Overview

Colorectal cancer (CRC) is the third most frequently diagnosed cancer in men and women in the United States. In 2009, an estimated 106,100 new cases of colon cancer and 40,870 new cases of rectal cancer will occur in the United States, and 49,920 people will die of colon and rectal cancers. Patients with localized colon cancer have a 90% 5-year survival rate.

CRC mortality can be reduced through early diagnosis and cancer prevention with polypectomy. Therefore, the goal of CRC screening is to detect cancer at an early, curable stage and to detect and remove clinically significant adenomas. Screening

Please Note

These guidelines are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network makes no representation or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their applications or use in any way.

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Disclosures for the NCCN Colorectal Cancer Screening Guidelines Panel

At the beginning of each NCCN guidelines panel meeting, panel members disclosed any financial support they have received from industry. Through 2008, this information was published in an aggregate statement in JNCCN and online. Furthering NCCN's commitment to public transparency, this disclosure process has now been expanded by listing all potential conflicts of interest respective to each individual expert panel member.

Individual disclosures for the NCCN Colorectal Cancer Screening Guidelines Panel members can be found on page 61. (To view the most recent version of these guidelines and accompanying disclosures, visit the NCCN Web site at NCCN.org.)

These guidelines are also available on the Internet. For the latest update, please visit NCCN.org.
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.

Current technology falls into 2 broad categories: structural and stool/fecal-based tests. Although some techniques are better established than others, panelists agreed 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. These 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 examinations require informed consent and sedation, and have related risks, including perforation and bleeding. Recently, a large cohort study of 53,220 Medicare patients between ages 66 and 95 years showed that risk for adverse events after colonoscopy increases with age.1

**Colonoscopy**

Colonoscopy is the most complete screening procedure, allowing the entire large bowel to be examined and polyps to be removed in one session. It is currently the preferred screening method and also the required procedure for confirming positive findings from other tests. Colonoscopy is also considered the current gold standard for assessing the efficacy of other screening methods. Although no randomized

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Text continues on p. 43
RISK ASSESSMENT FOR COLON CANCER

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

Increased risk:
- Personal history
  - Adenoma/sessile serrated polyp (SSP)
  - Colorectal cancer
  - Inflammatory bowel disease (ulcerative colitis, Crohn’s disease)
- Positive family history

High-risk syndromes:
- Lynch syndrome/hereditary nonpolyposis colorectal cancer (HNPCC)
- Polyposis syndromes
  - Classical familial adenomatous polyposis
  - Attenuated familial adenomatous polyposis
  - MYH-associated polyposis
  - Peutz-Jeghers syndrome
  - Juvenile polyposis syndrome
  - Hyperplastic polyposis syndrome

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\*Not having 1 first-degree or 2 second-degree relatives with colorectal cancer or multiple cases of Lynch syndrome/HNPCC-related cancers in the family.

\*SSP is synonymous with sessile serrated adenoma but does not include classical hyperplastic polyp.

Clinical trials: The NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise noted.
SCREENING MODALITY AND SCHEDULE<sup>c,d</sup>

<table>
<thead>
<tr>
<th>Colonoscopy&lt;sup&gt;e,f&lt;/sup&gt; (preferred if available)</th>
<th>Evaluation of positive screening findings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Negative/no polyps</td>
</tr>
<tr>
<td></td>
<td>Positive/polyps</td>
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<tr>
<td></td>
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<tr>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Stool based:&lt;sup&gt;g&lt;/sup&gt;</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Positive</td>
</tr>
<tr>
<td>or</td>
<td>Negative/no polyps</td>
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<tr>
<td></td>
<td>Positive/polyps</td>
</tr>
<tr>
<td></td>
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</tr>
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</tbody>
</table>

or

<table>
<thead>
<tr>
<th>Flexible sigmoidoscopy</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative/no polyps</td>
<td>Repeat flexible sigmoidoscopy in 5 y&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Positive/polyps</td>
<td>Biopsy</td>
</tr>
<tr>
<td></td>
<td>Adenoma/SSP&lt;sup&gt;i&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>c</sup>See Screening Modality and Schedule (pages 16 and 17).
<sup>d</sup>Currently there is no 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 extracolonic lesions. However, the data available suggests that if CT colonography is negative/no polyps, then CT colonography should be repeated in 5 y; and if positive/polyps lesions, colonoscopy should be performed.
<sup>e</sup>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.
<sup>f</sup>If colonoscopy incomplete, consider other screening modalities or repeat colonoscopy at discretion of physician.
<sup>g</sup>Emerging technologies, such as stool DNA, have shown increasing evidence as reasonably accurate screening tests but data are limited for determining an interval between screening. Currently, stool DNA is not considered a first-line screening test except in specific circumstances.
<sup>h</sup>Studies at the present time have shown that fecal immunohistochemical testing (FIT) is as good as, if not superior to, guaiac-based testing.
<sup>i</sup>SSPs are managed the same as adenomas.
Increased-risk patients: personal history of adenomas/SSPs found at colonoscopy

<table>
<thead>
<tr>
<th>Low-risk adenoma:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• ≤ 2 polyps</td>
</tr>
<tr>
<td>• &lt; 1 cm</td>
</tr>
<tr>
<td>• Tubular</td>
</tr>
</tbody>
</table>

- Repeat colonoscopy within 5 y

- Negative/ no polyps

- Repeat colonoscopy every 5-10 y

- Positive/ polyps

- Repeat colonoscopy within 3 y

- Negative/ no polyps

- Repeat colonoscopy within 5 y

- Individual management

- Consider a polyposis syndrome

- See Hereditary Colorectal Cancer Pathway (page 19)

- Repeat colonoscopy within 2-6 mo (timing dependent on endoscopic and pathologic findings)

- Malignant polyp

- See NCCN Clinical Practice Guidelines in Oncology: Colon Cancer

*To view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org.

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*See Screening Modality and Schedule (pages 16 and 17).

SSPs are managed the same as adenomas.

Fewer than 10 polyps in the setting of a strong family history or younger age (< 40 y) may be associated with an inherited polyposis syndrome.

Ink lesion for later identification.
### INCREASED RISK BASED ON PERSONAL HISTORY OF COLORECTAL CANCER

<table>
<thead>
<tr>
<th>RISK STATUS</th>
<th>SURVEILLANCE</th>
<th>FOLLOW-UP OF CLINICAL FINDINGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personal history of curative intent resected colorectal cancer&lt;sup&gt;l,m&lt;/sup&gt;</td>
<td>Colonoscopy in 1 y, (within 3-6 mo if there was no or incomplete preoperative colonoscopy)</td>
<td>Repeat colonoscopy in 1-3 y&lt;sup&gt;n&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adenoma/ SSP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Negative/ no polyps</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Repeat colonoscopy in 2-3 y, then every 3-5 y based on findings</td>
</tr>
</tbody>
</table>

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<sup>l</sup>Identify colorectal patients who meet Bethesda criteria; these patients may require genetic counseling or individualized management. (See High-Risk Syndromes [page 19] and Lynch Syndrome [page 22].)

<sup>m</sup>In addition to the colonoscopy, patients with rectal cancer should also undergo periodic limited endoscopic evaluation of the rectal anastomosis to identify local recurrence. Optimal timing for surveillance is not known. Expert opinion supports repeat evaluation every 3-6 mo for the first 2-3 y of surveillance. No specific data clearly support rigid versus flexible sigmoidoscopy. The usefulness of routine endoscopic ultrasound for early surveillance is not defined. See surveillance section of NCCN Clinical Practice Guidelines in Oncology: Rectal Cancer (to view the most recent version of these guidelines, visit the NCCN Website at www.NCCN.org).

<sup>n</sup>The recommendation for intensive surveillance immediately after resection is based on studies that found a high rate of metachronous colorectal cancer and/or resectable recurrences in the 4-5 y after colorectal cancer resections, although the studies did not fully exclude patients with HNPCC.
### 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</td>
<td>8-10 y after onset of symptoms&lt;sup&gt;o&lt;/sup&gt;</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 expert GI pathologist desirable</td>
<td>Surgical consultation for resection&lt;sup&gt;s&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>o</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>q</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 on the individual findings.

<sup>r</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>s</sup>See Definitions of Common Colorectal Resections (page 18).
## Increased Risk Based on Positive Family History

### Family History Criteria

<table>
<thead>
<tr>
<th>Criteria Description</th>
<th>Screening Protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-degree relative with colorectal cancer at age 50-60 y</td>
<td>Colonoscopy beginning at age 40 y, Repeat every 5 y^w</td>
</tr>
<tr>
<td>First-degree relative with colorectal cancer at ≤ 50 y&lt;sup&gt;u,v&lt;/sup&gt;</td>
<td>Colonoscopy beginning at age 40 y, or 10 y before earliest diagnosis of colorectal cancer, Repeat every 3-5 y depending on other family history</td>
</tr>
<tr>
<td>First-degree relative with colorectal cancer at ≥ 60 y&lt;sup&gt;u&lt;/sup&gt;</td>
<td>Colonoscopy beginning at age 50 y, Repeat every 5 y</td>
</tr>
<tr>
<td>Two related first-degree relatives with colorectal cancer at any age&lt;sup&gt;x&lt;/sup&gt;</td>
<td>Colonoscopy beginning at age 40 y, or 10 y before earliest diagnosis of colorectal cancer, Repeat every 3-5 y depending on other family history</td>
</tr>
<tr>
<td>Two related second-degree relatives with colorectal cancer at any age</td>
<td>Colonoscopy beginning at age 50 y, Repeat every 5 y</td>
</tr>
</tbody>
</table>
| One second-degree relative or any third-degree relative with colorectal cancer or First-degree relative with non-advanced adenomas | • Treat as average-risk patients  
• Colonoscopy is preferred screening |

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<sup>1</sup>If a patient meets the criteria for an inherited colorectal syndrome, see Criteria for Further Risk Evaluation for High-Risk Syndromes (page 19).
<sup>u</sup>First-degree relatives with advanced adenoma may confer the same risk as first-degree relatives with colorectal cancer, and any adenoma < age 40 y may confer a similar risk to colorectal cancer < age 50 y.
<sup>v</sup>In this circumstance or if any one of the revised Bethesda criteria (page 26) are met, IHC/MSI testing should be performed on the colon tumor of youngest family member with available colorectal cancer tissue. Also see Lynch syndrome guidelines (page 22).
<sup>w</sup>Shorter intervals may be needed depending upon the family history.
SCREENING MODALITY AND SCHEDULE

- Colon cancer prevention should be the primary goal of colorectal cancer screening.
- Screening of average-risk individuals can reduce colorectal cancer mortality by detecting cancer at an early, curable stage and detecting and removing clinically significant adenomas. It has been shown to be cost-effective compared with 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 y, or
- Flexible sigmoidoscopy every 5 y, or
- CT colonography every 5 y

**Screening Modalities that Primarily Detect Cancer**

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

**Colonoscopy**

- Colonoscopy is the primary method employed for colorectal cancer screening in average- and high-risk populations. However, screening with any of the available modalities is preferable to no screening.
- Caveats for every-10-years interval:
  - A 1-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, 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 substantial variability exists in the quality and, by extension, the clinical effectiveness of colonoscopy. Improving the overall impact of screening colonoscopy requires a programmatic approach that addresses quality issues at several levels.
- These colonoscopy quality indicators include:
  - Cecal intubation rates
  - Withdrawal time
  - Adenoma detection rates
  - Appropriate intervals between endoscopic studies based on family and personal history, number, and histologic type of polyps on last colonoscopy
  - Minor and major complications rates
  - Pre-procedure medical evaluation
  - Appropriate preparation instructions
  - Standardized colonoscopy reports that contain, at a minimum:
    - Patient demographic and clinical factors
    - Procedure indications
    - Endoscopic findings
    - Photographic documentation of endoscopic landmarks
    - Estimate of quality of bowel preparation
    - Documentation of follow-up planning, including pathology results
    - Sedation administered

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1. If other modalities are not available, double-contrast barium enema every 5 y may be useful.
2. Currently, there is no 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 extracolonic lesions. However, available data suggest that if CT colonography is negative/no polyps, then CT colonography should be repeated in 5 y, and if positive/polyps lesions, colonoscopy should be performed.
3. Annual stool-based testing with every 5-y flexible sigmoidoscopy can be used in combination for screening.
4. Emerging technologies, such as stool DNA, have shown increasing evidence as a reasonably accurate screening test, but data are limited for determining an interval between screening. Currently, stool DNA is not considered a first-line screening test except in specific circumstances.
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Colon cancer prevention should be the primary goal of colorectal cancer screening.

