >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 >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, Rodriguez-Girondo 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.

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

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

PMS2 LYNCH SYNDROME: SURVEILLANCE/PREVENTION STRATEGIES[q,r]

Site	Surveillance
Colorectal cancer	• High-quality colonoscopy[s] at age 30–35 y or 2–5 y prior to the earliest CRC if it is diagnosed before age 30 y[t] and repeat every 1–3 y.[u,v] See Follow-up of Surveillance Colonoscopy 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 *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.

[q] Other than CRC and EC, 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 PV-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* PV, age >40 y, 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 y for *MSH2* LS, age 35 repeating every 3 y for *MSH6* LS, and age 40 repeating every 3 y 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 y 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 y 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. Daily low-dose (81 mg/d) aspirin use in pregnancy is considered safe and is associated with a low likelihood of serious maternal or fetal complications related to use. 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.

PMS2 LYNCH SYNDROME: SURVEILLANCE/PREVENTION STRATEGIES[q,r]

Site	Surveillance
Endometrial cancer	• *PMS2* carriers appear to be at only a modestly increased risk of EC in contrast to *MLH1, MSH2*, and *MSH6*. • Because EC 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 EC mortality, but can reduce the incidence of EC. 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 EC vary by LS gene. Given the higher risks of EC in *PMS2*, hysterectomy with BSO may be considered starting at age 50 y. • EC 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 y starting at age 30–35 y can be considered. • Transvaginal ultrasound to screen for EC 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 *PMS2* PV carriers. *PMS2* PV 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 LS gene. Hysterectomy with BSO may be considered starting at age 50 y. As premature menopause due to oophorectomy can cause detriments to bone health, cardiovascular health, and generalized quality of life, estrogen replacement therapy should be considered. • Data do not support routine ovarian cancer screening for LS. CA-125 and pelvic ultrasound are recommended for preoperative planning. • Salpingectomy has been shown to reduce the risk of ovarian cancer in the general population and is an option for premenopausal patients with hereditary cancer risk who are not yet ready for oophorectomy. • Consider risk-reduction agents for endometrial and ovarian cancers, including oral contraceptive pills and progestin intrauterine systems (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.

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

Footnotes on LS-E 3 of 5

PMS2 LYNCH SYNDROME: SURVEILLANCE/PREVENTION STRATEGIES[q,r]

Site	Surveillance
Gastric and small bowel cancer	• Consider upper GI surveillance with high-quality EGD starting at age 30–40 y and repeat every 2–4 y, 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 <2 y 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 *H. pylori* (with treatment indicated if *H. pylori* 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 *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.
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 y 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 y 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 PV(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.

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

Footnotes on LS-E 3 of 5

SURVEILLANCE COLONOSCOPY FINDINGS	FOLLOW-UP[a]
No pathologic findings	• Continued surveillance every 1–3 y.[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 PV.[d,e] After surgery, if colon or rectum remain, colonoscopy surveillance should be performed every 1–2 y.[b] • For patients with rectal adenocarcinoma, proctectomy or TPC is indicated depending on the clinical scenario and factors such as age, PV, relationship to the anal sphincter, and anticipated need for pelvic radiation.
Adenomas	• Complete endoscopic polypectomy with follow-up colonoscopy every 1–2 y for *MSH2/MLH1*[b] and every 1–3 y for *PMS2/MSH6*.
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 y.[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* PV, age >40 y, 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 PV should be considered, as risk for metachronous tumors varies by PV 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.

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

SURGICAL OPTIONS FOR TREATING THE COLON IN PATIENTS WITH LS[a]

	Segmental Resection	Extended Resection (subtotal colectomy/total abdominal colectomy)
Indications for consideration	• Unresectable (endoscopically) advanced adenoma • Pre-existing bowel and/or sphincter dysfunction • Older age	• Synchronous colon adenocarcinoma(s)/advanced adenoma(s) • Younger age • Family history suggestive of more penetrant disease regardless of underlying germline mutation
Average recurrence risk: Metachronous adenocarcinoma[b]	• At 10 years: ~10%–32%	• At 10 years: ~0%–12%
Overall survival[c]	• At 10 years: ~90%	• At 10 years: ~90%
Bowel functional outcomes	• Often (but not uniformly) associated with preserved function	• Compromised function and altered quality of life despite long-term adaptation ▸ Greater stool evacuation frequency/diarrhea ▸ Greater food avoidance behavior ▸ More interference with daily activities and greater social impact
Additional factors to consider	• High-quality surveillance endoscopy access and adherence • Technically less complex operation, lower perioperative risk profile • Repetitive/iterative abdominal surgery (cumulative morbidity) for metachronous neoplasia ▸ Metachronous colon cancer localized (stage 1 or 2, >75%) • Patient preferences ▸ 4:1 to 5:1 opt segmental ▸ Psychologic considerations poorly understood (fear of recurrence, secondary cancers) • Survival difference (long-term) uncertain • Risk/future impact of other LS-related cancer(s) (eg, endometrial)	• Increased perioperative morbidity and mortality risk • Possibly reduced fertility • Potentially increased abdominal adhesions, higher risk for future bowel obstruction(s) • Metachronous colorectal neoplasia despite extended resection (ie, not completely preventative operation) • Survival difference (long-term) uncertain • Risk/future impact of other LS-related cancer(s) (eg, endometrial treated with pelvic radiation; duodenal/pancreatic following resection) ▸ Absorption/motility impact • Flexible sigmoidoscopy surveillance rather than colonoscopy

[a] Care should be taken to take into account genotype, phenotype, family history, and personal considerations. For example, extended colectomy may be more favorably considered for individuals with higher risk genotype (eg, *MLH1/MSH2*) or stronger family history of CRC.
[b] Metachronous risks cited are from studies which included a range of LS genes (*MLH1, MSH2, EPCAM, MSH6*, and *PMS2*).
[c] Colon cancer-specific survival limited/insufficient data.

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

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2024
Adenomatous Polyposis Testing Criteria

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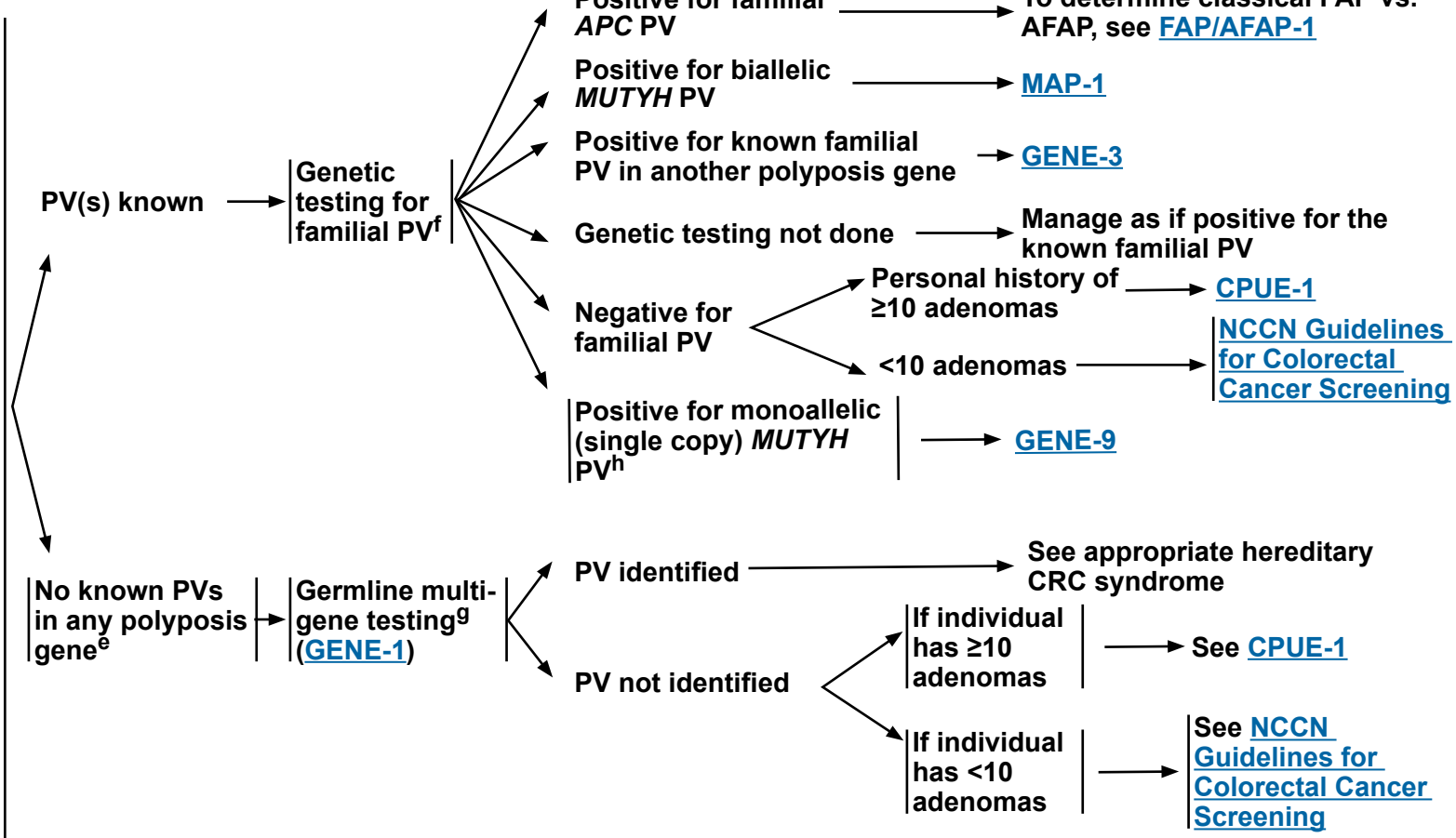
ADENOMATOUS POLYPOSIS TESTING CRITERIA

- Recommend testing if a personal history of ≥1 of the following criteria:
  - ≥20 cumulative adenomas
  - Known PV in adenomatous polyposis gene in family
  - Multifocal/bilateral congenital hypertrophy of retinal pigment epithelium (CHRPE)[a]
  - Cribriform-morular variant of papillary thyroid cancer
  - Family history of polyposis and family unwilling/unable to have testing
- Consider testing if a personal history of ≥1 of the following criteria:
  - Between 10–19 cumulative adenomas,[b] desmoid tumor, hepatoblastoma, unilateral CHRPE, or individual meets criteria for SPS (SPS-1) with at least some adenomas
- In individuals with any cancer with a P/LP APC variant identified on tumor-only genomic testing, germline testing should be considered for:[c,d]
  1. Those meeting one or more of the other adenomatous testing criterion above after reevaluation of personal and family history
  2. Those diagnosed age <30 y with any cancer



Footnotes on POLYP-1A

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

FOOTNOTES

[a] Also known as retinal pigment epithelium (RPE) hamartomas associated with FAP (RPEH-FAP).
[b] 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.
[c] This should prompt a careful evaluation of personal and family history of the individual to determine the yield of germline sequencing. Somatic *APC* P/LP variants are common in many tumor types in absence of a germline P/LP variant.
[d] Mandelker D, et al. Ann Oncol 2019;30:1221-1231.
[e] There are clinically relevant yet rarer genes that can cause a polyposis syndrome that may be phenotypically indistinguishable from *APC/MUTYH* polyposis.
[f] Additional testing may be indicated based on personal and family medical history.
[g] Multigene panel should include all polyposis and CRC genes (Stanich P, et al. Clin Gastroenterol Hepatol 2019;17:2008-2015).
[h] Siblings of a patient with MAP are recommended to have site-specific testing for the familial PVs. 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* PV, testing the adult offspring for the familial *MUTYH* PVs 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).

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

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2024
APC-Associated Polyposis

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PHENOTYPE

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

Cancer Risks (FAP-A)

AFAP:[b,e]
- Germline *APC* PV
- 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/periampullary 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

RISK STATUS

- Personal history of classical FAP → Treatment and Surveillance (FAP-1)
- Family history of classical FAP, family member at risk, family PV known → Genetic Testing and Surveillance (FAP-2)
- Personal history of AFAP → Treatment and Surveillance (AFAP-1)
- Family history of AFAP, family member at risk, family PV 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. Identification of a germline APC PV confirms the diagnosis of FAP.
[b] MGPT is recommended to differentiate *APC* from MAP and other adenomatous polyposis syndromes and CPUE. See HRS-A for CRC/polyposis gene list and GENE-1 for surveillance recommendations.
[c] Individuals with ≥100 polyps occurring at older ages (≥35–40 y) may be found to have AFAP.
[d] There is a 30% spontaneous new PV rate; thus, family history may be negative. This is especially noteworthy if onset age <50 y.
[e] 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* PV is identified.

