<table>
<thead>
<tr>
<th>Name</th>
<th>Institution/Center</th>
</tr>
</thead>
<tbody>
<tr>
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<td>Chair, Huntsman Cancer Institute at the University of Utah</td>
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<td>University of Alabama at Birmingham Comprehensive Cancer Center</td>
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<td>Mary Dwyer, MS</td>
<td>NCCN</td>
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</tbody>
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## NCCN Colorectal Cancer Screening Panel Members

**Summary of the Guidelines Updates**
- **Risk Assessment for Colorectal Cancer** (CSCR-1)
- **Average Risk**
  - **Average Risk** (CSCR-2)
- **Increased Risk**
  - **Personal History of Adenomatous or Sessile Serrated Polyps** (CSCR-3)
  - **Personal History of Colorectal Cancer** (CSCR-4)
  - **Personal History of Inflammatory Bowel Disease** (CSCR-5)
  - **Based on Positive Family History** (CSCR-6)
  - **Screening Modality and Schedule** (CSCR-A)
  - **Definitions of Common Colorectal Resections** (CSCR-B)

## Clinical Trials

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

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

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

## NCCN Colorectal Cancer Screening Panel Members

### High-Risk Syndromes
- **Criteria for Further Risk Evaluation, Risk Assessment** (HRS-1)
- **Obtaining a Comprehensive Assessment for Hereditary Colorectal Cancer** (HRS-A)

### Non-Polyposis Syndrome
- **Lynch Syndrome** (Hereditary Nonpolyposis Colorectal Cancer) (LS-1)
  - **Principles of IHC and MSI Testing for Lynch Syndrome** (LS-A)
  - **Revised Bethesda Guidelines** (LS-B)
  - **Amsterdam Criteria I and II** (LS-C)
  - **Cancer Risk Up to Age 70 Years in Individuals with Lynch Syndrome Compared to the General Population** (LS-D)

### Polyposis Syndromes
- **APC and MUTYH Genetic Testing Criteria** (APC/MUTYH-1)
- **Familial Adenomatous Polyposis/AFAP (FAP/AFAP-1)**
  - **Familial Adenomatous Polyposis (FAP-1)**
    - **Surgical Management Options with FAP** (FAP-A)
  - **Attenuated Familial Adenomatous Polyposis (AFAP-1)**
  - **MUTYH-Associated Polyposis (MAP-1)**
- **Peutz-Jeghers Syndrome** (PJS-1)
- **Juvenile Polyposis Syndrome** (JPS-1)
- **Serrated Polyposis Syndrome** (SPS-1)
- **Colonic Adenomatous Polyposis of Unknown Etiology** (CPUE-1)

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Updates to the 2.2013 version of the NCCN Guidelines for Colorectal Cancer Screening from the 1.2013 version include:

**CSCR-A 1 of 4**
- A footnote was removed: “If other modalities are not available, double-contrast barium enema every 5 years may be useful.”

**Lynch syndrome**

**LS-1**
- Lynch syndrome testing criteria
  - 2nd bullet was added: “All CRC patients or CRC patients diagnosed at <70 y and also those ≥70 y who meet the Bethesda guidelines (See LS-B)”

**LS-A**
- Last bullet was revised by adding: “Recommend LS screening at the time of diagnosis of CRC with either approach: All CRC patients or CRC patients diagnosed at <70 y and also those ≥70 y who meet the Bethesda guidelines (See LS-B).”

**MS-1**
- The Discussion section was updated to reflect the changes in the algorithm.

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Updates in Version 1.2013 of the NCCN Guidelines for Colorectal Cancer Screening from Version 2.2012 include:

**CSCR-1**
- Cowden syndrome and Li-Fraumeni syndrome were added as examples of high-risk syndromes with a link to the NCCN Guidelines for Genetics/Familial High-Risk Assessment: Breast and Ovarian.
- Footnote
  - Footnote “a” was added: “See Discussion for further information on age of screening in African Americans.”

**CSCR-2**
- For colonoscopy with polyps found, “hyperplastic, right-sided, non-SSP, and <1cm” with “repeat colonoscopy in 5 y” was added.
- Footnotes
  - Footnote “h” was revised from “Studies at the present time have demonstrated that fecal immunochemical testing (FIT) is as good as, if not superior to, guaiac-based testing” to “Recent studies have demonstrated that FIT is more sensitive than guaiac-based testing.”
  - Footnote “k” was added: “Left-sided includes splenic flexure, descending colon, sigmoid colon and rectum. Right-sided includes cecum, ascending colon and transverse colon.”
  - Footnote was removed: “Other screening modalities such as double contrast barium enema should be reserved for those who are not able to undergo colonoscopy, or colonoscopy is technically incomplete.”

**CSCR-3**
- Low-risk adenomatous polyps, after repeat colonoscopy within 5 y, if negative/no polyps, “repeat colonoscopy” was changed from “every 5-10 y” to “every 10 y.”
- Footnotes
  - Footnote “n” was modified by adding text from a previous footnote: “Other factors in determining intervals might include the results of the prior examinations and the presence of comorbid conditions. Generally, the results of the first two screening examinations may predict the patient's overall colon cancer risk. (USPSTF, Screening for colorectal cancer: U.S. Preventive Service Task Force recommendation statement. Ann Intern Med 2008;149:627-637).
  - Footnote was removed: “The decision to choose a 5- or 10-year interval after a low-risk exam is a patient-specific one. The factors...”

**CSCR-4**
- Increased Risk Based on Personal History of Colorectal Cancer
  - A new column titled “Testing” was added regarding MSI and IHC testing for a personal history of CRC.
  - The surveillance recommendations were removed and the reader is now directed to the surveillance recommendations in “NCCN Guidelines for Colon Cancer” and “NCCN Guidelines for Rectal Cancer.”

**CSCR-6**
- Increased Risk Based on Positive Family History
  - The following family history criteria were removed
    - 2 second-degree relatives with CRC at any age
    - 1 second-degree relative and ≥2 third-degree relatives with CRC at any age
    - Grandparent aged >50 y with CRC
    - Aunt/uncle aged >50 y with CRC or 3 third-degree relatives with CRC at any age
  - 1 second-degree relative with CRC aged <50 y, the follow-up screening was revised: “Repeat every 5-10 y per colonoscopy findings.”
  - First-degree relative with advanced adenoma(s), the follow-up screening was revised: “Repeat every 7-8 y per colonoscopy findings.”
- Footnotes
  - Footnote “bb” has been revised: “Multiple (2 or more) negative colonoscopies may support stepwise lengthening in the colonoscopy interval by 1 year. (eg, every 5 y = ages 50, 55, 61, 68, and 75-76).”
Updates in Version 1.2013 of the NCCN Guidelines for Colorectal Cancer Screening from Version 2.2012 include:

**CSCR-A 2 of 4**
- 3rd bullet was modified by adding: “A number of quality indicators such as withdrawal time have been examined. Quality indicators for colonoscopy are an important part of the fidelity of findings.”

**CSCR-A 3 of 4**
- Stool-based screening, 1st bullet was added: “Annual stool occult blood testing should not be performed if colonoscopy is used as a screening measure in an average-risk patient.”
- FIT
  - 5th bullet was added: “Recent studies have demonstrated that FIT is more sensitive than guaiac-based testing.” with 3 corresponding references.

**CSCR-A 4 of 4**
- Footnote “13” was modified by updating the link to the most recent version of the “AGA Standards for Gastroenterologists for Performing and Interpreting Diagnostic Computed Tomography Colonography: 2011 Update.”

**High-Risk Syndromes**

**HRS-1**
- Criteria, “Individual with a desmoid tumor” was added.

**Lynch Syndrome**

**LS-1**
- After “Positive mutation found in MLH1, MSH2, MSH6, or PMS2,” the recommendation was clarified as: “Consider genetic testing for at-risk family members.”

**LS-2**
- The surveillance recommendations were specified as being for MLH1 and MSH2 mutation carriers
  - Colonoscopy
    - 2nd bullet was added: “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.”
    - Gastric and small bowel cancer, bullet was revised: “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) at 2- to 3-y every 3.5-5 y intervals beginning at age 30-35 y. Consider capsule endoscopy for small bowel cancer at 2- to 3-y intervals beginning at age 30-35 y.
  - Pancreatic cancer was revised: “Due to limited data, 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 bullet was added: “There have been suggestions that there is an increased risk for breast cancer in LS patients; however, due to limited data no screening recommendation is possible at this time.”
- Footnote

**LS-3**
- Surveillance recommendations were added for MSH6 and PMS2 mutation carriers.

**LS-D**
- The table has been updated with the addition of cancer risk associated with MSH6 and PMS2 gene mutations.
Updates in Version 1.2013 of the NCCN Guidelines for Colorectal Cancer Screening from Version 2.2012 include:

**APC and MUTYH Genetic Testing Criteria**

**APC/MUTYH-1**
- A new page was added describing APC and MUTYH genetic testing criteria, testing strategies, and treatment/surveillance.

**Familial Adenomatous Polyposis/AFAP**

**FAP/AFAP-1**
- Phenotype
  - For both FAP and AFAP, “germline APC mutation” was added.
  - FAP
    - 5th bullet was modified: “hepatoblastoma (1%-2%, usually age ≤5 y)”
    - 8th bullet was added: “Duodenal cancers (4%-12%)”
  - AFAP
    - 2nd bullet was revised: “Presence of 10-100 adenomas”
    - 5th bullet was revised: “Upper GI findings, thyroid and duodenal cancer risks are similar to classical FAP”

- Footnotes
  - Footnote “a” was added: “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.”
  - Footnote “d” was added: “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.”

**Familial Adenomatous Polyposis**

**FAP-1**
- Surveillance, colon cancer
  - 3rd bullet was changed from “Consider nonsteroidal anti-inflammatory drug (NSAID) chemoprevention to reduce polyp burden as a pharmacological adjunct to endoscopic surveillance. A clinical trial is encouraged” to “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 polypl regression medication, it is not known if the decrease in polypl burden decreases cancer risk.” Also for AFAP-1.

**FAP-2**
- Surveillance, extracolonic
  - Gastric cancer,
    - 1st sub-bullet was revised: “…For this reason, special screening or surgery is not needed unless should only be considered in the presence of high-grade dysplasia is present.”
    - 2nd sub-bullet was added: “Non-fundic gland polyps should be managed endoscopically if possible. Patients with polyps that cannot be removed endoscopically but have high-grade dysplasia or invasive cancer detected on biopsy should be referred for gastrectomy.”

**FAP-4**
- Genetic testing was revised: “Recommend APC gene testing for familial mutation for at-risk family member.”

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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.
Updates in Version 1.2013 of the NCCN Guidelines for Colorectal Cancer Screening from Version 2.2012 include:

**Attenuated Familial Adenomatous Polyposis (AFAP)**
- Genetic testing, “APC gene testing” was removed along with two footnotes “APC gene testing is recommended in a proband to confirm a diagnosis of AFAP and allow for mutation-specific testing in other family members. Additionally, knowing the location of the APC mutation can be helpful in determining extracolonic cancer risks in affected individuals” and “MUTYH testing if an APC mutation is not found or if recessive pattern patients with a family history of apparent in pedigree (See MAP-1).”
- Footnote “c” was revised: “Earlier surgical intervention should be considered in patients with a family history of cancer before age 40 or noncompliant patients.”

**AFAP-2**
- Genetic testing was revised: “Recommend APC gene testing for familial mutation for at-risk family member.”

**MUTYH-Associated Polyposis (MAP)**
- The algorithms related to MAP were extensively revised.

**Peutz-Jeghers Syndrome (PJS)**
- Screening Procedure and Interval
  - Pancreas was modified by removing: “CA 19-9 at similar intervals.”
  - Small intestine was modified: “Small bowel visualization (CT enterography, small bowel enteroclysis)...”

**Colonic Adenomatous Polyposis of Unknown Etiology (CPUE)**
- A new page describing the management/surveillance of colonic adenomatous polyposis of unknown etiology was added.