Stool-based screening

CT colonography every 5 y

Flexible sigmoidoscopy every 5 y,  or

Colonoscopy every 10 y, or

immunochemical-based testing, annually , or

Guaiac-based testing, a

Recommended every 5 y for average-risk screening

Stool-Based Screening

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

Annual guaiac-based should not be performed if screening colonoscopy is used as a screening measure in an average-risk patient

Fecal immunohistochemical testing (FIT)

Detects human globin

Prescribed diet is not required

Requires single stool annually

Any positive test requires further evaluation

Radiographic

CT colonography (CTC)\(^5,6,7\)

Accuracy

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 y is based solely on computer simulation models

All visualized extracolonic findings should be described and recommendations provided as to appropriate follow-up

The increased risk for cancer rising from the performance of a single CTC is estimated to be < 0.14%

CTC interpretation should be accomplished only by those trained according to American Gastroenterological Association\(^5\) or

American College of Radiology (ACR)\(^6\) guidelines

Procedure quality should be tracked and assured using current ACR practice guidelines for patient preparation, image acquisition,

study interpretation, and reporting

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\(^{5}\)See American Gastroenterological Association CT Colonography Standards.

\(^{6}\)See American College of Radiology Practice Guideline for the Performance of CT Colonography in Adults.

\(^{7}\)Currently, there is not consensus on the use of CTC 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 extracolonic lesions. However, available data suggest

that if CTC is negative/no polyps, then CTC should be repeated in 5 y, and if positive/polyps lesions, colonoscopy should be

performed.
Clinical trials: The NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise noted.

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

Individual meeting the revised Bethesda guidelines\(^a\) (see page 26)

or

Individual from a family meeting Amsterdam criteria (see page 27)

or

> 10 adenomas in same individual (see pages 29 and 38)

or

Individual with multiple gastrointestinal hamartomatous polyps (see pages 40 and 41) or hyperplastic polyps (see page 42)

or

Individual from a family with a known hereditary syndrome associated with colorectal cancer, with or without known mutation (see appropriate hereditary syndrome)

### RISK ASSESSMENT/GENETIC COUNSELING\(^{b,c}\)

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

### HEREDITARY SYNDROME

- Lynch syndrome (see page 22)
- Classical FAP (see page 29)
- Attenuated FAP (see page 35)
- MYH-associated polyposis (see page 38)
- Peutz-Jeghers syndrome\(^d\) (page 40)
- Juvenile polyposis syndrome\(^d\) (page 41)
- Hyperplastic polyposis syndrome (page 42)

No syndromes, but familial risk present

See Positive Family History (page 15)

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

\(^b\) See Obtaining a Comprehensive Risk Assessment for Hereditary Colorectal Cancer (page 20).

\(^c\) 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.
### Obtaining a Comprehensive Assessment for Hereditary Colorectal Cancer

**Family History of Colorectal Cancer and Expanded Pedigree**
- It is essential to obtain a detailed family history, including:
  - Parents
  - Children
  - Siblings/half-siblings
  - Aunts and uncles
  - Grandparents
  - Great-grandparents
  - Cousins
  - Nieces and nephews

  See Common Pedigree Symbols (facing page) and Pedigree: First-, Second-, and Third-degree Relatives of Proband (facing page)

- Minimal data set on each relative:
  - Current age and age at diagnosis of cancer (medical record documentation of cancer 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, Turcot, Peutz-Jeghers, juvenile polyposis)¹
  - All other inherited conditions and birth defects

**Detailed Medical and Surgical History**
- Polyps
- Inflammatory bowel disease
- Inherited syndromes:
  - Lynch syndrome
  - Muir-Torre syndrome
  - FAP and associated syndromes
    - Attenuated FAP
    - Gardner syndrome
    - Turcot syndrome
  - MYH-associated polyposis (MAP)
  - Peutz-Jeghers syndrome
  - Juvenile polyposis syndrome
  - PTEN-associated syndromes
    - Cowden syndrome
    - Bannayan-Riley-Ruvalcaba syndrome
    - Pathology verification strongly encouraged

**Directed Examination for Related Manifestations**
- Colonoscopy
- Esophagogastroduodenoscopy
- Eye examination
- Skin, soft-tissue, and bone examination
- Oral examination

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Minimal data set on each relative:

- Current age and age at diagnosis of cancer (medical record documentation of cancer strongly encouraged)
- Age/availability of tumor sample and cause of death
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- All other inherited conditions and birth defects

Detailed Medical and Surgical History

- Polyps
- Inflammatory bowel disease
- Inherited syndromes: Lynch syndrome, FAP and associated syndromes, MYH-associated polyposis (MAP), Peutz-Jeghers syndrome, juvenile polyposis syndrome, PTEN-associated syndromes
- Pathology verification strongly encouraged
- Muir-Torre syndrome
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Directed Examination for Related Manifestations

- Colonoscopy
- Esophagogastroduodenoscopy
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- Skin, soft-tissue, and bone examination
- Oral examination

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


3 First-degree relatives: parents, siblings, and children; second-degree relatives: grandparents, aunts, uncles, nieces, nephews, and half-siblings; third-degree relatives: great-grandparents and cousins.
LYNCH SYNDROME

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LYNCH SYNDROME

**GENETIC COUNSELING/TESTING OF ELIGIBLE FAMILY MEMBERS**

**MUTATION STATUS**

- Not tested
  - Tailored surveillance based on individual- and family-risk assessment
  - No familial mutation found
    - Mutation of unknown significance found
      - Positive familial mutation MLH1, MSH2, MSH6, or PMS2 found
        - Positive gene test (mutation present)
          - See Lynch Syndrome Surveillance and Follow-up (page 24)
        - Negative gene test (mutation not present)
          - Average-risk screening (see page 11)
  
**Mismatch repair gene mutation unknown**
- Consider genetic testing of affected family member if possible to find a disease causing mutation
  - Genetic testing should begin with the gene most likely to harbor the mutation based on IHC results. If IHC testing cannot be performed or is uninformative, first test MSH2 or MLH1 and then MSH6 or PMS2 if a mutation is not found in the first 2 genes

**Familial mismatch repair gene mutation known**
- Consider genetic testing of at-risk family member to find a disease causing mutation

---

1At-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.
SURVEILLANCE\textsuperscript{a,h}

Colon cancer:
- Colonoscopy\textsuperscript{i} at age 20-25 y, or 10 y before the youngest age at diagnosis in the family, whichever comes first, and repeat every 1-2 y.
- Extracolonic:
  - Endometrial and ovarian cancer:
    - Consider referral to gynecologic oncologist for screening for gynecologic tumors.
    - Encourage patient education and prompt response to endometrial cancer symptoms.
    - Prophylactic hysterectomy and bilateral salpingo-oophorectomy is a risk-reducing option for women who have completed childbearing.
  - Gastric and duodenal cancer: consider upper GI endoscopy (including side-viewing examination) at age 25-30 y and repeat every 1-3 y, depending on findings.
  - Urothelial cancer: consider annual urinalysis.
  - CNS cancer: annual physical examination; no additional screening recommendations have been made.
  - Pancreatic cancer: no recommendations have been made.

Adenomas not amenable to endoscopic resection or high-grade dysplasia
- Adenocarcinomas
- No pathologic findings

FOLLOW-UP

- Continued screening\textsuperscript{j}
- Consider prophylactic total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAH/BSO) if postmenopausal or family completed
- See appropriate NCCN disease-specific treatment guidelines at www.NCCN.org
- Endoscopic polypectomy with follow-up colonoscopy every 1-2 y, depending on:
  - Location, character
  - Surgical risk
  - Patient preference
- Total abdominal colectomy with ileorectal anastomosis\textsuperscript{k}
- Endoscopic rectal exam every 1-2 y

\textsuperscript{a}See Cancer Risk in Individuals with HNPCC up to Age 70 Years Compared With the General Population (page 28).
\textsuperscript{h}Other than colon and endometrial cancer, screening recommendations are expert opinion rather than evidence-based.
\textsuperscript{i}Given the later average age of onset for MSH6 mutation carriers, consider starting colonoscopy at the age of 30-35 y, or 10 y before the youngest age of diagnosis in the family, whichever comes first.
\textsuperscript{j}May consider subtotal colectomy if patient is not a candidate for optimal screening.
\textsuperscript{k}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 (page 18).
IHC and MSI analyses are screening tests (either by themselves or in conjunction), typically performed on colon cancer tissue to identify individuals at risk for Lynch syndrome.

**Immunohistochemistry**

- IHC refers to staining tumor tissue for protein expression of the 4 mismatch genes known to be mutated in Lynch syndrome: 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 1 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.
- 10% to 15% of sporadic colon cancers exhibit abnormal IHC, often from abnormal methylation of the MLH1 gene promoter, but occasionally from an inherited mutation from 1 of the mismatch repair genes. Thus the presence of an abnormal IHC test increases the possibility of Lynch syndrome but does not make a definitive diagnosis. Genetic testing of peripheral blood DNA to find a disease-causing mutation of 1 of the mismatch repair genes should then be performed. Most patients will be found to have sporadic colon cancer and not a germline mutation. Those with a germline mutation are then identified as having Lynch syndrome.
- There is a 5%–10% false-negative rate with IHC testing.

**Microsatellite Instability**

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

- The Bethesda Criteria were developed in response to the emerging understanding of the pathologic spectrum and molecular characteristics of Lynch syndrome-related tumors. These criteria were intended to help identify patients with colon cancer whose tumors should be tested for MSI, thereby identifying patients with a greater chance of having Lynch syndrome. The revised Bethesda Guidelines (see page 26) 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 page 27), up to 30% of patients with Lynch syndrome fail to meet even the revised Bethesda Guidelines.
- Recently, IHC and/or MSI screening of all endometrial and colorectal cancers, regardless of age at diagnosis or family history, has been implemented at some centers to identify individuals at risk for Lynch syndrome.
LYNCH SYNDROME

THE REVISED BETHESDA GUIDELINES
FOR TESTING COLORECTAL TUMORS FOR MICROSATELLITE INSTABILITY (MSI)¹

Tumors from individuals should be tested for MSI in the following situations:

- Colorectal cancer² diagnosed in a patient < 50 years.
- Presence of synchronous or metachronous Lynch syndrome-associated tumors,³ regardless of age.
- Colorectal cancer with the MSI-H histology⁴ diagnosed in a patient < 60 years.
- Colorectal cancer diagnosed in a patient with 1 or more first-degree relatives with a Lynch syndrome-related cancer,³ with 1 of the cancers being diagnosed < 50 years of age.
- Colorectal cancer diagnosed in a patient with 2 or more first- or second-degree relatives with Lynch syndrome-related cancers³ regardless of age.

² Endometrial cancer at age < 50 y is not included in the revised Bethesda Guidelines; however, recent evidence suggests that these individuals should be evaluated for Lynch syndrome.
³ Lynch syndrome-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, and 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.

Clinical trials: The NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise noted.
LYNCH SYNDROME

THE REVISED BETHESDA GUIDELINES FOR TESTING COLORECTAL TUMORS FOR MICROSATellite INSTABILITY (MSI) 1

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- Colorectal cancer diagnosed in a patient with 2 or more first- or second-degree relatives with Lynch syndrome-related cancers regardless of age.