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

PERSONAL HISTORY OF CLASSICAL FAP

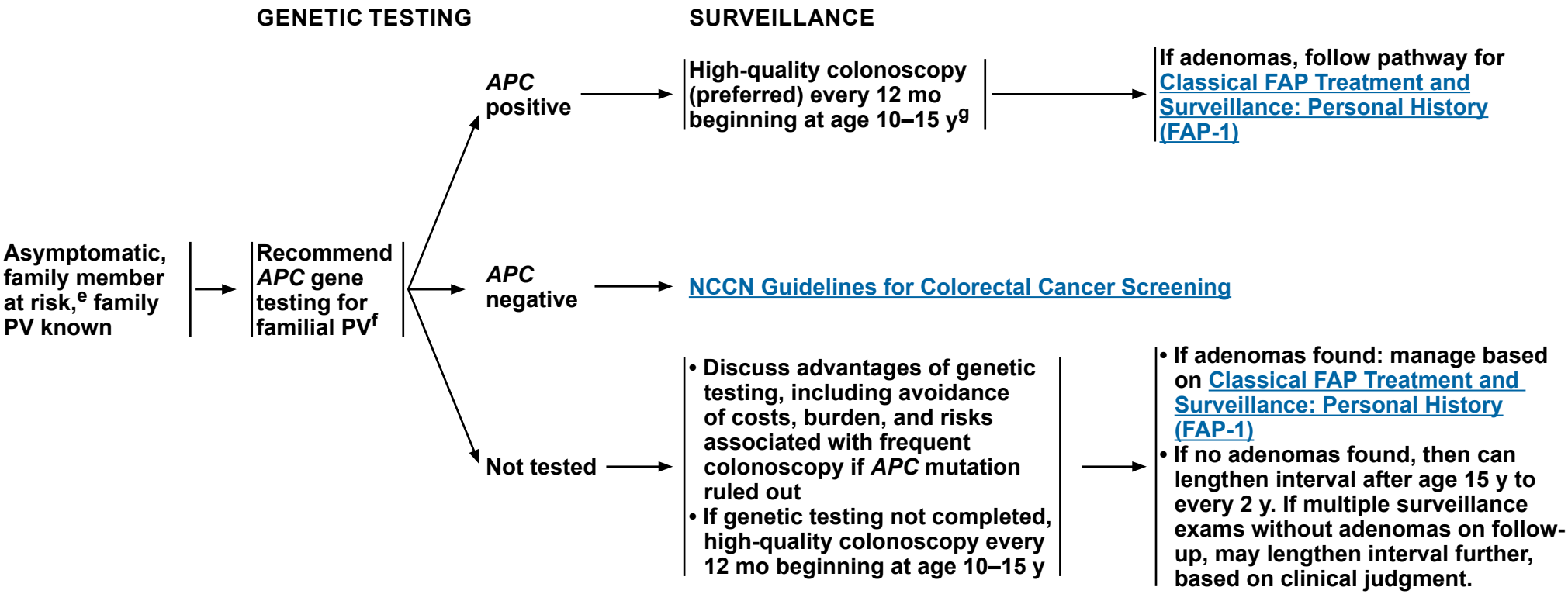
TREATMENT

Personal history of classical FAP[a] → **Proctocolectomy or colectomy[b,c,d]** → **Surveillance (FAP-B)**

[a] Cancer Risks (FAP-A).
[b] *APC* genetic testing is recommended in a proband to confirm a diagnosis of FAP and allow for PV-specific testing in other family members. Additionally, knowing the location of the PV 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-E).
[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.

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 PV 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.

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

FAP: CANCER RISKS

Site[a]	Estimated Average Age of Presentation	Cumulative Risk for Diagnosis Through Age 80 y[b]	Cumulative Risk for Diagnosis Through Lifetime for General Population[g]	References
Colorectal cancer (without colectomy)	39 years (median)	Approaches 100%	4.1%	Reference: 1
Rectal/Pouch 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%[c] Pouch and ATZ/rectal cuff (s/p IPAA): <1%–3%	4.1%	References: 2–10
Duodenal or periampullary cancer	50–52 years	<1%–10%	—[h]	References: 11–19
Gastric cancer	52–57 years	0.1%–7.1%[d]	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%[e] Mutations in the 3' end of the *APC* gene have a higher risk[f]	—[h]	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%	—[h]	References: 44–48
CNS cancer (predominantly medulloblastoma)	18 years	1%	0.6%	References: 49–50

ATZ = anal transition zone
IPAA = ileal pouch-anal anastomosis
IRA = ileorectal anastomosis

Footnotes on FAP-A 2 of 3
References on FAP-A 2 of 3 and FAP- A 3 of 3

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

FOOTNOTES

[a] There is one report showing increased pancreas cancer risk, but this study had significant limitations (Karstensen J, et al. Gastro 2023;165:573-581; see Discussion); whether pancreatic cancer risk is increased remains uncertain.

[b] 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.

[c] These estimates are based on older studies that were performed prior to newer practices for case selection of ileorectal anastomosis (IRA) candidates.

[d] The cumulative risks at the higher end of the range have been reported in Asian populations in Japan and Korea.

[e] Studies have shown that the median time to development of desmoid tumors after abdominal surgery is 28.8–36 mo (range 1–474 mo) 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).

[f] Genotype-phenotype correlation shows that higher risk (≤37%) is associated with mutations in the 3' end (Church J, et al. Dis Colon Rectum 2015;58:444-448).

[g] 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.

[h] 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.

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

CLASSICAL FAP: PERSONAL HISTORY - SURVEILLANCE STRATEGIES[a,b]

Site	Surveillance	
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	• See FAP-D for follow-up of gastric findings.	
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.	
CNS cancer	• There is currently no support for routine surveillance imaging. However, 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 abdominal imaging. Patients should be educated regarding signs and symptoms of intra-abdominal desmoids and the importance of prompt reporting of abdominal symptoms to their physicians. See NCCN Guidelines for Soft Tissue Sarcoma.	
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 or CT/MRI enterography), 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 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).

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

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 and surgical consultation for consideration of duodenectomy**

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).

Footnotes
Continued

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

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 endoscopic 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 (GAs), 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.
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Note: All recommendations are category 2A unless otherwise indicated.

GASTRIC FINDINGS AND MANAGEMENT

Endoscopic and Histologic Findings:

- **The majority of patients with FAP have proximal gastric polyposis involving the gastric body and fundus. The majority of proximal gastric polyps are FGP with or without low-grade foveolar dysplasia. Polyps with other histologic subtypes can be admixed in the proximal stomach. Gastric adenomas (GAs) and hyperplastic polyps are often found in the antrum.**
- **Focal low-grade dysplasia is commonly noted in FGP and is typically non-progressive.**
- **An approach to management of gastric polyps may be facilitated by histologic subtype. Gastric polyp pathology in FAP can be divided into high-risk (lesions that have an increased propensity to turn into cancer) and low-risk lesions.**

Low-Risk Pathology	High-Risk Pathology
• FGP with or without low-grade dysplasia	• Pyloric gland adenoma (PGA) with or without high-grade dysplasia • GA with or without high-grade dysplasia • FGP with high-grade dysplasia • Hyperplastic polyp[a] with or without high-grade dysplasia

- **GAs and PGAs can be mixed in with FGP, are precursors to gastric cancer, and are more commonly found in individuals with FAP who develop gastric cancer.[b]**
- **Emerging evidence suggests that there are some endoscopic features that may be associated with lower- versus higher-risk pathology:[c]**
  - **Lower-risk features include same color as the surrounding mucosa, closed pit pattern, smooth surface, and more features seen on narrow band imaging (NBI) compared to white light endoscopy.**
  - **Higher-risk features include lighter or darker color than the surrounding mucosa, open pit pattern, irregular surface, and features that appear similar in both NBI and white light endoscopy.**
- **Additional endoscopic markers of the detection of advanced gastric pathology:[b,d]**
  - **White mucosal patches in the proximal body or fundus – of note, the high-risk finding can be in the white mucosal patch itself or elsewhere in the stomach**
  - **Carpeting of gastric polyposis (difficult to see any intervening normal mucosa)**
  - **Mounds of polyps ≥20 mm**
  - **Large, solitary polyps ≥10 mm**

[a] Orlowska J, et al. Am J Gastroenterol 1995;90:2152-2159.
[b] Leone PJ, et al. Gastrointest Endosc 2019;89:961-968.
[c] Mankaney G, et al. Gastreointest Endosc 2020;92:755-762.
[d] Mankaney G, et al. Fam Cancer 2017;16:371-376.

Continued

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

GASTRIC FINDINGS AND MANAGEMENT

Management:[d,e,f]

- **Recommend representative sampling of polyps <10 mm that appear as FGP by multiple biopsies or endoscopic resection at baseline exam to determine histology.**
- **Resect polyps ≥10 mm, as well as any polyps with endoscopic markers of advanced pathology or high-risk features. If there is suspicion for malignancy in a lesion, recommend referral to an expert center for management (endoscopic submucosal dissection [ESD] vs. surgery).**
- **Recommend considering referral to an expert center for management by endoscopists with expertise in FAP for management of mounds of gastric polyps that are limiting accuracy, and resection of polyps with high-risk/advanced pathology. Mounds of gastric polyps may limit accuracy of endoscopic surveillance. If other high-risk characteristics are present, consider endoscopic management to debulk proximal polyposis.**
- **Due to the fact that adenomas and hyperplastic polyps are the predominant polyp in the antrum, recommend resection of all polyps in the antrum.**
- **Patients with high-risk lesions that cannot be removed by standard endoscopic techniques (including snare removal with or without endoscopic mucosal resection [EMR]) should be referred to a specialized center for consideration of ESD versus gastrectomy.**
- **Gastrectomy is indicated for multifocal high-grade dysplasia and intramucosal or invasive cancer (see NCCN Guidelines for Gastric Cancer).**
- **Roux-en-Y esophago-jejunostomy reconstruction after total gastrectomy may require balloon-assisted enteroscopy for continued duodenal polyposis and ampullary surveillance.**

[d] Mankaney G, et al. Fam Cancer 2017;16:371-376.
[e] Yang J, et al. Gastrointest Endosc 2020;91:963-982.
[f] Bianchi LK, et al. Clin Gastroentrol Hepatol 2008;6:180-185.

Continued

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

GASTRIC FINDINGS AND MANAGEMENT

Gastric Polyp Characteristics and Recommended Surveillance Intervals:[g,h]

Histology	Size	Dysplasia	Surveillance Interval[i]
Fundic gland polyps (FGP)	<1 cm	None or low grade	3 y
	≥1 cm	None or low grade	1 year (6 mo if piecemeal resection or unable to remove all large polyps in a single procedure)
	Any size	High grade*	3–6 mo and consider endoscopic management at an expert center or surgical evaluation
Gastric adenomas (GA) or Pyloric gland adenomas (PGA)	<1 cm	—	1 y
	≥1 cm	—	1 year (6 mo if piecemeal resection or unable to remove all large polyps in a single procedure)
	Any size	High grade*	3–6 mo and consider endoscopic management at an expert center or surgical evaluation
Any proximal polypoid mounds – FGP, PGA, GA	N/A	None or low grade	3–6 mo
		High grade*	Referral for endoscopic management at expert center and surgical evaluation
Intramucosal or invasive adenocarcinoma	N/A	N/A	Surgical evaluation for possible gastrectomy

* Multifocal high-grade dysplasia should prompt referral for surgical evaluation for possible gastrectomy.

- **If partial gastrectomy is performed for antral neoplasia, then continue surveillance of the remaining stomach as above.**
- **Intervals for upper endoscopy surveillance should be determined based on gastric and/or duodenal findings and whichever requires more frequent surveillance should be applied.**

[g] Adapted from Stanich P, et al. Gastrointest Endosc Clin N Am 2022;32:113-130 and Mankaney G, et al. Fam Cancer 2017;16:371-376.
[h] These pages do not address gastric findings and management for gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS) due to mutations in APC promoter 1B (for management recommendations of GAPPS, see GENE-4).
[i] Length of surveillance intervals can be shortened or lengthened as clinically indicated based on number and size of gastric polyps, as well as completion of endoscopic resection.

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

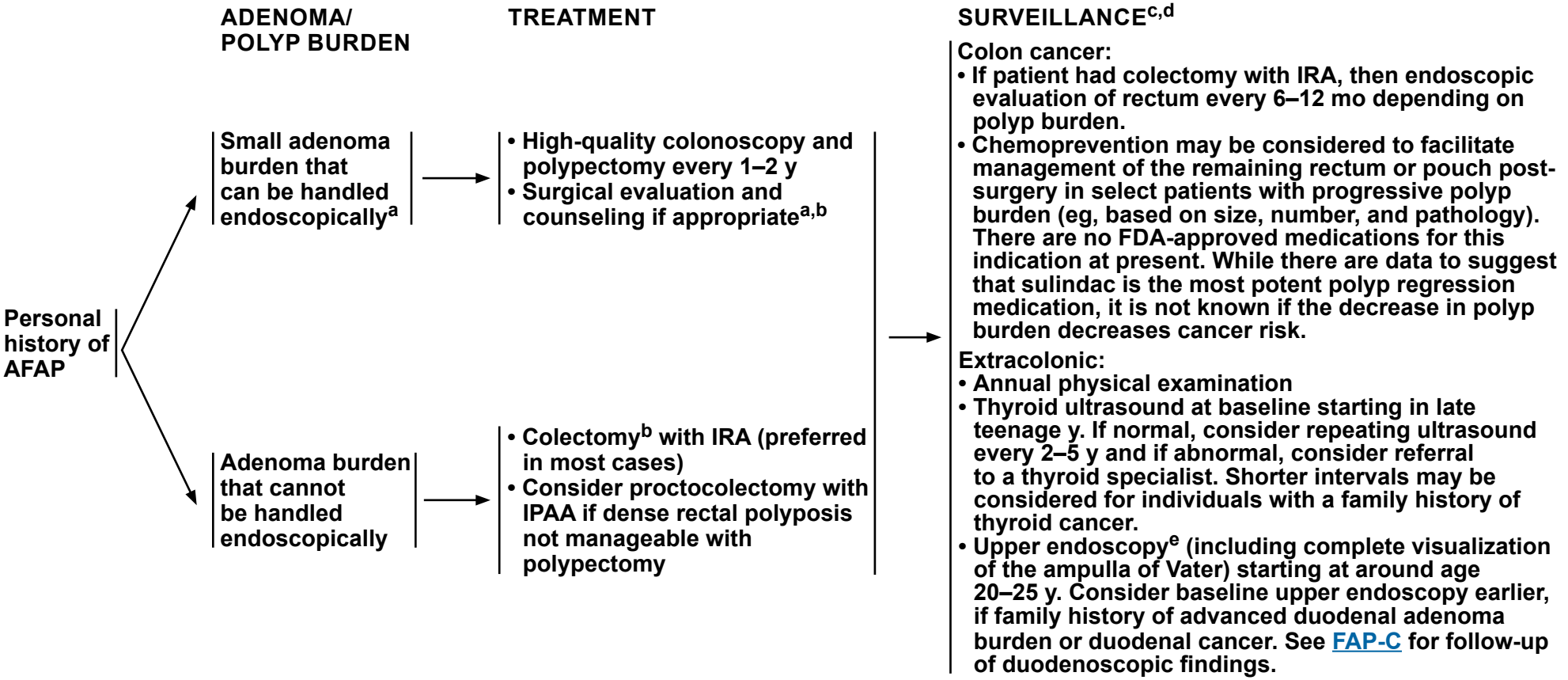
SURGICAL OPTIONS FOR TREATING THE COLON AND RECTUM IN PATIENTS WITH FAP[a]

	Total Abdominal Colectomy with Ileorectal Anastomosis (TAC/IRA)	Proctocolectomy with Ileal Pouch-Anal Anastomosis (PC/IPAA)	Proctocolectomy with End Ileostomy (PC/EI)
Indications	• The decision to remove the rectum is dependent on whether the polyps are amenable to endoscopic surveillance and resection.	• Severe disease in colon and/or rectum • After TAC/IRA with endoscopically unmanageable disease in the rectum • Curable rectal cancer	• 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
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	• Reduced rectal cancer risk • No permanent stoma • Reasonable bowel function	• Removes rectal cancer risk • One operation
Disadvantages	• Risk of metachronous cancer in the remaining rectum	• 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	• 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

[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.

