National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Colorectal Cancer Screening

Version 2.2012

NCCN.org

Continue

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2012 Panel Members
Colorectal Cancer Screening

NCCN Guidelines Index
Colorectal Screening TOC
Discussion

* **Randall W. Burt, MD/Chair** ¤ Δ
Huntsman Cancer Institute at the University of Utah

James S. Barthel, MD ¤ Þ
H. Lee Moffitt Cancer Center & Research Institute

Jamie A. Cannon, MD ¶
University of Alabama at Birmingham Comprehensive Cancer Center

Donald S. David, MD ¤
City of Hope Comprehensive Cancer Center

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

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

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

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

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

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

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

Mohammad K. Ismail, MD ¤
St. Jude Children's Research Hospital/ University of Tennessee Cancer Institute

Kory Jasperson, MS, CGC Δ
Huntsman Cancer Institute at the University of Utah

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

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

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

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

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

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

Moshe Shike, MD ¤ Þ
Memorial Sloan-Kettering Cancer Center

Gideon Steinbach, MD, PhD ¤ Þ
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

NCCN
Mary Dwyer, MS
Deborah Freedman-Cass, PhD

¤ Gastroenterology
Δ Cancer Genetics
Þ Internal Medicine
† Medical Oncology
≠ Pathology
¶ Surgery/Surgical Oncology
* Writing Committee Member

Continue

NCCN Guidelines Panel Disclosures

NCCN Guidelines Version 2.2012 Table of Contents
Colorectal Cancer Screening

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

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

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

See NCCN Categories of Evidence and Consensus.

NCCN Guidelines Version 2.2012 Updates
Colorectal Cancer Screening

Updates to the 2.2012 version of the Colorectal Cancer Screening Guidelines from the 1.2012 version include:

- **The addition of the discussion to reflect the changes in the algorithm (MS-1).**

Updates in Version 1.2012 of the Colorectal Cancer Screening Guidelines from Version 2.2011 include:

CSCR-1

- **Footnote was removed from the page: "A negative family history is not having a first-degree relative or two second-degree relatives with colorectal cancer (advanced adenoma) or multiple cases of Lynch syndrome/HNPCC-related cancers in the family."**

CSCR-2

- **Evaluation of positive screening findings, qualifiers were added after hyperplastic, "left-sided, non SSP, and <1 cm."**
- **Footnotes**
  - **Footnote "d" was added: "There is direct evidence from randomized controlled trials that fecal occult blood testing (Mandel JS, et al. NEJM 1993: 328:1365-1371; Hardcastle JD, et al. Lancet 1996; 348: 1472-77; Kronborg O, et al. Lancet 1996; 348: 1467-71) and flexible sigmoidoscopy (Atkin WS, et al. Lancet 2010; 375:1624-33) will reduce mortality from colorectal cancer. Given the available evidence from case control and cohort studies, however, it is the consensus opinion of the panel that colonoscopy should be the preferred method of screening, due to its potential ability to prevent colorectal cancer (with its associated morbidity), and cancer deaths (Kahi CJ, et al. Clin Gastro Hep 2009;7:710-715; Baxter NN, et al. Ann Intern Med. 2009;150:1-8)."**
  - **Footnote "f" was modified as: "If colonoscopy is incomplete *or preparation is suboptimal*, consider other screening modality..."**
  - **Footnote "j" was added: "There is controversy over whether SSP should be called "sessile serrated adenomas." These terms are equivalent and these guidelines will use "SSPs." However, any serrated lesions in the proximal colon should be followed similarly to adenomatous polyps."**

CSCR-3

- **Footnote "m" was added: "Shorter intervals may be necessary when there is uncertainty about completeness of removal in large and/or sessile polyps. Shorter intervals may be necessary if the colonic preparation was suboptimal."**
- **Footnote "n" was added: "The decision to choose a 5- or 10-year interval after a low-risk exam is a patient-specific one. The factors that can be taken into account to formulate this decision include: adequacy of the preparation and other technical considerations, the results of the prior examinations, and the presence of other co-morbid conditions. Generally the results of the first two screening examinations may predict the patient's overall colon cancer risk. (USPSTF, Screening for colorectal cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2008;149:627-637)."**

CSCR-4

- **Footnote "p" was modified as: "Expert opinion supports repeat evaluation *every 6 mo x 5 y for patients' status post LAR* ~~every 3-6 months for the first 2-3 years of surveillance~~."**

CSCR-5

- **Initiation of screening was modified as, "8-10 y after onset of symptoms *of pancolitis*" and "*12 y after onset of left-sided colitis.*"**
- **Evaluation of positive screening findings, "Sporadic colorectal adenoma" was added with corresponding footnote "u," "Patients with ulcerative colitis develop sporadic colorectal adenomas at the same rate as the general population. Lesions that appear endoscopically and histologically similar to a sporadic adenoma, with no dysplasia in the flat mucosa in the surrounding area or elsewhere in the colon and without invasive carcinoma in the polyp, can be treated safely by polypectomy and continuous surveillance."**
- **Footnotes**
  - **Footnote "s," "Winawer S, Fletcher R, Rex D, et al. Gastroenterology 2003;124:544-560" was replaced with "Levin B, Lieberman DA, McFarland B, et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology..."**
  - **Footnote "t" was added: "Biopsies can be better targeted to abnormal-appearing mucosa using chromoendoscopy, narrow-band imaging, autofluorescence, or confocal endomicroscopy. Targeted biopsies have been found to improve detection of dysplasia, and should be considered for surveillance colonoscopies in patients with ulcerative colitis."**

CSCR-6

- **"Increased risk based on positive family history" has been extensively revised.**

Continued on next page

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

NCCN Guidelines Version 2.2012 Updates
Colorectal Cancer Screening

Updates in Version 1.2012 of the Colorectal Cancer Screening Guidelines from Version 2.2011 include:

CSCR-A 2 of 4
- 1st bullet was modified as: "*In the US*, colonoscopy is the primary method employed for colorectal cancer screening..."

CSCR-A 3 of 4
- FIT, 3rd bullet was modified from "Requires single stool annually" to "Many brands require only a single stool annually."
- Footnote "9" was added: "There is category 1 data that guaiac-based FOBT and flexible sigmoidoscopy reduce mortality from colorectal cancer."

CSCR-A 4 of 4
- Footnote "12" was modified by adding: "However, the data available suggests that if CT colonography is negative/no polyps, then repeat CT colonography in 5 years and if CT colonography is positive/polyps lesions >*5 mm*, colonoscopy should be performed."

Lynch Syndrome

LS-1
- Footnote "a" was modified by adding: "An infrastructure needs to be in place to handle the screening results."

LS-2
- Surveillance
  - Endometrial and ovarian cancer,
    - 2nd sub-bullet was modified from "Perform patient education which would include recommending prompt response to endometrial cancer symptoms" to "Patients must be aware that dysfunctional uterine bleeding warrants evaluation."
    - 3rd sub-bullet was modified as: "However, annual office endometrial sampling *is an option* ~~may be useful in select patients~~."
    - 4th sub-bullet has been modified as: "Transvaginal ultrasound for ovarian and endometrial cancer *has not been shown to be sufficiently sensitive or specific as to support a positive recommendation, but* may be considered at the clinician's discretion."
  - Gastric and small bowel cancer, sub-bullet was added, "There is no clear evidence to support screening for gastric and small bowel cancer for LS, may consider:" and the following was removed, "Preliminary data suggests other screening may be considered as follows: Baseline gastric biopsies to evaluate for chronic inflammation, atrophic gastropathy, and intestinal metaplasia and consider shorter screening intervals in persons with extensive histological change and longer intervals in persons with normal histology. Evaluate for H. pylori on the biopsies and by serology and treat those with evidence of infection. Consider enteroscopy at the time of EGD to evaluate the distal duodenum and jejunum."
  - Urothelial cancer was revised as: "Consider annual urinalysis starting at 25-30 y."
  - Central nervous system cancer was revised as: "Annual physical examination starting at 25-30 y."
- Footnote
  - Footnote "h" was added: "Since the average age of colon cancer onset for *MSH6* or *PMS2* mutation carriers is somewhat older than for *MLH1* and *MSH2* mutation carriers...depending on ages of cancers observed in family members."

LS-A 1 of 2
- Immunohistochemistry, 2nd bullet, 3rd sentence was changed from, "Genetic testing of peripheral blood DNA to find a disease causing mutation of one of the mismatch repair genes should then be done." to "Individuals with abnormal IHC or MSI results should preferably be referred for genetic counseling so that the appropriate follow-up testing can be offered to the patient. In some cases, this would include testing for abnormal methylation of the MLH1 promoter and in others, it would include germline genetic testing of one or more of the mismatch repair genes."

LS-A 2 of 2
- For the gene known as TACSTD1, "EPCAM" was added as an alternative name.

LS-B
- 2nd bullet was clarified as: "Presence of synchronous, or metachronous, *colorectal or other* Lynch syndrome-associated tumors, regardless of age."

LS-D
- The table has been updated.

Continued on next page

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

NCCN Guidelines Version 2.2012 Updates Colorectal Cancer Screening

Updates in Version 1.2012 of the Colorectal Cancer Screening Guidelines from Version 2.2011 include:

Familial Adenomatous Polyposis

FAP-1

- Attenuated FAP phenotype, 5th bullet was modified as, "Other extraintestinal manifestations, including CHRPE and desmoids. are unusual ~~rare~~."

FAP-3

- Surveillance, 1st bullet was modified as: "Duodenal or periampullary cancer: Baseline upper endoscopy (including side-viewing examination), ~~repeat every 1-3 y depending on severity of polyposis. repeat every 1-3 y depending on severity of polyposis~~." The bullet is directed to "See Duodenoscopic Findings."

FAP-A

- A statement regarding the surgical options was added: "TAC/IRA is preferred for AFAP and TPC/IPAA is generally recommended for FAP."
- Total abdominal colectomy with ileorectal anastomosis,
  - Indications, sub-bullet was modified from "Patients with few (<20) rectal polyps and mild colonic disease (<100) polyps" to "The decision to remove the rectum is dependent on whether the polyps are amenable to endoscopic surveillance and resection."
  - Advantages, 5th sub-bullet was modified from "Avoids risk of proctectomy (sexual or bladder dysfunction)" to "Avoids the risks of sexual or bladder dysfunction that can occur following proctectomy."
- Total proctocolectomy with end ileostomy,
  - Disadvantages, 1st subbullet was modified as: "Risks of ~~proctectomy~~ *sexual or bladder dysfunction*."
- Total proctocolectomy with ileal pouch anal anastomosis,
  - Disadvantages, 3rd sub-bullet was modified as: "Risks of ~~proctectomy~~ *sexual or bladder dysfunction,*" and 4th subbullet was modified as, "Functional results ~~can be unpredictable~~ *are variable*."

MUTYH-Associated Polyposis

MAP-1

- Phenotype, "Consanguinity" was added.
- Footnote "a" was added: "Hyperplastic polyps may also be seen in this setting."

Juvenile Polyposis Syndrome

JPS-1

- Surveillance considerations, 1st bullet was modified as: "*Approximately 50% of* JPS cases occur due to mutations in the BMPR1A and SMAD4 genes..." and a corresponding footnote, "In individuals with SMAD4 mutations, recommend screening for vascular lesions associated with hereditary hemorrhagic telangiectasia" was added.

Serrated Polyposis Syndrome

SPS-1

- Previously known as "hyperplastic polyposis syndrome."
- This page had been extensively revised.

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

NCCN Guidelines Version 2.2012
Colorectal Cancer Screening

NCCN Guidelines Index
Colorectal Screening TOC
Discussion

RISK ASSESSMENT FOR COLON CANCER

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

→ See Average-Risk Screening and Evaluation (CSCR-2)

Increased risk:
- Personal history
  - Adenoma/sessile serrated polyp (SSP)[a] → See Follow-up of Clinical Findings: Adenomatous Polyp or Sessile Serrated Polyp (CSCR-3)
  - CRC → See Increased Risk Screening Based on Personal History of Colorectal Cancer (CSCR-4)
  - Inflammatory bowel disease (ulcerative colitis, Crohn's disease) → See Increased Risk Screening Based on Personal History of Inflammatory Bowel Disease (CSCR-5)
- Positive family history → See Increased Risk Screening Based on Positive Family History (CSCR-6)

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

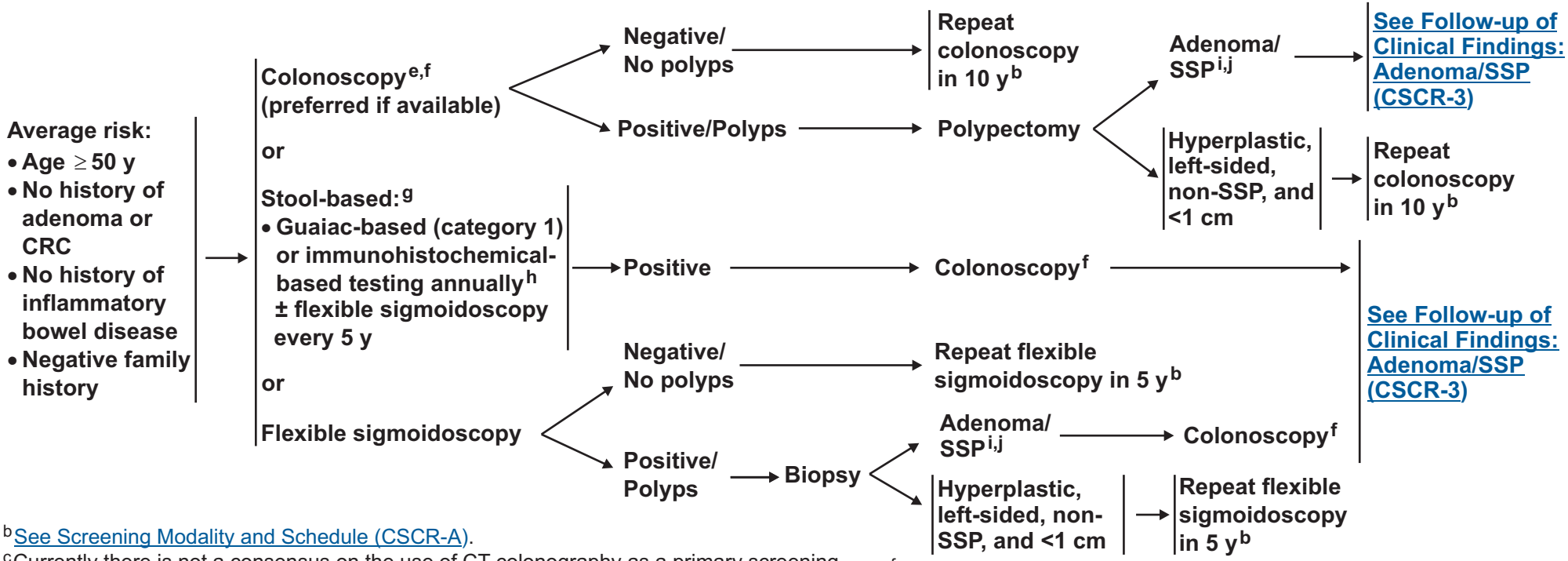
→ See Criteria for Further Risk Evaluation for High-Risk Syndromes (HRS-1)

[a]SSP is synonymous with sessile serrated adenoma but does not include classical hyperplastic polyp.

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

NCCN Guidelines Version 2.2012
Colorectal Cancer Screening

NCCN Guidelines Index
Colorectal Screening TOC
Discussion



[b] See Screening Modality and Schedule (CSCR-A).

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

[d] There is direct evidence from randomized controlled trials that fecal occult blood testing (Mandel JS, et al. NEJM 1993: 328:1365-1371; Hardcastle JD, et al. Lancet 1996; 348:1472-77, Kronborg O, et al. Lancet 1996; 348:1467-71) and flexible sigmoidoscopy (Atkin WS, et al. Lancet 2010; 375:1624-33) will reduce mortality from colorectal cancer. Given the available evidence from case control and cohort studies, however, it is the consensus opinion of the panel that colonoscopy should be the preferred method of screening, due to its potential ability to prevent colorectal cancer (with its associated morbidity), and cancer deaths (Kahi CJ, et al. Clin Gastro Hep 2009;7:770-775; Baxter NN, et al. Ann Intern Med 2009;150:1-8).

[e] Other screening modalities such as double contrast barium enema should be reserved for those who are not able to undergo colonoscopy, or colonoscopy is technically incomplete.

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

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

[h] Studies at the present time have demonstrated that fecal immunohistochemical testing (FIT) is as good as, if not superior to, guaiac-based testing.

[i] SSPs are managed the same as adenomas.

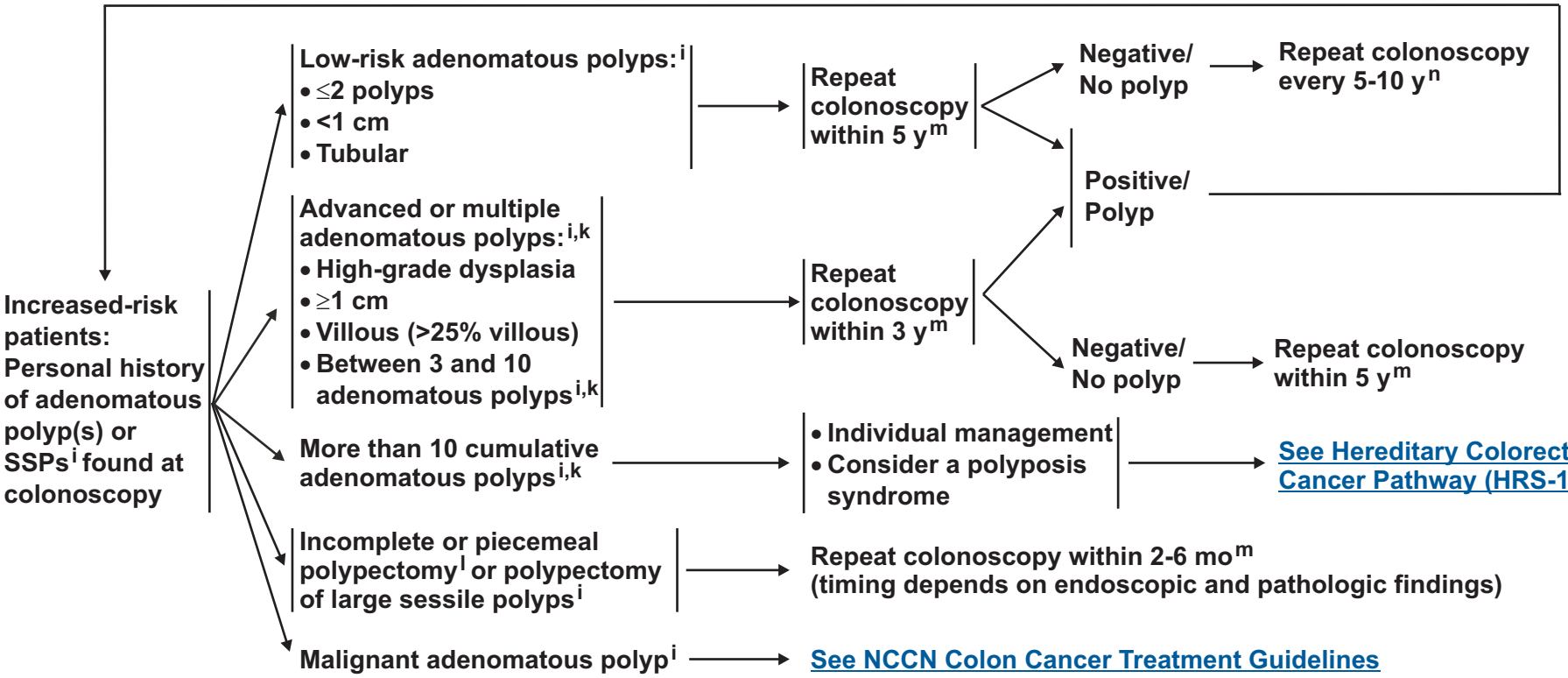
[j] There is controversy over whether SSPs should be called "sessile serrated adenomas." These terms are equivalent and these guidelines will use "SSPs." However, any serrated lesions in the proximal colon should be followed similarly to adenomatous polyps.

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

NCCN Guidelines Version 2.2012
Colorectal Cancer Screening

NCCN Guidelines Index
Colorectal Screening TOC
Discussion

INCREASED RISK BASED ON PERSONAL HISTORY OF ADENOMATOUS POLYP OR SESSILE SERRATED POLYP[i]



[b] See Screening Modality and Schedule (CSCR-A).

[i] SSPs are managed the same as adenomas.

[k] Ten or fewer polyps in the setting of a strong family history or younger age (< 40 y) may sometimes be associated with an inherited polyposis syndrome.