Endometrial cancer at age < 50 y is not included in the revised Bethesda Guidelines; however, recent evidence suggests that these individuals should be evaluated for Lynch syndrome.

Lynch syndrome-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, and sebaceous gland adenomas and keratoacanthomas, as seen in Muir-Torre syndrome.

Presence of tumor infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern.

MINIMUM CRITERIA FOR CLINICAL DEFINITION OF HNPCC (AMSTERDAM CRITERIA I) 1,2

At least 3 relatives with colorectal cancer; all of the following criteria should be present:

- One should be a first-degree relative of the other 2
- At least 2 successive generations must be affected
- At least 1 of the relatives with colorectal cancer must have received the diagnosis < 50 years of age
- Familial adenomatous polyposis (FAP) should be excluded
- Tumors should be verified by pathologic examination

REVISED MINIMUM CRITERIA FOR CLINICAL DEFINITION OF HNPCC (AMSTERDAM CRITERIA II) 1,2

At least 3 relatives must have a cancer associated with HNPCC (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 2
- At least 2 successive generations must be affected
- At least 1 of the relatives with cancer associated with HNPCC should be diagnosed < 50 years of age
- FAP should be excluded in the colorectal cancer cases (if any)
- Tumors should be verified whenever possible

2 Approximately 50% of patients with HNPCC will be missed by these criteria and approximately 50% of patients will meet the criteria and not have HNPCC, but have a high familial risk of uncertain etiology.
# Cancer Risk in Individuals with HNPCC Up to Age 70 Years Compared with the General Population

<table>
<thead>
<tr>
<th>Cancer</th>
<th>General Population Risk</th>
<th>HNPCC</th>
<th>Mean Age of Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>5.5%</td>
<td>80%</td>
<td>44 y</td>
</tr>
<tr>
<td>Endometrium</td>
<td>2.7%</td>
<td>20%-60%</td>
<td>46 y</td>
</tr>
<tr>
<td>Stomach</td>
<td>&lt; 1%</td>
<td>11%-19%</td>
<td>56 y</td>
</tr>
<tr>
<td>Ovary</td>
<td>1.6%</td>
<td>9%-12%</td>
<td>42.5 y</td>
</tr>
<tr>
<td>Hepatobiliary tract</td>
<td>&lt; 1%</td>
<td>2%-7%</td>
<td>Not reported</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>&lt; 1%</td>
<td>4%-5%</td>
<td>~ 55 y</td>
</tr>
<tr>
<td>Small bowel</td>
<td>&lt; 1%</td>
<td>1%-4%</td>
<td>49 y</td>
</tr>
<tr>
<td>Brain/central nervous system</td>
<td>&lt; 1%</td>
<td>1%-3%</td>
<td>~ 50 y</td>
</tr>
</tbody>
</table>

---

Table 1: HNPCC Risks

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Risk Mean Age of Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>80%</td>
</tr>
<tr>
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</tr>
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<td>1%-4%</td>
</tr>
<tr>
<td>Brain/central nervous system</td>
<td>1%-3%</td>
</tr>
</tbody>
</table>

Classical Familial Adenomatous Polyposis (FAP):
- 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 (usually ≤ 5 y)
- Pancreatic cancers (< 2%)
- Gastric cancers (< 1%)

Attenuated FAP
- Presence of < 100 adenomas (average of 30 polyps)
- Frequent right-sided distribution of polyps
- Adenomas and cancers at age older than classic FAP (mean age > 50)
- Upper GI findings and thyroid cancer risk are similar to classic FAP
- Other extraintestinal manifestations, including CHRPE and desmoids, are rare

*RISK ASSESSMENT*

- **Personal history classical FAP**
  - Family mutation known → See Genetic Testing and Surveillance (page 32)
  - Family mutation unknown → See Genetic Testing and Surveillance (page 33)

- **Personal history attenuated FAP**
  - Family mutation known → See Genetic Testing and Surveillance (page 36)
  - Family mutation unknown → See Genetic Testing and Surveillance (page 37)

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Individuals with ≥ 100 or more polyps occurring at older ages (≥ 35-40 years) may be found to have attenuated FAP.

30% spontaneous new mutation rate, thus family history may be negative. Especially noteworthy if onset < 50 years of age.
### FAMILIAL ADENOMATOUS POLYPOSIS

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

All recommendations are category 2A unless otherwise noted.

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<table>
<thead>
<tr>
<th>TREATMENT</th>
<th>SURVEILLANCE</th>
<th>Proctectomy if dense polyposis or severe dysplasia</th>
</tr>
</thead>
</table>
| Colon cancer: | - Annual sigmoidoscopy and polypectomy or polyp ablation if adenoma burden is low (in patients with retained rectum).<sup>5</sup>  
- Consider NSAID chemoprevention to reduce polyp burden as pharmacologic adjunct to endoscopic surveillance. Clinical trial is encouraged. |  |
| Extracolonic: | - Duodenal or periampullary cancer: baseline upper endoscopy (including side-viewing examination) at the time of colectomy or at age 25-30 y, whichever comes first, and repeat every 1-3 y, depending on severity of polyposis.<sup>6</sup>  
- Gastric cancer: same as duodenal cancer.<sup>6</sup>  
- Thyroid cancer: annual thyroid examination, starting in late teenage years.<sup>6</sup>  
- CNS cancer: annual physical examination; no additional screening recommendations have been made.<sup>6</sup>  
- Intra-abdominal desmoids: annual abdominal palpation; after colectomy, consider abdominal and pelvic CT or MRI every 3 y, especially if family history of desmoids.<sup>6</sup>  
- 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.<sup>6</sup>  
- Hepatoblastoma: consider liver palpation, abdominal ultrasound and measurement of AFP, every 3-6 mo, during first 5 y of life. Screening in a clinical trial is preferred.<sup>6</sup>  
- Pancreatic cancer: no recommendations have been made.<sup>6</sup> |  |
| **Personal history of classical FAP** | **Proctocolectomy or colectomy**<sup>4,6,8</sup> |  |

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<sup>5</sup> 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.

<sup>6</sup> See Surgical Options for Treating the Colon And Rectum in Patients with FAP (page 34).

<sup>4</sup> Timing of colectomy in patients < 18 y 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. Annual colonoscopy if surgery is delayed.

<sup>8</sup> 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.

<sup>9</sup> Other than colon cancer, screening recommendations are expert opinion rather than evidence based.
FAMILIAL ADENOMATOUS POLYPOSIS

**Personal history of classical FA P**

- 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.

See Surgical Options for Treating the Colon And Rectum in Patients with FAP (page 34).

- Timing of colectomy in patients < 18 y 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. Annual colonoscopy if surgery is delayed.
- 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.
- Other than colon cancer, screening recommendations are expert opinion rather than evidence based.

**CLASSICAL FAP TREATMENT AND SURVEILLANCE: PERSONAL HISTORY**

- **Colon cancer:**
  - Annual sigmoidoscopy and polypectomy or polyp ablation if adenoma burden is low (in patients with retained rectum).
  - Consider NSAID chemoprevention to reduce polyp burden as pharmacologic adjunct to endoscopic surveillance. Clinical trial is encouraged.
- **Extracolonic:**
  - Duodenal or periampullary cancer: baseline upper endoscopy (including side-viewing examination) at the time of colectomy or at age 25-30 y, whichever comes first, and repeat every 1-3 y, depending on severity of polyposis.
  - Gastric cancer: same as duodenal cancer.
  - Thyroid cancer: annual thyroid examination, starting in late teenage years.
  - CNS cancer: annual physical examination; no additional screening recommendations have been made.
  - Intra-abdominal desmoids: annual abdominal palpation; after colectomy, consider abdominal and pelvic CT or MRI every 3 y, especially if family history of desmoids.
  - 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: AFP. Screening in a clinical trial is preferred.
  - Pancreatic cancer: no recommendations have been made. Consider liver palpation, abdominal ultrasound and measurement of , every 3-6 mo, during first y of life.

**SURVEILLANCE**

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

**DUODENOSCOPIC FINDINGS**

- 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, and 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 and dense polyposis or high-grade dysplasia that cannot be managed endoscopically.
FAMILIAL ADENOMATOUS POLYPOSIS  Colorectal Cancer Screening Version 1:2010

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

Genetic Testing

- APC gene positive
  - Flexible sigmoidoscopy or colonoscopy every 12 mo beginning at age 10-15 y
  - If adenomas, follow pathway for Personal History of Classical FAP (page 30)

- APC gene negative
  - Average-risk screening
  - Not tested
    - Flexible sigmoidoscopy or colonoscopy beginning at age 10-15 y:
      - Every 12 mo until age 24 y
      - Every 2 y until age 34 y
      - Every 3 y until age 44 y
      - Then every 3-5 y thereafter
      - Consider substituting colonoscopy every 5 y beginning at age 20 y for the chance that patient may have attenuated FAP

Surveillance

- Family history of classical FAP, mutation known
  - APC gene testing for at-risk family member
    - APC gene testing for at-risk family member
      - APC gene positive
      - APC gene negative
      - Not tested

  - If mutation found, follow pathway for Family History of Classical FAP, Mutation Known (opposite page)

  - Mutation in family not found
    - Affected family member not available
      - Consider APC gene testing for at-risk family member

  - APC gene testing of affected family member
    - Consider MYH testing

  - Not tested
    - Family history of classical FAP, mutation unknown
      - APC gene testing for at-risk family member
        - APC gene testing for at-risk family member
          - APC gene positive
          - APC gene negative
          - Not tested

      - If polyposis detected, follow pathway on (page 30)

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.
**CLASSICAL FAP GENETIC TESTING AND SURVEILLANCE: FAMILY HISTORY OF CLASSICAL FAP MUTATION UNKNOWN**

**GENETIC TESTING**

If mutation found, follow pathway for Family History of Classical FAP, Mutation Known (opposite page)

Mutation in family not found

**SURVEILLANCE**

Flexible sigmoidoscopy or colonoscopy beginning at age 10-15 y:
- Every 12 mo until age 24 y
- Every 2 y until age 34 y
- Every 3 y until age 44 y
- Then every 3-5 y thereafter

Consider substituting colonoscopy every 5 y beginning at age 20 y in addition to the sigmoidoscopy examinations

If polyposis detected, follow pathway on (page 30)

---

**Family history of classical FAP, mutation unknown**

APC gene testing of affected family member

Consider MYH testing

Affected family member not available

APC gene testing of affected family member not available

Consider MYH testing

Mutation in family not found

No mutation found

Not tested

---

**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.**

**See MYH-Associated Polyposis (page 38).**

**When polyposis is present in a single person with negative family history, testing for a de novo APC mutation should be considered; if negative, testing for MYH should follow. When family history is positive only for a sibling, recessive inheritance should be considered and testing for MYH should occur first. In a polyposis family with clear autosomal dominant inheritance and absence of APC mutation, MYH testing is unlikely to be informative. These families are treated according to the polyposis phenotype, including classical or attenuated FAP.**
### Total Abdominal Colectomy With Ileorectal Anastomosis (TAC/IRA)

- **Indications:**
  - Asymptomatic patient with few (< 20) rectal polyps and mild colonic disease (< 100) polyps
  - Attenuated FAP with rectal sparing

- **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 function outcome
  - No permanent or temporary stoma
  - Avoids risk for proctectomy (sexual or bladder dysfunction)

- **Disadvantages:**
  - Functional results can be unpredictable

### Total Proctocolectomy With Ileal Pouch Anal Anastomosis (TPC/IPAA)

- **Indications:**
  - After TAC/IRA with unstable rectum
  - Patient unreliable for follow-up after TAC/IRA
  - Severe disease in colon and/or rectum
  - Curable colon or rectal cancer

- **Contraindications:**
  - Incurable cancer
  - Intra-abdominal desmoid
  - Advanced low rectal cancer
  - Patient not a candidate for IPAA (e.g., has concomitant Crohn’s disease or anal sphincter dysfunction)

