NCCN Colorectal Cancer Screening Panel Members

- Randall W. Burt, MD/Chair △
  Huntsman Cancer Institute at the University of Utah

- James S. Barthel, MD △ ∥
  H. Lee Moffitt Cancer Center and Research Institute

- Donald S. David, MD △
  City of Hope

- Ernesto Drelichman, MD
  University of Alabama at Birmingham Comprehensive Cancer Center

- James M. Ford, MD † △ ∥
  Stanford Comprehensive Cancer Center

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

- Stephen B. Gruber, MD, PhD, MPH † △
  University of Michigan Comprehensive Cancer Center

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

- Stanley Hamilton, MD ≠
  The University of Texas M. D. Anderson Cancer Center

- Wendy Kohlmann, MS, CGC △
  Huntsman Cancer Institute at the University of Utah

- Audrey J. Lazenby, MD ≠
  UNMC Eppley Cancer Center at The Nebraska Medical Center

- Kirk A. Ludwig, MD ∥
  Duke Comprehensive Cancer Center

- Patrick M. Lynch, MD, JD △
  The University of Texas M. D. Anderson Cancer Center

- Christopher Marino, MD △
  St. Jude Children’s Research Hospital/University of Tennessee Cancer Institute

- Edward W. Martin, Jr., MD ∥
  Arthur G. James Cancer Hospital & Richard J. Solove Research Institute at The Ohio State University

- Robert J. Mayer, MD †
  Dana-Farber/Brigham and Women’s Cancer Center | Massachusetts General Hospital Cancer Center

- Reid M. Ness, MD △
  Vanderbilt-Ingram Cancer Center

- Ashwani Rajput, MD ∥
  Roswell Park Cancer Institute

- M. Sambasiva Rao, MD ≠ △
  Robert H. Lurie Comprehensive Cancer Center of Northwestern University

- Moshe Shike, MD △ ∥
  Memorial Sloan-Kettering Cancer Center

- Gideon Steinbach, MD, PhD ∥
  Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance

- Jonathan P. Terdiman, MD △
  UCSF Helen Diller Family Comprehensive Cancer Center

- David Weinberg, MD, MSc △
  Fox Chase Cancer Center

- Sidney J. Winawer, MD ∥
  Memorial Sloan-Kettering Cancer Center

△ Gastroenterology
△ Cancer Genetics
∥ Internal Medicine
† Medical Oncology
‡ Hematology/Hematology Oncology
≠ Pathology
∥∥ Surgery/Surgical Oncology
* Writing Committee Member

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**References**

**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.

To find clinical trials online at NCCN member institutions, click here:
ncn.org/clinical_trials/physician.html

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

See NCCN Categories of Evidence and Consensus

These guidelines are a statement of evidence and 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 representations nor warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way. These guidelines are copyrighted by National Comprehensive Cancer Network. All rights reserved. These guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN. ©2008.
Summary of the Guidelines updates

Summary of changes in the 2.2008 version of the Colorectal Cancer Screening guidelines from the 1.2008 version is the addition of the updated manuscript representing the changes to the algorithm.

Summary of changes in the 1.2008 version of the Colorectal Cancer Screening guidelines from the 1.2007 version include:

CSCR-1

- Footnote a, “There should be particular attention that African Americans receive the suggested colorectal screening due to the higher risks of colon cancer and mortality,” is new to the page.

CSCR-2

- Footnote d, was clarified by adding the option of “repeat colonoscopy,” if the colonoscopy is incomplete.

CSCR-3

- Advanced or multiple adenoma, “severe dysplasia” was added to “high-grade dysplasia”.
- Incomplete polypectomy was clarified by adding, “piecemeal” and “polypectomy of large sessile polyps”
- Footnote I, “A recent study has shown that the identification of villous architecture and high-grade dysplasia is associated with poor reproducibility among pathologists routinely evaluating adenomas. Golembeski CP, McKenna, BJ, Appelman HD. “Advanced” adenomas: Pathologists don’t agree. Mod Pathol 2007;20 (suppl 2):115A” is new to the page.
- Footnote m, “An adenoma that shows features of severe dysplasia or carcinoma in situ (CIS) can be categorized as high-grade dysplasia. Severe dysplasia: marked reduction of interglandular stromas with complex irregularity of glands and papillary infolding and cytological abnormalities include marked irregularity of nuclear membranes; nuclear chromatin cleared, vesicular, irregularly clumped, or densely hyperchromatic; and large and irregular nucleoli. Carcinoma in situ: severe architectural disturbance of glands, such as cribiform or back-to-back patterns or growth in solid sheets in association with cytological features of dysplasia. O'Brien MJ, Winawer SJ, Zauber AG, et al. The National Polyp Study. Patient and polyp characteristics associated with high-grade dysplasia in colorectal adenomas. Gastroenterology 1990; 98:371-379. CIS is a term previously used by pathologist to describe colon polyps and cancer and is currently being replaced by high-grade dysplasia.” is new to the page.

CSCR-4

- Footnote ‘r’ was clarified by adding, “See surveillance section of NCCN Colon Cancer Guidelines and NCCN Rectal Cancer Guidelines.”

CSCR-6

- “First-degree relative with colorectal cancer” was clarified by adding, “at age ≥ 50 y.”

CSCR-7

- Inclusion criteria was clarified by adding, “Individuals with multiple primary HNPCC-related cancers, or Individuals with an HNPCC-related cancer who have one or more first-degree relatives with an HNPCC-related cancer prior to age 50 or two or more first or second degree relatives with an HNPCC related cancer diagnosed at any age”
- “Hepatobiliary/pancreas and brain tumors (particularly glioblastomas)” were added to HNPCC-related cancers. (Also for CSCR-8)

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

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

Continued on next page
### Summary of the Guidelines updates (Continued)

**CSCR-8**
- Risk assessment was modified with the addition of the following:
  - Colon cancer or “other HNPCC-related cancers” in first- or second-degree family member
  - Right-sided colon cancer predominance “and/or MSI-H histology”
- Footnote gg was modified by adding, “There is a 5-10% false negative rate with IHC testing.”
- Footnote hh, “There is a 5-10% false negative rate with MSI testing,” is new to the page.

**CSCR-10**
- Footnote ll, “See Cancer Risk in Individuals with HNPCC up to Age 70 Years Compared to the General Population (CSCR-H)” is new to the page.

**CSCR-11**
- For MYH associated polyposis, risk assessment, the 2nd bullet was clarified by adding, “or colon cancers.”

**CSCR-12**
- Baseline endoscopy surveillance for personal history of FAP was modified by adding, “at the time of colectomy” or at age 25-30 y, “whichever comes first; then every 1-3 y depending on severity of polyposis.”

**CSCR-14**
- Reference to a “family history consistent with recessive inheritance” with MYH-associated polyposis was removed throughout the guidelines.

**CSCR-15**
- Treatment for significant polyposis was clarified by adding, “with IRA (preferred in most cases)” after colectomy and “based on burden of disease in rectum” after proctocolectomy.

**CSCR-16**
- Surveillance for Stage IV was modified by adding “duodenectomy or Whipple procedure if duodenal papilla is involved” to “complete mucosectomy.”

**CSCR-A**
- “Consanguinity” was added as information to be obtained on each relative when taking a family history.

**CSCR-D**
- Removed “young” from TAC/IRA indication for “Asymptomatic patient with few (<20) rectal polyps and mild colonic disease (<100) polyps.”
- Removed the surgical option of “total proctocolectomy with continent ileostomy (TPC/CI).”

**CSCR-E**
- Additional histology features seen in HNPCC or Lynch syndrome tumors and references were added to footnote 4.

**CSCR-H**
- “Cancer risks in individuals with HNPCC up to age 70 years compared to the general population” table is new to the guideline.

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### RISK ASSESSMENT

**Average risk:**
- Age ≥ 50 y
- No history of adenoma
- No history of inflammatory bowel disease
- Negative family history\(^b\)

**Increased risk:**
- **Personal history**
  - Adenoma
  - Colorectal cancer
  - Endometrial/Ovarian cancer < age 60 y
  - Inflammatory bowel disease

- **Positive family history:**
  - A first degree relative with colorectal cancer or adenoma
  - Two second degree relatives (related to each other) with colorectal cancer

- Clustering of colorectal cancer or HNPCC related cancers in the family (See CSCR-7)

**Hereditary high risk:**
- Colorectal cancer at age < 50 y or clustering of colorectal cancer or HNPCC related cancers in the family, or personal or family history of polyposis.
- Polyposis syndromes
- HNPCC

---

\(^a\)There should be particular attention that African Americans receive the suggested colorectal screening due to the higher risks of colon cancer and mortality.

\(^b\)Not having a first-degree relative or two second-degree relatives with colorectal cancer or clustering of HNPCC related cancers in the family.
# Colorectal Cancer Screening

## Guidelines for Average Risk Patients

### Risk Assessment
- **Average risk:**
  - Age ≥ 50 y
  - No history of adenoma
  - No history of inflammatory bowel disease
  - Negative family history

### Screening Modality and Schedule

<table>
<thead>
<tr>
<th>Modality</th>
<th>Schedule</th>
<th>Findings</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colonoscopy (preferred if available)</td>
<td>Age 50 y, Negative family history</td>
<td>Polyps</td>
<td>Biopsy</td>
</tr>
</tbody>
</table>
| or FOBT annually (category 1) and flexible sigmoidoscopy every 5 y | Positive FOBT | Hyperplastic | Repeat colonoscopy in 10 y
| or Double-contrast barium enema every 5 y | | | Routine screening |

### Evaluation of Positive Screening Findings

- **Biopsy:**
  - Hyperplastic
  - Adenoma
  - Serrated adenoma

- **Polyps:**
  - Repeat colonoscopy in 10 y

### Additional Notes
- **Not having a first-degree relative or two second-degree relatives with colorectal cancer or clustering of HNPCC related cancers in the family.**
- **If FOBT positive and colonoscopy negative, proceed with additional workup.**
- **If colonoscopy incomplete, consider double-contrast barium enema or CT colonography or repeat colonoscopy at discretion of physician.**
- **Other screening options preferred over double contrast barium enema.**
- **If using 10 y interval, patient must have no identifiable risk factors except age and preparation must be adequate.**
- **Patients with large hyperplastic polyps (> 10 mm) or > 10 hyperplastic polyps, especially right-sided or with diffuse distribution, may need to be screened more frequently. Serrated adenomas have an association with adenocarcinoma, but pathologic classification is currently controversial and guidelines for screening are not established at present. Patients with these lesions may need more frequent screening than patients with a hyperplastic polyp.**
- **Lesions > 1 cm may not need biopsy because they are almost always adenomas and should be referred directly to colonoscopy.**

### Additional Information
- **Fecal Occult Blood Test (FOBT):**
  - Any positive test requires evaluation
  - 3 successive stool specimens
  - Prescribed diet
  - Not via digital rectal examination
  - Guaiac-based nonrehydrated
  - Immunochemical techniques under investigation
  - Coordinated by health care provider
  - Annual FOBT need not be performed if screening colonoscopy or double-contrast enema are used as a screening measure in an average-risk patient.