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-E).

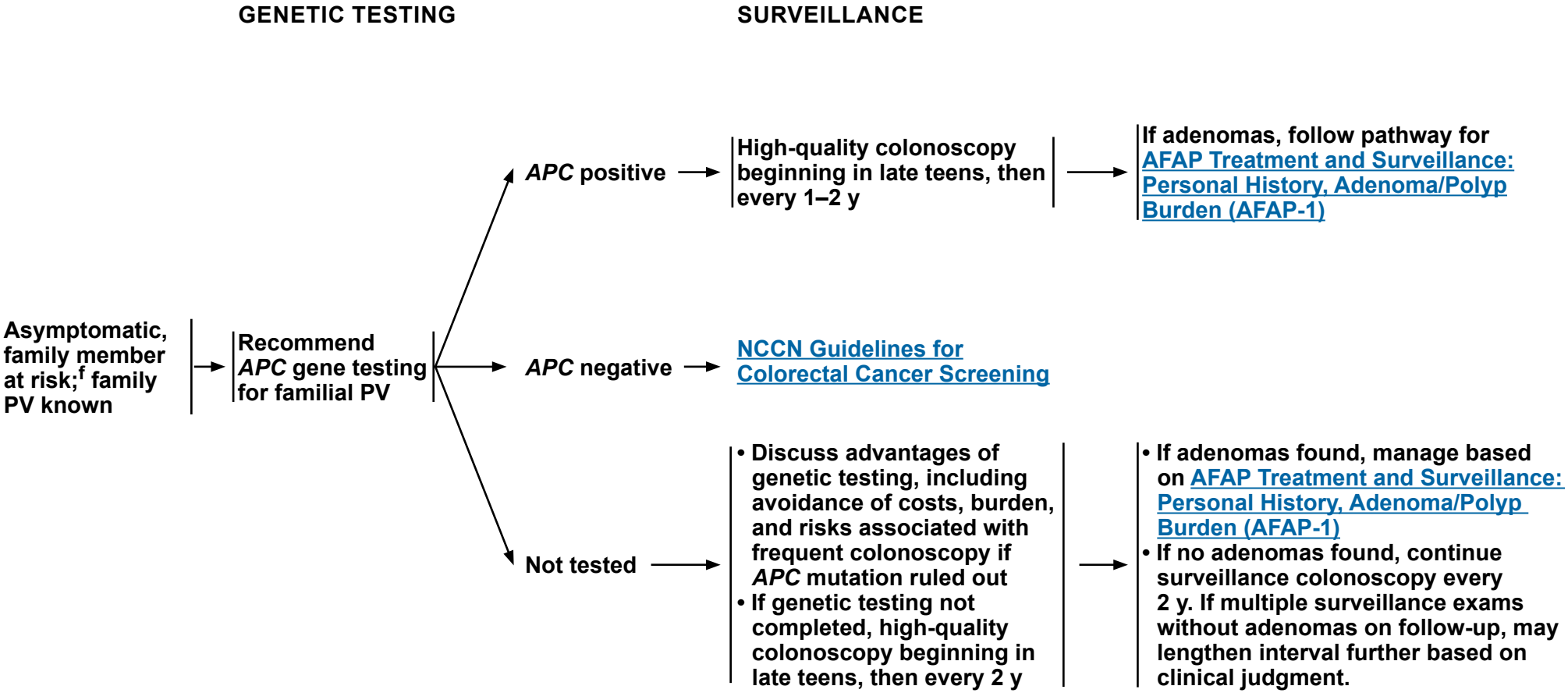
[c] It is recommended that patients receive care by physicians or centers with expertise in FAP/AFAP and that care be individualized to account for genotype, phenotype, and personal considerations.

[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.

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



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

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

NCCN Guidelines Version 1.2024
MUTYH-Associated Polyposis

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PHENOTYPE

- **Biallelic *MUTYH* PVs**
- **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**

RISK STATUS

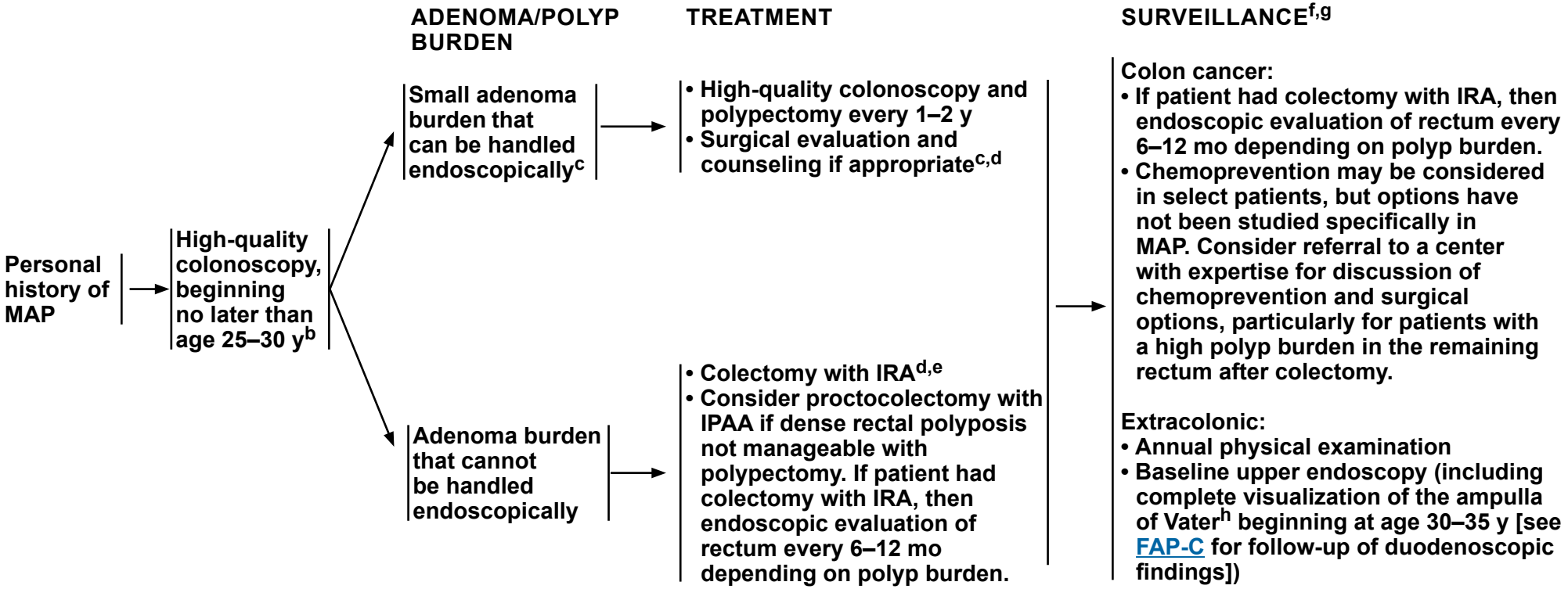
Personal history of MAP → **Treatment and Surveillance (MAP-2)**

Asymptomatic family member at risk; family PV 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.

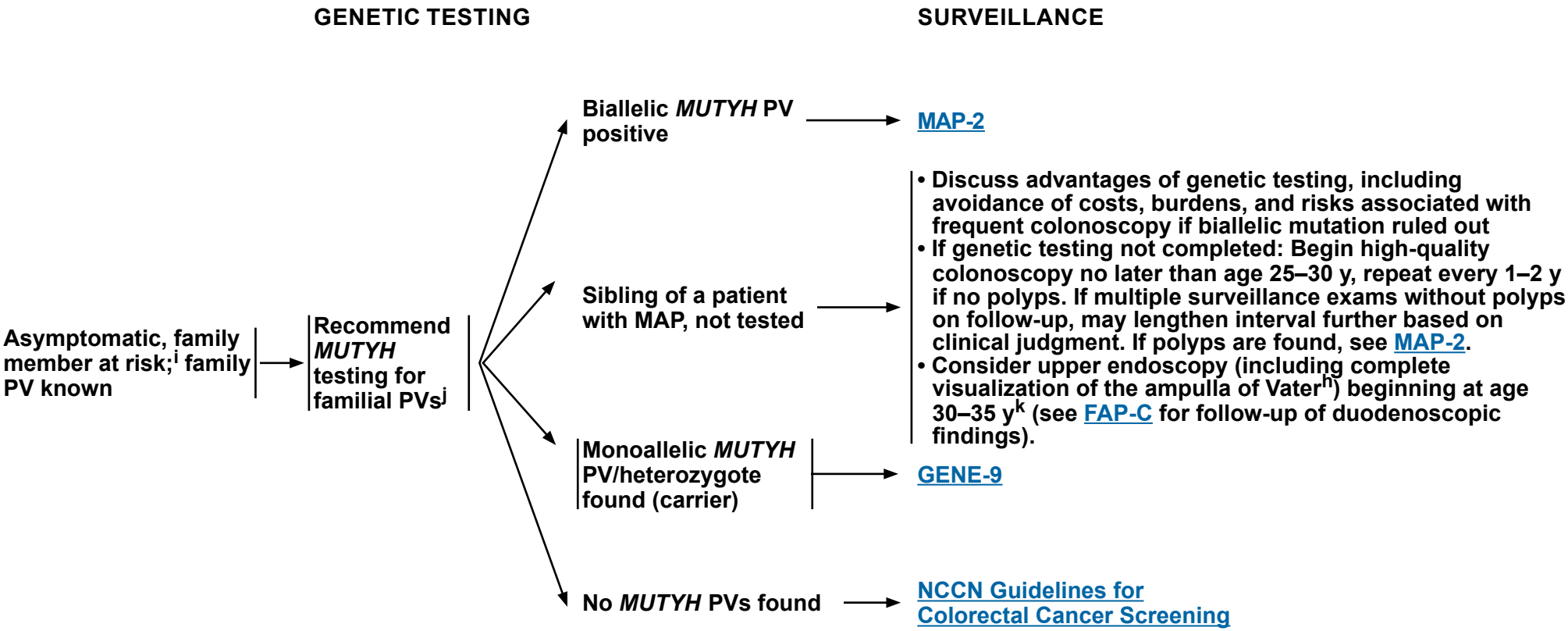
MAP TREATMENT AND SURVEILLANCE: PERSONAL HISTORY



[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-E).
[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.

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



[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* PV.
[j] Siblings of a patient with MAP are recommended to have site-specific testing for the familial PVs. 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 an *MUTYH* PV, 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* PV, testing the adult children for the familial *MUTYH* PVs is indicated.
[k] 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.

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

COLONIC ADENOMATOUS POLYPOSIS OF UNKNOWN ETIOLOGY (CPUE)

(CPUE is defined as an individual with cumulative lifetime ≥10–20 adenomas without a PV 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 (including complete visualization of the ampulla of Vater[d]) at time of next colonoscopy surveillance by age 20–25 y as on page FAP-B 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 y ▸ Repeat at short interval based on residual polyp burden[c] • Baseline upper endoscopy (including complete visualization of the ampulla of Vater[d]) at time of next colonoscopy surveillance by age 20–25 y as on page FAP-B and repeat following duodenal surveillance guidelines on page FAP-C. • Surgical evaluation may be considered if polyps are 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 (including complete visualization of the ampulla of Vater[d]) at time of next colonoscopy surveillance by age 20–25 y as on page FAP-B 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]. See NCCN Guidelines for Colorectal Cancer Screening.

[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). PVs associated with adenomatous polyposis include, but are not limited to monoallelic PVs in *APC, GREM1, POLE, POLD1,* and *AXIN2,* and biallelic PVs in *NTHL1, MUTYH, MBD4, MLH3,* and *MSH3*. Updated genetic testing may be considered in patients who have previously had limited genetic testing as clinically indicated. See HRS-A for CRC/polyposis gene list and GENE-1 for surveillance recommendations.

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

[d] 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.

COLONIC ADENOMATOUS POLYPOSIS OF UNKNOWN ETIOLOGY (CPUE)
(CPUE is defined as an individual with cumulative lifetime ≥10–20 adenomas without a PV 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[e,f] AND meets one of the following criteria: **1) Family member tested, with no PV identified; OR** **2) Family member not tested and the unaffected individual with family history has been tested, with no PV 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[e,f] AND meets one of the following criteria: **1) Family member tested, with no PV identified; OR** **2) Family member not tested and the unaffected individual with family history has been tested, with no PV 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 PV identified; OR** **2) Family member not tested and the unaffected individual with family history has been tested, with no PV 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. See NCCN Guidelines for Colorectal Cancer Screening.
[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). PVs associated with adenomatous polyposis include, but are not limited to monoallelic PVs in *APC, GREM1, POLE, POLD1,* and *AXIN2,* and biallelic PVs in *NTHL1, MUTYH, MBD4, MLH3,* and *MSH3*. Updated genetic testing may be considered in patients who have previously had limited genetic testing as clinically indicated. See HRS-A for CRC/polyposis gene list and GENE-1 for surveillance recommendations.
[e] Recommend genetic testing (POLYP-1) in family member affected with polyposis.
[f] 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.

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**

Indications for Genetic Testing for 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 PVs in the *STK11 (LKB1)* gene.**
- ***STK11* P/LP variant detected by tumor genomic testing on any tumor type in the absence of germline analysis**
  - **This should prompt a careful evaluation of personal and family history of the individual to determine the yield of germline sequencing. Somatic *STK11* P/LP variants are common in many tumor types in absence of a germline P/LP variant.**

General Treatment and Surveillance Considerations:[c]

- **For patients who meet clinical criteria for PJS or with a PV 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.

