National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

# Genetic/Familial High-Risk Assessment: Colorectal

Version 3.2017 — October 10, 2017

NCCN.org

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# NCCN Guidelines Version 3.2017 Panel Members
# Genetic/Familial High-Risk Assessment: Colorectal

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Discussion

* Dawn Provenzale, MD, MS/Chair ¤ Þ
Duke Cancer Institute

* Samir Gupta, MD/Vice-chair ¤
UC San Diego Moores Cancer Center

Dennis J. Ahnen, MD ¤
University of Colorado Cancer Center

Travis Bray, PhD ¥
Hereditary Colon Cancer Foundation

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

Gregory Cooper, MD ¤
Case Comprehensive Cancer Center/
University Hospitals Seidman Cancer
Center and Cleveland Clinic Taussig
Cancer Institute

Dayna S. Early, MD ¤
Siteman Cancer Center at Barnes-
Jewish Hospital and Washington
University School of Medicine

James M. Ford, MD † Þ Δ
Stanford Cancer Institute

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

William Grady, MD ¤
Fred Hutchinson Cancer Research
Center/Seattle Cancer Care Alliance

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

Amy L. Halverson, MD ¶
Robert H. Lurie Comprehensive Cancer
Center of Northwestern University

Stanley R. Hamilton, MD ≠
The University of Texas
MD Anderson Cancer Center

Heather Hampel, MS, CGC Δ
The Ohio State University Comprehensive
Cancer Center - James Cancer Hospital
and Solove Research Institute

Jason B. Klapman, MD ¤
Moffitt Cancer Center

David W. Larson, MD, MBA¶
Mayo Clinic Cancer Center

Audrey J. Lazenby, MD ≠
Fred & Pamela Buffett Cancer Center

Xavier Llor, MD, PhD ¤ Þ
Yale Cancer Center/
Smilow Cancer Hospital

Patrick M. Lynch, MD, JD ¤
The University of Texas
MD Anderson Cancer Center

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

Robert J. Mayer, MD † Þ
Dana-Farber/Brigham and Women's
Cancer Center

Reid M. Ness, MD, MPH ¤
Vanderbilt-Ingram Cancer Center

Scott E. Regenbogen, MD ¶
University of Michigan
Comprehensive Cancer Center

Niloy Jewel Samadder, MD ¤
Huntsman Cancer Institute at the
University of Utah

Moshe Shike, MD ¤ Þ
Memorial Sloan Kettering Cancer Center

Thomas P. Slavin Jr, MD Δ
City of Hope Comprehensive
Cancer Center

Shajanpeter Sugandha, MD ¤
University of Alabama at Birmingham
Comprehensive Cancer Center

Jennifer M. Weiss, MD, MS ¤
University of Wisconsin
Carbone Cancer Center

NCCN
Mary Dwyer, MS
Ndiya Ogba, PhD

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≠ Pathology
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¥ Patient advocacy
* Discussion Writing Committee Member

NCCN Guidelines Panel Disclosures

# NCCN Guidelines Version 3.2017 Panel Members
# Genetic/Familial High-Risk Assessment: Colorectal



**MULTI-GENE TESTING SUBCOMMITTEE**
**Samir Gupta, MD ¤**
**UC San Diego Moores Cancer Center**

**Dennis J. Ahnen, MD ¤**
**University of Colorado Cancer Center**

**Heather Hampel, MS, CGC Δ**
**The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute**

**NCCN gratefully acknowledges the following individuals for participating in the review of the Lynch syndrome management recommendations for ovarian and endometrial cancer:**

**Travis Bray, PhD ¥**
**Hereditary Colon Cancer Foundation**

**Lee-may Chen, MD Ω**
**UCSF Helen Diller Family Comprehensive Cancer Center**

**Marta Ann Crispens, MD Ω**
**Vanderbilt-Ingram Cancer Center**

**Molly Daniels, MS, CGC Δ**
**The University of Texas MD Anderson Cancer Center**

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¥ Patient advocacy
* Discussion Writing Committee Member

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

To find clinical trials online at NCCN Member Institutions, click here: nccn.org/clinical_trials/physician.html.

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

See NCCN Categories of Evidence and Consensus.

# NCCN Guidelines Version 3.2017 Updates Genetic/Familial High-Risk Assessment: Colorectal

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**Updates in Version 3.2017 of the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal from Version 2.2017 include:**

**MS-1**

- The discussion section was updated to reflect the changes in the algorithm.

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**Updates in Version 2.2017 of the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal from Version 1.2017 include:**

**HRS-1**

- Assessment for hereditary cancer
  - After "Is there a personal history of a known genetic mutation or known genetic mutation in the family?" and the reply is "No," the following criteria was added, "Family history of: ≥1 relative with polyposis".
    - ◊ If the response to these criteria is "No" the next question was revised as, "Is there a personal history of ~~colorectal cancer (CRC), endometrial or~~ a Lynch syndrome-related cancer?"
    - ◊ If the response to this question is "No" the next question was revised as, "Is there a family history of ~~colorectal, endometrial or~~ a Lynch syndrome-related cancer?
    - ◊ If the response to this question is "No", then "See NCCN Guidelines for Colorectal Cancer Screening - Average risk," was clarified by adding, "unless other significant personal or family history that may indicate increased risk for hereditary cancer syndrome."
- Footnote a was added to this page, "LS-related cancers include colorectal, endometrial, gastric, ovarian, pancreas, ureter and renal pelvis, brain (usually glioblastoma), small intestinal cancers, as well as sebaceous adenoma, sebaceous carcinomas, and keratoacanthomas as seen in Muir-Torre Syndrome.
- Footnote b was added, "Increased risk warranting genetic evaluation many be indicated by, but not restricted to personal history of congenital hypertrophy of the retinal pigment epithelium, osteomas, supernumerary teeth, desmoid tumor, cribriform variant of papillary thyroid cancer, and hepatoblastoma."

**HRS-2**

- Footnote f was added to the page, "If evaluation is based on family history of ≥1 relative with polyposis, then type of polyps in affected relative (if known) may guide testing."

**HRS-3**

- The "Criteria For Further Risk Evaluation For High-Risk Syndromes For Unaffected (No Personal History of Colorectal or Endometrial Cancer or Concerning Polyposis)" heading has been revised as, "Evaluation to Exclude Lynch Syndrome."
  - The bullets were updated for both a personal history and family history of a Lynch syndrome-related cancer.
- Footnote g was added, "Tumor screening for mismatch repair deficiency is appropriate for all colorectal and endometrial cancers regardless of age at diagnosis, however, germline genetic testing is generally reserved for patients with early-age at diagnosis; positive family history; or abnormal tumor testing results: MSI or loss of mismatch repair protein expression. See LS-A for details on tumor screening for Lynch syndrome."

**LS-1**

- After "No known LS mutation," the criteria was revised as, "No tumor available or insufficient tumor *or affected relative unavailable*." Footnotes b and c were added to this criterion.

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# NCCN Guidelines Version 3.2017 Updates Genetic/Familial High-Risk Assessment: Colorectal

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**Updates in Version 1.2017 of the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal from Version 2.2016 include:**

**HRS-1**

- A new algorithm for the "Assessment for Hereditary CRC Syndrome" was added.
- This page now directs to
  - Risk Assessment/Genetic Evaluation for Possible Polyposis Syndromes (HRS-2)
  - Strategies for Evaluating for Lynch Syndrome (LS) (LS-1)
  - Criteria for Further Risk Evaluation for High-Risk Syndromes for Unaffected (No Personal History of Colorectal or Endometrial Cancer or Concerning Polyposis) (HRS-3)

**HRS-2**

- Risk Assessment/Genetic Evaluation for Possible Polyposis Syndromes has been adpated from a previous page.

**HRS-3**

- The "Criteria for Further Risk Evaluation for High-Risk Syndromes for Unaffected" has been revised to be for "Criteria For Further Risk Evaluation For High-Risk Syndromes For Unaffected (No Personal History of Colorectal or Endometrial Cancer or Concerning Polyposis)"
  - The bullets related to personal history were removed from the page.
  - Criteria were removed,
    - ◊ "Individual with multiple GI hamartomatous polyps (See PJS-1 and JPS-1 and NCCN Guidelines for Cowden Syndrome) or serrated polyposis syndrome (See SPS-1)."
    - ◊ "Individual with a desmoid tumor, multifocal or bilateral CHRPE, cribriform morular variant of papillary thyroid cancer, or hepatoblastoma."

**HRS-A 1 of 3**

- Directed examination for related manifestations
  - ◊ 3rd bullet was added, "Indicated only if suspicion of a specific syndrome" above eye exam, skin, oral exam, and measurement of head circumference.
- Footnote 1 was added, "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 mutation arising in the patient (de novo mutation), variable penetrance of a pathogenic mutation, autosomal recessive inheritance of risk, and mosaicism."

**Lynch Syndrome**

- Clinical Testing Criteria for Lynch Syndrome was removed and the appropriate criteria have been incorporated into other pages. The revised Bethesda criteria and Amsterdam II criteria will now be available in the discussion only.
- The algorithm page title, "Routine Tumor Testing Criteria For Lynch Syndrome" has been removed and the content incorporated into LS-1.

**LS-1**

- This page was previously for "Meets testing criteria for Lynch syndrome" and is now titled, "Strategies For Evaluating For Lynch Syndrome."
- Deleterious LS mutation known,
  - For genetic testing not done, a category 2B designation was added, along with a footnote, "The recommendation to manage patients in whom genetic testing was not done using LS-management recommendations is category 2B."
- Footnotes
  - Footnote a was moved to the page, "The panel recommends universal screening of all CRCs to maximize sensitivity for identifying individuals with Lynch syndrome and to simplify care processes. However, evidence suggests an alternate option would be to limit screening to individuals with CRC diagnosed <70 y plus those >70 meeting Bethesda guidelines. 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."
  - Footnote b was added, "Criteria that justify LS testing may include meeting Bethesda Guidelines (See Discussion), Amsterdam Criteria (See Discussion), cancer diagnosis prior to age 50, or having a predicted risk for Lynch syndrome >5% on one of the following prediction models: MMRpro, PREMM 1,2,6 or MMRpredict."
  - Footnote f was added, "The panel recommends tumor testing with IHC and/or MSI be used as the primary approach for pathology-lab based universal screening. If tumor is available, LS-specific testing or multi gene testing without IHC or MSI should only be utilized in select cases under direction of a clinician with expertise in genetics, and not be used as a universal testing strategy."
  - Footnote h was added, "This approach may be preferred in patients with a strong family history or if diagnosed age <50 y (Pearlman R, e al JAMA Oncol 2016; Yurgelun M eta l. J Clin Oncol 2017;35:1086-1095)."

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UPDATES

# NCCN Guidelines Version 3.2017 Updates
# Genetic/Familial High-Risk Assessment: Colorectal



**Updates in Version 1.2017 of the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal from Version 2.2016 include:**

**LS-2**
- **Lynch Syndrome Management**
  - **Footnote n was added, "The panel recognizes that there is limited population-based studies on the lifetime risk for most of the cancers related to each of these genes. Although, there are some mutation-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." (Also for LS-3 and LS-4)**
  - **Footnote o was added, "For MSH6, consider a later age of onset for colonoscopy."**
- **Other Extracolonic Cancers**
  - **Gastric and small bowel cancer recommendation was revised, "There are no clear data to support ~~screening~~ *surveillance* for gastric, duodenal, and small bowel cancer for LS. Selected individuals *with a family history of gastric, duodenal, or small bowel cancer* or those of Asian descent..."**
  - **Urothelial cancer recommendation was revised, "*Selected individuals such as with a family history of urothelial cancer or individuals with MSH2 mutations (especially males) may want to consider screening. Surveillance options may include* ~~Consider~~ annual urinalysis starting at 30–35 y. *However, there is insufficient evidence to recommend a particular surveillance strategy."***

**LS-3**
- **Other Extracolonic Cancers**
  - **Surveillance recommendations for endometrial and ovarian cancer were separated and extensively revised.**

**LS-5**
- **No pathologic findings and adenomas not amenable to endoscopic resection or high-grade dysplasia, the bullet "Consider prophylactic hysterectomy/BSO if postmenopausal or childbearing completed" wasremoved.**
- **Adenomas not amenable to endoscopic resection or high-grade dysplasia, "lower endoscopic exam every 1–2 y" was replaced with, "Examine all remaining colonic mucosa every 1–2 y."**

**LS-A 1 of 5**
- **IHC,**
  - **3rd bullet was revised by adding last the sentence, "BRAF testing is less specific than methylation testing of the MLH1 promoter and therefore there may be a role for methylation testing to rule out Lynch syndrome in MSI-H tumors in which no BRAF mutation is found."**
  - **4th bullet was added, "If clinical suspicion for Lynch syndrome is high despite a normal IHC screening result, consider genetic evaluation and testing."**

**LS-A 2 of 5**
- **The information on this page related to IHC was added.**

**LS-A 3 of 5**
- **"Pros and Cons of Universal Tumor Screening for LS Using Colonoscopy-Based Biopsy Versus Surgical Rsection Specimen" was added to this page.**

**LS-A 4 of 5**
- **"NOTE: If younger than age 50 regardless of LS test results, consider genetic evaluation" was added to the page.**

**LS-A 5 of 5**
- **The content of footnote d was extensively updated.**

**Continued on next page**

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**UPDATES**

# NCCN Guidelines Version 3.2017 Updates
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**Updates in Version 1.2017 of the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal from Version 2.2016 include:**

**LS-B 1 of 2**

- Colon, the general population risk was updated from 5.5% to 4.5%.
- Ovary risk was moved to LS-B 2 of 2 and for each gene, the cumulative risk from ages 40 to 70 y was added.

**Familial Adenomatous Polyposis**

**FAP-1**

- Footnote f was added, "A single pilot study among patients with FAP suggests the omega-3 polyunsaturated fatty acid eicosapentaenoic acid has potential to reduce size and number of polyps on follow up (West NJ, Clark SK, Phillips RK, et al. Gut 2010;59:918-925). However, 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."

**FAP-3**

- Footnote g, bullet 2 was revised, "Recommend examination with side-viewing endoscope, use of Spigelman's or other standardized staging, ~~and extensive biopsy of dense lesions to evaluate for advanced histology~~."

**FAP-4**

- APC positive and Not tested, the surveillance was revised from "Flexible sigmoidoscopy or colonoscopy every 12 mo beginning at age 10–15 y" to "Colonoscopy (preferred) or flexible sigmoidoscopy every 12 mo beginning at age 10–15 y."
- Not tested, "Consider substituting colonoscopy every 5 y beginning at age 20 y for the chance that the patient may have AFAP" was removed.

**Peutz-Jeghers Syndrome**

**PJS-2**

- Site
  - Ovary, "typically sex cord/Sertoli cell tumors" was added.
  - Cervix, "typically cervical adenoma malignum" was added.
  - Testes, "typically sex cord/Sertoli cell tumors" was added.
- Screening Procedure and Interval
  - Small intestine was revised, "Small bowel visualization (CT or MRI enterography *or video capsule endoscopy* baseline at 8–10 y..."

**Juvenile Polyposis Syndrome**

**JPS-1**

- Footnote d was added, "In families without an identified genetic mutation, consider substituting endoscopy every 5 y beginning at age 20 and every 10 years beginning at age 40 y in patients in whom no polyps are found."

**Multi-Gene Testing**

**GENE-3**

- Examples of clinical scenarios for which multi-gene testing should NOT be considered:
  - 1st bullet was revised from "A family with a known mutation" to "An individual from a family with a known mutation and no other reason for multi-gene testing."

**GENE-4, GENE-5, and GENE-6**

- The tables for "High-Risk CRC Genes on Multi-Gene Panels" and "Low- To Moderate-Risk CRC Genes On Multi-Gene Panels" were combined into "Evaluation of CRC Genes Commonly Included on Multi-Gene Panels." This is now Table 4.
- Table 4
  - A new column for "Strength of Evidence" was added for each gene.
  - AXIN2, MSH3 and NTHL1 were added.

**GENE-7**

- Table 5,
  - The heading was revised, "Recommended Management for Genes that May Confer ~~High Or Moderate~~ a Riskor Colorectal Cancer."
  - BLM heterozygotes and GALNT12 were removed.
  - AXIN2, MSH3, and NTHL1 were added.
  - For MUTYH heterozygotes, the recommendations were separated into its own row as follows:
    - ◊ For probands unaffected by colorectal cancer with a first-degree relative with colorectal cancer: Colonoscopy screening every 5 years, beginning at age 40 y or 10 years prior to age of first-degree relative's age at CRC diagnosis.
    - ◊ For probands unaffected by colorectal cancer with NO family history of colorectal cancer: Data are uncertain if specialized screening is warranted.

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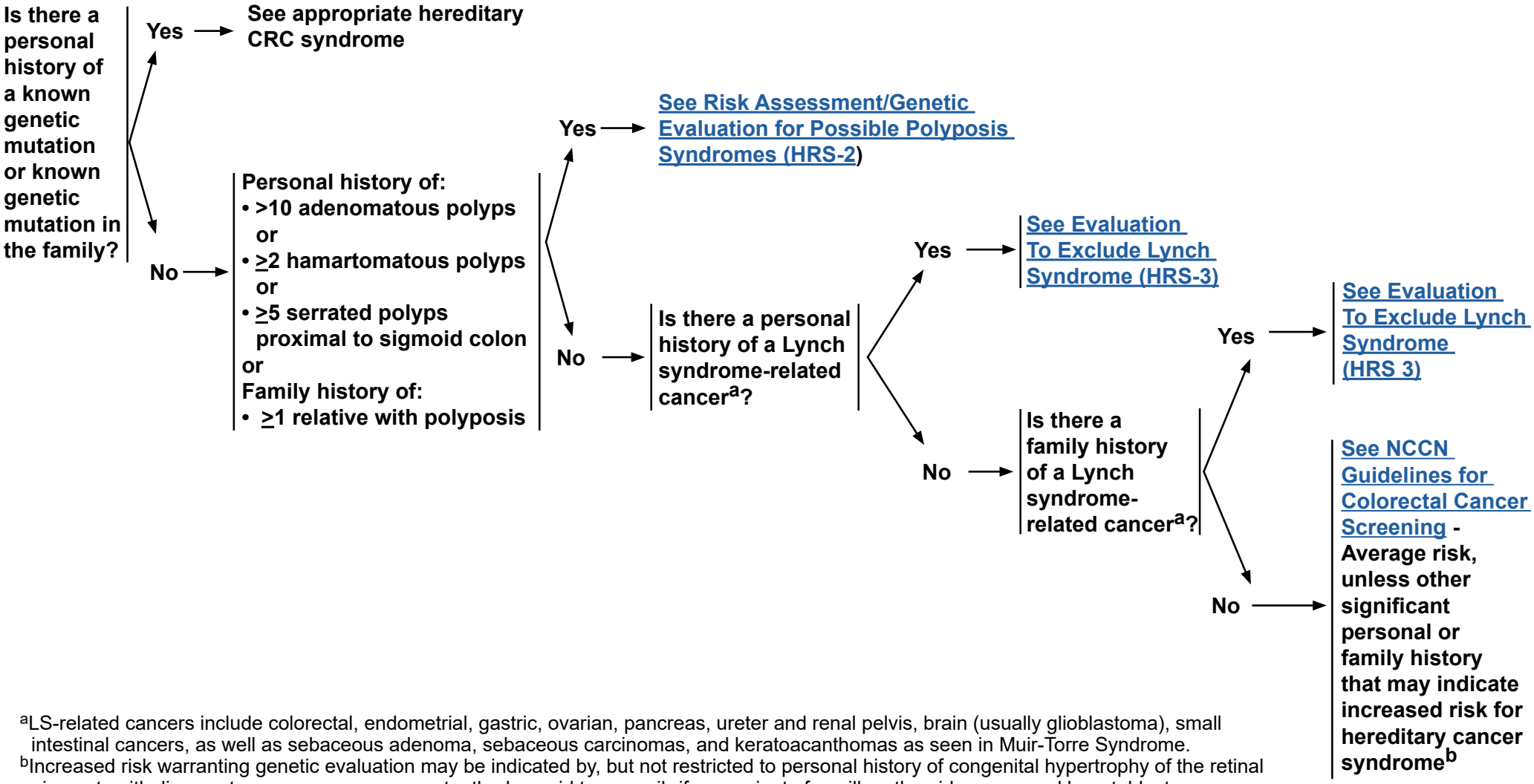
**UPDATES**

## ASSESSMENT FOR HEREDITARY CRC SYNDROME




[a]LS-related cancers include colorectal, endometrial, gastric, ovarian, pancreas, ureter and renal pelvis, brain (usually glioblastoma), small intestinal cancers, as well as sebaceous adenoma, sebaceous carcinomas, and keratoacanthomas as seen in Muir-Torre Syndrome.
[b]Increased risk warranting genetic evaluation may be indicated by, but not restricted to personal history of congenital hypertrophy of the retinal pigment epithelium, osteomas, supernumerary teeth, desmoid tumor, cribriform variant of papillary thyroid cancer, and hepatoblastoma.

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### RISK ASSESSMENT/GENETIC EVALUATION FOR POSSIBLE POLYPOSIS SYNDROMES[c,d,e]

- Detailed family history[f]
- Detailed medical and surgical history
- Directed examination for related manifestations
- Psychosocial assessment and support
- Risk counseling
- Education support
- Discussion of genetic testing[d]
- Informed consent
- Patient advocacy support

**>10 adenomas** →
- Classical familial adenomatous polyposis (FAP)
- Attenuated FAP (AFAP)
- *MUTYH*-associated polyposis (MAP)

→ See *APC* and *MUTYH* Genetic Testing Criteria (APC/MUTYH-1)

**>2 hamartomatous polyps** →
- Peutz-Jeghers syndrome (PJS) (See PJS-1)
- Juvenile polyposis syndrome (JPS) (See JPS-1)
- Cowden/PTEN hamartoma tumor syndrome (See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian)

**≥5 serrated polyps** → Serrated polyposis syndrome (SPS) (See SPS-1)

[c] See Obtaining a Comprehensive Assessment for Hereditary Colorectal Cancer (HRS-A).
[d] 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.
[e] If personal history of CRC and more than one syndrome might explain the presentation, consider multi-gene testing.
[f] If evaluation is based on family history of ≥1 relative with polyposis, then type of polyps in affected relative (if known) may guide testing.

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### EVALUATION TO EXCLUDE LYNCH SYNDROME

- **Known Lynch syndrome mutation in the family**
- **An individual with colorectal or endometrial cancer diagnosed <50 y**
- **An individual with colorectal or endometrial cancer and another synchronous or metachronous LS-related cancer[a]**
- **An individual with colorectal or endometrial cancer and ≥1 first-degree or second-degree relative with LS-related cancer[a] diagnosed <50 y**
- **An individual with colorectal or endometrial cancer and ≥2 first-degree or second-degree relatives with LS-related cancers;[a] regardless of age**
- **An individual with colorectal or endometrial cancer at any age with tumor showing evidence of mismatch repair deficiency, either by MSI or loss of mismatch repair protein expression[g]**
- **Family history of ≥1 first-degree relative with colorectal or endometrial cancer diagnosed <50 y**
- **Family history of ≥1 first-degree relative with colorectal or endometrial cancer and another synchronous or metachronous LS-related cancer[a]**
- **Family history of ≥2 first-degree or second-degree relative with LS-related cancer,[a] including ≥1 diagnosed <50 y**
- **Family history of ≥3 first-degree or second-degree relatives with LS-related cancers,[a] regardless of age**
- **An individual with a LS-related cancer or unaffected individual with a ≥5% risk of having an MMR gene mutation based on predictive models (PREMM5, MMRpro, MMRpredict)**

→ See Strategies For Evaluating LS (LS-1)

[a]LS-related cancers include colorectal, endometrial, gastric, ovarian, pancreas, ureter and renal pelvis, brain (usually glioblastoma), small intestinal cancers, as well as sebaceous adenoma, sebaceous carcinomas, and keratoacanthomas as seen in Muir-Torre Syndrome.