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FOLLOW-UP OF CLINICAL FINDINGS: ADENOMA

Increased risk patients: Personal history of adenoma(s) or adenoma found at colonoscopy

- Low-risk adenoma:
  - ≤ 2 polyps, < 1 cm, tubular
  - Repeat colonoscopy within 5 y
    - Normal → Repeat colonoscopy every 5-10 y
    - Abnormal → Repeat colonoscopy within 5 y

- Advanced or multiple adenomas:
  - High-grade dysplasia (severe dysplasia or carcinoma in situ)
  - ≥ 1 cm
  - Villous (> 25% villous)
  - Between 3 and 10 polyps
  - More than 10 adenomas or > 15 cumulative adenomas in 10 y
  - Incomplete or piecemeal polypectomy or polypectomy of large sessile polyps
  - Malignant polyp

- Consider a polyposis syndrome

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

- See NCCN Colon Cancer Treatment Guidelines

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

<table>
<thead>
<tr>
<th>Personal history of curative intent resected colorectal cancer&lt;sup&gt;q,r&lt;/sup&gt;</th>
<th>Colonoscopy in 1 y, (within 3-6 mo if there was no or incomplete preoperative colonoscopy)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Personal history of ovarian or endometrial cancer at age &lt; 60 y&lt;sup&gt;s&lt;/sup&gt;</td>
<td>Begin colonoscopy at age 40 y (or at age of diagnosis of ovarian/endometrial cancer)</td>
<td></td>
</tr>
</tbody>
</table>

### FINDINGS

- **Adenoma** → Repeat colonoscopy in 1-3 y<sup>t</sup>
- **Normal** → Repeat colonoscopy in 2-3 y
- Repeat colonoscopy at every 5 y if normal

<sup>q</sup>Identify colorectal patients who meet Bethesda criteria. Those patients may require genetic counseling or individualized management. See (CSCR-7, CSCR-8).

<sup>r</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 months for the first 2-3 years of surveillance. No specific data clearly support rigid versus flexible sigmoidoscopy. The utility of routine endoscopic ultrasound for early surveillance is not defined. See surveillance section of NCCN Colon Cancer Guidelines and NCCN Rectal Cancer Guidelines.

<sup>s</sup>Women with endometrial and ovarian cancer diagnosed prior to age 60 y are at mildly elevated risk for colorectal cancer. Risk is highest for women with the primary diagnosis prior to age 50 y. However, this observation is based on data that did not exclude patients with HNPCC who may account for some of the observed risk.

<sup>t</sup>The recommendation for intensive surveillance immediately following resection is based on studies that found a high rate of metachronous colorectal cancer and/or resectable recurrences in the 4-5 years following colorectal cancer resections, though the studies did not fully exclude patients with HNPCC.

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### Colorectal Cancer Screening

#### RISK ASSESSMENT

- Inflammatory bowel disease
  - Ulcerative colitis
  - Crohn's disease

#### INITIATION OF SCREENING

- 8-10 y after onset of symptoms

#### SCREENING MODALITY AND SCHEDULE

- Colonoscopy every 1–2 y
  - When clinically quiescent, 4 quadrant biopsies every 10 cm with > 30 total samples using large cup forceps (preferred)
  - Additional extensive sampling of strictures and masses
  - Endoscopic polypectomy when appropriate with biopsies of surrounding mucosa for the assessment of dysplasia

#### EVALUATION OF POSITIVE SCREENING FINDINGS

- Dysplasia/Intraepithelial neoplasia
  - Confirmation by expert GI pathologist desirable

#### FOLLOW-UP OF CLINICAL FINDINGS

- Prophylactic proctocolectomy with ileoanal pouch (preferred)

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**Information regarding the value of endoscopic surveillance of long-standing Crohn's disease is limited. Surveillance is at the discretion of the physician.**

**Optimal management of Crohn's-related dysplasia remains undefined. Patient and physician preference should be considered. Extent of resection for Crohn's-related dysplasia needs to be based upon the individual findings.**

**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.**

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**INCREASED RISK**

**POSITIVE FAMILY HISTORY**

- **First-degree relative with colorectal cancer < age 50 y, two first-degree relatives with colorectal cancer at any age, or clustering of HNPCC-related cancers, or polyposis in close relatives.** See Evaluation for Genetic Screening (CSCR-7) and (CSCR-8)

- **First-degree relative with colorectal cancer at age ≥ 50 y**

- **Two related second-degree relatives with colorectal cancer at any age**

- **One second-degree relative or any third-degree relative(s) with colorectal cancer**

- **First-degree relative with adenoma(s)**

**SCREENING**

- If not meeting criteria for a defined syndrome, consider beginning screening colonoscopy at age 40 y or 10 y prior to earliest cancer in family → Repeat every 1-5 y

- Colonoscopy beginning at age 40 y or 10 y prior to earliest colorectal cancer in family → Repeat every 5 y

- Risk equivalent to one affected first degree relative

- • Screen as average risk
  • Individualized evaluation, including a careful family history, is encouraged

- Colonoscopy beginning at age 50 or at the age of diagnosis of the adenoma in the relative, whichever is earlier → Repeat every 5-10 y

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\(^\text{Y}\) Consider the shorter interval when advanced or multiple adenomas are diagnosed prior to age 60 y. The guideline is based on Winawer SJ, Zauber AG, Gerdes H, et al. Risk of colorectal cancer in the families of patients with adenomatous polyps. NEJM 1996;334:82-87.

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INCLUSION CRITERIA

Early-age-onset colorectal cancer (< age 50)
or
Individuals with multiple primary HNPCC-related cancers or
Individuals with an HNPCC-related cancer who have one or more first-degree relatives with an HNPCC-related cancer prior to age 50 or two or more first or second-degree relatives with an HNPCC-related cancer diagnosed at any age
Related cancers include:
- Colorectal
- Endometrial
- Ovarian
- Duodenal/small bowel
- Stomach
- Sebaceous adenomas or sebaceous carcinomas
- Ureteral/renal pelvis
- Hepatobiliary/pancreas
- Brain tumors (particularly glioblastomas)
or
Multiple colorectal carcinomas or >10 adenomas in same individual or
Family with known hereditary syndrome associated with cancer with or without mutation (eg, polyposis)

HEREDITARY SYNDROME

HNPCC or Lynch syndrome criteria met (See CSCR-8)

Classical FAP criteria met (See CSCR-11)

Attenuated FAP criteria met (See CSCR-11)

MYH-associated polyposis criteria met (See CSCR-19)

Peutz-Jeghers syndrome or juvenile polyposis criteria met

No syndromes, but familial risk present

RISK/GENETIC COUNSELING

Risk assessment and counseling:
- Psychosocial assessment and support
- Risk counseling
- Education support
- Discussion of genetic testing
- Informed consent

Referral to specialized team recommended

See HNPCC pathway (CSCR-8)
See Classical FAP pathway (CSCR-11)
See Attenuated FAP pathway (CSCR-11)
See MYH pathway (CSCR-19)
See Positive Family History (CSCR-6)

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

Directed examination for related manifestations:
- Colonoscopy
- Esophagastroduodenoscopy
- Eye examination
- Skin, soft-tissue, and bone examination
- Oral examination

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.

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HEREDITARY PREDISPOSITION: HNPCC OR LYNCH SYNDROME SCREENING

**RISK ASSESSMENT**

**Extended pedigree**
- HNPCC or Lynch syndrome risk factors present:
  - Autosomal dominant inheritance pattern
  - Colon cancer or other HNPCC-related cancers in first- or second-degree family member
  - Colon cancer at age < 50 y
  - Multiple primaries
    - Colorectal
    - Endometrial
    - Ovarian
    - Duodenal/small bowel
    - Stomach
    - Ureteral/renal pelvis
    - Sebaceous adenomas or sebaceous carcinomas
  - Right-sided colon cancer predominance and/or MSI-H histology

**RISK STATUS**

- Tumor available from affected family member
  - Meets Revised Bethesda guidelines
  - Familial mismatch repair mutation not known
- Tumor not available
  - Familial mismatch mutation known
- Individual management

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

IHC abnormal or Microsatellite instability high (MSI-H)
- Does not meet Amsterdam I or Amsterdam II criteria
- Meets Amsterdam I or Amsterdam II criteria

See Consider Genetic Testing for Mutations of the Mismatch Repair Genes (CSCR-9)

Tailored colonoscopic monitoring based on individual risk assessment

See Consider Gene Testing of At-Risk Family Members (CSCR-9)

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dd See Revised Bethesda Guidelines (CSCR-E).

ee With informed consent as designated by local practice and IRB standards.

ff An alternative and efficient approach when a family meets the Amsterdam Criteria or one of the first three of the classical Bethesda Criteria, is to proceed directly to genetic testing (whether or not tumor tissue is available) in the person most likely to carry the putative genetic mutation (usually the youngest living person in the family with colon or other HNPCC cancer). If a mutation of MLH1 or MSH2 is not found, then one may consider MSI and/or immunohistochemistry testing of colon cancer tissue for the possibility of difficult to detect mutations in MLH1 or MSH2 or mutations in MSH6 or PMS2.

gg IHC=Immunohistochemistry, refers to staining for protein expression of the four mismatch genes known to be mutated in HNPCC: MLH1, MSH2, MSH6, and PMS2. A normal IHC test implies all four mismatch repair proteins are normally expressed and thus no underlying mismatch repair gene mutation present. An abnormal test means that one of the proteins is not expressed and an inherited mutation may be present in the related gene. Ten to 15% of sporadic colon cancers exhibit abnormal IHC, often due to abnormal methylation of the MLH1 gene promoter, but occasionally due to an inherited mutation of one of the mismatch repair genes. There is a 5-10% false negative rate with IHC testing.

hh There is a 5-10% false negative rate with MSI testing.

ii See Amsterdam I Criteria (CSCR-F).

jj See Amsterdam II Criteria (CSCR-G).

kk Loss of protein expression by immunohistochemistry (IHC) in any one of the mismatch repair genes guides genetic testing (mutation detection) to the gene where protein expression is not observed.
HEREDITARY PREDISPOSITION: HNPCC OR LYNCH SYNDROME SCREENING

GENETIC COUNSELING/TESTING OF ELIGIBLE FAMILY MEMBERS

Mismatch repair gene mutation unknown:
Consider genetic testing to find a disease causing mutation in MSH2 or MLH1 of affected family member if possible and in MSH6 or PMS2 if a mutation is not found in the first two.