- **Advantages:**
  - Negligible risk for rectal cancer
  - No permanent stoma
  - Reasonable bowel function

- **Disadvantages:**
  - Complex operation
  - Usually involves temporary stoma
  - Risks of proctectomy (sexual or bladder dysfunction)
  - Functional results can be unpredictable

### 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 contraindication to IPAA

- **Advantages:**
  - Removes risk for colorectal cancer
  - One operation

- **Disadvantages:**
  - Risks for proctectomy
  - Permanent stoma
  - May discourage family members from seeking evaluation for fear of permanent stoma
## ATTENUATED FAP TREATMENT AND SURVEILLANCE: PERSONAL HISTORY

<table>
<thead>
<tr>
<th>ADENOMA/POLYP BURDEN</th>
<th>TREATMENT</th>
<th>SURVEILLANCE f,g</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 21 y with small adenoma burden c</td>
<td>• Colonoscopy and polypectomy every 1-2 y&lt;br&gt;• Surgical evaluation and counseling</td>
<td>• If colectomy, annual endoscopic examination of the rectum&lt;br&gt;• Annual physical examination&lt;br&gt;• Consider NSAID and chemoprevention to reduce polyp burden as pharmacologic adjunct to endoscopic surveillance. Clinical trial is encouraged.</td>
</tr>
<tr>
<td>≥ 21 y with small adenoma burden c</td>
<td>• Colectomy d and ileorectal anastomosis (IRA) e or colonoscopy and polypectomy every 1-2 y&lt;br&gt;• Surgical evaluation and counseling</td>
<td>• Baseline upper endoscopy beginning at age 25-30 y&lt;br&gt;See Duodenoscopic Findings (page 31)</td>
</tr>
<tr>
<td>≥ 40 y with small adenoma burden c</td>
<td>• Strongly consider colectomy d and IRA e&lt;br&gt;• Surgical evaluation and counseling</td>
<td></td>
</tr>
<tr>
<td>Significant polyposis not manageable with polypectomy</td>
<td>• Colectomy d with IRA (preferred in most cases) or proctocolectomy with ileal J-pouch anal anastomosis based on burden of disease in rectum e</td>
<td></td>
</tr>
</tbody>
</table>

---

a APC gene testing is recommended in a proband to confirm a diagnosis of attenuated FAP 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.
b Consider MYH testing if APC mutation not found (see page 38).
c Small adenoma burden is defined (somewhat arbitrarily) as < 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. Surgery is strongly advised when polyp burden is > 20, some polyps have reached a size > 1 cm, or advanced histology is encountered in any polyp.
d See Surgical Options for Treating the Colon and Rectum in Patients with FAP (opposite page).
e Earlier surgical intervention should be considered in patients < 40 years with family history of cancer or those who are noncompliant.
f 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.
g Surveillance for upper gastrointestinal findings for attenuated FAP is similar to that for classical FAP.
**ATTENUATED FAMILIAL ADENOMATOUS POLYPOSIS**  
Colorectal Cancer Screening Version 1:2010

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

**GENETIC TESTING**

- Family history of attenuated FAP, mutation known → APC testing for at-risk family member
  - APC positive → Colonoscopy beginning in late teens, then every 2-3 y
  - APC negative → Average-risk screening
- Not tested → Colonoscopy beginning in late teens, then every 2-3 y

**SURVEILLANCE**

- If adenomas, follow pathway for Personal history of attenuated FAP, adenoma/polyp burden (page 35)
- If no polyps, continue screening

---

*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.*
ATTENUATED FAP GENETIC TESTING AND SURVEILLANCE: FAMILY HISTORY OF ATTENUATED FAP MUTATION UNKNOWN

GENETIC TESTING

If APC mutation found, follow pathway for family mutation known (opposite page)

- Family history of attenuated FAP, mutation unknown
  - Consider APC testing of affected family member
    - Consider MYH testing

APC mutation in family not found

- No mutation found
  - Colonoscopy beginning in late teens, then every 2-3 y
  - If adenoma, see page 35
  - Not tested

- APC mutation found
  - Consider APC testing for at-risk family member
    - Consider MYH testing
      - If APC mutation negative
  - Affected family member not available

SURVEILLANCE

- Colonoscopy beginning in late teens, then every 2-3 y

h 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.

i See MYH-Associated Polyposis (page 38).

j When polyposis is present in a single person with negative family history, consider testing for a de novo APC mutation; if negative, follow with testing for MYH. When family history is positive only for a sibling, recessive inheritance should be considered and testing for MYH should occur first. In a polyposis family with clear autosomal dominant inheritance and absence of APC mutation, MYH testing is unlikely to be informative. These families are treated according to the polyposis phenotype, including classical or attenuated FAP.
MYH-ASSOCIATED POLYPOSIS

MYH-Associated Polyposis (MAP):
- Polyposis or colon cancers consistent with autosomal recessive inheritance (i.e., parents unaffected, siblings affected)
- < 100 adenomas (range 0-100’s and uncommonly > 1000)
- Adenomas and colorectal cancer at age older than classical FAP (median CRC age > 50 y)
- Duodenal adenomas are uncommon
- Attenuated polyposis with negative APC gene mutation

RISK ASSESSMENT

Personal history
or
Family history
(i.e., known mutation in patient or sibling)

PHENOTYPIC FEATURES

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MYH-ASSOCIATED POLYPOSIS

**GENETIC COUNSELING/TESTING OF ELIGIBLE FAMILY MEMBERS**

- **Personal history of multiple adenomatous polyps (> 10 adenomas with negative APC mutation testing)**
  - Counseling and testing for MYH mutations
  - Biallelic MYH mutation negative → Manage individually as multiple adenomatous polyps (page 29)
  - Biallelic MYH mutation positive
    - Small adenoma burden manageable by colonoscopy and polypectomy
    - Dense polyposis or large polyps not manageable by polypectomy

- **Family history of sibling with MYH polyposis, asymptomatic; Counseling and testing for the familial mutations is recommended**
  - Mutation status unknown or biallelic MYH mutations known
  - Counseling and testing for MYH mutations

**TREATMENT/SURVEILLANCE**

- **Biallelic MYH mutation negative**
  - Colonoscopy and polypectomy every 1-2 y
  - Consider upper endoscopy and side-viewing duodenoscopy beginning at age 30-35 y and every 3-5 y
  - Patients with duodenal adenomas are treated as FAP (See Duodenoscopic Findings; page 31)

- **Biallelic MYH mutation positive**
  - Small adenoma burden manageable by colonoscopy and polypectomy
  - Dense polyposis or large polyps not manageable by polypectomy
  - Counseling regarding surgical options
  - Subtotal colectomy or proctocolectomy depending on adenoma density and distribution
  - Upper endoscopy and side-viewing duodenoscopy at age 30-35 y and every 3-5 y
  - Patients with duodenal adenomas are treated as FAP (See Duodenoscopic Findings; page 31)

- **Mutation status unknown or biallelic MYH mutations known**
  - Colonoscopy and polypectomy every 1-2 y
  - Consider upper endoscopy and side-viewing duodenoscopy at age 30-35 y and every 3-5 y
  - Patients with duodenal adenomas are treated as FAP (See Duodenoscopic Findings; page 31)

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a When polyposis is present in a single person with negative family history, consider testing for a de novo APC mutation; if negative, follow with testing for MYH. When family history is positive only for a sibling, consider recessive inheritance and test for MYH first. In a polyposis family with clear autosomal dominant inheritance, and absence of APC mutation, MYH testing is unlikely to be informative. Such families are treated according to the polyposis phenotype, including classical or attenuated FAP.

b In patients with MYH, the absolute risk of colorectal cancer and the role of surgery and endoscopically manageable adenomas is not known. The lifetime colon cancer risk may be very high.
**Peutz-Jeghers Syndrome (PJS) Definition:**
- A clinical diagnosis of PJS can be made when an individual has 2 or more of the following features:
  - Two or more PJS-type hamartomatous polyps of the small intestine
  - Mucocutaneous hyperpigmentation of the mouth, lips, nose, eyes, genitalia, or fingers
  - Family history of PJS

**Surveillance Considerations:**
- More cases occur because of mutations in the STK11/LKB1 gene and 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 (see below) if symptoms have not already occurred; any early symptoms should be evaluated thoroughly.
- The surveillance guidelines (see below) 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 efficacy of the tests. Data are limited regarding the efficacy of various screening modalities in PJS.

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

<table>
<thead>
<tr>
<th>Site (% Risk)</th>
<th>Screening Procedure and Interval</th>
<th>Initiation Age (y)</th>
</tr>
</thead>
</table>
| Breast (45%-50%) | • Mammogram and breast MRI annually  
 • Clinical breast exam every 6 mo | ~ 25 y |
| Colon (39%) | Colonoscopy every 2-3 y | ~ Late teens |
| Pancreas (11%-36%) | • Magnetic resonance cholangiopancreatography and/or endoscopic ultrasound every 1-2 years  
 • CA 19-9 at similar intervals | ~ 30 y |
| Stomach (29%) and small intestine (13%) | Upper endoscopy every 2-3 y and small bowel visualization (CT enterography, small bowel enteroclysis) every 2-3 y, or with symptoms | ~ 10 y |
| Ovary (18%-21%), cervix (10%), uterus (9%) | • Pelvic examination and PAP smear annually  
 • Consider transvaginal ultrasound | ~ 18-20 y |
| Testes | Annual testicular exam and observation for feminizing changes | ~ 10 y |
| Lung (15%-17%) | No specific recommendations have been made. Provide education about symptoms and smoking cessation. | |

2 Because of the rarity of the syndrome and complexities of diagnosing and managing individuals with PJS, referral to a specialized team is recommended.
Juvenile Polyposis Syndrome (JPS) Definition:\(^1\)
- A clinical diagnosis of JPS is considered in an individual who meets at least 1 of the following criteria:
  - At least 3-5 juvenile polyps of the colon
  - Multiple juvenile polyps found throughout the gastrointestinal tract
  - Any number of juvenile polyps in an individual with a family history of JPS

Surveillance Considerations:
- Some JPS cases occur due to mutations in the BMPR1A and SMAD4 genes and clinical genetic testing is available.
- Referral to a specialized team is recommended and participation in clinical trials is especially encouraged.
- Surveillance should begin at these approximate ages listed below if symptoms have not already occurred; any early symptoms should be evaluated thoroughly.
- The following surveillance guidelines for the multiple organs at risk for cancer may be considered. Limited data exist regarding the efficacy of various screening modalities in juvenile polyposis syndrome.

### Juvenile Polyposis Syndrome: Cancer Risk and Surveillance Guidelines

<table>
<thead>
<tr>
<th>Site (% Risk)</th>
<th>Screening Procedure and Interval</th>
<th>Initiation Age (y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon (40%-50%)</td>
<td>Colonoscopy: repeat annually if polyps are found; if no polyps, repeat every 2-3 y</td>
<td>~ 15 y</td>
</tr>
<tr>
<td>Stomach (21% if multiple polyps)</td>
<td>Upper endoscopy: repeat annually if polyps are found; if no polyps, repeat every 2-3 y</td>
<td>~ 15 y</td>
</tr>
<tr>
<td>Small intestine (rare, undefined)</td>
<td>No recommendations have been made</td>
<td></td>
</tr>
<tr>
<td>Pancreas (rare, undefined)</td>
<td>No recommendations have been made</td>
<td></td>
</tr>
</tbody>
</table>

\(^1\)Because of the rarity of the syndrome and complexities of diagnosing and managing individuals with JPS, referral to a specialized team is recommended.
Hyperplastic Polyposis Syndrome Definition: ¹
- A clinical diagnosis of hyperplastic polyposis is considered in anyone who meets at least 1 of the following criteria:
  - > 20-30² cumulative hyperplastic polyps distributed throughout the colon³
  - > 5 hyperplastic polyps proximal to the sigmoid colon with 2 > 1 cm
  - > 1 hyperplastic polyp proximal to the sigmoid colon and a first-degree relative with hyperplastic polyposis
- Hyperplastic polyposis syndrome is rarely inherited

Surveillance Recommendations for Individuals With Hyperplastic Polyposis:
- Colonoscopy with polypectomy until all polyps ≥ 5 mm are removed, then colonoscopy every 1-3 y depending on number and size of polyps. Clearing of all polyps is preferable but not always possible.
- Consider surgical referral if colonoscopic treatment and/or surveillance inadequate or if high-grade dysplasia occurs.

