NCCN Guidelines Version 1.2015 Panel Members
Genetic/Familial High-Risk Assessment: Colorectal

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

See NCCN Categories of Evidence and Consensus.
Updates in Version 1.2015 of the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal from Version 2.2014 include:

**High-Risk Colorectal Cancer Syndromes**

**HRS-1**
- Last criterion was expanded by adding, “Individual with a desmoid tumor, cribriform-morular variant of papillary thyroid cancer, or hepatoblastoma.”
- Footnote was removed, “Referral to a specialized team is recommended.”

**Lynch Syndrome**

**LS-1**
- Clinical Testing Criteria for Lynch Syndrome (based on personal and family history)
  - For risk status, no criteria met, the strategy was revised, “Individual management, Colonoscopic monitoring CRC screening based on individual risk assessment.” (Also for LS-2)
  - For risk status, no known LS mutation with tumor available, the testing strategy was revised, “Tumor testing (See LS-A) consider both with IHC and/or MSI.”

**LS-2**
- Routine Tumor Testing Criteria for Lynch Syndrome
  - For risk status, tumor available, the testing strategy was revised, “Tumor testing (See LS-A) consider with IHC and/or MSI.”

**LS-3**
- The title “Lynch Syndrome Management” was added to the page. (Also for LS-4).
- Surveillance
  - Extracolonic, last bullet regarding breast cancer surveillance was revised, “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 due to limited data no screening-recommendation is possible at this time.”

**LS-4**
- Bullets regarding risks to relatives and reproductive options were added.

**LS-A 2 of 3**
- The table for “Tumor Testing Results and Additional Testing Strategies” was extensively revised.

**LS-C**
- The following text was removed from the title of the Amsterdam Criteria I and II definitions, “Minimum Criteria for Clinical Definition of LS.”

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Lynch Syndrome (continued)

**LS-A 3 of 3**
- Footnote “c” was revised by adding, “...or additional features of hereditary cancer syndromes (multiple colon polyps) are present,...”
- Footnote “d” was extensively revised.
- Footnote “f” was added, “Germline LS genetic testing may include testing of the gene/s that are indicated (See 'Plausible Etiologies' for possibilities) by the abnormal tumor test results, or instead multi-gene testing that includes MLH1, MSH2, MSH6, PMS2, and EPCAM concurrently may be performed.”
- Footnote “g” was added, “Evaluation for constitutional MLH1 epimutation involves MLH1 promoter hypermethylation studies on blood or other sources of normal tissue.”
- Footnote “h” was added, “Somatic MMR genetic testing of the corresponding gene(s) (see “Plausible Etiologies” for possibilities) could be performed on tumor DNA to assess for somatic mutations that might explain the abnormal IHC and/or MSI results.”
- Footnote “i” was added, “Absent MSH6 in rectal tumor tissue may be due to treatment effect (neoadjuvant chemoradiotherapy).”

Continued on next page
Updates in Version 1.2015 of the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal from Version 2.2014 include:

**APC and MUTYH Genetic Testing Criteria**

**APC/MUTYH-1**
- APC testing criteria was revised:
  - 1st bullet, “Personal history of ≥10 20 adenomas.”
  - 3rd bullet, “Consider testing if a personal history of a desmoid tumor, hepatoblastoma, cribriform-morular variant of papillary thyroid cancer, or between 10–20 adenomas.”

- MUTYH testing criteria was revised:
  - 1st bullet, “Personal history of ≥10 20 adenomas.”
  - 2nd bullet, “Known deleterious biallelic MUTYH mutation(s) in family.”
  - 3rd bullet, “Consider testing if personal history of between 10–20 adenomas or if individual meets criteria 1 or 3 for SPS (see SPS-1) with at least some adenomas.”

- Footnote “a” is new, “Age of onset, family history, and/or presence of other features may influence whether genetic testing is offered in these situations.”
- Footnote “b” the last sentence was revised, “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, or cribriform-morular variant of papillary thyroid cancer.”
- Footnote “c” was revised, “Siblings of a patient with MAP are recommended to have site-specific testing for the familial biallelic 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.” (Also for MAP-3, footnote h)

**Attenuated Familial Adenomatous Polyposis**

**AFAP-1**
- Personal history of classical FAP, after surveillance for colon cancer, the option for surgery was revised, “Proctectomy or colectomy if dense polyposis or severe dysplasia.” If cancer found, a link was added to “see appropriate NCCN Guidelines for Treatment of Cancer by Site.”

**FAP-2**
- Surveillance
  - Extracolonic, second bullet was revised, “Gastric cancer: Examine stomach at time of duodenoscopy upper endoscopy.”
  - Fundic gland polyps occur in a majority of FAP patients, and focal low grade dysplasia is typical can occur but is almost invariably typically non-progressive. For this reason, special screening or surgery should only be considered in the presence of high-grade dysplasia.”

**FAP-A**
- Surgical Options for Treating the Colon and Rectum in Patients with FAP
  - TAC/IRA,
    - Contraindications, sub-bullet was removed, “Curable cancer in rectum.”
    - Advantages, last sub-bullet was revised, “Avoids the risks of sexual or bladder dysfunction and decreased fecundity that can occur following proctectomy.”
    - Disadvantages, new sub-bullet was added, “Risk of metachronous cancer in the remaining rectum”

**MAP-3**
- Footnote “g” was revised, “An at-risk family member can be defined as a first-degree relative sibling 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. Other individuals in a family may also be at risk of having MAP or a monoallelic MUTYH mutation.”

**Additional High-Risk Syndromes Associated with Colorectal Cancer Risk**

**ADDIT-1**
- This page was added to the Guidelines and Li-Fraumeni Syndrome and PTEN Hamartoma Tumor Syndrome/Cowden Syndrome were added as examples of other syndromes that have a risk for colon cancer.
NCCN Guidelines Version 1.2015
High-Risk Colorectal Cancer Syndromes

CRITERIA FOR FURTHER RISK EVALUATION FOR HIGH-RISK SYNDROMES

- Individual meeting the revised Bethesda Guidelines (See LS-B)
- Individual from a family meeting Amsterdam criteria (See LS-C)
- Individuals 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 from a family with a known high-risk syndrome associated with colorectal cancer (CRC), with or without a known mutation (See appropriate high-risk syndrome)
- Individual with a desmoid tumor, cribriform-morular variant of papillary thyroid cancer, or hepatoblastoma

Note: All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
OBTAINING A COMPREHENSIVE ASSESSMENT FOR HEREDITARY COLORECTAL CANCER

Family history of CRC 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 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)¹
  › 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
  › PTEN-Hamartoma tumor syndromes
    ◊ Cowden syndrome
    ◊ Bannayan-Riley-Ruvalcaba syndrome

Directed examination for related manifestations

• Colonoscopy
• Esophagogastroduodenoscopy (EGD)
• Eye examination
• Skin, soft-tissue, and bone examination
• Oral examination


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Obtaining a Comprehensive Assessment for Hereditary Colorectal Cancer

Common Pedigree Symbols

- **Male, Female**
- **Mating**
- **Sibship**
- **Proband** (patient initiating genetic workup)
- **Affected with trait**
- **Deceased**
- **Adopted into a family**
- **Dizygotic twins**
- **Monozygotic twins**

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OBTAINING A COMPREHENSIVE ASSESSMENT FOR HEREDITARY COLORECTAL CANCER

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

3First-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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**LS-2**

**NCCN Guidelines Version 1.2015**

**Lynch Syndrome**

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### ROUTINE TUMOR TESTING CRITERIA FOR LYMPH SYNDROME

- **All CRC patients**
- **CRC patients diagnosed at <70 y and also those ≥70 y who meet the Bethesda Guidelines (See LS-B)**

#### RISK STATUS

- **Tumor available**
- **No tumor available or insufficient tumor**

#### TESTING STRATEGY

- **Tumor testing (See LS-A)** with IHC or MSI
- **Consider testing all 4 MMR genes and EPCAM**

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<table>
<thead>
<tr>
<th>Criteria met (See LS-B)</th>
<th>Consider testing all 4 MMR genes and EPCAM</th>
<th>Positive mutation found in MLH1, MSH2, MSH6, PMS2, or EPCAM</th>
</tr>
</thead>
<tbody>
<tr>
<td>No criteria met (See LS-B)</td>
<td>• Individual management</td>
<td></td>
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<tr>
<td>- CRC screening/surveillance based on individual risk assessment</td>
<td></td>
<td></td>
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</tbody>
</table>

- **See NCCN Guidelines for Colorectal Cancer Screening** for average risk and for increased risk

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**a** Testing of unaffected family members when no affected member is available should be discussed. Significant limitations of interpreting test results should be discussed.