No familial mutation found

Positive familial mutation of unknown significance found

Positive familial mutation MSH2 or MLH1 found

Follow familial mismatch mutation known pathway below

Positive gene test (mutation present)

Not tested

Negative gene test (mutation not present)

Average risk screening

Specific mismatch repair gene mutation known:
Consider genetic testing of at-risk family member

Positive gene test (mutation present)

See Follow-up (CSCR-10)

Not tested

Average risk screening

See Follow-up (CSCR-10)

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Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
HEREDITARY PREDISPOSITION: HNPCC OR LYNCH SYNDROME FOLLOW-UP

SURVEILLANCE

Colonoscopy at age 20-25 y or 10 y younger than the youngest age at diagnosis in the family, whichever comes first
Repeat every 1-2 y

Consider periodic evaluation for associated intra-abdominal malignancies

Consider annual urinalysis with cytology and imaging of the renal collecting system

For women:
• Encourage patient education and prompt response to endometrial cancer symptoms
• Screening for endometrial cancer with transvaginal ultrasound and office endometrial sampling annually starting by age 30-35 y or 5-10 y earlier than the earliest age of first diagnosis of these cancers in the family, and screening for ovarian cancer with concurrent transvaginal ultrasound (preferably day 1-10 of cycle for premenopausal women) + CA-125 every 6-12 mo
• Prophylactic hysterectomy and bilateral salpingo-oophorectomy is a risk reducing option for women who have completed childbearing. Chemoprevention may be considered

No pathologic findings

Continued screening
• Consider prophylactic total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAH/BSO)

Adenocarcinomas

See NCCN Colon Cancer Treatment Guidelines

Adenomas

Endoscopic polypectomy with follow-up colonoscopy every 1-2 y depending on:
• location, character
• surgical risk
• patient preference

Adenomas not amenable to endoscopic resection or high-grade dysplasia

• Total abdominal colectomy with ileorectal anastomosis
• Consider TAH/BSO at time of colon surgery if postmenopausal or family completed

Endoscopic rectal exam every 1-2 y

II See Cancer Risk in Individuals with HNPCC up to Age 70 Years Compared to the General Population (CSCR-H)

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

The type of surgical procedure chosen should be based on individual considerations and discussion of risk.

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

PHENOTYPE

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 of medulloblastoma, papillary carcinoma of the thyroid (<2%), hepatoblastoma (usually ≤ age 5 y)
- Pancreatic cancers (<2%)
- Gastric cancers (<1%)

Attenuated FAP
- Fewer than 100 adenomas (range 0 - > 1000)
  - Adenomas and cancers at age older than classic FAP (mean cancer age > 50)

MYH associated polyposis (MAP)
- Autosomal recessive (parents’ phenotype negative)
- Fewer than 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 occur uncommonly

RISK ASSESSMENT

- Personal history
  - No symptoms, positive family history
    - Family mutation known
    - Family mutation unknown
  - Personal or family history (ie, known mutation, in patient or sibling)
    - Polyposis or colon cancers consistent with recessive inheritance
    - Attenuated polyposis with negative APC mutation

- Family mutation known

- Family mutation unknown

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

**TREATMENT**

- Personal history of Classical FAP
- Proctocolectomy or colectomy

**SURVEILLANCE**

- **POSTCOLECTOMY**
  
  - Annual sigmoidoscopy and polypectomy or polyp ablation if adenoma burden is low (in patients with retained rectum).
  
  - Physical examination annually, including thyroid exam.
  
  - Consider NSAID chemoprevention after colectomy to reduce polyp burden as pharmacological adjunct to endoscopic surveillance. Clinical trial is encouraged.
  
  - Baseline upper endoscopy at the time of colectomy or at age 25-30 y, whichever comes first; then every 1-3 y depending on severity of polyposis.

- **Precolectomy**
  
  - Annual sigmoidoscopy and polypectomy or polyp ablation if adenoma burden is low (in patients with retained rectum).
  
  - Physical examination annually, including thyroid exam.
  
  - Consider NSAID chemoprevention after colectomy to reduce polyp burden as pharmacological adjunct to endoscopic surveillance. Clinical trial is encouraged.
  
  - Baseline upper endoscopy at the time of colectomy or at age 25-30 y, whichever comes first; then every 1-3 y depending on severity of polyposis.

- **Proctectomy if dense polyposis or severe dysplasia**

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

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

**References**

- See Primary Surgical Management of FAP (CSCR-D).
- Timing of colectomy in patients under age 18 y is unresolved. In patients under 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.

**See Duodenoscopic Findings (CSCR-16)**
HEREDITARY PREDISPOSITION: CLASSICAL FAP SCREENING

GENETIC TESTING

Family history of Classical FAP, familial mutation known

APC positive

Flexible sigmoidoscopy or colonoscopy every 12 mo beginning at age 10-15 y

If adenomas, follow pathway for Personal history of Classical FAP (CSCR-12)

APC testing for at-risk family member

APC negative

Average risk screening

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 for chance that patient may have attenuated FAP.

Not tested

If adenomas, follow pathway for Personal history of Classical FAP (CSCR-12)

If no polyps, continue screening

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

GENETIC TESTING

- **If mutation found,** follow pathway for family mutation known (CSCR-13)

SURVEILLANCE

If polyposis detected, follow pathway on (CSCR-12)

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

1. **Consider APC testing of affected family member**
2. **Consider MYH testing if APC mutation negative**

**Mutation in family not found**

- **Consider APC testing of affected family member not available**
- **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 in addition to the sigmoidoscopy examinations

**APC positive**

- **Consider APC testing for at-risk family member**
- **No mutation found**

**See APC Positive (CSCR-13)**

**See MYH-Associated Polyposis (CSCR-19).**

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

ADENOMA/POLYP BURDEN | TREATMENT | SURVEILLANCE
---|---|---
< 21y with small adenoma burden\(^{vv}\) | • Colonoscopy and polypectomy every 1-2 y  
• Surgical evaluation and counseling |  
\(^{vv}\)Small adenoma burden is defined (somewhat arbitrarily) as fewer than 20 adenomas, all < 1 cm in diameter and none with advanced histology, so that colonoscopy with polypectomy can be used to effectively eliminate the polyps. Colectomy may be indicated before this level of polyp profusion, especially if colonoscopy is difficult. Surgery is strongly advised when polyp burden is greater than 20, some polyps have reached a size > 1 cm, or advanced histology is encountered in any polyp.

≥ 21y with small adenoma burden\(^{vv}\) | • Colectomy\(^{qq}\) and ileorectal anastomosis (IRA)\(^{ww}\)  
or colonoscopy and polypectomy every 1-2 y  
• Surgical evaluation and counseling |  
\(^{qq}\)See Primary Surgical Management of FAP (CSCR-D).  
\(^{ww}\)It is recommended that patients be managed by physicians or centers with expertise in FAP and that management would be individualized to account for genotype, phenotype and personal considerations.

≥ 40y with small adenoma burden\(^{vv}\) | • Strongly consider colectomy\(^{qq}\) and ileorectal anastomosis\(^{ww}\)  
• Surgical evaluation and counseling |  

Significant polyposis not manageable with polypectomy | • Colectomy\(^{qq}\) with IRA (preferred in most cases)  
or proctocolectomy based on burden of disease in rectum and ileorectal anastomosis\(^{ww}\) |  
\(^{qq}\)See Primary Surgical Management of FAP (CSCR-D).  
\(^{ww}\)Earlier surgical intervention should be considered in patients with family history of cancer under age 40 or noncompliant patients.

Personal history of Attenuated FAP  
APC testing\(^{pp,uu}\)  

\(^{pp}\)APC testing may not change clinical management of affected individuals but is recommended for familial risk assessment.  
\(^{uu}\)Consider MYH testing if APC mutation not found (See CSCR-19).  

\(^{qq}\)See Primary Surgical Management of FAP (CSCR-D).  
\(^{ww}\)It is recommended that patients be managed by physicians or centers with expertise in FAP and that management would be individualized to account for genotype, phenotype and personal considerations.

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

Stage 0, No polyposis $\rightarrow$ Repeat endoscopy every 4 y

Stage I, Minimal polyposis (1-4 tubular adenomas, size 1-4 mm) $\rightarrow$ Repeat endoscopy every 2-3 y

Stage II, Mild polyposis (5-19 tubular adenomas, size 5-9 mm) $\rightarrow$ Repeat endoscopy every 1-3 y

Stage III, Moderate polyposis ($\geq$ 20 lesions, or size $\geq$ 1 cm) $\rightarrow$ Repeat endoscopy every 6-12 mo

Stage IV, Dense polyposis or high grade dysplasia $\rightarrow$ 
- Surgical evaluation
- Expert surveillance every 6-12 mo
- Complete mucosectomy or duodenectomy, or Whipple procedure if duodenal papilla is involved

**SURVEILLANCE**

It is recommended that patients be managed by physicians or centers with expertise in FAP and that management be individualized to account for genotype, phenotype, and personal considerations, including potential risks and benefits. Management that includes endoscopic treatment may require shorter intervals.