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**RISK ASSESSMENT FOR COLORECTAL CANCER**

**Average risk:**
- Age \( \geq 50 \) y
- No history of adenoma or colorectal cancer (CRC)
- No history of inflammatory bowel disease
- Negative family history

\[ \text{See Average-Risk Screening and Evaluation (CSCR-2)} \]

**Increased risk:**
- Personal history
  - Adenoma/sessile serrated polyp (SSP)
  - CRC
  - Inflammatory bowel disease (ulcerative colitis, Crohn’s disease)

- Positive family history

**High-risk syndromes:**
- Lynch syndrome (hereditary nonpolyposis colorectal cancer [HNPCC]) \( (LS-1) \)
- Polyposis syndromes
  - Classical Familial Adenomatous Polyposis \( (FAP-1) \)
  - Attenuated Familial Adenomatous Polyposis \( (AFAP-1) \)
  - \( MUTYH \)-Associated Polyposis \( (MAP-1) \)
  - Peutz-Jeghers Syndrome \( (PJS-1) \)
  - Juvenile Polyposis Syndrome \( (JPS-1) \)
  - Serrated Polyposis Syndrome \( (SPS-1) \) (rarely inherited)

\[ \text{See Criteria for Further Risk Evaluation for High-Risk Syndromes (HRS-1)} \]

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NCCN Guidelines Version 2.2013
Colorectal Cancer Screening

**RISK STATUS**

**SCREENING MODALITY AND SCHEDULE**

- **Average risk:**
  - Age ≥50 y
  - No history of adenoma or CRC
  - No history of inflammatory bowel disease
  - Negative family history

<table>
<thead>
<tr>
<th>Screening Modality and Schedule</th>
<th>Evaluation of Positive Screening Findings</th>
</tr>
</thead>
</table>
| Colonoscopy (preferred if available) | Repeat colonoscopy in 10 y
| or
| Stool-based:
  - Guaiac-based (category 1)
  - or immunochemical-based testing annually
| Hyperplastic, left-sided, non-SSP, and <1 cm
| Repeat colonoscopy in 10 y
| or
| Flexible sigmoidoscopy | Repeat flexible sigmoidoscopy in 5 y
| or
| Colonoscopy (preferred if available) | Repeat colonoscopy in 5 y
| or
| Flexible sigmoidoscopy | Repeat flexible sigmoidoscopy in 5 y

**EVALUATION OF POSITIVE SCREENING FINDINGS**

- **Negative/No polyps**
  - Repeat colonoscopy in 10 y

- **Positive/Polyps**
  - Polypectomy

- **Positive/Polyps**
  - Colonoscopy

- **Biopsy**
  - Hyperplastic, left-sided, non-SSP, and <1 cm
  - Repeat flexible sigmoidoscopy in 5 y

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**Discussion**

- Currently there is not a consensus on the use of CT colonography as a primary screening modality, and it is evolving with regards to recommended/programmatic frequency, polyp size leading to referral for colonoscopy, and protocol for evaluating extra colonic lesions. However, the data available suggest that, if CT colonography is negative/no polyps, then repeat CT colonography in 5 y, and if positive/polyps lesions, colonoscopy should be performed.


- If colonoscopy is incomplete or preparation is suboptimal, consider other screening modality or repeat colonoscopy at discretion of physician.

- Emerging technologies such as stool DNA have shown increasing evidence as a reasonably accurate screening modality, but there are limited data to determine an interval between screening. At present, stool DNA is not considered a primary screening modality.

- Recent studies have demonstrated that FIT is more sensitive than guaiac-based testing.

- SSPs are managed the same as adenomas. Rex et al. Am J Gastro 2012;107:1315–1329.

- There is controversy over whether SSPs should be called “sessile serrated adenomas.” These terms are equivalent and these guidelines will use “SSPs.” However, any serrated lesions in the proximal colon should be followed similarly to adenomatous polyps.

- Left-sided includes splenic flexure, descending colon, sigmoid colon and rectum. Right-sided includes cecum, ascending colon and transverse colon.
INCREASED RISK BASED ON PERSONAL HISTORY OF ADENOMATOUS POLYP OR SESSILE SERRATED POLYP

**RISK STATUS**

- Increased-risk patients: Personal history of adenomatous polyp(s) or SSPs found at colonoscopy

**CLINICAL FINDINGS**

- Low-risk adenomatous polyps:
  - ≤2 polyps
  - <1 cm
  - Tubular

- Advanced or multiple adenomatous polyps:
  - High-grade dysplasia
  - ≥1 cm
  - Villous (>25% villous)
  - Between 3 and 10 adenomatous polyps

- More than 10 cumulative adenomatous polyps

- Incomplete or piecemeal polypectomy or polypectomy of large sessile polyps

- Malignant adenomatous polyp

**FOLLOW-UP OF CLINICAL FINDINGS**

- Repeat colonoscopy within 5 y

- Repeat colonoscopy within 3 y

- Repeat colonoscopy within 2-6 mo

See NCCN Guidelines for Colon Cancer

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### INCREASED RISK BASED ON PERSONAL HISTORY OF COLORECTAL CANCER

<table>
<thead>
<tr>
<th>RISK STATUS</th>
<th>TESTING</th>
<th>SURVEILLANCE</th>
</tr>
</thead>
</table>
| Personal history of CRC | • Recommend Lynch syndrome (LS) screening at the time of diagnosis with either approach below:  
  ➢ All CRC patients  
  or  
  ➢ CRC patients diagnosed at <70 y and also those ≥70 y who meet the Bethesda guidelines  
  (See LS-B)  
  • LS screening is done by:°  
    ➢ Microsatellite instability (MSI) testing and/or  
    ➢ Immunohistochemistry (IHC) for the 4 mismatch repair proteins (MLH1, MSH2, MSH6, and PMS2) followed by BRAF testing or MLH1 promoter methylation testing if MLH1 is not expressed by IHC  
    ➢ For patients with high MSI or abnormal IHC tumors that do not have a BRAF mutation or MLH1 promoter methylation, the patient should be referred to cancer genetics for follow-up counseling and further testing. | See NCCN Guidelines for Colon Cancer and See NCCN Guidelines for Rectal Cancer |


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### Increased Risk Based on Personal History of Inflammatory Bowel Disease

<table>
<thead>
<tr>
<th>Risk Status</th>
<th>Initiation of Screening</th>
<th>Screening Modality and Schedule</th>
<th>Evaluation of Positive Screening Findings</th>
<th>Follow-up of Clinical Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personal history of inflammatory bowel disease&lt;br&gt;- Ulcerative colitis&lt;br&gt;- Crohn's disease, especially if pancolitis</td>
<td>- 8-10 y after onset of symptoms of pancolitis&lt;br&gt;- 12 y after onset of left-sided colitis</td>
<td>Colonoscopy every 1-2 y&lt;br&gt;• When clinically quiescent, 4 quadrant biopsies every 10 cm with &gt;30 total samples (preferred)&lt;br&gt;• Additional extensive sampling of strictures and masses&lt;br&gt;• Endoscopic polypectomy when appropriate with biopsies of surrounding mucosa for the assessment of dysplasia</td>
<td>• Dysplasia/intraepithelial neoplasia&lt;br&gt;▷ Confirmation by an expert GI pathologist is desirable&lt;br&gt;• Sporadic colorectal adenoma</td>
<td>Surgical consultation for resection&lt;br&gt;&lt;sup&gt;§&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

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<sup>1</sup>Information regarding the value of endoscopic surveillance of long-standing Crohn’s disease is limited. Surveillance is at the discretion of the physician.


<sup>3</sup>Biopsies can be better targeted to abnormal-appearing mucosa using chromoendoscopy, narrow-band imaging, autofluorescence, or confocal endomicroscopy. Targeted biopsies have been found to improve detection of dysplasia, and should be considered for surveillance colonoscopies in patients with ulcerative colitis.

<sup>4</sup>Patients with ulcerative colitis develop sporadic colorectal adenomas at the same rate as the general population. Lesions that appear endoscopically and histologically similar to a sporadic adenoma, with no dysplasia in the flat mucosa in the surrounding area or elsewhere in the colon and without invasive carcinoma in the polyp, can be treated safely by polypectomy and continued surveillance.

<sup>5</sup>Optimal management of Crohn’s-related dysplasia remains undefined. Patient and physician preference should be considered. Extent of resection for Crohn’s-related dysplasia needs to be based upon the individual findings.

<sup>6</sup>Appropriate management of adenomatous polyps in the setting of ulcerative colitis is dependent on various factors and should be at the discretion of the treating physician.

<sup>7</sup>See Definitions of Common Colorectal Resections (CSCR-B).

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**INCREASED RISK BASED ON POSITIVE FAMILY HISTORY**

**FAMILY HISTORY CRITERIA**

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Screening</th>
</tr>
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<tbody>
<tr>
<td>1 first-degree relative with CRC aged &lt;50 y or 2 first-degree relatives with CRC at any age</td>
<td>Colonoscopy beginning at age 40 y or 10 y before earliest diagnosis of CRC → Repeat every 3-5 y depending on individual family history</td>
</tr>
<tr>
<td>First-degree relative with CRC aged ≥50 y</td>
<td>Colonoscopy beginning at age 50 y or 10 y before earliest diagnosis of CRC → Repeat every 5 y</td>
</tr>
<tr>
<td>1 second-degree relative with CRC aged &lt;50 y</td>
<td>Colonoscopy beginning at age 50 y → Repeat per colonoscopy findings</td>
</tr>
<tr>
<td>First-degree relative with advanced adenoma(s)</td>
<td>Colonoscopy beginning at age 50 y or at age of onset, whichever is first → Repeat per colonoscopy findings</td>
</tr>
</tbody>
</table>


- **If a patient meets the criteria for an inherited colorectal syndrome, see Criteria for Further Risk Evaluation for High-Risk Syndromes (HRS-1).**

- **In this circumstance or if any one of the revised Bethesda criteria (see LS-B) are met, IHC/MSI testing should be performed on the colon tumor of the youngest family member with available colorectal cancer tissue. Also see Lynch Syndrome guidelines (LS-1).**

**Notes:**

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- **The 50-59 y subgroup is associated with a somewhat higher risk than the >60 y group and requires more intensive risk assessment.**

- **Colonoscopy intervals should be further modified based on personal and family history as well as on individual preferences. Factors that modify colonoscopy intervals include: specifics of the family history, including number and age of onset of affected second- and third-degree relatives; size of family; completeness of the family history; and participation in screening and colonoscopy findings in family members.**

- **Multiple (2 or more) negative colonoscopies may support stepwise lengthening in the colonoscopy interval.**
Colon cancer prevention and early detection should be the primary goals of CRC screening.

Screening of average-risk individuals can reduce CRC mortality by detecting cancer at an early, curable stage and by detecting and removing adenomas. It has also been shown to be cost-effective compared to other screening programs.

Although patient preferences and availability of resources play an important role in the selection of screening options, tests that are designed to detect both early cancer and adenomatous polyps should be encouraged.

**Screening modalities that detect adenomatous polyps and cancer**

- Colonoscopy every 10 years,
- Flexible sigmoidoscopy every 5 years,
- CT colonography (CTC) every 5 years

**Screening modalities that primarily detect cancer**

- Stool-based screening
  - Guaiac-based testing annually,
  - Immunochemical-based testing annually,
  - Stool DNA test with high sensitivity (interval for screening is uncertain)

---


4. Currently there is not a consensus on the use of CT colonography as a primary screening modality, and it is evolving with regards to recommended/programmatic frequency, polyp size leading to referral for colonoscopy, and protocol for evaluating extra colonic lesions. However, the data available suggest that if CT colonography is negative/no polyps, then repeat CT colonography in 5 years, and if CT colonography is positive/polyps lesions, colonoscopy should be performed.

5. Emerging technologies such as stool DNA have shown increasing evidence as a reasonably accurate screening modality, but there are limited data to determine an interval between screening. At present, stool DNA is not considered a primary screening modality except in specific circumstances.

---

**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.
Colonoscopy

In the United States, colonoscopy is the primary method employed for CRC screening in average- and high-risk populations. However, screening with any of the available modalities is preferable to no screening.

Caveats for the 10-year interval:
- A 10-year interval is appropriate for average-risk patients who had an optimal procedure.
- Shorter intervals may be indicated based on the quality and completeness of the colonoscopy.
- Individual risk factors and physician judgment should be included in the interval determination.
- The number and characteristics of polyps as well as family history and medical assessment should influence judgment regarding the interval between colonoscopies.
- Colonoscopy has limitations and may not detect all cancers and polyps.

Accumulating data suggest that there is substantial variability in the quality, and by extension, the clinical effectiveness of colonoscopy. A number of quality indicators such as withdrawal time have been examined. Quality indicators for colonoscopy are an important part of the fidelity of findings. Improving the overall impact of screening colonoscopy requires a programmatic approach that addresses quality issues at several levels.

These colonoscopy quality indicators may include:
- Cecal intubation rates
- Withdrawal time
- Adenoma detection rates
- Appropriate intervals between endoscopic studies based on family and personal history and number and histologic type of polyps on last colonoscopy
- Minor and major complication rates
- Pre-procedure medical evaluation
- Appropriate prep instructions

Standardized colonoscopy reports that contain, at a minimum:
- Patient demographic, clinical factors, adenoma and cancer history, and GI family history
- Procedure indications
- Endoscopic findings, including polyp number, size, location, and method of excision
- Photographic documentation of endoscopic landmarks
- Estimate of quality of bowel preparation
- Documentation of follow-up planning, including pathology results
- Sedation administered
- Written communication of the findings and plans to the patient and referring physician is encouraged.