[l] Ink lesion for later identification, sterile carbon black ink preferred.

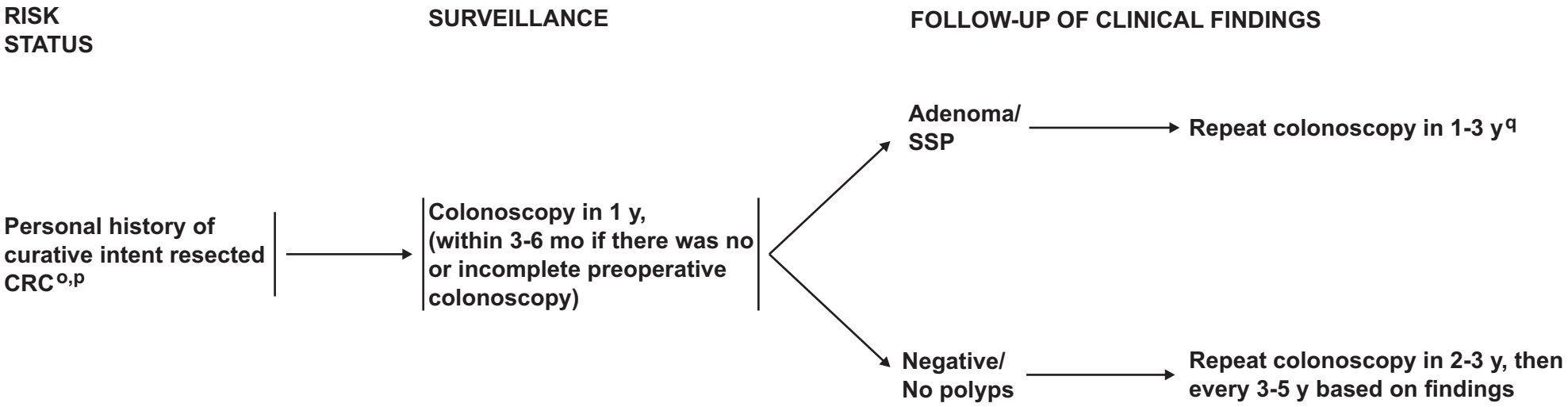
[m] Shorter intervals may be necessary when there is uncertainty about completeness of removal in large and/or sessile polyps. Shorter intervals may be necessary if the colonic preparation was suboptimal.

[n] The decision to choose a 5- or 10-year interval after a low-risk exam is a patient-specific one. The factors that can be taken into account to formulate this decision include: adequacy of the preparation and other technical considerations, the results of the prior examinations, and the presence of other co-morbid conditions. Generally the results of the first two screening examinations may predict the patient's overall colon cancer risk. (USPSTF, Screening for colorectal cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2008;149:627-637).

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

NCCN Guidelines Version 2.2012
Colorectal Cancer Screening

INCREASED RISK BASED ON PERSONAL HISTORY OF COLORECTAL CANCER



[o] Identify colorectal patients who meet Bethesda criteria. Those patients may require genetic counseling or individualized management. (See High Risk Syndromes, HRS-1 and Lynch Syndrome, LS-1).

[p] 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 6 mo x 5 y for patients' status post LAR. 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 Rectal Cancer Guidelines.

[q] 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.

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

NCCN Guidelines Version 2.2012
Colorectal Cancer Screening

NCCN Guidelines Index
Colorectal Screening TOC
Discussion

INCREASED RISK BASED ON PERSONAL HISTORY OF INFLAMMATORY BOWEL DISEASE

RISK STATUS	INITIATION OF SCREENING	SCREENING MODALITY AND SCHEDULE	EVALUATION OF POSITIVE SCREENING FINDINGS	FOLLOW-UP OF CLINICAL FINDINGS[v,w]
Personal history of inflammatory bowel disease[r] • Ulcerative colitis • Crohn's disease, especially if pancolitis	→ • 8-10 y after onset of symptoms of pancolitis[s] • 12 y after onset of left-sided colitis[s]	→ Colonoscopy every 1-2 y • When clinically quiescent, 4 quadrant biopsies every 10 cm with >30 total samples (preferred)[t] • Additional extensive sampling of strictures and masses • Endoscopic polypectomy when appropriate with biopsies of surrounding mucosa for the assessment of dysplasia	→ • Dysplasia/intraepithelial neoplasia ➤ Confirmation by an expert GI pathologist is desirable • Sporadic colorectal adenoma[u]	→ Surgical consultation for resection[x]

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

[s] Levin B, Lieberman DA, McFarland B, et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: A joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. CA Cancer J Clin 58:130-160.

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

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

[v] 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.

[w] 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.

[x] See Definitions of Common Colorectal Resections (CSCR-B).

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

NCCN Guidelines Version 2.2012
Colorectal Cancer Screening

NCCN Guidelines Index
Colorectal Screening TOC
Discussion

INCREASED RISK BASED ON POSITIVE FAMILY HISTORY

FAMILY HISTORY CRITERIA[y]	SCREENING	
1 first-degree relative with CRC aged <50 y[z] or 2 first-degree relatives with CRC at any age[z]	Colonoscopy beginning at age 40 y or 10 y before earliest diagnosis of CRC	Repeat every 3-5 y depending on individual family history[bb]
First-degree relative with CRC aged ≥ 50 y[aa]	Colonoscopy beginning at age 50 y or 10 y before earliest diagnosis of CRC	Repeat every 5 y[bb,cc]
1 second-degree relative with CRC aged <50 y	Colonoscopy beginning at age 50 y	Repeat every 5 y[bb,cc]
≥ 2 second-degree relatives with CRC at any age	Colonoscopy beginning at age 50 y	Repeat every 7-8 y (every 5 y if grandparent with CRC)[cc]
1 second-degree relative and ≥ 2 third-degree relatives with CRC at any age	Colonoscopy beginning at age 50 y	Repeat every 7-8 y[cc]
Grandparent aged >50 y with CRC	Colonoscopy beginning at age 50 y	Repeat every 7-8 y[cc]
Aunt/uncle aged >50 y with CRC or 3 third-degree relatives with CRC at any age	Colonoscopy beginning at age 50 y	Repeat every 10 y
First-degree relative with advanced adenoma(s)	Colonoscopy beginning at age 50 y or at age of onset, whichever is first	Repeat every 7-8 y[cc] or per colonoscopy findings

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

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

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

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

[cc] Multiple (2 or more) negative colonoscopies may support stepwise increases in the colonoscopy interval by 1 year. (eg, every 5 y = ages 50, 55, 61, 68, and 75-76).

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

NCCN Guidelines Version 2.2012
Colorectal Cancer Screening

NCCN Guidelines Index
Colorectal Screening TOC
Discussion

SCREENING MODALITY AND SCHEDULE (1 of 4)

- **Colon cancer prevention and early detection should be the primary goal of CRC screening.**
- **Screening of average-risk individuals can reduce CRC mortality by detecting cancer at an early, curable stage and by detecting and removing adenomas. It has also been shown to be cost-effective compared to other screening programs.**
- **Although patient preferences and availability of resources play an important role in the selection of screening options, tests that are designed to detect both early cancer and adenomatous polyps should be encouraged.**

Screening modalities that detect adenomatous polyps and cancer[1,2,3,4]

- **Colonoscopy every 10 years,**
- **Flexible sigmoidoscopy every 5 years,**
- **CT colonography every 5 years**[5]

Screening modalities that primarily detect cancer[2,3,4,6]

- **Stool-based screening**
  - **Guaiac-based testing annually,**
  - **Immunochemical-based testing annually,**
  - **Stool DNA test with high sensitivity (interval for screening is uncertain)**[7]

Continued on next page

[1] If other modalities are not available, double-contrast barium enema every 5 years may be useful.

[2] Levin B, et al. Screening and Surveillance for the Early Detection of Colorectal Cancer and Adenomatous Polyps, 2008: A Joint Guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. Gastroenterology 2008;134:1570-1595.

[3] USPSTF, Screening for colorectal cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2008;149:627-637.

[4] Rex DK, et al. American College of Gastroenterology guidelines for colorectal cancer screening 2008. Am J Gastroenterol 2009;104:739-750.

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

[6] Annual stool-based testing with every 5-year flexible sigmoidoscopy can be used in combination for screening.

[7] Emerging technologies such as stool DNA have shown increasing evidence as a reasonably accurate screening test, but there are limited data to determine an interval between screening. At present, stool DNA is not considered a first-line screening test except in specific circumstances.

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

SCREENING MODALITY AND SCHEDULE (2 of 4)

Colonoscopy

- In the US, colonoscopy is the primary method employed for CRC screening in average and high-risk populations. However, screening with any of the available modalities is preferable to no screening.
- Caveats for the 10-year interval:
  - A 10-year interval is appropriate for average-risk patients who had an optimal procedure.
  - Shorter intervals may be indicated based on the quality and completeness of the colonoscopy.
  - Individual risk factors and physician judgment should be included in the interval determination.
  - The number and characteristics of polyps as well as family history and medical assessment should influence judgment regarding the interval between colonoscopies.
  - Colonoscopy has limitations and may not detect all cancers and polyps.
- Accumulating data suggest that there is substantial variability in the quality, and by extension, the clinical effectiveness of colonoscopy. Improving the overall impact of screening colonoscopy requires a programmatic approach that addresses quality issues at several levels.
- These colonoscopy quality indicators include:
  - Cecal intubation rates
  - Withdrawal time
  - Adenoma detection rates
  - Appropriate intervals between endoscopic studies based on family and personal history and number and histological type of polyps on last colonoscopy
  - Minor and major complication rates
  - Pre-procedure medical evaluation
  - Appropriate prep instructions
- Standardized colonoscopy reports that contain, at a minimum:[8]
  - Patient demographic, clinical factors, adenoma and cancer history, and GI family history
  - Procedure indications
  - Endoscopic findings, including polyp number, size, location, and method of excision
  - Photographic documentation of endoscopic landmarks
  - Estimate of quality of bowel preparation
  - Documentation of follow-up planning, including pathology results
  - Sedation administered
  - Written communication of the findings and plans to the patient and referring physician is encouraged.
- Pathology should also include polyp number, size and location in addition to histopathology.

Continued on next page

[8] Lieberman D, Nadel M, Smith RA, et al. Standardized colonoscopy reporting and data system: Report of the Quality Assurance Task Group of the National Colorectal Cancer Roundtable. Gastrointestinal Endoscopy 2007;65:757-766.

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.

SCREENING MODALITY AND SCHEDULE (3 of 4)

Flexible sigmoidoscopy[9]

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

Stool-based screening

- Guaiac-based, nonrehydrated[9]
  - Requires 3 successive stool specimens annually (not via digital rectal examination), prescribed diet, and coordination by health care provider
  - Any positive test requires further evaluation
  - Annual guaiac-based testing should not be performed if screening colonoscopy is used as a screening measure in an average-risk patient
- Fecal immunohistochemical testing (FIT)
  - Detects human globin
  - Prescribed diet is not required
  - Many brands require only a single stool annually
  - Any positive test requires further evaluation

Continued on next page

[9]There is category 1 data that guaiac-based FOBT and flexible sigmoidoscopy reduce mortality from colorectal cancer.

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.

SCREENING MODALITY AND SCHEDULE (4 of 4)

Radiographic

CT colonography (CTC)[10,11,12]

- **Accuracy**
  - **>10 mm lesions can be identified by CTC with an accuracy similar to colonoscopy**
  - **Lesions 5-9 mm can be identified with an acceptable accuracy that is less than that identified for colonoscopy**
  - **Lesions <5 mm cannot be identified with acceptable accuracy**
- **Follow-up of identified lesions**
  - **All identified lesions >5 mm should be referred for colonoscopy**
  - **When identified, lesions <5 mm generally do not need to be referred for colonoscopy**
- **The recommended performance interval of every 5 years is based solely on computer simulation models**
- **All visualized extracolonic findings should be described and recommendations should be provided as to appropriate follow-up**
- **The increased risk of cancer arising from the performance of a single CTC is estimated to be <0.14%**
- **CTC interpretation should be accomplished only by those trained according to American Gastroenterological Association[5] or American College of Radiology (ACR)[6] guidelines**
- **Procedure quality should be tracked and assured using current ACR practice guidelines for patient preparation, image acquisition, study interpretation, and reporting**

[10] See American Gastroenterological Association CT Colonography Standards.

[11] See American College of Radiology Practice Guideline for the Performance of Computed Tomography (CT) Colonography in Adults.

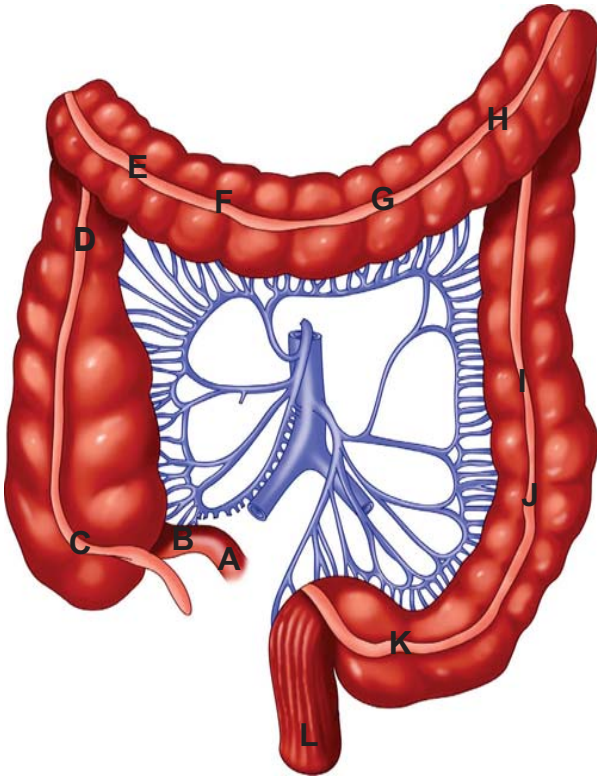
[12] Currently there is not a consensus on the use of CT colonography as a primary screening modality, and it is evolving with regards to recommended/ programmatic frequency, polyp size leading to referral for colonoscopy, and protocol for evaluating extra colonic lesions. However, the data available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

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.

DEFINITIONS OF COMMON COLORECTAL RESECTIONS

The extent of colorectal resection depends upon the location of the tumor, any underlying condition (eg, inflammatory bowel disease, hereditary syndrome), and the vascular supply to the colorectum.

Definitions of common colorectal resections are as follows:[1]



A through C Ileocecetomy

A through D Ascending colectomy

A through F Right hemicolectomy

A through G Extended right hemicolecotmy

E through H Transverse colectomy

G through I Left hemicolectomy

F through I Extended left hemicolectomy

J through K Sigmoid colectomy

A through J Subtotal colectomy

A through K Total colectomy

K through L Low anterior resection with sphincter preservation

K through L Abdominoperineal resection without sphincter preservation

[1] Adapted and reprinted with permission from Bullard KM and Rothenberger DA. (2005). Colon, Rectum, and Anus. In Brunicardi C (Ed.) Schwartz's Principles of Surgery, 8th Edition, page 1069. McGraw Hill: New York, NY.

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

NCCN Guidelines Version 2.2012
High-Risk Syndromes

NCCN Guidelines Index
Colorectal Screening TOC
Discussion

CRITERIA FOR FURTHER RISK EVALUATION FOR HIGH-RISK SYNDROMES

Individual meeting the revised Bethesda guidelines[a] (See LS-B)

or

Individual from a family meeting Amsterdam criteria (See LS-C)

or

>10 adenomas in same individual (See FAP-1 and MAP-1)

or

Individual with multiple GI hamartomatous polyps (See PJS-1 and JPS-1) or serrated polyposis syndrome (See SPS-1)

or

Individual from a family with a known hereditary syndrome associated with CRC, with or without a known mutation (See appropriate hereditary syndrome)

→

RISK ASSESSMENT/ GENETIC COUNSELING[b,c]

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

→

HEREDITARY SYNDROME

- Lynch syndrome (LS) (See LS-1)
- Classical familial adenomatous polyposis (FAP) (See FAP-1)
- Attenuated FAP (AFAP) (See AFAP-1)
- *MUTYH*-associated polyposis (MAP) (See MAP-1)
- Peutz-Jeghers syndrome (PJS)[d] (See PJS-1)
- Juvenile polyposis syndrome (JPS)[d] (See JPS-1)
- Serrated polyposis syndrome (SPS) (See SPS-1)
- No syndromes, but familial risk present → See Positive Family History (CSCR-6)

[a] Endometrial cancer <50 y is not included in the revised Bethesda guidelines; however recent, evidence suggests that these individuals should be evaluated for LS.
[b] See Obtaining a Comprehensive Risk Assessment for Hereditary Colorectal Cancer (HRS-A).
[c] A genetic counselor and/or medical geneticist should be involved early in counseling patients who (potentially) meet criteria for an inherited syndrome. Genetic counseling is advised when genetic testing is offered.
[d] Referral to a specialized team is recommended.

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

NCCN Guidelines Version 2.2012
High-Risk Syndromes

NCCN Guidelines Index
Colorectal Screening TOC
Discussion

OBTAINING A COMPREHENSIVE ASSESSMENT FOR HEREDITARY COLORECTAL CANCER

Family history of colorectal cancer and expanded pedigree

- It is essential to obtain a detailed family history, including:
  - Parents
  - Children
  - Siblings/half-siblings
  - Aunts and uncles
  - Grandparents
  - Great-grandparents
  - Cousins
  - Nieces and nephews

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

- Minimal data set on each relative:
  - Current age and age at diagnosis of cancer (medical record documentation of cancer is strongly encouraged)
  - Age/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 (eg, Muir-Torre syndrome, Turcot syndrome, Peutz-Jeghers, juvenile polyposis)[1]
  - All other inherited conditions and birth defects

Detailed medical and surgical history

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

Directed examination for related manifestations

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

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

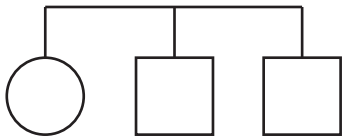
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

OBTAINING A COMPREHENSIVE ASSESSMENT FOR HEREDITARY COLORECTAL CANCER

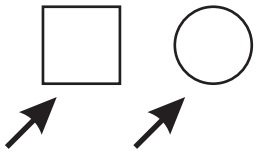
COMMON PEDIGREE SYMBOLS[2]

Male, Female

Mating

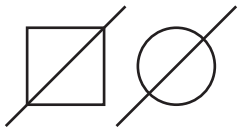


Sibship

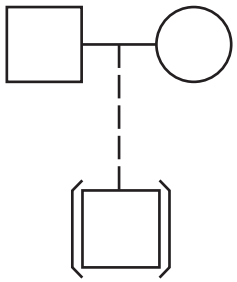


Proband (patient initiating genetic workup)

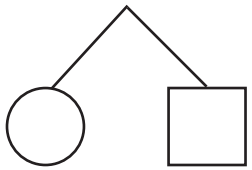
Affected with trait



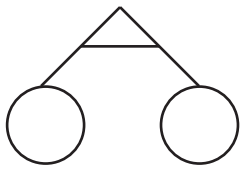
Deceased



Adopted into a family



Dizygotic twins



Monozygotic twins

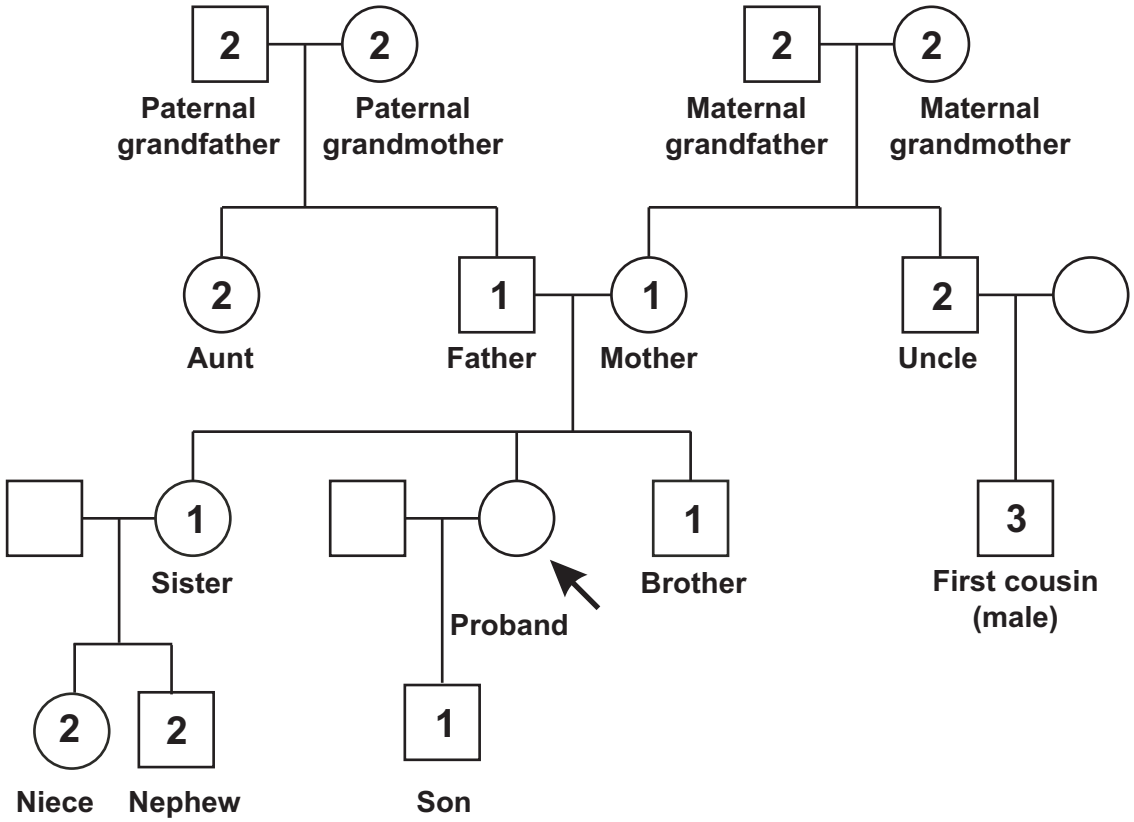
See Pedigree: First-, Second-, and Third-Degree Relatives of Proband (HRS-A 3 of 3)