[g]Tumor screening for mismatch repair deficiency is appropriate for all colorectal and endometrial cancers regardless of age at diagnosis, however, germline genetic testing is generally reserved for patients with early-age at diagnosis; positive family history; or abnormal tumor testing results: MSI or loss of mismatch repair protein expression. See LS-A for details on tumor screening for Lynch syndrome.

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### OBTAINING A COMPREHENSIVE ASSESSMENT FOR HEREDITARY COLORECTAL CANCER[1]

**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
  - Great-grandparents
  - Cousins
  - Nieces and nephews

See Common Pedigree Symbols (HRS-A 2 of 3)
and
Pedigree: First-, Second-, and Third-Degree Relatives of Proband (HRS-A 3 of 3)

- Minimal data set on each affected relative:
  - Current age and age at diagnosis of cancer (medical record documentation of cancer is strongly encouraged)
  - Age and cause of death
  - Type of cancer (note multiple primaries)
  - Ethnicity/country of origin
  - Consanguinity
  - Suspected colon cancer syndromes and additional syndrome-specific features (eg, Muir-Torre syndrome, Turcot syndrome, PJS, juvenile polyposis)[2]
  - All other inherited conditions and birth defects

**Detailed medical and surgical history**

- Pathology verification strongly encouraged
- Polyps
- Inflammatory bowel disease
- Inherited syndromes:
  - Lynch syndrome (LS)
    - ◊ Muir-Torre syndrome
    - ◊ Turcot syndrome
  - FAP and associated syndromes
    - ◊ AFAP
    - ◊ Gardner syndrome
    - ◊ Turcot syndrome
  - MAP
  - PJS
  - JPS
  - *PTEN*-Hamartoma tumor syndromes
    - ◊ Cowden syndrome
    - ◊ Bannayan-Riley-Ruvalcaba syndrome

**Directed examination for related manifestations**

- Colonoscopy
- Esophagogastroduodenoscopy (EGD)
- Indicated only if suspicion of a specific syndrome
  - Eye examination
  - Skin, soft-tissue, and bone examination
  - Oral examination
  - Measurement of head circumference (≥97%, 58 cm in adult women, 60 cm in adult men)

[1]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 mutation arising in the patient (de novo mutation), variable penetrance of a pathogenic mutation, autosomal recessive inheritance of risk, and mosaicism.

[2]Burt R and Neklason DW. Genetic testing for inherited colon cancer. Gastroenterology 2005;128:1696-1716.

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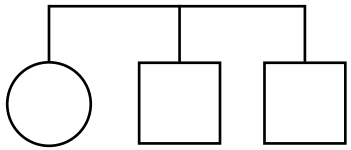
### OBTAINING A COMPREHENSIVE ASSESSMENT FOR HEREDITARY COLORECTAL CANCER

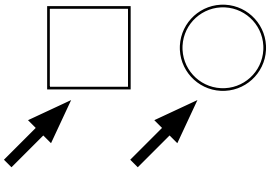
### COMMON PEDIGREE SYMBOLS[3]

Male, Female

Mating

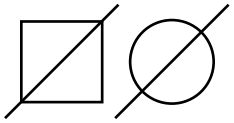


Sibship

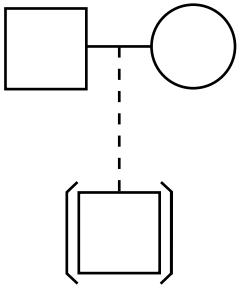


Proband (patient initiating genetic workup)

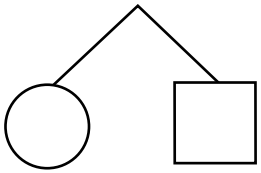
Affected with trait



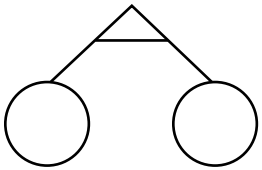
Deceased



Adopted into a family

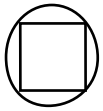


Dizygotic twins



Monozygotic twins

Female to male transsexual



Male to female transsexual

See Pedigree: First-, Second-, and Third-Degree Relatives of Proband (HRS-A 3 of 3)

[3]Bennett RL, Steinhaus KA, Uhrich SB, et al. Recommendations for standardized human pedigree nomenclature. Am J Hum Genet 1995;56:745-752.

**Note: All recommendations are category 2A unless otherwise indicated.**
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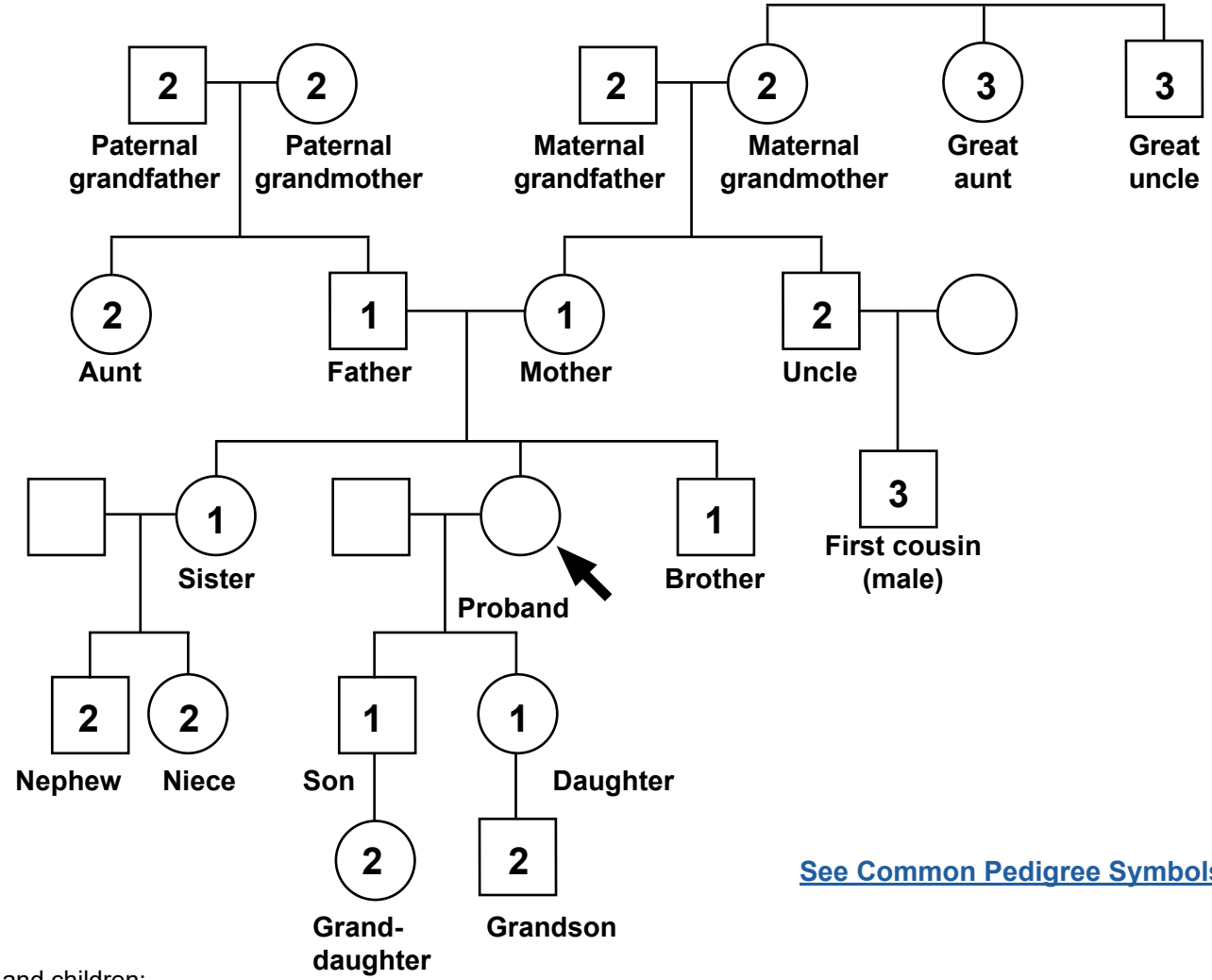
### OBTAINING A COMPREHENSIVE ASSESSMENT FOR HEREDITARY COLORECTAL CANCER

### PEDIGREE: FIRST-, SECOND-, AND THIRD-DEGREE RELATIVES OF PROBAND[4]




See Common Pedigree Symbols (HRS-A 2 of 3)

[4]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, and first cousins.

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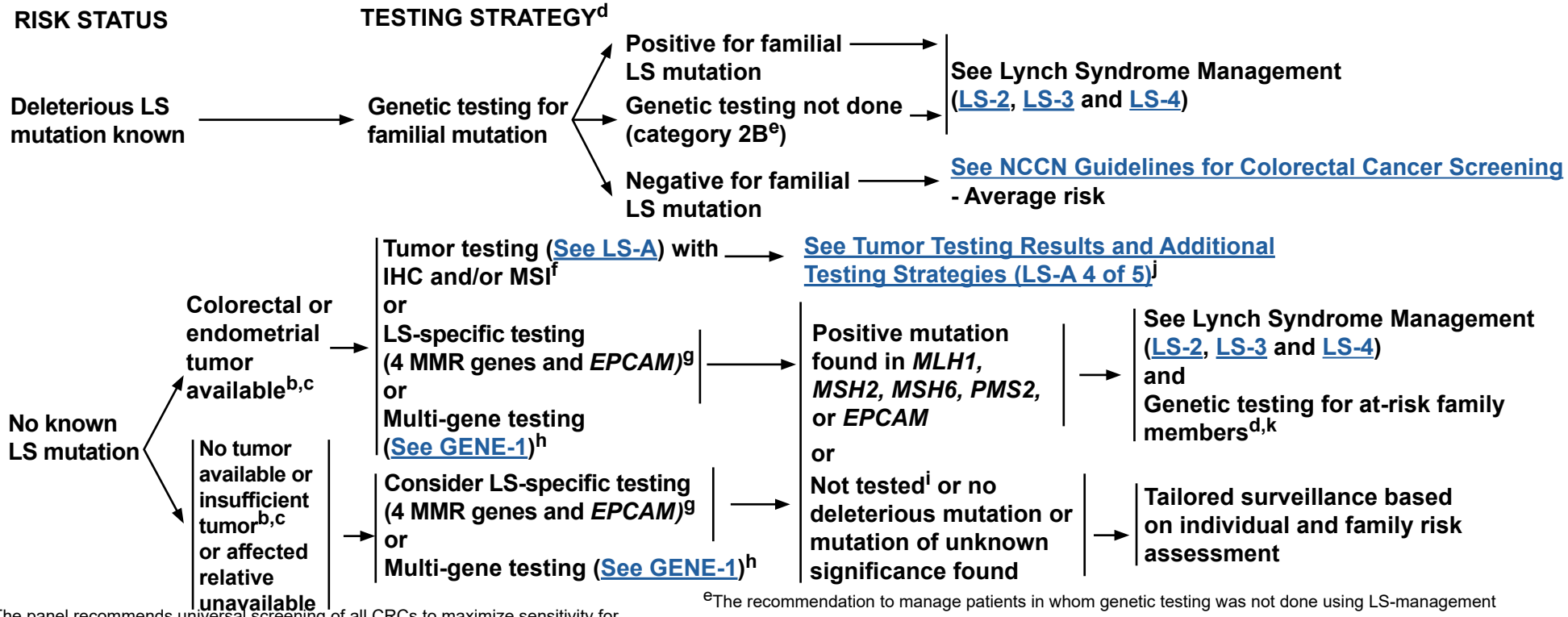
## STRATEGIES FOR EVALUATING FOR LYNCH SYNDROME[a]




[a] The panel recommends universal screening of all CRCs to maximize sensitivity for identifying individuals with Lynch syndrome and to simplify care processes. However, evidence suggests an alternate option would be to limit screening to individuals with CRC diagnosed <70 y plus those >70 meeting Bethesda guidelines. 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.

[b] Criteria that may justify LS testing include meeting Bethesda Guidelines (See Discussion), Amsterdam Criteria (See Discussion), cancer diagnosis prior to age 50, or having a predicted risk for Lynch syndrome >5% on one of the following prediction models: MMRpro, PREMM5 or MMRpredict.

[c] If there is more than one affected family member, first consider: youngest age at diagnosis, multiple primaries, and colorectal or endometrial cancers. Limitations of interpreting test results should be discussed if testing tumors other than colorectal or endometrial cancers. If IHC/MSI previously done, see LS-A 4 of 5.

[d] Proper pretest counseling should be done by an individual with expertise in genetics.

[e] The recommendation to manage patients in whom genetic testing was not done using LS-management recommendations is category 2B.

[f] The panel recommends tumor testing with IHC and/or MSI be used as the primary approach for pathology-lab–based universal screening. If tumor is available, LS-specific testing or multi-gene testing without IHC or MSI should only be utilized in select cases under direction of a clinician with expertise in genetics, and should not be used as a universal testing strategy.

[g] The decision to test all 4 MMR genes and *EPCAM* concurrently versus sequentially (stepwise) is left to the discretion of the clinician.

[h] This approach may be preferred in patients with a strong family history or if diagnosed age <50 y (Pearlman R, et al. JAMA Oncol 2016; Yurgelun M, et al. J Clin Oncol 2017;35:1086-1095).

[i] Testing of unaffected family members when no affected member is available should be considered. Significant limitations of interpreting test results should be discussed.

[j] For individuals found to have a deleterious LS mutation, see LS management recommendations.

[k] An at-risk family member can be defined as a first-degree relative of an affected individual and/or proband. If a first-degree relative is unavailable or unwilling to be tested, more distant relatives should be offered testing for the known mutation in the family.

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## LYNCH SYNDROME MANAGEMENT

**Surveillance for *MLH1*, *MSH2*, *MSH6, PMS2,* and *EPCAM* Mutation Carriers[l,m,n]**

- **Colon cancer:**
  - **Colonoscopy at age 20–25 y[o] or 2–5 y prior to the earliest colon cancer if it is diagnosed before age 25 y and repeat every 1–2 y.**
  - **There are data to suggest that aspirin may decrease the risk of colon cancer in LS but optimal dose and duration of aspirin therapy are uncertain**

→ See Follow-up of Surveillance Findings (LS-5)

**Other Extracolonic Cancers**

- **Gastric and small bowel cancer:**
  - **There are no clear data to support surveillance for gastric, duodenal, and small bowel cancer for LS. Selected individuals with a family history of gastric, duodenal, or small bowel cancer or those of Asian descent (Vasen HF, et al. Gut 2013;62:812-823) have an increased risk and may benefit from surveillance. If surveillance is performed, may consider upper endoscopy with visualization of the duodenum at the time of colonoscopy every 3–5 y beginning at age 30–35 y. Consider testing and treating H. pylori.**
- **Urothelial cancer:**
  - **Selected individuals such as with a family history of urothelial cancer or individuals with MSH2 mutations (especially males) may want to consider screening. Surveillance options may include annual urinalysis starting at 30–35 y. However, there is insufficient evidence to recommend a particular surveillance strategy.**
- **Central nervous system (CNS) cancer:**
  - **Consider annual physical/neurologic examination starting at 25–30 y; no additional screening recommendations have been made.**
- **Pancreatic cancer:**
  - **Despite data indicating an increased risk for pancreatic cancer, no effective screening techniques have been identified; therefore, no screening recommendation is possible at this time.**
- **Breast cancer:**
  - **There have been suggestions that there is an increased risk for breast cancer in LS patients; however, there is not enough evidence to support increased screening above average-risk breast cancer screening recommendations.**

**Lynch Syndrome Management continued on LS-3 and LS-4**

[l] See Cancer Risk Up to Age 70 Years in Individuals with Lynch Syndrome Compared to the General Population (LS-B).
[m] Other than colon and endometrial cancer, screening 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 mutation-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] For *MSH6*, consider a later age of onset for colonoscopy.

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## LYNCH SYNDROME MANAGEMENT

**Surveillance for *MLH1*, *MSH2*, *MSH6, PMS2,* and *EPCAM* Mutation Carriers[l,m,n]**

**Other Extracolonic Cancers**

- **Endometrial cancer:**
  - **Because endometrial cancer can often be detected early based on symptoms, women 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.**
  - **Hysterectomy has not been shown to reduce endometrial cancer mortality, but can reduce the incidence of endometrial cancer. Therefore, hysterectomy is a risk-reducing option that should be considered.**
  - **Timing of hysterectomy should be individualized based on whether childbearing is complete, comorbidities, family history, and LS gene, as risks for endometrial cancer vary by mutated gene.**
  - **Endometrial cancer screening does not have proven benefit in women with LS. However, endometrial biopsy is both highly sensitive and highly specific as a diagnostic procedure. Screening via endometrial biopsy every 1 to 2 years can be considered.**
  - **Transvaginal ultrasound to screen for endometrial cancer in postmenopausal women 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 women 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 by women who have completed childbearing 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 mutated gene.**
  - **Since there is no effective screening for ovarian cancer, women 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 woman's baseline should prompt her to seek evaluation by her physician.**
  - **While there may be circumstances where clinicians find screening helpful, data do not support routine ovarian cancer screening for LS. Transvaginal ultrasound for ovarian cancer screening has not been shown to be sufficiently sensitive or specific as to support a routine recommendation, but may be considered at the clinician's discretion. Serum CA-125 is an additional ovarian screening test with caveats similar to transvaginal ultrasound.**
- **Consider risk reduction agents for endometrial and ovarian cancers, including discussing risks and benefits (See Discussion for details).**

[l] See Cancer Risk Up to Age 70 Years in Individuals with Lynch Syndrome Compared to the General Population (LS-B).
[m] Other than colon and endometrial cancer, screening 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. However, there are some mutation-specific data available and a generalized screening approach is suggested. Screening and the option of risk-reducing surgeries should be individualized after risk assessment and counseling.

**Lynch Syndrome Management continued on LS-4.**

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## LYNCH SYNDROME MANAGEMENT

### Surveillance for *MLH1*, *MSH2*, *MSH6, PMS2,* and *EPCAM* Mutation Carriers[l,m,n]

**Reproductive Options**

- **For patients of reproductive age, advise about options for prenatal diagnosis and assisted reproduction including pre-implantation genetic diagnosis. 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 (constitutional MMR deficiency [CMMRD syndrome] Wimmer K, et al. J Med Genet 2014;51:355-365.) if both partners are a carrier of a mutation/s in the same MMR gene or *EPCAM* (for example, if both partners carry a mutation in the *PMS2* gene, then their future offspring have a risk for 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 at-risk relatives.**

[l] See Cancer Risk Up to Age 70 Years in Individuals with Lynch Syndrome Compared to the General Population (LS-B).
[m] Other than colon and endometrial cancer, screening 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. However, there are some mutation-specific data available and a generalized screening approach is suggested. Screening and the option of risk-reducing surgeries should be individualized after risk assessment and counseling.

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| SURVEILLANCE COLONOSCOPY FINDINGS | FOLLOW-UP |
|---|---|
| No pathologic findings | • Continued surveillance[p] |
| Adenocarcinomas | See appropriate NCCN Guidelines for Treatment of Cancer by Site |
| Adenomas | • Endoscopic polypectomy with follow-up colonoscopy every 1–2 y depending on:<br>▸ location, character<br>▸ surgical risk<br>▸ patient preference |
| Adenomas not amenable to endoscopic resection or high-grade dysplasia | • Segmental or extended colectomy depending upon clinical scenario[q] → Examine all remaining colonic mucosa every 1–2 y |

[p]May consider subtotal colectomy if patient is not a candidate for optimal surveillance.
[q]The type of surgical procedure chosen should be based on individual considerations and discussion of risk. Surgical management is evolving. See Definitions of Common Colorectal Resections (CSCR-B) in the NCCN Guidelines for Colorectal Cancer Screening.

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## PRINCIPLES OF IHC AND MSI TESTING FOR LYNCH SYNDROME

**General**

- IHC and MSI analyses are screening tests (either by themselves or in conjunction) that are typically done on colon and endometrial cancer tissue to identify individuals at risk for LS. Greater than 90% of LS tumors are MSI-H (microsatellite instability-high) and/or lack expression of at least one of the mismatch repair (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 (an inherited mutation of one of the MMR genes or *EPCAM*). Mutant BRAF V600E is found in the majority of sporadic MSI CRCs and is rarely found in LS-related CRCs. Thus, the presence of an abnormal MLH1 IHC test increases the possibility of LS but does not make a definitive diagnosis. Those with a germline mutation are then identified as LS patients. Also, sporadic endometrial cancers may exhibit abnormal MSI/IHC due to abnormal methylation of the MLH1 promoter. Somatic MMR genetic testing of the corresponding gene(s) (see "Plausible Etiologies" for possibilities on LS-A 4 of 5) could be performed on tumor DNA to asses for somatic mutations that might explain the abnormal IHC and/or MSI results.
- The Bethesda criteria (See LS-1) are intended to help identify CRC patients whose tumors should be tested for MMR defects, by MSI and/or IHC analysis, thereby identifying patients with a greater chance of having LS. Although more sensitive than the Amsterdam criteria, up to 50% of patients with LS do not meet even the revised Bethesda Guidelines.

**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 mutation is present. An abnormal test means that at least one of the proteins is not expressed and an inherited mutation may be present in the related gene. Loss of protein expression by IHC in any one of the MMR genes guides genetic testing (mutation 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 presence of expression.
- Abnormal MLH1 IHC should be followed by tumor testing for presence of *BRAF* V600E mutation (or with IHC for *BRAF*) or hypermethylation of the *MLH1* promoter, which are associated with sporadic colorectal tumors (or for sporadic endometrial tumors hypermethylation of *MLH1* promoter only), and subsequently by genetic testing if the latter are negative (See LS-A 4 of 5). Those with a germline mutation are then identified as LS patients. *BRAF* V600E mutation tumor testing does not apply to endometrial cancer. BRAF testing is less specific than methylation testing of the MLH1 promoter and therefore there may be a role for methylation testing to rule out Lynch syndrome in MSI-H tumors in which no BRAF mutation is found.
- If clinical suspicion for Lynch syndrome is high despite a normal IHC screening result, consider genetic evaluation and testing.
- There is a 5%–10% false-negative rate with IHC testing.