Pathology should also include polyp number, size, and location in addition to histopathology.

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Flexible sigmoidoscopy

- May be performed alone or in combination with stool-based screening
- Issues surrounding sigmoidoscopy are similar to colonoscopy except the colon is only examined distal to the splenic flexure
- Recommended every 5 years for average-risk screening

Stool-based screening

- Annual stool occult blood testing should not be performed if colonoscopy is used as a screening measure in an average-risk patient.
- Guaiac-based, nonrehydrated
  - Requires 3 successive stool specimens annually (not via digital rectal examination), prescribed diet, and coordination by health care provider
  - Any positive test requires further evaluation
- Fecal immunochemical testing (FIT)
  - Detects human globin
  - Prescribed diet is not required
  - Many brands require only a single stool annually
  - Any positive test requires further evaluation
  - Recent studies have demonstrated that FIT is more sensitive than guaiac-based testing.\(^9,\,10,\,11\)

\(^8\)There are category 1 data that guaiac-based fecal occult blood test (FOBT) and flexible sigmoidoscopy reduce mortality from colorectal cancer.


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SCREENING MODALITY AND SCHEDULE (4 of 4)

Radiographic
CTC\textsuperscript{12,13,14}

- **Accuracy**
  - >10 mm lesions can be identified by CTC with an accuracy similar to colonoscopy
  - Lesions 5-9 mm can be identified with an acceptable accuracy that is less than that identified for colonoscopy
  - Lesions <5 mm cannot be identified with acceptable accuracy

- **Follow-up of identified lesions**
  - All identified lesions >5 mm should be referred for colonoscopy
  - When identified, lesions <5 mm generally do not need to be referred for colonoscopy

- The recommended performance interval of every 5 years is based solely on computer simulation models
- All visualized extracolonic findings should be described and recommendations should be provided as to appropriate follow-up
- The increased risk of cancer arising from a single CTC is estimated to be <0.14%
- CTC interpretation should be accomplished only by those trained according to American Gastroenterological Association\textsuperscript{12} or American College of Radiology (ACR)\textsuperscript{13} guidelines
- Procedure quality should be tracked and assured using current ACR practice guidelines for patient preparation, image acquisition, study interpretation, and reporting

\textsuperscript{12} See American Gastroenterological Association CT Colonography Standards.
\textsuperscript{13} See American College of Radiology Practice Guideline for the Performance of Computed Tomography (CT) Colonography in Adults.
\textsuperscript{14} Currently there is not a consensus on the use of CT colonography as a primary screening modality, and it is evolving with regards to recommended/programmatic frequency, polyp size leading to referral for colonoscopy, and protocol for evaluating extra colonic lesions. However, the data available suggest that if CT colonography is negative/no polyps, then repeat CT colonography in 5 years, and if CT colonography is positive/polyps lesions >5 mm, colonoscopy should be performed.
The extent of colorectal resection depends on the location of the tumor, any underlying condition (e.g., inflammatory bowel disease, hereditary syndrome), and the vascular supply to the colorectum.

Definitions of common colorectal resections are as follows:

- A through C: Ileocecectomy
- A through D: Ascending colectomy
- A through F: Right hemicolecotomy
- A through G: Extended right hemicolecotomy
- E through H: Transverse colectomy
- G through I: Left hemicolecotomy
- F through I: Extended left hemicolecotomy
- J through K: Sigmoid colectomy
- A through J: Subtotal colectomy
- A through K: Total colectomy
- K through L: Low anterior resection with sphincter preservation
- K through L: Abdominoperineal resection without sphincter preservation

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**NCCN Guidelines Version 2.2013**

**High-Risk Syndromes**

**CRITERIA FOR FURTHER RISK EVALUATION FOR HIGH-RISK SYNDROMES**

- Individual meeting the revised Bethesda guidelines\(^a\) (See LS-B)
- Individual from a family meeting Amsterdam criteria (See LS-C)
- >10 adenomas in same individual (See APC/MUTYH-1)
- Individual with multiple GI hamartomatous polyps (See PJS-1 and JPS-1) or serrated polyposis syndrome (See SPS-1)
- Individual from a family with a known high-risk syndrome associated with CRC, with or without a known mutation (See appropriate high-risk syndrome)
- Individual with a desmoid tumor

**RISK ASSESSMENT/GENETIC COUNSELING\(^b,c\)**

- Detailed family history
- Detailed medical and surgical history
- Directed examination for related manifestations
- Psychosocial assessment and support
- Risk counseling
- Education support
- Discussion of genetic testing\(^b\)
- Informed consent

**HIGH-RISK SYNDROME**

- LS (See LS-1)
- Classical familial adenomatous polyposis (FAP)
- Attenuated FAP (AFAP)
- MUTYH-associated polyposis (MAP)
- Peutz-Jeghers syndrome (PJS)\(^d\) (See PJS-1)
- Juvenile polyposis syndrome (JPS)\(^d\) (See JPS-1)
- Serrated polyposis syndrome (SPS) (See SPS-1)
- No syndromes, but familial risk present
  - See Positive Family History (CSCR-6) or Colonic Adenomatous Polyposis of Unknown Etiology (CPUE-1)

---

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

\(^b\)See Obtaining a Comprehensive Assessment for Hereditary Colorectal Cancer (HRS-A).

\(^c\)A genetic counselor and/or medical geneticist should be involved early in counseling patients who (potentially) meet criteria for an inherited syndrome. Genetic counseling is advised when genetic testing is offered.

\(^d\)Referral to a specialized team is recommended.

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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.
**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

- Minimal data set on each relative:
  - Current age and age at diagnosis of cancer (medical record documentation of cancer is strongly encouraged)
  - Age/availability of tumor sample and cause of death
  - Type of cancer (note multiple primaries)
  - Ethnicity/country of origin
  - Consanguinity
  - Suspected colon cancer syndromes and additional syndrome-specific features
    - (e.g., 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:
  - LS
  - Muir-Torre syndrome
  - Turcot syndrome
  - FAP and associated syndromes
    - AFAP
    - Gardner syndrome
    - Turcot syndrome
  - MAP
  - PJS
  - JPS
  - \(PTEN\)-Hamartoma tumor syndromes
    - Cowden syndrome
    - Bannayan-Riley-Ruvalcaba syndrome

---

**Directed examination for related manifestations**

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

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COMMON PEDIGREE SYMBOLS

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

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

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

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.

See Common Pedigree Symbols (HRS-A 2 of 3)
LYNCH SYNDROME TESTING CRITERIA

- Meets revised Bethesda guidelines (See LS-B) or Amsterdam criteria (See LS-C)
- All CRC patients or CRC patients diagnosed at <70 y and also those ≥70 y who meet the Bethesda guidelines (See LS-B)
- Endometrial cancer at age <50 y
- Known LS in family

RISK STATUS

- Deleterious LS mutation known
  - Genetic testing for familial mutation
  - Positive for familial LS mutation
    - See Lynch Syndrome Surveillance (LS-2 and LS-3)
  - Genetic testing not done
  - See Average-Risk Colorectal Cancer Screening (CSCR-2)

- No known LS mutation
  - Tumor available
    - Tumor testing (See LS-A)
      - Consider both IHC and MSI
      - See Tumor Testing Results and Additional Testing Strategies (LS-A 2 of 2)
    - Not tested or no familial mutation or mutation of unknown significance found
      - Tailored surveillance based on individual and family risk assessment
    - Positive mutation found in MLH1, MSH2, MSH6, or PMS2
      - See Lynch Syndrome Surveillance (LS-2 and LS-3)
      - and Genetic testing for at-risk family members

- No tumor available or insufficient tumor
  - Individual management
    - Colonoscopic monitoring based on individual risk assessment (See CSCR-2 for average risk and see CSCR-6 for increased risk)

- No criteria met

*IHC and/or MSI screening of all colorectal and endometrial cancers, 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. Genetics in Medicine 2009;11:35-41). An infrastructure needs to be in place to handle the screening results.

*If there is more than one affected family member, first consider: youngest age at diagnosis, multiple primaries, and colorectal or endometrial cancers. Limitations of interpreting test results should be discussed if testing tumors other than colorectal or endometrial cancers.

*For recommendations to have a deleterious LS mutation, see LS surveillance recommendations (LS-2 and LS-3). In addition, individuals with loss of MSH2 and/or MSH6 protein expression via immunohistochemistry, regardless of germline mutation status, should be followed as though they have LS.

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

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

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SURVEILLANCE FOR MLH1 AND MSH2 MUTATION CARRIERS\textsuperscript{f,g}

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.

Extra colonic:
- 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\textsuperscript{h} 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 cancer: Annual physical 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, due to limited data no screening recommendation is possible at this time.

\textsuperscript{f}See Cancer Risk Up to Age 70 Years in Individuals with Lynch Syndrome Compared to the General Population (LS-D).
\textsuperscript{g}Other than colon and endometrial cancer, screening recommendations are expert opinion rather than evidence-based.
SURVEILLANCE FOR MSH6 AND PMS2 MUTATION CARRIERS

**MSH6**
- Colon cancer:
  - Colonoscopy at age 30-35 y (may need to be earlier in some families, depending on ages of cancers observed) every 2-3 y, and then after age 40 y every 1-2 y

- Extra colonic:
  - Consider prophylactic hysterectomy and BSO in women who have completed childbearing.
  - The risk of other LS-related cancers is reportedly low; however, due to limited data no screening recommendation is possible at this time.

**PMS2**
- Colon cancer:
  - Colonoscopy at age 35-40 y (may need to be earlier in some families, depending on ages of cancers observed) every 2-3 y, and then after age 50 y every 1-2 y

- Extra colonic:
  - The risk of other LS-related cancers is reportedly low; however, due to limited data no screening recommendation is possible at this time.

*See Cancer Risk Up to Age 70 Years in Individuals with Lynch Syndrome Compared to the General Population (LS-D).*
### NCCN Guidelines Version 2.2013

**Lynch Syndrome**

#### SURVEILLANCE FINDINGS

<table>
<thead>
<tr>
<th>FINDINGS</th>
<th>FOLLOW-UP</th>
</tr>
</thead>
<tbody>
<tr>
<td>No pathologic findings</td>
<td>• Continued surveillance&lt;sup&gt;i&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>• Consider prophylactic hysterectomy/BSO if postmenopausal or family completed</td>
</tr>
<tr>
<td>Adenocarcinomas</td>
<td>See appropriate NCCN Guidelines for Treatment of Cancer by Site</td>
</tr>
<tr>
<td>Adenomas</td>
<td>• Endoscopic polypectomy with follow-up colonoscopy every 1-2 y depending on:</td>
</tr>
<tr>
<td></td>
<td>▶ location, character</td>
</tr>
<tr>
<td></td>
<td>▶ surgical risk</td>
</tr>
<tr>
<td></td>
<td>▶ patient preference</td>
</tr>
<tr>
<td>Adenomas not amenable to endoscopic resection or high-grade dysplasia</td>
<td>• Total abdominal colectomy with ileorectal anastomosis&lt;sup&gt;j&lt;/sup&gt; ▶ Endoscopic rectal exam every 1-2 y</td>
</tr>
<tr>
<td></td>
<td>• Consider prophylactic hysterectomy/BSO at time of colon surgery if postmenopausal or family completed</td>
</tr>
</tbody>
</table>

<sup>i</sup>May consider subtotal colectomy if patient is not a candidate for optimal surveillance.

<sup>j</sup>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).

### 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.
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 cancer tissue to identify individuals at risk for LS.

• The Bethesda criteria were developed in response to the emerging understanding of the pathologic spectrum and molecular characteristics of LS-related tumors. These criteria were intended to help identify colon cancer patients whose tumors should be tested for MSI, thereby identifying patients with a greater chance of having LS. The revised Bethesda guidelines (see LS-B) are now widely used to identify tumors that should be tested for mismatch repair defects, either by MSI and/or IHC analysis. Although more sensitive than the Amsterdam criteria (See LS-C), up to 30% of patients with LS fail to meet even the revised Bethesda guidelines.

IHC
• IHC refers to staining tumor tissue for protein expression of the four mismatch repair genes known to be mutated in LS: MLH1, MSH2, MSH6, and PMS2. A normal IHC test implies all 4 mismatch repair proteins are normally expressed and thus no underlying mismatch repair 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 mismatch repair genes guides genetic testing (mutation detection) to the gene where protein expression is not observed.