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

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

OBTAINING A COMPREHENSIVE ASSESSMENT FOR HEREDITARY COLORECTAL CANCER

PEDIGREE: FIRST-, SECOND-, AND THIRD-DEGREE RELATIVES OF PROBAND[3]



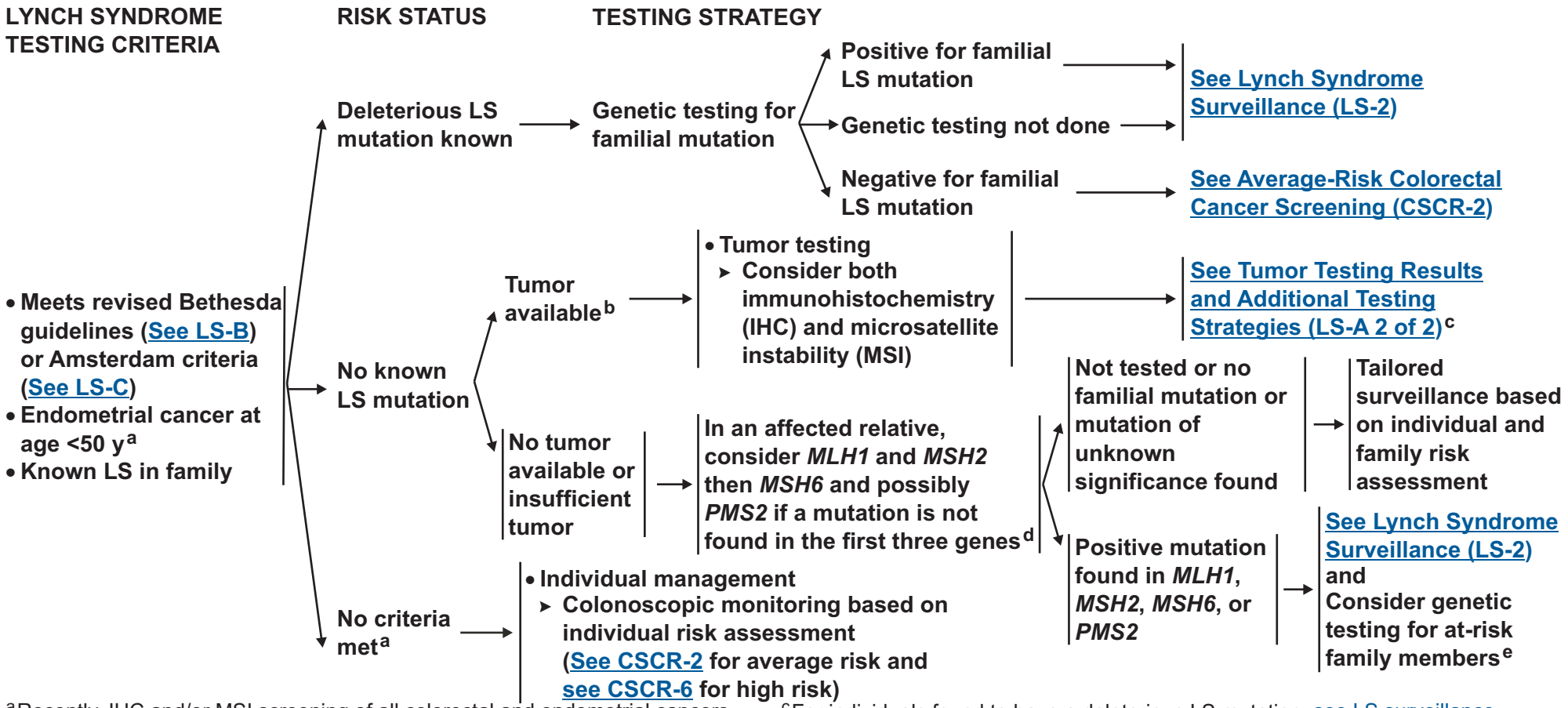
See Common Pedigree Symbols (HRS-A 2 of 3)

[3]First-degree relatives: parents, siblings, and children;
Second-degree relatives: grandparents, aunts, uncles, nieces, nephews, and half-siblings;
Third-degree relatives: great-gandparents and cousins.

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

NCCN Guidelines Version 2.2012
Lynch Syndrome

NCCN Guidelines Index
Colorectal Screening TOC
Discussion



[a] Recently, IHC and/or MSI screening of all colorectal and endometrial cancers, regardless of age at diagnosis or family history, has been implemented at some centers to identify individuals at risk for LS. This approach was recently endorsed for colorectal cancer by the Evaluation of Genomic Applications in Practice and Prevention Working Group from the CDC and shown to be cost-effective (EGAPP Recommendation Statement. Genetics in Medicine 2009;11:35-41). An infrastructure needs to be in place to handle the screening results.

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

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

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

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

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.

SURVEILLANCE[f,g]

Colon cancer:

- **Colonoscopy at age 20-25 y[h] or 2-5 y prior to the earliest colon cancer if it is diagnosed before age 25 y and repeat every 1-2 y.**

Extra colonic:

- **Endometrial and ovarian cancer:**
  - **Prophylactic hysterectomy and bilateral salpingo-oophorectomy is a risk-reducing option that should be considered by women who have completed childbearing.**
  - **Patients must be aware that dysfunctional uterine bleeding warrants evaluation.**
  - **There is no clear evidence to support screening for endometrial cancer for LS. However, annual office endometrial sampling is an option.**
  - **While there may be circumstances where clinicians find screening helpful, data do not support routine ovarian screening for LS. Transvaginal ultrasound for ovarian and endometrial cancer has not been shown to be sufficiently sensitive or specific as to support a positive recommendation, but may be considered at the clinician's discretion. Serum CA-125 is an additional ovarian screening test with caveats similar to transvaginal ultrasound.**
- **Gastric and small bowel cancer:**
  - **There is no clear evidence to support screening for gastric and small bowel cancer for LS, may consider:**
    - **Esophagogastroduodenoscopy (EGD) with extended duodenoscopy (to distal duodenum or into the jejunum) at 2- to 3-y intervals beginning at age 30-35 y. Consider capsule endoscopy for small bowel cancer at 2- to 3-y intervals beginning at age 30-35 y.**
- **Urothelial cancer: Consider annual urinalysis starting at 25-30 y.**
- **Central nervous system cancer: Annual physical examination starting at 25-30 y; no additional screening recommendations have been made.**
- **Pancreatic cancer: Due to limited data, no recommendation is possible at this time.**

→ See Follow-up of Surveillance Findings (LS-3)

[f] See Cancer Risk in Individuals with HNPCC Up to Age 70 Years Compared to the General Population (LS-D).

[g] Other than colon and endometrial cancer, screening recommendations are expert opinion rather than evidence based.

[h] Since the average age of colon cancer onset for *MSH6* or *PMS2* mutation carriers is somewhat older than for *MLH1* and *MSH2* mutation carriers, the start of colon screening may be delayed 5 years (ie, to age 30 years), but may need to be earlier than age 30 in some families, depending on ages of cancers observed in family members.

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

NCCN Guidelines Version 2.2012
Lynch Syndrome

SURVEILLANCE FINDINGS	FOLLOW-UP
No pathologic findings	• Continued surveillance[i] • Consider prophylactic total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAH/BSO) if postmenopausal or family completed
Adenocarcinomas	See appropriate NCCN 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[j] → Endoscopic rectal exam every 1-2 y • Consider TAH/BSO at time of colon surgery if postmenopausal or family completed

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

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

PRINCIPLES OF IHC AND MSI TESTING FOR LYNCH SYNDROME

IHC and MSI analyses are screening tests (either by themselves or in conjunction), typically done on colon cancer tissue to identify individuals at risk for LS.

IHC

- **IHC refers to staining tumor tissue for protein expression of the four mismatch genes known to be mutated in LS: *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 is present. An abnormal test means that at least one of the proteins is not expressed and an inherited mutation may be present in the related gene. Loss of protein expression by IHC in any one of the mismatch repair genes guides genetic testing (mutation detection) to the gene where protein expression is not observed.**
- **Ten percent to 15% of sporadic colon cancers exhibit abnormal IHC, often due to abnormal methylation of the *MLH1* gene promoter, but occasionally due to an inherited mutation of one of the mismatch repair genes. Thus, the presence of an abnormal IHC test increases the possibility of LS but does not make a definitive diagnosis. Individuals with abnormal IHC or MSI results should preferably be referred for genetic counseling so that the appropriate follow-up testing can be offered to the patient. In some cases, this would include testing for abnormal methylation of the MLH1 promoter and in others, it would include germline genetic testing of one or more of the mismatch repair genes. Most patients will be found to have sporadic colon cancer and not a germline mutation. Those with a germline mutation are then identified as LS patients.**
- **There is a 5-10% false negative-rate with IHC testing.**

MSI

- **MSI-H (microsatellite instability-high) in tumors refers to changes in two or more of the five microsatellite markers in the National Cancer Institute-recommended panel. Its significance, use, and implications are similar to that of IHC, although the tests are slightly complementary.**
- **There is a 5-10% false negative-rate with MSI testing.**

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

- **Recently, IHC and/or MSI screening of all CRCs and endometrial cancers regardless of age at diagnosis or family history, have been implemented at some centers to identify individuals at risk for LS. This approach was recently endorsed for colon cancer by the Evaluation of Genomic Applications in Practice and Prevention Working Group from the CDC and shown to be cost-effective.[1]**

[1] EGAPP Recommendation Statement. Genetics in Medicine 2009;11:35-41.

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

NCCN Guidelines Version 2.2012
Lynch Syndrome

NCCN Guidelines Index
Colorectal Screening TOC
Discussion

TUMOR TESTING RESULTS AND ADDITIONAL TESTING STRATEGIES

Tumor Testing[a]							Plausible Etiologies	Additional Testing
IHC				MSI	BRAF V600E[b]	MLH1 Promoter Methylation		
MLH1	MSH2	MSH6	PMS2					
+	+	+	+	MSS/MSI-Low	N/A	N/A	1) Sporadic cancer	1) None[c]
+	+	+	+	MSI- High	N/A	N/A	1) Germline mutation in any one of the known mismatch repair genes	1) Consider germline testing of *MLH1* and *MSH2* followed by *MSH6* and possibly *PMS2*
N/A	N/A	N/A	N/A	MSI- High	N/A	N/A	1) Sporadic cancer or germline mutation in any one of the known mismatch repair genes	1) Consider IHC testing to guide genetic testing 2) If IHC not done, *MLH1* and *MSH2* genetic testing followed by *MSH6* and possibly *PMS2*
--	+	+	--	N/A	N/A	N/A	1) Sporadic cancer 2) Germline mutation *MLH1*	1) Consider *BRAF*[b]/methylation studies 2) *MLH1* genetic testing if no *BRAF* mutation and/or hypermethylation, or testing not done
--	+	+	--	N/A	Positive	N/A	1) Sporadic cancer	1) None[c]
--	+	+	--	N/A	Negative	Positive	1) Sporadic cancer 2) Rarely germline mutation *MLH1* or constitutional *MLH1* epimutation	1) None, unless young age of onset or significant family history; then consider *MLH1* genetic testing or if young onset consider evaluation for constitutional *MLH1* epimutation
--	+	+	--	N/A	Negative	Negative	1) Germline mutation *MLH1*	1) *MLH1* genetic testing
+	--	--	+	N/A	N/A	N/A	1) Germline mutation *MSH2* 2) Germline mutation in *TACSTD1* (*EPCAM*); rarely germline mutation in *MSH6*	1) *MSH2* genetic testing, if negative TACSTD1 (EPCAM) testing 2) Consider *MSH6* genetic testing, if *MSH2* and *TACSTD1* (*EPCAM*) are negative
--	+	+	+	N/A	N/A	N/A	1) Germline mutation *MLH1*	1) *MLH1* genetic testing
+	+	+	--	N/A	N/A	N/A	1) Germline mutation *PMS2* 2) Rarely germline mutation *MLH1*	1) *PMS2* genetic testing 2) *MLH1* genetic testing, if negative *PMS2*
+	--	+	+	N/A	N/A	N/A	1) Germline mutation *MSH2*	1) *MSH2* genetic testing
+	+	--	+	N/A	N/A	N/A	1) Germline mutation *MSH6* 2) Germline mutation *MSH2*	1) *MSH6* genetic testing 2) Consider *MSH2* genetic testing, if negative *MSH6*

[a] Tumor testing strategies apply to colorectal and endometrial cancers. Limited data exists regarding the efficacy of tumor testing in other LS tumors.
[b] Testing is not appropriate for tumors other than colorectal cancer.
[c] If strong family history (ie, Amsterdam criteria) is present, additional testing may be warranted in the proband, or consider tumor testing in another affected family member due to the possibility of a phenocopy.

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

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[1]

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

- **Colorectal cancer[2] diagnosed in a patient who is less than 50 years of age.**
- **Presence of synchronous, or metachronous, colorectal or other LS-associated tumors,[3] regardless of age.**
- **Colorectal cancer with the MSI-H histology[4] 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 LS-related cancer,[3] 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 LS-related cancers[3] regardless of age.**

Many NCCN institutions have implemented IHC and/or MSI screening of all newly diagnosed colorectal cancers regardless of age or for age <70 years in order to identify individuals at risk for LS. This approach was endorsed for colorectal cancer by the Evaluation of Genomic Applications in Prevention and Practice group from the CDC and shown to be cost-effective (EGAPP Recommendation Statement. Genetics in Medicine 2009;11:35-41.). Also see: Ladabaum, U., et al. Strategies to identify the Lynch syndrome among patients with colorectal cancer: A cost-effectiveness analysis. Ann Intern Med 2011;155:69-79.
An infrastructure needs to be in place to handle the screening results.

[1] Adapted with permission from Umar A, Boland CR, Terdiman JP, et al. Revised Bethesda Guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. J Natl Cancer Inst 2004;96:261-268.
[2] Endometrial cancer <50 y is not included in the revised Bethesda guidelines; however, recent evidence suggests that these individuals should be evaluated for LS.
[3] LS-related cancers include colorectal, endometrial, gastric, ovarian, pancreas, ureter and renal pelvis, biliary tract, brain (usually glioblastoma as seen in Turcot syndrome), and small intestinal cancers, as well as sebaceous gland adenomas and keratoacanthomas as seen in Muir-Torre syndrome.
[4] Presence of tumor infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern.

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

NCCN Guidelines Version 2.2012
Lynch Syndrome

NCCN Guidelines Index
Colorectal Screening TOC
Discussion

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

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)[1,2]

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.**

[1] From Vasen HFA. Clinical diagnosis and management of hereditary colorectal cancer syndromes. J Clin Oncol 2000;18(suppl 1):81s-92s.
[2] Approximately 50% of patients with HNPCC will be missed by these criteria, and approximately 50% of patients will meet the criteria and not have HNPCC but a high familial risk of uncertain etiology.

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

NCCN Guidelines Version 2.2012
Lynch Syndrome

NCCN Guidelines Index
Colorectal Screening TOC
Discussion

Cancer Risk in Individuals with HNPCC up to Age 70 Years Compared to the General Population[1]

Cancer	General Population Risk	Lynch Syndrome *MLH1* and *MSH2* heterozygotes	
		Risks	Mean Age of Onset
Colon	5.5%	52%-82%	44-61 years
Endometrium	2.7%	25%-60%	48-62 years
Stomach	<1%	6%-13%	56 years
Ovary	1.6%	4%-12%	42.5 years
Hepatobiliary tract	<1%	1.4%-4%	Not reported
Urinary tract	<1%	1%-4%	~55 years
Small bowel	<1%	3%-6%	49 years
Brain/central nervous system	<1%	1%-3%	~50 years
Sebaceous neoplasms	<1%	1%-9%	Not reported
Pancreas[2]	<1%	1%-6%	Not reported

[1] Adapted from Kohlmann W, Gruber SB (Updated August 11, 2011) Lynch Syndrome. In: GeneReviews at GeneTests: Medical Genetics Information Resource (database online). Copyright, University of Washington, Seattle. 1997-2011. Available at http://www.genetests.org. Accessed March 6, 2012.
[2] Kastrinos F, Mukherjee B, Tayob N, et al. Risk of pancreatic cancer in families with Lynch syndrome. JAMA 2009;302:1790-1795.

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

NCCN Guidelines Version 2.2012
Familial Adenomatous Polyposis

NCCN Guidelines Index
Colorectal Screening TOC
Discussion

PHENOTYPE

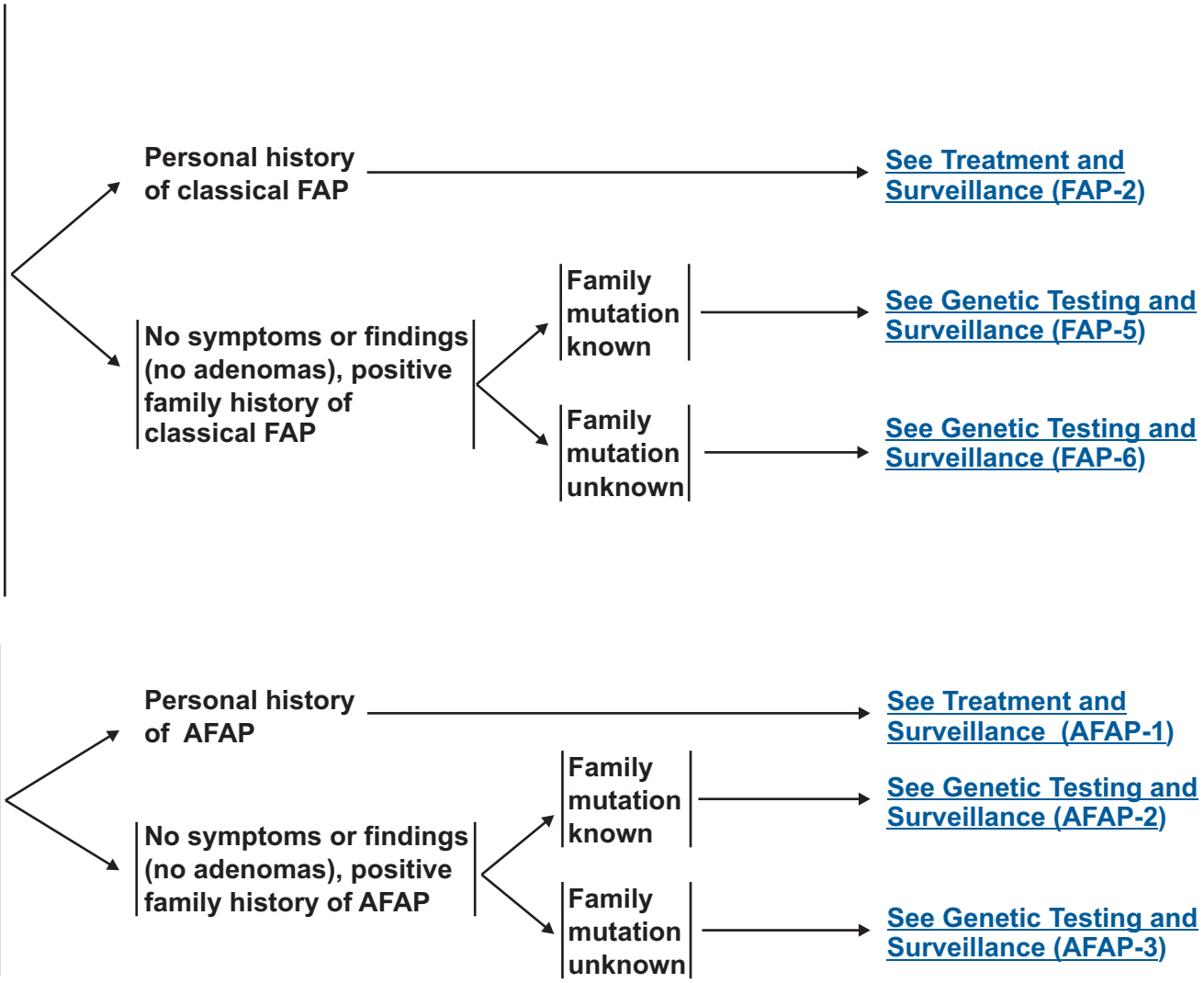
Classical FAP:

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

AFAP

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

RISK ASSESSMENT



[a] Individuals with 100 or more polyps occurring at older ages (35 to 40 years or older) may be found to have AFAP.
[b] There is a thirty percent spontaneous new mutation rate, thus family history may be negative. Especially noteworthy if onset age <50 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.