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## PRINCIPLES OF IHC AND MSI TESTING FOR LYNCH SYNDROME

**IHC (continued)**

- **Adenomas:**
  - **IHC can also be performed on colorectal adenomas if cancer tissue is not available. Abnormal 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.[1,2,3] The suboptimal sensitivity of IHC performed on polyps means this approach should not be used to exclude LS. An abnormal polyp IHC result should be referred for genetic evaluation and testing. If PMS2 and MLH1 are missing, further tumor testing should be considered before referring for genetic testing.**
- **Rectal cancers treated with neoadjuvant chemotherapy and radiation therapy:[4]**
  - **False abnormal IHC has been reported in rectal cancer resection specimens after neoadjuvant chemo and RT. As a result, some member institutions avoid doing IHC on rectal cancers after neoadjuvant chemo and RT. Others still perform IHC on rectal cancers after neoadjuvant chemo and RT, but if expression is absent (particularly MSH6 or PMS2) the testing is repeated on the pretreatment biopsy.**
- **Sebaceous neoplasms:[5-9]**
  - **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.**
- **Metastatic colorectal cancer (liver, lymph node, and other metastases):[10]**
  - **There are data showing that the MSI and the IHC results in primary tumors matches the MSI and IHC results in the metastatic tissue from the same tumor, so this should be an acceptable alternative if the primary tumor is not available.**

Continued on next page

[1]Pino MS, et al. Deficient DNA mismatch repair is common in Lynch syndrome-associated colorectal adenomas. J Mol Diagn 2009;11:238-247.
[2]Walsh MD, et al. Immunohistochemical testing of conventional adenomas for loss of expression of mismatch repair proteins in Lynch syndrome mutation carriers: a case series from the Australasian site of the colon cancer family registry. Mod Pathol 2012;25:722-730.
[3]Yurgelun MB, Goel A, Hornick JL, et al. Microsatellite instability and DNA mismatch repair protein deficiency in Lynch syndrome colorectal polyps. Cancer Prev Res (Phila) 2012;5:574-582.
[4]Vilkin A, Halpern M, Morgenstern S, et al. How reliable is immunohistochemical staining for DNA mismatch repair proteins performed after neoadjuvant chemoradiation? Hum Pathol 2014;45:2029-2036.
[5]Roberts ME, Riegert-Johnson DL, Thomas BC, et al. Screening for Muir-Torre syndrome using mismatch repair protein immunohistochemistry of sebaceous neoplasms. J Genet Couns 2013;22:393-405.
[6]Hampel H, Frankel WL, Martin E, et al. Feasibility of screening for Lynch syndrome among patients with colorectal cancer. J Clin Oncol 2008;26: 5783-5788.
[7]Hampel H, Stephens JA, Pukkala E, et al. Cancer risk in hereditary nonpolyposis colorectal cancer syndrome: later age of onset. Gastroenterology 2005;129:415-421.
[8]Lindor NM, Burgart LJ, Leontovich O, et al. Immunohistochemistry versus microsatellite instability testing in phenotyping colorectal tumors. J Clin Oncol 2002;20:1043-1048.
[9]Roberts ME, Riegert-Johnson DL, Thomas BC, et al. A clinical scoring system to identify patients with sebaceous neoplasms at risk for the Muir-Torre variant of Lynch syndrome. Genet Med. 2014;16:711-716.
[10]Haraldsdottir S, Roth R, Pearlman R, et al. Mismatch repair deficiency concordance between primary colorectal cancer and corresponding metastasis. Fam Cancer 2017;15:253-260.

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## PRINCIPLES OF IHC AND MSI 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.[11]**
- **There is a 5%–10% false-negative rate with MSI testing.**

### Pros and Cons of Universal Tumor Screening for LS Using Colonoscopy-Based Biopsy Versus Surgical Resection Specimen[12,13]

**Pre-surgical testing considerations**

- **Enables surgical decision-making (subtotal vs. segmental resection)**
- **Rectal tumors have not yet been exposed to neoadjuvant chemotherapy and RT so IHC is more reliable than after neoadjuvant chemotherapy[14,15]**
- **Often not enough tumor or normal tissue to do MSI analysis**
- **Screening could be done twice (once on biopsy and once on surgical resection), thereby decreasing cost effectiveness**
- **Patient may be lost to follow-up if he/she doesn't have surgery or has surgery elsewhere**

**Surgical testing considerations**

- **Cannot inform surgical decision-making**
- **Rectal tumors with neoadjuvant chemotherapy and RT could have false absence of MSH6**
- **Can perform MSI and/or IHC**
- **Ensures test is only done once**
- **Patient may be less likely to be lost to follow-up**

Continued on next page

[11]Xicola RM, Llor X, Pons E. Performance of different microsatellite marker panels for detection of mismatch repair-deficient colorectal tumors. J Natl Cancer Inst. 2007;99:244-52.
[12]Kumarasinghe AP, de Boer B, Bateman AC, Kumarasinghe MP. DNA mismatch repair enzyme immunohistochemistry in colorectal cancer: a comparison of biopsy and resection material. Pathology 2010;42:414-420.
[13]Shia J, Stadler Z, Weiser MR, et al. Immunohistochemical staining for DNA mismatch repair proteins in intestinal tract carcinoma: How reliable are biopsy samples? Am J Surg Pathol 2011;35:447-454.
[14]Bao F, Panarelli NC, Rennert H, et al. Neoadjuvant therapy induces loss of MSH6 expression in colorectal carcinoma. Am J Surg Pathol 2010;34:1798-1804.
[15]Radu OM, Nikiforova MN, Farkas LM, Krasinskas AM. Challenging cases encountered in colorectal cancer screening for Lynch syndrome reveal novel findings: nucleolar MSH6 staining and impact of prior chemoradiation therapy. Hum Patho 2011;42:1247-128.

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## TUMOR TESTING RESULTS AND ADDITIONAL TESTING STRATEGIES

| Tumor Testing[a] | | | | | | | Plausible Etiologies | Additional Testing[d,e] NOTE: If younger than age 50 regardless of LS test results, consider genetic evaluation. |
|---|---|---|---|---|---|---|---|---|
| IHC | | | | MSI | *BRAF* V600E[b] | MLH1 Promoter Methylation | | |
| *MLH1* | *MSH2* | *MSH6* | *PMS2* | | | | | |
| + | + | + | + | MSS/MSI-Low | N/A | N/A | 1) Sporadic cancer<br>2) Other (not Lynch syndrome) hereditary CRC syndrome | 1) None[c] |
| + | + | + | + | MSI- High | N/A | N/A | 1) Germline mutation in any LS gene<br>2) Sporadic cancer | 1) Germline LS genetic testing[f]<br>2) If germline testing negative, consider somatic MMR genetic testing[h] |
| N/A | N/A | N/A | N/A | MSI- High | N/A | N/A | 1) Sporadic cancer<br>2) Germline mutation in any of the LS genes | 1) Consider IHC analysis and additional testing depending on IHC results<br>2) If IHC not performed, consider germline LS genetic testing[f] |
| -- | + | + | -- | N/A | N/A | N/A | 1) Sporadic cancer<br>2) Germline mutation *MLH1* or rarely *PMS2* | 1) Consider *BRAF*[b]/methylation studies<br>2) Germline LS genetic testing[f] |
| -- | + | + | -- | N/A | Positive | N/A | 1) Sporadic cancer<br>2) Rarely germline *MLH1* mutation or constitutional *MLH1* epimutation | 1) None, unless young age of onset or significant family history; then consider constitutional *MLH1* epimutation testing[g] and/or germline LS genetic testing[f] |
| -- | + | + | -- | N/A | Negative | Positive | 1) Sporadic cancer<br>2) Rarely germline *MLH1* mutation or constitutional *MLH1* epimutation | |
| -- | + | + | -- | N/A | Negative | Negative | 1) Germline mutation *MLH1* or rarely *PMS2*<br>2) Sporadic cancer | 1) Germline LS genetic testing[f]<br>2) If germline testing negative, consider somatic MMR genetic testing[h] |
| + | -- | -- | + | N/A | N/A | N/A | 1) Germline mutation *MSH2*/*EPCAM*; rarely germline mutation in *MSH6*<br>2) Sporadic cancer | |
| + | + | + | -- | N/A | N/A | N/A | 1) Germline mutation *PMS2*<br>2) Germline mutation *MLH1* | |
| + | -- | + | + | N/A | N/A | N/A | 1) Germline mutation *MSH2/EPCAM*<br>2) Sporadic cancer | |
| + | + | -- | + | N/A | N/A | N/A | 1) Germline mutation *MSH6*<br>2) Germline mutation *MSH2*<br>3) Sporadic cancer/Treatment effect[i] | 1) Germline LS genetic testing[f]<br>2) If applicable, consider MSI analysis or repeat IHC testing on nontreated tumor[i]<br>3) If germline testing negative, consider somatic MMR genetic testing[h] |
| -- | + | + | + | N/A | N/A | N/A | 1) Germline mutation *MLH1*; possibly sporadic cancer or *PMS2* mutation | 1) Germline LS genetic testing[f]<br>2) If germline testing of *MLH1* negative, consider *BRAF*[b]/methylation studies<br>3) If germline testing negative, consider somatic MMR genetic testing[h] |
| -- | -- | -- | -- | N/A | N/A | N/A | 1) Germline mutation in *any* LS gene<br>2) Sporadic cancer | |

N/A = Either testing was not done or results may not influence testing strategy. + normal staining of protein -- absent staining of protein

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See Footnotes on LS-A 5 of 5

## TUMOR TESTING RESULTS AND ADDITIONAL TESTING STRATEGIES

**Footnotes from LS-A 4 of 5**

[a]Tumor testing strategies apply to colorectal and endometrial cancers. Limited data exist regarding the efficacy of tumor testing in other LS tumors.

[b]Testing is not appropriate for tumors other than colorectal cancer.

[c]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.

[d]Studies have shown that 45%–68% of cases with unexplained defective MMR (MSI-high and/or abnormal IHC with no evidence of MLH1 promoter hypermethylation when indicated) have double somatic mutations (either two pathogenic sequence mutations or one pathogenic sequence mutation and loss of heterozygosity) in the MMR genes. (Sourrouille I, Coulet F, Lefevre JH, et al. Fam Cancer 2013;12:27-33. Mensenkamp A, Vogelaar I, van Zelst-Stams W, et al. Gastroenterology 2014;146:643-646. Geurts-Giele W, Leenen C, Dubbink H, et al. J Pathol 2014;234:548-559. Haraldsdottir S, Hampel H, Tomsic J, et al. Gastroenterology 2014;147:1308-1316.) As a result, tumor sequencing may be helpful for individuals with tumor testing showing deficient MMR and no germ-line mutation detected. If double somatic mutations are identified or if the testing does not help clarify the result, *it is recommended that these patients and their close relatives be managed based on their family history and NOT as if they have Lynch syndrome.* However, if one somatic mutation only or LOH of one allele only is identified in the tumor, this could mean that the patient has Lynch syndrome due to an unidentifiable germline mutation and these represent the “second hit” in the tumor. For these patients, it is recommended that they and their close relatives follow Lynch syndrome surveillance guidelines. Genetic consultation should be considered for interpretation of complex results.

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

[f]Germline LS genetic testing may include testing of the gene/s that are indicated (see “Plausible Etiologies” for possibilities on LS-A 4 of 5) by the abnormal tumor test results, or instead, multi-gene testing that includes *MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM* concurrently may be performed.

[g]Evaluation for constitutional *MLH1* epimutation involves *MLH1* promoter hypermethylation studies on blood or other sources of normal tissue.

[h]Somatic MMR genetic testing of the corresponding gene(s) (see “Plausible Etiologies” for possibilities on LS-A 4 of 5) could be performed on tumor DNA to asses for somatic mutations that might explain the abnormal IHC and/or MSI results.

[i]Absent *MSH6* in rectal tumor tissue may be due to treatment effect (neoadjuvant chemoradiotherapy).

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

# NCCN Guidelines Version 3.2017
# Lynch Syndrome

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**Cancer Risk Up to Age 70 Years in Individuals with Lynch Syndrome Compared to the General Population**

| Cancer | General Population Risk[1] | *MLH1* or *MSH2*[1,2] | | *MSH6*[2,3] | | *PMS2*[4] | |
|---|---|---|---|---|---|---|---|
| | | Risk | Mean Age of Onset | Risk | Mean Age of Onset | Risk | Mean Age of Onset |
| Colon | 4.5% | 52%–82% | 44–61 years | 10%–22% | 54 years | 15%–20% | 61–66 years |
| Endometrium | 2.7% | 25%–60% | 48–62 years | 16%–26% | 55 years | 15% | 49 years |
| Stomach | <1% | 6%–13% | 56 years | ≤3% | 63 years | † | 70–78 years |
| Ovary | 1.6% | See LS-B 2 of 2 | | | | | |
| Hepatobiliary tract | <1% | 1%–4% | 50–57 years | Not reported | Not reported | † | Not reported |
| Urinary tract | <1% | 1%–7%[6] | 54–60 years | <1% | 65 years | † | Not reported |
| Small bowel | <1% | 3%–6% | 47–49 years | Not reported | 54 years | † | 59 years |
| Brain/CNS | <1% | 1%–3% | ~50 years | Not reported | Not reported | † | 45 years |
| Sebaceous neoplasms | <1% | 1%–9% | Not reported | Not reported | Not reported | Not reported | Not reported |
| Pancreas[5] | <1% | 1%–6% | Not reported | Not reported | Not reported | Not reported | Not reported |

[1]Adapted from Kohlmann W, Gruber SB (Updated May 22, 2014) Lynch Syndrome. In: GeneReviews at GeneTests: Medical Genetics Information Resource (database online). Copyright, University of Washington, Seattle. 1993-2014. Available at http://www.genetests.org. Accessed June 2, 2017.
[2]Bonadona V, et al. JAMA 2011;305:2304-2310.
[3]Baglietto L, Lindor NM, Dowty JG, et al. J Natl Cancer Inst 2010;102:193-201.
[4]Senter L, et al. Gastroenterology 2008;135:419-428.
[5]Kastrinos F, et al. JAMA 2009;302:1790-1795.
[6]Risk for MSH2 mutations may be higher (Joost P, et al. Urology 2015;86:1212-1217).
†The combined risk for renal pelvic, stomach, ovary, small bowel, ureter, and brain is 6% to age 70 (Senter L, et al. Gastroenterology 2008;135:419-428).

**Note: All recommendations are category 2A unless otherwise indicated.**
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## Cancer Risk Up to Age 70 Years in Individuals with Lynch Syndrome Compared to the General Population

| Cancer | General Population Risk | Ref.[7] | *MLH1* | | | | | Ref.[7] | *MSH2* | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Cumulative Risk by Age in Years, % (95% confidence interval) | | | | Mean Age of Onset | | Cumulative Risk by Age in Years, % (95% confidence interval) | | | | Mean Age of Onset |
| Ovary | 1.6% | | 40 | 50 | 60 | 70 | | | 40 | 50 | 60 | 70 | |
| | | Ref. 1 | 0 (0-2) | 4 (0-11) | 15 (1-45) | 20 (1-65) | 45 years | Ref. 1 | 1 (0-3) | 4 (1-9) | 11 (2-28) | 24 (3-52) | 43 years |
| | | Ref. 2 | 1 (0-3.6) | 7 (2.2-11.2) | 9 (2.9-12.2) | 11 (3.2.19.8) | | Ref. 2 | 4 (0.0-8.9) | 12 (4.2-20.2) | 15 (5.5-24.4) | 15 (5.5-24.4) | |
| | | | | | | | | | | | | | |
| | | | *MSH6*[8] | | | | | | *PMS2*[8] | | | | |
| | | | Cumulative Risk by Age in Years, % (95% confidence interval) | | | | Mean Age of Onset | | Cumulative Risk by Age in Years, % (95% confidence interval) | | | | Mean Age of Onset |
| | | | 40 | 50 | 60 | 70 | | | 40 | 50 | 60 | 70 | |
| | | Ref. 1 | 0 | 0 (0-1) | 1 (0-2) | 1 (0-3) | 46 years | Ref. 3 | † | † | † | † | 42 years |
| | | Ref. 2 | 0 (-) | 0 (-) | 0 (-) | 0 (-) | | Ref. 2 | 0 (-) | 0 (-) | 0 (-) | 0 (-) | |

Reference 1: Bonadona V, et al. JAMA 2011;305:2304-2310.
Reference 2: Moller P, et al. Gut 2017;66:464–472.
Reference 3: Senter L, et al. Gastroenterology 2008;135:419-428.

[7]In both of the referenced papers by Bonadona V et al and Moller P et al, some women received prophylactic oophorectomy; thus risk estimates might be underestimated.

[8]Sample size of women with *MSH6* and *PMS2* mutations were small in both the Bonadona V et al and Moller P et al studies; larger studies may clarify risk for *MSH6* and *PMS2* mutation carriers.

†The combined risk for renal pelvic, stomach, ovary, small bowel, ureter, and brain is 6% to age 70 (Senter L, et al. Gastroenterology 2008;135:419-428).

**Note: All recommendations are category 2A unless otherwise indicated.**
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# NCCN Guidelines Version 3.2017
# *APC* and *MUTYH* Genetic Testing Criteria

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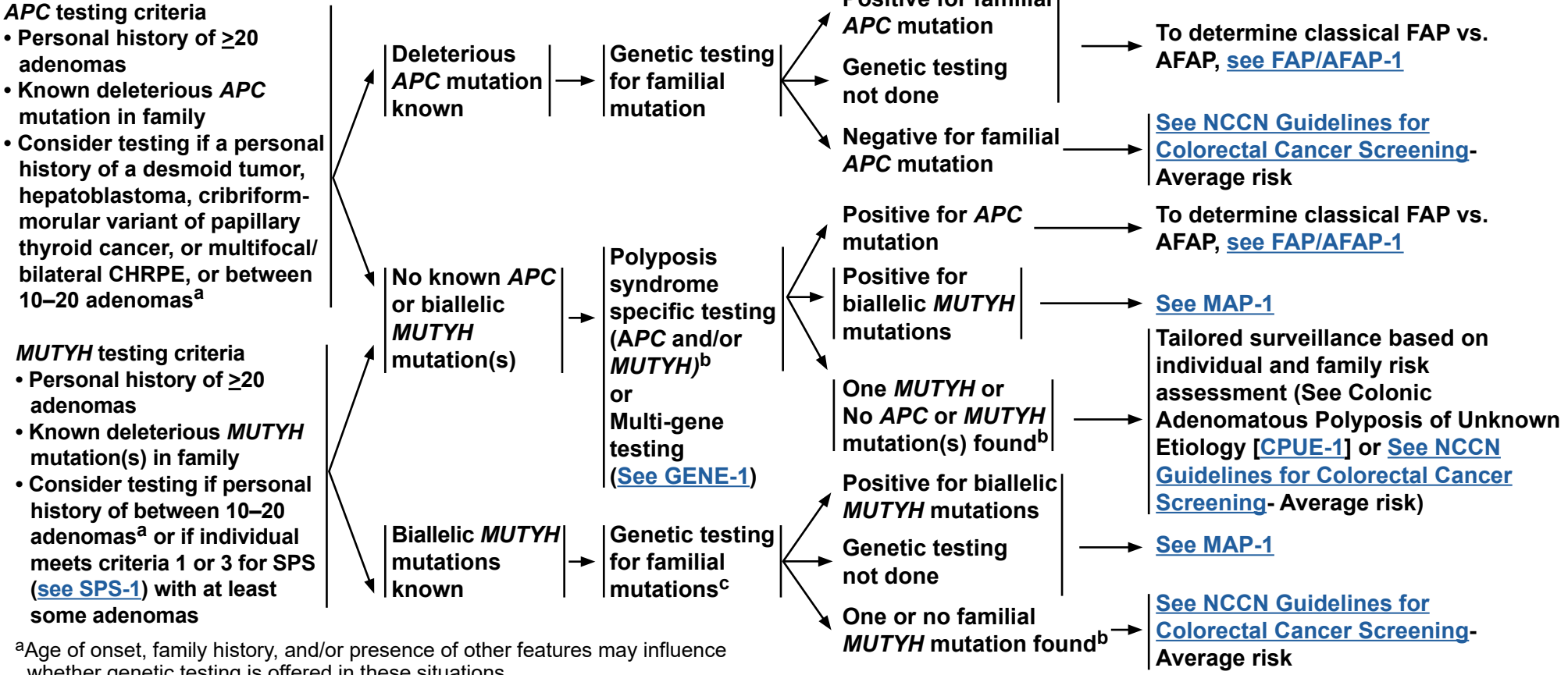


[a]Age of onset, family history, and/or presence of other features may influence whether genetic testing is offered in these situations.

[b]When colonic polyposis is present in a single person with a negative family history, consider testing for a *de novo APC* mutation; if negative, follow with testing of *MUTYH* (targeted testing for the two common northern European founder mutations c.536A>G and c.1187G>A may be considered first followed by full sequencing if biallelic mutations are not found). When colonic polyposis is present only in siblings, consider recessive inheritance and test for *MUTYH* first. Order of testing for *APC* and *MUTYH* is at the discretion of the clinician. *MUTYH* genetic testing is not indicated based on a personal history of a desmoid tumor, hepatoblastoma, cribriform-morular variant of papillary thyroid cancer, or multifocal/bilateral CHRPE.

[c]Siblings of a patient with MAP are recommended to have site-specific testing for the familial mutations. Full sequencing of *MUTYH* may be considered in an unaffected parent when the other parent has MAP. If the unaffected parent is found to not have a *MUTYH* mutation, 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 children. If the unaffected parent is found to have one *MUTYH* mutation, testing the children for the familial *MUTYH* mutations is indicated.

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

# NCCN Guidelines Version 3.2017
# Familial Adenomatous Polyposis/AFAP

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**PHENOTYPE**

**RISK STATUS**

**Classical FAP:[a]**
- **Germline *APC* mutation**
- **Presence of ≥100 polyps[b] (sufficient for clinical suspicion of FAP) or fewer polyps at younger ages, especially in a family known to have FAP**
- **Autosomal dominant inheritance[c] (except with de novo mutation)**
- **Possible associated additional findings**
  - **Congenital hypertrophy of retinal pigment epithelium (CHRPE)**
  - **Osteomas, supernumerary teeth, odontomas**
  - **Desmoids, epidermoid cysts**
  - **Duodenal and other small bowel adenomas**
  - **Gastric fundic gland polyps**
- **Increased risk for medulloblastoma, papillary carcinoma of the thyroid (<2%), and hepatoblastoma (1%–2%, usually age ≤5 y)**
- **Pancreatic cancers (<1%)**
- **Gastric cancers (<1%)**
- **Duodenal cancers (4%–12%)**

**Personal history of classical FAP** → **See Treatment and Surveillance (FAP-1)**

**Family history of classical FAP, unaffected (no symptoms, findings, adenomas), family mutation known** → **See Genetic Testing and Surveillance (FAP-4)**

**AFAP[d]**
- **Germline *APC* mutation**
- **Presence of 10–<100 adenomas (average of 30 polyps)**
- **Frequent right-sided distribution of polyps**
- **Adenomas and cancers at age older than classical FAP (mean age of cancer diagnosis >50 y)**
- **Upper GI findings, thyroid and duodenal cancer risks are similar to classical FAP**
- **Other extraintestinal manifestations, including CHRPE and desmoids, are unusual**

**Personal history of AFAP** → **See Treatment and Surveillance (AFAP-1)**

**Family history of AFAP, unaffected (no symptoms, findings, adenomas), family mutation known** → **See Genetic Testing and Surveillance (AFAP-2)**

[a]A clinical diagnosis of FAP is suspected when >100 polyps are present at a young age; however, genetic testing of *APC* and *MUTYH* is important to differentiate FAP from MAP or colonic polyposis of unknown etiology. Identification of a germline *APC* mutation confirms the diagnosis of FAP.
[b]Individuals with >100 polyps occurring at older ages (35–40 years or older) may be found to have AFAP.
[c]There is a 30% spontaneous new mutation rate; thus, family history may be negative. This is especially noteworthy if onset age <50 y.
[d]There is currently no consensus on what constitutes a clinical diagnosis of AFAP. AFAP is considered when >10–<100 adenomas are present and is confirmed when an *APC* mutation is identified. Genetic testing of *APC* and *MUTYH* is important to differentiate AFAP from MAP or colonic polyposis of unknown etiology.