• Ten percent to 15% of sporadic colon cancers exhibit abnormal IHC, often due to abnormal methylation of the MLH1 gene promoter, but occasionally due to an inherited mutation of one of the mismatch repair genes. Thus, the presence of an abnormal IHC test increases the possibility of LS but does not make a definitive diagnosis. Individuals with abnormal IHC or MSI results should preferably be referred for genetic counseling so that the appropriate follow-up testing can be offered to the patient. In some cases, this would include testing for abnormal methylation of the MLH1 promoter and in others, it would include germline genetic testing of one or more of the mismatch repair genes. Most patients will be found to have sporadic colon cancer and not a germline mutation. 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 (microsatellite instability-high) in tumors refers to changes in 2 or more of the 5 microsatellite markers in the National Cancer Institute-recommended panel. 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.

• Recommend LS screening at the time of diagnosis of CRC with either approach: All CRC patients or CRC patients diagnosed at <70 y and also those ≥70 y who meet the Bethesda guidelines (See LS-B). IHC and/or MSI screening of all newly diagnosed CRCs and endometrial cancers, regardless of age at diagnosis or family history, have been implemented at some centers to identify individuals at risk for LS. This approach has been endorsed for colon cancer by the Evaluation of Genomic Applications in Practice and Prevention Working Group from the Centers for Disease Control and Prevention (Genetics in Medicine 2009;11:35-41) and has been shown to be cost-effective. An infrastructure needs to be in place to handle the screening results.
# Tumor Testing Results and Additional Testing Strategies

<table>
<thead>
<tr>
<th>Tumor Testing&lt;sup&gt;a&lt;/sup&gt;</th>
<th>IHC</th>
<th>MSI</th>
<th>BRAF V600E&lt;sup&gt;b&lt;/sup&gt;</th>
<th>MLH1 Promoter Methylation</th>
<th>Plausible Etiologies</th>
<th>Additional Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>MLH1</td>
<td>MSH2</td>
<td>MSH6</td>
<td>PMS2</td>
<td>MSS/MSI-</td>
<td>Low</td>
<td>N/A</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>MSS/MSI-Low</td>
<td>N/A</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>MSI- High</td>
<td>N/A</td>
</tr>
<tr>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>+</td>
<td>MSI- High</td>
<td>N/A</td>
</tr>
</tbody>
</table>

| --   | +    | +    | --   | N/A     | N/A | N/A | 1) Sporadic cancer | 1) None<sup>c</sup> |
| --   | +    | +    | --   | N/A     | Negative | Positive | N/A | 1) Sporadic cancer 2) Rarely germline mutation MLH1 or constitutional MLH1 epimutation | 1) None, unless young age of onset or significant family history; then consider MLH1 genetic testing or if young onset consider evaluation for constitutional MLH1 epimutation |
| --   | +    | +    | --   | N/A     | Negative | Negative | N/A | 1) Germline mutation MLH1 | 1) MLH1 genetic testing |
| +    | --   | --   | +    | N/A     | N/A | N/A | 1) Germline mutation MSH2 2) Germline mutation in TACSTD1 (EPCAM); rarely germline mutation in MSH6 | 1) MSH2 genetic testing, if negative TACSTD1 (EPCAM) testing 2) Consider MSH6 genetic testing, if MSH2 and TACSTD1 (EPCAM) are negative |
| --   | +    | +    | +    | N/A     | N/A | N/A | 1) Germline mutation MLH1 | 1) MLH1 genetic testing |
| +    | +    | +    | --   | N/A     | N/A | N/A | 1) Germline mutation PMS2 2) Rarely germline mutation MLH1 | 1) PMS2 genetic testing 2) MLH1 genetic testing, if negative PMS2 |
| +    | --   | +    | +    | N/A     | N/A | N/A | 1) Germline mutation MSH2 | 1) MSH2 genetic testing |
| +    | +    | +    | --   | N/A     | N/A | N/A | 1) Germline mutation MSH6 2) Germline mutation MSH2 | 1) MSH6 genetic testing 2) Consider MSH2 genetic testing, if negative MSH6 |

<sup>a</sup>Tumor testing strategies apply to colorectal and endometrial cancers. Limited data exist regarding the efficacy of tumor testing in other LS tumors.

<sup>b</sup>Testing is not appropriate for tumors other than colorectal cancer.

<sup>c</sup>If strong family history (ie, Amsterdam criteria) is present, additional testing may be warranted in the proband, or consider tumor testing in another affected family member due to the possibility of a pheno
copy.

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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.
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.


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.
MINIMUM CRITERIA FOR CLINICAL DEFINITION OF LS
(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.

REVISED MINIMUM CRITERIA FOR CLINICAL DEFINITION OF LS
(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.

²Approximately 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.

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.
### 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</th>
<th>MLH1 and MSH2&lt;sup&gt;1,2&lt;/sup&gt;</th>
<th>MSH6&lt;sup&gt;2&lt;/sup&gt;</th>
<th>PMS2&lt;sup&gt;3&lt;/sup&gt;</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%&lt;sup&gt;5&lt;/sup&gt;</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&lt;sup&gt;4&lt;/sup&gt;</td>
<td>&lt;1%</td>
<td>1%-6%</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
</tbody>
</table>


<sup>5</sup>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).

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

---

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

**Clinical Trials:** NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
## APC and MUTYH Genetic Testing Criteria

### Testing Criteria

**APC Testing Criteria**
- Personal history of >10 adenomas
- Personal history of a desmoid tumor
- Known deleterious APC mutation in family

**MUTYH Testing Criteria**
- Personal history of >10 adenomas
- Individual meeting criteria for SPS (see SPS-1) with at least some adenomas
- Known deleterious biallelic MUTYH mutations in family

### 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 MUTYH mutations**

### Results

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

### Treatment/Surveillance

- To determine classical FAP vs. AFAP, see FAP/AFAP-1
- See Average-Risk Colorectal Screening (CSCR-2)
- See MAP-1
- Tailored surveillance based on individual and family risk assessment (See Colonic Adenomatous Polyposis of Unknown Etiology [CPUE-1] or Average-Risk Colorectal Screening [CSCR-2])

- See Average-Risk Colorectal Screening (CSCR-2)

### Notes

- **a:** When colonic polyposis is present in a single person with a negative family history, consider testing for a *de novo* APC mutation; if negative, follow with testing of MUTYH (targeted testing for the two common northern European founder mutations c.536A>G and c.1187G>A may be considered first followed by full sequencing if biallelic mutations are not found). When colonic polyposis is present only in siblings, consider recessive inheritance and test for MUTYH first. Order of testing for APC and MUTYH is at the discretion of the clinician.

- **b:** MUTYH genetic testing is not indicated based on a personal history of a desmoid tumor.

- **c:** Siblings of a patient with MAP are recommended to have site-specific genetic testing for the familial biallelic mutations. Children of an affected parent with MAP are recommended to have site-specific genetic testing for the familial mutation/s. If positive for one MUTYH mutation, full sequencing of MUTYH is recommended. Full sequencing of MUTYH also may be considered in an unaffected parent when the other parent has MAP. If the unaffected parent is found to not be heterozygous for a MUTYH mutation, genetic testing in children is not necessary. If he or she is found to have a MUTYH mutation, testing for the familial mutations in the children is recommended.

---

**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.
# Familial Adenomatous Polyposis (FAP)/AFAP

## PHENOTYPE

### Classical FAP:
- **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%)**

### AFAP
- **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 >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

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

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

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

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

---

**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 to 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

<table>
<thead>
<tr>
<th>TREATMENT</th>
<th>SURVEILLANCE(^d,e) (POSTCOLECTOMY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon cancer:</td>
<td></td>
</tr>
<tr>
<td>• If patient had colectomy with ileorectal anastomosis, then endoscopic evaluation of the rectum every 6-12 mo depending on polyp burden.</td>
<td></td>
</tr>
<tr>
<td>• 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.</td>
<td></td>
</tr>
<tr>
<td>• 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.</td>
<td></td>
</tr>
<tr>
<td>Extracolonic Surveillance (See FAP-2)</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) 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.

---

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\(^d,e\) (POSTCOLECTOMY)

Extracolonic:

- Duodenal or periampullary cancer: Baseline upper endoscopy (including side-viewing examination).
- Gastric cancer: Examine stomach at time of duodenoscopy.
  - Fundic gland polyps occur in a majority of FAP patients, and focal dysplasia is typical but is almost invariably non-progressive. For this reason, special screening or surgery should only be considered in the presence of high-grade dysplasia.
  - Non-fundic gland polyps should be managed endoscopically if possible. Patients with polyps that cannot be removed endoscopically but with high-grade dysplasia or invasive cancer detected on biopsy should be referred for gastrectomy.
- Thyroid cancer: Annual thyroid examination, starting in late teenage years. Annual thyroid ultrasound may be considered, though data to support this recommendation are lacking.
- CNS cancer: An annual physical examination; due to limited data, no additional screening recommendation is possible at this time.
- Intra-abdominal desmoids: Annual abdominal palpation. If family history of symptomatic desmoids, consider abdominal MRI or CT 1-3 y post-colectomy and then every 5-10 y. Suggestive abdominal symptoms should prompt immediate abdominal imaging.
- Small bowel polyps and cancer: Consider adding small bowel visualization to CT or MRI for desmoids as outlined above, especially if duodenal polyposis is advanced.
- Hepatoblastoma: No recommendations have been made for FAP; however, there are other situations where the high risk for hepatoblastoma has been observed and the following recommendations have been considered:
  - Liver palpation, abdominal ultrasound, and measurement of AFP, every 3-6 mo, during the first 5 y of life. Screening in a clinical trial is preferred.
- Pancreatic cancer: Due to limited data, no screening recommendation is possible at this time.

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

\(^e\) Other than colon cancer, screening recommendations are expert opinion rather than evidence-based.
Familial Adenomatous Polyposis

**DUODENOSCOPIC FINDINGS**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Surveillance Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0, No polyposis</td>
<td>Repeat endoscopy every 4 y</td>
</tr>
<tr>
<td>Stage I, Minimal polyposis (1-4 tubular adenomas, size 1-4 mm)</td>
<td>Repeat endoscopy every 2-3 y</td>
</tr>
<tr>
<td>Stage II, Mild polyposis (5-19 tubular adenomas, size 5-9 mm)</td>
<td>Repeat endoscopy every 1-3 y</td>
</tr>
<tr>
<td>Stage III, Moderate polyposis (≥20 lesions, or size ≥1 cm)</td>
<td>Repeat endoscopy every 6-12 mo</td>
</tr>
<tr>
<td>Stage IV, Dense polyposis or high-grade dysplasia</td>
<td>Surgical evaluation&lt;br&gt;• Expert surveillance every 3-6 mo&lt;br&gt;• Complete mucosectomy or duodenectomy, or&lt;br&gt;Whipple procedure if duodenal papilla is involved</td>
</tr>
</tbody>
</table>

**SURVEILLANCE**

Surgical evaluation<br>Expert surveillance every 3-6 mo<br>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.

---

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 Genetic Testing and Surveillance: Family History of Classical FAP Mutation Known

**Genetic Testing**

- APC positive
  - Flexible sigmoidoscopy or colonoscopy every 12 mo beginning at age 10-15 y
- APC negative
  - Flexible sigmoidoscopy or colonoscopy every 12 mo until age 24 y
  - Then every 3-5 y thereafter
  - Consider substituting colonoscopy every 5 y beginning at age 20 y for the chance that the patient may have AFAP.
- Not tested
  - If no polyps, continue surveillance

**Surveillance**

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

---

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.

---

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

TAC/IRA is preferred 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:
  - Curable cancer in colon or rectum
  - Severe rectal or colon 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 that can occur following proctectomy

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 colon or 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
**ATTENUATED FAP TREATMENT AND SURVEILLANCE: PERSONAL HISTORY**

<table>
<thead>
<tr>
<th>ADENOMA/POLYP BURDEN</th>
<th>TREATMENT</th>
<th>SURVEILLANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;21 y with small adenoma burden&lt;sup&gt;a&lt;/sup&gt;</td>
<td>- Colonoscopy and polypectomy every 1-2 y &lt;br&gt;- Surgical evaluation and counseling</td>
<td>Colon cancer: &lt;br&gt;- If patient had colectomy with IRA, then endoscopic evaluation of rectum every 6-12 mo depending on polyp burden. &lt;br&gt;- 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.</td>
</tr>
<tr>
<td>≥21 y with small adenoma burden&lt;sup&gt;a&lt;/sup&gt;</td>
<td>- Colonoscopy and polypectomy every 1-2 y &lt;br&gt;- Colectomy&lt;sup&gt;b&lt;/sup&gt; and IRA&lt;sup&gt;c&lt;/sup&gt; may be considered &lt;br&gt;- Surgical evaluation and counseling if appropriate</td>
<td>Extracolonic: &lt;br&gt;- Annual physical examination &lt;br&gt;- Annual thyroid examination &lt;br&gt;- Baseline upper endoscopy beginning at age 25-30 y</td>
</tr>
<tr>
<td>Significant polyposis not manageable with polypectomy</td>
<td>- Colectomy&lt;sup&gt;b&lt;/sup&gt; with IRA (preferred in most cases) or proctocolectomy with IPAA based on burden of disease in rectum</td>
<td>See Duodenoscopic Findings (FAP-3)</td>
</tr>
</tbody>
</table>

<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 greater than 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).