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

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)

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

Peutz-Jeghers Syndrome: Adult Surveillance

Cancer Site	% Lifetime Risk[e]	Screening Procedure and Interval	Initiation Age (y)
Breast (female)	32%–54%	• Mammogram and breast MRI annually[f] • Clinical breast exam every 6–12 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[d])	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] Formerly known as cervical adenoma malignum.
[e] 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.
[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.

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

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2024
Juvenile Polyposis Syndrome

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Discussion

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**

Indications for Genetic Testing for 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 PVs detected in the *BMPR1A* or *SMAD4*[c] genes.**
  - **In families with a known *BMPR1A* PV, 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* PV in the family, genetic testing should be performed within the first 6 mo of life due to the coexistence of *SMAD4*-related JPS-hereditary hemorrhagic telangiectasia (HHT) overlap, which requires specialized surveillance.**
- ***BMPR1A* or *SMAD4* P/LP variants detected by tumor genomic testing on any tumor type in the absence of germline analysis**
  - **This should prompt a careful evaluation of personal and family history of the individual to determine the yield of germline sequencing.**

General Treatment and Surveillance Considerations:

- **For patients who meet clinical criteria for JPS or with a PV 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.

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 an *SMAD4* PV, screen for signs, symptoms, and vascular lesions associated with HHT.[a,e]	• 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.
[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] For consensus guidelines for the management and prevention of HHT-related symptoms and complications, see Faughnan M, et al. Ann Intern Med 2020;173:989-1001.

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

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 y. Intervals should be based on polyp size, number, and pathology.[d]	~18 y
	No PV identified	Undefined	• High-quality colonoscopy every 1–3 y. Intervals should be based on polyp size, number, and pathology.[d] If no polyps, consider increasing interval to every 5 y.[h]	
Stomach	*SMAD4*	Up to 21% especially if multiple gastric polyps present	• Upper endoscopy every 1–3 y. Intervals should be based on polyp size, number, and pathology.[d,i]	~18 y
	BMPR1A	Rare[f]	• Upper endoscopy every 1–3 y. Intervals should be based on polyp size, number, and pathology.[d] If no polyps, consider increasing interval to every 5 y.[h]	
	No PV identified	Undefined		
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.
[f] In a meta-analysis of 204 patients (Singh AD, et al. Gastrointest Endosc 2023;97:407-414) with *BMPR1A*, only one patient with gastric cancer was identified.
[g] O'Malley M, et al. Hered Cancer Clin Pract 2011;9(Suppl 1):O5.
[h] MacFarland SP, et al. Cancer Prev Res (Phila) 2021;14:215-222.
[i] While *SMAD4* PV carriers often have severe upper GI tract involvement, *BMRP1A* PV carriers may have a less severe upper GI tract phenotype and may merit lengthened surveillance intervals in the absence of polyps. Gastric cancer risk for *BMPR1A* PV carriers may be lower than for *SMAD4* PV carriers. Latchford A, et al. Dis Colon Rectum 2012;55:1038-1043. Aytac E, et al. Br J Surg 2015;102:114-118.

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

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. PVs in *RNF43* have been identified as a rare cause, as have biallelic PVs 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 y 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 y**
  - **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 y if no polyps are found. If proximal serrated polyps or multiple adenomas are found, consider colonoscopy every 1–3 y.**

[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, eds. 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, et al. Gastroenterology 2017;153:106-112).
[e] Boparai KS, et al. Gut 2010;59:1222-1225.

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

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 PV 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 PVs. 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 PVs in a gene may pose higher or lower risk than other PVs in that same gene. Therefore, it may be difficult to use a known PV 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, et al. JAMA 2018;320:1266-1274.
[b] Slavin T, et al. J Natl Cancer Inst 2018;110:1059-1066.
[c] Slavin T, et al. Oncotarget 2019;10:417-423.
[d] David K, et al. Genet Med 2019;21:769-771.

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

MULTIGENE TESTING

Table 1: Multigene Testing Definitions

Term	Definition
Multigene panel	Laboratory test that includes testing for PVs 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	PV 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 PVs 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 PVs for which clinical management is uncertain. Estimates suggest that 3%–4%[f,i] of PVs identified are not clearly clinically actionable, such as finding a PV 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 PVs for which clinical management is uncertain are incorrectly interpreted.

[a] Mersch J, et al. JAMA 2018;320:1266-1274.
[b] Slavin T, et al. J Natl Cancer Inst 2018;110:1059-1066.
[e] Hall M, et al. J Natl Compr Canc Netw 2014;12:1339-1346.
[f] Yurgelun M, et al. Gastroenterology 2015;149:604-613.
[g] Idos G, et al. MJCO Precis Oncol 2019;3:PO.18.00217.
[h] Uson PLS Jr, et al. Clin Gastroenterol Hepatol 2022;20:e508-e528.
[i] Cragun D, et al. Clin Genet 2014:86:510-520.

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

Continued

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
***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 y of age and 95% by age 35 y. FAP may also present with gastric FGP/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[j,k]**	• **Estimated Absolute Risk:** 5%–10% • **Management:** ▸ For probands with CRC and this PV: 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: In the Ashkenazi Jewish population in the United States, the *APC* c.3920T>A (p.I1307K) variant is reported in 11.5% of those diagnosed with CRC and 7.2% of those not diagnosed with CRC (Valle L, et al. J Med Genet 2023;60:1035-1043). The incidence of CRC in probands and family members is similar for both Ashkenazi Jewish *APC* I1307K heterozygotes and non-Jewish *APC* I1307K heterozygotes. The same screening recommendations apply to all *APC* I1307K variant heterozygotes.		

Continued
Footnotes on GENE-15
References on GENE-16

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

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
***APC* promoter 1B/ Gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS)**	• **Estimated Absolute Risk:** Insufficient data to define • **Management:** Baseline colonoscopy at time of first EGD 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 FGP, some having regions of dysplasia • **Absolute Risk:** Stomach cancer - 12%–25% • **Management:** ▸ No current guidelines ▸ Consider risk-reducing total gastrectomy from third decade, annual EGD 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.		

Continued
References on GENE-16

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

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
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, 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 ectodermal dysplasia. Polymorphisms in *AXIN2* have also been associated with CRC and other cancers, but the information above is referring to individuals with P/LP 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. Cunniff C, et al. 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 - see comment • **Management:** See Juvenile Polyposis Syndrome (JPS-2) • **Strength of Evidence:** Strong
	Comment: Not associated with features of HHT. In a meta-analysis of 204 patients (Singh A, et al. Gastrointest Endosc 2023;97:407-414.e1) with *BMPR1A*, only one patient with gastric cancer was identified. For management, see JPS-3.		

Continued

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

References on GENE-16

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
CHEK2[j,k]	See GENE-17 for updated references • **Estimated 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 guidelines: NCCN Guidelines for Colon Cancer, NCCN Guidelines for Rectal Cancer, and NCCN Guidelines for Colorectal Cancer Screening • **Strength of Evidence:** Strong	• 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	• No polyposis • Polyp spectrum can include adenomas and sessile serrated lesions	**Other Cancers** • Lynch Syndrome (LS-C)
	Comment: Counsel for risk of rare autosomal recessive condition, CMMRD syndrome, in offspring. CMMRD can occur if both parents are a carrier of a PV in the same DNA MMR gene. Only large deletions including 3' untranslated regions of EPCAM cause LS. Single loss of function (LOF) PVs do not cause LS but are carriers of an autosomal recessive condition called congenital tufting enteropathy.		
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

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

Continued
References on GENE-16
Footnotes on GENE-15

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
GREM1[k]**/ 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, 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
	Comment: There is a common SCG5 upstream duplication in Ashkenazi Jewish individuals, but other duplications in non-Ashkenazi Jewish individuals have also been reported (Rohlin A, et al. Genes Chromosomes Cancer 2016;55:95-106; Venkatachalam R, et al. Int J Cancer 2011;129:1635-1642; McKenna DB, et al. Fam Cancer 2019;18:63-66).		
***MBD4* biallelic pathogenic variants/*MBD4*-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
	Comment: The colorectal polyposis phenotype and CRC risk for individuals with a heterozygous *MBD4* PV is unknown. One case report described a patient with a heterozygous *MBD4* PV and history of 30 adenomatous polyps (Tanakaya K, et al. Oncol Rep 2019;42:1133-1140). Unilateral and bilateral schwannomas have also been reported in at least three individuals with biallelic *MBD4* mutations (Blombery P, et al. Br J Haematol 2022;198:196-199).		
***MLH1*/ 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)
	Comment: Counsel for risk of rare autosomal recessive condition, CMMRD syndrome, in offspring. CMMRD can occur if both parents are a carrier of a PV in the same DNA MMR gene.		
***MSH2*/ 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)
	Comment: Counsel for risk of rare autosomal recessive condition, CMMRD syndrome, in offspring. CMMRD can occur if both parents are a carrier of a PV in the same DNA MMR gene.		

Continued
Footnotes on GENE-15
References on GENE-16

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

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
***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 PV 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, 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. *MSH3* 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, 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. *MLH3* heterozygote cancer risks are unclear.		

Continued
Footnotes on GENE-15
References on GENE-16

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

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
***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 FGP - 11% • **Management:** See *MUTYH*-Associated Polyposis (MAP-2)
	Comment: Limited evidence of increased risk for EC 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 (not explained by MAP): increased screening as per the relevant guidelines: NCCN Guidelines for Colon Cancer, 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 *MUTYH* 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 *MUTYH* 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 *MUTYH* heterozygosity in individuals of European ancestry (Thompson A, et al. Fam Cancer 2022;231:415-422). A large metanalysis (Ma X, et al. Gut 2014;63:326-336) of monoallelic *MUTYH* 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 *MUTYH* heterozygotes who underwent at least one surveillance colonoscopy did not identify any CRCs 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 *MUTYH* 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).		

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

Continued
References on GENE-16

MULTIGENE TESTING

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Gene/Syndrome	Colon Cancer Risk and Management	Colorectal Phenotype (polyposis defined as ≥10 polyps)	Other Risks and Management
***NTHL1* biallelic pathogenic variants[k]/ *NTHL1* 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, 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 are not yet enough data to support increased breast cancer surveillance ▸ Endometrial: Because EC 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 EC 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: *NTHL1* heterozygotes do not appear to be at increased risk for polyposis and/or CRC (Elsayed FA, et al. Gastroenterology 2020;159:2241-2243; Beck SH, et al. Fam Cancer 2022;21:453-462).		

Continued
Footnotes on GENE-15
References on GENE-16

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

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
POLD1[k]**/ Polymerase proofreading-associated polyposis**	• **Estimated Absolute Risk:** >20% • **Management:** ▸ Begin high-quality colonoscopy at age 25–30 y or 2–5 y prior to the earliest CRC in the family if it is diagnosed before age 25 y and repeat every 2–3 y if negative. If polyps are found, colonoscopy every 1–2 y with consideration of surgery if the polyp burden becomes unmanageable. ▸ Surgical evaluation if appropriate. • **Strength of Evidence:** Strong	• 30–100 • Adenomas	**Other Cancers** • See comment
	Comment: Information about cancer risk in *POLD1* PV carriers is limited by small sample sizes. In one study (Mur P, et al. Genome Med 2023;15:85), the cancers with risk greater than that of the general population were colon cancer (27/48) and EC (11/36). Limited evidence of increased risk for breast cancer, brain cancers, and possibly other cancers (Mur P, et al. Genome Med 2023;15:85; Palles C, et al. Fam Cancer 2022;21:197-209; 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. Gain-of-function P/LP variants in the exonuclease domain [*POLD1* amino acids 304–533] are associated with polymerase proofreading-associated polyposis (PPAP). LOF PV and PV outside of the exonuclease domain are associated with autosomal dominant mandibular hypoplasia, deafness, progeroid features, and lipodystrophy (MDPL) syndrome.		
POLE[k]**/ Polymerase proofreading-associated polyposis**	• **Estimated Absolute Risk:** >20% • **Management:** ▸ Begin high-quality colonoscopy at age 25–30 y or 2–5 y prior to the earliest CRC in the family if it is diagnosed before age 25 y and repeat every 2–3 y if negative. If polyps are found, colonoscopy every 1–2 y with consideration of surgery if the polyp burden becomes unmanageable. ▸ Surgical evaluation if appropriate. • **Strength of Evidence:** Strong	• 30–100 • Adenomas	**Other Cancers** • See comments
	Comments: Information about cancer risk in *POLE* PV carriers is limited by small sample sizes. In one study (Mur P, et al. Genome Med 2023;15:85), the cancers with risk greater than that of the general population were colon (102/164), endometrial (11/87), ovarian (8/87), brain (17/164), and extracolonic GI cancer (12/102). There is limited evidence of increased risk for breast cancer, melanoma, and possibly other cancers (Mur P, et al. Genome Med 2023;15:85; Palles C, et al. Fam Cancer 2022;21:197-209; 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). Gain-of-function P/LP variants in the exonuclease domain [*POLE* amino acid 268-471 (exons 9–14)] are associated with PPAP. LOF variants and those outside exonuclease domain are not likely to be pathogenic for PPAP but are associated with carrier status for autosomal recessive FILS (facial dysmorphism-immunodeficiency-livedo-short stature syndrome) (Mur P, et al. Genet Med 2020;22:2089-2100) and IMAGE-1 (intrauterine growth retardation, metaphyseal dysplasia, adrenal hypoplasia congenita, genital anomalies, immunodeficiency, and diffuse large B-cell lymphoma) (Mur P, et al. Genome Med 2023;15:85).		

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

Continued
Footnotes on GENE-15
References on GENE-16

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 PV in the same DNA MMR gene.		
***PTEN*/ *PTEN* hamartoma tumor syndrome**	• **Estimated Absolute Risk:** 9%–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: Multiple non-cancer features, which are included in major/minor criteria. (NCCN Guildines for Genetic/Famial 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: PVs in *RNF43* have been identified as a rare cause of SPS.		