**b**Proper pretest counseling should be done by an individual with expertise in genetics.

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

**d** 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.

**g** IHC and/or MSI screening of all colorectal and endometrial cancers (usually from surgical resection but may be performed on biopsies), regardless of age at diagnosis or family history, has been implemented at some centers to identify individuals at risk for LS. This approach was recently endorsed for colorectal cancer by the Evaluation of Genomic Applications in Practice and Prevention Working Group from the CDC and shown to be cost-effective (EGAPP Recommendation Statement. Genet Med 2009;11:35-41). 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.

**h** For individuals found to have a deleterious LS mutation, see LS surveillance recommendations (LS-3 and LS-4).

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LYNCH SYNDROME MANAGEMENT

Surveillance for *MLH1, MSH2*, and *EPCAM* Mutation Carriers

**Colon cancer:**
- Colonoscopy at age 20–25 y 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; however, at this time the data are not sufficiently robust to make a recommendation for its standard use.

**Extracolonic:**
- Endometrial and ovarian cancer:
  - Prophylactic hysterectomy and bilateral salpingo-oophorectomy (BSO) is a risk-reducing option that should be considered by women who have completed childbearing.
  - Patients must be aware that dysfunctional uterine bleeding warrants evaluation.
  - There is no clear evidence to support screening for endometrial cancer for LS. However, annual office endometrial sampling is an option.
  - While there may be circumstances where clinicians find screening helpful, data do not support routine ovarian screening for LS. Transvaginal ultrasound for ovarian and endometrial cancer 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. Serum CA-125 is an additional ovarian screening test with caveats similar to transvaginal ultrasound.
- Gastric and small bowel cancer: There is no clear evidence to support screening for gastric, duodenal, and small bowel cancer for LS. Selected individuals or families or those of Asian descent may consider EGD with extended duodenoscopy (to distal duodenum or into the jejunum) every 3–5 y beginning at age 30–35 y.
- Urothelial cancer: Consider annual urinalysis starting at 25–30 y.
- Central nervous system (CNS) cancer: 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.

1See Cancer Risk Up to Age 70 Years in Individuals with Lynch Syndrome Compared to the General Population (LS-D).
2Other than colon and endometrial cancer, screening recommendations are expert opinion rather than evidence-based.

**Surveillance for MSH6 and PMS2 Mutation Carriers (LS-4)**

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

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LYNCH SYNDROME MANAGEMENT

Surveillance for *MSH6* and *PMS2* Mutation Carriers

- Colon cancer:
  - Colonoscopy at age 25–30 y or 2–5 y prior to the earliest colon cancer if it is diagnosed before age 30 y and repeat every 1–2 y

- Extracolonic:
  - For endometrial and ovarian cancer, see surveillance for *MLH1*, *MSH2*, and *EPCAM* mutation carriers (See LS-3).
  - The risk of other LS-related cancers is reportedly low; however, due to limited data no screening recommendation is possible at this time.

Risk to Relatives

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

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 mismatch repair deficiency [CMMRD syndrome]) if both partners are a carrier of a mutation/s in the same MMR gene or *EPCAM* (example, both partners carry a mutation in the *PMS2* gene, then their future offspring have a risk for CMMRD syndrome).

See Cancer Risk Up to Age 70 Years in Individuals with Lynch Syndrome Compared to the General Population (LS-D).

There are limited data to suggest definitive recommendations for when to initiate screening. Current data suggest that *MSH6* and *PMS2* mutation carriers have significantly lower risks for colorectal and certain extracolonic cancers compared to *MLH1*, *MSH2*, and *EPCAM* mutation carriers. However, given the limited data and variability in the ages of onset and penetrance among *MSH6* and *PMS2* carriers, colonoscopies starting at younger or later ages may be considered in some families.

### Lynch Syndrome

**SURVEILLANCE FINDINGS**

<table>
<thead>
<tr>
<th>Findings</th>
<th>FOLLOW-UP</th>
</tr>
</thead>
</table>
| No pathologic findings                                                  | • Continued surveillance
• Consider prophylactic hysterectomy/BSO if postmenopausal or childbearing completed                                          |
| Adenocarcinomas                                                         | **See appropriate NCCN Guidelines for Treatment of Cancer by Site**                                                                      |
| Adenomas                                                                | • Endoscopic polypectomy with follow-up colonoscopy every 1–2 y depending on:  
  ‣ location, character  
  ‣ surgical risk  
  ‣ patient preference                                                                 |
| Adenomas not amenable to endoscopic resection or high-grade dysplasia   | • Total abdominal colectomy with ileorectal anastomosis  
• Consider prophylactic hysterectomy/BSO at time of colon surgery if postmenopausal or family completed |

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

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 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). 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.
- The Bethesda criteria (See LS-B) 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 (See LS-C), up to 50% of patients with LS fail to 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.
- 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, and subsequently by genetic testing if the latter are negative (See LS-A 2 of 3). Those with a germline mutation are then identified as LS patients.
- There is a 5%–10% false-negative rate with IHC testing.

MSI

- MSI-H in tumors refers to changes in 2 or more of the 5 microsatellite markers. Its significance, use, and implications are similar to that of IHC, although the tests are slightly complementary.
- There is a 5%–10% false-negative rate with MSI testing.

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### Tumor Testing Results and Additional Testing Strategies

<table>
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<th>IHC</th>
<th>MSI</th>
<th>BRAF V600E</th>
<th>MLH1 Promoter Methylation</th>
<th>Plausible Etiologies</th>
<th>Additional Testing[^de]</th>
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<td>1) Sporadic cancer</td>
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<td>+</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1) Germline mutation MSH2/EPCAM, rarely germline mutation in MSH6</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2) Sporadic cancer</td>
<td></td>
</tr>
<tr>
<td>+</td>
<td>+</td>
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<td>--</td>
<td>N/A</td>
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<td></td>
<td></td>
<td></td>
<td>1) Germline mutation PMS2</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>2) Germline mutation MLH1</td>
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<tr>
<td>+</td>
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<td>+</td>
<td>+</td>
<td>N/A</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1) Germline mutation MSH2/EPCAM</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>2) Sporadic cancer</td>
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<td>+</td>
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<td>+</td>
<td>N/A</td>
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<td></td>
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<td></td>
<td></td>
<td>1) Germline mutation MSH6</td>
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<td>2) Germline mutation MSH2</td>
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<td></td>
<td>3) Sporadic cancer/Treatment effect</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1) Germline LS genetic testing[^f]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2) If applicable, consider MSI analysis or repeat IHC testing on nontreated tumor[^g]</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>3) If germline testing negative, consider somatic MMR genetic testing[^h]</td>
</tr>
<tr>
<td>--</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1) Germline mutation MLH1; possibly sporadic cancer or PMS2 mutation</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2) Sporadic cancer</td>
<td></td>
</tr>
<tr>
<td>--</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1) Germline mutation in any LS gene</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2) Sporadic cancer</td>
<td></td>
</tr>
</tbody>
</table>

[^de]: Either testing was not done or results may not influence testing strategy. + normal staining of protein -- absent staining of protein

[^c]: None

[^f]: Germline LS genetic testing

[^h]: Somatic MMR genetic testing

[^i]: Treatment effect

[^j]: Germline LS genetic testing

[^k]: Germline LS genetic testing

[^l]: Somatic MMR genetic testing

[^m]: Germline LS genetic testing
Footnotes from LS-A 2 of 3

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 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 should be managed as LS (See LS-3 and LS-4) or managed based on personal/family history (See NCCN Guidelines for Colorectal Cancer Screening, for average risk and for increased risk). Growing evidence suggests that the majority of these individuals with abnormal tumor results and no germline mutation found have double somatic mutations/changes in the mismatch repair (MMR) genes. Although the efficacy 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 mismatch repair (MMR) genes likely do not have LS and management should be based on personal/family history.

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) 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) could be performed on tumor DNA to assess 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).
Tumors from individuals should be tested for MSI in the following situations:

- CRC\(^2\) diagnosed in a patient who is younger than 50 years of age.

- Presence of synchronous, or metachronous, colorectal, or other LS-related tumors,\(^3\) regardless of age.

- CRC with the MSI-H histology\(^4\) diagnosed in a patient who is younger than 60 years of age.

- CRC diagnosed in a patient with one or more first-degree relatives with an LS-related cancer,\(^3\) with one of the cancers being diagnosed before age 50 years.

- CRC diagnosed in a patient with two or more first- or second-degree relatives with LS-related cancers\(^3\) regardless of age.

---


\(^2\)Endometrial cancer <50 y is not included in the revised Bethesda Guidelines; however, recent evidence suggests that these individuals should be evaluated for LS.