<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 Gl 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.
ATTENUATED FAP GENETIC TESTING AND SURVEILLANCE: FAMILY HISTORY OF ATTENUATED FAP MUTATION KNOWN

**GENETIC TESTING**

- APC positive
  - Colonoscopy beginning in late teens, then every 2-3 y
  - If adenomas, follow pathway for AFAP Treatment and Surveillance: Personal History, Adenoma/Polyp Burden (AFAP-1)

- APC negative
  - Colonoscopy beginning in late teens, then every 2-3 y
  - If no polyps, continue surveillance

- Not tested
  - Colonoscopy beginning in late teens, then every 2-3 y
  - If adenomas, follow pathway for AFAP Treatment and Surveillance: Personal History, Adenoma/Polyp Burden (AFAP-1)
  - If no polyps, continue surveillance

---

**SURVEILLANCE**

Unaffected, at-risk family member; APC mutation known

- Recommend APC gene testing for familial mutation

---

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.

---

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.
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 polyp, 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.
**MAP TREATMENT AND SURVEILLANCE: PERSONAL HISTORY**

**ADENOMA/POLYP BURDEN**

- **<21 y with small adenoma burden**
  - Colonoscopy and polypectomy every 1-2 y
  - Surgical evaluation and counseling

- **≥21 with small adenoma burden**
  - Colonoscopy and polypectomy every 1-2 y
  - Colectomy and IRA may be considered
  - Surgical evaluation and counseling if appropriate

- **Significant polyposis not manageable with polypectomy**
  - Colectomy with IRA (preferred in most cases) or proctocolectomy with IPAA based on burden of disease in rectum

**SURVEILLANCE**

- 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.

- Extracolonic:
  - Annual physical examination
  - Baseline upper endoscopy beginning at age 30-35 y

---

**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 greater than 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.

---

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

GENETIC TESTING

Biallelic MUTYH mutation positive

SURVEILLANCE

- 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).

Unaffected, at-risk family member; family mutation known

Recommend MUTYH testing for familial mutations

Not tested

One MUTYH mutation found or No APC or MUTYH deleterious mutations found

See Average-Risk Colorectal Screening (CSCR-2)

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9 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.

h Siblings of a patient with MAP are recommended to have site-specific genetic testing for the familial biallelic mutations. Children of an affected parent with MAP are recommended to have site-specific genetic testing for the familial mutation/s. If positive for one MUTYH mutation, full sequencing of MUTYH is recommended. Full sequencing of MUTYH also may be considered in an unaffected parent when the other parent has MAP. If the unaffected parent is found to not be heterozygous for a MUTYH mutation, genetic testing in children is not necessary. If he or she is found to have a MUTYH mutation, testing for the familial mutations in the children is recommended.

**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 clinical diagnosis of PJS can be made when an individual has two or more of the following features:
  - Two or more Peutz-Jeghers-type hamartomatous polyps of the small intestine
  - Mucocutaneous hyperpigmentation of the mouth, lips, nose, eyes, genitalia, or fingers
  - Family history of PJS

**Surveillance considerations:**

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

**See Cancer Risk and Surveillance Guidelines (PJS-2)**

---


*b* Due to the rarity of the syndrome and complexities of diagnosing and managing individuals with Peutz-Jeghers syndrome, referral to a specialized team is recommended.
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>
<tbody>
<tr>
<td>Breast</td>
<td>45%-50%</td>
<td>• Mammogram and breast MRI annually&lt;br&gt;• Clinical breast exam every 6 mo</td>
<td>~ 25 y</td>
</tr>
<tr>
<td>Colon</td>
<td>39%</td>
<td>• Colonoscopy every 2-3 y</td>
<td>~ Late teens</td>
</tr>
<tr>
<td>Stomach</td>
<td>29%</td>
<td>• Upper endoscopy every 2-3 y</td>
<td>~ Late teens</td>
</tr>
<tr>
<td>Pancreas</td>
<td>11%-36%</td>
<td>• Magnetic resonance cholangiopancreatography and/or endoscopic ultrasound every 1-2 years</td>
<td>~ 25-30 y</td>
</tr>
<tr>
<td>Small intestine</td>
<td>13%</td>
<td>• Small bowel visualization (CT 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</td>
<td>~ 8-10 y</td>
</tr>
<tr>
<td>Ovary&lt;sup&gt;C&lt;/sup&gt; &lt;br&gt;Cervix&lt;br&gt;Uterus</td>
<td>18%-21%&lt;br&gt;10%&lt;br&gt;9%</td>
<td>• Pelvic examination and Pap smear annually&lt;br&gt;• Consider transvaginal ultrasound</td>
<td>~ 18-20 y</td>
</tr>
<tr>
<td>Testes</td>
<td></td>
<td>• Annual testicular exam and observation for feminizing changes</td>
<td>~ 10 y</td>
</tr>
<tr>
<td>Lung</td>
<td>15%-17%</td>
<td>• Provide education about symptoms and smoking cessation&lt;br&gt;• No other specific recommendations have been made</td>
<td></td>
</tr>
</tbody>
</table>

<sup>C</sup>Although the absolute risk of adenocarcinoma of the ovary is elevated in PJS, ovarian sex cord tumors are the most common ovarian pathology found in these patients.

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: Cancer 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>
</tbody>
</table>

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.  
bIn individuals with SMAD4 mutations, recommend screening for vascular lesions associated with hereditary hemorrhagic telangiectasia.

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.
Serrated polyposis syndrome (previously known as hyperplastic polyposis) definition: a,b,c

• A clinical diagnosis of serrated polyposis is considered in an individual who meets at least one of the following empiric criteria:
  1) At least 5 serrated polyps\textsuperscript{d} proximal to the sigmoid colon with 2 or more of these being >10 mm
  2) Any number of serrated polyps\textsuperscript{d} proximal to the sigmoid colon in an individual who has a first-degree relative with serrated polyposis
  3) Greater than 20 serrated polyps\textsuperscript{e} of any size, but distributed throughout the colon\textsuperscript{f}

• Occasionally, more than one affected case of serrated polyposis is seen in a family.\textsuperscript{g}

• 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 \( \geq 5 \) 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.

\textsuperscript{a}The serrated polyposis syndrome guidelines are based on expert opinion on the current data available.


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

\textsuperscript{d}Serrated polyps include hyperplastic polyps, sessile serrated adenomas/polyps, and traditional serrated adenomas.

\textsuperscript{e}The total number of polyps necessary to make a diagnosis of serrated polyposis is unclear. A lower threshold number of polyps (<20) has also been used to make a diagnosis of serrated polyposis.

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

### COLONIC ADENOMATOUS POLYPOSIS OF UNKNOWN ETIOLOGY

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

#### Phenotype

**Personal history of ≥100 adenomas**

Manage as FAP (See FAP-1)

**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 preferable but not always possible

- Dense polyposis or large polyps not manageable by polypectomy
  
  Subtotal colectomy or proctocolectomy depending on adenoma density and distribution

**Family history of ≥100 adenomas diagnosed at age <40 y in a first-degree relative**

<table>
<thead>
<tr>
<th>Personal history of &gt;10-&lt;100 adenomas</th>
<th>Management/Surveillance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small adenoma burden manageable by colonoscopy and polypectomy</td>
<td>Colonoscopy and polypectomy every 1-2 years</td>
</tr>
<tr>
<td>Dense polyposis or large polyps not manageable by polypectomy</td>
<td>Subtotal colectomy or proctocolectomy depending on adenoma density and distribution</td>
</tr>
</tbody>
</table>

**Family history of >10-<100 adenomas in a first-degree relative**

Colonoscopy and polypectomy every 3-5 y\(^{b}\) 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**

Colonoscopy and polypectomy every 2-3 y\(^{b}\) starting at age 40 y if uncomplicated by cancer

\(^a\)Consider genetic testing (See APC/MUTYH-1) in family member affected with polyposis.

\(^b\)If multiple polyps are found, then colonoscopy every 1-3 years depending on type, number, and size of polyps.

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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.
NCCN Guidelines Version 2.2013
Colorectal Cancer Screening

Discussion

NCCN Categories of Evidence and Consensus

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

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

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

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

All recommendations are category 2A unless otherwise 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), and MutY human homolog (MUTYH)-associated polyposis (MAP). Other entities include Muir-Torre, Turcot, Gardner, Cowden, Bannayan-Riley-Ruvalcaba, Peutz-Jeghers, juvenile polyposis, and serrated polyposis syndromes (SPS).

CRC mortality can be reduced both by early diagnosis and by cancer prevention through polypectomy. Hence, the goals of CRC screening are to detect cancer at an early, curable stage and to detect and remove adenomatous polyps. According to the Centers for Disease Control and Prevention (CDC), the screening rate among U.S. adults aged 50 to 75 years has increased from approximately 42% in 2000 to 59% in 2010.

These NCCN Guidelines for Colorectal Cancer Screening describe various colorectal screening modalities as well as recommended screening schedules for patients at average or increased risk of developing CRC. In addition, the guidelines provide recommendations for the management of patients with high-risk syndromes, including Lynch syndrome, FAP, MAP, Peutz-Jeghers syndrome, juvenile polyposis syndrome, and SPS.

Colorectal Cancer Screening

Current technology falls into two broad categories: structural tests and stool/fecal-based tests. There is direct evidence from randomized controlled trials that fecal occult blood testing (FOBT) and flexible sigmoidoscopy (discussed in detail below) reduce mortality from CRC. Given the available evidence from case control and cohort studies, however, it is the consensus opinion of the panel that colonoscopy should be the preferred method of screening because of its potential ability to prevent CRC (with its associated morbidity) and cancer deaths. Screening tests that can detect both early cancer and adenomatous polyps are encouraged, although the panel recognizes that patient preference and resource accessibility play a large role in test selection. Overall, while some techniques are better established than others, panelists agree that any screening is better than none.

Structural Screening Tests

Structural tests are able to detect both early cancer and adenomatous polyps using endoscopic or radiologic imaging. Endoscopic tests have several limitations including their relative invasiveness, the need for dietary preparation and bowel cleansing, and the time dedicated to the...
examination (typically a day). Endoscopic exams require informed consent and usually the need for sedation and have related risks including perforation and bleeding. A large cohort study of 53,220 Medicare patients between age 66 to 95 years showed that the risks of adverse events after colonoscopy increase with age.\textsuperscript{14}

**Colonoscopy**
Colonoscopy is the most complete screening procedure, allowing examination of the entire large bowel and the removal of polyps in one session. It is currently the preferred screening method and also the required procedure for confirmation of positive findings from other tests. Colonoscopy is also considered the current gold standard for assessment of the efficacy of other screening methods. Although there are no randomized controlled trials that directly demonstrate mortality reduction by colonoscopy, findings from case-control and cohort studies show significant impact of colonoscopy and polypectomy on CRC, with an estimated >50% reduction in incidence.\textsuperscript{15-19} Rabeneck and colleagues recently reported an inverse correlation between colonoscopy use and death from CRC from a large population study involving close to 2.5 million Canadians.\textsuperscript{20} For every 1% increase in colonoscopy rate, the risk of death decreased by 3%.

Interestingly, in a Canadian case-control study that matched each of 10,292 individuals who died of CRC to 5 controls, colonoscopy was associated with lower mortality from left-sided CRC (adjusted conditional OR, 0.33; 95% CI, 0.28–0.39) but not right-sided CRC (OR, 0.99; CI, 0.86–1.14).\textsuperscript{21} Part of this finding may be related to significant variation in the quality of this widely used procedure in the community that can lead to variable effectiveness.\textsuperscript{22,23} Another study that compared CRC mortality of 715 patients who underwent colonoscopy over a median follow-up period of 8 years to expected rates of colorectal mortality based on the SEER database found a 65% relative reduction in CRC mortality following colonoscopy.\textsuperscript{24}

A recent follow-up on the National Polyp Study evaluated the long-term mortality effects of colonoscopy with polypectomy.\textsuperscript{17,25} The mortality of 2,602 patients with adenomas removed was compared to the incidence-based mortality from CRC in the SEER database. With a median 15.8 years follow-up, 12 deaths were attributed to CRC in the screened group, compared with an expected 25.4 deaths in the general population, suggesting a 53% decrease in mortality.