Continued
References on GENE-16

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

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
RPS20	• **Absolute Risk:** Insufficient data to define • **Management:** Colonoscopy every 5 y beginning at age 20. If the patient had a hematopoietic cell transplant prior to age 20, colonoscopy is recommended to begin one year after transplant. See NCCN Guidelines for Colorectal Cancer Screening • **Strength of Evidence:** Limited	• Unknown	**Other Cancers** • Unknown or insufficient evidence
	Comment: Four families who meet Amsterdam I criteria have been reported with PVs in the *RPS20* gene, including one where all the CRCs were MSS (familial CRC type X). In addition, one individual with a PV in *RPS20* had metachronous CRC primaries by age 39 (Nieminen T, et al. Gastroenterology 2014;147:595-598; Broderick P, et al. Gastroenterology 2017;152:75-77; Thompson B, et al. Clin Genet 2020;97:943-944). The earliest CRC diagnosis reported thus far was at age 24. In one of the mutation-positive Amsterdam I families, two individuals had >10 polyps. Diamond-Blackfan anemia (DBA) is a rare inherited bone marrow failure syndrome characterized by red blood cell failure, congenital anomalies, poor linear growth, and cancer predisposition (most commonly CRC and osteogenic sarcoma). The vast majority of cases result from LOF mutations/deletions in 1 of 23 genes encoding either a small or large subunit-associated ribosomal protein (RPS or RPL) (Lipton JM, et al. Pediatr Blood Cancer 2021;68:e28984). Two unrelated children with 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). Increased CRC surveillance has been recommended for patients with DBA (Lipton JM, et al. Pediatr Blood Cancer 2021;68:e28984). While the link between *RPS20* PVs and DBA is uncertain at present, we recommend that individuals with *RPS20* PVs follow the DBA CRC surveillance recommendations given the early ages of CRC in the *RPS20* families.		
***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 mo of life. See Juvenile Polyposis Syndrome (JPS-1) for additional information.		

References on GENE-16

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

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
***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: *STK11* 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: *TP53* 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.		

Continued
References on GENE-16

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

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 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.

[k] Katona BW, Yurgelun MB, Garber JE, et al. A counseling framework for moderate-penetrance colorectal cancer susceptibility genes. Genet Med 2018;20:1324-1327; Breen KE, Katona BW, Catchings A, et al. An updated counseling framework for moderate-penetrance colorectal cancer susceptibility genes. Genet Med 2022;24:2587-2590.

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

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

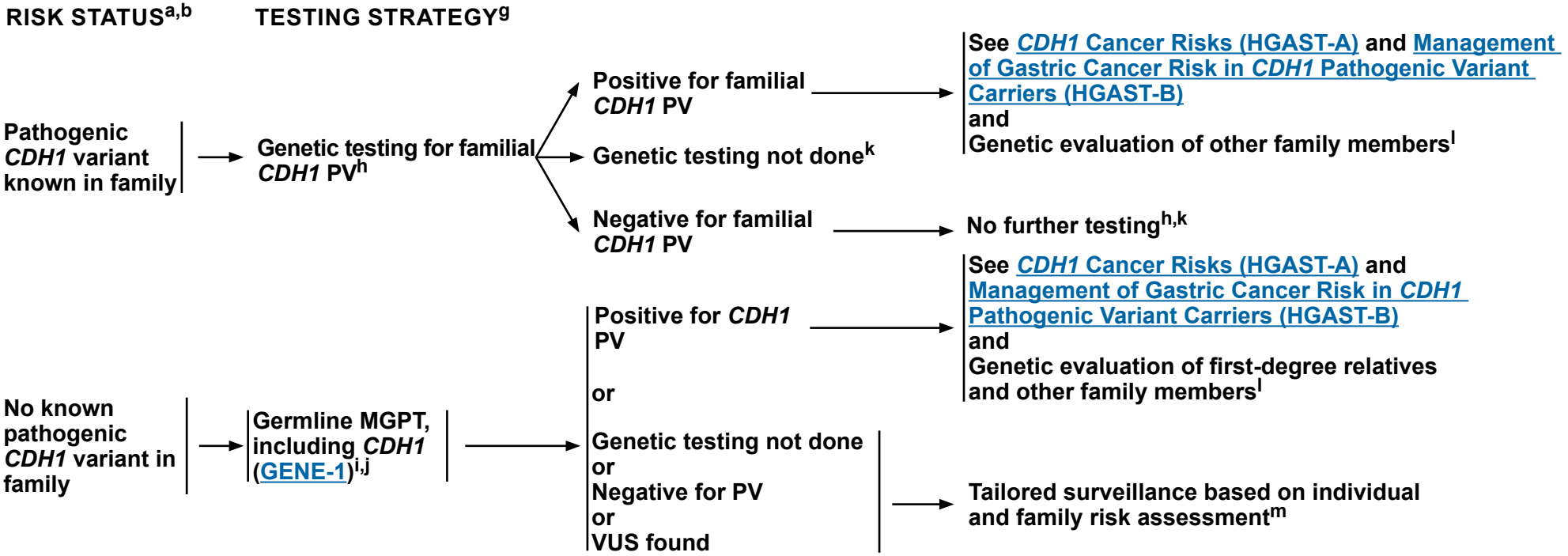
TESTING CRITERIA FOR HEREDITARY DIFFUSE GASTRIC CANCER (*CDH1*[a,b,c])[d,e,f]

- **Individual with a known *CDH1* PV in the family**
- **An individual with diffuse gastric cancer (DGC)[f] at any age**
- **Family history of ≥2 first-degree or second-degree relatives with gastric cancer with at least one diagnosed at age ≤50 y or at least one confirmed to be DGC at any age**
- **Individual meeting criteria for *CDH1* testing based on NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic - Testing Criteria For High-Penetrance Breast Cancer Susceptibility Genes**

→ HGAST-2

[a] The Panel recognizes that there are other causes of hereditary gastric cancer, which will be included in future versions of these Guidelines.
[b] *CTNNA1* has also been associated with HDGC. Management of gastric cancer risk for individuals with P/LP variants in *CTNNA1* will be developed for future versions of this guideline.
[c] Nomenclature of *CDH1*-associated DGC is evolving; OMIM nomenclature refers to this as “diffuse gastric and lobular breast cancer syndrome (DGLBC)."
[d] The Panel recognizes that based on clinical judgment, additional individuals may warrant testing for *CDH1*; these may include families that have DGC and other manifestations such as cleft lip/palate and Maori ancestry.
[e] Lerner BA, et al. J Med Genet 2023;60:36-40. These criteria identified 87% of mostly unselected mutation carriers independent of clinical phenotype and would not result in a high number of patients unnecessarily tested.
[f] Intramucosal signet ring cell carcinoma (SRCC) is the histologic lesion associated with *CDH1* PVs. The term "diffuse gastric cancer" refers to the histologic appearance of diffuse-type, poorly cohesive gastric cancer, often with a residual component of SRCC morphology, extending beyond the submucosa [WHO 2022]. The term "diffuse gastric cancer" is also clinically recognized as having the phenotype, "linitis plastica."

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



[a] The Panel recognizes that there are other causes of hereditary gastric cancer, which will be included in future versions of these Guidelines.
[b] *CTNNA1* has also been associated with HDGC. Management of gastric cancer risk for individuals with P/LP variants in *CTNNA1* will be developed for future versions of this guideline.
[g] 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 (EVAL-A).
[h] Additional testing may be indicated based on personal and family medical history.
[i] The Panel recommends that germline testing include *CDH1*, as well as the following genes: *APC, BMPR1a, BRCA1, BRCA2, CTNNA1, EPCAM, MLH1, MSH2, MSH6, PMS2, PTEN, SMAD4, STK11,* and *TP53*. The Panel recognizes that not all of these genes have been linked to DGC. Management of gastric cancer risk for individuals with P/LP variants in *CTNNA1* will be developed for future versions of this guideline. Testing for *KIT* may also be considered in families where there is a clinical concern for gastrointestinal stromal tumors (GIST).
[j] If there is more than one affected family member, first consider testing the family member with youngest age at diagnosis or multiple primaries. Testing of unaffected family members when no affected member is available should be considered. Limitations of interpreting test results should be discussed.
[k] Comprehensive care of individuals who do not have confirmatory genetic testing or negative genetic testing should be individualized based on personal and family history of cancer.
[l] If a first-degree relative is unavailable or unwilling to be tested, testing their children can help identify the mutation status if any of them test positive for the familial mutation (obligate carrier).
[m] Others have offered recommendations for individuals meeting this clinical scenario (Blair VR, et al. Lancet Oncol 2020;21:e386-e397).

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

CDH1[a] GASTRIC CANCER RISKS

- **Hereditary diffuse gastric cancer (HDGC) is an autosomal dominant cancer susceptibility syndrome that is characterized by increased risk for DGC and lobular breast cancer. Nearly all *CDH1* carriers have small foci (0.1–10 mm) of intramucosal SRCC limited to the superficial gastric mucosa (pT1a) (ie, intramucosal carcinoma),[1] but likelihood of progression to stage >pT1a advanced DGC is uncertain. Heterozygous germline PVs in *CDH1* are a major cause of HDGC with a prevalence of 1/5000 to 1/8000 in unselected population studies.[2] *CDH1* gene encodes e-cadherin, a cell adhesion protein that is important for maintenance of cell morphology and cell-cell adhesion. Neoplastic transformation requires somatic inactivation of the second *CDH1* allele resulting in complete loss of E-cadherin function.[3]**

Site	Estimated Average Age of Presentation	Cumulative Risk for Diagnosis Through Age 80 y	Cumulative Risk for Diagnosis Through Lifetime for General Population[f]	References
Stomach (Diffuse or signet ring cell carcinoma[b])[c]	47–49 years	Females: 13.6%–33% for any stage gastric cancer; 6.5% for advanced-stage[e] gastric cancer Males: 20.5%–42% for any stage gastric cancer; 10.3% for advanced-stage[e] gastric cancer	0.8%	References 4, 5, 6
Breast (Lobular)[d]	51–54 years	36.8%–55% females	12.9% females	References 5, 6

[a] The Panel recognizes that there are other causes of hereditary gastric cancer, which will be included in future versions of these Guidelines.
[b] Intramucosal SRCC is the histologic lesion associated with *CDH1* PVs. The term "diffuse gastric cancer" refers to extensive involvement of poorly differentiated carcinoma, often with a residual component of SRCC morphology, extending beyond the submucosa. DGC is also clinically recognized as having the phenotype, "linitis plastica."
[c] Estimates for lifetime risk may include a mix of individuals who developed DGC as well as those with only limited foci of stage T1a SRCC.[5]
[d] Studies have demonstrated the predominance of lobular histopathology (Stanich PP, et al. Am J Gastroenterol 2022;117:1877-1879).
[e] In the study reporting on advanced-stage gastric cancer, advanced stage was defined as AJCC stage 2 or higher.[6]
[f] 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, 2023 via SEER*Explorer.

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

MANAGEMENT OF GASTRIC CANCER RISK IN *CDH1* PATHOGENIC VARIANT CARRIERS

Overview[a]

- Given the still limited understanding and rarity of this syndrome, it is recommended for *CDH1* PV carriers to be referred to institutions with expertise in managing risks for cancer associated with *CDH1*.
- The primary gastric cancer risk in *CDH1* PV carriers is for SRCC.[b]
- Nearly all carriers of *CDH1* PV will have at least intramucosal SRCC stage 1a (pT1a). Intramucosal SRCC is observed even in very young individuals.
  - Based on analysis of risk-reducing gastrectomy specimens, prevalence of gastric cancer of any stage is 88%–97%.[1-4] In part, variation in reported prevalence is attributable to the techniques used for analysis of gastrectomy specimens.[5] Most risk-reducing gastrectomy specimens with SRCC are stage pT1a.[1-4]
  - Prevalence of ≥pT1b SRCC at gastrectomy is 2%–3%.[3,4]
  - While pT1a SRCC is an invasive carcinoma, it is suspected that most carriers of these early lesions will not develop advanced gastric cancer in their lifetime as many of these pT1a lesions will not progress to more advanced stage.[2,6-8]
- There is significant paucity of data regarding the natural history of the progression from SRCC stage pT1a to more advanced cancer.
- Lifetime risk for pT1b or greater stage gastric cancer has not been well established. One modeling study has estimated lifetime risk for stage 2 or higher gastric cancer to be 10.3% for males and 6.5% for females.[9]
- Lifetime risk for gastric cancer mortality among *CDH1* carriers has not been well established.
  - Some families with *CDH1* PVs have been reported to have high rates of gastric cancer mortality, including at a young age.[10,11]
  - Some families with *CDH1* PVs have no reported gastric cancer incidence or mortality.[12,13]
- Based on limited data, no specific *CDH1* genotypes have been associated with risk for incident and fatal gastric cancer.
- Risk-reducing gastrectomy completely eliminates risk for gastric cancer incidence and mortality, if no more than limited stage SRCC is found at time of gastrectomy.[2,3,14]
- A strategy of surveillance upper endoscopy with biopsies, regardless of the biopsy protocol utilized, has suboptimal sensitivity for detection of SRCC (which is present in nearly all *CDH1* carriers).[7,15]
- Current strategies for endoscopic biopsies at surveillance EGD, when SRCC is detected, cannot usually distinguish between stage pT1a (limited to the lamina propria) and stage pT1b (invasion into submucosa) disease due to the superficial nature of the biopsies.
- There are limited data on the outcomes of *CDH1* carriers who choose to pursue endoscopic surveillance with respect to risk for developing stage pT1b or higher gastric cancer or gastric cancer mortality.
- Across available reports of surveillance, no gastric cancer deaths have been reported in patients who elected for surveillance, though available studies are limited by short follow-up time and high rates of election for risk-reducing gastrectomy over time, even when SRCCs were not detected as part of endoscopic surveillance.[2,3,6,8,14,16,17]

[a] The Panel recognizes that there are other causes of hereditary gastric cancer, which will be included in future versions of these Guidelines.
[b] Intramucosal SRCC is the histologic lesion associated with *CDH1* PVs. The term "diffuse gastric cancer" refers to extensive involvement of poorly differentiated carcinoma, often with a residual component of SRCC morphology, extending beyond the submucosa. DGC is also clinically recognized as having the phenotype, "linitis plastica."