Recommend examination with side-viewing endoscope, use of Spigelman's or other standardized staging, and extensive biopsy of dense lesions to evaluate for advanced histology. More intensive surveillance and/or treatment is required in patients with large or villous adenomas, and with advancing age, > 50 y. Surgical counseling is advisable for patients with stage IV polyposis (Spigelman AD, Williams CB, Talbot IC et al. Upper gastrointestinal cancer in patients with familial adenomatous polyposis. Lancet 1989;2(8666): 783-785).

Endoscopic treatment options include endoscopic papillectomy in addition to excision or ablation of resectable large (> 1 cm) or villous adenomas, as well as mucosectomy of resectable advanced lesions, including contained high grade dysplasia, to potentially avert surgery while observing pathology guidelines for adequate resection.

Surgery is recommended for invasive carcinoma as well as dense polyposis or high grade dysplasia that cannot be managed endoscopically.

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

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
HEREDITARY PREDISPOSITION TESTING AND SURVEILLANCE: FAMILY HISTORY OF AFAP

**GENETIC TESTING**

- **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 (CSCR-15)**

**Family history of Attenuated FAP, mutation known**

- APC testing for at-risk family member

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

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
HEREDITARY PRE-DISPOSITION: FAMILY HISTORY OF ATTENUATED FAP

**GENETIC TESTING**

- If APC mutation found, follow pathway for family mutation known (CSCR-17)
- Consider APC testing of affected family member
  - Consider MYH testing if APC mutation negative
- APC mutation in family not found
  - Affected family member not available
  - Consider APC testing for at-risk family member
    - Consider MYH testing if APC mutation negative
- APC mutation found
  - No mutation found
  - Not tested

**SURVEILLANCE**

- Colonoscopy beginning in late teens, then every 2-3 y
  - See MYH-Associated Polyposis (CSCR-19)
  - Colonoscopy beginning in late teens, then every 2-3 y

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

**tt** See MYH-Associated Polyposis (CSCR-19).
**MYH-ASSOCIATED POLYPOSIS**

### INCLUSION CRITERIA

**Family history of sibling with MYH polyposis, asymptomatic**
- Counseling and testing for the familial mutations is recommended

**Personal history of adenomatous polyposis (>10 adenomas or >15 cumulative adenomas in 10 y)**
- Counseling and testing for MYH mutations

### MUTATION STATUS

- **Mutation status unknown or biallelic MYH mutations known**
- **Biallelic MYH mutation negative**
  - Manage individually as multiple adenomatous polyps (CSCR-7)
- **Biallelic MYH mutation positive**
  - Dense polyposis or large polyps not manageable by polypectomy
  - Counseling and testing for MYH mutations
  - Small adenoma burden manageable by colonoscopy and polypectomy

### TREATMENT/SURVEILLANCE

**Begin colonoscopy at age 25-30 y and every 3-5 y if negative (consider shorter intervals with advancing age)**

**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 FAP CSCR-16)
- 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 FAP CSCR-16)
- 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 FAP CSCR-16)

---

**yy** This is a recently described syndrome. The present guidelines are working guidelines awaiting prospective data. One colorectal cancer at age 21 was reported.

**zz** When polyposis is present in a single person with negative family history, consider and test for 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.

**aaa** The absolute risk of colorectal cancer and the role of surgery in patients with MYH and endoscopically manageable adenomas is not known.
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

- 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

COMMON PEDIGREE SYMBOLS


Note: All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
SURGICAL OPTIONS FOR TREATING THE COLON AND RECTUM IN PATIENTS WITH 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 of proctectomy (sexual or bladder dysfunction)

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 (ie, concomitant Crohn’s disease, anal sphincter dysfunction, etc)

Advantages:
- Negligible risk of 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 of colorectal cancer
- One operation

Disadvantages:
- Risks of proctectomy
- Permanent stoma
- May discourage family members from seeking evaluation for fear of permanent stoma

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
THE REVISED BETHESDA GUIDELINES FOR TESTING COLORECTAL TUMORS FOR MICROSATELLITE INSTABILITY (MSI)

The Bethesda Criteria were developed in response to the emerging understanding of the pathologic spectrum and molecular characteristics of HNPCC-associated tumors. These criteria were intended to help identify tumors that should be tested for microsatellite instability, thereby identifying HNPCC patients. Although more inclusive (and therefore more sensitive) than Amsterdam Criteria, the Bethesda Criteria are not intended specifically for routine clinical application. It is generally understood that the greater the number of criteria satisfied, the greater the chance that subsequent molecular diagnostics will identify a mismatch repair deficit; however, colon cancer risk for individuals meeting these criteria, alone or in combination, cannot be adequately stratified at present. The greatest clinical utility of the Bethesda Criteria is to suggest the possibility of HNPCC in patients.

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

- Colorectal cancer diagnosed in a patient who is less than 50 years of age.
- Presence of synchronous, or metachronous HNPCC-associated tumors, regardless of age.
- Colorectal cancer with the MSI-H histology diagnosed in a patient who is less than 60 years of age.
- Colorectal cancer diagnosed in a patient with one or more first-degree relatives with an HNPCC-related cancer, with one of the cancers being diagnosed under age 50 years.
- Colorectal cancer diagnosed in a patient with two or more first- or second-degree relatives with HNPCC-related cancers, regardless of age.


Hereditary nonpolyposis colorectal cancer (HNPCC)-related cancers include colorectal, endometrial, stomach, ovarian, pancreas, ureter and renal pelvis, biliary tract, brain (usually glioblastoma as seen in Turcot syndrome), and small intestinal cancers, as well as sebaceous gland adenomas and keratoacanthomas in Muir-Torre syndrome.

MSI-H=microsatellite instability-high in tumors refers to changes in two or more of the five National Cancer Institute-recommended panels of microsatellite markers.


There was no consensus among the workshop participants on whether to include the age criteria in guideline 3 above; participants voted to keep less than 60 years of age in the guidelines.
MINIMUM CRITERIA FOR CLINICAL DEFINITION OF HNPCC
(AMSTERDAM CRITERIA I)\(^1\)

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

- One should be a first-degree relative of the other two;
- At least two successive generations must be affected;
- At least one of the relatives with colorectal cancer must have received the diagnosis before the age of 50 years;
- 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

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

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

Cancer Risk in Individuals with HNPCC up to Age 70 Years Compared to 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 years</td>
</tr>
<tr>
<td>Endometrium</td>
<td>2.7%</td>
<td>20%-60%</td>
<td>46 years</td>
</tr>
<tr>
<td>Stomach</td>
<td>&lt;1%</td>
<td>11%-19%</td>
<td>56 years</td>
</tr>
<tr>
<td>Ovary</td>
<td>1.6%</td>
<td>9%-12%</td>
<td>42.5 years</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 years</td>
</tr>
<tr>
<td>Small bowel</td>
<td>&lt;1%</td>
<td>1%-4%</td>
<td>49 years</td>
</tr>
<tr>
<td>Brain/central nervous system</td>
<td>&lt;1%</td>
<td>1%-3%</td>
<td>~50 years</td>
</tr>
</tbody>
</table>

Colorectal Cancer Screening

Manuscript

NCCN Categories of Evidence and Consensus

Category 1: Based on high-level evidence and uniform consensus.

Category 2A: Based on lower-level evidence including clinical experience and uniform consensus.

Category 2B: Based on lower-level evidence including clinical experience and nonuniform consensus (but no major disagreement).

Category 3: Based on any level of evidence but reflects major disagreement.

All recommendations are category 2A unless otherwise noted.

Overview

Colorectal cancer is the third most frequently diagnosed cancer in men and women in the United States. In 2008, an estimated 108,070 new cases of colon cancer and 40,740 new cases of rectal cancer will occur in the United States. During the same year, it is estimated that 49,960 people will die from colon and rectal cancer. Colorectal cancer mortality can be reduced by early diagnosis as well as by screening and polypectomy. Patients with localized colon cancer have 90% five-year survival rate. Thus, screening is a critical and particularly effective procedure for colorectal cancer prevention. Fecal occult blood test (FOBT) has been demonstrated to be an effective screening tool to reduce mortality associated with colorectal cancer by 33%. Other options for screening include colonoscopy, sigmoidoscopy, combined FOBT and sigmoidoscopy, computed tomographic (CT) colonography (also known as virtual colonoscopy) or double-contrast barium enema combined with proctoscopy.

Risk Assessment

The colorectal cancer screening guidelines stratify patients into three groups depending on their risk of getting colorectal cancer (CSCR-1). Colorectal screening is particularly important for African Americans since they have a higher risk of developing colon cancer and mortality.

Average Risk

The individuals at average risk of getting colorectal cancer are those 50 years or older with no history of adenoma and inflammatory bowel disease and negative family history.

Increased Risk

Individuals with personal history of adenomas, colorectal cancer, endometrial/ovarian cancer before 60 years of age, or inflammatory bowel disease as well as those with a positive family history are considered to be at increased risk for getting colorectal cancer.

Hereditary High Risk

Individuals who have had colorectal cancer before the age of 50 years, those with family history of clustering of colorectal cancer or hereditary nonpolyposis colon cancer (HNPCC) related cancers, personal or family history of polyposis syndromes are considered to be in the high risk category.

Individuals at Average Risk

Colorectal cancer risk assessment in persons without known family history is advisable by age 40 years to determine the appropriate age for initiating screening. Individuals with a negative family history for colorectal neoplasia and associated hereditary syndromes, and a negative personal history of colorectal neoplasia, HNPCC associated cancers and inflammatory bowel diseases represent the group at average risk for development of colorectal cancer. It is recommended...
that average risk screening begin at age 50 after discussions of the available options.

**Colorectal Cancer Screening for Persons at Average Risk**

Currently recommended options include colonoscopy every 10 years, annual FOBT (category 1) and flexible sigmoidoscopy every 5 years using a 60 cm or longer scope (CSCR-2). These recommendations are based on data from three randomized, controlled trials of FOBT conducted in the United States and Europe and two case-control studies of flexible sigmoidoscopy.10,11

If available, colonoscopy is the preferred screening modality for individuals at average risk. If the colonoscopy is incomplete, double-contrast barium enema or CT colonography or repeat colonoscopy would be an alternative screening option, at the discretion of the physician.