Surveillance Recommendations for Individuals With a Family History of Hyperplastic Polyposis:
- The risk for colorectal cancer in relatives of individuals with hyperplastic polyposis is still unclear.
- First-degree relatives should be encouraged to undergo average-risk screening colonoscopy. Increased screening may be warranted for individuals with a family history of multiple adenomas and/or colorectal cancer.

¹ Sessile serrated polyps, traditional serrated polyps, and/or mixed adenomas can be substituted for hyperplastic polyps in all parts of the definition.
² The total number of polyps necessary to make a diagnosis of hyperplastic polyposis is unclear. A lower threshold of polyps (> 20) has also been used to diagnose hyperplastic polyposis.
³ Multiple hyperplastic polyps localized to the rectal sigmoid is unlikely to be hyperplastic polyposis syndrome.
controlled trials directly show mortality reduction with colonoscopy, findings from case-control and cohort studies show significant impact of colonoscopy and polypectomy on CRC incidence, estimated at a more than 50% reduction.1-6

In a recent 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 odds ratio [OR], 0.33; 95% CI, 0.28–0.39) but not right-sided (OR, 0.99; CI, 0.86–1.14).7 Part of this finding may be related to significant variation in the quality of this widely used procedure within the community, which can lead to variable effectiveness.8,9 The quality indicators of colonoscopy (e.g., withdrawal times) and minimum requirements of a colonoscopy report are listed on pages 16 and 17. 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° view of front and back side of all folds, withdrawal time longer than 10 minutes, and complete excision of polyps (may require extra snare/biopsy or cautery after initial polypectomy).

An optimal screening protocol should have an interval during which there is a low likelihood of developing cancer and be cost-effective based on the duration of risk reduction after 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 emphasizes 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.10 Only 1 of 154 individuals had a polyp 1 cm or larger. These results suggest that an interval of repeat colonoscopy after an initial negative colonoscopy beyond 5 years is safe.

Imperiale et al.11 reported on 2436 individuals with no adenomas at baseline colonoscopy. No cancers were found at rescreening at a mean of 5.3 years later. Adenomas were identified in 16%, and only 1.3% had advanced adenomas. The authors recommended a rescreening interval of 5 years or longer. Lieberman et al.12 reported that advanced adenomas were found in only 2.4% of individuals on repeat colonoscopy within 5.5 years after a baseline normal colonoscopy. In this study, individuals with adenomatous polyps smaller than 1 cm at baseline also had a low rate of developing advanced neoplasia.

Further studies have evaluated the durability of risk reduction 10 years after an endoscopic evaluation. In an early study evaluating the value of rigid sigmoidoscopy for CRC screening, individuals who underwent rigid sigmoidoscopy within 10 years before being diagnosed with colon cancer were compared with a cohort of matched controls.13 The negative association was 0.41 risk reduction (95% CI, 0.25–0.69) in the proctosigmoidoscopy group. In a population-based retrospective analysis using a physician billing claims database of individuals who underwent a screening colonoscopy, Singh et al.14 also assessed the time that risk reduction persists after colonoscopy. They compared incidence of CRC among patients in the surveillance cohort with that in the general population. 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 who had a previous negative colonoscopy;15 the adjusted OR 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. In a study of 564 participants, Robertson et al.16 recently reported that combining results of 2 prior colonoscopies can help predict the likelihood of high-risk findings (advanced adenomas or cancers) on the third screen.

Flexible Sigmoidoscopy
Flexible sigmoidoscopy followed by colonoscopic polypectomy significantly reduced mortality risk in earlier case-control studies.6,17 Currently, 4 randomized studies are ongoing in the United States and Europe.18-21 Compared with colonoscopy, this technique requires no sedation and less bowel preparation, but is limited to examination of the lower half of the colon tract. 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 polyps (SSP; flat adenomas are unusual and may be missed during colonoscopy). Patients with lesions larger than 1 cm should be referred directly for a colonoscopy, because these lesions are almost always adenomas associated with a risk for proximal colonic neoplasms.

**Double-Contrast Barium Enema**
The availability of and physicians’ experience with double-contrast barium enema are decreasing. This technique is typically only used as an alternative for patients who cannot undergo colonoscopy.

**CT Colonography**
CT colonography (CTC; see page 17), also known as virtual colonoscopy, is evolving as a promising technique for CRC screening. CTC has the advantages of being noninvasive and not requiring sedation, and the risk for test-related complications is very low. However, a positive finding requires a colonoscopy, and extra-colonic findings—which are present in up to 16% of patients—pose a dilemma.22,23 These findings require further investigation and have a potential for benefit and harm. Data are currently insufficient to determine the clinical impact of these findings.

The recently completed National CT Colonography Trial (ACRIN 6664) organized by the American College of Radiology assessed the accuracy of CTC in detecting polyps or cancers measuring 10 mm or more.24 Among the 2531 patients participating in the study, 128 large adenomas or carcinomas were found in 109. CTC detected polyps or cancers in 90% of patients who had lesions measuring 10 mm or larger found with colonoscopy. There were 18 lesions found on CTC, but not colonoscopy, for which a subsequent colonoscopy was performed; 5 of these lesions were confirmed to include 4 adenomas and 1 inflammatory polyp. CTC performance in this study was better than that reported in earlier studies25,26 and similar to what was reported by Pickhardt et al.27

In 2005, 2 meta-analysis reviewed the performance of CTC for detecting colorectal polyps.28,29 In one meta-analysis, CTC showed high average sensitivity (93%) and specificity (97%), both of which decreased to 86% when medium polyps were included in the analysis. The sensitivity of CTC was heterogeneous but improved as the polyp size increased in another meta-analysis (48% for polyps < 6 mm, 70% for those 6–9 mm, and 85% for those > 9 mm). The specificity was uniform (92%) for detection of all the polyps. Kim et al.30 compared CTC with colonoscopy for detecting advanced neoplasia. Although this study was not randomized, detection rates were comparable between the groups (3.2% for CTC and 3.4% for colonoscopy).

The technical aspects of CTC, including imaging, preprocedure preparation, use of stool tagging, and expertise of the interpreter, differ among studies and have not been standardized. Long-term follow-up studies of patients screened with CTC are not yet available.

The issue of radiation exposure also requires consideration. The reported dose of radiation exposure during CTC is approximately 10 mSv. The precise risk from life-long screening cannot be estimated, but experts have suggested that 1 additional person in 1000 would develop cancer in a lifetime after being exposed to radiation at the dose used for CTC.31

Available data indicate that CTC may be useful for detecting larger polyps. However, this technique is still evolving in terms of 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 no consensus on the use of CTC as a primary screening tool.

**Fecal-Based Screening Tests**
Fecal tests are designed to detect signs of cancer in stool samples, specifically occult blood or, more recently, alterations in exfoliated DNA. In contrast with 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 for structural tests. Any positive stool test must be followed by colonoscopy.

**Fecal Occult Blood Test**
Two fecal occult blood tests (FOBT) are currently available: guaiac-based and immunochemical. These may be used alone annually or in combination with flexible sigmoidoscopy. Based on the pseudoperoxi-
Stool DNA test 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 single-target markers such as K-ras produced less than 40% sensitivity. To improve sensitivity, newer tests with multipanel markers were developed.

### Risk Assessment

These guidelines stratify patients into 3 groups depending on their risk for CRC (page 10). Colorectal screening is particularly important for African Americans because of a higher risk for incidence and mortality. Communicating to the patient and referring physician any updated CRC risk assessment and screening plan based on family history, colonoscopy, and pathology findings is highly encouraged.

#### Average Risk

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

#### Increased Risk

Individuals with personal history of adenomas/

Hemoccult II and Hemoccult II Sensa, which is the most sensitive and reader-friendly. One major disadvantage of the guaiac FOBT is that it may miss tumors that bleed in smaller amounts, intermittently, or not at all. To compensate for intermittent bleeding, guaiac FOBTs should be performed on 3 successive stool specimens obtained while the patient adheres to a prescribed diet. Another limitation is the high false-positive rate resulting from reaction with non-human heme in food and blood from the upper gastrointestinal tract.

The technique currently recommended is Hemoccult II SENSa, which is the most sensitive and reader-friendly. One major disadvantage of the guaiac FOBT is that it may miss tumors that bleed in smaller amounts, intermittently, or not at all. To compensate for intermittent bleeding, guaiac FOBTs should be performed on 3 successive stool specimens obtained while the patient adheres to a prescribed diet. Another limitation is the high false-positive rate resulting from reaction with non-human heme in food and blood from the upper gastrointestinal tract.

The 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 (25%–72%) and specificity (59%–97%) vary widely, as illustrated by a recent German study that assessed 6 different FIT methods on 1319 participants.

Comparative studies generally show that detection rates for FIT are comparable, if not superior, to guaiac FOBT depending on the test used. For example, in the study by Allison et al., FIT had a sensitivity of 69% for cancer, which was between that for Hemoccult II and Hemoccult II Sensa. An update study by the same group showed that a newer FIT had a higher sensitivity for detecting cancer than Hemoccult Sensa (82% vs. 64%). A recent Dutch randomized study also showed that FIT had higher detection rates for advanced neoplasia (2.4%) than guaiac FOBT (1.1%), although both were less reliable than flexible sigmoidoscopy (8%).

To ensure adequate follow-up, health care professionals should coordinate FOBT testing so that patients with positive results enter the health care system in a responsible way. FOBT of a single specimen obtained at digital rectal examination is not recommended because of exceptionally low sensitivity.

### Stool DNA Test

Stool DNA test 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 single-target markers such as K-ras produced less than 40% sensitivity. To improve sensitivity, newer tests with multipanel markers were developed. In a large multicenter study of 4404 patients, eligible subjects submitted 1 stool specimen for DNA analysis, underwent standard Hemoccult II testing, and then had a colonoscopy. In a subgroup analysis, the multitarget DNA assay SDT-1 (21 mutations) detected 52% of CRC compared with 13% by Hemoccult at 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 (APC, K-ras, and vimentin methylation). A total of 3764 average-risk healthy adults underwent screening colonoscopy, Hemoccult, Hemoccult Sensa, SDT-1, and SDT-2. The sensitivities of SDT-1 and Hemoccult Sensa were very similar for screen-relevant neoplasms (20% and 21%, respectively), whereas the sensitivity of SDT-2 was 40%.
SSP, CRC, or inflammatory bowel disease, and those with a positive family history of CRC or advanced adenomas are considered at increased risk for developing CRC.

High-Risk Syndromes
Individuals with family history of Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer [HNPCC]), or personal or family history of polyposis syndromes are considered high-risk.

Individuals at Average Risk
CRC risk assessment in persons without known family history is advisable by 40 years of age to determine the appropriate age for initiating screening. It is recommended that screening for persons at average risk begin at age 50 years after discussion of available options (page 11).

Currently recommended options include colonoscopy every 10 years, annual fecal-based tests, flexible sigmoidoscopy every 5 years using a 60 cm or longer scope, combination of annual fecal tests and sigmoidoscopy every 5 years, or CTC every 5 years. However, any screening is better than none.