\(^3\)LS-related cancers include colorectal, endometrial, gastric, ovarian, pancreas, ureter and renal pelvis, biliary tract, brain (usually glioblastoma as seen in Turcot syndrome), and small intestinal cancers, as well as sebaceous gland adenomas and keratoacanthomas as seen in Muir-Torre syndrome.

\(^4\)Presence of tumor-infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern.
AMSTERDAM CRITERIA I\(^1,2\)

At least three relatives with CRC; all of the following criteria should be present:

- One should be a first-degree relative of the other two;
- At least two successive generations must be affected;
- At least one of the relatives with CRC must have received the diagnosis before the age of 50 years;
- FAP should be excluded;
- Tumors should be verified by pathologic examination.

AMSTERDAM CRITERIA II\(^1,2\)

At least three relatives must have a cancer associated with LS (colorectal, cancer of endometrium, small bowel, ureter, or renal-pelvis); all of the following criteria should be present:

- One must be a first-degree relative of the other two;
- At least two successive generations must be affected;
- At least one relative with cancer associated with LS should be diagnosed before age 50 years;
- FAP should be excluded in the CRC case(s) (if any);
- Tumors should be verified whenever possible.


\(^2\)Approximately 50% of patients with LS will be missed by these criteria, and approximately 50% of patients will meet the criteria and not have LS but a high familial risk of uncertain etiology.

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

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

<table>
<thead>
<tr>
<th>Cancer</th>
<th>General Population Risk(^1)</th>
<th>MLH1 or MSH2(^1,2)</th>
<th>MSH6(^2)</th>
<th>PMS2(^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk</td>
<td>Mean Age of Onset</td>
<td>Risk</td>
<td>Mean Age of Onset</td>
</tr>
<tr>
<td>Colon</td>
<td>5.5%</td>
<td>40%–80%</td>
<td>10%–22%</td>
<td>54 years</td>
</tr>
<tr>
<td>Endometrium</td>
<td>2.7%</td>
<td>25%–60%</td>
<td>16%–26%</td>
<td>55 years</td>
</tr>
<tr>
<td>Stomach</td>
<td>&lt;1%</td>
<td>1%–13%</td>
<td>≤3%</td>
<td>63 years</td>
</tr>
<tr>
<td>Ovary</td>
<td>1.6%</td>
<td>4%–24%(^5)</td>
<td>1%–11%</td>
<td>46 years</td>
</tr>
<tr>
<td>Hepatobiliary tract</td>
<td>&lt;1%</td>
<td>1.4%–4%</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>&lt;1%</td>
<td>1%–4%</td>
<td>&lt;1%</td>
<td>65 years</td>
</tr>
<tr>
<td>Small bowel</td>
<td>&lt;1%</td>
<td>3%–6%</td>
<td>Not reported</td>
<td>54 years</td>
</tr>
<tr>
<td>Brain/CNS</td>
<td>&lt;1%</td>
<td>1%–3%</td>
<td>~50 years</td>
<td>Not reported</td>
</tr>
<tr>
<td>Sebaceous neoplasms</td>
<td>&lt;1%</td>
<td>1%–9%</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Pancreas(^4)</td>
<td>&lt;1%</td>
<td>1%–6%</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

---


\(^5\)The 24% risk reported in Bonadona V et al. (JAMA 2011;305:2304-2310) included wide confidence intervals (1%–65% for MLH1; 3%–52% for MSH2).

\(\dagger\)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).

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**NCCN Guidelines Version 1.2015**

**APC and MUTYH Genetic Testing Criteria**

### TESTING CRITERIA

#### APC testing criteria
- Personal history of ≥20 adenomas
- Known deleterious APC mutation in family
- Consider testing if a personal history of a desmoid tumor, hepatoblastoma, cribriform-morular variant of papillary thyroid cancer, or between 10–20 adenomas

#### MUTYH testing criteria
- Personal history of ≥20 adenomas
- Known deleterious MUTYH mutation(s) in family
- Consider testing if personal history of between 10–20 adenomas or if individual meets criteria 1 or 3 for SPS (see SPS-1) with at least some adenomas

### RISK STATUS

- Deleterious APC mutation known
- No known APC or biallelic MUTYH mutation(s)
- Biallelic MUTYH mutations known

### TESTING STRATEGY

- Genetic testing for familial mutation
- Comprehensive genetic testing of APC and/or MUTYH
- Genetic testing for familial mutations

### RESULTS

- Positive for familial APC mutation
- Genetic testing not done
- Negative for familial APC mutation
- Positive for APC mutation
- Positive for biallelic MUTYH mutations
- One MUTYH or No APC or MUTYH mutation(s) found
- Positive for biallelic MUTYH mutations
- Genetic testing not done
- One or no familial MUTYH mutation found

### TREATMENT/SURVEILLANCE

- To determine classical FAP vs. AFAP, see FAP/AFAP-1
- See NCCN Guidelines for Colorectal Cancer Screening-Average risk
- See MAP-1
- Tailored surveillance based on individual and family risk assessment (See Colonic Adenomatous Polyposis of Unknown Etiology [CPUE-1] or See NCCN Guidelines for Colorectal Cancer Screening-Average risk)
- See MAP-1
- See NCCN Guidelines for Colorectal Cancer Screening-Average risk

---

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# Familial Adenomatous Polyposis/AFAP

## PHENOTYPE

### Classical FAP:a
- **Germline APC mutation**
- Presence of ≥100 polyps (sufficient for clinical diagnosis) or fewer polyps at younger ages, especially in a family known to have FAP
- Autosomal dominant inheritance (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%), hepatoblastoma (1%–2%, usually age ≤5 y)
- Pancreatic cancers (<1%)
- Gastric cancers (<1%)
- Duodenal cancers (4%–12%)

### AFAPd
- **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

## RISK STATUS

<table>
<thead>
<tr>
<th>Personal history of classical FAP</th>
<th>See Treatment and Surveillance (FAP-1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family history of classical FAP, unaffected (no symptoms, findings, adenomas), family mutation known</td>
<td>See Genetic Testing and Surveillance (FAP-4)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Personal history of AFAP</th>
<th>See Treatment and Surveillance (AFAP-1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family history of AFAP, unaffected (no symptoms, findings, adenomas), family mutation known</td>
<td>See Genetic Testing and Surveillance (AFAP-2)</td>
</tr>
</tbody>
</table>

---

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

---

*a* A clinical diagnosis of FAP is made 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.
CLASSICAL FAP TREATMENT AND SURVEILLANCE: PERSONAL HISTORY

### TREATMENT

Colon cancer:
- If patient had colectomy with ileorectal anastomosis, then endoscopic evaluation of the rectum every 6–12 mo depending on polyp burden.
- 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.
- The use of chemoprevention 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.

### SURVEILLANCE\(^d,e\) (POSTCOLECTOMY)

Extracolonic Surveillance (See FAP-2)

---

\(a\) 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 colectomy in patients <18 y of age is not established. In patients <18 y with mild polyposis and without family history of early cancer or severe genotype, the timing of colectomy can be individualized. An annual colonoscopy 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.

---

\(\text{Note: All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.}\)
CLASSICAL FAP SURVEILLANCE: PERSONAL HISTORY

SURVEILLANCE\textsuperscript{d,e} (POSTCOLECTOMY)

Extracolonic:

\begin{itemize}
  \item Duodenal or periampullary cancer: Upper endoscopy (including side-viewing examination) starting at age 20–25 y. Consider baseline upper endoscopy earlier, if colectomy before age 20 y.
  \item Gastric cancer: Examine stomach at time of upper endoscopy.
    \begin{itemize}
      \item 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.
      \item 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.
    \end{itemize}
  \item Thyroid cancer: Annual thyroid examination, starting in late teenage years. Annual thyroid ultrasound may be considered, though data to support this recommendation are lacking.
  \item CNS cancer: An annual physical examination; due to limited data, no additional screening recommendation is possible at this time.
  \item Intra-abdominal desmoids: Annual abdominal palpation. If family history of symptomatic desmoids, consider abdominal MRI or CT 1–3 y post-colectomy and then every 5–10 y. Suggestive abdominal symptoms should prompt immediate abdominal imaging.
  \item 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.
  \item 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:
    \begin{itemize}
      \item 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.
    \end{itemize}
  \item Pancreatic cancer: Due to limited data, no screening recommendation is possible at this time.
\end{itemize}

\textsuperscript{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.

\textsuperscript{e}Other than colon cancer, screening recommendations are expert opinion rather than evidence-based.