In addition, a recent population-based, case-controlled study in Germany demonstrated that colonoscopy in the preceding 10 years gave an overall 77% decrease in the risk for CRC.\textsuperscript{26} While risk reduction was strongest for left-sided cancer, a 56% risk reduction was seen for right-sided disease as well. Similar results were seen in a recent large case-control study using the SEER-Medicare database.\textsuperscript{27}

A current randomized controlled trial is comparing one-time colonoscopy with biennial fecal immunochemical testing (FIT; see discussion of FIT below) with the primary outcome of death due to CRC at 10 years. Interim results from this trial show that subjects are more likely to participate in FIT screening (34.2% vs. 24.6%; \(P < .001\)).\textsuperscript{28} The two tests identified similar numbers of cancers in initial screening, but colonoscopy identified significantly more advanced and non-advanced adenomas.

A recent meta-analysis of 14 randomized controlled trials and other controlled studies found that while endoscopic surveillance detected more advanced neoplasms than stool testing, its advantage was offset by a lower participation rate.\textsuperscript{29}
Recommendations made by the panel are based on the premise of complete, high-quality colonoscopies as reflected by: colonoscopy to cecum; rectal retroflexion; excellent preparation or endoscopic clearing of residual stool; sufficient distention and full 360 degree view of front and back side of all folds; withdrawal time >10 minutes; and complete excision of polyps (may require extra snare/biopsy or cautery following initial polypectomy). A recent European report on a screening program involving more than 45,000 subjects confirmed that the endoscopist’s rate of adenoma detection is an important predictor of the risk of interval CRC ($P = .008$), highlighting the need for meticulous inspection of the large intestinal tract. The study did not demonstrate statistical significance with cecal intubation rate, another widely recognized quality indicator. One explanation is that the importance of this factor is restricted to the right colon, which gives rise to a small number of cancer cases. In an effort to enhance screening quality, the Quality Assurance Task Group of the National Colorectal Cancer Roundtable developed a standardized reporting system for colonoscopy. The algorithm lists the common quality indicators of colonoscopy and minimum requirements of a colonoscopy report. Quality indicators, including withdrawal time, are an important part of the fidelity of colonoscopy findings.

An optimal screening protocol should have an interval during which there is a low likelihood of developing cancer and it should be cost effective based on the duration of risk reduction following an initial negative colonoscopy. The general consensus is that a 10-year interval is appropriate for most individuals (average risk), although shorter intervals may be indicated depending on the completeness and quality of the colonoscopy. The panel emphasized the importance of family history in the screening scheme. Individual risk factors, the number or characteristics of polyps found, and physician judgment should also be included in the interval determination. A 1996 study reported that 27% of individuals had adenomatous polyps identified on repeat colonoscopy a mean of 66 months after an initial negative colonoscopy, but none had colon cancer and only one of 154 individuals had a polyp ≥1 cm. These results suggest that an interval of repeat colonoscopy after an initial negative colonoscopy beyond 5 years is safe. Imperiale et al reported on 2,436 individuals with no adenomatous polyps at baseline colonoscopy. No cancers were found at rescreening at a mean of 5.3 years later. Adenomatous polyps were identified in 16% of individuals and only 1.3% had advanced adenomatous polyps. The authors recommended a rescreening interval of 5 years or longer. Lieberman and colleagues reported that advanced adenomatous polyps were found in only 2.4% of individuals on repeat colonoscopy within 5 years after a baseline normal colonoscopy. In this study, individuals with 1 or 2 adenomatous polyps <1 cm at baseline also had a low rate of developing advanced neoplasia.

Singh et al assessed the time that risk reduction persists after colonoscopy. This study was a population-based retrospective analysis utilizing a physician billing claims database of individuals who had a negative screening colonoscopy. Patients in the surveillance cohort were compared to the general population regarding incidence of CRC. A negative colonoscopy was associated with a standardized incidence ratio of 0.28 (95% CI, 0.09–0.65) at 10 years. A similar study calculated the adjusted relative risk for CRC among subjects with a previous negative colonoscopy. The adjusted odds ratio was 0.26 (95% CI, 0.16–0.40). The low risk was seen even if the colonoscopy had been performed up to 20 or more years previously. A recent analysis showed that the risk reduction seen following negative colonoscopy holds even for patients with a family history of CRC, but not for current smokers.
Flexible Sigmoidoscopy
Flexible sigmoidoscopy followed by colonoscopic polypectomy in patients with lesions >1 cm significantly reduced mortality risk in early case-control studies.\textsuperscript{19,38} There is now direct evidence from randomized controlled trials that flexible sigmoidoscopy reduces mortality from CRC.\textsuperscript{39} A recent British randomized population screening study of over 110,000 individuals attributed a 23\% and 31\% reduction in CRC incidence and mortality, respectively, to flexible sigmoidoscopy offered once between ages 55 and 64 compared to no screening.\textsuperscript{39} The reductions in colorectal incidence and mortality for those individuals who accepted screening were 33\% and 43\%, respectively. In addition, the SCORE trial randomized 34,272 subjects to one-time sigmoidoscopy or no screening and recently reported incidence and mortality results after >10 years median follow-up.\textsuperscript{40} Per-protocol analysis demonstrated a 31\% reduction in incidence and a 38\% reduction in mortality.

On the other hand, the Norwegian Colorectal Cancer Prevention (NORCCAP) Study Group performed a randomized controlled trial of flexible sigmoidoscopy in over 55,000 participants aged 55 to 64 years.\textsuperscript{41} After 7 years of follow-up, the researchers reported no difference in the incidence of CRC between individuals screened once compared to unscreened participants. However, a non-significant trend towards reduced mortality from CRC was observed in the screened arm, and longer follow-up may reveal a mortality benefit.

The Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening group recently reported CRC mortality rates from their randomized, controlled flexible sigmoidoscopy screening trial, which screened >64,000 participants with flexible sigmoidoscopy and 59\% of those participants a second time at 3 or 5 years.\textsuperscript{42-44} A 26\% reduction in deaths from CRC was seen in the screened group (RR, 0.74; 95\% CI, 0.63–0.87; \(P < .001\)), with a 50\% reduction seen in mortality from distal disease and no mortality from proximal disease.\textsuperscript{42} This strong effect was seen despite an estimated 46\% contamination rate of sigmoidoscopy or colonoscopy in the control arm, suggesting that the true benefit of screening is even greater.

A recent meta-analysis of randomized controlled trials (including the PLCO trial) supports the conclusion that screening by flexible sigmoidoscopy significantly reduces the incidence and mortality of CRC.\textsuperscript{45} A recent analysis of a 5\% random Medicare sample of the SEER database found a similar reduction in distal CRC after both colonoscopy and sigmoidoscopy, with a reduction in proximal CRC after colonoscopy but not sigmoidoscopy.\textsuperscript{46} A similar result was seen in a nested case-control study of 4 U.S. health plans, in which the reduction of stage IIB or higher CRC was only seen on the left side.\textsuperscript{47}

Compared to colonoscopy, sigmoidoscopy requires no sedation and less bowel preparation, but is limited to examination of the lower half of the colon tract. A recent analysis of cancers not detected by flexible sigmoidoscopy in the PLCO trial showed that 37\% of undetected lesions were beyond the reach of the sigmoidoscope.\textsuperscript{48} In fact, the authors estimated that an additional 15\% to 19\% of cancers may have been detected during screening had colonoscopy been used.

Flexible sigmoidoscopy should be performed using a scope 60 cm or longer. Polyps identified should be biopsied by trained personnel to determine if they are hyperplastic, adenomatous, or sessile serrated (flat adenomatous polyps are unusual and may be missed during screening). Patients with lesions larger than 1 cm should be referred...
directly to colonoscopy, since they are almost always adenomatous polyps associated with a risk of proximal colonic neoplasms.

**Computed Tomographic Colonography**

CT colonography, also known as virtual colonoscopy or CTC, is evolving as a promising technique for CRC screening. CTC has the advantages of being noninvasive and not requiring sedation. The risk of test-related complications is also very low. However, a positive finding requires a colonoscopy, and extracolonic findings, which are present in up to 16% of patients, pose a dilemma. These findings require further investigations and have a potential for both benefit and harm. At the present time there are no sufficient data to determine the clinical impact of these findings.

The accuracy of CTC in detecting polyps or cancers measuring 10 mm or more was assessed in the National CT Colonography Trial (ACRIN 6664) organized by the American College of Radiology Imaging Network. In this study, 2,531 participants underwent CTC followed by traditional optical colonoscopy. Colonoscopy identified 128 large adenomatous polyps or carcinomas in 109 patients. CTC detected 90% of patients who had lesions measuring 10 mm or larger found by colonoscopy. There were also 30 lesions found on CTC, but not colonoscopy, for which 15 of 27 participants underwent a subsequent colonoscopy. Five of 18 lesions were confirmed: 4 adenomatous polyps and 1 inflammatory polyp. The CTC performance in this study (sensitivity of 90% and specificity of 86%) was better than that reported from some earlier studies and similar to what was reported by Pickhardt and colleagues in a prospective study with a similar design as the ACRIN trial.

Kim et al also compared CTC with colonoscopy for the detection of advanced neoplasia. Although this study was not randomized, the detection rates were comparable between the two groups of >3,100 patients each (3.2% for CTC and 3.4% for colonoscopy).

In 2005, 2 meta-analyses reviewed the performance of CTC in the detection of colorectal polyps. In one of these studies, CTC showed high average sensitivity (93%) and specificity (97%) for polyps ≥1 cm, both of which decreased to 86% when medium polyps (6–9 mm) were included in the analysis. In the other meta-analysis, the sensitivity of CTC, although heterogeneous, improved as the polyp size increased (48% for polyps less than 6 mm, 70% for 6- to 9-mm polyps, and 85% for polyps larger than 9 mm). The specificity was 92% to 97% for the detection of all the polyps.

Two additional meta-analyses were published in 2011. An analysis of 49 studies found the sensitivities for detection of CRC by colonography and colonoscopy to be 96.1% and 94.7%, respectively, with overlapping confidence intervals. Another analysis focused only on studies of average-risk participants and found the sensitivity and specificity of CTC for the detection of adenomas ≥1 cm to be 87.9% and 97.6%, respectively.

Importantly, CTC may be a more acceptable option to many individuals. A recent randomized study compared participation rates when members of the general population were offered CRC screening by either colonoscopy or CTC. Significantly more people accepted the invitation for CTC (34% vs. 22%). While colonoscopy had a greater diagnostic yield in screened participants, the yields were similar when determined per the invited population. More recently, laxative-free CTC has shown good sensitivity and specificity for detecting lesions 1 cm or larger. This technique is likely to be even more acceptable to patients.
The technical aspects of CTC differ from study to study and have not been standardized. These details include the imaging, pre-procedure preparation, use of stool tagging, and the expertise of the interpreter. Long-term follow-up studies of patients who were screened by CTC are not yet available.

The issue of radiation exposure also requires consideration. Using the screening protocol for the ACRIN trial, Berrington de Gonzalez et al estimated the effective dose of low-dose CTC to be 9 mSv for women and 8 mSv for men, corresponding to 5 radiation-related cancer cases per 10,000 individuals undergoing one scan at age 60. Risks increase with repeated scanning. The 2009 American College of Radiology (ACR) practice guidelines for the use of CTC recommend the use of a multi-detector CT scanner and low-dose, non-enhanced technique to minimize radiation exposure to the patient. Absorbed doses should not exceed 12.5 mGy total per scan.

Overall, available data indicate that CTC may be useful for the detection of larger polyps. However, it is still an evolving technique, and there are little data with regards to screening intervals, polyp size leading to referral for colonoscopy, and protocol for evaluating extracolonic lesions. The best evidence currently available seems to support repeating the procedure every 5 years and referring patients with identified polyps larger than 5 mm to colonoscopy. The panel views colonoscopy as the preferred screening modality, and there is a lack of consensus on the use of CTC as a primary screening tool.

Fecal-Based Screening Tests
Fecal tests are designed to detect signs of CRC in stool samples, specifically occult blood or, more recently, alterations in exfoliated DNA. In contrast to structural tests, they are noninvasive and no bowel clearance is necessary. However, stool tests are less likely to detect adenomatous polyps for cancer prevention. Also, sensitivity can be limited by inadequate specimen collection or suboptimal processing and interpretation and is significantly lower than that of structural tests.

Any positive stool test needs to be followed by colonoscopy. To ensure adequate follow-up, a health care professional should coordinate testing so that the patient who has a positive result enters the health care system in a responsible way.

Fecal Occult Blood Test
Two FOBTs are currently available: guaiac-based and immunochemical. These tests are recommended annually, alone, or in combination with flexible sigmoidoscopy every 5 years. Annual FOBT should not be performed in combination with colonoscopy in an average-risk patient. Any positive result on FOBT, however, should be followed up with colonoscopy. It is important for FOBT to be performed annually, because the sensitivity in detecting advanced adenomas in a single test is fairly low.