Flexible sigmoidoscopy followed by colonoscopic polypectomy has been used as the screening method and demonstrated a 45-79% of mortality reduction in case-control studies. Randomized, controlled trials of flexible sigmoidoscopy are still in progress in the United States and in the United Kingdom.12,13 It is recommended that polyps identified at sigmoidoscopy be biopsied by trained personnel to determine if polyps are hyperplastic or adenomatous or serrated adenoma. Patients with lesions larger than 1 cm should be referred directly to colonoscopy, since they are almost always adenomas, which also confer a risk of more proximal colonic neoplasms.

**Hyperplastic polyps**

A large body of literature indicates that hyperplastic polyps are not associated with significantly increased risk of colorectal cancer, and supports the recommendation that persons with hyperplastic polyps be screened as average risk. Recent literature, however, suggests that a small and poorly defined subset of persons with numerous large, right sided hyperplastic polyps may be at increased risk for colorectal cancer. This observation is based on two main lines of evidence. First, a few small series of patients with hyperplastic polyposis have been reported in whom high risk for cancer was observed. The majority, however, had concomitant adenomas or serrated adenomas.14 Secondly, there is accumulating literature suggesting that some cancers with extensive DNA methylation and microsatellite instability might derive from hyperplastic polyps.15 Based on these observations, it is recommended that more frequent screening and surveillance be considered in patients with large multiple right sided hyperplastic polyps (greater than 10 mm or more than 10 polyps). There are insufficient data regarding appropriate colonoscopic intervals. Such polyps should also be examined for presence of dysplasia, as well as for histological features of serrated adenomas.

**Adenoma**

Biopsy-proven adenoma or serrated adenoma as well as positive FOBT should be followed with colonoscopy (CSCR-2). Colonoscopy is also indicated for individuals in whom an abnormality is detected by a double-contrast barium enema or CT colonography. In patients undergoing colonoscopy, any polyps found should be removed, and follow-up strategies should be based on the endoscopic and pathologic findings (CSCR-3).

**Serrated adenoma**

Serrated adenomas have been associated with adenocarcinoma, but the pathologic classification is currently controversial and guidelines for screening such polyps are not established yet. Patients with these findings may need more frequent screening than those with hyperplastic polyps. Pending additional data, individuals with serrated adenomas are considered to be at similar risk to those with tubular adenomas and should be treated following the same guidelines.
Fecal Occult Blood Test

Two methods are currently available to determine the presence of fecal occult blood: guaiac and immunochemical. At present, guaiac-based, non-rehydrated technology is used (CSCR-2). Fecal occult blood testing should be performed on three successive stool specimens obtained while the patient adheres to a prescribed diet. Previously in the United States, Hemoccult™ test slides were rehydrated (ie, a drop of distilled water was added before adding the developer). However, this technique contributes significantly to a high incidence of false-positive results and is not recommended by the manufacturer. Hemoccult™ II SENSA is the guaiac technique currently recommended. It appears to be as sensitive as the original Hemoccult test and is more “reader friendly.” In the future, however, physicians will probably switch to immunochemical techniques, which are currently being investigated on a larger scale than in the past. To ensure adequate follow-up, a health care professional should coordinate this testing, so that the patient who has a positive FOBT result enters the health care system in a responsible way.16

Digital rectal examination (DRE) is not a proven method for colorectal screening and it has been shown that DRE is not associated with reduction in mortality from distal rectal cancer. Fecal occult blood testing of a specimen obtained at digital rectal examination is not recommended.17

Alternative Screening Options

Double-contrast Barium Enema

Double-contrast barium enema can be performed every 5 years in patients who are average risk of developing colon cancer. Although a double-contrast barium enema is relatively sensitive and specific for detecting large neoplasms, its availability is limited. Experience with this procedure is decreasing, because radiologists in training receive minimum exposure to this technique.

Computed Tomographic Colonography

CT colonography is evolving as a very promising technique for colorectal cancer screening.5 Various studies have demonstrated that virtual colonoscopy is very specific, especially in detecting polyps larger than 9 mm in individuals at average risk of developing colorectal cancer.18-22 Wide range of sensitivity for CT colonography (55-94%) was observed in all the studies. The accuracy of CT colonography for the detection of clinically important colorectal neoplasia, with at least one proven lesion measuring at least 1 cm was assessed in a multi-institutional retrospective diagnostic study (ACRIN-6656) involving 341 patients.23 Colonoscopy was used as the reference standard. The average sensitivity and specificity were 75% and 73% respectively. The performance of CT colonography was comparable to that of FOBT, flexible sigmoidoscopy and barium enema.

In 2005, two meta-analysis reviewed the performance of CT colonography in the detection of colorectal polyps.24,25 In one meta-analysis, CT colonography 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 CT colonography was heterogenous but improved as the polyps size increased in another meta-analysis (48% for polyps less than 6 mm, 70% for 6-9mm polyps and 85% for polyps larger than 9 mm. The specificity was uniform (92%) for the detection of all the polyps.

Preliminary results from the recently completed National CT Colonography Trial (ACRIN 6664) presented at the 2007 Annual Meeting of ACRIN also showed that CT colonography was comparable to colonoscopy for the detection of intermediate to large (90% sensitivity and 86% specificity for adenomas 10 mm or larger).2
Recently, Kim et al compared primary screening with CT colonography with primary screening with colonoscopy for the detection of advanced neoplasia. Although this study was not randomized, the detection rates were comparable between the two groups (3.2% for CT colonography and 3.4% for colonoscopy).

Available data indicate that CT colonography may be useful for the detection of intermediate (6-9mm) or larger polyps (larger than 10mm). Colonoscopy is still the preferred screening modality for all patients 50 years or older. If colonoscopy is not readily available or if it is contraindicated, then CT colonography or any other alternative technique will be appropriate.

**Stool DNA Test**

Stool DNA test is an emerging non-invasive diagnostic tool for colorectal cancer screening. Detection of molecular alterations in fecal DNA was studied initially using single-target DNA marker involving K-ras oncogene mutations. However, the overall sensitivity for detecting colorectal cancer using a single DNA-marker has been less than 40%, with the exception of adenomatous polyposis coli (APC) assay which has higher sensitivity for both the cancer and large adenomas.

Multitargeted DNA stool testing have been reported in several studies, based on the assay developed by Exact Sciences. In a prospective multicenter study conducted by Imperiale et al, multitargeted analysis of stool DNA was found to be more efficient than Hemoccult II in detecting colorectal neoplasm. One such DNA stool test for colorectal cancer screening has been made available for use by physicians. However, this test has not yet been approved by the FDA. Investigation is underway to test the efficacy of fecal DNA testing.

**Individuals at Increased Risk**

**Personal History of Adenoma**

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

Low risk adenomas are tubular, 2 or fewer, and less than 1 cm. In this group, colonoscopy should be repeated within 5 years. Emerging data suggest that the longer intervals are usually appropriate. If this examination is normal, colonoscopy should be repeated every 5-10 years (CSCR-3).

Advanced adenomas (10 mm or larger with greater than 25% villous histology or high-grade dysplasia) have been associated with increased risk. Recent study has shown that the identification of villous architecture and high-grade dysplasia is associated with poor reproducibility among pathologists. 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 cytological features of dysplasia).

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

Individuals with more than 10 adenomas or more than 15 cumulative adenomas in 10 years are recommended to undergo evaluation for a polyposis syndrome, though 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 with a strong family history. Hence, a detailed family history is crucial in patients with multiple adenomas.

Polypectomy of large sessile polyps is associated with a high rate of recurrence, attributed to the presence of residual adenoma tissue at the time of polypectomy. Hence, follow-up colonoscopy, within 2-6 months is appropriate in this setting, or when polypectomy is incomplete or involves removal of large sessile polyps. The NCCN Colon Cancer Guidelines provide suggestions for management if a malignant polyp is found at colonoscopy.

**Personal History of Colorectal Cancer**

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

In addition to colonoscopy, patients with rectal cancer should also undergo periodic limited endoscopic evaluation of the rectal anastomosis to identify local recurrence. Expert opinion supports repeat evaluation every 3-6 months for the first 2-3 years. No specific data clearly support rigid versus flexible sigmoidoscopy. The utility of routine endoscopic ultrasound for early surveillance is not defined.

Women with a personal history of endometrial or ovarian cancer prior to age 60 y are considered to be at mildly increased risk for colorectal cancer. Risk is highest for those women with a primary diagnosis prior to 50 y. However, this data is derived from populations that include persons with HNPCC who may account for some of the observed risk. Screening colonoscopy is recommended in this group at 5 year intervals beginning at age 40 y or at the age of diagnosis of ovarian or endometrial cancer.

**Inflammatory Bowel Disease**

It is well recognized that individuals with symptoms of pancolitis for 8 or more years are at an increased risk for colorectal cancer. Screening should be initiated 8-10 years after the onset of symptoms and should be performed by an endoscopist, who is familiar with the appearance of chronic inflammatory bowel disease (ulcerative colitis, Crohn’s
disease). When the disease is clinically quiescent, multiple four-quadrant biopsies (every 10 cm with 30 or more samples) should be taken for histologic examination using large cup forceps (CSCR-5). Strictures that are suggestive (particularly in ulcerative colitis) should be evaluated thoroughly using biopsy and brush cytology. Any masses, including so-called dysplasia-associated lesions, are, of course, of extreme concern. Endoscopic polypectomy should be performed when appropriate with biopsies of surrounding mucosa for the assessment of dysplasia.

Interpretation of dysplasia or intraepithelial neoplasia can be difficult. Pathologist experienced in interpreting inflammatory bowel disease lesions, should evaluate biopsies. Most findings of high-grade, multifocal or repeated low-grade dysplasia place the ulcerative colitis patient at high-risk for developing colorectal cancer. Prophylactic proctocolectomy with ileoanal anastomosis is preferred. These individuals should be referred to an experienced inflammatory bowel disease surgeon to discuss surgical options.

**Family History**

Family history is the most important risk factor for colorectal cancer. It is essential to obtain detailed family history including first-degree relatives (parents, siblings, and offspring), second-degree relatives (aunts, uncles, grandparents, great-grandparents, and half-siblings), and additional relatives with cancer (cousins, nieces and nephews). Sometimes, a great deal of information can be obtained by looking at first cousins as well. Grandchildren are often not old enough to manifest any of the clinical phenotypes of cancer syndromes (CSCR-A).