If available, colonoscopy is the preferred screening modality for individuals at average risk. If the colonoscopy is incomplete, other screening methods (including double-contrast barium enema) 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, such as stool tests, flexible sigmoidoscopy (biopsy-proven adenoma), CTC, and double-contrast barium enema. 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 given to polyps on the right side of the colon tract, because 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 Individuals at Increased Risk, opposite column). Villous adenomas have a greater chance of harboring cancer and having adenomas or cancer found on follow-up.

SSP and Flat Adenomas: SSP, also known as sessile serrated adenomas, are rare forms of polyps associated with adenocarcinoma. The pathologic classification is currently controversial and guidelines for screening these polyps are not clearly established. Patients with SSP may need more frequent screening than those with hyperplastic polyps. Pending additional data, individuals with SSP should be treated following the same guidelines for those with adenomas.

Flat adenomas 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 contribution to CRC risk. Meanwhile, all identified flat adenomas should be removed and patients should undergo routine post-adenoma follow-up.

Hyperplastic Polyps: A large body of literature indicates that hyperplastic polyps are not associated with 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—the hyperplastic polyposis syndrome (HPP; see page 42 for definition)—have a 26% to 70% risk for developing CRC. Most of these had concomitant adenomas or SSP. Additionally, evidence suggests that some cancers with extensive DNA methylation and MSI might derive from hyperplastic polyps.

Based on these observations, all hyperplastic polyps larger than 5 mm should be removed during the initial colonoscopy and polypectomy session, and patients should undergo colonoscopy every 1 to 3 years thereafter. Ideally, all detected polyps should be removed, but this is not always possible. Removed polyps should also be examined for degree of dysplasia and histologic features of SSP. HPP is rarely reported to be inherited, and the risk for developing CRC in individuals with affected relatives remains unclear.

Individuals at Increased Risk

Personal History of Adenoma/SSP
Individuals with adenomas are at increased risk for developing recurrent adenomas and CRC. To minimize risk for developing CRC, a surveillance program is recommended after screening colonoscopy and complete polypectomy. For patients with a
completely resected adenomatous polyp, the surveillance schedule depends on risk for recurrence, which is in turn related to the number of adenomatous polyps and their size and histology.

Low-risk adenomas are tubular, 2 or fewer in number, and smaller than 1 cm. In this group, colonoscopy should be repeated within 5 years. Emerging data suggest that longer intervals are usually appropriate. If this examination is normal, colonoscopy should be repeated every 5 to 10 years.

Advanced or multiple adenomas (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 carcinoma in situ (severe architectural disturbance of glands along with cytologic features of dysplasia). Carcinaoma in situ is a term previously used by pathologists to describe colon polyps and cancer, and is currently being replaced by the term high-grade dysplasia. A study by Golombetski et al. showed that identification of villous architecture and high-grade dysplasia is associated with poor reproducibility among pathologists.

Because studies have used 1 cm as the standard measure, data are lacking on the relative significance of intermediate-sized adenomas (5–10 mm). Individuals with high-risk adenomas 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. Reassessing risk, including contributing medical and personal factors, number and characteristics of adenomas, and family history, is appropriate at each interval before and after procedures.

Individuals with more than 10 cumulative adenomas are recommended to undergo evaluation for a polyposis syndrome, although only a small fraction of those with no family history and low adenoma burden will have a defined hereditary syndrome. Fewer than 10 polyps may infrequently be associated with an inherited polyposis syndrome, especially in patients younger than 40 years or with a strong family history. Hence, a detailed family history is crucial in patients with multiple adenomas. 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 polypectomy. Hence, follow-up colonoscopy within 2 to 6 months is appropriate, or when polypectomy is incomplete or involves removal of large sessile polyps.

The NCCN Clinical Practice Guidelines in Oncology: Colon Cancer (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org) provide suggestions for management if a malignant polyp is found at colonoscopy.

**Personal History of CRC**

Individuals with a personal history of CRC who underwent colonic resection with curative intent are at increased risk for recurrent adenomas and cancer. The recommendation for intensive surveillance immediately after resection is based on studies that found a high recurrence rate in the 4 to 5 years after CRC resections. An analysis of 3278 patients with resected stage II and III CRC found that recurrence rate is especially high in the immediate 5 years after surgery, suggesting that intense surveillance be considered during that period (Intergroup 0089 study). However, the studies did not exclude patients with Lynch syndrome who are at greater than 30% risk for synchronous and metachronous cancers. The guidelines recommend a complete colonoscopy preoperatively and at 1 year after surgery (within 3–6 months if preoperative colonoscopy was incomplete). If this examination is normal, colonoscopy should be repeated in 2 to 3 years. Shorter intervals (1–3 years) are recommended if adenomas or SSP are found. Subsequent colonoscopic intervals are individualized and generally should not exceed 5 years.

Patients with rectal cancer should also undergo periodic rigid or flexible sigmoidoscopy of the rectal anastomosis to identify local recurrence. Expert opinion supports repeat evaluation every 3 to 6 months for the first 2 to 3 years. The usefulness of routine endoscopic ultrasound for early surveillance is not defined.

**Inflammatory Bowel Disease**

Individuals with a personal history of inflammatory bowel disease are known to be at increased risk for developing CRC. Screening with colonoscopy every 1 to 2 years should be initiated 8 to 10 years after the onset of symptoms and be performed by an en-
A doscopist who is familiar with the appearance of ulcerative colitis or Crohn’s disease. When the disease is clinically quiescent, multiple 4-quadrant biopsies (every 10 cm with ≥ 30 samples) should be taken for histologic examination using large-cup forceps. Strictures, particularly those in ulcerative colitis, that are suggestive should be evaluated thoroughly using biopsy and brush cytology. Any masses, including so-called “dysplasia-associated” lesions, are of extreme concern. Endoscopic polypectomy should be performed when appropriate with biopsies of surrounding mucosa to assess dysplasia.

Interpretation of dysplasia or intraepithelial neoplasia can be difficult. Pathologists experienced in interpreting inflammatory bowel disease lesions should evaluate biopsies. Most findings of high-grade, multifocal, or repeat low-grade dysplasia place patients with ulcerative colitis at high-risk for developing CRC. Prophylactic proctocolectomy with ileoanal anastomosis is preferred. These individuals should be referred to a surgeon experienced in inflammatory bowel disease to discuss surgical options. See page 18 for common colorectal resections.

**Family History**

Family history is the most important risk factor for CRC. A detailed family history must be obtained, including first-degree relatives (parents, siblings, and offspring), second-degree relatives (aunts, uncles, grandparents, and half-siblings), and other 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 relative, current age and age at diagnosis of any cancer; availability of a tumor sample; or date, age, and cause of death are very important in 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.

**Positive Family History:** Individuals with 1 or more first-degree relative diagnosed with CRC are at increased risk for developing the malignancy (see page 15). Colonoscopy every 5 years beginning at 40 years of age is recommended for those with a first-degree relative diagnosed with CRC between 50 and 60 years. If the relative was diagnosed at 60 years of age or older, screening should begin at 50 years and repeated every 5 years. The same screening schedule is recommended for individuals who have 2 second-degree relatives diagnosed with CRC at any age.

For individuals with 1 first-degree relative diagnosed with CRC before 50 years of age or 2 diagnosed with CRC at any age, screening colonoscopy is recommended beginning at 40 years, or 10 years before earliest CRC in family, whichever is earlier. Screening interval will depend on other family history but should be between every 3 and 5 years. Additionally, this family history (or if any of the revised Bethesda criteria are met) suggests the possibility of Lynch syndrome (page 22), and immunohistochemical (IHC)/MSI testing on the colon tumor of the youngest affected family member is warranted.

Having a first-degree relative with advanced adenomas may confer similar CRC risk as having one with CRC. Similarly, having one with early-onset adenomas (< 40 years of age) may confer similar CRC risk as having one with early-onset CRC (< 50 years of age).

Persons who have a second-degree or any number of third-degree relatives with CRC, or individuals with a first-degree relative with nonadvanced adenomas are screened as average-risk individuals, with colonoscopy as the preferred method. However, individualized risk assessment is recommended and should include a careful family history to determine whether a familial clustering of cancers is present in the extended family.

In all cases, further risk evaluation and counseling as outlined on page 19 are required for patients who meet the criteria for an inherited CRC syndrome.

**Inherited Colon Cancer**

Genetic susceptibility to CRC includes well-defined inherited syndromes, such as Lynch syndrome (HNPCC), familial adenomatous polyposis (FAP), and MYH-associated polyposis (MAP).

Other entities that are important to recognize include suspected colon cancer syndromes, such as Muir-Torre, Turcot, and Peutz-Jeghers syndromes, juvenile polyposis, or HPP. These syndromes are also critical to understanding what could be the potential genetic basis for cancer in the family. If
a concern exists about the presence of a hereditary syndrome, the guidelines recommend referring the patient to a genetic service or counselor. Inclusion criteria and details for risk evaluation are listed on pages 20 through 21.

The newly developed test for I1307K, a mutation found among Ashkenazi Jews that predisposes them to CRC, has been excluded from the guidelines because very little evidence is available on what kind of screening should be offered to individuals with this mutation.

After evaluation, individuals 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 (page 40) or juvenile polyposis (page 41). Individuals with a familial risk and no syndrome should be managed as described for those with positive family history.

Lynch Syndrome (HNPCC)

Lynch syndrome is the most common form of a genetically determined colon cancer predisposition, accounting for 2% to 3% of all CRC cases. This hereditary syndrome results from germline mutations in DNA mismatch repair (MMR) genes (MLH1, MSH2, MSH6, and PMS2), although associations with 3 other genes (MLH3, PMS1, EXO1) have also been found. MMR mutations are detected in more than 50% of individuals meeting the clinical criteria of Lynch syndrome, and the lifetime risk for CRC approaches 80% in affected individuals carrying a mutation in 1 of these genes. MSI occurs in 85% to 90% of resulting CRCs. Surveillance has been shown to reduce the risk for developing CRC and may be beneficial for early diagnosis of endometrial cancer. Site-specific evaluation and heightened attention to symptoms are also advised for other cancers that occur with increased frequency in affected persons, including gastric, ovarian, pancreas, urethral, brain (glioblastoma), and small intestinal cancers, and sebaceous gland adenomas and keratoacanthomas, although efficacy of surveillance for these sites has not been clearly shown (reviewed by Lindor et al.).

Risk factors for the presence of Lynch syndrome related to the extended family history for individuals are listed on page 22. Because of the high risk for CRC in individuals with Lynch syndrome, intensive screening is essential, though the exact interval has not been fully established in clinical trials. Recommendations in this area are based on the best available evidence, but more data are still needed.

Molecular Workup

Genetic testing for Lynch syndrome is somewhat complicated because several different genes contribute to its development. MSI and IHC analysis of CRC specimens are frequently first used to identify individuals who might have Lynch syndrome (page 25). IHC analysis is used to detect the protein expression of the 4 MMR genes in tumor tissue. If one of the genes is not expressed, then underlying dysfunction of that gene is indicated. Both MSI and IHC have false-negative rates of 5% to 10%. 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 on which strategy is optimal.

MSI analysis of colon cancer tissue is very sensitive but less specific than IHC testing. The classical Bethesda guidelines provide several criteria for testing colorectal tumors for MSI. The National Cancer Institute introduced the revised Bethesda guidelines in 2002 (see page 26) to clarify selection criteria for the MSI testing. Bethesda guidelines are useful for determining which individuals should have MSI testing, leading to subsequent identification of MLH1 and MSH2 germline mutations. One study reported that MLH1 and MSH2 mutations were detected in 65% of patients with MSI of the colon cancer tissue who met the Bethesda criteria. MSI test is particularly helpful when the family history is not strongly suggestive of Lynch syndrome. Families that meet the minimal criteria for consideration, such as diagnosis before the age of 50 years (but meet no other criteria), may not represent the disorder. Microsatellite stable tumors arising within a patient with disease onset at a young age is unlikely to represent the disorder. Proceeding with genetic testing in this setting will probably not yield informative results.