FOBT of a single specimen obtained at digital rectal examination is not recommended due to exceptionally low sensitivity. Unfortunately, a recent survey of over 1,000 primary care physicians revealed that inappropriate in-office testing is still widely used (25% used in-office testing only and 53% used both in-office and home testing), suggesting the need for strengthened education.

Guaiac FOBT
Based on the pseudoperoxidase activity of heme in human blood, guaiac FOBT is the most common stool test in use for CRC screening. There is direct evidence from randomized controlled trials that guaiac FOBT reduces the mortality from CRC. In the Minnesota Colon Cancer Control Study, more than 46,000 participants were randomized
to receive FOBT once a year, once every 2 years, or no screening. The 13-year cumulative mortality from CRC per 1000 was 5.88 and 8.83 in the annual and unscreened groups, respectively, and this 33% difference was statistically significant. While this study did not demonstrate a decrease in CRC mortality with biennial screening, other large randomized studies have. In fact, a recently published long-term follow-up of the Nottingham trial showed that individuals randomized to the biennial guaiac FOBT screening arm had a 13% reduction in CRC mortality at a median follow-up of 19.5 years (95% CI, 3% to 22%), despite a 57% participation rate. Following adjustment for non-compliance, the reduction in CRC mortality was 18%.

A systematic review of 4 randomized controlled trials involving more than 320,000 participants showed a 16% reduction in relative risk for CRC death with guaiac FOBT screening (95% CI, 0.78–0.90). The sensitivity of different guaiac FOBT for cancer detection ranged from 37% to 79% in a study of about 8,000 participants by Allison and colleagues. In the UK National Health Service Bowel Cancer Screening Programme (BCSP), cancer was detected in 11.8% of individuals who had a colonoscopy following an abnormal or weak positive FOBT. Adenomas were found in an additional 49.7% of participants.

One major disadvantage for guaiac FOBT is that it may miss tumors that bleed in smaller amounts, intermittently, or not at all. Another limitation is the high false-positive rate resulting from reaction with non-human heme in food and blood from the upper gastrointestinal tract. To compensate for intermittent limitations, guaiac FOBT should be performed on three successive stool specimens obtained while the patient adheres to a prescribed diet.

**Fecal Immunochemical Test**
FIT, approved by the FDA in 2001, directly detects human globin within hemoglobin. Unlike guaiac FOBT, FIT does not require dietary restrictions, and a single testing sample is sufficient. However, sensitivity (11%–58% for detecting any adenoma) and specificity (59%–97%) vary widely for FIT as illustrated by a 2009 German study that assessed six different FIT methods on 1,319 participants. More recent comparative studies have shown that FIT is more sensitive than guaiac FOBT. For example, one study demonstrated a higher sensitivity for cancer by FIT compared to Hemoccult® Sensa (82% vs. 64%). A Dutch randomized study also demonstrated higher detection rates of advanced neoplasia by FIT (2.4%) than guaiac FOBT (1.1%), although both were less reliable than flexible sigmoidoscopy (8.0%). An expert panel in Ontario recently conducted an extensive literature analysis and concluded that FIT is superior to guaiac FOBT in both participation rates and in detection of advanced adenomas and CRC.

**Stool DNA Test**
Stool DNA testing is an emerging screening tool for CRC. It detects the presence of known DNA alterations during colorectal carcinogenesis in tumor cells sloughed into stool. Early proof-of-principle tests involving a single-target marker such as KRAS produced less than 40% sensitivity. In an effort to improve sensitivity, newer tests with multi-panel markers were developed. In a large multicenter study of 4,404 patients, eligible subjects submitted a stool specimen for DNA analysis, underwent Hemoccult® II testing, and then had a colonoscopy. In a subgroup analysis, the multi-target DNA assay SDT-1 (21 mutations in APC, KRAS, and p53 plus 2 other markers) detected 52% of CRC compared with 13% by Hemoccult® II, with specificities of 94% and 95%, respectively. The SDT-1 assay did not perform as well in another large, multicenter, prospective, triple-blinded trial that also assessed a
second-generation combination test SDT-2 (mutations in \textit{APC} and \textit{K-ras} plus \textit{vimentin} methylation). In this study, a total of 3,764 average-risk healthy adults underwent screening colonoscopy, Hemoccult®, Hemoccult® Sensa, SDT-1, and SDT-2. Very similar sensitivities for detection of CRCs, high-grade dysplasias, and adenomas were observed for SDT-1 and Hemoccult® Sensa (20% and 21%, respectively), whereas the sensitivity of SDT-2 was 40%. Other stool DNA tests are being developed and tested.

For those unwilling or unable to have screening colonoscopy, there is increasing evidence that a stool DNA test may provide a valuable noninvasive option. More research is necessary to determine the optimal testing interval. Only one stool DNA test, ColoSure™ detecting methylated \textit{vimentin}, is currently available in the United States. However, stool DNA testing has not yet been approved by the FDA, and is currently not considered a first-line screening tool.

**Risk Assessment**

The NCCN Guidelines for Colorectal Cancer Screening stratify patients into 3 groups depending on their risk of getting CRC. Colorectal screening is particularly important for African Americans since they have a higher risk of incidence and mortality (see Increased Risk, below). Communication with the patient and referring physician of any updated CRC risk assessment and screening plan based on family history, colonoscopy, and pathology findings is highly encouraged.

CRC risk assessment in persons without a known family history is advisable by age 40 years to determine the appropriate age for initiating screening.

**Average Risk**

Individuals at average risk of developing CRC are those 50 years or older with a negative family history and no history of adenoma, CRC, or inflammatory bowel disease.

**Increased Risk**

Individuals with a personal history of adenomatous polyps/sessile serrated polyps (SSPs) (see description below), CRC, or inflammatory bowel disease, and those with a positive family history of CRC or advanced adenomatous polyps are considered to be at increased risk for developing CRC. Individuals with diabetes mellitus or a history of \textit{BRCA}-positive breast cancer also have a higher risk, although these are not considered to affect the screening guidelines.

Registry data suggest an increased incidence for CRC in African Americans prior to age 50. This increased risk has led some to recommend beginning population CRC screening in African Americans at age 45. However, mortality from CRC is multifactorial and is related to host factors, tumor biology, environmental exposures, disparities in access to screening, differences in stage at diagnosis, and treatments received. In addition, mortality from CRC has been decreasing in African Americans and whites since 1999. Therefore, based on the available data, methods to further enhance access to screening in African American populations should be endorsed.

**High-Risk Syndromes**

Individuals with a family history of Lynch syndrome (also known as HNPCC) or with a personal or family history of polyposis syndromes are considered to be in the high-risk category (see Inherited Colon Cancer, below).
Screening of Individuals at Average Risk

It is recommended that screening for persons at average risk begin at age 50 after discussions of the available options. Currently recommended options include colonoscopy every 10 years, annual fecal-based tests, flexible sigmoidoscopy every 5 years using a 60 cm or longer scope, a combination of annual fecal tests and sigmoidoscopy every 5 years, or CTC every 5 years. If available, colonoscopy is the preferred screening modality for individuals at average risk. However, any screening is better than none. Recent data suggest that following up with less invasive tests, such as annual fecal tests, provides approximately the same benefit with lower risks and costs than colonoscopy.

If a colonoscopy is incomplete or preparation is suboptimal, other screening methods or repeat colonoscopy should be considered based on physician judgment.

Interpretation of Findings

Colonoscopy is indicated as follow-up of abnormal findings from other screening modalities—stool tests, flexible sigmoidoscopy (biopsy-proven adenoma), or CTC. During colonoscopy, any polyps found should be removed, and follow-up strategies should be based on the endoscopic and pathologic findings. Special attention should be paid to polyps located on the right side of the colon tract, as these tend to be associated with microsatellite instability (MSI) and hence greater cancer risk that warrants additional surveillance.

Adenoma/Adenomatous Polyps

Adenomas or adenomatous polyps (most often found to be tubular), the most common form of polyps, are associated with an increased risk for CRC (see the following section on Screening of Individuals at Increased Risk). Villous adenomatous polyps have a greater risk of harboring cancer and finding additional adenomatous polyps or cancer on follow-up.

Flat Adenoma

Flat adenomatous polyps are unusual and can be easily missed during colonoscopy because they are not protruding from the colon wall. More prospective studies are required to clarify their role in CRC risk. In the meantime, all flat adenomatous polyps should be removed upon identification with routine post-adenoma follow-up.

Serrated Polyps

SSPs, also known as sessile serrated adenomatous polyps, are rare forms of polyps that have been associated with adenocarcinoma. Any serrated lesion in the proximal colon should be followed similarly to adenomatous polyps, due to their significant risk of neoplastic progression.

Hyperplastic polyps are another type of serrated polyp. A large body of literature indicates that hyperplastic polyps are not associated with a significantly increased risk for CRC, and supports the recommendation that persons with hyperplastic polyps be screened as average risk. Recent literature, however, suggests that a small subset of persons with multiple or large hyperplastic polyps have SPS (see Serrated Polyposis Syndrome, below), with a 26% to 70% risk for CRC. The majority of these persons had concomitant adenomatous polyps or SSP. Additionally, there is evidence suggesting that some cancers with extensive DNA methylation and MSI might derive from hyperplastic polyps.

Ideally, all detected polyps should be removed, but this is not always possible. Removed polyps should be examined for degree of dysplasia, as well as for histologic features of SSP. Hyperplastic polyps that are <1
cm without SSP features indicate average risk for follow-up screening when they occur on the left side (ie, splenic flexure, descending colon, sigmoid colon, rectum), while those on the right side (ie, cecum, ascending colon, transverse colon) should be followed with repeat colonoscopy in 5 years. Larger polyps and SSPs should be followed as adenomas. SPS is rarely reported to be inherited, and the CRC risk of individuals with affected relatives remains unclear (see Serrated Polyposis Syndrome, below).

Screening of Individuals at Increased Risk

**Personal History of Adenoma/SSP**

Individuals with adenomatous polyps are at increased risk for recurrent adenomatous polyps and CRC. To minimize the risk of developing CRC, a surveillance program is recommended for patients with adenomatous polyps following screening colonoscopy and complete polypectomy. For patients with completely resected adenomatous polyps, the surveillance schedule depends on the risk of recurrence, which in turn is related to the number, size, and histology of adenomatous polyps. Furthermore, when there is uncertainty about the completeness of removal in large and/or sessile polyps and when the colonic preparation was suboptimal, shorter screening intervals may be necessary.

Low-risk adenomatous polyps are tubular, 2 or fewer, and <1 cm. In this group, colonoscopy should be repeated within 5 years, although emerging data suggest that longer intervals may be appropriate. If this examination is normal, colonoscopy should be repeated every 10 years. Generally the results of the first 2 screening examinations may predict the patient’s overall colon cancer risk. Robertson et al reported on a study of 564 participants who had their first adenoma identified by colonoscopy and underwent 2 additional colonoscopies. The study found that combining results of two prior colonoscopies can help predict the likelihood of high-risk findings (advanced adenomatous polyps or cancers) on the third screen. If no adenomas were found on the second exam, results of the first screening predicted results of the third. In this case, if the first colonoscopy showed only low-risk findings, then the chance of high-risk findings on the third colonoscopy was 4.9%, whereas high-risk findings on the first colonoscopy gave a 12.3% risk of high-risk findings on the third colonoscopy (P = .015).

Advanced or multiple adenomatous polyps (3–10 polyps, ≥10 mm with >25% villous histology or high-grade dysplasia) have been associated with increased risk. High-grade dysplasia is defined as an adenoma that shows features of severe dysplasia (marked reduction of interglandular stromas with complex irregularity of glands, papillary infolding, and cytogenetic abnormalities) or high-grade dysplasia (severe architectural disturbance of glands along with cytologic features of dysplasia). Carcinoma in situ is a term previously used by pathologists to describe colon polyps and cancer that has been replaced by the term high-grade dysplasia. A study by Golembeski and colleagues has shown that the identification of villous architecture and high-grade dysplasia is poorly reproducible among pathologists. Individuals with advanced or multiple adenomatous polyps should have repeat colonoscopy within 3 years, although new data suggest that intervals of 5 years may be appropriate.

Because studies have used 1 cm as the standard measure, data are lacking on the relative significance of intermediate size adenomatous polyps (size 5–10 mm). Individuals with high-risk adenomatous polyps are recommended to repeat colonoscopy within 3 years. Subsequent surveillance colonoscopies are recommended within 5 years, depending on colonoscopic findings. Longer intervals are recommended for persons with normal follow-up colonoscopies. It is appropriate to reassess risk, including contributing medical and personal factors,
number and characteristics of adenomatous polyps, and family history at each interval prior to and following procedures.