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

# NCCN Guidelines Version 3.2017
# Familial Adenomatous Polyposis

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## CLASSICAL FAP TREATMENT AND SURVEILLANCE: PERSONAL HISTORY

| | TREATMENT | SURVEILLANCE[d,e] (POSTCOLECTOMY) | |
|---|---|---|---|
| Personal history of classical FAP | → Proctocolectomy or colectomy[a,b,c] | → **Colon cancer:**<br>• If patient had colectomy with ileorectal anastomosis, then endoscopic evaluation of the rectum every 6–12 mo depending on polyp burden.<br>• If patient had total proctocolectomy (TPC) with ileal pouch-anal anastomosis (IPAA) or ileostomy, then endoscopic evaluation of the ileal pouch or ileostomy every 1–3 y depending on polyp burden. Surveillance frequency should be increased to every 6 mo for large, flat polyps with villous histology and/or high-grade dysplasia.<br>• The use of chemoprevention[f] is to facilitate management of the remaining rectum post-surgery. 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.<br><br>**Extracolonic surveillance (See FAP-2)** | → **In retained rectosigmoid, colectomy if dense polyposis or severe dysplasia**<br><br>**If cancer found, see appropriate NCCN Guidelines for Treatment of Cancer by Site** |

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

[b] See Surgical Options for Treating the Colon and Rectum in Patients with FAP (FAP-A).

[c] 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.

[d] It is recommended that patients be managed by physicians or centers with expertise in FAP and that management be individualized to account for genotype, phenotype, and personal considerations.

[e] Other than colon cancer, screening recommendations are expert opinion rather than evidence-based.

[f] A single pilot study among patients with FAP suggests the omega-3 polyunsaturated fatty acid eicosapentaenoic acid has potential to reduce size and number of polyps on follow up (West NJ, Clark SK, Phillips RK, et al. Gut 2010;59:918-925). However, 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.

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

## CLASSICAL FAP SURVEILLANCE: PERSONAL HISTORY

**SURVEILLANCE[d,e] (POSTCOLECTOMY)**

**Extracolonic:**

- **Duodenal or periampullary cancer: Upper endoscopy (including complete visualization of the ampulla of Vater) starting at around age 20–25 y. Consider baseline upper endoscopy earlier, if colectomy before age 20 y.**

→ See Duodenoscopic Findings (FAP-3)

- **Gastric cancer: Examine stomach at time of upper endoscopy.**
  - **Fundic gland polyps occur in a majority of FAP patients, and focal low-grade dysplasia can occur but is typically non-progressive. For this reason, special screening or surgery should only be considered in the presence of high-grade dysplasia.**
  - **Non-fundic gland polyps should be managed endoscopically if possible. Patients with polyps that cannot be removed endoscopically but with high-grade dysplasia or invasive cancer detected on biopsy should be referred for gastrectomy.**
- **Thyroid cancer: Annual thyroid examination, starting in late teenage years. Annual thyroid ultrasound may be considered, though data to support this recommendation are lacking.**
- **CNS cancer: An annual physical examination; due to limited data, no additional screening recommendation is possible at this time.**
- **Intra-abdominal desmoids: Annual abdominal palpation. If family history of symptomatic desmoids, consider abdominal MRI with and without contrast or CT with contrast within 1–3 y post-colectomy and then every 5–10 y. Suggestive abdominal symptoms should prompt immediate abdominal imaging. Data to support screening and treatment are limited.**
- **Small bowel polyps and cancer: Consider adding small bowel visualization to CT or MRI for desmoids as outlined above, especially if duodenal polyposis is advanced.**
- **Hepatoblastoma: No recommendations have been made for FAP; however, there are other situations where the high risk for hepatoblastoma has been observed and the following recommendations have been considered:**
  - **Liver palpation, abdominal ultrasound, and measurement of AFP every 3–6 mo during the first 5 y of life. Screening in a clinical trial is preferred.**
- **Pancreatic cancer: Due to limited data, no screening recommendation is possible at this time.**

[d]It is recommended that patients be managed by physicians or centers with expertise in FAP and that management be individualized to account for genotype, phenotype, and personal considerations.
[e]Other than colon cancer, screening recommendations are expert opinion rather than evidence-based.

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| DUODENOSCOPIC FINDINGS | SURVEILLANCE[g] |
|---|---|
| **Stage 0, No polyposis** | **Repeat endoscopy every 4 y** |
| **Stage I, Minimal polyposis (1–4 tubular adenomas, size 1–4 mm)** | **Repeat endoscopy every 2–3 y** |
| **Stage II, Mild polyposis (5–19 tubular adenomas, size 5–9 mm)** | **Repeat endoscopy every 1–3 y** |
| **Stage III, Moderate polyposis (≥20 lesions, or size ≥1 cm)** | **Repeat endoscopy every 6–12 mo** |
| **Stage IV, Dense polyposis or high-grade dysplasia** | **• Surgical evaluation<br>• Expert surveillance every 3–6 mo<br>• Complete mucosectomy or duodenectomy, or Whipple procedure if duodenal papilla is involved** |

[g]Duodenal Surveillance:

- It is recommended that patients be managed by physicians or centers with expertise in FAP and that management be individualized to account for genotype, phenotype, and personal considerations, including potential risks and benefits. Management that includes endoscopic treatment may require shorter intervals.
- Recommend examination with side-viewing endoscope and use of Spigelman's or other standardized staging. More intensive surveillance and/or treatment is required in patients with large or villous adenomas, and with advancing age >50 y. Surgical counseling is advisable for patients with stage IV polyposis. (Spigelman AD, Williams CB, Talbot IC, et al. Upper gastrointestinal cancer in patients with familial adenomatous polyposis. Lancet 1989;2:783-785).
- Endoscopic treatment options include endoscopic papillectomy in addition to excision or ablation of resectable large (>1 cm) or villous adenomas, as well as mucosectomy of resectable advanced lesions, including contained high-grade dysplasia, to potentially avert surgery while observing pathology guidelines for adequate resection.
- Surgery is recommended for invasive carcinoma as well as for dense polyposis or high-grade dysplasia that cannot be managed endoscopically.

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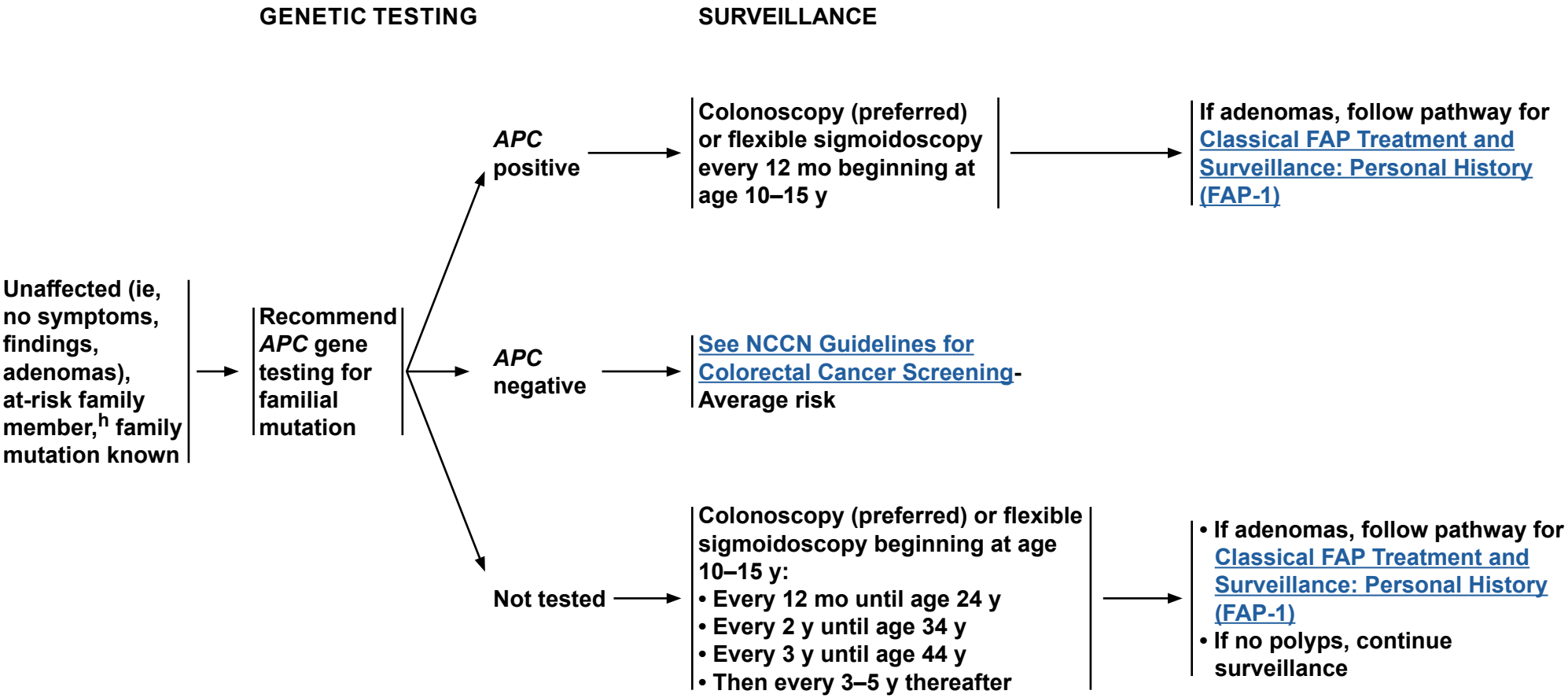
## CLASSICAL FAP GENETIC TESTING AND SURVEILLANCE: FAMILY HISTORY OF CLASSICAL FAP MUTATION KNOWN




[h]An at-risk family member can be defined as a first-degree relative of an affected individual and/or proband. If a first-degree relative is unavailable or unwilling to be tested, more distant relatives should be offered testing for the known mutation in the family.

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

**TAC/IRA is generally recommended for AFAP and TPC/IPAA is generally recommended for FAP.[b]**

### TOTAL ABDOMINAL COLECTOMY WITH ILEORECTAL ANASTOMOSIS (TAC/IRA)

- Indications:
  - The decision to remove the rectum is dependent on whether the polyps are amenable to endoscopic surveillance and resection.
- Contraindications:
  - Severe rectal disease (size or number of polyps)
  - Patient not reliable for follow-up surveillance of retained rectum
- Advantages:
  - Technically straightforward
  - Relatively low complication rate
  - Good functional outcome
  - No permanent or temporary stoma
  - Avoids the risks of sexual or bladder dysfunction and decreased fecundity that can occur following proctectomy
- Disadvantages
  - Risk of metachronous cancer in the remaining rectum

### TOTAL PROCTOCOLECTOMY WITH END ILEOSTOMY (TPC/EI)

- Indications:
  - Very low, advanced rectal cancer
  - Inability to perform IPAA
  - Patient with IPAA with unacceptable function
  - Patient with a contraindication to IPAA
- Advantages:
  - Removes risk of CRC
  - One operation
- Disadvantages:
  - Risks of sexual or bladder dysfunction
  - Permanent stoma
  - May discourage family members from seeking evaluation for fear of permanent stoma

### TOTAL PROCTOCOLECTOMY WITH ILEAL POUCH-ANAL ANASTOMOSIS (TPC/IPAA)

- Indications:
  - Severe disease in colon and/or rectum
  - After TAC/IRA with unstable rectum
  - Curable rectal cancer
  - Patient unreliable for follow-up after TAC/IRA
- Contraindications:
  - 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)
- Advantages:
  - Minimal risk of rectal cancer
  - No permanent stoma
  - Reasonable bowel function
- Disadvantages:
  - Complex operation
  - Usually involves temporary stoma
  - Risks of sexual or bladder dysfunction
  - Functional results are variable

[a] It is recommended that patients be managed by physicians or centers with expertise in FAP and that management be individualized to account for genotype, phenotype, and personal considerations.

[b] In certain circumstances such as AFAP with mainly proximal polyps, the extent of colectomy may be modified based on the burden of adenoma distribution and number.

**Note: All recommendations are category 2A unless otherwise indicated.**
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# NCCN Guidelines Version 3.2017
# Attenuated Familial Adenomatous Polyposis

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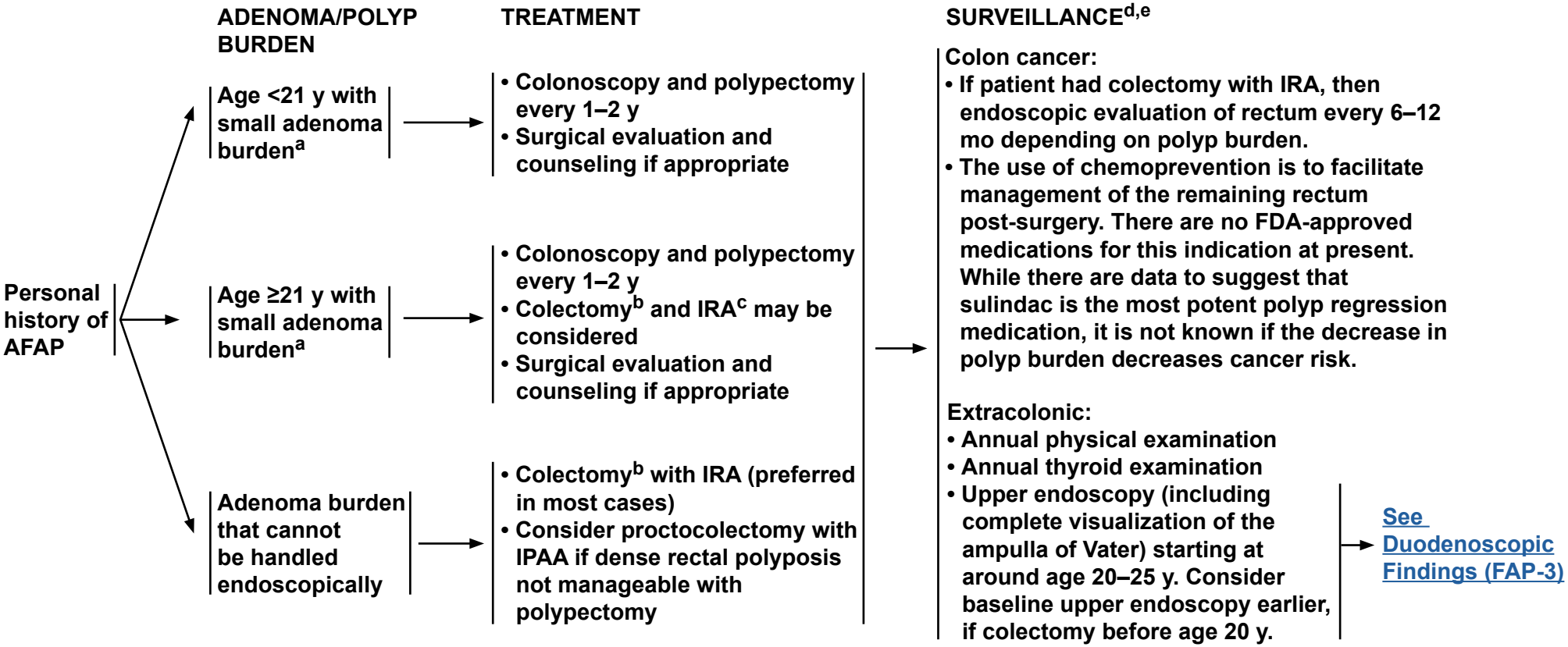
## ATTENUATED FAP TREATMENT AND SURVEILLANCE: PERSONAL HISTORY




[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 profusion, especially if colonoscopy is difficult and polyp control is uncertain. Surgery should 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]See Surgical Options for Treating the Colon and Rectum in Patients with FAP (FAP-A).

[c]Earlier surgical intervention should be considered in noncompliant patients.

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

[e]Surveillance for upper GI findings for AFAP is similar to classical FAP.

**Note: All recommendations are category 2A unless otherwise indicated.**
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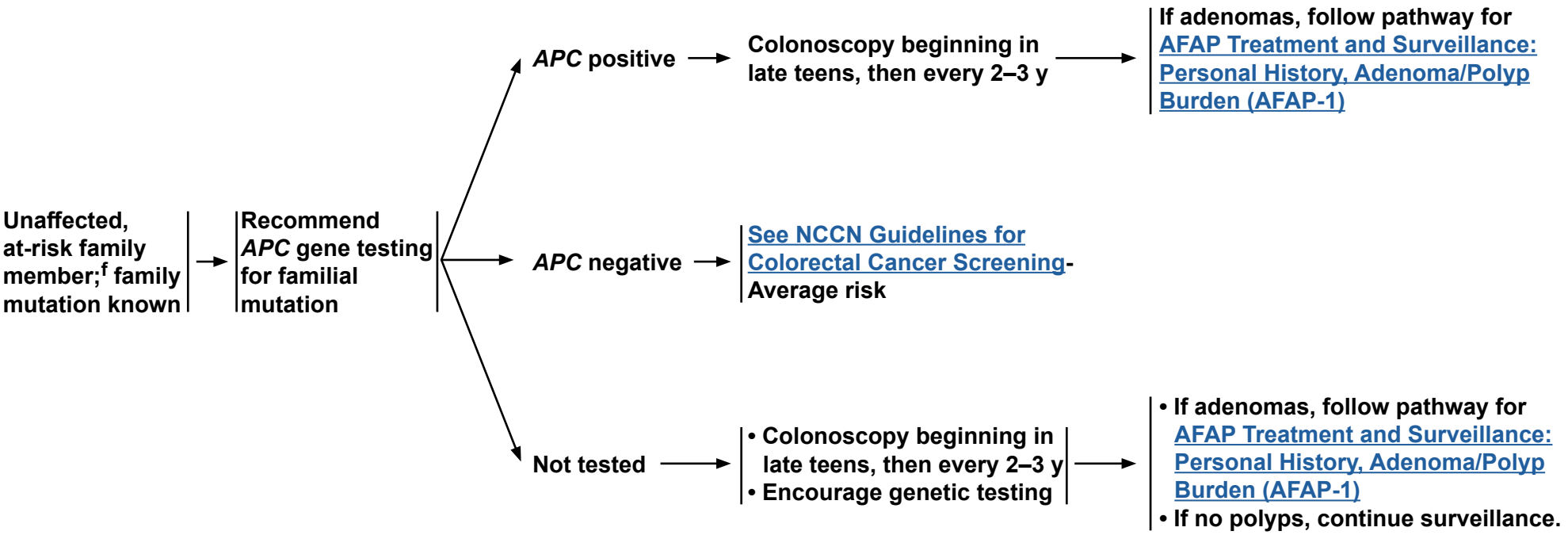
## ATTENUATED FAP GENETIC TESTING AND SURVEILLANCE: FAMILY HISTORY OF ATTENUATED FAP MUTATION KNOWN




[f]An at-risk family member can be defined as a first-degree relative of an affected individual and/or proband. If a first-degree relative is unavailable or unwilling to be tested, more distant relatives should be offered testing for the known mutation in the family.

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# NCCN Guidelines Version 3.2017
# *MUTYH*-Associated Polyposis

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**PHENOTYPE**

- **Biallelic *MUTYH* mutations**
- **Polyposis or colon cancers consistent with autosomal recessive inheritance (ie, parents unaffected, siblings affected)**
- **Consanguinity**
- **Fewer than 100 adenomas[a] (range 0–100s and uncommonly >1000)**
- **Adenomas and CRC at age older than classical FAP (median CRC age >50 y)**
- **Duodenal cancer (5%)**
- **Duodenal polyps**

**RISK STATUS**

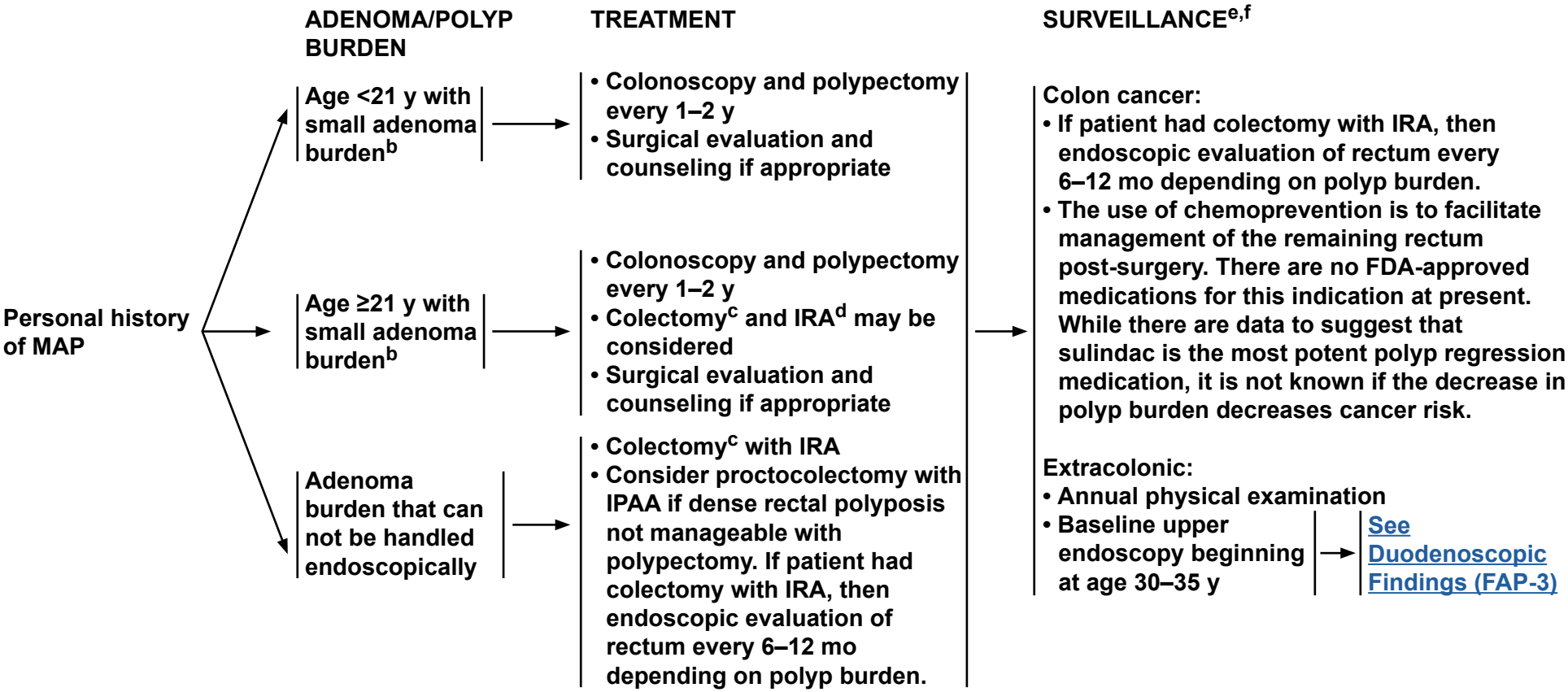
**Personal history of MAP** → **See Treatment and Surveillance (MAP-2)**

**Unaffected, at-risk family member; family mutation known** → **See 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 serrated polyposis syndrome.

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

## MAP TREATMENT AND SURVEILLANCE: PERSONAL HISTORY




[b]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 profusion, especially if colonoscopy is difficult and polyp control is uncertain. Surgery should 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.

[c]See Surgical Options for Treating the Colon and Rectum in Patients with FAP (FAP-A).

[d]Earlier surgical intervention should be considered in noncompliant patients.