References on HGAST-B 5 of 5

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

MANAGEMENT OF GASTRIC CANCER RISK IN *CDH1* PATHOGENIC VARIANT CARRIERS

Management Options[a]

- **Management options for *CDH1* PV carriers include gastrectomy versus endoscopic surveillance.**

- **Gastrectomy is recommended for *CDH1* PV carriers meeting any of the following criteria:**
  - **Established stage pT1b or higher SRCC**
  - **Persistent signs and symptoms that may be associated with more advanced-stage SRCC that are unexplained by other medical conditions, including:**
    - **Weight loss, early satiety, anemia, and abdominal pain**
      - **Evidence to support sign-/symptom-based referral for gastrectomy is lacking, and this recommendation is based on expert opinion.**
  - **Endoscopic findings that may suggest presence of more advanced SRCC include:**
    - **Poor distensibility of the stomach suggestive of linitis plastica, gastric ulcerations, thickened rigid gastric folds, disturbed vascular pattern and a coarse pit pattern, and mucosal irregularities, even if biopsies only show T1a SRCC or in the absence of biopsy-proven SRCC in the absence of biopsy-proven SRCC.[15]**
      - **The sensitivity and specificity of these findings for identification of >pT1a SRCC have not been well established.**

- **Individuals without any of the above features should have the opportunity to engage in shared decision-making offering the option of risk-reducing gastrectomy versus endoscopic surveillance taking into account pros and cons of surveillance and patient preference (see HGAST-B 3 of 5). Shared decision-making should include a multidisciplinary team of clinicians with expertise in genetics, endoscopic surveillance, and surgical oncology. Age for prophylactic gastrectomy and/or initiation of surveillance, including among children aged <18 y should be based on a multidisciplinary discussion taking into account personal and family history and patient preference.**
  - **Gastrectomy**
    - **may be preferred by patients who put a higher value on maximizing prevention of developing advanced gastric cancer and gastric cancer death, and a lower value on the risks of gastrectomy and lifestyle changes associated with gastrectomy. Decision to undergo gastrectomy may be influenced by experiences with gastric cancer in a patient's family.**
  - **Endoscopic surveillance**
    - **may be preferred by patients who put a higher value on avoiding risks and lifestyle changes associated with gastrectomy and uncertain likelihood of developing and dying from gastric cancer, and a lower value on the uncertain data with regard to whether a program of upper endoscopy surveillance can prevent development of advanced gastric cancer and gastric cancer mortality.**

[a] The Panel recognizes that there are other causes of hereditary gastric cancer, which will be included in future versions of these Guidelines.

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

References on HGAST-B 5 of 5

MANAGEMENT OF GASTRIC CANCER RISK IN *CDH1* PATHOGENIC VARIANT CARRIERS

	Risk-Reducing Gastrectomy	Endoscopic Surveillance
Pros	• Risk-reducing gastrectomy maximizes reduction in risk for advanced gastric cancer and gastric cancer mortality to <1%.[3,13,17]	• Endoscopic surveillance avoids immediate gastrectomy and may avoid delay or need for gastrectomy on follow-up. • There is a low risk for endoscopic complications. • There are emerging data that patients under surveillance rarely develop greater than stage pT1a gastric carcinoma, although in most studies the follow-up time is short.[2,6,7,8]
Cons	• In a systematic review that included 353 patients who underwent risk-reducing prophylactic gastrectomy, the rate of major complications was 19.2%, with the most common complications including anastomotic leak and pulmonary complications. Five patients required re-operation because of incomplete removal of gastric tissue. Perioperative mortality was <1%.[18] • Other post-surgical complications may include internal bleeding, bile reflux into the eosphagus with potential for scarring and strictures, development of ulcers/hernia, dysmotility of the GI tract, dumping syndrome, bronchitis/ pneumonia, bile reflux, nausea/vomiting, diarrhea, nutritional deficiencies (including of multiple vitamins), and unintended weight loss. • Quality of life is often significantly impacted by risk-reducing gastrectomy in *CDH1* carriers. While a recent study has shown a return to baseline quality of life 6–12 mo after gastrectomy (according to the physical, social, emotional, and functional well-being parameters used), most patients continued experiencing high levels of intrusive GI symptoms as already described in other publications including dumping, bile reflux, diarrhea, discomfort when eating, fatigue, weight loss, eating restrictions, as well as body image, and regret for having had gastrectomy after one year.[19,20,21,22] • Studies on decisional regret and satisfaction regarding surgery are mixed, with some suggesting low levels of regret and dissatisfaction, and others suggesting substantial levels of decisional regret after risk-reducing gastrectomy.[21,23]	• Current biopsy strategies are unable to consistently distinguish between pT1a and more advanced-stage disease. This means advanced-stage disease could go undetected. • Long-term risk of progression of pT1a gastric carcinoma, which is present in nearly all *CDH1* PV carriers, is unknown. • Best approaches for maximizing sensitivity of upper endoscopy for detecting SRCC with stage >pT1a with respect to frequency of surveillance, examination techniques, and biopsy techniques have not been well established. • At least annual upper endoscopy (EGD) surveillance will be required.

References on HGAST-B 5 of 5

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

MANAGEMENT OF GASTRIC CANCER RISK IN *CDH1* PATHOGENIC VARIANT CARRIERS

Approach to Endoscopic Surveillance[a]

- **The goal of endoscopic surveillance is not to find stage pT1a lesions. Endoscopic surveillance should seek to identify individuals who are at risk for harboring stage >pT1a SRCC at time of surveillance.**

- **For individuals electing for endoscopic surveillance, the following strategies are recommended:**
  - **Upper endoscopy surveillance should be performed at centers with expertise in *CDH1* gastric cancer.**
  - **History of *CDH1* should be clearly indicated on pathology requisition. Multidisciplinary discussion of any abnormal findings is encouraged.**
  - **Exams should be high quality and defined as including:**
    - ◊ **Careful white light examination of the entire stomach with a high-definition endoscope**
    - ◊ **Clearance of all mucus and debris**
    - ◊ **Evaluation of stomach distensibility**
    - ◊ **Targeted cold forceps biopsies of any mucosal abnormalities, such as thickened rigid gastric folds, disturbed vascular pattern and a coarse pit pattern, or mucosal irregularities**
    - ◊ **If confirmation of presence of stage pT1a SRCC would influence patient decision-making regarding gastrectomy, even in light of knowledge that nearly all *CDH1* PV carriers have at least stage pT1a SRCC, biopsies of normal-appearing gastric mucosa utilizing random biopsy protocols such as the Cambridge protocol may be considered.[c]**
  - **For patients who do not meet criteria for recommended gastrectomy (HGAST-B 2 of 5) after surveillance exam episode:**
    - ◊ **There should be discussion of endoscopic findings, as well as pros and cons of ongoing surveillance versus risk-reducing gastrectomy after each surveillance episode.**
    - ◊ **Repeat endoscopy in 6 to 12 mo if patient continues to express preference for endoscopic surveillance.**
  - **For patients who meet criteria for gastrectomy (HGAST-B 2 of 5) after surveillance exam episode but decline gastrectomy:**
    - ◊ **Repeat endoscopy in 6 mo.**

[a] The Panel recognizes that there are other causes of hereditary gastric cancer, which will be included in future versions of these Guidelines.

[c] Endoscopic sampling that is more extensive than the modified Cambridge protocol, such as the Bethesda protocol, should be used in research settings as the clinical utility of additional random biopsies beyond those specified by the Cambridge protocol is not well established (Asif B, et al. Lancet Oncol 2023;24:383-391). The modified Cambridge protocol includes recommendations to take biopsies from each of the following areas: prepyloric area (2 biopsies); antrum (4 biopsies); transitional zone (4 biopsies); body (6 biopsies); fundus (4 biopsies); and cardia (4 biopsies) (Lee CYC, et al. Lancet Oncol 2023;24:107-116).

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

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

ABBREVIATIONS

AFAB	assigned female at birth
AFAP	attenuated familial adenomatous polyposis
AMAB	assigned male at birth
AML	acute myeloid leukemia
BSO	bilateral salpingo-oophorectomy
CBC	complete blood count
CHRPE	congenital hypertrophy of retinal pigment epithelium
CLIA	Clinical Laboratory Improvement Amendments
CMMRD	constitutional mismatch repair deficiency
CNS	central nervous system
CPUE	colonic adenomatous polyposis of unknown etiology
CRC	colorectal cancer
CS	Cowden syndrome
ctDNA	circulating tumor DNA
DBA	Diamond-Blackfan anemia
DGC	diffuse gastric cancer
DGLB	diffuse gastric and lobular breast cancer syndrome
dMMR	mismatch repair deficient
DTC	direct to consumer
EC	endometrial cancer
EGD	esophagogastroduodenoscopy
EI	end ileostomy
EMR	endoscopic mucosal resection
ERCP	endoscopic retrograde cholangiopancreatography
ESD	endoscopic submucosal dissection
EUS	endoscopic ultrasound
FA	Fanconi anemia
FAP	familial adenomatous polyposis
FGP	fundic gland polyp
FILS	facial dysmorphism-immunodeficiency-livedo-short stature syndrome
GA	gastric adenoma
GAPPS	gastric adenocarcinoma and proximal polyposis of the stomach
GI	gastrointestinal
GIM	gastric intestinal metaplasia
GINA	Genetic Information Nondiscrimination Act of 2008
GIST	gastrointestinal stromal tumor
HDGC	hereditary diffuse gastric cancer
HHT	hereditary hemorrhagic telangiectasia
IHC	immunohistochemistry
IMAGE-1	intrauterine growth retardation, metaphyseal dysplasia, adrenal hypoplasia congenita, genital anomalies, immunodeficiency, and diffuse large B-cell lymphoma
IPAA	ileal pouch-anal anastomosis
IRA	ileorectal anastomosis
JPS	juvenile polyposis syndrome
LFS	Li-Fraumeni syndrome
LOF	loss of function
LOH	loss of heterozygosity
LS	Lynch syndrome
MAP	*MUTYH*-associated polyposis
MDPL	mandibular hypoplasia, deafness, progeroid features, and lipodystrophy
MGPT	multigene panel test
MMR	mismatch repair
MRCP	magnetic resonance cholangiopancreatography
MSI	microsatellite instability
MSI-H	microsatellite instability-high
MSI-I	microsatellite instability-intermediate
MSI-L	microsatellite instability-low
MSS	microsatellite stable

ABBREVIATIONS

NBI	**narrow band imaging**
NGS	**next-generation sequencing**
PC	**proctocolectomy**
PCR	**polymerase chain reaction**
PGA	**pyloric gland adenoma**
PHTS	**PTEN hamartoma tumor syndrome**
PJS	**Peutz-Jeghers syndrome**
P/LP	**pathogenic/likely pathogenic**
PPAP	**polymerase proofreading-associated polyposis**
PRS	**polygenic risk score**
PV	**pathogenic variant**
RPE	**retinal pigment epithelium**
RPEH-FAP	**retinal pigment epithelium hamartomas associated with familial adenomatous polyposis**
RRSO	**risk-reducing salpingo-oophorectomy**
SCTAT	**sex cord tumor with annular tubules**
SNP	**single nucleotide polymorphism**
SPS	**serrated polyposis syndrome**
SRCC	**signet ring cell carcinoma**
TAC	**total abdominal colectomy**
TMB	**tumor mutational burden**
TPC	**total proctocolectomy**
UAAB	**unassigned at birth**
VAF	**variant allele frequency**
VUS	**variant of uncertain significance**

NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence (≥1 randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus (≥50%, but <85% support of the Panel) 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.

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

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2024 Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric

Discussion

This discussion corresponds to the NCCN Guidelines for NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal. Last updated: October 30, 2023.

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NCCN Guidelines Version 1.2024 Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric

Overview

Colorectal cancer (CRC) is the fourth most frequently diagnosed cancer and the second leading cause of cancer death in the United States. In 2023, an estimated 106,970 new cases of colon cancer and 46,050 new cases of rectal cancer will occur in the United States. During the same year, it is estimated that 52,550 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 (LS), 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 Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Genetic/Familial High-Risk Assessment: Colorectal provide recommendations for the care of patients with high-risk syndromes, including LS, 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.

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Practice Guidelines; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies. The data from key PubMed articles as well as articles from additional sources deemed as relevant to these guidelines as discussed by the panel during the Guidelines update have been included in this version of the Discussion section. Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

Sensitive/Inclusive Language Usage

NCCN Guidelines strive to use language that advances the goals of equity, inclusion, and representation. NCCN Guidelines endeavor to use language that is person-first; not stigmatizing; anti-racist, anti-classist, anti-misogynist, anti-ageist, anti-ableist, and anti-weight-biased; and inclusive of individuals of all sexual orientations and gender identities. NCCN Guidelines incorporate non-gendered language, instead focusing on organ-specific recommendations. This language is both more accurate and more inclusive and can help fully address the needs of individuals of all sexual orientations and gender identities. NCCN Guidelines will continue to use the terms men, women, female, and male when citing statistics, recommendations, or data from organizations or sources that do not use inclusive terms. Most studies do not report how sex and gender data are collected and use these terms interchangeably or inconsistently. If sources do not differentiate gender from sex assigned at birth or organs present, the information is presumed to predominantly represent cisgender individuals. NCCN encourages researchers to collect more specific data in future studies and organizations to use more inclusive and accurate language in their future analyses.

Assessment for Hereditary CRC Syndrome (HRS-1)

Genetic susceptibility to CRC includes well-defined inherited syndromes such as LS, 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 syndromes is warranted. A pathogenic variant in this case includes likely pathogenic variants.[9] 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 LS 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 LS-associated cancers beyond CRC should be elicited. LS-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 LS 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 LS-related cancers or MMR deficiency should undergo further evaluation (See LS-1 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-morular variant of papillary thyroid cancer, brain cancer (typically medulloblastoma), and hepatoblastoma.