Minimal data are needed on each of the relatives. For instance, current age and age at diagnosis of any cancer as well as a date, age, cause of death, and availability of a tumor sample are very important for discerning whether relatives were at risk of 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 who have a first degree relative with a colorectal cancer prior to 50 years of age, or two first degree relatives with colorectal cancer at any age, or either clustering of HNPCC-related tumors or polyposis in close relatives are at increased risk for colorectal cancer. They should undergo hereditary evaluation and screening as outlined in CSCR-7 and CSCR-8. Screening colonoscopy (every 5 years) beginning at the age of 40 years old or 10 years prior to earliest cancer in family is recommended for those not meeting criteria for a defined syndrome or those with a first degree relative who has a colorectal cancer (CSCR-6).

Persons who have a second degree or any third degree relatives with colorectal cancer are screened as average risk individuals. However, it is recommended that risk assessment be individualized and include a careful family history to determine whether a familial clustering of cancers is present in the extended family. Individuals with a first-degree relative with adenoma should have screening colonoscopy beginning at the age of 50 or at the age of diagnosis of adenoma in the relative, whichever is sooner.

**Inherited Colon Cancer**

Genetic susceptibility to colorectal cancer includes defined inherited syndromes, such as hereditary nonpolyposis colorectal cancer (HNPCC, also known as Lynch syndrome), familial adenomatous polyposis (FAP), MYH-associated polyposis (MAP), Peutz-Jeghers syndrome, and juvenile polyposis as well as nonsyndromic familial colorectal cancer.
HNPCC is the most common form of a genetically determined colon cancer predisposition. This hereditary syndrome results from the germline mutations in DNA mismatch repair (MMR) genes (MLH1, MSH2, MSH6 and PMS2).\textsuperscript{43,44} The lifetime risk of colorectal cancer approaches 80\% in individuals carrying a mutation in an HNPCC gene. Hereditary nonpolyposis colorectal cancer is relatively common, accounting for 2-3\% of all colorectal cancer cases. Surveillance has been shown to reduce the risk of colorectal cancer and may be of benefit in the early diagnosis of endometrial cancer.\textsuperscript{45,46} Site-specific evaluation and heightened attention to symptoms is also advised for other cancers that occur with increased frequency in HNPCC, such as ovarian, gastric, and urethral cancers, though efficacy of surveillance of these sites has not been demonstrated.

FAP is an autosomal dominant condition characterized by a germline mutation in the APC gene, located on chromosome 5q21.\textsuperscript{47} Although FAP accounts for approximately 1\% of all colorectal cancers, its importance has been recognized as a paradigm for treating individuals at increased risk of cancer.\textsuperscript{48} The lifetime risk of cancer in individuals with classic FAP approaches 100\% by the age of 50. Management includes early screening and colectomy or proctocolectomy after the onset of polyposis. Genetic testing can be used to help manage cancer risk in patients and their family members.\textsuperscript{49} 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. This distinction makes an important difference in clinical management.

MAP is a recently described autosomal recessive hereditary syndrome that predisposes some individuals to attenuated adenomatous polyposis and colorectal cancer.\textsuperscript{50,51} It is reported in approximately 0.4\% of colorectal cancer patients. MAP is caused by biallelic germ line 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 thought to result from such transversions occurring within the APC gene.

Other entities that are important to recognize include suspected colon cancer syndromes, such as Muir-Torre, Turcot, and Peutz-Jeghers syndromes, and juvenile polyposis.\textsuperscript{52} These syndromes are also critical to understanding what could be the potential genetic basis for cancer in the family. If there is a concern about the presence of a hereditary syndrome, the guidelines recommend referring the patient to a genetic service or genetic counselor.

The newly developed test for I1307K, a mutation found among Ashkenazi Jews that predisposes them to colorectal cancer, has been intentionally excluded from the guidelines because there is very little evidence to date indicating what kinds of screening guidelines should be offered to individuals with this mutation.

**Inclusion Criteria for Inherited Colon cancer**

Individuals with the following risk factors should be evaluated for inherited colon cancer.

- Diagnosis of colorectal cancer at the age 50 years or younger
- Multiple primary HNPCC-related cancers or those with HNPCC-related cancer who have one or more first-degree relatives with HNPCC-related cancer prior to the age of 50 or two or more first or second degree relatives with an HNPCC related cancer diagnosed at any age. HNPCC-related cancers include colorectal, ovarian, endometrial, small bowel, stomach, sebaceous carcinomas or adenomas, ureteral or renal pelvic cancer, hepatobiliary, pancreatic or brain cancer especially glioblastomas.
Multiple colorectal adenomas or more than 10 adenomas.

Family with known hereditary syndrome associated with cancer with or without mutation.

**Evaluation for Inherited Colon Cancer**

A detailed family history, including ethnicity, as well as a detailed medical and surgical history and physical examination, is paramount in screening for inherited colorectal cancer syndromes (CSCR-7). The history should include questions about colon cancer syndromes or syndrome-specific features such as, polyps, inflammatory bowel disease, Gardner’s syndrome, Turcot’s syndrome, Juvenile polyposis, Muir-Torre, Peutz-Jeghers, Bannayan-Riley-Ruvalcaba, Cowden and MYH-associated polyposis. 

Pathologic verification is strongly encouraged. Directed examination for related manifestations should include colonoscopy, eye examination, esophagogastroduodenoscopy, skin, soft tissue and bone examination, and oral examination. Certain physical features that may be helpful in the recognition of FAP include congenital hypertrophy of retinal pigment epithelium (CHRPE), osteomas, odontomas, supernumerary teeth, epidermoid cysts, desmoids, and duodenal and other small-bowel adenomas.

Following evaluation, those with HNPCC, Classical or Attenuated FAP or MYH-associated polyposis are managed as described in the appropriate sections below. Referral to specialized team is recommended for those with Peutz-Jeghers syndrome or juvenile polyposis. Individuals with a familial risk and no syndrome should be managed as described for those with positive family history in CSCR-6.

**Hereditary Nonpolyposis Colorectal Cancer or Lynch Syndrome**

HNPCC is autosomal dominant syndrome that is responsible for 2-3% of all cases of colorectal cancer and it is characterized by germline mutations in MMR genes and microsatellite instability (MSI) of the colon cancers. Although seven genes (MSH2, MSH6, MLH1, MLH3, PMS1, PMS2 and EXO1) have been associated with HNPCC, mutations in four of these genes (MLH1, MSH2, MSH6 and PMS2) are known to cause HNPCC. Individuals with these mutations are at higher risk for developing colorectal, endometrial, and ovarian cancer. MMR mutations are found in about 60% of persons and families meeting the clinical criteria of HNPCC and MSI occurs in 85-90% of colon cancers that occur as a part of HNPCC.

Risk factors for the presence of HNPCC in a patient include autosomal dominant inheritance pattern affecting multiple generations, colon cancer in a first- or second-degree family member, colon cancer diagnosed under the age of 50 years, multiple primary cancers, including ovarian, endometrial, urethral/renal pelvis, small bowel, and stomach cancers, and predominance of right-sided colon cancer (CSCR-8). Breast cancer is not included in the guidelines as a risk factor and remains a fairly controversial aspect of what constitutes the clinical phenotype of HNPCC.

Due to the high risk for colorectal cancer, intensive screening is essential, though the exact interval has not been fully established in clinical trials. The recommendations in this area are based on the best evidence available to date, but more data are still needed.

**Molecular Work-up**

Genetic testing for HNPCC is somewhat more complicated than testing for FAP because several different genes contribute to the development of HNPCC. MSI and immunohistochemical (IHC) analysis done on colon cancer specimens are frequently first used to identify individuals who might have HNPCC. IHC analysis is used to detect the protein expression of MMR genes (MLH1, MSH2, MSH6 and PMS2) 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 5-10%. 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.\(^6\),\(^6\)\(^1\) Identification of the MSH6 mutation provides valuable information for HNPCC prevention, treatment, clinical management, and prognosis.\(^6\),\(^6\)\(^3\) Mixed strategy (MSI tumor testing for all colorectal cancer patients followed by germline MSH2 and MLH1 testing of MSI-high tumors) has been shown as the most cost-effective approach for HNPCC screening.\(^6\) However, conclusive data are not yet available that establishes which test is the most cost-effective screening mechanism in HNPCC.\(^6\),\(^6\),\(^6\),\(^6\)

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 microsatellite instability (CSCR-E).\(^6\)\(^9\) The National Cancer Institute introduced the revised Bethesda guidelines in 2002 to clarify selection criteria for the MSI testing.\(^7\)\(^0\) Bethesda guidelines are useful for the detection of MSI, leading to subsequent identification of MLH1 and MSH2 germline mutations. One study reported that MLH1 and MSH2 mutations were detected in 68% of the patients with MSI of the colon cancer tissue who met the Bethesda criteria.\(^7\)\(^1\)

MSI test is particularly helpful when the family history is not strongly suggestive of HNPCC. Families that meet the minimal criteria for consideration such as diagnosis before the age of 50, but no other criteria may not represent HNPCC. Microsatellite stable tumor arising within a young onset patient is very unlikely to represent HNPCC. Proceeding with genetic testing in this setting is unlikely to yield an informative result.

IHC analysis is usually performed for family members that meet the Amsterdam criteria I or II, since the there is a 50-92% chance of identifying a mutation in one of the four MMR genes in these individuals.\(^5\)\(^9\) The first version of the minimum criteria for clinical definition of HNPCC (Amsterdam criteria) was introduced in 1991 (CSCR-F), and these criteria were modified (Amsterdam II criteria) in 1999 (CSCR-G).\(^7\)\(^2\) MMR gene mutations are found in 88% of patients with MSI-positive tumors and who meet the Amsterdam criteria. Among patients with MSI-negative tumors, only 29% were found to have MMR gene mutations.\(^7\)

**Genetic Testing**

If HNPCC is suspected, an analysis of the tumor block for MSI provides diagnostic information, as well as guidance regarding the likelihood of informative predictive testing. Genetic screening for MSI is cost-effective for patients with newly diagnosed colon cancer as well as for the siblings and children of mutation carriers.\(^7\)\(^4\)

When a mutation is found in the family, it offers an opportunity to provide predictive testing for at-risk family members. Predictive testing can save people a lot of unnecessary procedures. It is important to consider genetic testing for at-risk family members when the family mutation is known (CSCR-8).