IHC analysis is usually performed for family members who meet the Amsterdam criteria I or II (page 27), because there is a 50% to 92% chance of identifying a mutation in 1 of the 4 MMR genes in these individuals. The first version of the mini-
Genetic Testing

Some centers now perform IHC (and sometimes MSI) testing on all CRCs to determine which patients should undergo genetic testing for Lynch syndrome. The cost-effectiveness of this approach is uncertain. If Lynch syndrome is suspected based on the extended pedigree, an analysis of the tumor block for MSI provides diagnostic information and guidance on the likelihood of informative predictive testing. Screening for MSI is cost-effective for patients with newly diagnosed CRC and for the siblings and children of mutation carriers.77

Mutations found within a family provide an opportunity to perform predictive testing for at-risk family members, which can prevent many unnecessary procedures. Genetic testing should be considered for at-risk family members when the family mutation is known (page 23). At-risk family members can be defined as first-degree relatives 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.

If the familial mutation is not known in an individual who meets the revised Bethesda guidelines, the management plan depends on the results of IHC staining and/or MSI analysis as outlined in page 22. Almost all tumors arising within the context of Lynch syndrome are microsatellite unstable. If tumor is available from the affected relative and shows abnormal IHC and/or high MSI, genetic testing for mutations should be considered (page 23). Testing should proceed in the following order: the gene mostly likely mutated according to IHC results (if available), MLH1 or MSH2, then MSH6 or PMS2. Those with normal IHC and/or low/stable MSI but do not meet the more stringent Amsterdam criteria should be monitored with colonoscopy based on individual risk assessment. If they meet the Amsterdam criteria or if tumor from an affected family member is not available, then genetic testing for MMR mutations is recommended.

Because of the challenges that exist with using MSI testing and IHC staining of tumor tissue, several computer models have been developed to predict detection of a priori risk for Lynch syndrome mutation.78–80

For individuals who do not meet the revised Bethesda guidelines or Amsterdam criteria, individualized management should be considered based on the severity of family history.

Many other issues are involved in genetic counseling of individuals undergoing presymptomatic testing for cancer susceptibility. Many individuals elect not to undergo testing, and these individuals must be counselled to continue with increased surveillance.

Surveillance and Treatment Options

Individuals with Lynch syndrome are at an increased lifetime risk for developing CRC compared with the general population (80% vs. 6%, respectively), endometrial cancer (20%–60% vs. 3%, respectively), and other cancers (page 28).81,82 Screening study data in the literature mainly concern colon and endometrial cancers. More data are needed to evaluate the risk and benefits of extracolonic cancer screening. If Lynch syndrome can be confirmed, colonoscopy is advised to start between ages 20 and 25 years, or 10 years younger than the youngest age at diagnosis in the family, whichever comes first, and be repeated every 1 to 2 years. This recommendation is based on a systematic review of data between 1996 and 2006 on the reduction in cancer incidence and mortality using colonoscopy.83 For women, referral to a gynecologic oncologist should be considered to screen for endometrial and ovarian cancers. Total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH/BSO) is an option for women who have completed childbearing. Because patients are also at increased risk for gastric and duodenal cancer, upper gastrointestinal endoscopy every 1 to 3 years based on findings starting at age 25 to 30 years should be considered.83 The endoscopy session should include side-viewing examination for ampullary cancers. Annual urinalysis, which provides relative ease and low cost compared with other tests, should also be considered to screen for urothelial cancers. Because of the current lack of data, annual history and physical examination is appropriate for screening of other cancers (e.g., brain, pancreatic).

If there are no pathologic findings, continued screening is recommended. If the patient is not a
candidate for routine screening, subtotal colectomy may be considered. This important feature often arises clinically 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 disease-specific guidelines (see the NCCN Clinical Practice Guidelines in Oncology Table of Contents at www.NCCN.org). For patients with adenomas, recommendations include endoscopic polypectomy with a follow-up colonoscopy every 1 to 2 years. This option depends on the tumor location and characteristics, surgical risk, and patient preference. If the adenomas identified cannot be endoscopically resected, or high-grade dysplasia is identified, total abdominal colectomy with an ileorectal anastomosis (IRA) is recommended (page 18). Because 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 up with endoscopic rectal examination every 1 to 2 years.

When an individual tests negative for a known familial Lynch syndrome mutation and has no symptoms, they are no longer at a heightened cancer risk based on the mutation identified in their family. This does not mean they are at zero risk; rather they are at average risk, and routine screening is recommended.

FAP

FAP is an autosomal dominant condition characterized by a germline mutation in the APC gene, located on chromosome 5q21. Although FAP accounts for less than 1% of all CRC, its importance has been recognized as a paradigm for treating individuals at increased risk for cancer.

Diagnosis: Classical Versus Attenuated FAP

Diagnosis of classical FAP is based on the presence of more than 100 polyps, or fewer polyps at younger ages, especially in patients with a family history of FAP. When fully developed, patients exhibit hundreds to thousands of colonic adenomas. The lifetime risk for cancer in individuals with classic FAP approaches 100% by 50 years of age. Most of the resulting cancers occur in the left colon. Family members are increasingly being diagnosed at adolescence through genetic testing for their specific familial mutation or through sigmoidoscopic screening in the second decade of life. Because cancer incidence rises dramatically early in the third decade, prophylactic proctocolectomy is usually indicated in the second decade.

Attenuated FAP is a recognized variant of FAP characterized by a later onset of disease and fewer adenomas, typically fewer than 100. These adenomas are more prone to occur in the right colon and may take the form of diminutive sessile adenomas. Phenotypic expression is often variable within families. The onset of CRC is typically delayed, but the incidence of cancer rises sharply after the age of 40 years and approaches 70% by 80 years of age.

Management of FAP includes early screening and colectomy or proctocolectomy after the onset of polyposis. Genetic testing can guide management of cancer risk in patients and their family members. It is important to note the distinction between individuals with a personal history of FAP and individuals who are considered at high risk based on a family history of FAP (but no symptoms or findings). This distinction makes a significant difference in clinical management. Again, at-risk family members can be defined as first-degree relatives 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.

Fundic gland polyps (FGP) occur in most patients with FAP, classical and attenuated, and often are too numerous to count. In FAP, FGPs usually have biallelic inactivation of the APC gene, and often display foci of dysplasia or microadenomas of the foveolar epithelium. However, malignant progression in FGPs is uncommon and the lifetime risk for gastric cancer in patients with FAP in Western countries is reported to range from 0.5% to 1%. Endoscopic biopsies of FGP are not routinely recommended. However, the recommendation is to observe carefully for polyps that stand out because they have an irregular shape or texture or are large, suggesting adenomas. Removal of polyps in the antrum or immediate preantrum is also recommended, if possible. These are less common and often adenomas.

Surgical Options

Three different surgical options are available for individuals with classical and attenuated FAP (page 34). The prime factors when choosing an opera-
tion for FAP are the personal and familial phenotype, including the rectal polyp burden and whether colon or rectal cancer is present at diagnosis (page 18). In patients presenting with the classical FAP phenotype, proctocolectomy, if possible, is the preferred procedure because it prevents both colon and rectal cancer.

**Total Proctocolectomy With Ileal Pouch Anal Anastomosis:** Total proctocolectomy with ileal pouch anal anastomosis (IPAA), usually with a temporary loop ileostomy, is offered to patients with classical FAP, those with attenuated FAP with severe phenotypes resulting in carpeting of the rectum, those with curable colon or rectal cancer complicating the polyposis, and those 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 or low rectal cancer, or patients who have an anatomic, physiologic, or pathologic contraindication to an IPAA.

The advantages of this operation are that the risks for 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 is associated with a small risk for bladder and sexual dysfunction after proctectomy. Bowel function, although usually reasonable, is also somewhat unpredictable. The ileal pouch requires surveillance, and the area of the IPAA should still be examined because of the imperfect nature of mucosectomy. The remaining controversy over performing total abdominal colectomy with IRA versus total proctocolectomy with IPAA centers on issues of relative quality of life. A modest reduction in life expectancy is expected in patients with classical FAP with rectal preservation. Proctoscopic examination of a retained rectum is indicated annually.

**Total Abdominal Colectomy With IRA:** A total abdominal colectomy with IRA is a fairly quick and straightforward operation with an overall low morbidity rate, and generally results in good bowel function. Most patients have 3 to 4 bowel movements per day after this procedure, and the risk for urgency, seepage, or fecal incontinence is low. Without proctectomy, no risk exists for bladder or sexual function problems, and even a temporary stoma is obviated. The major disadvantages of total abdominal colectomy with IRA are high risk for rectal cancer development and associated morbidity and mortality, frequent need to undergo subsequent proctectomy because of severe rectal polyposis, and real need for regular endoscopic surveillance of the retained rectum (every 6–12 months).

In a review of 659 patients in the Dutch-Scandinavian collaborative national polyposis registries who underwent colectomy with IRA, Vasen et al., 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. The investigators estimated that 12.5% of patients undergoing this procedure would die of rectal cancer by 65 years of age even if compliant with endoscopic screening. They concluded that proctocolectomy is the preferred procedure for most patients with the classical FAP phenotype, although some controversy remains. They and others also observed that patients could not be reliably selected for colectomy based on genotype alone. However, studies have reported that the risk for rectal cancer development associated with total abdominal colectomy and IRA has declined since the 1980s when IPAA first became available for high-risk patients with severe polyposis.

However, IRA is the preferred surgery for most patients with attenuated FAP who have either 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 in attending follow-up endoscopic examinations. The risk to the rectal stump rises considerably after the age of 50 years, and if the rectum becomes unstable a proctectomy with either an IPAA or end ileostomy is recommended.

**Total Proctocolectomy With Ileostomy:** A total proctocolectomy with end ileostomy 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 family. Fear of a permanent stoma may make family members reluctant to undergo screening. The operation removes all risk of colon and rectal cancer, but is associated with the risk for bladder or sexual function disorders. This operation may be offered to patients with a low, locally advanced rectal cancer, those who cannot have an ileal pouch because of a desmoid tumor, those with a poorly functioning ileal
pouch, and those who have a contraindication for an IPAA (e.g., concomitant Crohn’s disease, poor sphincter function).

Total proctocolectomy with continent ileostomy is offered to patients who are motivated to avoid end ileostomy because they either are not suitable for total proctocolectomy with IPAA or have a poorly functioning IPAA. This is a complex operation with a significant risk for re-operation.

**Surveillance After Surgery**

For all patients with FAP, proctocolectomy surveillance involves annual physical examination, sigmoidoscopy, and polypectomy. In practice, some patients have few or no recurrent polyps in the rectum and the follow-up interval can probably be cautiously lengthened. Major surveillance in patients with a personal history of FAP or attenuated FAP after colectomy involves the upper gastrointestinal tract. It is recommended that physicians or centers with expertise in FAP manage patients, and that management should be individualized based on genotype, phenotype, and other personal considerations. In patients with retained rectum, polyp ablation can be performed if adenoma burden is low. In the case of attenuated FAP, surveillance involves annual physical and endoscopic examination if colectomy has been performed. Again, if rectal adenomas do not recur, longer follow-up intervals may be safely followed.

APC testing is recommended in the proband for several reasons: it confirms the diagnosis and allows other family members to clarify their risks through mutation-specific testing. Additionally, identifying the location of the APC mutation can be useful in predicting the severity of colonic polyposis generally and the severity of rectal involvement (for FAP) and risks for extracolonic cancers in affected patients.

Most classical and attenuated FAP patients will develop duodenal adenomas that can become cancerous (see Duodenoscopic Findings, opposite column).