Management After Diagnosis with a Genetic Syndrome

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

Lynch Syndrome

LS is the most common form of genetically determined colon cancer predisposition, accounting for 2% to 4% of all CRC cases.[10-14] LS 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 LS.[16,17] Identification of LS is important both for individuals with cancer, because of high personal risk for metachronous LS 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 LS, 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 LS, as well as other cancer risk genes, are evolving. Previously, the NCCN panel has endorsed the following strategies for identifying individuals with LS, 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 LS, 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 who do not already meet criteria based on having personal history suspicious for a polyposis syndrome or diagnosis 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 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 (LS-1)

If an individual has a personal or family history of a LS-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 LS:

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

  - ≥1 first-degree relative with a CRC or endometrial cancer and another synchronous or metachronous LS-related cancer regardless of age
  - ≥2 first-degree or second-degree relatives with LS-related cancer; including ≥1 diagnosed at <50 years
  - ≥3 first-degree or second-degree relatives with LS-related cancers, 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 (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 LS is not required if multi-gene testing 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.[26]

Strategies for Evaluating for Lynch Syndrome in Individuals Meeting Criteria for the Evaluation of Lynch Syndrome (LS-2)

Deleterious Lynch syndrome pathogenic variant in family is known:
When a known LS 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 LS outlined below (See *Lynch Syndrome Management).* In addition, genetic testing should be offered to family members who are at risk. However, the recommendation to treat patients in whom genetic testing was not done is category 2B. Individuals who test negative for the familial LS 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 LS has generally used 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 LS in a family with a proband affected by CRC or any other LS-associated cancer (ie, endometrial, small bowel, ureter, renal-pelvic cancers), and two relatives with a LS-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 LS-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 LS.[29]

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

- CRC diagnosed in a patient <50 years
- Synchronous, metachronous, colorectal, or other tumor associated with LS
- 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 at <50 years and associated with LS. If more than one relative was diagnosed with a LS-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 Bethesda criteria had an odds ratio (OR) for carrying a germline P/LP variant in *MLH1* or *MSH2* of 33.3 (95% CI, 4.3–250; *P* = .001). Still, a considerable number of patients with LS fail to meet even the revised Bethesda Guidelines.[12]

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 LS.[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 LS-associated pathogenic variant, the panel recommends additional evaluation for LS 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 LS 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 LS 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 LS 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 LS.[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 LS 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 LS 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 tumor specimen.[46] Greater than 90% of LS 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 patients who are high risk who may have *MLH1*, *MSH2*, and *MSH6* germline P/LP variants.[41,49,50] In 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 the two testing methods is high (99.1%).[18] The panel recommends using only one test initially. If normal results are found and LS is strongly suspected, then the other test may be carried out. Alternatively, emerging studies suggest a role for NGS panels in LS tumor testing.[26,51,52]

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 LS (*MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM*) simultaneously. Reductions in cost of sequencing, and recognition that some patients meeting LS testing criteria may have germline P/LP variants not associated with LS have led to growing use of so called "multi-gene" panels in clinical practice. These panels test not only for LS-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.[19,53]

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 LS-associated, cancer.[43,46,54,55]

Follow-up of Genetic Test Results
If a pathogenic variant for familial LS is found, the panel recommends that LS management guidelines be followed (See *Lynch Syndrome Management*).

If no pathogenic variant for familial LS 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 LS. 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 LS 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 biallelic somatic variants.[18] Individuals found to have biallelic somatic P/LP variants/changes in the MMR genes are unlikely to have LS, though biallelic 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 LS

When a LS P/LP variant is found in the family, it offers an opportunity to provide predictive testing for family members who are at increased risk. 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 LS. Compared to the general population, these patients are at increased lifetime risk for CRC (46%–61% vs. 4.1%), endometrial cancer (34%–54% vs. 3.1%), and other cancers including of the stomach and ovary.[56-59] Within LS 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).[60]

Existing data on surveillance 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. Surveillance and the option of risk-reducing surgeries should be individualized after risk assessment and counseling.

Colon Cancer Surveillance

If LS is confirmed, a high-quality colonoscopy is advised. The age to start CRC surveillance 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.[42,43,54,55,61,62] 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.[59,63]

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.[64] Some patients may benefit from a shorter 1-year versus a longer 2-year surveillance interval.[65] 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.[65,66]

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 families with LS (*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.[67] 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 LS.[68] It was 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.

A prospective comparison of CRC incidence in carriers of an MMR P/LP variant in the Prospective Lynch syndrome Database and the International Mismatch Repair Consortium cohorts showed that colonoscopy may not prevent all CRC in individuals with LS.[69] This may be due to some cancers developing from dMMR crypts that do not form an intermediate adenoma.[70] A study from a Canadian registry including 429 patients with LS showed that colonoscopy screening every 1 to 2 years beginning at ages 20 to 25 years was particularly efficient at detecting adenomas, and any new adenomas detected at screening decreased CRC incidence by 11.3%.[71]

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 LS.[72] 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.[73] A more recent meta-analysis including four randomized studies showed that adenoma detection rate in patients with LS 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.[74] Chromoendoscopy may be considered in patients with LS, but larger prospective randomized trials are needed to better understand its role in LS.

Endometrial Cancer Surveillance

Women with LS are at heightened risk for endometrial cancer.[56,61,75,76] With a lifetime risk of up to 60%, endometrial cancer is the second most common cancer in women with LS.[75] 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.[56,58,59,66,77-80] 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 LS. 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.[81-86]

Routine transvaginal ultrasound to screen for endometrial cancer in postmenopausal individuals has not been shown to be sufficiently sensitive or specific to warrant a positive recommendation,[82-87] but may be considered at the clinician's discretion. However, transvaginal ultrasound is not recommended as a screening tool in premenopausal individuals 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.[54,62,81,83,88,89] The timing of a hysterectomy can be individualized based on whether childbearing is complete, comorbidities, family history, and LS 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 (hazard ratio [HR], 0.39; 95% CI, 0.23–0.64; $P < .001$).[90] However, prospective data are needed before hormonal contraceptives are recommended for prevention of gynecologic cancers in patients with LS. In general, risk reduction agents should be considered, with detailed discussion between the physician and patient outlining the associated risks and benefits.

Ovarian Cancer Surveillance

Women with LS 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).[56,61,66,75,76,79] There are circumstances where clinicians may find screening helpful; however, the data do not support routine ovarian cancer screening for LS. Transvaginal ultrasound and serum CA-125 testing to screen for ovarian cancer in postmenopausal individuals has not been shown to be sufficiently sensitive or specific to warrant a routine recommendation,[82-87] 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.[54,62,81,83,88,89] The decision and timing of BSO as an option should be individualized based on whether childbearing is complete, menopausal status, comorbidities, family history, and LS 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

LS 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 LS 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.[56,58,76,91-93] 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% to 4%).[56,58,76,92] Studies specific to LS have not reported cumulative small bowel cancer risk higher than 0.1% for *PMS2*.[80] However, the panel did not interpret these data as suggesting risk for a LS carrier would be lower than for the general population. There are data demonstrating that upper GI surveillance in LS detects upper GI cancers at early stages.[94-96] Upper GI surveillance also identifies pre-neoplastic lesions of the upper GI tract in LS.[95,96] At this time, it remains uncertain whether upper GI surveillance reduces upper GI cancer mortality in LS. For individuals with *MLH1*, *MSH2*, *MSH6*, or *EPCAM* P/LP variants, upper GI surveillance with esophagogastroduodenoscopy (EGD) starting at age 30 to 40 years and repeated every 2 to 4 years, preferably performed in conjunction with colonoscopy, is recommended.[94-96] 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 *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 LS 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.[97] 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 *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 LS, 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 LS 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%–7%) and *MSH6* (ranging from 0.7%–8.2%) P/LP variant carriers.[56,58,92,98] 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 LS.[75,76,99,100] Although there are limited data on pancreatic risk in *MSH2* and *MSH6* carriers, the panel recommends that patients with LS with a P/LP variant in *MLH1, MSH2*, or *MSH6* and a family history of ≥1 first- or second-degree relatives from the same family side as the identified pathogenic germline variant with pancreatic cancer begin screening for pancreatic cancer at age 50, or 10 years younger than the earliest familial exocrine pancreatic cancer diagnosis, whichever is earlier.[101] The International Cancer of the Pancreas Screening (CAPS) Consortium recommends that patients with LS due to a P/LP variant in *MLH1, MSH2,* and *MSH6* and one first-degree relative with pancreatic cancer should be considered for screening.[102] *PMS2* carriers have not been shown to be at increased risk for pancreatic cancer.[58] 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 no increased risk for prostate cancer in individuals with LS, though prostate cancer risk in individuals with LS is not expected to be lower than that for the general population.[77,92,103] Though the panel found insufficient evidence to conclude increased risk for prostate cancer in LS, 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.[77] 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 (available at www.NCCN.org) recommend that patients with LS may consider beginning shared decision-making about prostate cancer screening at age 40 years and screening at annual intervals rather than every other year.

While studies have found that 42% to 51% of breast cancers in patients with LS are dMMR with abnormal IHC corresponding to their germline pathogenic MMR gene variant,[104,105] there are insufficient data supporting an increased risk for breast cancer for patients with LS.[77,92,106-110] 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 LS[111,112]; 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.[111,112] The panel recommends consideration of a skin exam every 1 to 2 years with a health care provider skilled in identifying LS-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.[113]

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.[65] 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.[65,66] 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 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. Patients who are post-colectomy 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. Patients who are post-colectomy 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 LS 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.[114] 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).[115] Adverse events in both groups were similar. Longitudinal 10-year follow-up showed that taking 2 to 4 years of resistant starch had no effect on risk of CRC but was associated with a 46% relative risk reduction for extracolonic cancers (specifically cancers of the upper GI tract).[116]

In an observational study including 1858 patients from the Colon Cancer Family Registry who have LS, 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.[117]

At this time, the panel suggests that aspirin may be used to reduce the future risk of CRC in patients with LS, but it is emphasized that the optimal dose and duration of therapy should be determined on an individual basis.[115] The CAPP2 trial used a dose of 600 mg per day,[114] though many clinicians who prescribe daily aspirin as chemoprevention in patients with

LS 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 LS-associated cancer incidence (NCT02497820), but results are not yet be available. The panel's recommendation to consider aspirin for chemoprevention is consistent with the stance of the American Gastroenterological Association.[55] Due to limited mature data,[114,118] the American College of Gastroenterology does not recommend standard use of aspirin for chemoprevention.[62] 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 during pregnancy is category D; as such, individuals with LS who have childbearing potential 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 adenomas.[73,119] Genetic testing is also recommended when an individual has a family history of a known P/LP variant in polyposis genes or if an individual has multifocal/bilateral CHRPE.[62]

Testing may also be considered if: 1) there is a personal history of a desmoid tumor, hepatoblastoma,[120] cribriform-morular variant of papillary thyroid cancer,[121,122] or unilateral CHRPE; 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 adenomatous polyposis coli (*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.[123] 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).[119] Notably, prevalence of P/LP variants in all genes of interest remained above 5% in all age and polyp cohorts.[119] 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.[119] 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.[119] 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, other known pathogenic variant in another polyposis gene), genetic testing can be considered for at-risk family members. A family member at risk 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 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 individuals at risk 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 individual at average risk 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.[124,125] Truncating P/LP variant of the *APC* gene is detectable in about 80% of patients with FAP using protein-truncating tests.[126,127] Approximately 20% to 30% of cases are due to *de novo APC* germline P/LP variants, and 11% to 20% of cases have been estimated to

be attributable to mosaicism.[128-131] A systematic review described studies in which somatic mosaic *APC* variants were found with more specific genetic testing strategies in 14 patients with previously unexplained FAP, indicating that the incidence of mosaicism may be underestimated with current testing methods.[130]

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), 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% to 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).[120,165-168] The majority of thyroid cancers seen in FAP are papillary thyroid carcinomas, with the rare cribriform-morular variant considered almost pathognomonic.[121] Cumulative risks for gastric cancer at the higher end of the range have been reported in Asian populations in Japan and 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 central nervous system [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 family members who are at risk.[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.[124,125] 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) 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 family members who are at risk. When the familial P/LP variant is known, genetic counseling and testing of asymptomatic, family members at risk is indicated. If the family member who is clinically affected is not available for testing, testing of other family members at risk can be considered. Genetic testing for FAP in children at risk 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 individuals with increased risk may be done by the late teens, the age range during which endoscopic surveillance would be initiated.

Preoperative Surveillance for FAP (FAP-2)

Surveillance for individuals with increased risk, 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 individual at average risk 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 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. 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 known P/LP familial variant:

Evaluating individuals who are asymptomatic and at risk in families for which there is no known P/LP variant at the time of evaluation presents a difficult problem. By far the best approach in this situation is additional attempts to identify a P/LP variant in an affected family member with multi-gene panel testing (MGPT) for all polyposis and CRC genes, even if the available person is not a first-degree relative. If a P/LP variant is found, then the individual at risk 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 individuals at risk can be considered. A positive test in a person who is asymptomatic 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 a person who is asymptomatic 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 individuals at risk for whom no P/LP variant is found is identical to that for individuals who are untested with a known familial P/LP variant (see section 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 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).

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 individual at average risk 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. 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 reduced 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 patients with severe polyposis who are high risk.[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 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.

Postoperative Surveillance for FAP (FAP-B, FAP-C, FAP-D)

Colorectal Cancer

Patients with FAP 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 Periampullary 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 <1% to 10%[140,141,143-146,193,195,196] of patients and usually patients who are >40 years. Duodenal adenoma burden 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 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 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,[62] 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 1.2% 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 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] Another retrospective analysis of thyroid ultrasound surveillance yield reviewed data in patients (n = 264) with confirmed FAP that had received at least 2 thyroid ultrasounds. A subset of 167 patients had a baseline thyroid ultrasound classified as normal based on the American Thyroid Association Guidelines. Of these 167 patients, none developed thyroid cancer over a 5.1-year follow-up. Thyroid cancer developed in 6 patients (2.3%) who had nodules present on baseline thyroid ultrasound.[207] 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%, with rates of thyroid nodule detection in individuals who had a normal baseline thyroid ultrasound ranged from 9% to 16.7%.[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, with consideration of 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.[120] 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.

Postoperative Surveillance 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 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 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 polyp 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.