CLASSICAL FAP TREATMENT AND SURVEILLANCE: PERSONAL HISTORY

Personal history of classical FAP → **Proctocolectomy or colectomy**[c,d,e] →

TREATMENT

SURVEILLANCE[f,g] **(POSTCOLECTOMY)**

Colon cancer:

- **If patient had colectomy with ileorectal anastomosis, then endoscopic evaluation of the rectum every 6-12 mo depending on polyp burden.**
- **If patient had total proctocolectomy with ileal pouch-anal anastomosis or ileostomy, then endoscopic evaluation of the ileal pouch or ileostomy every 1-3 y depending on polyp burden. Surveillance frequency should be increased to every 6 mo for large, flat polyps with villous histology and/or high-grade dysplasia.**
- **Consider nonsteroidal anti-inflammatory drug (NSAID) chemoprevention to reduce polyp burden as a pharmacological adjunct to endoscopic surveillance. A clinical trial is encouraged.**

Extracolonic Surveillance **(See FAP-3)**

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

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

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

[e] Timing of colectomy in patients <18 y of age is not established. In patients <18 y with mild polyposis and without family history of early cancer or severe genotype, the timing of colectomy can be individualized. An annual colonoscopy if surgery is delayed.

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

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

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

CLASSICAL FAP SURVEILLANCE: PERSONAL HISTORY

SURVEILLANCE[f,g] (POSTCOLECTOMY)

Extracolonic:

- **Duodenal or periampullary cancer: Baseline upper endoscopy (including side-viewing examination).** → See Duodenoscopic Findings (FAP-4)
- **Gastric cancer: Examine stomach at time of duodenoscopy. Fundic gland polyps occur in a majority of FAP patients, and focal dysplasia is typical but is almost invariably non-progressive. For this reason, special screening or surgery is not needed unless high-grade dysplasia is present.**
- **Thyroid cancer: Annual thyroid examination, starting in late teenage years. Annual thyroid ultrasound may be considered, though data to support this recommendation are lacking.**
- **CNS cancer: An annual physical examination; due to limited data, no recommendation is possible at this time.**
- **Intra-abdominal desmoids: Annual abdominal palpation. If family history of symptomatic desmoids, consider abdominal MRI or CT 1-3 y post-colectomy and then at 5 - 10 y intervals. Suggestive abdominal symptoms should prompt immediate abdominal imaging.**
- **Small bowel polyps and cancer: Consider adding small bowel visualization to CT or MRI for desmoids as outlined above, especially if duodenal polyposis is advanced.**
- **Hepatoblastoma: No recommendations have been made for FAP; however there are other situations where the high risk for hepatoblastoma has been observed and the following recommendations have been considered:**
  - **Liver palpation, abdominal ultrasound, and measurement of AFP, every 3-6 mo, during the first 5 y of life. Screening in a clinical trial is preferred.**
- **Pancreatic cancer: Due to limited data, no recommendation is possible at this time.**

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

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

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

NCCN Guidelines Version 2.2012
Familial Adenomatous Polyposis

NCCN Guidelines Index
Colorectal Screening TOC
Discussion

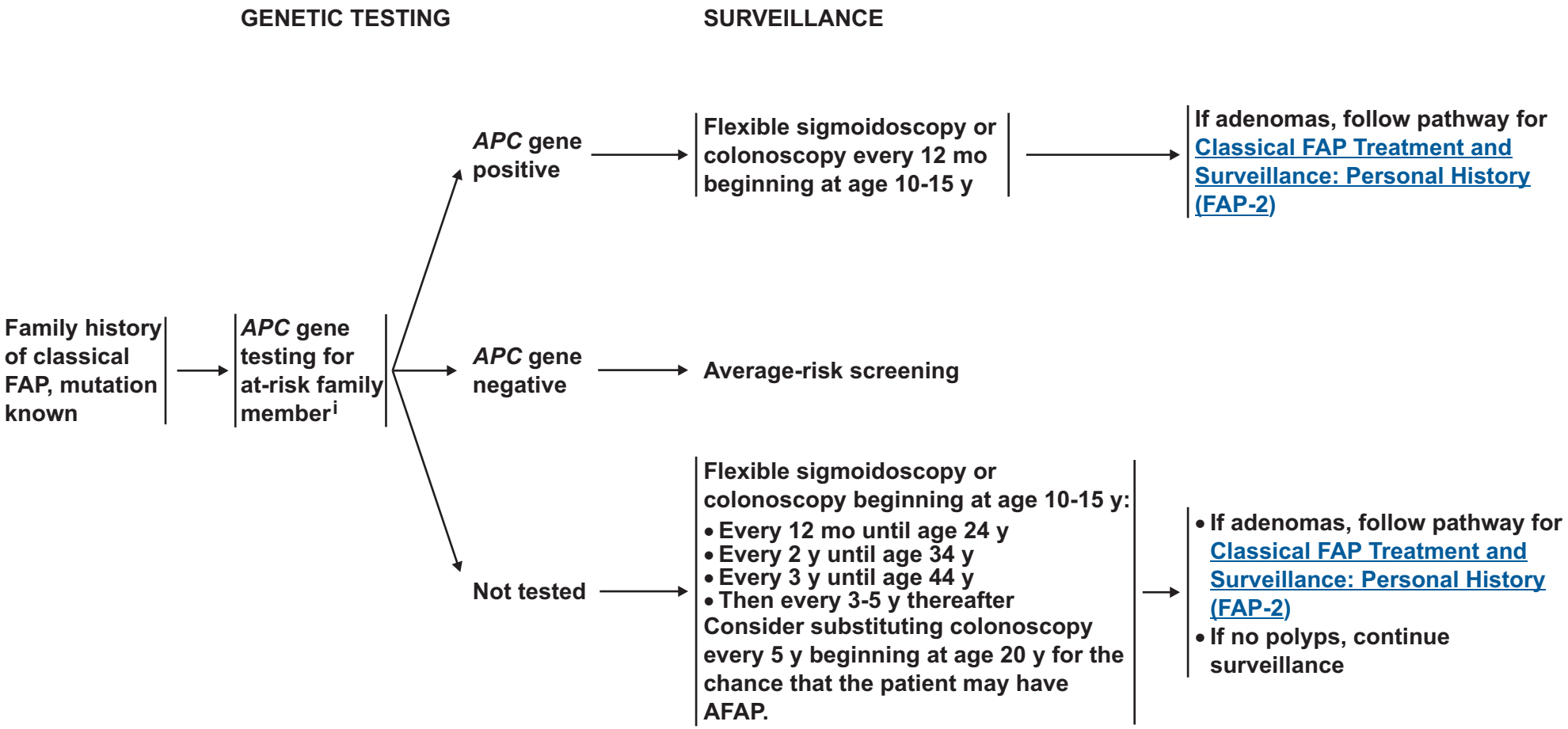
DUODENOSCOPIC FINDINGS	SURVEILLANCE[h]
Stage 0, No polyposis	**Repeat endoscopy every 4 y**
Stage I, Minimal polyposis (1-4 tubular adenomas, size 1-4 mm)	**Repeat endoscopy every 2-3 y**
Stage II, Mild polyposis (5-19 tubular adenomas, size 5-9 mm)	**Repeat endoscopy every 1-3 y**
Stage III, Moderate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

[h] Duodenal Surveillance:

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

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

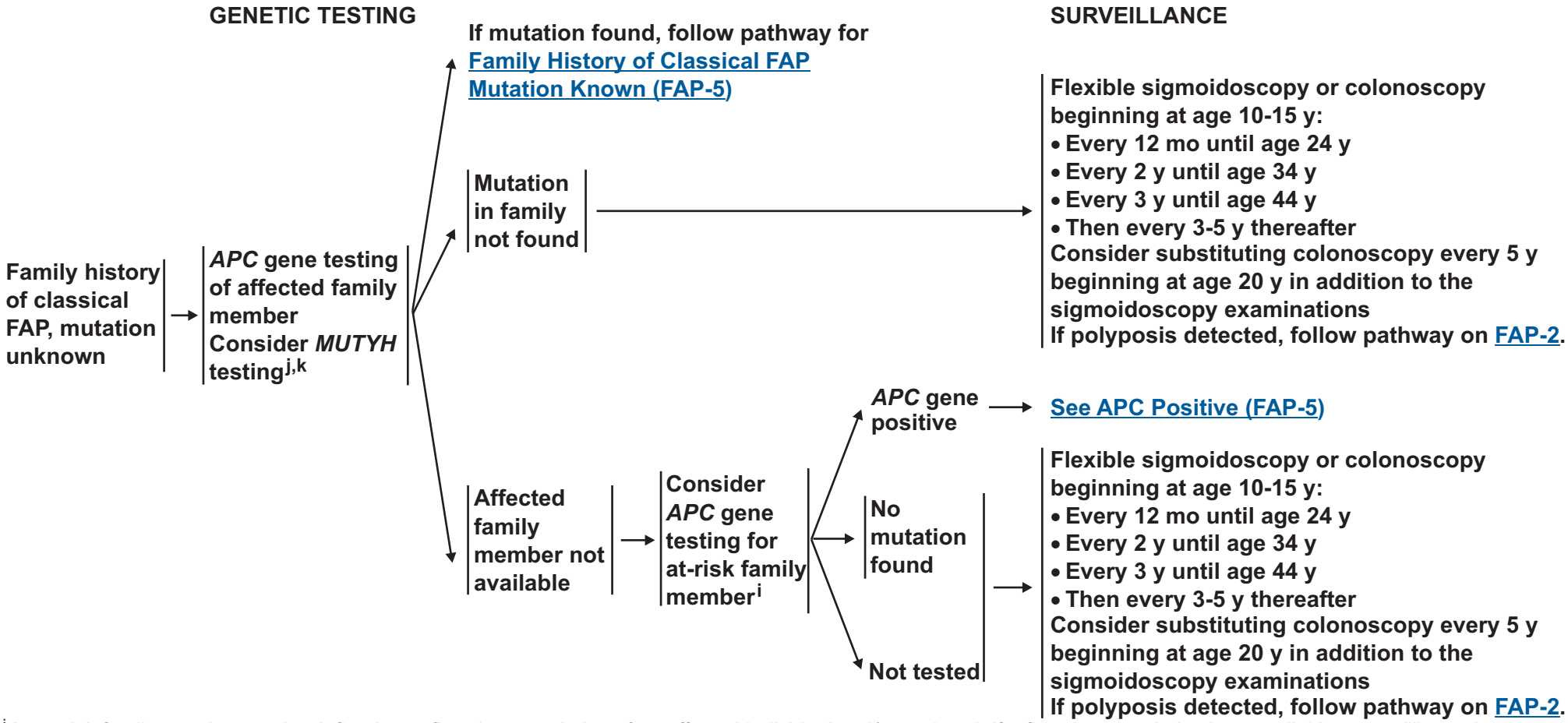
CLASSICAL FAP GENETIC TESTING AND SURVEILLANCE: FAMILY HISTORY OF CLASSICAL FAP MUTATION KNOWN



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

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

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



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

[j] See MUTYH-Associated Polyposis (MAP-1).

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

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

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

TOTAL ABDOMINAL COLECTOMY WITH ILEORECTAL ANASTOMOSIS (TAC/IRA)

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

TOTAL PROCTOCOLECTOMY WITH END ILEOSTOMY (TPC/EI)

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

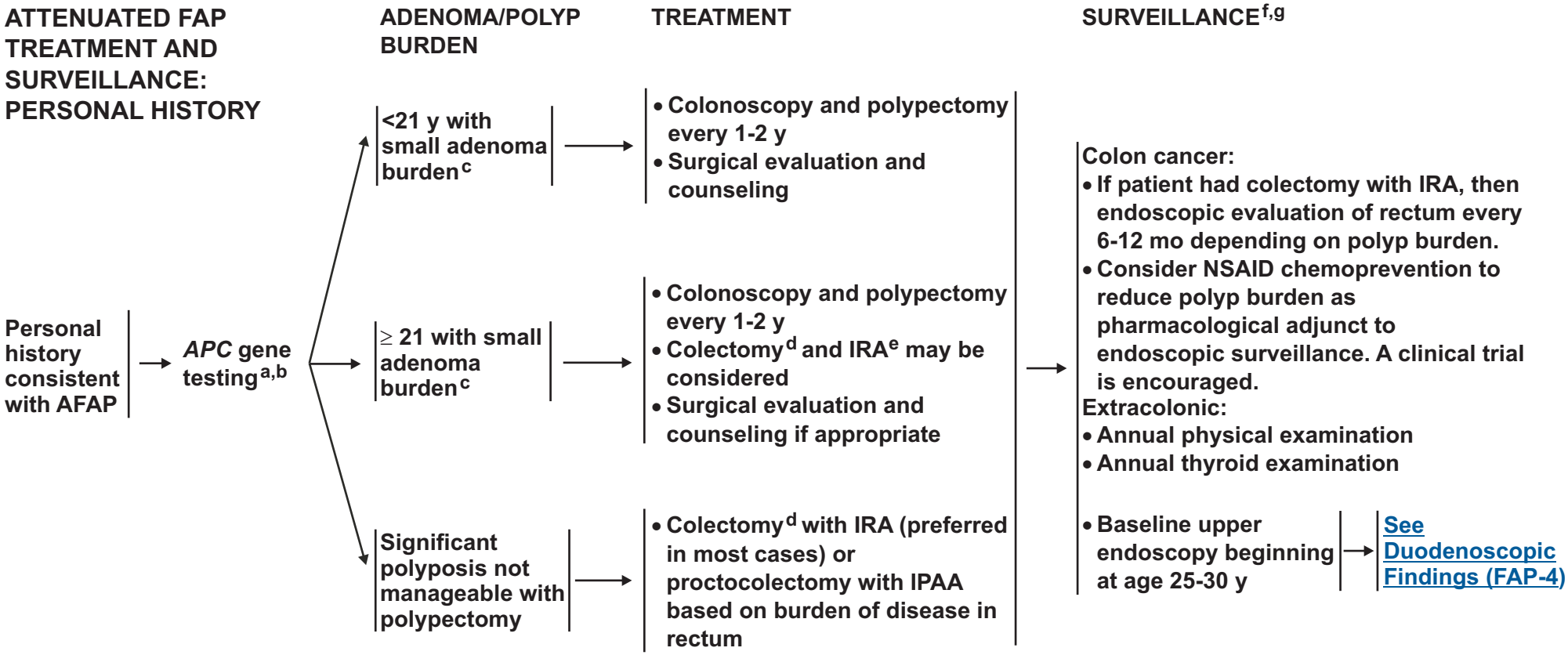
TOTAL PROCTOCOLECTOMY WITH ILEAL POUCH ANAL ANASTOMOSIS (TPC/IPAA)

- Indications:
  - Severe disease in colon and/or rectum
  - After TAC/IRA with unstable rectum
  - Curable colon or rectal cancer
  - Patient unreliable for follow-up after TAC/IRA
- Contraindications:
  - Intra-abdominal desmoid that would interfere with completion of surgery
  - Patient is not a candidate for IPAA (eg, concomitant Crohn's disease, anal sphincter dysfunction)
- Advantages:
  - Minimal risk of rectal cancer
  - No permanent stoma
  - Reasonable bowel function
- Disadvantages:
  - Complex operation
  - Usually involves temporary stoma
  - Risks of sexual or bladder dysfunction
  - Functional results are variable

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

NCCN Guidelines Version 2.2012
Attenuated Familial Adenomatous Polyposis

NCCN Guidelines Index
Colorectal Screening TOC
Discussion



[a] *APC* gene testing is recommended in a proband to confirm a diagnosis of AFAP and allow for mutation-specific testing in other family members. Additionally, knowing the location of the *APC* mutation can be helpful in determining extra-colonic cancer risks in affected individuals.

[b] *MUTYH* testing if an *APC* mutation is not found or if recessive pattern apparent in pedigree (See MAP-1).

[c] Small adenoma burden is defined (somewhat arbitrarily) as fewer than 20 adenomas, all <1 cm in diameter and none with advanced histology, so that colonoscopy with polypectomy can be used to effectively eliminate the polyps. Colectomy may be indicated before this level of polyp profusion, especially if colonoscopy is difficult and polyp control is uncertain. Surgery should be considered when polyp burden is greater than 20 at any individual examination, when polyps have been previously ablated, when some polyps have reached a size >1 cm, or when advanced histology is encountered in any polyp.

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

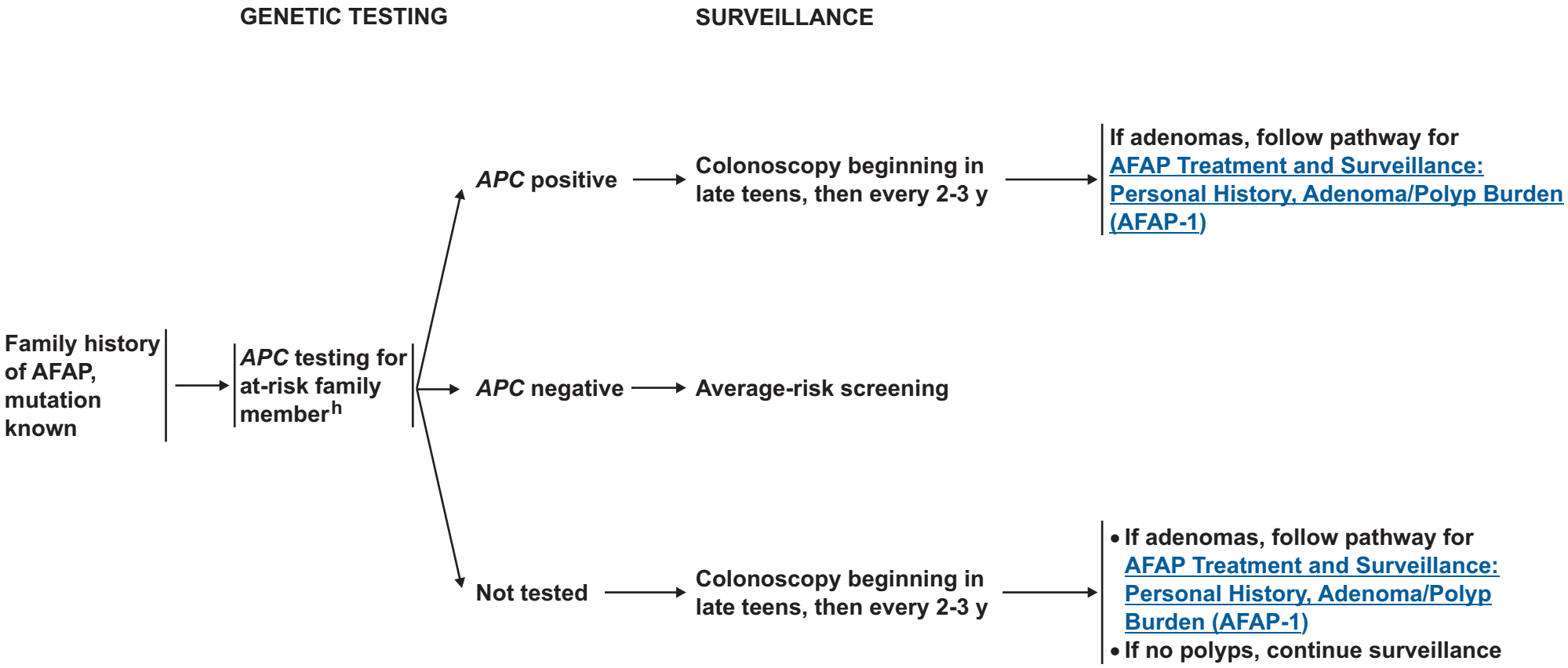
[e] Earlier surgical intervention should be considered in patients with a family history of cancer before age 40 or noncompliant patients.