\textbf{Note: All recommendations are category 2A unless otherwise indicated.}

\textbf{Clinical Trials:} NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
NCCN Guidelines Version 1.2015
Familial Adenomatous Polyposis

DUODENOSCOPIC FINDINGS

Stage 0, No polyposis

Stage I, Minimal polyposis (1–4 tubular adenomas, size 1–4 mm)

Stage II, Mild polyposis (5–19 tubular adenomas, size 5–9 mm)

Stage III, Moderate polyposis (≥20 lesions, or size ≥1 cm)

Stage IV, Dense polyposis or high-grade dysplasia

SURVEILLANCE

Repeat endoscopy every 4 y

Repeat endoscopy every 2–3 y

Repeat endoscopy every 1–3 y

Repeat endoscopy every 6–12 mo

• Surgical evaluation
• Expert surveillance every 3–6 mo
• Complete mucosectomy or duodenectomy, or Whipple procedure if duodenal papilla is involved

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, use of Spigelman's or other standardized staging, and extensive biopsy of dense lesions to evaluate for advanced histology. 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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Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
CLASSICAL FAP GENETIC TESTING AND SURVEILLANCE: FAMILY HISTORY OF CLASSICAL FAP MUTATION KNOWN

**GENETIC TESTING**

- **APC positive**
  - **Unaffected (ie, no symptoms, findings, adenomas), at-risk family member, family mutation known**
  - Recommend APC gene testing for familial mutation

- **APC negative**
  - **Not tested**
  - Flexible sigmoidoscopy or colonoscopy every 12 mo beginning at age 10–15 y

**SURVEILLANCE**

- If adenomas, follow pathway for Classical FAP Treatment and Surveillance: Personal History (FAP-1)

- If no polyps, continue surveillance

---

9An 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

TAC/IRA is generally recommended for AFAP and TPC/IPAA is generally recommended for FAP.

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

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

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
ATTENUATED FAP TREATMENT AND SURVEILLANCE: PERSONAL HISTORY

<table>
<thead>
<tr>
<th>ADENOMA/POLYP BURDEN</th>
<th>TREATMENT</th>
<th>SURVEILLANCE&lt;sup&gt;d,e&lt;/sup&gt;</th>
</tr>
</thead>
</table>
| **Age <21 y with small adenoma burden**<sup>a</sup> | • Colonoscopy and polypectomy every 1–2 y  
• Surgical evaluation and counseling if appropriate | Colon cancer:  
• If patient had colectomy with IRA, then endoscopic evaluation of rectum every 6–12 mo depending on polyp burden.  
• The use of chemoprevention 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. |
| **Age ≥21 y with small adenoma burden**<sup>a</sup> | • Colonoscopy and polypectomy every 1–2 y  
• Colectomy<sup>b</sup> and IRA<sup>c</sup> may be considered  
• Surgical evaluation and counseling if appropriate | Extracolonic:  
• Annual physical examination  
• Annual thyroid examination  
• Upper endoscopy (including side-viewing examination) starting at age 20–25 y. Consider baseline upper endoscopy earlier, if colectomy before age 20 y.  
See [Duodenoscopic Findings (FAP-3)](http://example.com) |
| **Significant polyposis not manageable with polypectomy** | • Colectomy<sup>b</sup> with IRA (preferred in most cases)  
• Consider proctocolectomy with IPAA if dense rectal polyposis not manageable with polypectomy | |

<sup>a</sup>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.

<sup>b</sup>See [Surgical Options for Treating the Colon and Rectum in Patients with FAP (FAP-A)](http://example.com).

<sup>c</sup>Earlier surgical intervention should be considered in noncompliant patients.

<sup>d</sup>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.

<sup>e</sup>Surveillance for upper GI findings for AFAP is similar to classical FAP.

Note: All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
ATENUATED FAP GENETIC TESTING AND SURVEILLANCE: FAMILY HISTORY OF ATTENUATED FAP MUTATION KNOWN

**GENETIC TESTING**

- Unaffected, at-risk family member; family mutation known
  - Recommend APC gene testing for familial mutation

**SURVEILLANCE**

- APC positive
  - Colonoscopy beginning in late teens, then every 2–3 y
- APC negative
  - Not tested
  - See NCCN Guidelines for Colorectal Cancer Screening - Average risk
- APC positive
  - Colonoscopy beginning in late teens, then every 2–3 y
  - Encourage genetic testing

If adenomas, follow pathway for AFAP Treatment and Surveillance: Personal History, Adenoma/Polyp Burden (AFAP-1)

- If no polyps, continue surveillance.

---

1An 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.

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

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

**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
- Gastric polyposis is uncommon

**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 cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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### MUTYH-Associated Polyposis

#### MAP TREATMENT AND SURVEILLANCE: PERSONAL HISTORY

<table>
<thead>
<tr>
<th>ADENOMA/POLYP BURDEN</th>
<th>TREATMENT</th>
<th>SURVEILLANCE&lt;sup&gt;e,f&lt;/sup&gt;</th>
</tr>
</thead>
</table>
| **Age <21 y with small adenoma burden**<sup>b</sup> | • Colonoscopy and polypectomy every 1–2 y  
• Surgical evaluation and counseling if appropriate | Colon cancer:  
• If patient had colectomy with IRA, then endoscopic evaluation of rectum every 6–12 mo depending on polyp burden.  
• The use of chemoprevention 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. |
| **Age ≥21 y with small adenoma burden**<sup>b</sup> | • Colonoscopy and polypectomy every 1–2 y  
• Colectomy<sup>c</sup> and IRA<sup>d</sup> may be considered  
• Surgical evaluation and counseling if appropriate | Extracolonic:  
• Annual physical examination  
• Baseline upper endoscopy beginning at age 30–35 y  
| **Significant polyposis not manageable with polypectomy** | • Colectomy<sup>c</sup> with IRA  
• Consider proctocolectomy with IPAA if dense rectal polyposis not manageable with polypectomy. If patient had colectomy with IRA, then endoscopic evaluation of rectum every 6–12 mo depending on polyp burden. | |

### Notes

**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.

**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.
MAP TREATMENT AND SURVEILLANCE: FAMILY HISTORY OF MAP MUTATION KNOWN

### GENETIC TESTING

Unaffected, at-risk family member;\(^g\) family mutation known

- Recommend MUTYH testing for familial mutations\(^h\)

Sibling of a patient with MAP, not tested

- One MUTYH mutation found or No MUTYH deleterious mutations found

### SURVEILLANCE

Biallelic MUTYH mutation positive

- Begin colonoscopy at age 25–30 y and every 2–3 y if negative. If polyps are found, see MAP-2.
- Consider upper endoscopy and side viewing duodenoscopy beginning at age 30–35 y (See FAP-3 for follow-up of duodenoscopic findings).

See NCCN Guidelines for Colorectal Cancer Screening - Average risk

---

\(^g\)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.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
**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 \textit{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 \textit{PJS-2} if symptoms have not already occurred, and any early symptoms should be evaluated thoroughly.
- The surveillance guidelines (See \textit{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.
## Peutz-Jeghers Syndrome: Cancer Risk and Surveillance Guidelines

<table>
<thead>
<tr>
<th>Site</th>
<th>% Lifetime Risk</th>
<th>Screening Procedure and Interval</th>
<th>Initiation Age (y)</th>
</tr>
</thead>
</table>
| Breast          | 45%–50%         | • Mammogram and breast MRI annually<sup>c</sup>  
• 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 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 or endoscopic ultrasound every 1–2 years           | ~ 30–35 y         |
| Ovary<sup>c</sup> | 18%–21%    | • Pelvic examination and Pap smear annually                                                       | ~ 18–20 y         |
| Cervix          | 10%             | • Consider transvaginal ultrasound                                                               |                    |
|                  | 9%              |                                                                                                   |                    |
| Testes          |                 | • Annual testicular exam and observation for feminizing changes                                   | ~ 10 y            |
| Lung            | 15%–17%         | • Provide education about symptoms and smoking cessation                                           |                    |
|                 |                 | • No other specific recommendations have been made                                                |                    |


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

**JPS definition:**
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* genes. If known *SMAD4* mutation in 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

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

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

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

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

Serrated polyposis syndrome (previously known as hyperplastic polyposis) definition:

- 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 proximal to the sigmoid colon with 2 or more of these being >10 mm
  2) Any number of serrated polyps proximal to the sigmoid colon in an individual who has a first-degree relative with serrated polyposis
  3) Greater than 20 serrated polyps of any size, but distributed throughout the colon
- Occasionally, more than one affected case of serrated polyposis is seen in a family.
- 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.