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 in the absence of endoscopic or surgical intervention.[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]

Approximately 1% to 2% of the general population are carriers of a *MUTYH* monoallelic P/LP variant.[19,230] A study comparing the prevalence of *MUTYH* heterozygotes in patients with colorectal, endometrial, or breast cancer who underwent genetic testing at a commercial testing laboratory compared to controls of European (non-Finnish) descent from GnomAD found no difference in the prevalence, suggesting there is no association between colorectal, endometrial, or breast cancer and *MUTYH* heterozygosity in individuals of European ancestry.[230] A large meta-analysis of carriers of a monoallelic *MUTYH* pathogenic variant found only a slight increase in CRC risk (OR, 1.17, 95% CI, 1.01—–1.34).[229] One report suggested increased risk of gastric and liver cancers,[231] but reports investigating associations with risk of breast and endometrial cancers have been conflicting.[230,232] A study including 125 carriers of a *MUTYH* heterozygote who underwent at least one surveillance colonoscopy did not identify any CRCs, and the adenoma rate was not high.[233] Therefore, screening beyond that which is recommended for the general population is not warranted for carriers of a *MUTYH* monoallelic P/LP variant. For monoallelic *MUTYH* carriers with CRC or a first-degree relative with CRC, see recommendations in the NCCN Guidelines for Colon Cancer, the NCCN Guidelines for Rectal Cancer, and the NCCN Guidelines for Colorectal Cancer Screening (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,[205,223,234] 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.

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 (specifically abdominopelvic RT and/or alkylating chemotherapy) 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).[235,236] 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. This can be repeated at short intervals depending on residual polyp burden; longer intervals between

colonoscopies may be used depending on clinical judgment. An upper endoscopy at time of next colonoscopy surveillance (by age 20–25 years) and repeat following duodenal surveillance guidelines as described above for patients with FAP (see FAP-C) is recommended. 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 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, stomach, small intestine, and lung. [239-241] 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%).[242] In a study of 72 patients with PJS, 12.5% had a GI malignancy.[243] 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, as well as cancer of the testes (Sertoli cell tumors.[239-241] The majority of PJS cases occur due to P/LP variants in the *STK11 (LKB1)* gene.[244,245] Molecular testing and identification techniques have identified mutations in *STK11/LKB1* in 66% to 94% of cases of PJS.[246,247] In an analysis of 20 patients with PJS, *STK11/LKB1* P/LP variants were identified in 16 cases (80%).[248] Even with modern techniques, however, the detection rate of *STK11/LKB1* P/LP variants in PJS has not approached 100%. This leaves the possibility of PJS as heterogenous genetic disease with other potential P/LP variants playing a role in disease development.[248]

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. The NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal include PJS surveillance recommendations for both adults and children. 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]

Adult Surveillance

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 approximately age 30 years. For surveillance for gastric cancer, upper endoscopy should be done every 2 to 3 years beginning around age 18 years. 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. 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. For lung cancer, education should be provided about symptoms and smoking cessation, if necessary. No other specific recommendations have been made for lung cancer.

Pediatric Surveillance

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. 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 should be initiated at an earlier age or repeated more frequently if signs or symptoms of GI obstruction or blood loss are present. 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.

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 *BMPR1A* and *SMAD4* genes.[62,254,258] 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).[261,262] 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.[263] 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 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.[62,264,265]

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.

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. CRC screening via colonoscopy should begin around age 18 years, since the mean age of diagnosis for juvenile polyps is 18.6 years.[259,266,267] High-quality colonoscopy should be repeated every 1 to 3 years for surveillance. Intervals should be based on polyp size, number, and pathology. 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.[258,268] 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.[269] 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 Cancer[249] 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.[62]

Serrated Polyposis Syndrome (SPS-1)

Serrated polyps include hyperplastic polyps, sessile serrated lesions (SSL), and traditional serrated adenomas.[270] SSLs are flat or slightly raised and usually occur on the right side, while traditional serrated adenomas are generally polypoid.[271] Serrated polyps are more difficult to detect during colonoscopy and account for a disproportionate amount of interval cancers.[272] Serrated lesions such as SSLs may account for as many as a third of CRCs, and should be managed similarly to adenomas.[272]

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.[273] 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.[274] Individuals with SPS have an increased risk for colon cancer.[275,276] A systematic review and meta-analysis including 36 studies with 2788 patients with SPS showed that the overall prevalence of CRC was 19.9% (95% CI, 15.3%–24.5%).[277] Relative to time of SPS diagnosis, CRC was diagnosed prior to SPS diagnosis for 7.0%; (95% CI, 4.6%–11.7%), concurrent to SPS diagnosis for 14.7% (95% CI, 11.4%–18.8%), and on surveillance after SPS diagnosis for 2.8% (95% CI, 1.8%–4.4%). One retrospective study found that 35% of patients developed CRC during a mean follow-up period of 5.6 years (range, 0.5–26.6 years).[275] 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.[278] Another

retrospective analysis of 64 patients with serrated polyposis showed an SIR of 18.72 (95% CI, 6.87–40.74) for CRC.[279] 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.[235,280]

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%.[281] 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.[282] The *RNF43* variants were associated with multiple serrated polyps (OR, 3.0; 95% CI, 0.9–8.9; *P* = .04).[282] 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.[283] A study from Spain also identified 10 variants in the *WNK2* gene in 12 patients with SPS.[284] Notably, some patients with a diagnosis of *MUTYH*-associated polyposis may have a phenotype also meeting criteria for SPS.[285] As such, patients meeting criteria with SPS and some conventional adenomas may benefit from genetic evaluation to exclude presence of biallelic *MUTYH* P/LP variants, though data on yield of genetic testing for patients with SPS are still emerging (see POLYP-1 in the algorithm).

Management 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.[62] 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 or CRC occurs.[62]

Treatment of First-Degree Relatives (SPS-1)

The risk for CRC is elevated in first-degree relatives of individuals with SPS.[286-288] 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).[286] 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.[288] 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.[289]

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 patients who are at increased risk, 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 syndrome-specific tests (ie, panels that test for only

one syndrome like LS, 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.[290] 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.[290] Multi-gene testing with panels that include genes associated with LS, as well as other highly penetrant genes associated with CRC, may be cost-effective,[291] and this approach may detect P/LP variants not found in single-gene testing.[292] Multi-gene testing has comparable, or even higher, yield for LS, 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.[290,293] 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.[294,295]

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.[293,296,297] This issue is compounded by the low prevalence of many pathogenic variants, leading to a difficulty in conducting adequately powered studies.[296] 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.[290,297-300] 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 *POLE* 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 tumor mutation burden-high (TMB-H) are necessary for determination of eligibility of ICI treatment of CRC.

Multi-gene tests also increase the likelihood of detecting VUS,[290,293,297,300-303] 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.[20,304-306] 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 identified through hereditary cancer testing have been reclassified and

downgraded to benign or likely benign categories.[9,307] 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.[308,309]

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.[290] Second, in some cases, NGS may miss some P/LP variants that would have been detected with traditional single-gene analysis.[290] Third, P/LP variants identified for more than one gene add complexity that may lead to difficulty in making risk management recommendations.[293] 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.[310] 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 LS 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, STK11,* and *TP53*.

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.

APC I1307K Pathogenic Variant

The *APC* gene is a tumor-suppressor gene associated with CRC.[311] 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.[312-317] 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).[312] 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).[312] 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).[315] 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.[318-320] 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.[319] 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 dominant trait caused by *APC* promoter 1B variants.[321,322] 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.[323] There is a 12% to 25% lifetime risk of developing gastric cancer in GAPPS.[324] 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.[325] Colonoscopy at time of diagnosis to exclude colon polyposis, if not previously done, is recommended.

ATM P/LP Variants

P/LP variants in the *ATM* (ataxia-telangiectasia mutated) gene may increase risk for CRC (absolute lifetime risk, 5%–10%),[326-329] breast cancer (20%–40%),[327,330-332] ovarian cancer (2%–3%),[333-335] and pancreatic cancer (5%–10%).[336-342] There is currently insufficient evidence to provide specific CRC risk management recommendations for carriers of an *ATM* P/LP 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).[343-347] 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.[343] Other studies support the association of *AXIN2* P/LP variants and oligodontia.[345,347] 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.[345] 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.[346] Carriers of the variant had a variable number of polyps, but no oligodontia or ectodermal dysplasia.[346] 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%).[329,348,349] 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 biallelic *BLM* P/LP variants; therefore, carriers of a heterozygous P/LP variant in *BLM* should be counseled accordingly.[350]

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; risk for CRC is uncertain, and heterogeneity may exist based on type of *CHEK2* pathogenic variant.[351-354] 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.[351] 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).[351] Significant associations between *CHEK2* P/LP variants and CRC risk have been identified in meta-analyses.[353,354] 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.[353] However, in a 2022 retrospective cohort of 3783 patients with one or more *CHEK2* PVs, *CHEK2* was not associated with CRC, and those with a *CHEK2* P/LP variant were less likely to have been diagnosed with CRC, compared to patients who did not carry a *CHEK2* P/LP variant (OR, 0.62; 95% CI, 0.51–0.76; P <.001). A similar result was reported when stratified by *CHEK2* 1100delC carriers, and CRC was less frequently diagnosed in 1100delC carriers compared to patients who did not carry a *CHEK2* P/LP variant (OR, 0.69; 95% CI, 0.53–0.88; P <.002).[355] For carriers of *CHEK2* P/LP variants with a personal history of 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 *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 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, but this model was published prior to availability of the aforementioned large cohort study showing no increased risk for CRC among CHEK2 P/LP variant carriers.[355,356]

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%).[357-360] 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.[361,362] HMPS is due to a 40 kb duplication upstream of the gremlin 1 gene (*GREM1*), which increases ectopic *GREM1* expression in normal epithelium.[361] 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.[363] For carriers of *GREM1* alterations, 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.

MBD4 Biallelic Pathogenic Variants/MBD4-Associated Neoplasia Syndrome

Methyl-CpG Binding Domain 4 *(MBD4)* is a gene involved in the DNA base excision repair pathway. Biallelic P/LP variants of *MBD4* may be implicated in causing colorectal polyposis and extracolonic neoplasia, a syndrome known as *MBD4*-Associated Neoplasia Syndrome. In a whole genome/whole exome sequencing study of 309 individuals with multiple adenomas and/or familial CRC, 2 individuals with P/LP *MBD4* variants were identified. A replication cohort of 1611 patients identified an individual with a homozygous *MBD4* mutation and four heterozygous carriers of loss of function variants of *MBD4*. The CRC risks and clinical phenotypes for both homozygous and heterozygous *MBD4* PV carriers are not well established given current data. In addition to adenomas, biallelic loss of function mutations in *MBD4* may lead to a higher risk of extracolonic manifestations, specifically AML and uveal melanoma.[364,365] For those with biallelic *MBD4* pathogenic variants/*MBD4*-associated neoplasia syndrome, the panel recommends high quality colonoscopy starting at age 18 to 20 years or at date of diagnosis, repeated every 2 to 3 years if negative. CBC at diagnosis and annual ophthalmologic exams starting at time of diagnosis are also recommended.

MSH3 Biallelic Pathogenic Variants

MutS homolog 3 (*MSH3*) is a DNA MMR gene implicated in tumorigenesis of colon cancer with MSI.[366] Some data have linked biallelic *MSH3* germline P/LP variants as a recessive subtype of colorectal adenomatous polyposis.[367,368] 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 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.

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.[369] For carriers of two *MLH3* 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.

NTHL1 Biallelic Pathogenic Variants

The endonuclease III-like 1 (*NTHL1*) gene is involved in base excision repair and acts on oxidized pyrimidine residues.[370] There is some evidence that biallelic *NTHL1* P/LP variants are associated with increased risk of colorectal polyposis.[371-373] Monoallelic *NTHL1* P/LP variants do not appear to be associated with increased risk of polyposis or CRC.[374] 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.[368] A systematic review of 21 papers including 47 patients with biallelic P/LP variants in *NTHL1* showed that 49% were diagnosed with CRC, and 55% of the female patients were diagnosed with breast cancer.[375] Colonoscopy findings from these patients showed colonic adenomas in 93% and duodenal adenomatosis in 6%. Another study including 29 carriers of biallelic *NTHL1* P/LP variants showed that 60% of females were diagnosed with breast cancer.[376] 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.[371] 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. Though breast cancer risk may be elevated, the evidence currently does not support screening beyond that which is recommended for the general population. 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. Screening for duodenal cancer includes baseline upper endoscopy (including complete visualization of the ampulla of Vater) beginning at age 30 to 35 years.

POLD1 and *POLE* P/LP Variants

DNA polymerases delta [δ]1 (*POLD1*) and epsilon [ε] (*POLE*) are involved in DNA proofreading and replication.[377] P/LP variants in the *POLD1* and *POLE* genes may be associated with polyposis and increased risk for CRC.[378-382] 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.[380] 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.[381] 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.[383] 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.[380-388] Presently, for carriers of *POLD1* and *POLE* 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. 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.[389] In an analysis of 67 *PTEN* P/LP variant carriers undergoing colonoscopy, colorectal polyps were found in 92.5% of patients.[390] About half of the patients undergoing colonoscopy had hyperplastic polyps, and about 25% had polyps that were hamartomatous, ganglioneuromatous, or adenomatous.[390] 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.[390] 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.[391] 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.[390] The lifetime risk for CRC has been estimated as 9% to 18%.[392-394]

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.[395,396] 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.[395,397] 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.[392,393,398] The lifetime risk for thyroid cancer (follicular or papillary) has been estimated at 3% to 10%.[395,399] In addition, brain tumors are occasionally seen in individuals with Cowden syndrome/PHTS, although the risks for developing these conditions are not well defined.[395,397] 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 Cowden syndrome/PHTS.

TP53/Li-Fraumeni Syndrome

LFS is a rare hereditary cancer syndrome associated with germline *TP53* P/LP variants.[400] 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%.[401] 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.[400,402-409] 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.[404] Hypodiploid acute lymphoblastic leukemia is also strongly associated with LFS.[410,411] 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.[373,412-415] *FOCAD* is 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 risk emerge, the panel expects that these surveillance recommendations will evolve.

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