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

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

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

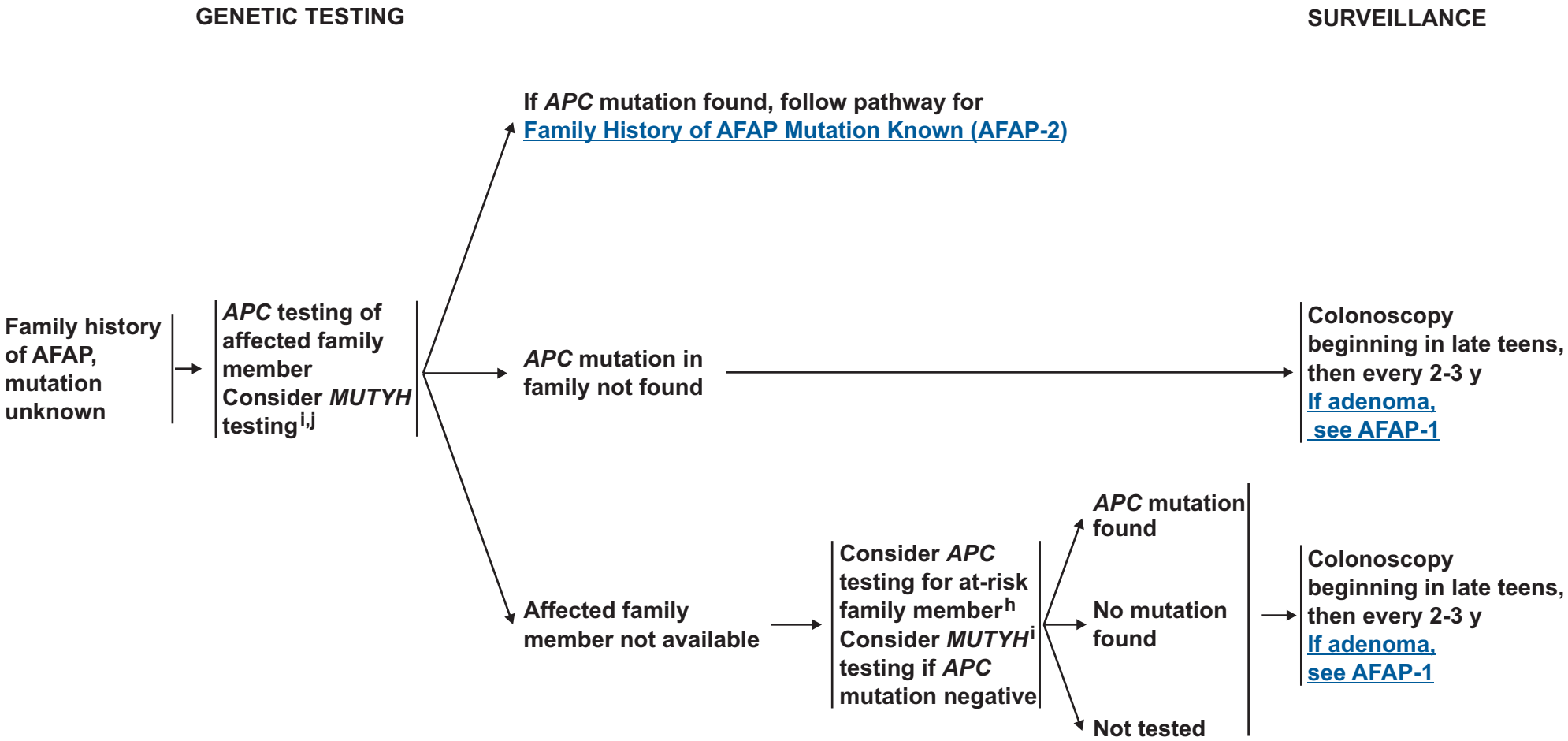
ATTENUATED FAP GENETIC TESTING AND SURVEILLANCE: FAMILY HISTORY OF ATTENUATED FAP MUTATION KNOWN



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

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

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



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

[i] See MUTYH-Associated Polyposis (MAP-1).

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

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

NCCN Guidelines Version 2.2012
MUTYH-Associated Polyposis

NCCN Guidelines Index
Colorectal Screening TOC
Discussion

PHENOTYPE

- **Polyposis or colon cancers consistent with autosomal recessive inheritance (ie, parents unaffected, siblings affected)**
- **Consanguinity**
- **Fewer than 100 adenomas (range 0-100s and uncommonly >1000)[a]**
- **Adenomas and CRC at age older than classical FAP (median CRC age >50 y)**
- **Duodenal adenomas are uncommon**
- **Attenuated polyposis with negative *APC* gene mutation**

RISK ASSESSMENT

Personal history
or
Family history
(ie, known mutation in patient or sibling)

See MUTYH-Associated Polyposis (MAP-2)

[a]Hyperplastic polyps may also be seen in this setting.

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

NCCN Guidelines Version 2.2012
MUTYH-Associated Polyposis

NCCN Guidelines Index
Colorectal Screening TOC
Discussion

GENETIC COUNSELING/TESTING OF ELIGIBLE FAMILY MEMBERS

TREATMENT/SURVEILLANCE

Personal history of multiple adenomatous polyps (>10 adenomas with negative *APC* mutation testing)[b]

→ **Counseling and testing for *MUTYH* mutations**

→ **Biallelic *MUTYH* mutation negative**

→ **Manage individually as multiple adenomatous polyps (FAP-1)**

→ **Biallelic *MUTYH* mutation positive**

→ **Small adenoma burden manageable by colonoscopy and polypectomy**

→
- **Colonoscopy and polypectomy every 1-2 y[c]**
- **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 FAP Duodenoscopic Findings (FAP-4))**

→ **Dense polyposis or large polyps not manageable by polypectomy**

→
- **Counseling regarding surgical options**
- **Subtotal colectomy or proctocolectomy depending on adenoma density and distribution[c]**
- **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 FAP Duodenoscopic Findings (FAP-4))**

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

→ **Mutation status unknown or biallelic *MUTYH* mutations known**

→
- **Begin colonoscopy at age 25-30 y and every 3-5 y if negative**
- **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 FAP Duodenoscopic Findings (FAP-4))**

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

[c] In patients with *MUTYH*, the absolute risk of colorectal cancer and the role of surgery and endoscopically manageable adenomas is not known. The lifetime colon cancer risk may be very high.

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

NCCN Guidelines Version 2.2012
Peutz-Jeghers Syndrome

PJS definition:[1,2]

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

Surveillance considerations:

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

See Cancer Risk and Surveillance Guidelines (PJS-2)

[1] Tomlinson IP, Houlston RS. Peutz-Jeghers syndrome. J Med Genet 1997;34:1007-1011.

[2] Due to the rarity of the syndrome and complexities of diagnosing and managing individuals with Peutz-Jeghers syndrome, referral to a specialized team is recommended.

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

Peutz-Jeghers Syndrome: Cancer Risk and Surveillance Guidelines

Site (% lifetime risk)	Screening Procedure and Interval	Initiation Age (y)
Breast (45-50%)	• Mammogram and breast MRI annually • Clinical breast exam every 6 mo	~ 25 y
Colon (39%)	• Colonoscopy every 2-3 y	~ Late teens
Stomach (29%)	• Upper endoscopy every 2-3 y	~ Late teens
Pancreas (11-36%)	• Magnetic resonance cholangiopancreatography and/or endoscopic ultrasound every 1-2 years • CA 19-9 at similar intervals	~ 25-30 y
Small intestine (13%)	• Small bowel visualization (CT enterography, small bowel enteroclysis) baseline at 8-10 y with follow-up interval based on findings but at least by age 18, then every 2-3 y. though this may be individualized, or with symptoms	~ 8-10 y
Ovary[1] (18-21%), cervix (10%), uterus (9%)	• Pelvic examination and Pap smear annually • Consider transvaginal ultrasound	~ 18-20 y
Testes	• Annual testicular exam and observation for feminizing changes	~ 10 y
Lung (15-17%)	• Provide education about symptoms and smoking cessation • No other specific recommendations have been made	

[1] Although the absolute risk of adenocarcinoma of the ovary is elevated in PJS, ovarian sex cord tumors are the most common ovarian pathology found in these patients.

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

NCCN Guidelines Version 2.2012
Juvenile Polyposis Syndrome

NCCN Guidelines Index
Colorectal Screening TOC
Discussion

JPS definition:[1]

- **A clinical diagnosis of JPS is considered in an individual who meets at least one of the following criteria:**
  - **At least 3 to 5 juvenile polyps of the colon**
  - **Multiple juvenile polyps found throughout the GI tract**
  - **Any number of juvenile polyps in an individual with a family history of JPS**

Surveillance considerations:

- **Approximately 50% of JPS cases occur due to mutations in the *BMPR1A* and *SMAD4*[2] genes. Clinical genetic testing is available.**
- **Referral to a specialized team is recommended and participation in clinical trials is especially encouraged.**
- **Surveillance should begin at the approximate ages listed below, if symptoms have not already occurred. Any early symptoms should be evaluated thoroughly.**
- **The following surveillance guidelines for the multiple organs at risk for cancer may be considered. Limited data exist regarding the efficacy of various screening modalities in JPS.**

Juvenile Polyposis Syndrome: Cancer Risk and Surveillance Guidelines

Site (% lifetime risk)	Screening/Surveillance Procedure and Interval	Initiation Age (y)
Colon (40-50%)	Colonoscopy: repeat annually if polyps are found and if no polyps, repeat every 2-3 years	~ 15 y
Stomach (21% if multiple polyps)	Upper endoscopy: repeat annually if polyps are found and if no polyps, repeat every 2-3 years	~ 15 y
Small intestine (rare, undefined)	No recommendations have been made	
Pancreas (rare, undefined)	No recommendations have been made	

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

[2] In individuals with *SMAD4* mutations, recommend screening for vascular lesions associated with hereditary hemorrhagic telangiectasia.

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

NCCN Guidelines Version 2.2012
Serrated Polyposis Syndrome

NCCN Guidelines Index
Colorectal Screening TOC
Discussion

Serrated polyposis syndrome (previously known as hyperplastic polyposis) definition:[1,2,3]

- **A clinical diagnosis of serrated polyposis is considered in an individual who meets at least one of the following empiric criteria:**
  - **1) At least 5 serrated polyps[4] proximal to the sigmoid colon with 2 or more of these being > 10 mm**
  - **2) Any number of serrated polyps[4] proximal to the sigmoid colon in an individual who has a first-degree relative with serrated polyposis**
  - **3) Greater than 20 serrated polyps[5] of any size, but distributed throughout the colon[6]**
- **Occasionally, more than one affected case of serrated polyposis is seen in a family.[7]**
- **Currently, no causative gene has been identified for serrated polyposis.**
- **The risk for colon cancer in this syndrome is elevated, although the precise risk remains to be defined.**

Surveillance recommendations for individuals with serrated polyposis:

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

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

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

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

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

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

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

[5] The total number of polyps necessary to make a diagnosis of serrated polyposis is unclear. A lower threshold number of polyps (< 20) has also been used to make a diagnosis of serrated polyposis.

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

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

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

Discussion

NCCN Categories of Evidence and Consensus

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

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

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

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

All recommendations are category 2A unless otherwise noted.

Overview

Colorectal cancer (CRC) is the fourth most frequently diagnosed cancer in the United States. In 2012, an estimated 103,170 new cases of colon cancer and 40,290 new cases of rectal cancer will occur in the United States. During the same year, it is estimated that 51,690 people will die from colon and rectal cancer.[1] Importantly, the incidence of colon and rectal cancers per 100,000 has decreased from 60.5 in 1976 to 46.4 in 2005.[2] The incidence of colorectal cancer continued to trend downward, with an average annual percentage change of -2.7% in men and -2.1% in women from 2004 to 2008.[3] In addition, mortality from colorectal cancer has decreased by almost 35% from 1990 to 2007,[4] likely because of both earlier diagnosis through screening and better treatment modalities. Currently, patients with stage I localized colon cancer have a 96% relative 5-year survival rate.[5]

Colorectal cancer often occurs sporadically, but familial cancer syndromes are also common in this disease. Genetic susceptibility to colorectal cancer includes well-defined inherited syndromes such as Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer, or HNPCC), familial adenomatous polyposis (FAP), and MUTYH-associated polyposis (MAP). Other entities include Muir-Torre, Turcot, Gardner, Cowden, Bannayan-Riley-Ruvalcaba, Peutz-Jeghers, juvenile polyposis, and serrated polyposis syndromes.[6-8]

CRC mortality can be reduced both by early diagnosis and by cancer prevention through polypectomy.[9-11] Hence the goals of CRC screening are to detect cancer at an early, curable stage and to detect and remove adenomatous polyps. According to the Centers for Disease Control and Prevention (CDC), the screening rate among U.S. adults aged 50-75 years has increased from 52% in 2002 to 63% in 2008.[12]

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

Colorectal Cancer Screening

Current technology falls into two broad categories: structural tests and stool/fecal-based tests.[13] There is direct evidence from randomized controlled trials that fecal occult blood testing and flexible sigmoidoscopy (discussed in detail below) reduce mortality from colorectal cancer. Given the available evidence from case control and cohort studies, however, it is the consensus opinion of the panel that colonoscopy should be the preferred method of screening because of

its potential ability to prevent colorectal cancer (with its associated morbidity) and cancer deaths. Screening tests that can detect both early cancer and adenomatous polyps are encouraged, although the panel recognizes that patient preference and resource accessibility play a large role in test selection. Overall, while some techniques are better established than others, panelists agree that any screening is better than none.

Structural Screening Tests

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

Colonoscopy

Colonoscopy is the most complete screening procedure, allowing examination of the entire large bowel as well as removal of polyps in one session. It is currently the preferred screening method and also the required procedure for confirmation of positive findings from other tests. Colonoscopy is also considered the current “gold standard” for assessment of the efficacy of other screening methods. Although there are no randomized controlled trials that directly demonstrate mortality reduction by colonoscopy, findings from case-control and cohort studies show significant impact of colonoscopy and polypectomy on CRC, with an estimated >50% reduction in incidence.[15-17] Rabeneck and colleagues recently reported an inverse correlation between colonoscopy use and death from CRC from a large population study involving close to 2.5 million Canadians.[18] For every 1% increase in colonoscopy rate, the risk of death decreased by 3%.

Interestingly, in a Canadian case-control study that matched each of 10,292 individuals who died of CRC to 5 controls, colonoscopy was associated with lower mortality from left-sided CRC (adjusted conditional OR, 0.33; 95% CI, 0.28-0.39) but not right-sided CRC (OR, 0.99; CI, 0.86-1.14).[19] Part of this finding may be related to significant variation in the quality of this widely-used procedure in the community that can lead to variable effectiveness.[20, 21] Another study that compared colorectal cancer mortality of 715 patients who underwent colonoscopy over a median follow-up period of 8 years to expected rates of colorectal mortality based on the SEER database found a 65% relative reduction in CRC mortality following colonoscopy.[22]

A recent follow-up on the National Polyp Study evaluated the long-term mortality effects of colonoscopy with polypectomy.[16, 23] The mortality of 2,602 patients with adenomas removed was compare to the incidence-based mortality from colorectal cancer in the SEER database. With a median 15.8 years follow-up, 12 deaths were attributed to colorectal cancer in the screened group, compared with an expected 25.4 deaths in the general population, suggesting a 53% decrease in mortality.

In addition, a recent population-based case-controlled study in Germany demonstrated that colonoscopy in the preceding 10 years gave an overall 77% decrease in the risk of colorectal cancer.[24] While risk reduction was strongest for left-sided cancer, a 56% reduction in risk was seen for right-sided disease as well.

A current randomized controlled trial is comparing 1-time colonoscopy with biennial fecal immunochemical testing (FIT; see discussion of FIT below) with the primary outcome of death due to colorectal cancer at 10

years. Interim results from this trial show that subjects are more likely to participate in FIT screening (34.2% vs. 24.6%; P<0.001).[25] The 2 tests identified similar numbers of cancers in initial screening, but colonoscopy identified significantly more advanced and non-advanced adenomas.

Recommendations made by the panel are based on the premise of complete, high quality colonoscopies as reflected by: colonoscopy to cecum, rectal retro-flexion, excellent preparation or endoscopic clearing of residual stool, sufficient distention and full 360 degree view of front and back side of all folds, withdrawal time >10 minutes, and complete excision of polyps (may require extra snare/biopsy or cautery following initial polypectomy). A recent European report on a screening program involving over 45,000 subjects confirmed that the endoscopist's rate of adenoma detection is an important predictor of the risk of interval CRC (P=0.008), highlighting the need for meticulous inspection of the large intestinal tract.[26] The study did not demonstrate statistical significance with cecal intubation rate, another widely recognized quality indicator; one explanation is that the importance of this factor is restricted to the right colon, which gives rise to a small number of cancer cases. In an effort to enhance screening quality, the Quality Assurance Task Group of the National Colorectal Cancer Roundtable developed a standardized reporting system for colonoscopy.[27] The algorithm lists the common quality indicators of colonoscopy and minimum requirements of a colonoscopy report.

An optimal screening protocol should have an interval during which there is a low likelihood of developing cancer and is cost effective based on the duration of risk reduction following an initial negative colonoscopy. The general consensus is that a 10-year interval is appropriate for most individuals (average risk), although shorter intervals may be indicated depending on the completeness and quality of the colonoscopy. The panel emphasized the importance of family history in the screening scheme. Individual risk factors, the number or characteristics of polyps found, and physician judgment should also be included in the interval determination. An 1996 study reported that 27% of individuals had adenomatous polyps identified on repeat colonoscopy a mean of 66 months after an initial negative colonoscopy, but none had colon cancer and only one of 154 individuals had a polyp $\geq$1cm.[28] These results suggest that an interval of repeat colonoscopy after an initial negative colonoscopy beyond 5 years is safe. Imperiale et al reported on 2,436 individuals with no adenomatous polyps at baseline colonoscopy.[29] No cancers were found at rescreening at a mean of 5.3 years later. Adenomatous polyps were identified in 16% and only 1.3% had advanced adenomatous polyps. The authors recommended a rescreening interval of 5 years or longer. Lieberman and colleagues reported that advanced adenomatous polyps were found in only 2.4% of individuals on repeat colonoscopy within 5.5 years after a baseline normal colonoscopy.[30] In this study, individuals with 1 or 2 adenomatous polyps <1cm at baseline also had a low rate of developing advanced neoplasia.

Singh et al assessed the time that risk reduction persists after colonoscopy.[31] This study was a population-based retrospective analysis utilizing a physician billing claims database of individuals who had a negative screening colonoscopy. Patients in the surveillance cohort were compared to the general population regarding incidence of colorectal cancer. A negative colonoscopy was associated with a standardized incidence ratio of 0.28 (95% CI, 0.09-0.65) at 10 years. A similar study calculated the adjusted relative risk of CRC among subjects with a previous negative colonoscopy.[32] The adjusted odds ratio was 0.26 (95% CI, 0.16-0.40). The low risk was seen even if the colonoscopy had been performed up to 20 or more years previously. A

recent analysis showed that the risk reduction seen following negative colonoscopy holds even for patients with a family history of colorectal cancer, but not for current smokers.[33]

Flexible sigmoidoscopy

Flexible sigmoidoscopy followed by colonoscopic polypectomy significantly reduced mortality risk in early case-control studies.[17, 34] There is now direct evidence from randomized controlled trials that flexible sigmoidoscopy reduces mortality from colorectal cancer.[35] A recent British randomized population screening study of over 110,000 individuals attributed a 23% and 31% reduction in CRC incidence and mortality, respectively, to flexible sigmoidoscopy offered once between ages 55 and 64 compared to no screening.[35] The reductions in colorectal incidence and mortality for those individuals who accepted screening were 33% and 43%, respectively. In addition, the SCORE trial randomized 34,272 subjects to one-time sigmoidoscopy or no screening and recently reported incidence and mortality results after >10 years median follow-up.[36] Per-protocol analysis demonstrated a 31% reduction in incidence and a 38% reduction in mortality.

On the other hand, the Norwegian Colorectal Cancer Prevention Study Group (NORCCAP) performed a randomized controlled trial of flexible sigmoidoscopy in over 55,000 participants aged 55-64 years.[37] After 7 years of follow-up, the researches reported no difference in the incidence of colorectal cancer between individuals screened once compared to unscreened participants. However, a non-significant trend towards reduced mortality from colorectal cancer was observed in the screened arm, and longer follow-up may reveal a mortality benefit.

The Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening group has yet to report colorectal cancer mortality rates from their randomized, controlled flexible sigmoidoscopy screening trial, which screened >67,000 participants with flexible sigmoidoscopy and 59% of those participants a second time at 3 or 5 years.[38, 39] A interim report from the PLCO screening group reported that the second sigmoidoscopy screening increased the yield of advanced adenomas by 26% in women and 34% in men.[39]

Compared to colonoscopy, this technique requires no sedation and less bowel preparation, but is limited to examination of the lower half of the colon tract. A recent analysis of cancers not detected by flexible sigmoidoscopy in PLCO trial showed that 37% of undetected lesions were beyond the reach of the sigmoidoscope.[40] The authors estimate that an additional 15-19% of cancers may have been detected during screening had colonoscopy been used.

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

Double-contrast barium enema

Both the availability and physicians' experience with double-contrast barium enema is decreasing. At present, this technique is typically only used as an alternative for patients who cannot undergo colonoscopy.

Computed tomographic colonography

Computed tomographic (CT) colonography, also known as virtual colonoscopy or CTC, is evolving as a promising technique for CRC screening. CTC has the advantages of being non-invasive and not requiring sedation. The risk of test-related complications is also very

low. However, a positive finding requires a colonoscopy, and extra-colonic findings, which are present in up to 16% of patients, pose a dilemma.[41, 42] These findings require further investigations and have a potential for both benefit and harm. At the present time there are no sufficient data to determine the clinical impact of these findings.

The accuracy of CT colonography in detecting polyps or cancers measuring 10 mm or more was assessed in the National CT Colonography Trial (ACRIN 6664) organized by the American College of Radiology Imaging Network.[43] In this study, 2,531 participants underwent CT colonography followed by traditional optical colonoscopy. Colonoscopy identified 128 large adenomatous polyps or carcinomas in 109 patients. CT colonography detected 90% of patients who had lesions measuring 10 mm or larger found by colonoscopy. There were also 30 lesions found on CT colonography, but not colonoscopy, for which 15 of 27 participants underwent a subsequent colonoscopy. Five of 18 lesions were confirmed: 4 adenomatous polyps and 1 inflammatory polyp. The CT colonography performance in this study (sensitivity of 90% and specificity of 86%) was better than that reported from some earlier studies[44, 45] and similar to what was reported by Pickhardt and colleagues in a prospective study with a similar design as the ACRIN trial.[46]

Kim et al also compared CT colonography with colonoscopy for the detection of advanced neoplasia.[47] Although this study was not randomized, the detection rates were comparable between the two groups of >3,100 patients each (3.2% for CT colonography and 3.4% for colonoscopy).

In 2005, 2 metaanalysis reviewed the performance of CT colonography in the detection of colorectal polyps.[48, 49] In one of these studies, CT colonography showed high average sensitivity (93%) and specificity (97%) for polyps ≥1 cm, both of which decreased to 86% when medium polyps (6-9 mm) were included in the analysis.[48] In another metaanalysis, the sensitivity of CT colonography, although heterogenous, improved as the polyp size increased (48% for polyps less than 6 mm, 70% for 6- to 9-mm polyps, and 85% for polyps larger than 9 mm). The specificity was 92-97% for the detection of all the polyps.

Two additional meta-analyses were published in 2011. An analysis of 49 studies found the sensitivities for detection of colorectal cancer by colonography and colonoscopy to be 96.1% and 94.7%, respectively, with overlapping confidence intervals.[50] Another analysis focused only on studies of average-risk participants and found the sensitivity and specificity of CT colonography for the detection of adenomas ≥1 cm to be 87.9% and 97.6%, respectively.[51]

Importantly, CT colonography may be a more acceptable option to many individuals. A recent randomized study compared participation rates when members of the general population were offered colorectal cancer screening by either colonoscopy or CT colonography.[52] Significantly more people accepted the invitation for CT colonography (34% vs. 22%). While colonoscopy had a greater diagnostic yield in screened participants, the yields were similar when determined per the invited population.

The technical aspects of CT colonography differ from study to study and have not been standardized. These details include the imaging, pre-procedure preparation, use of stool tagging, and the expertise of the interpreter.[53, 54] Long-term follow-up studies of patients who were screened by CT colonography are not yet available.

The issue of radiation exposure also requires consideration. Using the screening protocol for the ACRIN trial, Berrington de Gonzalez et al recently estimated the effective dose of low-dose CT colonography to be 9 mSv for women and 8 mSv for men, corresponding to 5 radiation-related cancer cases per 10,000 individuals undergoing 1 scan at age 60.[55] Risks increase with repeated scanning. The 2009 ACR practice guidelines for the use of CT colonography recommend the use of a multi-detector CT scanner and low-dose, non-enhanced technique to minimize radiation exposure to the patient.[56] Absorbed doses should not exceed 12.5 mGy total per scan.

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

Fecal-Based Screening Tests

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

Any positive stool test needs to be followed by colonoscopy. To ensure adequate follow-up, a healthcare professional should coordinate FOBT testing, so that the patient who has a positive result enters the health care system in a responsible way. FOBT of a single specimen obtained at digital rectal examination is not recommended due to exceptionally low sensitivity.[57, 58] Unfortunately, a recent survey of over 1,000 primary care physicians revealed that inappropriate in-office testing is still widely used (25% used in-office testing only and 53% used both in-office and home testing), suggesting the need for strengthened education.[59]

Fecal occult blood test (FOBT)

Two fecal occult blood tests are currently available: guaiac-based and immunochemical. These may be used alone annually or in combination with flexible sigmoidoscopy every 5 years.

Guaiac FOBT

Based on the pseudoperoxidase activity of heme in human blood, guaiac FOBT is the most common stool test in use for CRC screening. There is direct evidence from randomized controlled trials that guaiac FOBT reduces the mortality from colorectal cancer.[60-62] In the Minnesota Colon Cancer Control Study, more than 46,000 participants were randomized to receive fecal occult blood testing once a year, once every 2 years, or no screening. The 13-year cumulative mortality from colorectal cancer per 1000 was 5.88 and 8.83 in the annual and unscreened groups, respectively, and this 33% difference was statistically significant.[62] While this study did not demonstrate a decrease in CRC mortality with biennial screening, other large randomized studies have.[60, 61] In fact, a recently published long-term follow-up of the Nottingham trial showed that individuals randomized to the biennial guaiac FOBT screening arm had a 13% reduction in colorectal cancer mortality at an median follow-up of 19.5 years (95% CI 3% to 22%), despite a 57% participation rate. Following adjustment for non-compliance, the reduction in CRC mortality was 18%.[63]

A systematic review of 4 randomized controlled trials involving over 320,000 participants showed a 16% reduction in relative risk for CRC death with guaiac FOBT screening (95% CI, 0.78-0.90).[64] The sensitivity of different guaiac FOBT for cancer detection ranges from 37% to 79% in a study of about 8,000 participants by Allison and colleagues.[65] In the UK National Health Service Bowel Cancer Screening Programme (BCSP), cancer was detected in 11.8% of individuals who had a colonoscopy following an abnormal or weak positive FOBT.[66] Adenomas were found in an additional 49.7% of participants.

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

Fecal immunochemical test (FIT)

FIT, approved by the FDA in 2001, directly detects human globin within hemoglobin. Unlike guaiac FOBT, FIT does not require dietary restrictions, and a single testing sample is sufficient. However, sensitivity (11-58% for detecting any adenoma) and specificity (59-97%) vary widely for FIT as illustrated by a recent German study that assessed six different FIT methods on 1,319 participants.[67] Comparative studies generally show that FIT is on par with, if not superior to, guaiac FOBT depending on the test used.[68] For example, in the study by Allison et al, FIT had a sensitivity of 69% for cancer, between that for Hemoccult™ II Sensa and Hemoccult™ II.[65] An update study by the same group demonstrated a higher sensitivity for cancer by a newer FIT compared to Hemoccult™ Sensa (82% vs. 64%).[69] A Dutch randomized study also demonstrated higher detection rates of advanced neoplasia by FIT (2.4%) than guaiac FOBT (1.1%), although both were less reliable than flexible sigmoidoscopy (8.0%).[70] An expert panel in Ontario recently conducted an extensive literature analysis and concluded that FIT is superior to guaiac FOBT in both participation rates and in detection of advanced adenomas and colorectal cancer.[71]

Stool DNA test

Stool DNA testing is an emerging screening tool for CRC. It detects the presence of known DNA alterations during colorectal carcinogenesis in tumor cells sloughed into stool. Early proof-of-principle tests involving a single-target marker such as *KRAS* produced less than 40% sensitivity.[72] In an effort to improve sensitivity, newer tests with multi-panel markers were developed. In a large multicenter study of 4,404 patients, eligible subjects submitted a stool specimen for DNA analysis, underwent Hemoccult™ II testing, and then had a colonoscopy.[73] In a subgroup analysis, the multi-target DNA assay SDT-1 (21 mutations in *APC*, *KRAS*, and *p53* plus 2 other markers) detected 52% of CRC compared with 13% by Hemoccult™ II, with specificities of 94% and 95%, respectively. The SDT-1 assay did not perform as well in another large multicenter, prospective, triple-blinded trial that also assessed a second-generation combination test SDT-2 (mutations in *APC* and *K-ras* plus *vimentin* methylation).[74] In this study, a total of 3,764 average-risk healthy adults underwent screening colonoscopy, Hemoccult™, Hemoccult™ Sensa, SDT-1, and SDT-2. Very similar sensitivities for detection of colorectal cancers, high-grade dysplasias, and adenomas were observed for SDT-1 and Hemoccult™ Sensa (20% and 21%, respectively), whereas the sensitivity of SDT-2 was 40%. Other stool DNA tests are being developed and tested.[75]

For those unwilling or unable to have screening colonoscopy, there is increasing evidence that a stool DNA test may provide a valuable noninvasive option. More research is necessary to determine the optimal testing interval. Only 1 stool DNA test, ColoSure™ detecting methylated vimentin, is currently available in the United States.[76] However, stool DNA testing has not yet been approved by the FDA, and is currently not considered a first-line screening tool.

Risk Assessment

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

Average Risk

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

Increased Risk

Individuals with personal history of adenomatous polyps/sessile serrated polyps (see description below), CRC, or inflammatory bowel disease, and those with a positive family history of CRC or advanced adenomatous polyps are considered to be at increased risk for developing CRC. Individuals with diabetes mellitus or a history of *BRCA*-positive breast cancer also have a higher risk,[77-79] although these are not considered to affect the screening guidelines.

Registry data suggest an increased incidence of colorectal cancer in African Americans prior to age 50.[80] This increased risk has led some to recommend beginning population colorectal cancer screening in African Americans at age 45.[81] However, mortality from colorectal cancer is multifactorial and is related to host factors, tumor biology, environmental exposures, disparities in access to screening, differences in stage at diagnosis, and treatments received. In addition, mortality from colorectal cancer has been decreasing in African Americans and whites since 1999.[1] Therefore, based on the available data, methods to further enhance access to screening in African American populations should be endorsed.

High Risk Syndromes

Individuals with family history of Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer, HNPCC) or with a personal or family history of polyposis syndromes are considered to be in the high risk category.

Individuals at Average Risk

CRC risk assessment in persons without known family history is advisable by age 40 years to determine the appropriate age for initiating screening. It is recommended that screening for persons at average risk begin at age 50 after discussions of the available options.

Currently recommended options include colonoscopy every 10 years, annual fecal-based tests, flexible sigmoidoscopy every 5 years using a 60 cm or longer scope, a combination of annual fecal tests and sigmoidoscopy every 5 years, or CT colonography every 5 years. If available, colonoscopy is the preferred screening modality for individuals at average risk. However, any screening is better than none.

If a colonoscopy is incomplete or preparation is suboptimal, other screening methods (including double-contrast barium enema) or repeat colonoscopy should be considered based on physician judgment.

Interpretation of Findings

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

Adenoma/adenomatous polyps

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

Flat adenoma

Flat adenomatous polyps are unusual and can be easily missed during colonoscopy because they are not protruding from the colon wall.[82] More prospective studies are required to clarify their role in CRC risk. In the meantime, all flat adenomatous polyps should be removed upon identification with routine post-adenoma follow-up.

Serrated polyps

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

Hyperplastic polyps are another type of serrated polyp. A large body of literature indicates that hyperplastic polyps are not associated with significantly increased risk of CRC, and supports the recommendation that persons with hyperplastic polyps be screened as average risk. Recent literature, however, suggests that a small subset of persons with multiple or large hyperplastic polyps have serrated polyposis syndrome, with a 26% to 70% risk of CRC.[83-85] The majority of these had concomitant adenomatous polyps or SSP.[86] Additionally, there is evidence suggesting that some cancers with extensive DNA methylation and microsatellite instability might derive from hyperplastic polyps.[87]

Ideally, all detected polyps should be removed, but this is not always possible. Removed polyps should be examined for degree of dysplasia, as well as for histological features of SSP. Hyperplastic polyps that are left-sided, non-SSP, and <1 cm indicate average risk for follow-up screening. Right-sided and larger polyps should be followed as adenomas. Serrated polyposis syndrome is rarely reported to be inherited, and the CRC risk of individuals with affected relatives remains unclear.

Individuals at Increased Risk

Personal History of Adenoma/SSP

Individuals with adenomatous polyps are at increased risk for recurrent adenomatous polyps and CRC. To minimize the risk of developing CRC, a surveillance program is recommended for patients with adenomatous polyps following screening colonoscopy and complete polypectomy.[88] For patients with completely resected adenomatous

polyps, the surveillance schedule depends on the risk of recurrence, which in turn is related to the number, size, and histology of adenomatous polyps. Furthermore, when there is uncertainty about the completeness of removal in large and/or sessile polyps and when the colonic preparation was suboptimal, shorter screening intervals may be necessary.

Low risk adenomatous polyps are tubular, 2 or fewer, and <1 cm. In this group, colonoscopy should be repeated within 5 years, although emerging data suggest that longer intervals may be appropriate. If this examination is normal, colonoscopy should be repeated every 5 to 10 years. The decision to choose a 5- or 10-year interval is a patient-specific one. The factors that can be taken into account include (1) adequacy of the preparation and other technical considerations; (2) the results of prior examinations; (3) the presence of other co-morbid conditions. Generally the results of the first 2 screening examinations may predict the patient's overall colon cancer risk.[11] Robertson et al reported on a study of 564 participants who had their first adenoma identified by colonoscopy and underwent 2 additional colonoscopies.[89] The study found that combining results of two prior colonoscopies can help predict the likelihood of high-risk findings (advanced adenomatous polyps or cancers) on the third screen. If no adenomas were found on the second exam, results of the first screening predicted results of the third. In this case, if the first colonoscopy showed only low-risk findings, then the chance of high-risk findings on the third colonoscopy was 4.9%, whereas high-risk findings on the first colonoscopy gave a 12.3% risk of high-risk finding on third colonoscopy (P=0.015).

Advanced or multiple adenomatous polyps (3-10 polyps, ≥10 mm with >25% villous histology or high-grade dysplasia) have been associated with increased risk. High-grade dysplasia is defined as an adenoma that shows features of severe dysplasia (marked reduction of interglandular stromas with complex irregularity of glands, papillary infolding, and cytogenetic abnormalities) or high-grade dysplasia (severe architectural disturbance of glands along with cytological features of dysplasia).[90] Carcinoma in situ is a term previously used by pathologist to describe colon polyps and cancer and is currently being replaced by the term high-grade dysplasia. A study by Golembeski and colleagues has shown that the identification of villous architecture and high-grade dysplasia is poorly reproducible among pathologists.[91]

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

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

Polypectomy of large sessile polyps is associated with a high rate of recurrence, attributed to the presence of residual adenoma tissue at the time of polypectomy.[92] Hence, follow-up colonoscopy, within 2 to 6

months is appropriate in this setting, or when polypectomy is suspected to be incomplete.

The NCCN Guidelines for Colon Cancer provide suggestions for management if a malignant polyp is found at colonoscopy.

Personal History of Colorectal Cancer

Individuals with a personal history of CRC who had undergone colonic resection with a curative intent are at increased risk for recurrent adenomatous polyps and cancer. The recommendation for intensive surveillance immediately following resection is based on studies that found a high recurrence rate in the 4 to 5 years following CRC resections.[93-96] Furthermore, an analysis of 3,278 patients with resected stage II and III CRC found that the rate of second primary CRC is especially high in the immediate 5 years following surgery and adjuvant chemotherapy, suggesting that intense surveillance should be considered during that period (Intergroup 0089 study).[97] However, the studies did not exclude patients with Lynch syndrome who are at greater than 30% risk for synchronous and metachronous cancers.

The guidelines recommend a complete colonoscopy preoperatively as well as at 1 year following surgery (within 3 to 6 months if preoperative colonoscopy was incomplete). If this examination is normal, colonoscopy should be repeated in 2 to 3 years. Shorter intervals (1 to 3 years) are recommended if adenomatous polyps or SSP are found. Subsequent colonoscopic intervals are individualized and generally should not exceed 5 years.

In addition to colonoscopy, patients with rectal cancer should also undergo periodic endoscopic evaluation of the rectal anastomosis to identify local recurrence, which has been reported to occur in 5-36% of patients.[98-100] Expert opinion supports repeat evaluation for patient status every 6 months for 5 years following low anterior resection (LAR). The utility of routine endoscopic ultrasound for early surveillance is not defined.

Advantages of more intensive follow-up of patients with stage II and/or stage III rectal cancer have been demonstrated prospectively in several studies[94, 101, 102] and in 3 meta-analyses of randomized controlled trials designed to compare low-intensity and high-intensity programs of surveillance.[103-105] Other studies impacting on the issue of post-treatment surveillance of colorectal cancer include results from an analysis of data from 20,898 patients enrolled in 18 large adjuvant colon cancer randomized trials.[95] The meta-analysis demonstrated that 80% of recurrences were in the first 3 years after surgical resection of the primary tumor. However, in the final analysis of Intergroup trial 0114 comparing bolus 5-FU to bolus 5-FU/LV in patients with surgically resectable rectal cancer, local recurrence rates continued to rise after 5 years.[106] Further, a population-based report indicated that long-term survival is possible in patients treated for local recurrence of rectal cancer (overall 5-year relative survival rate of 15.6%), thereby providing support for more intensive post-treatment follow-up in these patients.[107] Nevertheless, controversies remain regarding selection of optimal strategies for following up patients after potentially curative colorectal cancer surgery.[108, 109]

Inflammatory Bowel Disease

It is well recognized that individuals with a personal history of inflammatory bowel disease are at an increased risk for CRC. Screening by colonoscopy every 1 to 2 years should be initiated 8 to 10 years after the onset of symptoms of pancolitis or 12 years after onset of left-sided colitis and should be performed by an endoscopist who is familiar with the appearance of ulcerative colitis or Crohn's disease.[9] 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. Strictures, particularly those in ulcerative colitis, that are suggestive should be evaluated thoroughly using biopsy and brush cytology. Biopsies can be better targeted to abnormal-appearing mucosa using chromoendoscopy, narrow-band imaging, autofluorescence, or confocal endomicroscopy. Targeted biopsies have been found to improve detection of dysplasia and should be considered for surveillance colonoscopies in patients with ulcerative colitis.[110] Any masses, including so-called dysplasia-associated lesions are 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. Lesions in patients with ulcerative colitis that appear endoscopically and histologically similar to sporadic adenoma, with no dysplasia in the flat mucosa in the surrounding area or elsewhere in the colon and without invasive carcinoma in the polyp, can be treated safely by polypectomy and continued surveillance. Most findings of high-grade, multifocal or repeat low-grade dysplasia place the ulcerative colitis patient at high risk for developing CRC. Prophylactic proctocolectomy with ileoanal anastomosis is preferred for these patients. All other individuals with positive findings should be referred to an experienced inflammatory bowel disease surgeon to discuss surgical options.

Family History

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

For each of the relatives, current age and age at diagnosis of any cancer as well as a date, age, cause of death, and availability of a tumor sample are very important for discerning whether relatives were at risk 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.

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

When any one of the revised Bethesda criteria[111] are met, the possibility of Lynch syndrome is suggested, and immunohistochemical staining (IHC) for the four mismatch repair proteins and/or microsatellite instability (MSI) testing on the colon tumor of the youngest affected family member is warranted. Please see Molecular Work-Up and Genetic Testing in the section on Lynch Syndrome, below, for more information on this topic.