---

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

**Clinical Trials:** NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
## COLONIC ADENOMATOUS POLYPOSISS OF UNKNOWN ETIOLOGY

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

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Management/Surveillance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personal history of ≥100 adenomas</td>
<td>Manage as FAP (<a href="#">See FAP-1</a>)</td>
</tr>
</tbody>
</table>
| Personal history of >10–<100 adenomas: Small adenoma burden manageable by colonoscopy and polypectomy | • Colonoscopy and polypectomy every 1–2 years  
  ‣ Clearing of all polyps is recommended. Repeat at short interval if residual polyps are present. |
| Personal history of >10–<100 adenomas: Dense polyposis or large polyps not manageable by polypectomy | • Subtotal colectomy  
  • 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  
  ‣ then every 1 y until age 24 y,  
  ‣ every 2 y from 24–34 y,  
  ‣ every 3 y from 34–44 y,  
  ‣ then every 3–5 y thereafter  
  • If polyposis is detected, follow pathway for Classical FAP Treatment and Surveillance: Personal History ([See FAP-1](#)). |
| Family history of >10–<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.

---

**Note:** All recommendations are category 2A unless otherwise indicated.  
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Li-Fraumeni Syndrome (See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian)
- TP53 gene
- Colon cancer risk: The lifetime risk for CRC is likely increased, especially at younger ages.
- Extracolonic cancer risks: Soft-tissue sarcomas, osteosarcomas, breast cancer, leukemia, adrenal cortical carcinomas, brain tumors, and a number of other cancers.

PTEN Hamartoma Tumor Syndrome/Cowden Syndrome (See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian)
- PTEN gene
- Colon cancer risk: Up to 92% of patients with Cowden syndrome have colon polyps and recent estimates suggest a 9%–18% prevalence of CRC
- Extracolonic cancer risks: Breast, endometrial, thyroid, and renal cancer
NCCN Guidelines Version 1.2015
Genetics/Familial High-Risk Assessment: Colorectal

Discussion

This discussion is being updated to correspond with the newly updated algorithm. Last updated 07/01/13

NCCN Guidelines Index
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NCCN Guidelines Version 1.2015
Genetics/Familial High-Risk Assessment: Colorectal

Discussion

This discussion is being updated to correspond with the newly updated algorithm. Last updated 07/01/13

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 noted.

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Overview

Colorectal cancer (CRC) is the fourth most frequently diagnosed cancer in the United States. In 2012, an estimated 102,480 new cases of colon cancer and 40,340 new cases of rectal cancer will occur in the United States. During the same year, it is estimated that 50,830 people will die from colon and rectal cancer. Importantly, the incidence of colon and rectal cancers per 100,000 decreased from 60.5 in 1976 to 46.4 in 2005. The incidence of CRC continued to trend downward, with an average annual percentage change of -2.7% in men and -2.1% in women from 2004 to 2008. In addition, mortality from CRC decreased by almost 35% from 1990 to 2007, likely because of earlier diagnosis through screening and better treatment modalities. Currently, patients with stage I localized colon cancer have a 96% relative 5-year survival rate.

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), MutY human homolog (MUTYH)-associated polyposis (MAP), Peutz-Jeghers syndrome, juvenile polyposis, and serrated polyposis syndromes (SPS).

These NCCN Guidelines for Colorectal Cancer Screening provide recommendations for the management of patients with high-risk syndromes, including Lynch syndrome, FAP, MAP, Peutz-Jeghers syndrome, juvenile polyposis syndrome, and SPS.

Inherited Colon Cancer

Genetic susceptibility to CRC includes well-defined inherited syndromes such as Lynch syndrome (HNPCC), FAP, MAP, and other less common syndromes. Understanding the potential genetic basis for cancer in the family is critical in inherited syndromes. If there is a concern about the presence of a hereditary syndrome, the guidelines recommend referring the patient to a genetic service or genetic counselor.

Following evaluation, those with Lynch syndrome, FAP, or MAP are managed as described in following sections. Referral to a specialized team is recommended for those with Peutz-Jeghers syndrome or juvenile polyposis; surveillance guidelines for these as well as for SPS are outlined in the algorithm. Individuals with a familial risk and no syndrome should be managed as described for those with a positive family history, above, or following the newly developed recommendations for Colonic Adenomatous Polyposis of Unknown Etiology, in the guidelines.

Lynch Syndrome (Hereditary Nonpolyposis Colorectal Cancer)

Lynch syndrome is the most common form of genetically determined colon cancer predisposition, accounting for 2% to 4% of all CRC cases. This hereditary syndrome usually results from a germline mutation in 1 of 4 DNA MMR genes (MLH1, MSH2, MSH6, or PMS2), although possible associations with three other genes (MLH3, PMS1, and EXO1) have also been found. Recent evidence has shown that 3 deletions in the EPCAM gene, which lead to hypermethylation of the MSH2 promoter and subsequent MSH2 silencing, are an additional cause of Lynch syndrome. EPCAM deletions likely account for 20% to 25% of cases in which MSH2 protein is not detected by IHC (see below) but germline MSH2 mutations are not found. MMR mutations are detected in more than half of persons meeting the clinical criteria of
Lynch syndrome, and the lifetime risk for CRC approaches 80% in affected individuals carrying a mutation in one of these genes.\textsuperscript{16} MSI occurs in 80% to 90% of resulting colorectal tumors.\textsuperscript{17,18} Surveillance in patients with Lynch syndrome has been shown to reduce the risk for CRC and may be of benefit in the early diagnosis of endometrial cancer, which is also common in these patients.\textsuperscript{19,20} Site-specific evaluation and heightened attention to symptoms is also advised for other cancers that occur with increased frequency in affected persons, including gastric, ovarian, pancreatic, urethral, brain (glioblastoma), and small intestinal cancers, as well as sebaceous gland adenomatous polyps and keratoacanthomas. However, efficacy of surveillance for these sites has not been clearly demonstrated (reviewed by Lindor et al\textsuperscript{20}).

Risk factors for the presence of Lynch syndrome related to the extended family history in an individual are listed in the guidelines. Due to the high risk for CRC in a person with the syndrome, intensive screening is essential, though the optimal interval has not been fully established in clinical trials. The recommendations in this area are based on the best evidence available to date, but more data are still needed.

**Molecular Workup and Genetic Testing for Lynch Syndrome**

While identifying a germline mutation in an MMR gene (\textit{MLH1}, \textit{MSH2}, \textit{MSH6}, and \textit{PMS2}) by sequencing is definitive for Lynch syndrome, patients with CRC usually undergo 2 rounds of selection before sequencing: the first based on family history or age and the second by initial tests on tumor tissue. As discussed in more detail below, many institutions now proceed directly to initial tests on tumor tissue in all patients regardless of age and family history.

**Criteria for Lynch Syndrome Testing**

Several different sets of criteria have been developed to identify patients who should be tested for possible Lynch syndrome. The first version of the minimum criteria for clinical definition of Lynch syndrome (Amsterdam criteria) was introduced in 1991, and these criteria were modified (Amsterdam II criteria) in 1999.\textsuperscript{21} Approximately 50% of families meeting the Amsterdam II criteria have a mutation in an MMR gene.\textsuperscript{22} These criteria are very stringent, however, and miss as many as 68% of patients with Lynch syndrome.\textsuperscript{23}

The classical Bethesda guidelines were later developed to provide broader criteria for testing colorectal tumors for MSI.\textsuperscript{24} The National Cancer Institute introduced the revised Bethesda guidelines in 2002 to clarify selection criteria for MSI testing.\textsuperscript{25} One study reported that \textit{MLH1} and \textit{MSH2} mutations were detected in 65% of patients with MSI of colon cancer tissue who met the Bethesda criteria.\textsuperscript{26} 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.\textsuperscript{27} Patients fulfilling the revised Bethesda criteria had an odds ratio for carrying a germline mutation in \textit{MLH1} or \textit{MSH2} of 33.3 (95% CI, 4.3–250; \(P = .001\)). Screening tumors of patients meeting the Bethesda criteria for MSI was shown to be cost-effective not only for patients with newly diagnosed CRC but also when considering benefit for the siblings and children of mutation carriers.\textsuperscript{28}

Some newer models have also been developed to assess the likelihood that a patient carries a mutation in a MMR gene.\textsuperscript{23,29-31} These computer programs give probabilities of mutations and/or of the development of future cancers based on family and personal history. The PREMM\textsubscript{1,2,6} model can be used online at [http://premm.dfci.harvard.edu/](http://premm.dfci.harvard.edu/) and the HNPCC predict model is available for online use at [http://hnpccpredict.hgu.mrc.ac.uk/](http://hnpccpredict.hgu.mrc.ac.uk/). MMRpro is available for free.
download at http://www4.utsouthwestern.edu/breasthealth/cagene/. These models may be particularly useful when there is no tumor or insufficient tumor available for IHC or MSI testing.