Individuals with more than 10 cumulative adenomatous polyps are recommended to undergo evaluation for a polyposis syndrome (see Inherited Colon Cancer, below), though only a small fraction of those with no family history and low adenoma burden will have a defined hereditary syndrome. Ten polyps or fewer may infrequently be associated with an inherited polyposis syndrome, especially in patients younger than age 40 or with a strong family history. Hence, a detailed family history is crucial in patients with multiple adenomatous polyps. Individual management is emphasized.

Polypectomy of large sessile polyps is associated with a high rate of recurrence, attributed to the presence of residual adenoma tissue at the time of polypectomy. Hence, follow-up colonoscopy within 2 to 6 months is appropriate in this setting, or when polypectomy is suspected to be incomplete.

The NCCN Guidelines for Colon Cancer provide recommendations for management if a malignant polyp is found at colonoscopy (available at www.NCCN.org).

Personal History of Colorectal Cancer
Individuals with a personal history of CRC should be followed according to the surveillance recommendations in the NCCN Guidelines for Colon Cancer and the NCCN Guidelines for Rectal Cancer (available at www.NCCN.org). These patients are at increased risk for recurrent adenomatous polyps and cancer. Studies have found a high recurrence rate in the 4 to 5 years following CRC resections. In patients with rectal cancer, local recurrence at the rectal anastomosis has been reported to occur in 5% to 36% of patients. Furthermore, an analysis of 3,278 patients with resected stage II and III CRC in the Intergroup 0089 study found that the rate of second primary CRC is especially high in the immediate 5 years following surgery and adjuvant chemotherapy. These results suggest that intense surveillance should be considered during that period, even though this analysis did not exclude patients with Lynch syndrome, who are at greater than 30% risk for synchronous and metachronous cancers.

The NCCN Guidelines for Colon Cancer and the NCCN Guidelines for Rectal Cancer recommend a complete colonoscopy preoperatively as well as at 1 year following surgery (within 3 to 6 months if preoperative colonoscopy was incomplete). If this examination is normal, colonoscopy should be repeated in 3 years, then every 5 years. Shorter intervals (1 year) are recommended if adenomatous polyps or SSP are found. Subsequent colonoscopic intervals are individualized and generally should not exceed 5 years.

In addition to colonoscopy, patients with rectal cancer also should undergo periodic endoscopic evaluation of the rectal anastomosis to identify local recurrence, which has been reported to occur in 5% to 36% of patients. Expert opinion supports repeat evaluation for patient status every 3 to 6 months for 2 years following low anterior resection (LAR), then every 6 months for a total of 5 years. The utility of routine endoscopic ultrasound for early surveillance is not defined.

Advantages of more intensive follow-up of patients with stage II and/or stage III rectal cancer have been demonstrated prospectively in several studies and in 3 meta-analyses of randomized controlled trials designed to compare low-intensity and high-intensity programs of surveillance. Other studies impacting the issue of post-treatment CRC surveillance include results from an analysis of data from 20,898 patients enrolled in 18 large adjuvant colon cancer randomized trials.
The meta-analysis demonstrated that 80% of recurrences were in the first 3 years after surgical resection of the primary tumor. However, in the final analysis of Intergroup trial 0114 comparing bolus 5-FU to bolus 5-FU/LV in patients with surgically resectable rectal cancer, local recurrence rates continued to rise after 5 years. Furthermore, a population-based report indicated that long-term survival is possible in patients treated for local recurrence of rectal cancer (overall 5-year relative survival rate of 15.6%), thereby providing support for more intensive post-treatment follow-up in these patients. Nevertheless, controversies remain regarding selection of optimal strategies for following up patients after potentially curative CRC surgery.

Patients with a personal history of CRC should also be considered for Lynch syndrome testing using one of the following approaches: 1) all CRC patients; or 2) all CRC patients diagnosed prior to age 70 years plus patients diagnosed at older ages who meet the Bethesda guidelines. Testing for Lynch syndrome is discussed in more detail below (see Molecular Workup and Genetic Testing for Lynch Syndrome).

**Inflammatory Bowel Disease**

It is well recognized that individuals with a personal history of inflammatory bowel disease (ie, ulcerative colitis, Crohn’s disease) are at an increased risk for CRC. Screening by colonoscopy every 1 to 2 years should be initiated 8 to 10 years after the onset of symptoms of pancolitis or 12 years after onset of left-sided colitis and should be performed by an endoscopist who is familiar with the appearance of ulcerative colitis or Crohn’s disease. A 2001 meta-analysis showed that patients with pancolitis have a higher risk of developing CRC than those with less extensive disease. Interpretation of dysplasia or intraepithelial neoplasia can be difficult. Pathologists experienced in interpreting inflammatory bowel disease lesions should evaluate biopsies. Lesions in patients with ulcerative colitis that appear endoscopically and histologically similar to sporadic adenoma, with no dysplasia in the flat mucosa in the surrounding area or elsewhere in the colon and without invasive carcinoma in the polyp, can be treated safely by polypectomy and continued surveillance. Most findings of high-grade, multifocal, or repeat low-grade dysplasia place the ulcerative colitis patient at high risk for developing CRC. Prophylactic proctocolectomy with ileoanal anastomosis is preferred for these patients. All other individuals with positive findings should be referred to an experienced inflammatory bowel disease surgeon to discuss surgical options.
Family History
Family history is one of the most important risk factors for CRC. It is essential to obtain a detailed family history including first-degree relatives (parents, siblings, and offspring), second-degree relatives (aunts, uncles, grandparents, and half-siblings), and additional relatives with cancer (cousins, great-grandparents, nieces, and nephews). Sometimes a great deal of information can be obtained by looking at first cousins. Grandchildren are often not old enough to manifest any of the clinical phenotypes of cancer syndromes.

For each of the relatives, current age and age at diagnosis of any cancer as well as a date, age, cause of death, and availability of a tumor sample are very important for discerning whether relatives were at risk for developing cancer, how long they were at risk, and what type of cancer they had. It is particularly important to note the occurrence of multiple primary tumors. Other inherited conditions and birth defects should be included in this family history. Ethnicity and country of origin are also important.

It is recommended that risk assessment be individualized and include a careful family history to determine whether a familial clustering of cancers is present in the extended family. If a patient meets the criteria for an inherited colorectal syndrome (see below), further risk evaluation and counseling, as outlined in the guidelines, is required.

When any one of the revised Bethesda criteria are met (listed in the guidelines, above), the possibility of Lynch syndrome is suggested, and immunohistochemical (IHC) staining for the four mismatch repair (MMR) proteins and/or MSI testing on the colon tumor of the youngest affected family member is warranted (see Molecular Workup and Genetic Testing in the section on Lynch Syndrome, below, for more information on this topic).

Positive Family History
Individuals with a family history of CRC have an increased risk for the disease themselves and should therefore undergo earlier and/or more frequent screening. The panel's recommendations are as follows:

- For patients with an affected first-degree relative diagnosed before age 50 years or 2 first-degree relatives with CRC at any age, colonoscopy is recommended every 3 to 5 years, beginning 10 years prior to the earliest diagnosis in the family or at age 40 at the latest.

- For those with one affected first-degree relative diagnosed at age 50 years or later, colonoscopy every 5 years should begin at age 50 or 10 years earlier than the age of diagnosis of the relative. Multiple (≥2) negative colonoscopies may support stepwise lengthening of the colonoscopy interval in these individuals.

- When one second-degree relative is diagnosed with CRC prior to age 50, colonoscopy should begin at age 50 years, with repeat colonoscopy based on findings.

- Individuals with a first-degree relative with a history of advanced adenoma(s) should undergo colonoscopy beginning 10 years prior to the relative’s age of onset or age 50 years at the latest, with repeat colonoscopy based on findings. Data suggesting an increased risk for CRC in this population is limited.

Colonoscopy intervals should be modified based on personal and family history as well as on individual preferences. A recent population-based study analyzed more than 2 million individuals to determine relative risks for the development of CRC depending on family history of CRC. Results showed that some combinations of affected first-, second-, and third-degree relatives may increase risk sufficiently to alter screening guidelines from the recommendations listed above. Other factors that modify colonoscopy intervals include the size of family;
completeness of the family history; participation of family members in screening; and colonoscopic findings in family members.

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.\textsuperscript{137-140} 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.\textsuperscript{141} 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.\textsuperscript{142,143} 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.\textsuperscript{143} 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{144} MSI occurs in 80% to 90% of resulting colorectal tumors.\textsuperscript{145,146} 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{147,148} 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{145}).

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 (MLH1, MSH2, MSH6, and 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. Approximately 50% of families meeting the Amsterdam II criteria have a mutation in an MMR gene. These criteria are very stringent, however, and miss as many as 68% of patients with Lynch syndrome.

The classical Bethesda guidelines were later developed to provide broader criteria for testing colorectal tumors for MSI. The National Cancer Institute introduced the revised Bethesda guidelines in 2002 to clarify selection criteria for MSI testing. One study reported that MLH1 and MSH2 mutations were detected in 65% of patients with MSI of colon cancer tissue who met the Bethesda criteria. 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. Patients fulfilling the revised Bethesda criteria had an odds ratio for carrying a germline mutation in MLH1 or MSH2 of 33.3 (95% CI, 4.3–250; P = .001). 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.

Some newer models have also been developed to assess the likelihood that a patient carries a mutation in a MMR gene. These computer programs give probabilities of mutations and/or of the development of future cancers based on family and personal history. The PREMM1,2,6 model can be used online at http://premm.dfci.harvard.edu/ and the HNPCC predict model is available for online use at http://hnppcpredict.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. 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.

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. IHC analysis has the advantage of predicting which gene is most likely mutated and thus the first candidate for germline sequencing. 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.

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. 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. 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,\textsuperscript{178} with the following priority: \textit{MLH1} and \textit{MSH2} first, then \textit{MSH6}, and lastly \textit{PMS2}. Due to its rarity, testing for \textit{PMS2} mutation is only necessary if no mutation is found in the other genes.

\textbf{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 \textit{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.\textsuperscript{176} 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 \textit{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.

\textit{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.

\textbf{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.\textsuperscript{180–185} For the 2013 version of the guidelines, the panel devised separate cancer screening recommendations for patients with mutations in \textit{MLH1}/\textit{MSH2}, \textit{MSH6}, and \textit{PMS2}. This decision was based on emerging data that show a smaller risk for cancer in the latter groups.\textsuperscript{180,183,186} For example, individuals with \textit{MSH6} and \textit{PMS2} mutations have a 10\% to 22\% risk for colon cancer up to age 70, while those with \textit{MLH1} and \textit{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.

\textbf{Colon Cancer Surveillance}

If Lynch syndrome with \textit{MLH1} or \textit{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.\textsuperscript{148}
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 (ie, 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. There 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 MLH1 or MSH2 mutations, physicians may consider upper esophagogastroduodenoscopy (EGD) extended to the distal duodenum or into the jejunum every 3 to 5 years starting at age 30 to 35.

Annual urinalysis starting at age 25 to 30 years should also be considered to screen for urothelial cancers in carriers of MLH1 or 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 APC gene, located on chromosome 5q21. Truncating mutation of the 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. 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 ≥100 polyps or fewer polyps at younger ages, especially in a patient with a family history of FAP. 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. 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. These adenomatous polyps are more prone to occur in the right colon and may take the form of diminutive sessile adenomatous polyps. Phenotypic expression is often variable within families. The onset of
CRC is typically delayed compared to FAP patients, 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%.\textsuperscript{216} 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.\textsuperscript{217} 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 polyp 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.\(^\text{231}\) 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%).\(^\text{232}\) The risk for duodenal cancer increases dramatically with stage IV disease.

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.\(^\text{233}\) 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%. The 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.\(^\text{234}\) 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%).\(^\text{234,235}\) 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.

**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. 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. 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. 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 \( P < .0001 \)). However, due to the increased risk of cardiovascular events associated with their use, COX-2 inhibitors are not recommended routinely for sporadic adenomatous polyps.

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. 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. 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. 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. 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). 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, 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. It is caused by biallelic germline mutations in the MUTYH gene. MUTYH encodes the A/G-specific adenine DNA glycosylase excision repair protein (also called hMYH), which is responsible for excising adenine nucleotides mismatched with 8-oxo-guanine, a product of oxidative damage to DNA. Dysfunctional hMYH protein can thus result in G:C to T:A transversions during DNA replication. Adenomatous polyposis is thought to result from such transversions occurring within the APC gene. Individuals with MAP also have an increased risk for extracolonic tumors including duodenal cancer.

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. 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, 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 ≥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 (i.e., 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 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.

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

**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). SSPs are flat or slightly raised and usually occur on the right side, while traditional serrated adenomas are generally polypoid. 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, 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


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