[e]It is recommended that patients be managed by physicians or centers with expertise in MAP and that management be individualized to account for genotype, phenotype, and personal considerations.

[f]Surveillance for upper GI findings for MAP is similar to classical FAP.

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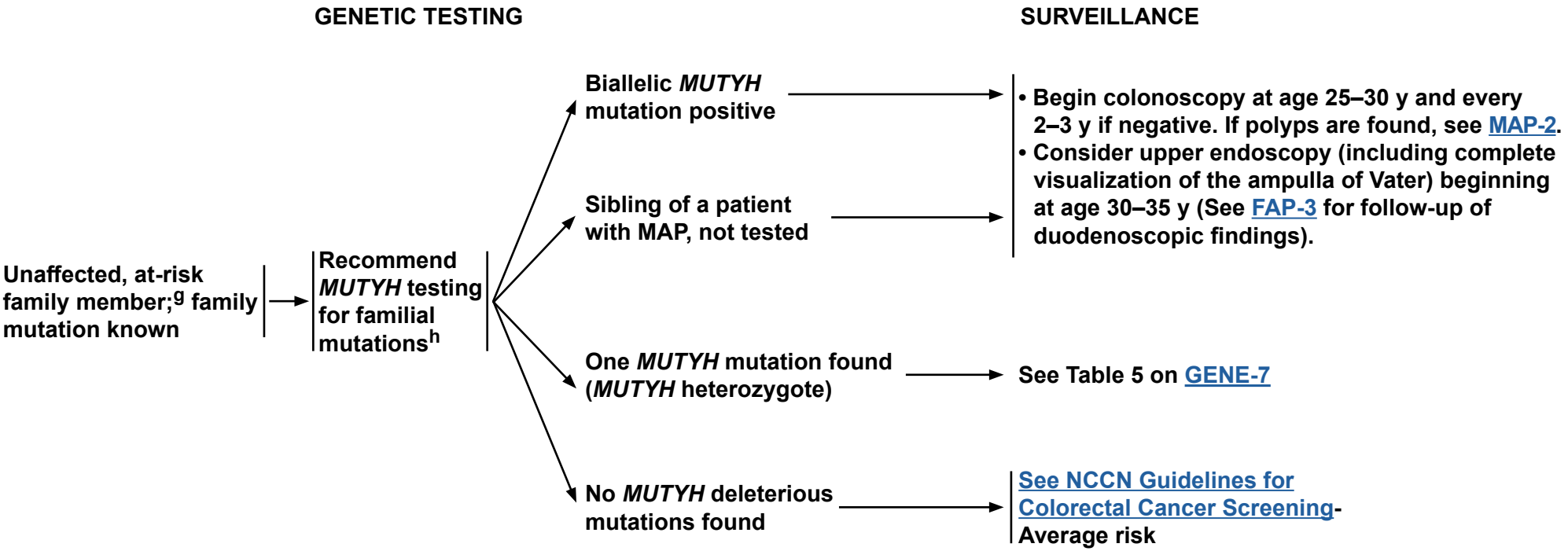
## MAP TREATMENT AND SURVEILLANCE: FAMILY HISTORY OF MAP MUTATION KNOWN




[g]An at-risk family member 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* mutation.

[h]Siblings of a patient with MAP are recommended to have site-specific testing for the familial mutations. Full sequencing of *MUTYH* may be considered in an unaffected parent when the other parent has MAP. If the unaffected parent is found to not have a *MUTYH* mutation, 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 children. If the unaffected parent is found to have one *MUTYH* mutation, testing the children for the familial *MUTYH* mutations is indicated.

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# NCCN Guidelines Version 3.2017
# Peutz-Jeghers Syndrome



**PJS definition**:[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 small intestine**
  - **Mucocutaneous hyperpigmentation of the mouth, lips, nose, eyes, genitalia, or fingers**
  - **Family history of PJS**

**Surveillance considerations**:

- **The majority of cases occur due to mutations in the *STK11 (LKB1)* gene. Clinical genetic testing is available.**
- **Referral to a specialized team is recommended and participation in clinical trials is especially encouraged.**
- **Surveillance should begin at the approximate ages on PJS-2 if symptoms have not already occurred, and any early symptoms should be evaluated thoroughly.**
- **The surveillance guidelines (See PJS-2) for the multiple organs at risk for cancer are provisional, but may be considered in view of the cancer risks in PJS and the known utility of the tests. There are limited data regarding the efficacy of various screening modalities in PJS.**

See Cancer Risk and Surveillance Guidelines (PJS-2)

[a]Tomlinson IP, Houlston RS. Peutz-Jeghers syndrome. J Med Genet 1997;34:1007-1011.
[b]Due to the rarity of the syndrome and complexities of diagnosing and managing individuals with Peutz-Jeghers syndrome, referral to a specialized team is recommended.

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

**Peutz-Jeghers Syndrome: Cancer Risk and Surveillance Guidelines**

| Site | % Lifetime Risk | Screening Procedure and Interval | Initiation Age (y) |
|---|---|---|---|
| Breast | 45%–50% | • Mammogram and breast MRI annually[c]<br>• Clinical breast exam every 6 mo | ~ 25 y |
| Colon | 39% | • Colonoscopy every 2–3 y | ~ Late teens |
| Stomach | 29% | • Upper endoscopy every 2–3 y | ~ Late teens |
| Small intestine | 13% | • Small bowel visualization (CT or MRI enterography or video capsule endoscopy baseline at 8–10 y with follow-up interval based on findings but at least by age 18, then every 2–3 y, though this may be individualized, or with symptoms) | ~ 8–10 y |
| Pancreas | 11%–36% | • Magnetic resonance cholangiopancreatography with contrast or endoscopic ultrasound every 1–2 years | ~ 30–35 y |
| Ovary[c] (typically benign sex cord/Sertoli cell tumors)<br>Cervix (typically cervical adenoma malignum)<br>Uterus | 18%–21%<br>10%<br>9% | • Pelvic examination and Pap smear annually<br>• Consider transvaginal ultrasound | ~ 18–20 y |
| Testes (typically sex cord/Sertoli cell tumors) | | • Annual testicular exam and observation for feminizing changes | ~ 10 y |
| Lung | 15%–17% | • Provide education about symptoms and smoking cessation<br>• No other specific recommendations have been made | |

[c] See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast/Ovarian (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 performed preferably days 7–15 of menstrual cycle for premenopausal women. The appropriateness of imaging modalities and scheduling is still under study. Lowry KP, et al. Annual screening strategies in *BRCA1* and *BRCA2* gene mutation carriers: a comparative effectiveness analysis. Cancer 2012; 118:2021-2030.

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

# NCCN Guidelines Version 3.2017
# Juvenile Polyposis Syndrome

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Discussion

**JPS definition**:[a]

- **A clinical diagnosis of JPS is considered in an individual who meets at least one of the following criteria:**
  - **At least 3 to 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**

**Genetic testing**:

- **Clinical genetic testing is recommended with approximately 50% of JPS cases occurring due to mutations in the *BMPR1A* and *SMAD4*[b] genes. If there is a known *SMAD4* mutation in the family, genetic testing should be performed within the first 6 months of life due to hereditary hemorrhagic telangiectasia (HHT) risk.**

**Surveillance considerations**:

- **Referral to a specialized team is recommended and participation in clinical trials is especially encouraged.**
- **Surveillance should begin at the approximate ages listed below, if symptoms have not already occurred. Any early symptoms should be evaluated thoroughly.**
- **The following surveillance guidelines for the multiple organs at risk for cancer may be considered. Limited data exist regarding the efficacy of various screening modalities in JPS.**

**Juvenile Polyposis Syndrome: Risk and Surveillance Guidelines**

| Site | % Lifetime Risk | Screening/Surveillance Procedure and Interval | Initiation Age (y) |
|---|---|---|---|
| Colon | 40%–50% | Colonoscopy: repeat annually if polyps are found and if no polyps, repeat every 2–3 years[d] | ~ 15 y |
| Stomach | 21% if multiple polyps | Upper endoscopy: repeat annually if polyps are found and if no polyps, repeat every 2–3 years[c,d] | ~ 15 y |
| Small intestine | Rare, undefined | No recommendations have been made | |
| Pancreas | Rare, undefined | No recommendations have been made | |
| HHT | Undefined | In individuals with *SMAD4* mutations, screen for vascular lesions associated with HHT[b] | Within first 6 mo of life |

[a] Due to the rarity of the syndrome and complexities of diagnosing and managing individuals with juvenile polyposis syndrome, referral to a specialized team is recommended.

[b] Faughnan M, Palda V, Garcia-Tsao G, et al. HHT Foundation International - Guidelines Working Group. International guidelines for the diagnosis and management of hereditary haemorrhagic telangiectasia. J Med Genet 2011;48:73-87.

[c] There may be management issues related to anemia from giant confluent polyps. If anemia develops requiring blood transfusion due to many stomach polyps, gastrectomy can be considered in severe cases.

[d] In families without an identified genetic mutation, consider substituting endoscopy every 5 y beginning at age 20 and every 10 years beginning at age 40 y in patients in whom no polyps are found.

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

# NCCN Guidelines Version 3.2017
# Serrated Polyposis Syndrome

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Discussion

**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:**
  1) **At least 5 serrated polyps[d] proximal to the sigmoid colon with 2 or more of these being >10 mm**
  2) **Any number of serrated polyps[d] proximal to the sigmoid colon in an individual who has a first-degree relative with serrated polyposis**
  3) **≥20 serrated polyps of any size, but distributed throughout the colon[e]**
- **Occasionally, more than one affected case of serrated polyposis is seen in a family.[f]**
- **Currently, no causative gene has been identified for serrated polyposis.**
- **The risk for colon cancer in this syndrome is elevated, although the precise risk remains to be defined.**

**Surveillance recommendations for individuals with serrated polyposis:**

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

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

- **The risk of CRC in relatives of individuals with serrated polyposis is still unclear. Pending further data it is reasonable to screen first-degree relatives at the youngest age of onset of serrated polyposis diagnosis, and subsequently per colonoscopic findings.**
- **First-degree relatives are encouraged to have colonoscopy at the earliest of the following:**
  - **Age 40**
  - **Same age as youngest diagnosis of serrated polyposis if uncomplicated by cancer**
  - **Ten years earlier than earliest diagnosis in family of CRC complicating serrated polyposis**
- **Following baseline exam, repeat every 5 years if no polyps are found. If proximal serrated polyps or multiple adenomas are found, consider colonoscopy every 1–3 years.**

[a]The serrated polyposis syndrome guidelines are based on expert opinion on the current data available.

[b]Snover DC, Ahnen DJ, Burt RW, Odze RD. Serrated polyps of the colon and rectum and serrated polyposis. In: Bosman FT, Carneiro F, Hruban RH, Theise ND, eds. WHO Classification of Tumours of the Digestive System: LYON: IARC, 2010:160-165.

[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]Serrated polyps include hyperplastic polyps, sessile serrated adenomas/polyps, and traditional serrated adenomas.

[e]Multiple hyperplastic polyps localized to the rectum and sigmoid are unlikely to contribute to SPS. Such distal polyps should not be counted toward the "qualifying" burden unless they a) are >10 mm; or b) display additional characteristics of serrated polyps (serrations extending to base of crypt, with widened or "boot"-shaped crypt base).

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

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

### COLONIC ADENOMATOUS POLYPOSIS OF UNKNOWN ETIOLOGY

**The following are surveillance/management recommendations for colonic adenomatous polyposis without known *APC* or biallelic *MUTYH* mutations.**

| Phenotype | Management/Surveillance |
|---|---|
| Personal history of ≥100 adenomas | Manage as FAP (See FAP-1) |
| Personal history of >20–<100 adenomas: Small adenoma burden manageable by colonoscopy and polypectomy | • Colonoscopy and polypectomy every 1–2 years<br>‣ Clearing of all polyps is recommended. Repeat at short interval if residual polyps are present. |
| Personal history of >20–<100 adenomas: Dense polyposis or large polyps not manageable by polypectomy | • Subtotal colectomy<br>• Consider proctocolectomy if there is dense rectal polyposis not manageable by polypectomy. |
| Family history of ≥100 adenomas diagnosed at age <40 y in a first-degree relative[a,b] | • Consider colonoscopy beginning at age 10–15 y<br>‣ then every 1 y until age 24 y,<br>‣ every 2 y from 24–34 y,<br>‣ every 3 y from 34–44 y,<br>‣ then every 3–5 y thereafter<br>• If polyposis is detected, follow pathway for Classical FAP Treatment and Surveillance: Personal History (See FAP-1). |
| Family history of >20–<100 adenomas in a first-degree relative[a,b] | Consider colonoscopy and polypectomy every 3–5 y[c] starting at the same age as the youngest diagnosis of polyposis in the family if uncomplicated by cancer or by age 40, whichever is earliest |
| Family history of >100 adenomas diagnosed at age ≥40 in a first-degree relative[a,b] | Consider colonoscopy and polypectomy every 2–3 y[c] starting at age 40 y if uncomplicated by cancer |

[a]Consider genetic testing (See APC/MUTYH-1) in family member affected with polyposis.
[b]There are limited data to suggest definitive recommendations for when to initiate screening or the interval of screening.
[c]If multiple polyps are found, then colonoscopy every 1–3 years depending on type, number, and size of polyps.

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## MULTI-GENE TESTING

**OVERVIEW**

- **The recent introduction of multi-gene testing for hereditary forms of cancer has rapidly altered the clinical approach to testing at-risk patients and their families. Based on next-generation sequencing technology, these tests simultaneously analyze a set of genes that are associated with a specific family cancer phenotype or multiple phenotypes. Given relative novelty of multi-gene testing, terminology and associated definitions used in this section of the guidelines are outlined in Table 1. Pros and cons of multi-gene testing are outlined in Table 2, and Table 3 provides examples of clinical scenarios for which multi-gene testing may be considered. Table 4 provides a list of genes that may be found on commercially available multi-gene panels with the strength of evidence, risk level, and phenotypic association, and Table 5 provides current recommendations for surveillance, based on gene mutation type.**
- **When more than one gene can explain an inherited cancer syndrome, then multi-gene testing may be more efficient and/or cost-effective than single gene testing.**
- **There is also a role for multi-gene 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.**
- **When multi-gene testing is performed, there is an increased likelihood of finding variants of unknown significance.**
- **Chances of finding a variant of uncertain significance or mutation with uncertain clinical management increase as the number of genes included in the multi-gene panel increases.**
- **As commercially available tests differ in the specific genes analyzed (as well as classification of variants and many other factors), choosing the specific laboratory and test panel is important.**
- **Multi-gene 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 mutations. Not all genes included on available multi-gene 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 mutations in a gene may pose higher or lower risk than other mutations in that same gene. Therefore, it may be difficult to use a known mutation alone to assign risk for relatives.**
- **In many cases the information from testing for moderate penetrance genes does not change risk management compared to that based on family history alone.**
- **It is for these and other reasons that multi-gene 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.**

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## MULTI-GENE TESTING

### TABLE 1: MULTI-GENE TESTING DEFINITIONS

| TERM | DEFINITION |
|---|---|
| Multi-gene panel | Laboratory test that includes testing for mutations of more than one gene. |
| Syndrome-specific test | Panel that only tests for one syndrome (eg, Lynch syndrome, 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 mutation | Mutation 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 re-classified as benign. |

### TABLE 2: PROS AND CONS OF MULTI-GENE TESTING FOR HEREDITARY COLORECTAL SYNDROMES[a]

| PROS | CONS |
|---|---|
| • More efficient testing when more than one gene may explain presentation and family history.<br>• Higher chance of providing proband with possible explanation for cause of cancer.<br>• Competitive cost relative to sequentially testing single genes. | • Higher chance of identifying pathogenic mutations for which clinical management is uncertain. Estimates suggest that 3%–4% (Gastroenterology. 2015 Sep;149:604-13.e20; Clin Genet 2014: 86: 510–520) of mutations identified are not clearly clinically actionable, such as finding a mutation in a moderate-risk gene for which management is unclear.<br>• Higher chance of identifying variants of uncertain significance that are not actionable; reported rates of finding variants of uncertain significance range from 17%–38%.<br>• Higher chance that patient will mistakenly receive overtreatment and overscreening if variants of uncertain significance or mutations for which clinical management is uncertain are incorrectly interpreted. |

[a]Hall MJ, et al. J Natl Compr Canc Netw 2014;12:1339-1346.

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## MULTI-GENE TESTING

### TABLE 3: EXAMPLES OF CLINICAL SCENARIOS FOR WHICH MULTI-GENE TESTING SHOULD AND SHOULD NOT BE CONSIDERED

**Examples of clinical scenarios for which multi-gene testing should be considered:**

- **Personal medical and/or family cancer history meets criteria for more than one hereditary cancer syndrome (ie, family meets both *BRCA*-related breast and/or ovarian cancer and Lynch syndrome clinical criteria or family history of young-onset CRC and oligopolyposis)**
- **Colonic polyposis with uncertain histology**
- **Family cancer history does not meet established testing guidelines, but consideration of inherited cancer risk persists and an appropriate panel is available**
- **Individuals concerned about cancer predisposition for whom family cancer history is limited or unknown**
- **Second-line testing for inherited cancer risk when first-line testing has been inconclusive**
- **Adenomatous polyposis (APC, MUTYH, POLE, POLD1)**

**Examples of clinical scenarios for which multi-gene testing should NOT be considered:**[b]

- **An individual from a family with a known mutation and no other reason for multi-gene testing**
- **As first-line testing when the family history is strongly suggestive of a known hereditary syndrome**

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[b]Syndrome-specific panels may be appropriate.

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## MULTI-GENE TESTING

### TABLE 4: EVALUATION OF CRC GENES COMMONLY INCLUDED ON MULTI-GENE PANELS[c]

| GENE | STRENGTH OF EVIDENCE | RISK LEVEL | ASSOCIATION | REFERENCE |
|---|---|---|---|---|
| *APC* | Well-established | High | Familial adenomatous polyposis (FAP) & Attenuated FAP | See *APC* and *MUTYH* Genetic Testing Criteria (APC/MUTYH-1) |
| *APC* I1307K mutation | Well-established | Moderate | Increased frequency in Ashkenazi Jewish individuals; increased risk for colorectal cancer | Boursi B, et al. Eur J Cancer 2013;49:3680-3685.<br>Liang J, et al. Am J Epidemiol 2013;177:1169-1179. |
| *ATM* | Not well-established | Unclear – moderate at most | Increased risk for breast cancer and colorectal cancer | Thompson D, et al. J Natl Cancer Inst 2005;97:813-822.<br>Olsen JH, et al. Br J Cancer 2005;93:260-265. |
| *AXIN2* | Not well-established | Uncertain – presumed high risk from limited case reports | Polyposis and oligodontia | Lammi L, et al. Am J Hum Genet 2004;74:1043-50.<br>Marvin ML, et al. Am J Med Genet A 2011;155A:898-902.<br>Rivera B, et al. Eur J Hum Genet 2014;22:423-6.<br>Lejuene S, et al. Hum Mutat 2006;27:1064.<br>Wong S, et al. Arch Oral Biol 2014;59:349-53. |
| *BLM* heterozygotes | Not well-established | Uncertain – none to low | Possible increased risk for colorectal cancer | Cleary et al. Cancer Res 2003;3:1769-71.<br>Baris et al. Isr Med Assoc J 2007;9:847-50.<br>Laitman Y, et al. Cancer Genet. 2016;209:70-4. |
| *BMPR1A* | Well-established | High | Juvenile polyposis syndrome | See Juvenile Polyposis Syndrome Guidelines (JPS-1) |
| *CHEK2* | Not well-established | Moderate | Increased risk for breast, colon, and other cancers | Xiang HP, et al. Eur J Cancer 2011;47:2546-2551.<br>Liu C, et al. Asian Pac J Cancer Prev 2012;13:2051-2055.<br>Gronwald J, et al. Br J Cancer 2009;100:1508-1512. |
| *EPCAM* | Well-established | High | Lynch syndrome | See Lynch Syndrome Guidelines (LS-1) |

[c]*RPS20* is an emerging gene that is potentially linked to CRC, and there are not enough data at present to include *RPS20* on this list.

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## MULTI-GENE TESTING

### TABLE 4: EVALUATION OF GENES COMMONLY INCLUDED ON MULTI-GENE PANELS[c] (CONTINUED)

| GENE | STRENGTH OF EVIDENCE | RISK STATUS | ASSOCIATION | REFERENCE |
|---|---|---|---|---|
| *GALNT12* | Not well-established | Uncertain – moderate at most | Increased risk for colorectal cancer | Guda K, et al. Proc Natl Acad Sci U.S.A. 2009;106:12921-12925.<br>Clarke E, et al. Hum Mutat 2012;33:1056-1058.<br>Segui N, et al. Hum Mutat 2014;35:50-52. |
| *GREM1* | Not well-established | Uncertain – presumed high risk from limited case reports | Hereditary mixed polyposis syndrome due to a 40kb duplication upstream of GREM1 in Ashkenazi Jewish ancestry only | Jaeger E, et al. Nat Genet 2012; 44:699-703. |
| *MLH1* | Well-established | High | Lynch syndrome | See Lynch Syndrome Guidelines (LS-1) |
| *MSH2* | Well-established | High | Lynch syndrome | |
| *MSH6* | Well-established | High | Lynch syndrome | |
| *MSH3* | Not well-established | Uncertain – presumed high risk from limited case reports | Polyposis | Adam R, et al. Am J Hum Genet 2016;99:337-51. |
| *MUTYH* biallelic mutations | Well-established | High | *MUTYH*-associated polyposis | See *APC* and *MUTYH* Genetic Testing Criteria (APC/MUTYH-1) |
| *MUTYH* heterozygotes | Not well-established | Uncertain – moderate at most | Possible increased risk for colorectal cancer | Win AK, et al. Gastroenterology 2014;146:1208-1211. |

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## MULTI-GENE TESTING

### TABLE 4: EVALUATION OF GENES COMMONLY INCLUDED ON MULTI-GENE PANELS[c] (CONTINUED)

| GENE | STRENGTH OF EVIDENCE | RISK STATUS | ASSOCIATION | REFERENCE |
|---|---|---|---|---|
| *NTHL1* | Not well-established | Uncertain – presumed high from limited case reports | Polyposis | Weren RD, et al. Nat Genet 2015;47:668-671. Rivera B, et al. N Engl J Med 2015;373:1985–1986. Broderick P, et al. BMC Cancer 2006:6:243. |
| *POLD1* | Not well-established | Uncertain – presumed high risk from limited case reports | Polymerase proofreading-associated polyposis | Palles C, et al. Nat Genet 2015; 45:136-144. Spier I, et al. Int J Cancer 2015;137:320-331. Bellido F, et al. Genet Med 2017;18:325-332. |
| *POLE* | Not well-established | Uncertain – presumed high risk from limited case reports | Polymerase proofreading-associated polyposis | Bellido F, et al. Genet Med 2017;18:325-332. |
| *PMS2* | Well-established | High | Lynch syndrome | See Lynch Syndrome Guidelines (LS-1) |
| *PTEN* | Well-established | Moderate-High | Cowden syndrome/ PTEN Hamartoma syndrome | See NCCN Guideline Genetic Familial High-Risk Assessment: Breast and Ovarian |
| *SMAD4* | Well-established | High | Juvenile polyposis syndrome | See Juvenile Polyposis Syndrome Guidelines (JPS-1) |
| *STK11* | Well-established | High | Peutz-Jeghers syndrome | See Peutz-Jegher syndrome Syndrome Guidelines (PJS-1) |
| *TP53* | Well-established | High | Li Fraumeni syndrome | See NCCN Guideline Genetic Familial High-Risk Assessment: Breast and Ovarian |

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[c]*RPS20* is an emerging gene that is potentially linked to CRC, and there are not enough data at present to include *RPS20* on this list.