Positive Family History

The panel extensively revised their screening recommendations for individuals with a positive family history in the 2012 version of the guidelines. These updated recommendations are largely based on a

population-based study that analyzed more than 2 million individuals to determine relative risks for the development of colorectal cancer depending on family history of colorectal cancer.[112] Colonoscopy is recommended every 3-5, beginning 10 years prior to the earliest diagnosis in the family for patients with ≥1 affected first-degree relative; colonoscopy should begin at age 50 at the latest for those with 1 affected first-degree relative and age 40 at the latest for those with ≥2 affected first-degree relatives. This same recommendation also applies if the first-degree relative was diagnosed with colorectal cancer at or under age 50 years. Individuals with various combinations of affected second- and third-degree relatives begin screening colonoscopy at age 50. The recommended screening intervals for these individuals range from 5 to 10 years. In addition, the panel recommends that individuals with a first-degree relative with history of advanced adenoma(s) should undergo colonoscopy every 7-8 years, beginning 10 years prior to the relative's age of onset or age 50 years at the latest.

Colonoscopy intervals should be modified based on personal and family history as well as on individual preferences. Factors that modify colonoscopy intervals include specifics of the family history, including number and age of onset of affected second- and third-degree relatives; size of family; completeness of the family history; participation of family member in screening; and colonoscopic findings in family members. In addition, for those with a weaker family history (ie, not those with a first-degree relative with colorectal cancer before age 50 nor those with 2 affected first-degree relatives), ≥2 negative colonoscopies may support 1-year stepwise increases in the colonoscopy interval (eg, every 5 years could be ages 50, 55, 61, 68, and 75-76).

Inherited Colon Cancer

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

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

Lynch Syndrome (Hereditary Nonpolyposis Colorectal Cancer)

Lynch syndrome is the most common form of genetically determined colon cancer predisposition, accounting for 2% to 4% of all CRC cases.[113-116] This hereditary syndrome usually results from a germline mutation in a DNA mismatch repair (MMR) gene (*MLH1*, *MSH2*, *MSH6*, or *PMS2*), although possible associations with three other genes (*MLH3*, *PMS1*, and *EXO1*) have also been found.[117] Recent evidence has shown that 3' deletions in the *EPCAM* gene, which lead to hypermethylation of the *MSH2* promoter and subsequent *MSH2* silencing, are an additional cause of Lynch Syndrome.[118, 119] *EPCAM* deletions likely account for 20-25% of cases in which MSH2 protein is not detected by IHC (see below) but germline *MSH2* mutations are not found.[119] MMR mutations are detected in more than half of persons

meeting the clinical criteria of Lynch syndrome, and the lifetime risk of CRC approaches 80% in affected individuals carrying a mutation in one of these genes.[120] Microsatellite instability (MSI) occurs in 80% to 90% of resulting CRCs.[121, 122] Surveillance in patients with Lynch Syndrome has been shown to reduce the risk of CRC and may be of benefit in the early diagnosis of endometrial cancer, which is also common in these patients.[123, 124] Site-specific evaluation and heightened attention to symptoms is also advised for other cancers that occur with increased frequency in affected persons, including gastric, ovarian, pancreas, urethral, brain (glioblastoma), and small intestinal cancers, as well as sebaceous gland adenomatous polyps and keratoacanthomas, though efficacy of surveillance for these sites has not been clearly demonstrated (reviewed by Lindor et al.[124]).

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

Molecular Workup and Genetic Testing

Mutation in one of the 4 MMR genes (*MLH1*, *MSH2*, *MSH6*, and *PMS2*) results in Lynch syndrome. While identifying a germline mutation in an MMR gene by sequencing is definitive for Lynch syndrome, patients usually undergo 2 rounds of selection before sequencing: the first based on family history and the second by initial tests on tumor tissue.

Family history criteria

Several different sets of criteria have been developed to identify patients who should be tested for possible Lynch Syndrome. The first version of the minimum criteria for clinical definition of Lynch Syndrome (Amsterdam criteria) was introduced in 1991, and these criteria were modified (Amsterdam II criteria) in 1999.[125] Approximately 50% of families meeting the Amsterdam II criteria have a mutation in an MMR gene.[126] These criteria are very stringent, however, and miss as many as 68% of patients with Lynch Syndrome.[127]

The classical Bethesda guidelines were later developed to provide broader criteria for testing colorectal tumors for microsatellite instability.[128] The National Cancer Institute introduced the revised Bethesda guidelines in 2002 to clarify selection criteria for MSI testing.[111] One study reported that *MLH1* and *MSH2* mutations were detected in 65% of patients with MSI of colon cancer tissue who met the Bethesda criteria.[129] Another study reported on the accuracy of the revised Bethesda criteria, concluding that the guidelines were useful for identifying patients who should undergo further testing.[130] Patients fulfilling the revised Bethesda criteria had an odds ratio for carrying a germline mutation in *MLH1* or *MSH2* of 33.3 (95% CI, 4.3-250; P=.001). Screening tumors of patients meeting the Bethesda criteria for MSI was shown to be cost-effective not only for patients with newly diagnosed CRC but also when considering benefit for the siblings and children of mutation carriers.[131]

Some newer models have also been developed to assess the likelihood that a patient carries a mutation in a MMR gene.[127, 132-134] These computer programs give probabilities of mutations and/or of the development of future cancers based on family and personal history. The PREMM1,2,6 model can used online at http://dana-farber.prod.dfcidev.org/pat/cancer/gastrointestinal/crc-calculator/default.asp, and the HNPCC predict model is available for online use at http://hnpccpredict.hgu.mrc.ac.uk/. MMRpro is available for free download at

http://www4.utsouthwestern.edu/breasthealth/cagene/. These models may be particularly useful when there is no tumor or insufficient tumor available for IHC or MSI testing.

Many NCCN institutions and other comprehensive cancer centers now perform IHC and sometimes MSI testing on all colorectal and endometrial cancers regardless of family history to determine which patients should have genetic testing for Lynch syndrome.[135, 136] The cost effectiveness of this approach, referred to as universal or reflex testing, has been confirmed for CRC, and this approach was endorsed by the Evaluation of Genomic Applications in Prevention and Practice (EGAPP) working group at the CDC.[137-139] An infrastructure needs to be in place to handle the screening results if reflex testing is established.

Initial testing methodologies

There are 2 main initial tests performed on CRC specimens to identify individuals who might have Lynch syndrome: immunohistochemical (IHC) analysis for MMR protein expression, which is often diminished due to mutation, and analysis for microsatellite instability (MSI), which results from MMR deficiency.[140] 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.[139, 141, 142] However, conclusive data are not yet available that establish which strategy is optimal.[117, 130, 143-146] The sensitivities of MSI and IHC testing have been estimated to be 77-89% and 83%, respectively; specificities have been estimated to be 90% and 89%, respectively.[139] Some experts advocate for using both methods when possible.[147]

MSI testing is particularly helpful when the family history is not strongly suggestive of Lynch syndrome. Families that meet the minimal criteria for consideration (diagnosis before the age of 50, but no other criteria) may not represent the disorder. A microsatellite stable tumor arising within a young onset patient without a strong family history of colorectal/endometrial cancer is very unlikely to represent the disorder.[148] Proceeding with genetic testing in this setting is unlikely to yield an informative result. On the other hand, among patients who met the Amsterdam criteria with MSI-negative tumors, 29% were found to have germline MMR gene mutations. MMR gene mutations were found in 88% of patients with MSI-positive tumors who met the Amsterdam criteria.[148]

IHC analysis is especially useful for family members that meet the Amsterdam criteria I or II, since there is a 50% to 92% chance of identifying a mutation in one of the four MMR genes in these individuals.[140] IHC analysis has the advantage of predicting which gene is most likely mutated and thus the first candidate for germline sequencing.[140] Testing the *BRAF* gene for mutation is indicated when MLH1 expression is absent in the tumor by IHC analysis. The presence of a *BRAF* mutation indicates that *MLH1* expression is down-regulated by somatic methylation of the promoter region of the gene and not by a germline mutation.[140]

Often, a patient presents with a strong family history of colorectal cancer, but no tumor sample is available for testing. A recent study showed that large (≥10mm) adenomatous colorectal polyps in patients with Lynch Syndrome display a loss of MMR protein expression by IHC and are MSI-positive.[149] These results indicate that MSI and/or IHC testing of large polyps when a tumor sample is not available is justified in high-risk families.[150] Importantly, a negative result would not rule out Lynch syndrome. An alternative approach is to go directly to germline sequencing in patients determined to have ≥5% risk of Lynch Syndrome when a tumor sample is not readily available.[151]

Definitive testing

Initial tests do not necessarily indicate that a patient has Lynch Syndrome. Abnormal results can occur in patients with sporadic colorectal cancer due to abnormal methylation of the *MLH1* gene promoter. Individuals with abnormal IHC or MSI results should be referred for genetic counseling so that the appropriate follow-up testing can be offered. Such tests might include one for abnormal *MLH1* promoter methylation and/or germline genetic testing of 1 or more of the mismatch repair genes. If a mutation is not found by sequencing, testing for large rearrangements and deletions of MMR genes may also be performed. Most patients will be found to have sporadic colorectal cancer; those with a germline alteration are identified as Lynch Syndrome patients.

Newly identified Lynch syndrome

When a mutation is found in the family, it offers an opportunity to provide predictive testing for at-risk family members. Predictive testing can save people a lot of unnecessary procedures. It is important to consider genetic testing for at-risk family members when the family mutation is known. At-risk family member can be defined as an FDR of an affected individual and/or proband. If an FDR is unavailable or unwilling to be tested, more distant relatives should be offered testing for the known family mutation.

There are many other issues involved in the genetic counseling process of individuals for presymptomatic testing for cancer susceptibility. A fair number of individuals elect not to undergo testing, and it is important to counsel these individuals so they continue with increased surveillance.

Panel Recommendation for Testing Criteria and Strategy

Testing for Lynch syndrome is advised for individuals who fit any of the following: 1) meets revised Bethesda guidelines or Amsterdam criteria; 2) diagnosed with endometrial cancer under age 50; 3) known Lynch syndrome in the family.

The testing strategy will depend on whether there is a known MMR mutation in the family. If so, the individual should be tested for the familial mutation. If tested positive or if testing is not performed for any reason, the individual should follow surveillance for Lynch syndrome outlined below. Individuals who test negative for the familial mutation are considered at average risk, not zero risk, for CRC and should follow the corresponding screening pathway.

In the case where no known familial MMR mutation has been previously identified, efforts should be made to identify the mutation. If a relevant CRC or endometrial tumor sample from an affected family member is available, consider both IHC and MSI testing on the sample. A table of IHC and MSI testing results as well as additional testing strategies is included in the algorithm section of this guideline. If no suitable sample is available, genetic testing on an affected relative should be considered with the following priority: *MLH1* and *MSH2* first, then *MSH6*, and lastly *PMS2*. Due to its rarity, testing for *PMS2* mutation is only necessary if no mutation is found in the other genes. Upon identification of a familial mutation, individuals who test positive should undergo surveillance for Lynch syndrome; testing for other at-risk family members should be considered. If no familial mutation is identified, surveillance should be tailored based on individual and family risk assessment.

As mentioned above, some centers perform universal IHC and/or MSI testing for all patients with CRC or endometrial cancer, even if relevant criteria is not met. Individual management is advised in this scenario.

Surveillance

The NCCN panel has had extensive discussions on the surveillance schemes for individuals with Lynch syndrome. These patients are at an increased lifetime risk compared to the general population for CRC (52-82% vs. 5.5%), endometrial cancer (25-60% vs. 2.7%), and other cancers including of the stomach and ovary.[152-156] Existing screening data in the literature is mainly on colon and endometrial cancers. More data are needed to evaluate the risk and benefits of extracolonic and extra-endometrial cancer screening, and recommendations are based on expert opinion.

If Lynch syndrome is confirmed, colonoscopy is advised to start between the ages of 20 to 25 or 2 to 5 years younger than the youngest diagnosis age in the family, whichever comes first, to be repeated every 1 to 2 years. This recommendation is based upon a systematic review of data between 1996 and 2006 on the reduction in cancer incidence and mortality by colonoscopy.[124] In addition, the panel points out that since the average age of colon cancer onset for *MSH6* or *PMS2* mutation carriers is somewhat older than for *MLH1* and *MSH2* mutation carriers,[152, 157] the start of colon screening may be delayed 5 years (ie, to age 30 years). However, screening may need to be initiated earlier than age 30 in some families, depending on ages of cancers observed in family members.

Women with Lynch syndrome are at heightened risk for endometrial and ovarian cancers (up to 60% and 12%, respectively).[124, 152, 153, 155] Education that enhances recognition of relevant symptoms (ie, dysfunctional uterine bleeding) is advised. Total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH/BSO) is an option that should be considered for risk reduction in women who have completed child-bearing.[158, 159] There is no clear evidence to support routine screening for gynecological cancers. Annual endometrial sampling is an option.[158, 160-163] Routine transvaginal ultrasound and serum CA-125 testing are not endorsed because they have not been shown to be sufficiently sensitive or specific,[158, 160-164] but the panel recognized that there may be circumstances where the clinician may find these tests helpful.

The lifetime risk for gastric cancer varies widely between individuals with Lynch syndrome in different populations, from 2% to 4% in the Netherlands to 30% in Korea.[124, 165] Most cases occur after age 40, and males have a stronger predisposition. There is no clear evidence to support screening for gastric cancer in patients with Lynch Syndrome.[166] Physicians may consider upper esophagogastroduodenoscopy (EGD) extended to the distal duodenum or into the jejunum every 2 to 3 years starting at age 30 to 35.

Lynch syndrome is also associated with a 4% to 8% risk for small bowel cancer.[167-169] There is no clear evidence to support screening for small bowel cancer in patients with Lynch syndrome. Non-invasive capsule endoscopy to screen for this cancer can be considered at a similar interval as for gastric cancer.[169]

Annual urinalysis starting at age 25-30 years should also be considered to screen for urothelial cancers, giving the relative ease and low cost compared to other tests. Although there is an increased risk of pancreatic and brain cancer,[153-156] because of the current lack of data, annual history and physical examination starting at age 25-30 years is appropriate for these cancers.

Surveillance Findings and Follow-up

If there are no pathologic findings, continued surveillance is recommended. If the patient is not a candidate for routine surveillance, subtotal colectomy may be considered. This important feature comes

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

Patients with confirmed adenocarcinoma should be treated following the appropriate NCCN Treatment Guidelines.

For patients with adenomatous polyps, recommendations include endoscopic polypectomy with a follow-up colonoscopy every 1 to 2 years. This option depends on the location and characteristics of the polyp, the surgical risk, and patient preference. If the adenomatous polyps identified cannot be endoscopically resected or high-grade dysplasia is identified, total abdominal colectomy with an ileorectal anastomosis is recommended. Since surgical management is evolving, the option of segmental or extended segmental colectomy is based on individual considerations and discussion of risks. These patients should be followed with endoscopic rectal exams every 1 to 2 years.

Chemoprevention in Lynch Syndrome

In the recent randomized CAPP2 trial, 861 participants with Lynch syndrome took either daily aspirin (600 mg) or placebo for up to 4 years; the primary endpoint was the development of colorectal cancer.[170] After a mean follow-up of >4 years, participants taking daily aspirin for at least 2 years had a 59% reduction in the incidence of colorectal cancer (HR, 0.41; 95% CI, 0.19-0.86; P=0.02). These participants also saw protection from non-colorectal Lynch Syndrome cancers (HR, 0.47; 95% CI, 0.21-1.06; P=0.07). There was no protection seen for participants who completed <2 years of the intervention.

Familial Adenomatous Polyposis

Classical FAP and attenuated FAP (AFAP) are autosomal dominant conditions characterized by a germline mutation in the *APC* gene, located on chromosome 5q21.[171, 172] Truncating mutation of the *APC* gene is detectable in about 80% of FAP patients using protein-truncating tests.[173, 174] Although FAP accounts for less than 1% of all CRC, it has been recognized as a paradigm for treating individuals at increased risk of cancer.

The I1307K polymorphism in the *APC* gene, found among Ashkenazi Jews, predisposes carriers to CRC.[175, 176] However, an available test for I1307K has been excluded from the guidelines because there is very little evidence to date indicating what kind of screening should be offered to individuals with this mutation.

Diagnosis: Classical vs Attenuated FAP

Diagnosis of classical FAP is based on the presence of >100 polyps or fewer polyps at younger ages especially in a patient with a family history of FAP.[171] When fully developed, patients exhibit hundreds to thousands of colonic adenomatous polyps. The lifetime risk of cancer in individuals with classic FAP approaches 100% by the age of 50. Most of the resulting cancers occur in the left colon. Possible associated findings of patients with FAP include desmoid tumors, which occur more frequently in patients with distal *APC* mutations, and congenital hypertrophy of retinal pigment epithelium (CHRPE), which occurs in patients with mutations in the central potion of the gene.[177, 178] 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.

Attenuated FAP is a recognized variant of FAP characterized by a later onset of disease and fewer adenomatous polyps, typically <100.[171, 172] These adenomatous polyps are more prone to occur in the right colon and may take the form of diminutive sessile adenomatous polyps.[179] Phenotypic expression is often variable within families. The onset of

CRC is typically delayed compared to FAP patients,[180] but the incidence of cancer rises sharply after the age of 40 and approaches 70% by age 80.

Genetic Testing for FAP and AFAP

When a familial mutation in *APC* is unknown, genetic testing for mutations in *APC* is recommended in the proband or an affected or at-risk family member for several reasons. It confirms the diagnosis and allows mutation-specific testing in other family members to clarify their risks. Additionally, identifying the location of the APC mutation can be useful in predicting the severity of colonic polyposis generally and the severity of rectal involvement (for FAP) and risks of extra-colonic cancers in affected patients. If a mutation is not found by sequencing, testing for large rearrangements and deletions of the *APC* gene may also be performed. If an alteration in *APC* is still not found, *MUTYH* mutation testing for MUTYH-associated polyposis (MAP) should be considered. As discussed below, MAP follows a recessive pattern of inheritance, so *MUTYH* testing can be performed prior to *APC* testing if a recessive pattern is apparent in the pedigree (eg, when family history is positive only for a sibling). If, on the other hand, a clear autosomal dominant inheritance pattern is observed, *MUTYH* testing is unlikely to be informative.

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. Counseling should be provided for at-risk individual so that they are able to make informed decisions about the implications involved in genetic testing, as well as the implications for their own management. Genetic testing in these individuals should be considered before or at the age of screening. The age for beginning screening should be based on the patient's symptoms, family phenotype, and other individual considerations. Fatal CRC is rare before the age of 18 years. If an individual at risk is found not to carry the *APC* gene mutation responsible for familial polyposis in the family, screening as an average risk individual is recommended. If an *APC* gene mutation is found, there is virtually a 100% probability that the individual will eventually develop familial polyposis.

Management of FAP and AFAP

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

It is important to note the distinction between individuals with a personal history of FAP and individuals who are considered at high risk based on a family history of FAP (but no symptoms or findings). This distinction makes a significant difference in clinical management. An at-risk family member for FAP can be defined as an FDR of an affected individual and/or proband. If an FDR is unavailable or unwilling to be tested, more distant relatives should be offered testing for the known family mutation. Preoperative surveillance schedules, surgical options, and surveillance following resection are discussed in more detail below.

Preoperative Surveillance

Family history of classical FAP

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

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

Positive genetic testing: If an *APC* gene mutation is found, flexible sigmoidoscopy or colonoscopy every 12 months, beginning at 10 to15 years of age is recommended. Once adenomas develop, surgical options should be reviewed (see below).

No genetic testing: Some people who undergo genetic counseling decide, for one reason or another, not to undergo genetic testing, which influences how their screening is managed. These individuals are considered to be potentially at risk and should be offered annual flexible sigmoidoscopy or colonoscopy beginning at age 10 to15 until the age of 24. Then if results continue to be negative, screening is scaled down to every 2 years until age 34, every 3 years until age 44, and every 3 to 5 years thereafter. One should also consider substituting colonoscopy every 5 years beginning at age 20 for a chance that a patient may have attenuated FAP.

There are several reasons why screening is recommended so often for these individuals. First, adenomatous polyps may begin to develop in adolescence. Most people with classic FAP present with polyps before the age of 25, so annual screening with sigmoidoscopy will detect the majority of patients with FAP. Less often, people with FAP will not develop polyps until a later age. The probability of FAP in a person without any polyps on annual screening begins to decrease with age around this time, so that screening does not need to be as frequent between the ages of 24 and 34, and can be even less frequent between the ages of 34 and 44. However, even this recommended schedule is more rigorous than screening guidelines for the general population, because serial negative examinations up to age 35 do not exclude the diagnosis of FAP. It is important to recognize that individuals with attenuated polyposis may not present until a later age and may have fewer polyps than those with classic FAP; yet enhanced screening is still warranted in these individuals.