Many NCCN Member Institutions and other comprehensive cancer centers now perform IHC and sometimes MSI testing on all newly diagnosed colorectal and endometrial cancers regardless of family history to determine which patients should have genetic testing for Lynch syndrome. The cost effectiveness of this approach, referred to as universal or reflex testing, has been confirmed for CRC, and this approach has been endorsed by the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) working group at the CDC. The Cleveland Clinic recently reported on their experiences implementing such a screening approach.

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. 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 level of sensitivity was better than that of both the revised Bethesda and Jerusalem (testing all patients diagnosed with CRC at age <70) recommendations. While this new selective strategy failed to identify 4.9% of Lynch syndrome cases, it resulted in approximately 35% fewer tumors undergoing MMR testing.

The NCCN Panel endorses using either this selective approach (testing all patients with CRC diagnosed <70 years plus patients diagnosed at older ages who meet the Bethesda guidelines) or the universal testing approach to select patients with CRC for Lynch syndrome testing. An infrastructure needs to be in place to handle the screening results in either case. In addition, testing for Lynch syndrome is advised for individuals who fit any of the following: 1) meets revised Bethesda guidelines or Amsterdam criteria; 2) diagnosed with endometrial cancer before age 50 years; 3) known Lynch syndrome in the family.

The testing strategy will depend on whether there is a known MMR mutation in the family. If so, the individual should be tested for the familial mutation (see Definitive Testing, below). If tested positive or if testing is not performed for any reason, the individual should follow surveillance for Lynch syndrome outlined below. Individuals who test negative for the familial mutation are considered to be at average risk, not zero risk, for CRC and should follow the corresponding screening pathway. If there is no known familial MMR mutation, initial tests should be performed on available tumor tissue, as described below.

**Initial Testing Methodologies**

There are 2 main initial tests performed on CRC specimens to identify individuals who might have Lynch syndrome: 1) IHC analysis for MMR protein expression, which is often diminished due to mutation; and 2) analysis for MSI, which results from MMR deficiency. 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. However, conclusive data are not yet available that establish which strategy is optimal. The sensitivities of MSI and IHC testing have been estimated to be 77% to 89% and 83%, respectively; specificities have been estimated to be 90% and 89%, respectively. Some experts advocate for using both methods when possible.

MSI testing is particularly helpful when the family history is not strongly suggestive of Lynch syndrome. Families that meet the minimal criteria for consideration (diagnosis before the age of 50, but no other criteria) may not represent the disorder. A microsatellite stable tumor arising within a young onset patient without a strong family history of
colorectal/endometrial cancer is very unlikely to represent the disorder.\(^{48}\) Proceeding with genetic testing in this setting is unlikely to yield an informative result. On the other hand, among patients who met the Amsterdam criteria with MSI-negative tumors, 29% were found to have germline MMR gene mutations. MMR gene mutations were found in 88% of patients with MSI-positive tumors who met the Amsterdam criteria.\(^{48}\)

IHC analysis is especially useful for family members who meet the Amsterdam criteria I or II, since there is a 50% to 92% chance of identifying a mutation in an MMR gene in these individuals.\(^{40}\) IHC analysis has the advantage of predicting which gene is most likely mutated and thus the first candidate for germline sequencing.\(^{40}\) Testing the \(BRAF\) gene for mutation is indicated when MLH1 expression is absent in the tumor by IHC analysis. The presence of a \(BRAF\) mutation indicates that \(MLH1\) expression is down-regulated by somatic methylation of the promoter region of the gene and not by a germline mutation.\(^{40}\)

Additional testing strategies and a table of IHC and MSI testing results are included in the algorithm section of these guidelines.

Often, a patient presents with a strong family history of Lynch syndrome-associated cancer, but no tumor sample is available for testing. A recent study showed that large (≥ 10 mm) adenomatous colorectal polyps in patients with Lynch syndrome display a loss of MMR protein expression by IHC and are MSI-positive.\(^{39}\) These results indicate that MSI and/or IHC testing of large polyps when a tumor sample is not available is justified in high-risk families.\(^{50}\) Importantly, a negative result would not rule out Lynch syndrome. An alternative approach is to go directly to germline sequencing in patients determined to have ≥5% risk for Lynch syndrome when a tumor sample is not readily available.\(^{51}\) with the following priority: \(MLH1\) and \(MSH2\) first, then \(MSH6\), and lastly \(PMS2\). Due to its rarity, testing for \(PMS2\) mutation is only necessary if no mutation is found in the other genes.

**Definitive Testing**

Initial tests do not necessarily indicate that a patient has Lynch syndrome. Abnormal results can occur in patients with sporadic CRC due to abnormal methylation of the \(MLH1\) gene promoter. A recent study estimated that 7.1% (95% CI, 2.8% to 18.2%) of patients with CRC with defective MMR have germline mutations associated with Lynch syndrome.\(^{52}\) Therefore, all individuals with abnormal IHC or MSI results should be referred for genetic counseling so that the appropriate follow-up testing can be offered. Such tests might include one for abnormal \(MLH1\) promoter methylation and/or germline genetic testing of one or more of the MMR genes. If a mutation is not found by sequencing, testing for large rearrangements and deletions of MMR genes may also be performed. Most patients will be found to have sporadic CRC; those with a germline alteration are identified as Lynch syndrome patients and should undergo surveillance for Lynch syndrome as describe below. If no familial mutation is identified, surveillance should be tailored based on individual and family risk assessment.

**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. Predictive testing can save people a lot of unnecessary procedures. It is important to consider genetic testing for at-risk family members when the family mutation is known. 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. A fair number of individuals elect not to undergo testing, and it is important to counsel these individuals so they continue with increased surveillance.

**Surveillance for Lynch Syndrome**

The NCCN Panel has had extensive discussions on the surveillance schemes for individuals with Lynch syndrome. These patients are at an increased lifetime risk compared to the general population for CRC (10%–80% vs. 5.5%), endometrial cancer (16%–60% vs. 2.7%), and other cancers including of the stomach and ovary. For the 2013 version of the guidelines, the panel devised separate cancer screening recommendations for patients with mutations in MLH1/MSH2, MSH6, and PMS2. This decision was based on emerging data that show a smaller risk for cancer in the latter groups. 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.

Existing screening data in the literature are mainly on colon and endometrial cancers. More data are needed to evaluate the risk and benefits of extracolonic and extra-endometrial cancer screening, and recommendations are based mainly on expert opinion.

**Colon Cancer Surveillance**

If Lynch syndrome with MLH1 or MSH2 mutation 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, to be repeated every 1 to 2 years. This recommendation is based upon a systematic review of data between 1996 and 2006 on the reduction in cancer incidence and mortality by colonoscopy.

Because the average age of colon cancer onset for MSH6 or PMS2 mutation carriers is somewhat older than for MLH1 and MSH2 mutation carriers, the start of colon screening may be delayed. MSH6 carriers should begin colonoscopic surveillance at age 30 to 35 years, and PMS2 carriers should begin at age 35 to 40 years. However, screening may need to be initiated earlier in some families, depending on ages of cancers observed in family members. This screening is recommended every 2 to 3 years until age 40 or 50 for MSH6 and PMS2 mutation carriers, respectively, at which time colonoscopy should be performed every 1 to 2 years.

**Endometrial and Ovarian Cancer Surveillance**

Women with Lynch syndrome are at heightened risk for endometrial and ovarian cancers (up to 60% and 24%, respectively). Education that enhances recognition of relevant symptoms (i.e., dysfunctional uterine bleeding) is advised. Total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH/BSO) is an option that should be considered for risk reduction in women who have completed childbearing and carry a MLH1, MSH2, or MSH6 mutation. There is no clear evidence to support routine screening for gynecologic cancers. Annual endometrial sampling is an option for carriers of MLH1 or MSH2 mutations. Routine transvaginal ultrasound and serum CA-125 testing are not endorsed because they have not been shown to be sufficiently sensitive or specific, but the panel recognized that there may be circumstances where the clinician may find these tests helpful.

**Surveillance for Other Cancers**

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. Most cases occur after age 40, and males have a stronger predisposition. Lynch syndrome is also associated with a 3% to 6% risk for small bowel cancer.
is no clear evidence to support screening for gastric, duodenal, and small bowel cancer in patients with Lynch syndrome. For selected individuals or families or those of Asian descent with \textit{MLH1} or \textit{MSH2} mutations, physicians may consider upper esophagogastrroduodenoscopy (EGD) extended to the distal duodenum or into the jejunum every 3 to 5 years starting at age 30 to 35.