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## MULTI-GENE TESTING

### TABLE 5: RECOMMENDED MANAGEMENT FOR GENES THAT MAY CONFER A RISK FOR COLORECTAL CANCER

| GENE | RECOMMENDATION |
|---|---|
| *APC* | See NCCN Guidelines for Familial Adenomatous Polyposis (FAP-1) |
| *BMPR1A* | See NCCN Guidelines for Juvenile Polyposis Syndrome (JPS-1) |
| *LS* syndrome genes *(MLH1, MSH2, MSH6, PMS2, EPCAM)* | See NCCN Guidelines for Lynch Syndrome (LS-2) |
| *MUTYH* biallelic mutations | See NCCN Guidelines for MUTYH-Associated Polyposis (MAP-1) |
| *PTEN* | See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian |
| *STK11* | See NCCN Guidelines for Peutz-Jeghers Syndrome (PJS-1) |
| *SMAD4* | See NCCN Guidelines for Juvenile Polyposis Syndrome (JPS-1) |
| *TP53* | See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian |
| *GREM1*[d] | • Begin colonoscopy at age 25–30 and 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.<br>• Surgical evaluation if appropriate. |
| *POLD1*[d] | |
| *POLE*[d] | |
| *AXIN2* | |
| *NTHL1* | |
| *MSH3* | |
| *APC* I1307K mutation[d]<br>*CHEK2*[d] | • For probands with colorectal cancer and one of these mutations:<br>‣ See surveillance recommendations for post-colorectal cancer resection<br>◊ NCCN Guidelines for Colon Cancer<br>◊ NCCN Guidelines for Rectal Cancer<br>• For probands unaffected by colorectal cancer with a first-degree relative with colorectal cancer:<br>‣ Colonoscopy screening every 5 years, beginning at age 40 or 10 years prior to age of first-degree relative's age at CRC diagnosis.<br>• For probands unaffected by colorectal cancer and no first-degree relative with colorectal cancer:<br>‣ Colonoscopy screening every 5 years, beginning at age 40. |
| *MUTYH* heterozygotes[d] | • For probands unaffected by colorectal cancer with a first-degree relative with colorectal cancer:<br>‣ Colonoscopy screening every 5 years, beginning at age 40 y or 10 years prior to age of first-degree relative's age at CRC diagnosis.<br>• For probands unaffected by colorectal cancer with NO family history of colorectal cancer:<br>‣ Data are uncertain if specialized screening is warranted. |

[d]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.

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## Discussion

**NCCN Categories of Evidence and Consensus**

**Category 1:** Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

**Category 2A:** Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

**Category 2B:** Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

**Category 3:** Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

**All recommendations are category 2A unless otherwise indicated.**

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## Overview

Colorectal cancer (CRC) is the fourth most frequently diagnosed cancer and the second leading cause of cancer death in the United States. In 2017, an estimated 95,520 new cases of colon cancer and 39,910 new cases of rectal cancer will occur in the United States. During the same year, it is estimated that 50,260 people will die from colon and rectal cancer.[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 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 in 2012 was down by 50% from peak mortality rates.[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 colorectal cancer registry found that the incidence of CRC in patients younger than 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.

CRC often occurs sporadically, but familial cancer syndromes are also common in this disease. Genetic susceptibility to CRC includes well-defined inherited syndromes such as Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer, or HNPCC), familial adenomatous polyposis (FAP), and MutY human homolog (*MUTYH*)-associated polyposis (MAP). Other entities include Muir-Torre, Turcot, Gardner, Cowden, Bannayan-Riley-Ruvalcaba, Peutz-Jeghers, Juvenile Polyposis, and Serrated Polyposis syndromes.[7-9]

These NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal provide recommendations for the management of patients with high-risk syndromes, including Lynch syndrome, FAP, MAP, Peutz-Jeghers syndrome (PJS), Juvenile Polyposis Syndrome (JPS), Serrated Polyposis Syndrome (SPS), and other high-risk syndromes associated with CRC risk (Li-Fraumeni syndrome [LFS] and Cowden syndrome/PTEN hamartoma tumor 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 between October 28, 2015 and October 10, 2016, 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). The PubMed database was chosen because it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.[10]

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 Trials; Meta-Analysis; Systematic Reviews; and Validation Studies.

The PubMed search resulted in 27 citations, and their potential relevance was examined. The data from key PubMed articles and articles from additional sources deemed as relevant to these guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available on the NCCN website (available at www.NCCN.org).

## Assessment for Hereditary CRC Syndrome (HRS-1)

Genetic susceptibility to CRC includes well-defined inherited syndromes such as Lynch syndrome, FAP, MAP, and other less common syndromes. Many approaches have been proposed for identifying individuals with hereditary CRC syndromes. NCCN recommends a stepwise approach. First, if an individual has a personal history of a known genetic mutation or a known genetic mutation in the family, further evaluation and management appropriate for established hereditary CRC syndromes is warranted. Second, if there is no known personal history of genetic mutation or known mutation in the family, 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 sigmoid colon, or
- a family history of ≥1 relative with polyposis

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, attenuated FAP (AFAP), or MAP; >2 hamartomatous polyps may be associated with PJS, JPS, or Cowden syndrome/PHTS (see the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian); and ≥5 serrated polyps may be associated with SPS.

Third, if the patient's personal history is not suspicious for a polyposis syndrome, personal and family history of Lynch syndrome-associated cancers should be elicited. Lynch syndrome-associated cancers include: colorectal, endometrial, gastric, ovarian, pancreatic, ureter and renal pelvis, brain (usually glioblastoma), and small intestinal cancers, as well as sebaceous adenoma, sebaceous carcinomas, and keratoacanthomas as seen in Muir-Torre syndrome. Those with personal or family history of Lynch syndrome-related cancers should have further evaluation to exclude Lynch syndrome (See *Evaluation to exclude Lynch Syndrome*).

Individuals not meeting any of the above criteria may be considered average risk for CRC, and follow the NCCN Guidelines for average risk colorectal cancer, unless other significant personal or family history that may indicate risk for a hereditary cancer syndrome is elicited. Increased risk warranting genetic evaluation may be indicated by, but not restricted to personal history of congenital hypertrophy of the retinal pigment epithelium, osteomas, supernumerary teeth, desmoid tumor, cribriform variant of papillary thyroid cancer, and hepatoblastoma.

### Evaluation to Exclude Lynch Syndrome (HRS-3)

If an individual has a personal or family history of a Lynch syndrome-related cancer, the panel has summarized measures that can be used to exclude a Lynch syndrome diagnosis including:

 

- Known Lynch syndrome mutation in the family
- An individual with CRC or endometrial cancer diagnosed at <50 years
- An individual with CRC or endometrial cancer and another synchronous or metachronous Lynch syndrome-related cancer
- An individual with CRC or endometrial cancer and ≥1 first-degree or second-degree relative with LS-related cancers <50 years
- An individual with CRC or endometrial cancer and ≥2 first-degree or second-degree relatives with LS-related cancers, regardless of age
- An individual with CRC or endometrial cancer at any age showing evidence of mismatch repair (MMR) deficiency, either by microsatellite instability (MSI) or loss of MMR protein expression
- Family history of ≥1 first-degree relative with CRC or endometrial cancer diagnosed <50 years
- Family history of ≥1 first-degree relative with CRC or endometrial cancer and another synchronous or metachronous Lynch syndrome-related cancer
- Family history of ≥2 first-degree or second-degree relatives with Lynch syndrome-related cancer; including ≥1 diagnosed <50 years
- Family history of ≥3 first-degree or second-degree relatives with Lynch syndrome-related cancers, regardless of age
- An individual with a Lynch syndrome-related cancer or unaffected individual with a ≥5% risk of having an MMR gene mutation based on predictive models (PREMM5,[11] MMRpro, MMRpredict)

Tumor screening for MMR deficiency is appropriate for all CRC and endometrial cancers regardless of age at diagnosis; however, germline genetic testing is generally reserved for patients diagnosed at an early age, with positive family history, or abnormal tumor testing results including MSI or loss of MMR protein expression.

### Management After Diagnosis with a Genetic Syndrome

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

## Lynch Syndrome (LS-1)

Lynch syndrome is the most common form of genetically determined colon cancer predisposition, accounting for 2% to 4% of all CRC cases,[12-15] and a consensus is emerging across medical specialty societies and expert groups regarding the best strategies for identifying patients with this condition. Lynch syndrome results from a germline mutation in 1 of 4 DNA MMR genes (*MLH1*, *MSH2*, *MSH6*, or *PMS2*).[16] Additionally, deletions in the *EPCAM* gene, which lead to hypermethylation of the *MSH2* promoter and subsequent *MSH2* silencing, cause Lynch syndrome.[17,18] Identification of Lynch syndrome is important both for individuals with cancer, because of high personal risk for metachronous Lynch syndrome cancers (ie, endometrial cancer after CRC or vice versa; second CRC), and for their families because of autosomal dominant inheritance and potentially high penetrance. After identification of Lynch syndrome, surveillance (particularly for first or metachronous CRC) offers an opportunity for early detection and perhaps even prevention of cancer among mutation 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 gland adenomatous polyps and keratoacanthomas.

**Strategies for Evaluating Lynch Syndrome (LS-1)**

**Deleterious Lynch syndrome mutation is known**: When a known MMR or *EPCAM* mutation exists in the family, the individual should be tested for the familial mutation. If the test is positive or if testing is not performed for any reason, the individual should follow surveillance for Lynch syndrome outlined below. However, the recommendation to manage patients in whom genetic testing was not done using Lynch syndrome-management recommendation is category 2B. Individuals who test negative for the familial mutation, or who do not have a family history of a Lynch syndrome-related cancer are considered to be at average risk for CRC and should follow the NCCN Guidelines for average risk colorectal cancer.

**No known Lynch syndrome mutation**: The traditional approach to identifying individuals at risk for Lynch syndrome has generally employed a 2-step screening process. First, patients meeting clinical criteria based on family history, personal history of cancer, and/or pathologic characteristics are identified, followed by additional application of screening with a molecular test.

Amsterdam II criteria outline increased risk for Lynch syndrome in a family with a proband affected by CRC or any other Lynch syndrome-associated cancer (ie, endometrial, small bowel, ureter, or renal-pelvic cancers), and 3 relatives with a Lynch syndrome-associated cancer provided the following family criteria are met:

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

Additionally, Amsterdam II criteria stipulate that FAP should be excluded, and tumors should be verified through pathologic examination.[19] Approximately 50% of families meeting the Amsterdam II criteria have a mutation in an MMR gene.[20] These criteria are very stringent, however, and miss as many as 68% of patients with Lynch syndrome.[21]

Bethesda Guidelines were later developed and updated to provide broader clinical criteria for Lynch syndrome screening.[22] Updated Bethesda criteria are as follows:[23]

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

One study reported that *MLH1* and *MSH2* mutations were detected in 65% of patients with MSI of colon cancer tissue who met the Bethesda criteria.[24] 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.[25] Patients fulfilling the revised Bethesda criteria had an odds ratio for carrying a

  

germline mutation in *MLH1* or *MSH2* of 33.3 (95% CI, 4.3–250; *P* = .001). Still, a considerable number of patients with Lynch syndrome fail to meet even the revised Bethesda Guidelines.[14]

Statistical models that predict risk for carrying a mutation in a DNA MMR gene are an additional commonly applied clinical approach to identifying individuals at risk for Lynch syndrome.[21,26-28] These models give probabilities of mutations and/or of the development of future cancers based on family and personal history. The PREMM5 model can be used online at http://premm.dfci.harvard.edu/ and the MMRpredict model is available for online use at http://hnpccpredict.hgu.mrc.ac.uk/. MMRpro is available for free download at http://www4.utsouthwestern.edu/breasthealth/cagene/.

Overall, based on clinical criteria the panel recommends additional evaluation for Lynch syndrome for individuals with no known Lynch syndrome mutation who meet the Amsterdam II criteria or Bethesda Guidelines, have a cancer diagnosis prior to age 50 years, or have a predicted risk for Lynch syndrome >5% on one of the following prediction models: MMRpro, PREMM5,[11] or MMRpredict.

A problem with nearly all clinically based criteria for identifying individuals with Lynch syndrome is suboptimal sensitivity. This has led several groups to study an alternative strategy, referred to as "universal screening," in which all individuals newly diagnosed with CRC have either MSI or immunohistochemistry (IHC) testing for absence of 1 of the 4 DNA MMR proteins. This approach provides a sensitivity of 100% (95% CI, 99.3%–100%) and a specificity of 93.0% (95% CI, 92.0%–93.7%) for identifying individuals with Lynch syndrome.[29] An alternative approach is to test all patients with CRC diagnosed prior to age 70 years plus patients diagnosed at older ages who meet the Bethesda Guidelines.[29] 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.

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 Centers for Disease Control and Prevention (CDC), the US Multi-Society Task Force on Colorectal Cancer, and the European Society for Medical Oncology (ESMO).[30-34]

As of 2016, the panel recommends universal screening of all CRCs, in order to maximize sensitivity for Lynch syndrome detection and simplify care processes.[29,35,36] However, evidence suggests an alternate strategy would be to limit screening to individuals with CRC diagnosed <70 years plus those >70 years meeting Bethesda Guidelines.[29,37] The panel emphasizes that great care must be taken in implementing system-level universal testing to avoid loss of follow-up for patients with abnormal tests and to avoid misinterpretation of the molecular screening tests, and accordingly recommends that an infrastructure needs to be in place to handle the screening results.[38] The panel concluded 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).

*Initial Tumor Testing Methodologies*

Screening for Lynch syndrome currently requires performance of 1 of 2 molecular tests (see *Principles of IHC and MSI 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.[39] Greater than 90% of Lynch syndrome tumors are MSI-H and/or lack expression of at least one of the MMR proteins by IHC.

IHC analysis has the advantage of predicting which gene is most likely to be mutated (the gene for the affected protein or its corresponding dimer partner) and thus the first candidate(s) for germline sequencing.[39] 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.[40] 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).[41] Sensitivity and positive predictive value of the panel including only mononucleotide markers (95.8% and 88.5%, respectively) were better, compared to the panel including both mononucleotide and dinucleotide markers (76.5% and 65.0%, respectively).

Some studies have shown that both IHC and MSI are cost-effective and useful for selecting high-risk patients who may have *MLH1*, *MSH2*, and *MSH6* germline mutations.[32,42,43] However, conclusive data are not yet available that establish which strategy is optimal.[16,25,44-47] A review showed that the sensitivities of MSI and IHC testing are 77% to 89% and 83%, respectively; specificities are 90% and 89%, respectively.[32] An analysis of 5,591 unrelated CRC probands undergoing both MSI and IHC testing showed a concordance rate of 97.5%.[29] Some experts advocate for using both methods when possible.[48] However, the panel recommends using only one test initially. If normal results are found and Lynch syndrome is strongly suspected, then the other test may be carried out.

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 mutations. The approach to mutation testing is evolving. Previously, a sequential approach in which 1 or 2 genes were sequenced guided by either disease prevalence or IHC results, followed by additional testing of other genes was followed. Recognition of scenarios in which IHC results were not available also allowed for syndrome-specific testing of the panel of genes that cause Lynch syndrome (*MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM*) simultaneously. Reductions in cost of sequencing, and recognition that some patients meeting Lynch syndrome testing criteria may have germline mutations not associated with Lynch syndrome have led to growing use of so called "multi-gene" panels in clinical practice. These panels test not only for Lynch syndrome-associated genes, but also for additional mutations. As of 2016, the panel recommends that for patients or families where colorectal or endometrial tumor is available, that 1 of 3 options should be considered for work up: 1) tumor testing with IHC or MSI; 2) Lynch syndrome-specific germline testing for the 4 MMR genes and EPCAM; or 3) multi-gene germline testing that includes the 4 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 colorectal or endometrial tumor is available, the panel recommends Lynch syndrome-specific testing or multi-gene testing without IHC or MSI should only be utilized in select cases under direction of a clinician

 

with expertise in genetics, and should not be used as a universal testing strategy.

If no tumor is available, tumor material is insufficient, or affected relative is unavailable, syndrome-specific testing or multi-gene testing may be considered that includes the 4 MMR genes and *EPCAM*. Multi-gene testing may be preferred in patients with a strong family history or if the age of diagnosis is less than 50 years.[49,50]

*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 colorectal 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 mutation. *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 mutation, either of which would be consistent with sporadic, rather than Lynch syndrome-associated, cancer.[34,39,51,52]

*Follow-up of Genetic Test Results*

If a deleterious mutation is found, the panel recommends that Lynch syndrome management guidelines be followed (See *Lynch Syndrome Management*).

If no deleterious mutation 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 deleterious mutation, or a variant of unknown significance (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 mutation detected in the corresponding gene(s) may still have undetected Lynch syndrome. At this time, no consensus has been reached as to whether these patients (sometimes referred to as having “Lynch-like syndrome”) should be managed as having Lynch syndrome or managed based on personal/family history. Growing evidence suggests a subset of these individuals may have double somatic mutations/changes in the MMR genes.[53] 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 mutations. Individuals found to have double somatic mutations/changes in the MMR genes may not have Lynch syndrome, but double somatic mutations might also be due to non-Lynch germline mutations. Thus, management should be based on personal/family history until further research on Lynch-like syndrome emerges. Additionally, germline testing may be normal despite a strong family history (ie, Amsterdam criteria) or additional features of hereditary cancer syndromes (multiple colon polyps) being present. In these cases, additional testing may be warranted in the proband (such as expanded multi-gene testing), or tumor testing in an affected family member could be considered due to the possibility of a phenocopy.

*Newly Identified Lynch Syndrome*

When a mutation is found in the family, it offers an opportunity to provide predictive testing for at-risk family members. An at-risk family member can be defined as a first-degree relative of an affected

 

individual and/or proband. If a first-degree relative is unavailable or unwilling to be tested, more distant relatives should be offered testing for the known family mutation.

There are many other issues involved in the genetic counseling process of individuals for presymptomatic 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-2)

The NCCN panel carefully considered surveillance schemes for individuals with Lynch syndrome. Compared to the general population, these patients are at increased lifetime risk for CRC (52%–82% vs. 5.5%), endometrial cancer (16%–60% vs. 2.7%), and other cancers including of the stomach and ovary.[54-59] Within Lynch syndrome carriers, risk may vary by specific type of DNA MMR gene mutation. For example, individuals with *MSH6* and *PMS2* mutations have a 10% to 22% risk for colon cancer up to age 70, while those with *MLH1* and *MSH2* mutations have a 40% to 80% risk. As of 2016, the panel recognizes that there continues to be controversy regarding whether mutation-specific risks should guide differential management.[60] The panel's current approach is to offer uniform recommendations for cancer surveillance and prevention, recognizing that, in some clinical scenarios, delaying initiation of surveillance (eg, later starting age for colonoscopy surveillance among *PMS2* carriers) may be appropriate, pending availability of large cohort studies of risk among specific mutation carriers.

Existing data on screening refer primarily to colon and endometrial cancers. More data are needed to evaluate the risks and benefits of extracolonic and extra-endometrial cancer screening, and recommendations are based mainly on expert opinion. The panel recognizes that there are limited population-based studies on lifetime risk for most of the cancers related to each of these genes. Although there are some mutation-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.

#### Colon Cancer Surveillance

If Lynch syndrome is confirmed, colonoscopy is advised to 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. For *MSH6* mutation carriers, consider a later age of onset for colonoscopy.[61,62] This recommendation is based on a systematic review of data between 1996 and 2006 on the reduction in cancer incidence and mortality by colonoscopy[63] and is consistent with recommendations made by the US Multi-Society Task Force on Colorectal Cancer, ESMO, ASCO, the American Gastroenterological Association, and the American College of Gastroenterology.[33,34,51,52,64] However, as previously mentioned, there is still some uncertainty regarding best age to initiate colonoscopic surveillance. For example, the results of a meta-analysis in which CRC risk in 1,114 Lynch syndrome families (*MLH1* and *MSH2* mutation carriers) was examined showed that 5-year CRC risk for those ages 20 to 29 years is about 1%, with the risk for those ages 30 to 39 years being 3% to 5%, with greater risk in men.[65] The investigators argued that annual colonoscopy in patients ages 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.

 

Chromoendoscopy is a relatively new technique that may be used during colonoscopy in which dye spray is used to enhance visualization. A systematic review of four studies indicated that chromoendoscopy is a promising technique for improving detection of lesions and flat adenomas in patients with Lynch syndrome.[66] 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.[67] Chromoendoscopy may be considered in patients with Lynch syndrome, but larger prospective randomized trials are needed to better understand its role in Lynch syndrome.

**Endometrial Cancer Surveillance (LS-3)**

Women with Lynch syndrome are at heightened risk for endometrial cancer.[54,56,58,63] With a lifetime risk of up to 60%, endometrial cancer is the second most common cancer in women with Lynch syndrome.[56] Education that enhances recognition and prompt reporting of relevant symptoms (ie, dysfunctional uterine bleeding or postmenopausal bleeding) is advised, to promote early endometrial cancer detection. The evaluation of these symptoms should include an endometrial biopsy. Endometrial cancer screening does not have proven benefit in women with Lynch syndrome. However, endometrial biopsy is highly sensitive and specific as a diagnostic procedure. Screening through endometrial biopsy every 1 to 2 years may be considered.[68-73] Routine transvaginal ultrasound to screen for endometrial cancer in postmenopausal women has not been shown to be sufficiently sensitive or specific to warrant a positive recommendation,[69-74] but may be considered at the clinician's discretion. However, transvaginal ultrasound is not recommended as a screening tool in premenopausal women due to the wide range of endometrial strip 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 in women who have completed childbearing and carry a *MLH1*, *MSH2*, *EPCAM*, *PMS2*, or *MSH6* mutation.[51,64,68,70,75,76] The timing of a hysterectomy should also be individualized based on comorbidities, family history, and Lynch syndrome gene, 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 mutations (HR, 0.39; 95% CI, 0.23—0.64, $P < .001$).[77] However, prospective data are needed before hormonal contraceptives are recommended for prevention of gynecologic cancers in patients with Lynch syndrome. In general, risk reduction agents should be considered, with detailed discussion between the physician and patient outlining the associated risks and benefits.