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 MSI analysis as outlined in CSCR-8. Almost all tumors arising within the context of HNPCC are microsatellite unstable. If tumor is available from the affected relative, and shows abnormal IHC or high MSI, genetic testing for mutations in MSH2, MLH1, MSH-6 and PMS2 should be considered. Those with normal IHC or low/stable MSI but do not meet the more stringent Amsterdam criteria, should be monitored with a colonoscopy based on individual risk assessment. If they meet the Amsterdam criteria or if a tumor is not available, then genetic testing for mutations in MSH2, MLH1, MSH-6 and PMS2 is recommended (CSCR-8). If a mutation of MLH1 or MSH2
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is not found, then MSI and/or IHC analysis of colon cancer tissue should be considered, to identify difficult to detect mutations in MLH1 or MSH2 or mutations in MSH6 or PMS2.

Because of the challenges that exist with the use of MSI testing and IHC staining of tumor tissue, several computer models have been developed for the prediction of a priori risk of HNPCC mutation detection.75,76,77,78

In those individuals who do not meet the revised Bethesda guidelines, the diagnosis of HNPCC should be reevaluated, and individualized management should be considered.

Screening, Follow-up Surveillance, and Treatment Options

Individuals with HNPCC are at an increased lifetime risk for colon cancer (80% vs. 5% respectively), endometrial cancer (20-60% vs. 3% respectively) and other cancers compared to the general population (CSCR-H). If HNPCC can be confirmed, colonoscopy is advised between the ages of 20 to 25 or 10 years younger than the youngest age at diagnosis in the family, whichever comes first, to be repeated every 1-2 years. This recommendation is based upon empiric data from a European trial of 251 patients that looked at the frequency and timing of colon cancer among individuals who carried known mutations for HNPCC or who did not carry mutations but were from HNPCC-like families. For women, an annual transvaginal ultrasound or endometrial aspirate, beginning at ages 25 to 35 years, should be considered. However, there are no definitive data to support the use of transvaginal ultrasound or endometrial biopsy to reduce the risk of cancer. Most of these individuals present with spotting or dysfunctional uterine bleeding, so that endometrial cancer can often be diagnosed relatively early.79

If there are no pathologic findings suggestive of HNPCC, continued screening is recommended. Total abdominal hysterectomy (TAH) and bilateral salpingo-oophorectomy (TAH/BSO) should be considered for this group of patients (CSCR-10). If the patient is not a candidate for routine screening, subtotal colectomy may be considered. This important feature comes up clinically often because some people cannot undergo a colonoscopy or decline to have one on a regular basis. Patients with confirmed adenocarcinoma should be treated following the NCCN Colon Cancer Guidelines.

If adenomas are not amenable to endoscopic resection or high-grade dysplasia is identified, total abdominal colectomy with an ileorectal anastomosis is recommended. The option of segmental or extended segmental colectomy is based on individual considerations and discussion of risks. Total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH/BSO) are not routinely recommended for HNPCC, although it is reasonable to discuss this option. If rectal cancer is involved, an appropriate surgical resection is recommended, with consideration of TAH/BSO at the time of rectal surgery. The guidelines also include endoscopic polypectomy with a follow-up colonoscopy every 1 to 2 years as a treatment option for patients with adenomas. This option depends on the location and character of the tumor, the surgical risk, and the patient's preference (CSCR-10).

When no familial mutation is found, follow-up includes colonoscopy at ages 20 to 25 or 10 years younger than the youngest age at diagnosis in the family, whichever comes first. Colonoscopy should be repeated every 1-2 years. Periodic evaluation (every 3-5 years) should be considered for associated intra-abdominal malignancies. Annual urinalysis with cytology and imaging of the renal collecting system are also should be considered. For female patients, follow up should also include annual endometrial sampling aspiration beginning at ages 25 to 35 or 5-10 years earlier than the earliest age of first diagnosis of these cancers in the family, and a transvaginal ultrasound (preferably
on day 1-10 of cycle for premenopausal women) with or without CA-125 testing every 6-12 months should be considered.

Presymptomatic individuals who have no symptoms and test negative for a known mutation in the family are not at risk of HNPCC based upon this particular mutation. This does not mean they are at zero risk; rather they are at average risk. Their cumulative lifetime risk is probably in the 6% range, or perhaps a little less; routine screening is recommended for these individuals.

Many other issues go into the genetic counseling associated with testing presymptomatic individuals for cancer susceptibility. A fair number of individuals elect not to undergo testing, and it is important to counsel these individuals so they continue with increased surveillance.

Familial Adenomatous Polyposis

Classical FAP

Diagnosis of classical FAP is based on the presence of over 100 polyps or fewer polyps at younger ages especially in a patient with a family history of FAP. Increasingly, family members are diagnosed at adolescence through genetic testing for their specific familial mutation or through sigmoidoscopic screening in the second decade of life. Because cancer incidence rises dramatically early in the third decade, prophylactic proctocolectomy is indicated in the second decade.

Fundic gland polyps (FGP) occur in the majority of FAP patients, 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 of gastric cancer in patients with FAP in Western countries is reported to be in the range of 0.5-1%. Endoscopic biopsies of FGP are not routinely recommended. However, the recommendation is to observe carefully for polyps that stand out because they appear irregular in shape or texture or large suggesting adenomas. It is also recommended that polyps in the antrum or immediate pre-antrum should be removed if possible. These are less common and are often adenomas. Patients with FAP are at risk for thyroid cancer with a lifetime risk of fewer than 2%, and female predominance (95%). Peak incidence is in the third decade of life with a mean age of 30 years. Yearly thyroid physical examination is recommended and is considered adequate for timely diagnosis and treatment.

Attenuated FAP

Attenuated FAP is a recently recognized variant of FAP characterized by a later onset of disease and fewer adenomas, typically less 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 colorectal cancer is typically delayed, but the incidence of cancer rises sharply after the age of 40 and is greater than 50%.

Surgical Options

Three different surgical options are available for individuals with classical and attenuated FAP (CSCR-D). The prime factors when choosing an operation for FAP are the personal and familial phenotype, including the rectal polyp burden and whether colon or rectal cancer is present at diagnosis. In patients with the classical FAP phenotype, proctocolectomy, if possible, is the procedure of choice, since it prevents both colon and rectal cancer.

Total proctocolectomy with ileal pouch anal anastomosis (IPAA)

Total proctocolectomy with ileal pouch anal anastomosis (IPAA), usually with a temporary loop ileostomy, is offered to patients with classical FAP, patient with attenuated FAP with severe phenotypes resulting in carpeting of the rectum, patients with curable colon or rectal...
cancer complicating the polyposis, and patients who underwent ileorectal anastomosis 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 ileal pouch anal anastomosis. The advantages of this operation are that the risks of developing rectal cancer are negligible and a permanent stoma is not needed. The disadvantages are that it is a complex operation, a temporary stoma is usually needed, and it carries a small risk of bladder and sexual dysfunction after proctectomy. Bowel function, although usually reasonable, is also somewhat unpredictable. The ileal pouch requires surveillance, and the area of the ileal pouch anal anastomosis should still be examined due to the imperfect nature of mucosectomy. The remaining controversy over the choice of total abdominal colectomy with ileorectal anastomosis versus total proctocolectomy with ileal pouch anal anastomosis centers on the issues of the relative quality of life. A modest reduction in life expectancy is expected in patients with classical FAP with rectal preservation. Proctoscopic examination of a retained rectum is indicated annually.

**Total abdominal colectomy with ileorectal anastomosis (IRA)**
A total abdominal colectomy with ileorectal anastomosis is a fairly quick, straightforward operation with an overall low morbidity rate. It generally results in good bowel function. Most patients have 3 to 4 bowel movements per day, and the risk of urgency, seepage, or fecal incontinence is low. Without proctectomy, there should be no risk of bladder or sexual function problems, and even a temporary stoma is obviated. The major disadvantages of IRA are the high risk of rectal cancer development and associated morbidity and mortality, the frequent need to undergo subsequent proctectomy because of severe rectal polyposis, and the real need for regular endoscopic surveillance of the retained rectum (every 6-12 months). Review of 659 patients in the Dutch-Scandinavian collaborative national polyposis registries who underwent colectomy with ileorectal anastomosis found a high rate of advanced and fatal rectal cancers even though 88% of the patients underwent an undiagnostic proctoscopy within 18 months of presentation. It was estimated that 12.5% of patients undergoing this procedure would die of rectal cancer by age 65 even if compliant with endoscopic screening. The authors concluded that proctocolectomy is the preferred procedure for most patients with the classical FAP phenotype, though some controversy remains regarding this choice. They and others also observed that patients could not be reliably selected for colectomy based on genotype alone. On the other hand, ileo-rectal anastomosis is the surgery of choice for the majority of patients with attenuated FAP who either have rectal sparing or endoscopically manageable rectal polyposis. It is not recommended for patients with curable colon or rectal cancer or those with extensive rectal or colonic polyposis. It is not recommended for patients with curable colon or rectal cancer or those with extensive rectal or colonic polyposis. Patients and families must be absolutely reliable for follow-up endoscopic examinations. The risk to the rectal stump rises considerably after the age of 50 and if the rectum becomes unstable, a proctectomy with either an ileal pouch anal anastomosis or end ileostomy is recommended.

**Total proctocolectomy with ileostomy (TPC)**
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 the 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 of bladder or sexual function disorders. This operation may be offered to patients with a low, locally advanced rectal cancer, patients who cannot have an ileal pouch
due to a desmoid tumor, patients with a poorly functioning ileal pouch, and patients who have a contraindication for an ileal pouch anal anastomosis (eg, 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 are either not suitable for total proctocolectomy with ileal pouch anal anastomosis (IPAA) or they have a poorly functioning IPAA. This is a complex operation with a significant risk for re-operation.