Patients with classical FAP also are at elevated risk for developing other extracolonic cancers, which warrants attention during surveillance (page 30). Patients are at heightened risk for thyroid cancer, with a lifetime risk of approximately 2% and female predominance (95%). Peak incidence is in the third decade of life, with a mean age of around 30 years. Yearly thyroid physical examination is recommended and considered adequate for timely diagnosis and treatment. Annual thyroid ultrasound can be used to supplement physical examination. These patients also have an increased risk for intra-abdominal desmoid tumors, most of which present within 5 years of colectomy. Because significant morbidity and mortality are associated with advanced tumors, early diagnosis is likely of benefit. If family history of desmoids is present, pelvic CT or MRI every 3 years postcolectomy should be considered, and performed immediately if 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.

The risk for hepatoblastoma is much higher in young children predisposed to FAP. Although the absolute risk is approximately 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 5 years of life may be considered. The optimal approach would be to perform this screening in a clinical trial.

Medulloblastoma accounts for most brain tumors found in patients with FAP, predominantly in women younger than 20 years. The incidence of pancreatic cancer in FAP is not well defined and likely very low. Giardiello et al. reported 4 retrospective cases (histology not documented) of 1391 FAP-related subjects. More studies are needed to elucidate the risk and benefit of screening for brain and pancreatic cancers; no specific recommendations are provided other than to undergo annual physical examination.

**Duodenoscopic Findings:** Duodenal adenomas develop in more than 90% of patients with FAP, and are classified into stages 0 to IV, as defined by Spigelman et al. based on macroscopic and histologic criteria (page 31). Duodenal cancer risk is uncommon in individuals younger than 40 years, and are rare in those younger than 30 years. The cumulative risk for developing severe duodenal polyposis (stage IV) has been estimated to be approximately 40% by 60 years of age. The risk for duodenal cancer increases dramatically with stage IV disease.

Surveillance using end- and side-view duodenoscopy, Spigelman’s or other standardized staging system, and extensive biopsy of dense lesions to evaluate advanced histology are recommended starting at age 25 to 30 years, although efficacy of surveillance of these sites has not been shown. More intensive surveillance and/or treatment is required in patients...
older than 50 years with large or villous adenomas.

Endoscopic treatment options include endoscopic polypectomy, in addition to excision or ablation of resectable large or villous adenomas, and mucosectomy of resectable advanced lesions to potentially avert surgery. 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 6 to 12 months for Spigelman’s stage IV polyposis. Surgical evaluation and expert surveillance every 6 to 12 months is recommended for stage IV polyps, invasive carcinoma, and high-grade dysplasia or dense polyposis that cannot be managed endoscopically. Surgical counseling is also advised for those with stage IV polyposis.

Chemoprevention: Nonsteroidal anti-inflammatory drugs (NSAIDs) have been shown to reduce the incidence and recurrence of colorectal adenomas, although long-term follow-up is needed to more precisely determine the role of this type of therapy. Long-term use of sulindac seems to be effective in poly regression and preventing recurrence of higher-grade adenomas in the retained rectal segment of patients with FAP. However, in a randomized, double-blind, placebo-controlled study, sulindac did not prevent the development of adenomas in those with FAP. NSAIDs are not effective as primary treatment of FAP. Prophylactic colectomy remains the preferred treatment to prevent CRC in patients with FAP. Chemoprevention with NSAIDs can be considered after initial prophylactic surgery for both classical and attenuated FAP as an adjunct to endoscopic surveillance to reduce the rectal polyp burden.

Cyclooxygenase-2 (COX-2) inhibitors are a form of NSAID that have been shown to be over-expressed in colorectal adenomas and cancers. International multicenter studies have been conducted to study the effect of these agents as chemoprevention of colorectal adenomas. Results from the Prevention of Colorectal Sporadic Adenomatous Polyps (PreSAP) trial showed that the use of celecoxib, a COX-2 inhibitor, significantly reduced the occurrence of colorectal adenomas within 3 years after polypectomy. The Adenoma Prevention with Celecoxib (APC) trial showed that celecoxib significantly lowered the formation of adenomas during a 3-year period in patients at high risk for CRC who had their polyps removed. Five-year safety and efficacy results showed that compared with placebo, the reduction in incidence of advanced adenomas over 5 years was 41% for those who received a lower dose of celecoxib compared with 26% in patients who received a higher dose (both P < .0001). However, because of the increased risk for cardiovascular events associated with their use, COX-2 inhibitors are not recommended routinely for sporadic adenomas.

Personal History of Classical FAP
Prophylactic surgery (proctocolectomy or colectomy) remains the primary preferred treatment for this group of individuals (page 30). 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 postsurgical surveillance should be followed. In patients who are younger than 18 years with mild polyposis and without family history of early cancers or genetic disposition, the timing of colectomy can be individualized, but annual colonoscopy is essential.

Personal History of Attenuated FAP
Treating patients with a personal history consistent with attenuated FAP varies depending on the patient’s age and adenoma burden (page 35). For young patients younger than 21 years 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 adenomas, colectomy and IRA are alternative treatment options to colonoscopy and polypectomy. Patients older than 40 years should strongly consider colectomy and IRA. Even patients older than 40 years with what seems to be an endoscopically manageable adenoma burden, particularly if responsive to a chemopreventative agent such as sulindac or celecoxib, may choose to defer consideration of colectomy. For those who have significant polyposis that is not manageable with polypectomy, colectomy with IRA is preferred, but IPAA is an option. Annual physical examination is recommended, and NSAIDs may be considered as chemoprevention. Surveillance of the rectum and upper gastrointestinal tract is similar to that for classical FAP.

Family History of Classical FAP
Management of individuals with a family history of FAP depends on whether the familial mutation is known or unknown. Individuals who have a fami-
ily history of FAP have 2 possible situations: known specific mutation that has caused familial polyposis or family history of polyposis with no known familial mutation.

**Familial Mutation Known:**

**Genetic Counseling:** When the mutation responsible for FAP within a family is known, screening can be appropriately directed to those at highest risk and APC testing can be considered for at-risk family members. At-risk individuals should be provided counseling so that they are able to make informed decisions about the implications of genetic testing and on their own management.

**Genetic Testing:** Genetic testing for the APC gene in individuals with familial polyposis should be considered before or at the age of screening. The age at which to begin screening should be based on symptoms, family phenotype, and other individual considerations. Fatal CRC is rare before 18 years of age.

If an APC gene mutation is found, individuals have virtually a 100% probability that they will eventually develop familial polyposis. Truncating mutation of the APC gene is detectable in approximately 80% of patients with FAP using protein-truncating tests.119,120 These patients need to undergo flexible sigmoidoscopy or colonoscopy every 12 months, beginning at 10 to 15 years of age.

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.

**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 they are 24 years of age. Then, if results continue to be negative, screening is scaled down to every 2 years until 34 years of age, every 3 years until 44 years of age, and every 3 to 5 years thereafter. Substituting colonoscopy every 5 years should be considered beginning at age 20 years because of the possibility that the patient may have attenuated FAP.

Screening is recommended so often for these individuals for several reasons. First, adenomas may begin to develop in adolescence. Most people with classic FAP present with polyps before 25 years of age, so annual screening with sigmoidoscopy will detect FAP in most of these patients. 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 24 and 34 years of age and can be even less frequent between 34 and 44 years of age. However, even this recommended screening schedule is more rigorous than screening guidelines for the general population, because serial negative examinations up to 35 years of age do not exclude the diagnosis of FAP. Individuals with attenuated polyposis may not present until a later age and may have fewer polyps than those with classic FAP, but enhanced screening is still warranted.

**Familial Mutation Unknown:** In some families, mutations cannot be found with available testing technology, recognizing that the sensitivity to identify APC gene mutations is currently only approximately 80%. In other families, affected individuals have died or are not immediately available. Under these circumstances, APC testing should be considered for at-risk family members. If the mutation responsible for FAP within a family is not found, it is important to remember the limitations of interpreting a gene test in a presymptomatic individual. Evaluating presymptomatic individuals at risk in these families presents a difficult problem, because the mutation responsible for FAP within the family is not known. Certainly, a positive test in a presymptomatic person is informative even when the familial mutation has not been previously identified. But interpreting a test in which “no mutation is found” in a presymptomatic person is not the same as a “negative test.”

The best approach in this situation is to attempt to identify the APC mutation in an affected family member, even if the available person is not a first-degree relative. Without this information, genetic testing in an unaffected individual offers less precision in estimating a person’s risk. If a mutation is found, they should be managed similar to those with known familial mutations. FAP is only 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). Physicians have recognized this particular issue as 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{121} MYH testing should be considered if APC gene mutation is negative and family history is consistent with a recessive inheritance.

Surveillance for these at-risk individuals who are not tested or have no mutation found after testing is identical to that in untested individuals with known familial mutation (see No Genetic Testing, page 55). Again, if polyposis is detected, then individuals should be managed the same as those with personal history of classical FAP.

**Family History of Attenuated FAP**
The same genetic counseling, testing, and surveillance considerations discussed previously for patients with a classical FAP family history apply to patients with a family history of attenuated FAP, except for the endoscopy approach (pages 36 and 37). 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. The recommended endoscopic schedule involves colonoscopy beginning 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. These recommendations apply to patients who have known gene familial mutations, those not tested, and those for whom a familial mutation is not known. Individuals should continue with screening until adenomas are found, at which point they should be managed as patients with personal history of attenuated FAP.

**MAP**
MAP is an autosomal recessive hereditary syndrome that predisposes some individuals to attenuated adenomatous polyposis and CRC.\textsuperscript{122,123} It is caused by biallelic germline mutations in the MutY human homolog (MYH) gene. MYH is an excision repair protein responsible for excising adenine nucleotides mismatched with 8-oxo-guanine, a product of oxidative damage to DNA. Dysfunctional MYH protein can thus result in G:C to T:A transversions during DNA replication. Adenomatous polyposis is believed to result from these transversions occurring within the APC gene.

Most individuals with MAP generally have fewer than 100 polyps, although a minority can present with more than 1000. The median age of presentation is in the mid-40s to late 50s. Duodenal polyposis is reported less frequently than in FAP, and the magnitude of risk for duodenal cancer is not yet defined. Individuals with MYH mutations also require colectomy at a later age than those with FAP.

Guidelines for screening and surveillance are based on limited retrospective data.\textsuperscript{124,125} Balaguer et al.\textsuperscript{126} recently reported that patients with CRC and more than 15 synchronous colorectal adenomas or those younger than 50 years might benefit from MYH genetic testing.

NCCN guidelines recommend genetic counseling and testing for germline MYH mutations for siblings of affected patients, and for patients who test negative for APC mutation with more than 10 cumulative adenomas (page 39). Genetic testing for MYH mutations may precede APC gene testing for families in which only siblings are affected (suggesting recessive inheritance).

Colonoscopy screening of asymptomatic individuals with affected siblings is recommended beginning at age 25 to 30 years at 3- to 5-year intervals (shorter intervals with advancing age). Patients with multiple adenomatous polyps but who tested negative for MYH mutation should be managed individually.

The lifetime risk for CRC in patients with MAP may be very high. If the individual tests MYH-positive, those with small adenoma burden are followed up with colonoscopy and complete polypectomy every 1 to 2 years. Surgery in the form of subtotal colectomy or proctocolectomy, depending on adenoma distribution and density, is recommended for patients with dense or large polyposis not manageable with polypectomy. Upper endoscopy and side-viewing duodenoscopy at 3- to 5-year intervals beginning at age 30 to 35 years are recommended for patients with dense polyposis and should also be considered for patients with small adenoma burden or those with unknown mutation status. If duodenal adenomas are identified, management is similar to that for FAP.

**References**
2. Levin B, Lieberman DA, McFarland B, et al. Screening and surveillance for the early detection of colorectal cancer and
Colorectal Screening


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Colorectal Cancer Screening


### Individual Disclosures for the NCCN Colorectal Cancer Screening Panel Members

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<thead>
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<th>Advisory Boards, Speakers Bureau, Expert Witness, or Consultant</th>
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<td>James S. Barthel, MD</td>
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<td>Myriad Genetic Laboratories, Inc.; and Archimedes Inc.</td>
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The NCCN guidelines staff have no conflicts to disclose.