**Ovarian Cancer Surveillance (LS-3)**

Women with Lynch syndrome are also at a heightened risk for ovarian cancer, which varies based on affected MMR gene and age.[54,56,58,63,78,79] There are circumstances where clinicians may find screening helpful; however, the data do not support routine ovarian cancer screening for Lynch syndrome. Transvaginal ultrasound and serum CA-125 testing to screen for ovarian cancer in postmenopausal women has not been shown to be sufficiently sensitive or specific to warrant a routine recommendation,[69-74] 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 her to seek evaluation by her physician. Bilateral salpingo-oophorectomy (BSO) may reduce the incidence of ovarian cancer.[51,64,68,70,75,76] The decision and timing of BSO as an option should

 

be individualized based on whether childbearing is complete, menopausal status, comorbidities, family history, and Lynch syndrome gene, as risks for ovarian cancer vary by mutated gene. 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-2)**

The lifetime risk for gastric cancer varies widely between individuals with Lynch syndrome in different populations, from 2% to 4% in the Netherlands to 30% in Korea.[63,80] Most cases occur after age 40 years, and males have a stronger predisposition. Lynch syndrome is also associated with a 3% to 6% risk for small bowel cancer.[54,57,79,81-83] There is no clear evidence to support screening for gastric, duodenal, and small bowel cancer in patients with Lynch syndrome.[84] For selected individuals with a family history of gastric, duodenal, or small bowel cancer or those of Asian descent with *MLH1*, *MSH2*, or *EPCAM* mutations who have an increased risk, physicians may consider upper esophagogastroduodenoscopy (EGD) extended to the distal duodenum or into the jejunum every 3 to 5 years starting at age 30 to 35 years.[85] Infection with Helicobacter pylori (H.pylori) is a cause of gastric cancer.[86,87] Given the increased risk for gastric cancer in patients with Lynch syndrome, testing and treating for H.pylori should be considered. This is consistent with recommendations by ASCO and ESMO.[33,51]

Risk for urinary tract cancer up to aged 70 years in patients with Lynch syndrome is 1% to 6.7%,[56,88] with greater risk among carriers of *MSH2* mutations (6.9%), relative to *MLH1* (2.9%) and *MSH6* (1.7%) mutation carriers.[88] There is insufficient evidence to recommend a particular surveillance strategy, but selected individuals with a family history of urothelial cancer or individuals with *MSH2* mutations (especially males) may benefit from annual urinalysis starting at age 30 to 35 years. Risk for pancreatic cancer and brain cancer is also elevated in Lynch syndrome.[56-59] However, no effective screening techniques have been identified for pancreatic cancer; therefore, no screening recommendation is possible at this time. Annual physical and neurologic examination starting at age 25 to 30 years may be considered for central nervous system (CNS) cancers, but data to support this practice are lacking.

In addition, there have been suggestions of an increased risk for breast cancer in the Lynch syndrome population;[89,90] however, there is insufficient evidence to support increased screening above average-risk breast cancer screening recommendations.[51,64] A study of 188 men with Lynch syndrome also showed a 5-fold increase in risk for prostate cancer.[91] However, there is insufficient evidence to support prostate cancer screening among males with Lynch syndrome.[51,64]

**Reproductive Options (LS-4)**

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 mutation(s) in the same MMR gene or *EPCAM* (eg, if both partners carry a mutation in the *PMS2* gene), then they should also be advised about the risk for constitutional MMR deficiency (CMMRD) syndrome, a rare recessive syndrome.[92]

**Lynch Syndrome Colonoscopy Surveillance Findings and Follow-up (LS-5)**

If there are no pathologic findings, continued surveillance is recommended. 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 of Cancer by Site (available at www.NCCN.org).

For patients with adenomatous polyps, recommendations include endoscopic polypectomy with a follow-up colonoscopy every 1 to 2 years. This option depends on the location and characteristics of the polyp, the surgical risk, and patient preference. If an adenomatous polyp cannot be completely resected endoscopically, then segmental or extended colectomy may be done. Post-colectomy patients should be followed with lower endoscopic exams every 1 to 2 years.

Because surgical management is evolving, 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 US Multi-Society Task Force on Colorectal Cancer recommends that surgery in those older than 60 to 65 years and those with underlying sphincter dysfunction should potentially be less extensive.[34] Surgical principles for polyps are similarly controversial. Practically, a patient who is unable or unlikely to comply with frequent colonoscopy should be considered for more extensive colectomy, especially if young. Post-colectomy patients should be followed with examination of all remaining colonic mucosa every 1 to 2 years.

**Chemoprevention in Lynch Syndrome**

In the randomized CAPP2 trial, 861 participants with Lynch syndrome took either daily aspirin (600 mg) or placebo for up to 4 years; the primary endpoint was the development of CRC.[93] After a mean follow-up of 55.7 months, participants taking daily aspirin for at least 2 years had a 63% reduction in the incidence of CRC (incidence rate ratio [IRR], 0.37; 95% CI, 0.18–0.78; *P* = .008). These participants also saw protection from all Lynch syndrome cancers (IRR, 0.42; 95% CI, 0.25–0.72; *P* = .001). There was no protection seen for participants who completed <2 years of the intervention. Subgroup analyses from this trial showed that the association between obesity and CRC in patients with Lynch syndrome may be attenuated by taking daily aspirin.[94] However, limitations of the CAPP2 trial highlight the need for larger and long-term randomized trials in this area.[95,96] In an observational study including 1858 patients from the Colon Cancer Family Registry who have Lynch syndrome, aspirin use was associated with reduced risk for CRC, both for patients who took aspirin for 5 or more years (HR, 0.25; 95% CI, 0.10–0.62; *P* = .003) and patients who took aspirin between 1 month and 4.9 years (HR, 0.49; 95% CI, 0.27–0.90; *P* = .02), compared to those who took aspirin for less than 1 month.[97]

At this time, the panel suggests that aspirin may be used to prevent cancer in patients with Lynch syndrome, but it is emphasized that the optimal dose and duration of therapy are currently unknown. The CAPP2 trial used a dose of 600 mg per day,[93] though many clinicians who prescribe daily aspirin as chemoprevention in patients with Lynch syndrome utilize a lower dose. The CAPP3 randomized double-blind trial is currently examining the effects of low, moderate, and high doses of daily aspirin on Lynch syndrome-associated cancer incidence (NCT02497820), but results are not yet available. The panel's recommendation to consider aspirin for chemoprevention is consistent with the stance of the American Gastroenterological Association.[52] The American College of Gastroenterology does not recommend standard use of aspirin for chemoprevention given the lack of evidence regarding its impact on CRC risk.[64]

 

**Genetic Testing for FAP, AFAP, and MAP (APC/MUTYH-1)**

Genetic testing of *APC* and/or *MUTYH* is important to differentiate between FAP/AFAP from MAP and colonic polyposis of unknown etiology. A cross-sectional study of >7000 individuals found that the prevalence of pathogenic *APC* mutations 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.[98] For the same groups, the prevalence of biallelic *MUTYH* mutations 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.

The Panel recommends comprehensive genetic testing when a patient presents with a known deleterious *APC* mutation in the family or a personal history of ≥20 cumulative adenomas. Testing may be considered if there is a personal history of a desmoid tumor, hepatoblastoma,[99] cribriform-morular variant of papillary thyroid cancer,[100,101] multifocal/bilateral congentical retinal pigment epithelial hypertrophy (CHRPE),[64] or between 10 and 20 cumulative adenomas.[51] Age of onset, family history, and/or presence of other features may influence whether genetic testing is offered in these situations.

As with *APC*, the panel recommends comprehensive genetic testing for patients with a known deleterious *MUTYH* mutation in the family or a personal history of ≥20 cumulative adenomas. In addition, testing may be considered if there is a personal history of 10 to 20 adenomas, with age of onset, family history, and/or presence of other features influencing whether testing may be offered. Note that some *MUTYH* mutation carriers might present with a mixed polyp phenotype, including adenomas and sessile serrated adenomas or polyps.[102]

If genetic testing is indicated, and a patient does not have a known *APC* or biallelic *MUTYH* mutation in the family, the panel recommends polyposis syndrome-specific testing (*APC* and/or *MUTYH*) or multi-gene testing. When colonic polyposis is present in a single person with a negative family history, polyposis syndrome-specific testing (eg, for *de novo APC* mutation or *MUTYH* mutations) or multi-gene testing may also be considered. When colonic polyposis is present only in siblings, consider recessive inheritance. For example, MAP follows a recessive pattern of inheritance, so *MUTYH* testing can be performed prior to *APC* testing 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. These guidelines recommend genetic counseling and testing for germline *MUTYH* mutations for asymptomatic siblings of patients with known *MUTYH* mutations, as well as for patients who are *APC* mutation-negative with more than 20 cumulative adenomatous polyps. Overall, the decision to order *APC*, *MUTYH*, or multi-gene testing including these genes should be at the discretion of the clinician.

Genetic testing confirms the diagnosis and allows mutation-specific testing in other family members to clarify their risks. Additionally, identifying the location of an *APC* mutation might be useful in predicting the general severity of colonic polyposis and the severity of rectal involvement (for FAP) and risks of extracolonic cancers in affected patients. If a mutation in *APC* is not found by sequencing, testing for large rearrangements and deletions of the *APC* gene may also be performed.

 

When a familial mutation is known (ie, deleterious *APC* mutation or biallelic *MUTYH* mutations), genetic testing can be considered for at-risk family members. An at-risk family member can be defined as a sibling of an affected individual and/or proband. Siblings of a patient with MAP are recommended to have site-specific testing for the familial mutations. Other individuals in a family may also be at risk of having MAP or a monoallelic *MUTYH* mutation. Full sequencing of *MUTYH* may be considered in an unaffected parent when the other parent has MAP. If the unaffected parent is found to not have a *MUTYH* mutation, then genetic testing in the children is not necessary to determine MAP status. 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* mutation, then testing the children for the familial *MUTYH* mutations is clinically indicated.

Counseling should be provided for at-risk individuals so that they are able to make informed decisions about the implications involved in genetic testing, as well as the implications for their own management. 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 mutation responsible for familial polyposis in the family, screening as an average-risk individual is recommended. If the familial mutation(s) is found, there is virtually a 100% probability that the individual will eventually develop familial polyposis.

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 a germline mutation in the *APC* gene, located on chromosome 5q21.[103,104] Truncating mutation of the *APC* gene is detectable in about 80% of patients with FAP using protein-truncating tests.[105,106] Although FAP accounts for less than 1% of all CRC, it has been recognized as a paradigm for treating individuals at increased risk for cancer.

### Diagnosis: Classical vs. Attenuated FAP

A clinical diagnosis of classical FAP is suspected with the early onset of at least 100 polyps in the large bowel. Fewer than 100 polyps may be observed in younger ages, especially in patients with a family history of FAP.[103] But at older ages, patients often exhibit hundreds to thousands of colonic adenomatous polyps. The lifetime risk for cancer in individuals with classic FAP approaches 100% by the age of 50. Most of the resulting cancers occur in the left colon. Individuals with FAP also have an increased risk for other cancers, including duodenal cancer (4%–12%), hepatoblastoma (1%–2%, usually by age 5 years), and thyroid cancer (<2%). FAP is associated with increased malignancy risk in cribriform-morular variant, a rare form of papillary thyroid carcinoma.[100] Other possible associated findings of patients with FAP include desmoid tumors, which occur more frequently in patients with distal *APC* mutations, and CHRPE, which occurs in patients with mutations in the central portion of the gene.[99,107-109] Increasingly, family members are diagnosed at adolescence through genetic testing for their specific familial mutation or through sigmoidoscopic screening in the second decade of life.[110]

AFAP is a recognized variant of FAP characterized by a later onset of disease and fewer adenomatous polyps than observed with FAP,

  

typically ranging from 10 to less than 100.[103,104] These adenomatous polyps are more prone to occur in the right colon and may take the form of diminutive sessile adenomatous polyps.[111] Phenotypic expression is often variable within families. The onset of CRC is typically delayed compared to patients with FAP,[112] but the incidence of cancer rises sharply after the age of 40 years and approaches 70% by age 80 years. Upper GI findings and thyroid and duodenal cancer risks are similar to that found in classical FAP.

However, there is currently no consensus on what constitutes a clinical diagnosis of AFAP and some patients may present with more than 100 polyps. To confirm the diagnosis of FAP or AFAP, a germline mutation in *APC* must be identified (see *Genetic Testing for FAP, AFAP, and MAP*, above). A family history may be negative, since approximately 30% of individuals have *de novo APC* germline mutations.[113,114]

**Management of FAP and AFAP**

It is recommended that physicians or centers with expertise in FAP should manage patients, and the management should be individualized based on genotype, phenotype, and other personal considerations. The surveillance interval should be adjusted according to the actual polyp burden. Management of FAP includes early screening and colectomy or proctocolectomy after the onset of polyposis. Because cancer incidence in FAP rises dramatically early in the third decade of life, prophylactic proctocolectomy is usually indicated in the second decade of life. Management of AFAP includes early screening, with colectomy or proctocolectomy when the polyp burden becomes significant and no longer manageable by polypectomy. Post-colectomy chemoprevention can also be considered (see below).

Preoperative surveillance schedules, surgical options, and surveillance following resection are discussed in more detail below.

**Preoperative Surveillance for Individuals with a Family History of Classical FAP (FAP-4)**

Management of individuals with a family history of FAP depends on whether the familial mutation is known or unknown (also see *Genetic Testing for FAP, AFAP, and MAP*, above). When the mutation is unknown, an affected family member should have genetic counseling and testing, followed by counseling and testing of at-risk family members. If affected family members are unavailable, testing of at-risk individuals can be considered. When the familial mutation is known, genetic counseling and testing of at-risk family members is indicated. Preoperative surveillance for at-risk individuals with a family history of FAP depends on genetic testing results, as described below.

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

*Positive genetic testing:* If an *APC* gene mutation is found, colonoscopy (preferred option) or flexible sigmoidoscopy every 12 months, beginning at 10 to 15 years of age, is recommended. If adenomas develop, surgical options should be reviewed (see below).

*No genetic testing:* Some people who undergo genetic counseling are determined to have high risk for FAP, but decide, for a variety of reasons, not to undergo genetic testing, which influences how their screening is managed. These individuals are considered to be potentially at risk and should be offered annual colonoscopy (preferred option) or flexible sigmoidoscopy beginning at 10 to 15 years of age until the age of 24 years. If results continue to be negative, the following surveillance intervals are recommended: every 2 years for patients >24 to ≤34 years of age; every 3 years for patients >34 to ≤44 years of age; and every 3 to 5 years for patients older than 44 years of age.

 

There are several reasons why surveillance is recommended so often for these individuals. First, adenomatous polyps may begin to develop in adolescence. Most people with classic FAP present with polyps 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 polyps until a later age. The probability of FAP in a person without any polyps 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. However, even 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 polyps 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 pathogenic mutation can allow for surveillance to rule in and rule out disease in unaffected relatives.

*No familial mutation found:* In some families, mutations cannot be found with available testing technology. The sensitivity to identify *APC* gene mutations is currently only about 70% to 90%.[115] Evaluating asymptomatic individuals at risk in these families presents a difficult problem. By far the best approach in this situation is additional attempts to identify the *APC* or *MUTYH* mutation in an affected family member, even if the available person is not a first-degree relative. If a mutation is found, then the at-risk individual should be managed similarly to those with known familial mutations. FAP can be excluded in a person at risk whose genetic testing results indicate no mutation is found when a mutation has been previously identified in an affected family member (a "true negative" test result).

If, however, a familial mutation is still not identified, genetic testing of at-risk individuals can be considered. Certainly, a positive test in an asymptomatic person is informative even when the familial mutation has not been previously identified. However, interpreting a test in which "no mutation is found" in an asymptomatic person is not the same as a "negative test." This particular issue is often a source of confusion and misinterpretation. Thus, it is critical that patients receive appropriate genetic counseling to avoid false-negative interpretations of test results.[116] Surveillance for these at-risk individuals for whom no mutation is found is identical to that for untested individuals with known familial mutation (see section above). Again, if polyposis is detected, patients should be managed in the same way as those with a personal history of classical FAP.

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

Treating patients with a personal history consistent with AFAP varies depending on the patient's age and adenoma burden. For young patients younger than age 21 years with small adenomatous polyp burden (defined as fewer than 20 adenomas, all <1 cm in diameter and none with advanced histology), colonoscopy and polypectomy are recommended every 1 to 2 years with surgical evaluation and counseling if appropriate. In patients aged 21 years and older with small adenomatous polyp burden, colectomy and ileorectal anastomosis (IRA) are alternative treatment options to colonoscopy and polypectomy that may be considered (see *Surgical Options in FAP and AFAP* below for further description of colectomy and IRA). Earlier surgical intervention should be considered in patients who are noncompliant.

If adenoma burden is endoscopically unmanageable, colectomy with IRA is preferred in most cases. When 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), proctocolectomy with ileal pouch anal anastomosis (IPAA) is recommended (see *Surgical Options in FAP and AFAP* below for further description).

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

Similar genetic counseling, testing, and surveillance considerations discussed previously for patients with a classical FAP family history apply to patients with a family history of AFAP, except for the endoscopy approach. It is important to recognize that individuals with attenuated polyposis may not present until a later age and may have fewer polyps 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* gene mutation responsible for polyposis in the family, screening as an average-risk individual is recommended.

*Positive genetic testing, no genetic testing, or no familial mutation found:* In the absence of a true negative genetic test result, an individual with a family history of AFAP should begin colonoscopy surveillance in late teens, with repeat examinations every 2 to 3 years. Thus, the late onset and right colon involvement is accommodated in contrast to classical FAP. Individuals should continue with surveillance until adenomatous polyps are found, at which point they should be managed as patients with a personal history of AFAP.

**Surgical Options in FAP and AFAP (FAP-A)**

Three different surgical options are available for individuals with classical FAP and AFAP: total proctocolectomy with IPAA (TPC/IPAA) (recommended for FAP), total abdominal colectomy with IRA (TAC/IRA) (recommended for AFAP), and TPC with permanent end ileostomy (TPC/EI).[117] 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, TPC/IPAA is generally recommended because it prevents both colon and rectal cancers. For patients with AFAP, TAC/IRA is generally recommended; TPC/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 younger than 18 years without severe polyposis and without a family history of early cancers or severe genotype, the timing of proctocolectomy can be individualized. If surgery is delayed, then annual colonoscopy is recommended. Patients should be managed by physicians or centers with expertise in FAP, and management should be individualized to account for genotype, phenotype, and personal considerations.

**Total Proctocolectomy with Ileal Pouch Anal Anastomosis:**

TPC/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 an unstable rectum in terms of polyp number, size, or histology. 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, or patients who have an anatomic, physiologic, or pathologic contraindication to an IPAA. The advantages of this operation are that the risks of developing rectal cancer are negligible 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 and sexual dysfunction after proctectomy. Functional results are variable. 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 is a straightforward operation with an overall low morbidity rate. It generally results in good bowel function. Most patients have 3 to 4 bowel movements per day, and the risk of urgency or fecal incontinence is low. Without proctectomy, there should be no risk of problems with bladder or sexual function, or decreased fertility, 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 need to undergo subsequent proctectomy due to severe rectal polyposis.[118-120] 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.[120] The authors concluded that proctocolectomy is the preferred procedure for most patients with the classical FAP phenotype, though some controversy remains regarding this choice. They and others also observed that patients could not reliably be selected for colectomy based on genotype alone. However, subsequent studies have reported that the risk for rectal cancer associated with TAC/IRA has declined since the 1980s when IPAA first became available for high-risk patients with severe polyposis.[121,122]

The choice of TAC/IRA versus TPC/IPAA centers on the issues of the relative quality of life.[123-128] A modest reduction in life expectancy is expected in patients with classical FAP with rectal preservation.[118,129] 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 the rectum becomes unstable, a proctectomy with either an IPAA or EI is recommended.[130]

**Total Proctocolectomy with Permanent End Ileostomy:** A TPC/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 function disorders. 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, and patients who have a contraindication to an IPAA (eg, concomitant Crohn's disease, poor sphincter function).

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

### Surveillance Following Surgery for FAP (FAP-1)

#### Colorectal Cancer

Patients with retained rectum should undergo endoscopic rectal examination every 6 to 12 months, depending on polyp burden. If the entire colorectal tract has been removed, the ileal pouch or ileostomy should be evaluated endoscopically every 1 to 3 years, depending on polyp burden; this should be increased to every 6 months if large flat polyps with villous histology and/or high-grade dysplasia are found. Chemoprevention may also be considered (see discussion of *Chemoprevention in FAP and AFAP* below).

#### Duodenal or Periampullary Cancer (FAP-2)

A major component of surveillance in patients with a personal history of FAP or AFAP after surgery relates to the upper GI tract. Duodenal adenomatous polyps develop in over 90% of patients with FAP. These adenomatous polyps are classified into stages 0 to IV, as defined by Spigelman based on macroscopic and histologic criteria (FAP-3).[131] Duodenal cancer is uncommon before age 40 years, and rare before age 30 years. The cumulative lifetime risk of developing severe duodenal polyposis (stage IV) has been estimated to be approximately 35% (95% CI, 25%–45%).[132] The risk for duodenal cancer increases dramatically with stage IV disease.

Surveillance following colectomy should be done with upper endoscopy (including complete visualization of the ampulla of Vater) and use of Spigelman's or other standardized staging, though efficacy of surveillance of these sites has not been demonstrated. More intensive surveillance and/or treatment is required in patients older than 50 years with large or villous adenomatous polyps. The panel recommends that surveillance begin at approximately 20 to 25 years of age. If colectomy was done before age 20 years, then an earlier baseline upper endoscopy could be considered.

The appropriate period for follow-up endoscopy relates to the burden of polyps, varying from every 4 years if no polyps are found to every 3 to 6 months for Spigelman's stage IV polyposis. Surgical evaluation and counseling and expert surveillance every 3 to 6 months is recommended for stage IV polyps, invasive carcinoma, and high-grade dysplasia or dense polyposis that cannot be managed endoscopically. Endoscopic treatment options include endoscopic papillectomy in addition to excision or ablation of resectable large or villous adenomatous polyps and mucosectomy of resectable advanced lesions to potentially avert surgery *(FAP-3)*.

#### Other Cancers (FAP-2)

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, FGPs usually have biallelic inactivation of the *APC* gene, and often display foci of dysplasia or microadenomatous polyps of the foveolar epithelium.[133] However, malignant progression in FGPs is uncommon and the lifetime risk for gastric cancer in patients with FAP in Western countries is reported to be in the range of 0.5% to 1%. Upper endoscopy for duodenal surveillance is adequate surveillance for gastric cancers. The recommendation is to carefully observe for gastric polyps that appear irregular in shape or texture or are large, suggesting

  

adenomatous polyps. It is also recommended that polyps in the antrum or immediate pre-antrum should be removed if possible. These are less common and are often adenomatous polyps. Special screening or surgery should only be considered in the presence of high-grade dysplasia. Non-FGPs should be managed endoscopically if possible. Patients with polyps that cannot be removed endoscopically, but with high-grade dysplasia or invasive cancer detected on biopsy, should be referred for gastrectomy.

Patients with classical FAP also have elevated risk for developing other extracolonic cancers that may warrant surveillance (FAP-2).[134] Several studies suggest that there is an increased lifetime risk for developing thyroid cancer in FAP patients when compared to the general population, with incidence ranging from approximately 1% to 12%.[135-139] The mean age of diagnosis in these patients ranges from 29 to 33 years.[137,139] In addition, thyroid cancers in FAP are most commonly papillary and occur predominantly in women.[134,137,138,140] Although there is currently no consensus for thyroid cancer screening in FAP patients, some studies have found that screening with thyroid ultrasound has potential to detect thyroid cancers.

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.[137] Another study performed thyroid ultrasounds on FAP patients during their annual colonoscopy and found that out of 205 patients screened, 38% had thyroid cancer.[140] 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%.[137 140] Thus, the benefit of regular surveillance for thyroid cancer is uncertain and more studies may be necessary to develop optimal management. Currently the panel has conditionally recommended annual thyroid physical examination starting in the late teenage years. Annual thyroid ultrasound may be considered to supplement physical examination, although supportive data are lacking.