**Personal History of Classical FAP**

Prophylactic surgery (proctocolectomy or colectomy) remains the primary treatment of choice for this group of individuals. 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 (CSCR-12). In patients who are less than 18 years with mild polyposis and without family history of early cancers or genetic disposition, timing colectomy can be individualized.

**Personal History of Attenuated FAP**

Treating patients with a personal history of attenuated FAP varies depending on the patient’s age and adenoma burden. For patients aged 21 and younger with a small adenoma burden, colonoscopy and polypectomy are recommended every 1-2 years with appropriate surgical evaluation and counseling. In patients aged 21 and older with small adenomas, colectomy and ileorectal anastomosis are alternative treatment options. For patients over the age of 40 years and those who have significant polyposis that is not manageable with polypectomy, a colectomy and ileorectal anastomosis is recommended. Even over age 40, subjects with what appears to be an endoscopically manageable adenoma burden, particularly if responsive to a chemopreventive agent such as sulindac or celecoxib, may choose to defer consideration of colectomy (CSCR-15).

**Surveillance**

In patients with FAP, proctocolectomy surveillance involves annual physical exam, sigmoidoscopy and polypectomy. In practice, some patients have few or no recurrent polyps in the rectum and the follow up interval can probably be lengthened, cautiously, in such cases. The major surveillance in patients with a personal history of FAP or attenuated FAP after colectomy relates to the upper gastrointestinal tract (CSCR-16). It is recommended that physicians or centers with expertise in FAP should manage patients and the management should be individualized based on genotype, phenotype and other personal considerations. 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 exam and endoscopic examination if colectomy has been performed. Again, if rectal adenomas do not recur, longer follow up intervals may be safely followed.

**Chemoprevention**

Nonsteroidal anti-inflammatory drugs (NSAID) have been shown to reduce the incidence and recurrence of colorectal adenomas. 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 polyp regression and preventing recurrence of higher-grade adenomas in the retained rectal segment of FAP patients. However, in a randomized, double-blinded placebo-controlled study, sulindac did not prevent the development of adenomas in persons with FAP. NSAIDs are not effective as primary treatment of familial adenomatous polyposis. Prophylactic surgery remains the treatment of choice to prevent colorectal cancer in patients with FAP. Chemoprevention with NSAIDs can be considered following initial prophylactic surgery, as an
adjunct to endoscopic surveillance, to reduce the rectal polyp burden (CSCR-12 and CSCR-15).

Cyclooxygenase-2 (COX-2) inhibitors have been shown to be overexpressed in colorectal adenomas and cancers. Therefore, international multicenter studies have been conducted to study the effect of COX-2 inhibitors in the chemoprevention of colorectal adenomas. Results from Prevention of colorectal sporadic adenomatous polyps (PreSAP) trial also showed that the use of celecoxib significantly reduced the occurrence of colorectal adenomas within three years after polypectomy. 

Five-year safety and efficacy results showed that chemoprevention with celecoxib may be safe and effective for some high risk colorectal adenoma patients. At 5-years, the reduction in the incidence of advanced adenomas was 41% for those who received lower dose of celecoxib compared to 25% in patients who received the higher dose. Due to the increased risk of cardiovascular events associated with their use, COX-2 inhibitors are not recommended routinely for sporadic adenomas.

Duodenoscopic findings

Duodenal adenomas develop in over 90% of patients with FAP. These adenomas are classified into five stages (stage 0 to stage IV), as defined by Spigelman, based on macroscopic and histologic criteria. Duodenal cancer risk is uncommon under age 40 years, and rare under age 30 years. The cumulative risk of developing severe duodenal polyposis (stage IV) has been estimated to be around 40% by age 60-70. The risk of duodenal cancer increases dramatically with stage IV disease.

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

Endoscopic treatment options include endoscopic papillectomy in addition to excision or ablation of resectable large or villous adenomas as well as 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 (CSCR-16). Surgical evaluation and expert surveillance every 6-12 months is recommended for Stage IV polyps, invasive carcinoma as well as high-grade dysplasia or dense polyposis that cannot be managed endoscopically. Surgical counseling is also advisable for those with stage IV polyposis.

Family History of Classical FAP

Management of individuals with a family history of FAP depends on whether the familial mutation is known or unknown. For those who have a family history of FAP, there are two possible situations:

- Specific mutation that has caused familial polyposis in that family is known.
- Familial mutation is not known, but that family has a history of familial polyposis.

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. This does not mean telling those individuals that they must have APC testing. Rather, it means providing them with genetic counseling so that they are able to make informed decisions about the implications involved in genetic testing, as well as the implications for their own management.

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 are offered the same screening recommendation that is proposed for those who are known to carry the mutation; namely, flexible sigmoidoscopy or colonoscopy every 12 months, beginning at age 10 to 15 until the age of 24. Then screening is scaled down to every 2 years until age 34, every 3 years until age 44, and every 3-5 years thereafter (CSCR-13). One should also consider substituting colonoscopy every 5 years beginning at age 20 for a chance that a patient may have attenuated FAP. There are several reasons why screening is recommended so often for these individuals. First, adenomas may begin to develop in adolescence. Most people with classic FAP present with polyps before the age of 25, so annual screening with sigmoidoscopy will detect the majority of patients with FAP. Less often, people with FAP will not develop polyps until a later age. The probability of FAP in a person without any polyps on annual screening begins to decrease with age around this time, so that screening does not need to be as frequent between the ages of 24 and 34, and can be even less frequent between the ages of 34 and 44. However, even this recommended screening schedule is more rigorous than screening guidelines for the general population, because serial negative examinations up to age 35 do not exclude the diagnosis of FAP. It is important to recognize that individuals with attenuated polyposis may not present until a later age and may have fewer polyps than those with classic FAP; yet enhanced screening is still warranted in these people.

**Genetic Testing**

Genetic testing in individuals with familial polyposis should be considered before or at the age of screening. The age for beginning screening should be based on the patient’s symptoms, family phenotype and other individual considerations. Fatal colorectal cancer is rare before the age of 18 years. Following genetic counseling, if at-risk family members agree to undergo genetic testing, two outcomes are possible.

**APC positive**

The first outcome is that an individual at risk is found to carry an APC gene mutation. If he or she does have an APC gene mutation, there is a 90% probability that the individual will develop familial polyposis. Truncating mutation of the APC gene is detectable in about 80% of FAP patients using protein-truncating tests. These patients need to undergo flexible sigmoidoscopy or colonoscopy every 12 months, beginning at 10 to 15 years of age.

**APC negative**

The second outcome following genetic counseling is that an individual at risk is found not to carry the APC gene mutation responsible for familial polyposis in the family. For such individuals, screening as an average-risk patient is recommended.

**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 about 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, since
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.”

By far the best approach in this situation is to attempt to identify the
mutation in an affected family member, even if the available person is
not a first-degree relative. Without this information, genetic testing
offers less precision in estimating a person’s risk. If a mutation is found,
then they should be managed similar to those with known familial
mutations (CSCR-13). Gene testing excludes FAP in a person at risk
only when no mutation is found in that person and a mutation has been
identified in an affected family member. 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.³⁵ MYH testing should
be considered if APC gene mutation is negative and family is consistent
with a recessive inheritance.

Surveillance

Surveillance is identical for at-risk individuals who do not undergo
testing as well those for whom no familial mutation is found and it
involves flexible sigmoidoscopy or colonoscopy every 12 months,
beginning at 10-15 years of age. Substituting with colonoscopy is
recommended beginning at age 20 then every 5 years (CSCR-14). If
polyposis is detected then they should be managed in the same way as
those with personal history of FAP (CSCR-12).

Family History of Attenuated FAP

The same 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 (CSCR-17 and
CSCR-18). It is important to recognize that individuals with attenuated
disorders 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
is colonoscopy beginning at age 13 to 15, with repeat examinations
every 2-3 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 in which a familial mutation is not known. Families
with severe phenotype are managed similarly to patients with classical
FAP (CSCR-12 and CSCR-13).

Nonsyndromic Hereditary Colon Cancer

Risk based on a familial susceptibility that is not FAP and not HNPCC
must also be considered. This patient population comprises a more
substantial portion of individuals at risk and probably accounts for 10%
to 15% of all colorectal cancer patients. In that situation, they are
considered to be at moderately high risk and screening should begin at
age 40 or 10 years before the earliest date of cancer onset in the
family.

MYH-associated polyposis

Most individuals with MAP generally have fewer than 100 polyps
(15-100) although some have been reported to present with more than
100 polyps. 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 of 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
retropective data which suggest that screening for MYH mutation
should be considered for patients with multiple polyps, early-onset of colorectal cancer and for patients who meet the clinical criteria for FAP, attenuate FAP or HNPCC in the absence of APC or MMR gene mutations respectively.\textsuperscript{115,116} Balaguer et al recently reported that patients with colorectal cancer and more than 15 synchronous colorectal adenomas or those younger than 50 years might benefit from MYH genetic testing.\textsuperscript{117}

NCCN guidelines recommend genetic counseling and testing for germ line MYH mutations for siblings of affected patients, as well as for patients with adenomatous polyposis (more than 10 adenomas or more than 15 cumulative adenomas in 10 y) whose family history is consistent with recessive inheritance (CSCR-19). Testing for APC gene mutations usually precedes testing for MYH mutations, except in families in which only siblings are affected (suggesting recessive inheritance rather than \textit{de novo} mutations).

Colonoscopy screening of asymptomatic patients with known mutations and of siblings of affected patients is recommended beginning at age 25 to 30 years at 3-5 year intervals (the shorter intervals with advancing age). Patients with colorectal adenomas are managed similarly to patients with attenuated FAP (CSCR-15). Those with small adenoma burden are followed up with colonoscopy and complete polypectomies of all polyps. Surgery (colectomy or proctocolectomy) is recommended, depending on adenoma distribution and density for those with dense polyposis not manageable by polypectomy. The absolute risk of colorectal cancer and the role of surgery in patients with MYH polyposis who are manageable by polypectomy are not known.

Upper endoscopy and side viewing duodenoscopy should be considered for affected patients, as well as for those at risk, starting at age 30 to 35 years for every 3-5 years. Patients with duodenal adenomas are managed similarly to patients with FAP (CSCR-16).

References


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