Annual urinalysis starting at age 25 to 30 years should also be considered to screen for urothelial cancers in carriers of \textit{MLH1} or \textit{MSH2} mutations, giving the relative ease and low cost compared to other tests. There is an increased risk for pancreatic and brain cancer in these individuals. However, no effective screening techniques have been identified for pancreatic cancer; therefore, no screening recommendation is possible at this time. Annual history and physical examination starting at age 25 to 30 years is appropriate for CNS cancer.

In addition, there have been suggestions of an increased risk for breast cancer in the Lynch syndrome population; however, because of limited data, no screening recommendation is possible at this time.

**Lynch Syndrome Surveillance Findings and Follow-up**

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. This important feature comes up clinically often because some people cannot undergo a colonoscopy or decline to have one on a regular basis.

Patients with confirmed adenocarcinoma should be treated following the appropriate NCCN Treatment Guidelines (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 the adenomatous polyps identified cannot be endoscopically resected or high-grade dysplasia is identified, total abdominal colectomy (TAC) with an ileorectal anastomosis (IRA) is recommended. Since surgical management is evolving, the option of segmental or extended segmental colectomy is based on individual considerations and discussion of risks. These patients should be followed with endoscopic rectal exams every 1 to 2 years.

**Chemoprevention in Lynch Syndrome**

In the recent 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. After a mean follow-up of >4 years, participants taking daily aspirin for at least 2 years had a 59% reduction in the incidence of CRC (HR, 0.41; 95% CI, 0.19–0.86; \( P = .02 \)). These participants also saw protection from non-colorectal Lynch syndrome cancers (HR, 0.47; 95% CI, 0.21–1.06; \( P = .07 \)). There was no protection seen for participants who completed <2 years of the intervention. Criticisms of this trial have been published.

At this time, the panel believes that the data are not sufficiently robust to recommend standard use of aspirin as chemoprevention in Lynch syndrome.

**Familial Adenomatous Polyposis**

Classical FAP and attenuated FAP (AFAP) are autosomal dominant conditions characterized by a germline mutation in the \textit{APC} gene, located on chromosome 5q21. Truncating mutation of the \textit{APC} gene is detectable in about 80% of FAP patients using protein-truncating tests. 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.
The I1307K polymorphism in the APC gene, found people of Ashkenazi Jewish decent, predisposes carriers to CRC.\textsuperscript{82-84} However, an available test for I1307K has been excluded from the guidelines because there is very little evidence to date indicating what kind of screening should be offered to individuals with this mutation.

**Diagnosis: Classical vs. Attenuated FAP**

A clinical diagnosis of classical FAP is based on the presence of $\geq 100$ polyps or fewer polyps at younger ages, especially in a patient with a family history of FAP.\textsuperscript{78} When fully developed, patients 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%). Other possible associated findings of patients with FAP include desmoid tumors, which occur more frequently in patients with distal APC mutations, and congenital hypertrophy of retinal pigment epithelium (CHRPE), which occurs in patients with mutations in the central portion of the gene.\textsuperscript{85,86} 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.

AFAP is a recognized variant of FAP characterized by a later onset of disease and fewer adenomatous polyps, typically 10 to $<100$.\textsuperscript{78,79} These adenomatous polyps are more prone to occur in the right colon and may take the form of diminutive sessile adenomatous polyps.\textsuperscript{87} Phenotypic expression is often variable within families. The onset of CRC is typically delayed compared to FAP patients,\textsuperscript{88} but the incidence of cancer rises sharply after the age of 40 and approaches 70% by age 80. Upper gastrointestinal findings and thyroid and duodenal cancer risks are similar to that in classical FAP.

To confirm the diagnosis of FAP or AFAP, a germline mutation in APC must be identified (see Genetic Testing for FAP, AFAP, and MAP, below).

**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, prophylactic proctocolectomy is usually indicated in the second decade. 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**

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, below). 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, flexible sigmoidoscopy or colonoscopy every 12 months, beginning at 10 to 15 years of age, is recommended. Once adenomas develop, surgical options should be reviewed (see below).

**No genetic testing:** Some people who undergo genetic counseling decide, for one reason or another, 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 flexible sigmoidoscopy or colonoscopy beginning at age 10 to 15 years until the age of 24. Then if results continue to be negative, screening is scaled down to every 2 years until age 34, every 3 years until age 44, and every 3 to 5 years thereafter. One should also consider substituting colonoscopy every 5 years beginning at age 20 for a chance that a patient may have AFAP.

There are several reasons why screening 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, so annual screening 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 screening begins to decrease with age around this time, so that screening does not need to be as frequent between the ages of 24 and 34, and can be even less frequent between the ages of 34 and 44. However, even this recommended schedule is more rigorous than screening guidelines for the general population, because serial negative examinations up to age 35 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 screening is still warranted in these individuals.

**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%. Evaluating presymptomatic 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 a presymptomatic person is informative even when the familial mutation has not been previously identified. However, interpreting a test in which “no mutation is found” in a presymptomatic 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. 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, they should be managed in the same way as those with a personal history of classical FAP.

**Preoperative Surveillance for Individuals with a Family History of AFAP**

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 screening 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 screenings 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 screening until adenomatous polyps are found, at which point they should be managed as patients with a personal history of AFAP.

**Preoperative Surveillance for Individuals with a Personal History of AFAP**

Treating patients with a personal history consistent with AFAP varies depending on the patient’s age and adenoma burden. For young patients under age 21 with a small adenoma burden, colonoscopy and polypectomy are recommended every 1 to 2 years with appropriate surgical evaluation and counseling. In patients aged 21 years and older with small adenomatous polyp burden, colectomy and IRA are alternative treatment options to colonoscopy and polypectomy that may be considered. Patients with what appears to be an endoscopically manageable adenoma burden may choose to defer colectomy.

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), surgery is recommended (see below). Colectomy may also be indicated before this level of polypl profusion, especially if colonoscopy is difficult and polyp control is uncertain. Earlier surgical intervention (usually after age 21) should also be considered in noncompliant patients.

**Surgical Options in FAP and AFAP**

Three different surgical options are available for individuals with classical FAP and AFAP: total proctocolectomy with ileal pouch anal anastomosis (TPC/IPAA), TAC with IRA (TAC/IRA), and TPC with permanent end ileostomy (TPC/EI). The prime factors to consider when choosing an operation for FAP and AFAP are the personal and familial phenotype, including the rectal polyp burden, and whether colon or rectal cancer is present at diagnosis. In patients presenting with the classical FAP phenotype, TPC/IPAA, if possible, is the procedure of choice, since it prevents both colon and rectal cancers. For patients with AFAP, TAC/IRA is preferred. 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 sections below. In
patients who are younger than 18 years with mild polyposis and without a family history of early cancers or genetic disposition, timing of colectomy can be individualized, but annual colonoscopy is essential.

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 colon or 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 fairly quick, 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 bladder or sexual function problems, and even a temporary stoma is obviated. The major disadvantages of TAC with IRA are the high risk for rectal cancer development and associated morbidity and mortality, the frequent need to undergo subsequent proctectomy because of severe rectal polyposis, and the real need for regular endoscopic surveillance of the retained rectum (every 6–12 months).

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. 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, studies have reported that the risk for rectal cancer associated with TAC and IRA has declined since the 1980s when IPAA first became available for high-risk patients with severe polyposis.

The choice of TAC with IRA versus TPC with IPAA centers on the issues of the relative quality of life. A modest reduction in life expectancy is expected in patients with classical FAP with rectal preservation. 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. It is not recommended for patients with curable colon or rectal cancer or those with extensive rectal or colonic polyposis. Patients and families must be absolutely reliable for follow-up endoscopic examinations. The risk to the rectal stump rises considerably after the age of 50 and if the rectum becomes unstable, a proctectomy with either an IPAA or EI is recommended.
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 for 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 re-operation.

Surveillance Following Surgery for FAP Colorectal Cancer: Patients with retained rectum should undergo endoscopic rectal examination every 6 to 12 months. If the entire colorectal tract has been removed, the ileal pouch or ileostomy should be evaluated endoscopically every 1 to 3 years; 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 below).

Duodenal or Periampullary Cancer: A major component of surveillance in patients with a personal history of FAP or AFAP after surgery relates to the upper gastrointestinal 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. 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 around 35% (95% CI, 25% to 45%).

Surveillance following colectomy with side-viewing duodenoscopy, use of Spigelman’s or other standardized staging system, and extensive biopsy of dense lesions to evaluate advanced histology is recommended, though efficacy of surveillance of these sites has not been demonstrated. More intensive surveillance and/or treatment are required in patients older than 50 years with large or villous adenomatous polyps.

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.