FAP is also associated with an increased risk for intra-abdominal desmoid tumors, the majority of which present within 5 years of colectomy. Since significant morbidity and mortality are associated with advanced desmoid tumors, early diagnosis is likely of benefit.[141] Although data to support screening and treatment are limited,[142,143] annual abdominal palpation during physical examination is advised. If family history of symptomatic desmoids is present, consider abdominal CT with contrast or MRI with or without contrast within 1 to 3 years post-colectomy, and then every 5 to 10 years. Immediate abdominal imaging is warranted if suggestive abdominal symptoms are present. For small bowel polyps and cancer, adding small bowel visualization to CT or MRI for desmoids as outlined above can be considered, especially if duodenal polyposis is advanced. The risk for hepatoblastoma is much higher in young children with FAP.[99] Although the absolute risk is about 1.5%, given the lethality of the disease (25% mortality), active screening by liver palpation, abdominal ultrasound, and alpha-fetoprotein (AFP) measurements every 3 to 6 months during the first five years of life may be considered. The optimal approach would be to perform this screening in a clinical trial.

Medulloblastoma accounts for most of the brain tumors found in patients with FAP, predominantly in females younger than age 20 years.[144] The incidence of pancreatic cancer in FAP is not well defined and is likely very low. Giardiello and colleagues reported 4 retrospective cases (histology not documented) out of 1391 FAP-related subjects.[136] More studies are needed to elucidate the risk and benefit of screening

 

for brain and pancreatic cancers, and there is no additional screening recommendation other than annual physical exam.

### Surveillance After Surgery for AFAP (AFAP-1)

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

#### Chemoprevention in FAP and AFAP (FAP-1/AFAP-1)

Aspirin has been shown to reduce the incidence and recurrence of colorectal adenomatous polyps in the general population.[145-150] Nonsteroidal anti-inflammatory drugs (NSAIDs) and aspirin have been shown in clinical trials to reduce recurrence of colorectal adenomatous polyps.

Cyclooxygenase-2 (COX-2) has been shown to be overexpressed in colorectal adenomatous polyps and cancers. The COX-2 inhibitor celecoxib is another NSAID that has been studied for its role in the chemoprevention of colorectal adenomatous polyps in the general population.[147,149,151-154] Results from the Prevention of Colorectal Sporadic Adenomatous Polyps (PreSAP) trial showed that the use of celecoxib significantly reduced the occurrence of colorectal adenomatous polyps within three years after polypectomy.[151] Similarly, the Adenoma Prevention with Celecoxib trial (APC trial) showed that in patients at high risk for CRC who had their polyps removed, celecoxib significantly lowered the formation of adenomatous polyps during a 3-year period.[154] Five-year safety and efficacy results of the APC trial showed that compared to placebo, the reduction in the incidence of advanced adenomatous polyps over 5 years was 41% for those who received the lower dose of celecoxib and 26% in patients who received the higher dose compared to the control arm (both $P < .0001$).[155] However, due to the increased risk of cardiovascular events associated with their use, COX-2 inhibitors are not recommended routinely for sporadic adenomatous polyps.[156,157]

NSAIDs have also 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.[158] 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.[159] Thus, NSAIDs may not be as effective as primary treatment of FAP. Some evidence suggests utility for NSAIDs when used in combination with other agents. Preclinical studies have demonstrated an association between COX-2 and the epidermal growth factor (EGFR) signaling pathways and the development of intestinal tumorigenesis.[160-162] A double blind, randomized, placebo-controlled trial examined the effect of sulindac and erlotinib, an EGFR inhibitor, on duodenal adenomas in patients with FAP.[163] Participants with FAP were randomized to receive placebo (n = 46) or 150 milligrams (mg) of sulindac twice a day and 75 mg of erlotinib once a day (n = 46) for 6 months.[163] 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; $P < .001$).[163]

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.[164] 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.[165] 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).[166] 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.

Overall, the panel notes that there are no FDA-approved medications for chemoprevention to facilitate management of the remaining rectum after surgery. While data suggest that sulindac, alone or combined with the EGFR inhibitor, erlotinib, may be a potent polyp-regression strategy,[158,163] addition studies with longer follow-up are needed to determine if the decrease in polyp burden decreases cancer risk.

## MUTYH-Associated Polyposis (MAP-1)

MAP is an autosomal recessive hereditary syndrome that predisposes individuals to attenuated adenomatous polyposis and CRC.[167-169] It is caused by biallelic germline mutations 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-oxo-guanine, 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. Individuals with MAP also have an increased risk for extracolonic tumors including duodenal cancer.[170]

Monoallelic carriers of *MUTYH* mutations may also be at increased risk for CRC, though study results are conflicting. A study of 2332 relatives of patients with CRC with monoallelic *MUTYH* mutations showed that carriers have an estimated 2.5-fold increased risk for CRC, relative to the general population.[171] Another study of 852 monoallelic *MUTYH* mutation 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).[172] In contrast, a population-based analysis of 198 monoallelic *MUTYH* mutation carriers showed that a monoallelic *MUTYH* mutation does not significantly increase CRC risk (OR, 1.07; 95% CI, 0.87–1.31; *P* = .55).[173]

Given that the largest population-based study suggests that monoallelic *MUTYH* carriers have increased risk for CRC,[171] the NCCN panel recommends specialized screening for CRC for some carriers (GENE-7). Specifically, the panel recommends that monoallelic *MUTYH* carriers unaffected by CRC with a first-degree relative with CRC receive colonoscopy screening every 5 years beginning at age 40 or 10 years prior to first-degree relative's age at CRC diagnosis. Notably, these are consistent with standard NCCN recommendations based on having a first-degree relative with CRC alone. For monoallelic *MUTYH* carriers unaffected by CRC with no family history of CRC, the data are uncertain if specialized screening is warranted. For monoallelic *MUTYH* carries with CRC, it is recommended that colonoscopy screenings occur at 1

 

year post-CRC resection. If an advanced adenoma is found, repeat annual screening. If there are no advanced adenomas detected, repeat at 3 years and then every 5 years. These recommendations are consistent with standard NCCN recommendations for surveillance of sporadic CRC (see NCCN Guidelines for Colon Cancer and the NCCN Guidelines for Rectal Cancer).

Most individuals with MAP generally have fewer than 100 polyps, although a minority can present with over 1000. Hyperplastic polyps, sessile serrated polyps (SSPs), and traditional serrated adenomas may also be seen in this setting. In fact, patients with MAP may also meet the criteria for SPS. The lifetime risk for CRC for patients with MAP may be very high.[174] The median age of presentation is approximately 45 to 59 years. 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* mutations (see *Genetic Testing for FAP, AFAP,* and *MAP*, above). With positive genetic testing (biallelic *MUTYH* mutations) or no testing in such individuals, surveillance colonoscopy should begin at age 25 to 30 years and should be repeated every 2 to 3 years if negative. If polyps are found, these patients should be managed 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, with follow-up as described above for patients with a personal history of FAP.

Genetic counseling and testing is recommended for patients with multiple adenomatous polyps (see *Genetic Testing for FAP, AFAP, and MAP*, above). Such individuals who have a negative test for *MUTYH* mutation should be managed individually as patients with FAP.

Individuals younger than 21 years of age with confirmed biallelic *MUTYH* mutations and small adenoma burden are followed with colonoscopy and complete polypectomy every 1 to 2 years. 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. Proctocolectomy with 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 can facilitate management of the remaining rectum postsurgery, although there are no FDA-approved medications for this indication at the present time. While there are data suggesting that sulindac is the most potent polyp-regression medication,[158] it is not known if the decrease in polyp burden decreases cancer risk.

In addition to evaluation of the rectum, an annual physical exam is recommended, with baseline upper endoscopy beginning at age 30 to 35 years. Follow-up of duodenoscopic findings is as described above for patients with FAP (see FAP-3).

 

## Peutz-Jeghers Syndrome (PJS-1)

PJS is an autosomal dominant condition mainly characterized by hamartomatous gastrointestinal (GI) polyps.[175] 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.[176] Medical treatment if 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.[175] Besides being associated with an increased risk for CRC, PJS is also associated with increased risk for cancers of the breast, pancreas, ovary, and gallbladder.[177-180] 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%).[181] In a study of 72 patients with PJS, 12.5% had a GI malignancy.[180] The majority of PJS cases occur due to mutations in the *STK11 (LKB1)* gene.[182,183] However, other genetic mutations may be involved, as an estimated half of patients with PJS do not have detectable *STK11/LKB1* mutations.[181]

A PJS clinical diagnosis is made when an individual has at least two of the following: two or more PJS-type polyps of the small intestine; mucocutaneous hyperpigmentation of the mouth, lips, nose, eyes, genitalia, or fingers; or family history of PJS. This is consistent with the statement from the American College of Gastroenterology regarding genetic testing and management of hereditary syndromes associated with CRC.[64] Since PJS is rare, referral to a specialized team is recommended.

### Management of Peutz-Jeghers Syndrome (PJS-2)

As there are limited data regarding the efficacy of various screening modalities in PJS, panel recommendations were made while taking into consideration cancer risk in PJS and the known utility of the specific screening modalities. Individuals with PJS should receive a colonoscopy every 2 to 3 years, beginning in the late teens.[184] To screen for breast cancer, a mammography and breast MRI should be done annually with a clinical breast exam conducted every six months, beginning at approximately age 25 years. For cancer of the stomach, upper endoscopy should be done every 2 to 3 years beginning in the late teen years. For small intestinal cancers, small bowel visualization should be performed with CT or MRI enterography or video capsule endoscopy 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) or be based on symptoms. To monitor for cancer of the pancreas, magnetic resonance cholangiopancreatography with contrast or endoscopic ultrasound should be done every 1 to 2 years beginning in one's early 30s. To monitor for gynecologic cancer, a pelvic exam and Pap smear should be done annually, beginning around ages 18 to 20 years. Transvaginal ultrasound may also be considered. In males, annual testicular exam and observation for feminizing changes should be done beginning at around age 10 years. For lung cancer, education should be provided about symptoms and smoking cessation, if necessary. No other specific recommendations have been made for lung cancer. The panel's recommendations for screening of extracolonic cancers in patients with PJS reflect recommendations from the American College of Gastroenterology.[64]

 

## Juvenile Polyposis Syndrome (JPS-1)

JPS is an autosomally dominant condition that is characterized by multiple hamartomatous polyps of the colon and rectum that usually manifests during childhood. Colonic polyps tend to be right-sided,[185] and 90% of patients present with bleeding and/or anemia.[186] 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.[176] 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.[187] About 50% to 64% of JPS cases occur due to mutations in the *BMPR1A* and *SMAD4* genes.[184,185] If there is a known *SMAD4* mutation in the family, genetic testing should be done within the first six months of life due to risk of hereditary hemorrhagic telangiectasia.[188] In a retrospective review of 44 patients with JPS from a polyposis registry in the United Kingdom, 9% had telangiectasia or vascular abnormalities.[185] Family history of juvenile polyposis is present in about half of patients with JPS.[186] 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.[189] The large number of polyps often found in JPS increases the risk of malignancy.[186] In a separate review of 218 patients with juvenile polyposis, malignancy developed in 17% of patients.[186] 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) at least three to five juvenile polyps of the colon; 2) multiple juvenile polyps found throughout the GI tract; and 3) at least one polyp in an individual with a family history of JPS.[190]

### Management of Juvenile Polyposis Syndrome

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

CRC screening via colonoscopy should begin around age 15 years, since the mean age of a juvenile polyp undergoing adenomatous changes is 18.6 years.[186] If polyps are found, colonoscopy should be repeated annually. If no polyps are found, then colonoscopy would only need to be done every 2 to 3 years. Screening for stomach cancer should also begin at age 15 years. An upper endoscopy screening schedule should match that of the colonoscopy screening schedule (ie, annually if polyps are found, every 2–3 years if no polyps are found). In families without an identified genetic mutation, consider substituting endoscopy every 5 years beginning at age 20 and every 10 years beginning at age 40 years in patients whom no colon or stomach polyps are found. However, there may be management issues related to anemia from giant confluent polyps. In severe cases, if anemia develops requiring blood transfusion due to many gastric polyps, gastrectomy can be considered. The panel has made no recommendations regarding surveillance of the small intestine and the pancreas, since cancer of these organs in patients with JPS is rare and/or undefined, though the American College of Gastroenterology recommends screening of the small intestine.[64]

## Serrated Polyposis Syndrome (SPS-1)

Serrated polyps include hyperplastic polyps, sessile serrated adenomas/polyps, and traditional serrated adenomas.[191] SSPs are flat or slightly raised and usually occur on the right side, while traditional

 

serrated adenomas are generally polyploid.[192] Serrated polyps are more difficult to detect during colonoscopy and account for a disproportionate amount of interval cancers.[193] These polyps are considered premalignant, may account for as many as a third of CRCs, and should be managed similarly to adenomas.[193] Serrated polyps are thought to progress to cancer via pathways that are different from those in adenomas and to have an unfavorable prognosis.[192,194-196]

A clinical diagnosis of SPS (previously known as hyperplastic polyposis) is considered in an individual meeting at least one of the following criteria established by the WHO: 1) at least 5 serrated polyps proximal to the sigmoid colon, 2 or more greater than 10 mm; 2) at least one serrated polyp proximal to the sigmoid colon and a first-degree relative with serrated polyposis; or 3) at least 20 serrated polyps throughout the colon.[191] Individuals with SPS have an increased risk for colon cancer, though data on CRC risk for patients with SPS are limited.[197,198] One retrospective study found that 35% of patients developed CRC during a mean follow-up period of 5.6 years (0.5–26.6 years).[197] In fact, in 6% of the patients, CRC was found during surveillance in diminutive polyps (4–16 mm) after a median interval of 11 months. 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.[199] Another retrospective analysis of 64 patients with serrated polyposis showed a standard incidence ratio of 18.72 (95% CI, 6.87–40.74) for CRC.[200] Emerging evidence links mutations in *RNF43*, a regulator of *ATM*/*ATR* (ataxia-telangiectasia mutated/ataxia-telangiectasia and Rad3-related protein) DNA damage response, to SPS.[201-204] 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 mutations in *RNF43* in 2 individuals.[201] The *RNF43* mutations were associated with multiple serrated polyps (OR, 3.0; 95% CI, 0.9–8.9; $P$ = .04).[201] A recent study identified a germline *RNF43* mutation in 1 out of 4 families with serrated polyposis.[204]

### Management of Serrated Polyposis (SPS-1)

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.[64] It may not always be possible to remove all polyps. Colonoscopic surveillance with consideration of surgical referral is recommended if colonoscopic treatment and/or surveillance is inadequate or if high-grade dysplasia occurs.[64]

#### Management of First-Degree Relatives (SPS-1)

The risk for CRC in relatives of individuals with SPS is still unclear, although several studies have found a significantly increased risk.[205] 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).[206] In addition, this study found that 4 first-degree relatives satisfied the criteria for serrated polyposis (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.[207] In addition, an increased risk for pancreatic cancer was observed. In a recent prospective study, 76% of first-degree relatives of patients with SPS were found to have SPS upon colonographic screening.[208]

Pending further data, the panel believes it is reasonable to screen first-degree relatives at the youngest age of onset of SPS diagnosis, 10 years earlier than earliest diagnosis of 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.

## Colonic Adenomatous Polyposis of Unknown Etiology (CPUE-1)

When genetic testing in an individual with polyposis reveals no *APC* and one or no *MUTYH* mutations, surveillance should be tailored based on individual and family risk assessment, as outlined in the guidelines. If the patient has a history of ≥100 adenomas, the panel recommends that the patient be managed as described above for patients with a personal history of classical FAP.

If the patient has a history of >20 but <100 adenomas, and the adenoma burden is small and considered to be manageable by colonoscopy and polypectomy, the panel recommends colonoscopy and polypectomy every 1 to 2 years. Clearing of all polyps is recommended and can be repeated at short intervals if residual polyps are present.

If the patient has a history of >20 but <100 adenomas, but the adenoma burden is dense and considered unmanageable by polypectomy, the panel recommends a subtotal colectomy. A proctocolectomy may be considered if there is a dense rectal polyposis that cannot be managed by polypectomy.

In patients with a family history of ≥100 adenomas diagnosed at age <40 years in a first-degree relative, there are limited data to suggest definitive recommendations for when to initiate screening or the interval of screening. The panel suggests consideration for colonoscopy screenings to begin at age 10 to 15 years with the following intervals post initial screen: every 1 year until age 24 years, every 2 years from 24 to 34 years, every 3 years from 34 to 44 years, and then every 3 to 5 years thereafter. If polyposis is detected, the panel recommends that patients be managed as described above for patients with a personal history of classical FAP. In addition, family members affected with polyposis should consider genetic testing as previously described for FAP and MAP.

In patients with a family history of >20 to <100 adenomas in a first-degree relative, there are limited data to suggest definitive recommendations for when to initiate screening or the interval of screening. The panel suggests considering colonoscopy screenings and polypectomy every 3 to 5 years starting at the same age as the youngest diagnosis of polyposis in the family if uncomplicated by cancer or by age 40 years, whichever is earliest. If multiple polyps are found during screenings, the interval for colonoscopies should occur every 1 to 3 years, depending on the type, number, and size of polyps. As described above, family members affected with polyposis should consider genetic testing as previously described for FAP and MAP.

In patients with a family history of >100 adenomas diagnosed at age ≥40 years in a first-degree relative, there are limited data to suggest definitive recommendations for when to initiate screening or the interval of screening. The panel suggests considering colonoscopy screenings and polypectomy every 2 to 3 years starting at age 40 years if uncomplicated by cancer. If multiple polyps are found during screenings, the interval for colonoscopies should occur every 1 to 3 years, depending on the type, number, and size of polyps. As described above, family members affected with polyposis should consider genetic testing as previously described for FAP and MAP.

## Multi-gene Testing (GENE-1)

Next-generation sequencing allows for the sequencing of multiple genes simultaneously. This is referred to as multi-gene testing. The NCCN panel added information regarding multi-gene testing for the 2016

  

update. The recent introduction of multi-gene testing for hereditary forms of cancer has rapidly altered the clinical approach to testing at-risk patients and their families. Multi-gene testing simultaneously analyzes a set of genes that are associated with a specific family cancer phenotype or multiple phenotypes. Multi-gene testing may include syndrome-specific tests (ie, panels that test for only one syndrome like Lynch syndrome), 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 could 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.[209] 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 mutation known to be clinically actionable; that is, whether the management of an individual patient is altered based on the presence or absence of a mutation. 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 gene mutation could potentially influence a condition, multi-gene testing may be more efficient and/or cost-effective.[209] Multigene testing with panels that include genes associated with Lynch syndrome, as well as other highly penetrant genes associated with CRC, may be cost effective,[210] and this approach may detect mutations not found in single-gene testing.[211] 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.[209,212]

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.[212-214] This issue is compounded by the low incidence rates of hereditary disease, leading to a difficulty in conducting adequately powered studies.[213] 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.[209,214-217] 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. Multi-gene tests also increase the likelihood of detecting VUS,[209,212,214,217-220] with likelihood rates ranging from 17% to 38%.[215,217,218,221] 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.

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. The specific laboratory and multi-gene test should be chosen carefully.[209] Second, in some cases, next-generation sequencing may miss some mutations that would have been detected with traditional single-gene analysis.[209] Third, mutations identified for more than one gene add complexity that may lead to difficulty in making risk management

 

recommendations.[212] A management plan should only be developed for identified gene mutations that are clinically actionable; care should be taken to ensure that overtreatment or overscreening 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 mutations are found for moderate-penetrance genes and when a VUS is found. For this reason, the NCCN panel recommends that multi-gene testing be 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.[222] Carriers of a genetic mutation 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 mutation and there is no other reason for multi-gene testing; 2) the patient's family history is strongly suggestive of a known hereditary syndrome; and, 3) the patient is diagnosed with CRC with MSI or loss of one or more DNA MMR proteins. In these three scenarios, syndrome-specific panels may be considered.

Multi-gene testing may be considered (but may not be limited to based on clinical judgement) the following scenarios:

- A patient has a personal or family history that meets criteria for more than one hereditary cancer syndrome (eg, Lynch syndrome and *BRCA*-related breast and/or ovarian cancer)
- Colonic polyposis with uncertain histology
- Adenomatous polyposis (specific to *APC, MUTYH, POLE,* and *POLD1*)
- Family history does not meet criteria for established testing guidelines, but there is suspicion of hereditary cancer, and an appropriate panel is available
- Family history is limited or unknown, but patient has concerns about hereditary cancer
- As second-line testing when first-line testing is inconclusive

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. For example, there is well-established evidence that the I1307K polymorphism in the *APC* gene, found in people of Ashkenazi Jewish decent, predisposes carriers to CRC.[223-226] Data are emerging for other genes associated with increased risk for CRC, though the data may not be as robust. For instance, one *GREM1* single nucleotide polymorphism (SNP) (rs16969681) has been shown to be associated with increased risk for CRC.[227,228] Additionally, mutations in the *POLE* and *POLD1* genes may be associated with increased risk for CRC.[229-232] In an analysis of 266 unrelated probands with polyposis or who met the Amsterdam criteria, a *POLE* mutation was found in 1.5% of patients.[233] In an analysis of 858 Spanish patients with early-onset and/or familial CRC and/or colonic polyposis, only one patient was found to have a *POLE* mutation.[231] Mutations in the *CHEK2* and *MSH3* genes may also be associated with increased risk for CRC.[234-239] For *CHEK2*, the 1100delC and I157T variants were found in meta-analytic reviews to be associated with both unselected and familial CRC.[237,239] Mutations in the protein-coding gene *GALNT12* is also believed to be associated with increased risk for CRC.[240-242] Heterozygous mutations in the *ATM* gene,[243] and heterozygous mutations in the DNA *RECQL*-helicase

gene *BLM*[244-246] may also increase risk for CRC. Mutations in the *AXIN2* and *NTHL1* genes are associated with polyposis and oligodontia.[247-254] There are emerging data that *RPS20* mutations ,ay be associated with increased risk for CRC, but more data are required to strengthen this association.[255]

Although research has demonstrated a potential risk for CRC associated with these mutations, 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.

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 (GENE-7). Screening recommendations for carriers of *GREM1, POLD1, POLE, AXIN2, NTHL1 and/or MSH3* mutations are as follows (GENE-7): begin colonoscopy at age 25 to 30 years, and receive follow-up colonoscopies every 2 to 3 years if negative. If polyps are found, screen with colonoscopy every 1 to 2 years with consideration of surgery if the polyp burden becomes unmanageable by colonoscopy. Surgical evaluation should be provided if appropriate. The panel recognizes that data to support the surveillance recommendations for *GREM*, *POLD*, *POLE, AXIN2, NTHL1,* and/or *MSH3* mutations are currently evolving. Therefore, caution should be used when implementing final colonoscopy surveillance regimens in the context of patient preferences and new knowledge that may emerge.

As with the surveillance recommendations for *GREM*, *POLD, POLE, AXIN2, NTHL1, and MSH3* mutations, data to support the surveillance recommendations for *APC* I1307K and *CHEK2* mutations are also currently evolving. Therefore, the panel recommends caution when implementing final colonoscopy surveillance regimens in the context of patient preferences and new knowledge that may emerge. For carriers of *APC* I1307K and *CHEK2* mutations with CRC, the panel recommends colonoscopy surveillance based on the NCCN Guidelines for Colon Cancer and the NCCN Guidelines for Rectal Cancer. For carriers of *APC* I1307K and *CHEK2* mutations unaffected by CRC with a first-degree relative with CRC, the panel recommends colonoscopy screening every 5 years beginning at age 40 or 10 years prior to the first-degree relative's age at CRC diagnosis (GENE-7). For carriers unaffected by CRC *without* a first-degree relative with CRC, the panel recommends colonoscopy screening every 5 years beginning at age 40 years (GENE-7).

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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