Other Cancers: Fundic gland polyps (FGP) of the stomach also occur in the majority of FAP and AFAP patients and often are too numerous to count. In FAP, FGPs usually have bi-allelic inactivation of the APC gene, and often display foci of dysplasia or microadenomatous polyps of the foveolar epithelium. 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 observe carefully for gastric polyps that stand out because they 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 warrants attention during surveillance. In the absence of rigorous data, there was extensive discussion among panelists on this area. Patients are at heightened risk for thyroid cancer with a lifetime risk of approximately 2% to 6% and female predominance (95%). Peak incidence is in the third decade of life with a mean age of around 30 years. Yearly thyroid physical examination starting in the late teenage years is recommended and is considered adequate for timely diagnosis and treatment. Annual thyroid ultrasound may be considered to supplement physical examination, although supportive data are lacking.

There is also 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. Annual abdominal palpation during physical examination is advised. If family history of symptomatic desmoids is present, consider abdominal CT or MRI 1 to 3 years post-colectomy and then at 5- to 10-year intervals. Immediate abdominal imaging is warranted if suggestive abdominal symptoms are present.

Data on screening for small bowel polyps and cancer are lacking, but adding small bowel visualization to CT or MRI for desmoids can be considered especially if duodenal polyposis is advanced. The risk for hepatoblastoma is much higher in young children with FAP. Although the absolute risk is about 1.5%, given the lethality of the disease (25% mortality), active screening by liver palpation, ultrasound, and AFP measurements every 3 to 6 months during the first five years of life may be considered. The optimal approach would be to do this screening in a clinical trial.

Medulloblastoma accounts for most of the brain tumors found in FAP patients, predominantly in females younger than age 20. 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 1,391 FAP-related subjects. More studies are needed to elucidate the risk and benefit of screening for brain and pancreatic cancers, and no additional screening recommendation other than annual physical exam is made.

**Surveillance After Surgery for AFAP**

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

**Chemoprevention in FAP and AFAP**

The nonsteroidal anti-inflammatory drug (NSAID) aspirin has been shown to reduce the incidence and recurrence of colorectal adenomatous polyps in the general population. 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.\textsuperscript{115,117,119-122} 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.\textsuperscript{119} 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.\textsuperscript{122} 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 $P < .0001$).\textsuperscript{121} However, due to the increased risk of cardiovascular events associated with their use, COX-2 inhibitors are not recommended routinely for sporadic adenomatous polyps.\textsuperscript{124,125}

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 adenomatous polyps in persons with FAP prior to surgical intervention.\textsuperscript{126} In addition, a recent randomized controlled trial failed to show a strong benefit to chemoprevention with aspirin in young patients with FAP prior to surgical intervention, despite non-significant trends to reduced polyp size and number.\textsuperscript{127} Thus, NSAIDs do not seem to be as effective as primary treatment of FAP.

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. In a randomized, double-blind, placebo-controlled study of 77 FAP patients 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.\textsuperscript{128} Long-term use of sulindac also seems to be effective in polyp regression and preventing recurrence of higher-grade adenomatous polyps in the retained rectal segment of FAP patients.\textsuperscript{129} 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 recent study looked at a possible similar postoperative chemopreventive role in FAP and AFAP for the omega-3 polyunsaturated fatty acid eicosapentaenoic acid (EPA).\textsuperscript{130} In this randomized, double-blind, placebo-controlled trial, 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.

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 is the most potent polyp-regression medication,\textsuperscript{126} it is not known if the decrease in polyp burden decreases cancer risk.

**MUTYH-Associated Polyposis**

MAP is an autosomal recessive hereditary syndrome that predisposes individuals to attenuated adenomatous polyposis and CRC.\textsuperscript{131-133} It is caused by biallelic germline mutations in the \textit{MUTYH} gene. \textit{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.\(^{134}\)

Most individuals with MAP generally have fewer than 100 polyps, although a minority can present with over 1,000. Hyperplastic 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 life-time risk for CRC for patients with MAP may be very high.\(^{135}\) 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. Gastric polyposis is uncommon. In addition, individuals with MAP generally require colectomy at a later age than those with FAP.

**Preoperative and Surgical Management of MAP**

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, below). With positive genetic testing (biallelic MUTYH mutations) or no testing in such individuals, surveillance colonoscopy should begin at age 25 to 30 years, 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 and side-viewing duodenoscopy can also be considered beginning at age 30 to 35 years, with follow-up as described above for patients with FAP.

With one or no mutations found in individuals with a family history of MAP and known MUTYH mutations, individuals should be screened as those at average risk (see Screening of Individuals at Average Risk, above).

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

Symptomatic individuals younger than 21 years of age with confirmed biallelic MUTYH mutations and a small adenoma burden are followed with colonoscopy and complete polypectomy every 1 to 2 years. Surgical evaluation and counseling is also recommended. Colectomy and IRA may be considered as the patient gets older. Surgery in the form of colectomy with IRA (preferred in most cases) or proctocolectomy with IPAA is recommended for patients with significant polyposis not manageable by polypectomy, based on the burden of disease in the rectum.

**Postoperative Surveillance in MAP**

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,\(^{126}\) it is not known if the decrease in polyp burden decreases cancer risk.

In addition to evaluation of the rectum, annual physical exam is recommended, with baseline upper endoscopy beginning at age 30 to 35 years. Follow-up of duodenoscopic findings is as described for patients with FAP, above.
Genetic Testing for FAP, AFAP, and MAP

Genetic testing of \( APC \) and/or \( MUTYH \) is important to differentiate between FAP/AFAP from MAP and colonic polyposis of unknown etiology. A recent cross-sectional study of >7000 individuals found that the prevalence of pathogenic \( APC \) mutations was 80%, 56%, 10%, and 5% for those with \( \geq 1000 \) adenomas, 100 to 999 adenomas, 20 to 99 adenomas, and 10 to 19 adenomas, respectively. For the same groups, the prevalence of biallelic \( MUTYH \) mutations was 2%, 7%, 7%, and 4%.

When a patient with no known familial mutation presents with a history of >10 adenomas or a desmoid tumor and/or meets the criteria for SPS (see below), then comprehensive genetic testing of \( APC \) and/or \( MUTYH \) is recommended, as outlined in the guidelines. 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 only on a personal history of a desmoid tumor. These guidelines recommend genetic counseling and testing for germline \( MUTYH \) mutations for asymptomatic siblings of patients with known \( MUTYH \) mutations, as well as for \( APC \) mutation-negative patients with more than 10 cumulative adenomatous polyps.

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

It is important to note that \emph{de novo} mutations can occur in \( APC \) or \( MUTYH \). Thus, when colonic polyposis is present in an individual with a negative family history, consideration should be given to genetic testing of \( APC \), followed by testing of \( MUTYH \) if no \( APC \) mutation is found.
Colonic Adenomatous Polyposis of Unknown Etiology

When comprehensive 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.

Serrated Polyposis Syndrome

Serrated polyps include hyperplastic polyps, sessile serrated adenomas/polyps, and traditional serrated adenomas (see Serrated Polyps, above). SSSPs are flat or slightly raised and usually occur on the right side, while traditional serrated adenomas are generally polyploid. Serrated polyps are more difficult to detect during colonoscopy and account for a disproportionate amount of interval cancers. These polyps are considered premalignant, may account for as many as a third of CRCs, and should be managed similarly to adenomas. Serrated polyps are thought to progress to cancer via pathways that are different from those in adenomas and to have an unfavorable prognosis.

A clinical diagnosis of serrated polyposis (previously known as hyperplastic polyposis) is considered in an individual with serrated polyps and/or a family history of SPS following the criteria outlined in the guidelines above. Individuals with serrated polyposis have an increased risk for colon cancer, although the precise risk remains to be defined. Although SPS is clearly inherited in some cases, no causative gene has yet been identified. Epigenetic and environmental factors are also thought to play a role in the syndrome.

Management of Serrated Polyposis

Data on patients with SPS are limited. 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). 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.

Based on available data and on expert consensus opinion, the panel outlined surveillance recommendations for individuals with serrated polyposis in the guidelines above. Colonoscopic surveillance with consideration of surgical referral is recommended if colonoscopic treatment and/or surveillance are inadequate or if high-grade dysplasia occurs.

Management of First-Degree Relatives

The risk for CRC in relatives of individuals with SPS is still unclear, although several studies have found a significantly increased risk. One recent 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 (RR, 5.4; 95% CI, 3.7–7.8; P < .001). 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 recently found a similar increase in risk for CRC in both first- and second-degree relatives of patients with SPS. In addition, an increased risk for pancreatic cancer was observed. In a recent prospective study, 76% of first-degree relatives of SPS patients were found to have SPS upon colonographic screening.

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.
References


NCCN Guidelines Version 1.2015
Genetics/Familial High-Risk Assessment: Colorectal