No familial mutation found: In some families, mutations cannot be found with available testing technology. The sensitivity to identify *APC* gene mutations is currently only about 70-90%.[181] Evaluating presymptomatic individuals at risk in these families presents a difficult problem. By far the best approach in this situation is additional attempts to identify the *APC* or *MUTYH* mutation in an affected family member, even if the available person is not a first-degree relative. If a mutation is found, then the at-risk individual should be managed similar to those with known familial mutations. FAP can be excluded in a person at risk whose genetic testing results indicate no mutation is found when a mutation has been previously identified in an affected family member (a “true negative” test result).

If, however, a familial mutation is still not identified, genetic testing of at-risk individuals can be considered. Certainly, a positive test in a

presymptomatic person is informative even when the familial mutation has not been previously identified. However, interpreting a test in which "no mutation is found" in a presymptomatic person is not the same as a "negative test." This particular issue is often a source of confusion and misinterpretation. Thus, it is critical that patients receive appropriate genetic counseling to avoid false-negative interpretations of test results.[182] Surveillance for these at-risk individuals for whom no mutation is found is identical to that for untested individuals with known familial mutation (see section above). Again, if polyposis is detected, they should be managed in the same way as those with personal history of classical FAP.

Family history of attenuated FAP

Similar genetic counseling, testing, and surveillance considerations discussed previously for patients with a classical FAP family history apply to patients with a family history of attenuated FAP, except for the endoscopy approach. It is important to recognize that individuals with attenuated polyposis may not present until a later age and may have fewer polyps than those with classical FAP. However, enhanced screening is still warranted for these patients.

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

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

Personal history of attenuated FAP

Treating patients with a personal history consistent with AFAP varies depending on the patient's age and adenoma burden. For young patients under age 21 with a small adenoma burden, colonoscopy and polypectomy are recommended every 1 to 2 years with appropriate surgical evaluation and counseling. In patients aged 21 years and older with small adenomatous polyp burden, colectomy and IRA are alternative treatment options to colonoscopy and polypectomy that may be considered. Patients with what appears to be an endoscopically manageable adenoma burden, particularly if responsive to a chemopreventative agent such as sulindac or celecoxib (see below), may choose to defer colectomy.

When polyposis becomes too significant to be managed by polypectomy (ie, when polyps number >20 at any individual examination or when a polyp ≥1 cm in diameter or with advanced histology is identified), surgery is recommended (see below). Colectomy may also be indicated before this level of polyp profusion, especially if colonoscopy is difficult and polyp control is uncertain. Earlier surgical intervention (usually after age 21) should also be considered in patients with a family history of cancer before age 40 or noncompliant patients.

Surgical Options

Three different surgical options are available for individuals with classical and attenuated FAP: total proctocolectomy with ileal pouch anal anastomosis (TPC/IPAA), total abdominal colectomy with ileorectal anastomosis (TAC/IRA), and total proctocolectomy with permanent end ileostomy (TPC/EI).[183] The prime factors to consider when choosing an

operation for FAP and AFAP are the personal and familial phenotype, including the rectal polyp burden, and whether colon or rectal cancer is present at diagnosis. In patients presenting with the classical FAP phenotype, TPC/IPAA, if possible, is the procedure of choice, since it prevents both colon and rectal cancer. For patients with AFAP, TAC/IRA is preferred. Surgery is performed either at the onset of polyposis or later, depending on the severity of the familial phenotype and genotype, the extent of polyposis at diagnosis, individual considerations, and local practices and expertise. Proper post-surgical surveillance should be followed as outlined in sections below. In patients who are younger than 18 years with mild polyposis and without family history of early cancers or genetic disposition, timing of colectomy can be individualized, but annual colonoscopy is essential.

Total proctocolectomy with ileal pouch anal anastomosis (TPC/IPAA)
TPC/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 that may interfere with the completion of surgery, 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. Functional results are variable. 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.

Total abdominal colectomy with ileorectal anastomosis (TAC/IRA)
A TAC/IRA is a fairly quick, straightforward operation with an overall low morbidity rate. It generally results in good bowel function. Most patients have 3 to 4 bowel movements per day, and the risk of urgency, 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 total abdominal colectomy with 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 IRA found a high rate of advanced and fatal rectal cancers even though 88% of the patients underwent a diagnostic proctoscopy within 18 months of presentation. It was estimated that 12.5% of patients undergoing this procedure would die of rectal cancer by age 65 even if compliant with endoscopic screening.[184] 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. However, studies have reported that the risk of rectal cancer associated with total abdominal colectomy and IRA has declined since the 1980s when IPAA first became available for high-risk patients with severe polyposis.[185, 186]

The choice of total abdominal colectomy with IRA versus total proctocolectomy with IPAA centers on the issues of the relative quality of life.[187-192] A modest reduction in life expectancy is expected in patients with classical FAP with rectal preservation.[193, 194] The decision to remove the rectum is dependent on whether the polyps are amenable to endoscopic surveillance and resection. Proctoscopic examination of a retained rectum is indicated annually. IRA is the surgery of choice for the majority of patients with 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. Patients and families must be absolutely reliable for follow-up endoscopic examinations. The risk to the rectal stump rises considerably after the age of 50 and if the rectum becomes unstable, a proctectomy with either an IPAA or end ileostomy is recommended.[195]

Total proctocolectomy with permanent end ileostomy (TPC/EI)
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 TPC/IPAA or they have a poorly functioning IPAA. This is a complex operation with a significant risk for re-operation.

Surveillance Following Surgery for FAP

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

Duodenal or periampullary cancer
A major component of surveillance in patients with a personal history of FAP or attenuated FAP after surgery relates to the upper gastrointestinal tract. Duodenal adenomatous polyps develop in over 90% of patients with FAP. These adenomatous polyps are classified into stages 0 to IV, as defined by Spigelman based on macroscopic and histologic criteria.[196] 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.[197] The risk of duodenal cancer increases dramatically with stage IV disease.

Surveillance following colectomy with side-viewing duodenoscopy, use of Spigelman's or other standardized staging system, and extensive biopsy of dense lesions to evaluate advanced histology is recommended, though efficacy of surveillance of these sites has not been demonstrated. More intensive surveillance and/or treatment are

required in patients over 50 years with large or villous adenomatous polyps.

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

Other cancers

Fundic gland polyps (FGP) of the stomach also occur in the majority of FAP and AFAP patients and often are too numerous to count. In FAP, FGPs usually have bi-allelic inactivation of the *APC* gene, and often display foci of dysplasia or microadenomatous polyps of the foveolar epithelium.[198] 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%. High-grade dysplasia that may warrant special screening is also uncommon on these gastric polyps, and endoscopic biopsies of FGP are not routinely recommended. The upper endoscopy for duodenal surveillance is adequate surveillance for gastric cancers. The recommendation is to observe carefully for gastric polyps that stand out because they appear irregular in shape or texture or are large, suggesting adenomatous polyps. It is also recommended that polyps in the antrum or immediate pre-antrum should be removed if possible. These are less common and are often adenomatous polyps.

Patients with classical FAP also have elevated risk for developing other extra-colonic cancers that warrants attention during surveillance.[199] In the absence of rigorous data, there was extensive discussion among panelists on this area. Patients are at heightened risk for thyroid cancer with a lifetime risk of approximately 2% to 6% and female predominance (95%).[199, 200] Peak incidence is in the third decade of life with a mean age of around 30 years. Yearly thyroid physical examination starting in the late teenage years is recommended and is considered adequate for timely diagnosis and treatment. Annual thyroid ultrasound may be considered to supplement physical examination, although supportive data is lacking.

There is also an increased risk of intra-abdominal desmoid tumors, the majority of which present within 5 years of colectomy. Since significant morbidity and mortality are associated with advanced desmoid tumors, early diagnosis is likely of benefit.[201] Annual abdominal palpation during physical examination is advised. If family history of symptomatic desmoids is present, consider abdominal CT or MRI 1 to 3 years post-colectomy and then at 5-10-year intervals. Immediate abdominal imaging is warranted if suggestive abdominal symptoms are present.

Data on screening for small bowel polyps and cancer is lacking but adding small bowel visualization to CT or MRI for desmoids can be considered especially if duodenal polyposis is advanced. The risk of hepatoblastoma is much higher in young children with FAP.[202] Although the absolute risk is about 1.5%, given the lethality of the disease (25% mortality), active screening by liver palpation, ultrasound, and AFP measurements every 3 to 6 months during the first five years of life may be considered. The optimal approach would be to do this screening in a clinical trial.

Medulloblastoma accounts for most of the brain tumors found in FAP patients, predominantly in females under age 20.[203] The incidence of pancreatic cancer in FAP is not well defined and likely very low. Giardiello and colleagues reported 4 retrospective cases (histology not documented) out of 1,391 FAP-related subjects.[204] More studies are needed to elucidate the risk and benefit of screening for brain and pancreatic cancers and no specific recommendation other than annual physical exam is made.

Surveillance following surgery for AFAP

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

Chemoprevention for FAP and AFAP

The nonsteroidal anti-inflammatory drug (NSAID) aspirin has been shown to reduce the incidence and recurrence of colorectal adenomatous polyps in the general population.[205-210]

COX-2 has been shown to be overexpressed in colorectal adenomatous polyps and cancers. The cyclooxygenase-2 (COX-2) inhibitor celecoxib is another NSAID that has been studied for its role in the chemoprevention of colorectal adenomatous polyps in the general population.[207, 209, 211-214] Results from the Prevention of Colorectal Sporadic Adenomatous Polyps (PreSAP) trial showed that the use of celecoxib significantly reduced the occurrence of colorectal adenomatous polyps within three years after polypectomy.[211] Similarly, the Adenoma Prevention with Celecoxib trial (APC trial) showed that in patients at high risk of CRC who had their polyps removed, celecoxib significantly lowered the formation of adenomatous polyps during a 3-year period.[214] Five-year safety and efficacy results of the APC trial showed that compared to placebo, the reduction in the incidence of advanced adenomatous polyps over 5 years was 41% for those who received lower dose of celecoxib and 26% in patients who received the higher dose compared to the control arm (both P<0.0001).[215] However, due to the increased risk of cardiovascular events associated with their use, COX-2 inhibitors are not recommended routinely for sporadic adenomatous polyps.[216, 217]

NSAIDS have also been studied for their role in chemoprevention in patients with FAP and AFAP. In a randomized, double-blind, placebo-controlled study, the NSAID sulindac did not prevent the development of adenomatous polyps in persons with FAP prior to surgical intervention.[218] In addition, a recent randomized, controlled trial failed to show a strong benefit to chemoprevention with aspirin in young FAP patients prior to surgical intervention, despite non-significant trends to reduced polyp size and number.[219] Thus NSAIDs do not seem to be effective as primary treatment of FAP.

Chemoprevention with NSAIDs, however, can be considered following initial prophylactic surgery for both classical and attenuated FAP as an adjunct to endoscopic surveillance and to reduce the rectal polyp burden, but long-term follow-up is needed to more precisely determine the role of this type of therapy. In a randomized double-blind, placebo-controlled study of 77 FAP patients who had not had their entire colon and rectum removed, patients treated twice daily with 400 mg of celecoxib for 6 months had a 28% reduction in polyp number (P=0.003) and a 31% decrease in sum of polyp diameters (P=0.001), whereas as patients receiving placebo had 4.5% and 4.9% reductions in those parameters, respectively.[220] Long-term use of sulindac also seems to be effective in polyp regression and preventing recurrence of higher-grade adenomatous polyps in the retained rectal segment of FAP patients.[221] It should be noted, however, the FDA indication for the

use of celecoxib in FAP was removed in 2011 due to the lack of phase IV (follow-up) data.

A recent study looked at a possible similar postoperative chemopreventive role in FAP and AFAP for the omega-3 polyunsaturated fatty acid eicosapentaenoic acid (EPA).[222] In this randomized, double-blind, placebo-controlled trial, patients receiving EPA demonstrated a significant 22.4% decrease in polyp number and a significant 29.8% decrease in sum polyp diameter after 6 months of treatment, while patients in the placebo arm saw a worsening of global polyp burden during this time. Although these results show promise, the panel feels they need to be reproduced before the use of EPA can be recommended in this setting.

MUTYH -Associated Polyposis (MAP)

MAP is an autosomal recessive hereditary syndrome that predisposes individuals to attenuated adenomatous polyposis and CRC.[223-225] It is caused by biallelic germline mutations in the *MutY human homolog* (*MUTYH*) gene. *MUTYH* encodes the A/G-specific adenine DNA glycosylase excision repair protein (also called hMYH), which is responsible for excising adenine nucleotides mismatched with 8-oxo-guanine, a product of oxidative damage to DNA. Dysfunctional hMYH protein can thus result in G:C to T:A transversions during DNA replication. Adenomatous polyposis is thought to result from such transversions occurring within the *APC* gene. Individuals with MAP also have an increased risk of extracolonic tumors including duodenal cancer.[226]

Most individuals with MAP generally have fewer than 100 polyps, although a minority can present with over 1,000. Hyperplastic polyps may also be seen in this setting. The life-time risk of CRC for patients with MAP may be very high.[227] The median age of presentation is approximately 45-59 years. The magnitude of risk of duodenal cancer is not well defined, but duodenal polyposis is reported less frequently in MAP than in FAP. In addition, individuals with MAP generally require colectomy at a later age than those with FAP.

Guidelines for screening for germine *MUTYH* mutations are based on limited retrospective data.[228, 229] Balaguer et al reported that patients with CRC and more than 15 synchronous colorectal adenomatous polyps or those younger than 50 years at the time of diagnosis with colorectal cancer might benefit from *MUTYH* genetic testing.[230] NCCN guidelines recommend genetic counseling and testing for germline *MUTYH* mutations for asymptomatic siblings of patients with known *MUTYH* mutations, as well as for *APC* mutation-negative patients with more than 10 cumulative adenomatous polyps. Genetic testing for *MUTYH* mutations may precede *APC* gene testing for families in which only siblings are affected (suggesting recessive inheritance).

Patients with multiple adenomatous polyps and a negative test for *MUTYH* mutation should be managed individually as FAP patients. Symptomatic individuals with confirmed biallelic *MUTYH* mutations and a small adenoma burden are followed with colonoscopy and complete polypectomy every 1 to 2 years. Surgery in the form of subtotal colectomy or proctocolectomy, depending on adenoma distribution and density, is recommended for patients with dense or large polyposis not manageable by polypectomy.

If the mutation status is unknown or if *MUTYH* biallelic mutations are found in an asymptomatic family member, colonoscopic surveillance is recommended beginning at age 25 to 30 years at 3 to 5 year intervals if results continue to be negative. If polyposis is observed, the patient should be followed every 1 to 2 years, as above.

Upper endoscopy and side-viewing duodenoscopy at 3 to 5 year intervals beginning at age 30 to 35 are recommended for patients with dense polyposis and should also be considered for asymptomatic patients, patients with small adenoma burden, or individuals with unknown mutation status and family history of MAP. If duodenal adenomatous polyps are identified, management is similar to that described for FAP patients with duodenal involvement (see above).

References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. CA Cancer J Clin 2012;62:10-29. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22237781.

2. Cheng L, Eng C, Nieman LZ, et al. Trends in Colorectal Cancer Incidence by Anatomic Site and Disease Stage in the United States From 1976 to 2005. Am J Clin Oncol 2011. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21217399.

3. Eheman C, Henley SJ, Ballard-Barbash R, et al. Annual Report to the Nation on the status of cancer, 1975-2008, featuring cancers associated with excess weight and lack of sufficient physical activity. Cancer 2012. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22460733.

4. Siegel R, Ward E, Brawley O, Jemal A. Cancer statistics, 2011: The impact of eliminating socioeconomic and racial disparities on premature cancer deaths. CA Cancer J Clin 2011. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21685461.

5. Gunderson LL, Jessup JM, Sargent DJ, et al. Revised TN categorization for colon cancer based on national survival outcomes data. J Clin Oncol 2010;28:264-271. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19949014.

6. Burt R, Neklason DW. Genetic testing for inherited colon cancer. Gastroenterology 2005;128:1696-1716. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15887160.

7. Giardiello FM, Offerhaus JG. Phenotype and cancer risk of various polyposis syndromes. Eur J Cancer 1995;31A:1085-1087. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7576997.

8. Hamilton SR, Liu B, Parsons RE, et al. The molecular basis of Turcot's syndrome. N Engl J Med 1995;332:839-847. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7661930.

9. Levin B, Lieberman DA, McFarland B, et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. CA Cancer J Clin 2008;58:130-160. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18322143.

10. Rex DK, Johnson DA, Anderson JC, et al. American College of Gastroenterology guidelines for colorectal cancer screening 2009 [corrected]. Am J Gastroenterol 2009;104:739-750. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19240699.

11. USPSTF. Screening for colorectal cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2008;149:627-637. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18838716.

12. Richardson LC, Rim SH, Plescia M. Vital Signs: Colorectal Cancer Screening Among Adults Aged 50-75 Years - United States, 2008. Morbidity and Mortality Weekly Report (Centers for Disease Control and Prevention) 2010;59:808-812. Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5926a3.htm?s_cid=mm5926a3_w.

13. Burt RW. Colorectal cancer screening. Curr Opin Gastroenterol 2010;26:466-470. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20664346.

14. Warren JL, Klabunde CN, Mariotto AB, et al. Adverse events after outpatient colonoscopy in the Medicare population. Ann Intern Med 2009;150:849-857, W152. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19528563.

15. Citarda F, Tomaselli G, Capocaccia R, et al. Efficacy in standard clinical practice of colonoscopic polypectomy in reducing colorectal cancer incidence. Gut 2001;48:812-815. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11358901.

16. Winawer SJ, Zauber AG, Ho MN, et al. Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. N Engl J Med 1993;329:1977-1981. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8247072.

17. Muller AD, Sonnenberg A. Prevention of colorectal cancer by flexible endoscopy and polypectomy. A case-control study of 32,702 veterans. Ann Intern Med 1995;123:904-910. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7486484.

18. Rabeneck L, Paszat LF, Saskin R, Stukel TA. Association between colonoscopy rates and colorectal cancer mortality. Am J Gastroenterol 2010;105:1627-1632. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20197758.

19. Baxter NN, Goldwasser MA, Paszat LF, et al. Association of colonoscopy and death from colorectal cancer. Ann Intern Med 2009;150:1-8. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19075198.

20. Barclay RL, Vicari JJ, Doughty AS, et al. Colonoscopic withdrawal times and adenoma detection during screening colonoscopy. N Engl J Med 2006;355:2533-2541. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17167136.

21. Radaelli F, Meucci G, Sgroi G, Minoli G. Technical performance of colonoscopy: the key role of sedation/analgesia and other quality indicators. Am J Gastroenterol 2008;103:1122-1130. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18445096.

22. Kahi CJ, Imperiale TF, Juliar BE, Rex DK. Effect of screening colonoscopy on colorectal cancer incidence and mortality. Clin Gastroenterol Hepatol 2009;7:770-775; quiz 711. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19268269.

23. Zauber AG, Winawer SJ, O'Brien MJ, et al. Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. N Engl J Med 2012;366:687-696. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22356322.

24. Brenner H, Chang-Claude J, Seiler CM, et al. Protection from colorectal cancer after colonoscopy: a population-based, case-control study. Ann Intern Med 2011;154:22-30. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21200035.

25. Quintero E, Castells A, Bujanda L, et al. Colonoscopy versus fecal immunochemical testing in colorectal-cancer screening. N Engl J Med 2012;366:697-706. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22356323.

26. Kaminski MF, Regula J, Kraszewska E, et al. Quality indicators for colonoscopy and the risk of interval cancer. N Engl J Med 2010;362:1795-1803. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20463339.

27. Lieberman D, Nadel M, Smith RA, et al. Standardized colonoscopy reporting and data system: report of the Quality Assurance Task Group of the National Colorectal Cancer Roundtable. Gastrointest Endosc 2007;65:757-766. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17466195.

28. Rex DK, Cummings OW, Helper DJ, et al. 5-year incidence of adenomas after negative colonoscopy in asymptomatic average-risk persons [see comment]. Gastroenterology 1996;111:1178-1181. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8898630.

29. Imperiale TF, Glowinski EA, Lin-Cooper C, et al. Five-year risk of colorectal neoplasia after negative screening colonoscopy. N Engl J Med 2008;359:1218-1224. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18799558.

30. Lieberman DA, Weiss DG, Harford WV, et al. Five-year colon surveillance after screening colonoscopy. Gastroenterology 2007;133:1077-1085. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17698067.

31. Singh H, Turner D, Xue L, et al. Risk of developing colorectal cancer following a negative colonoscopy examination: evidence for a 10-year interval between colonoscopies. JAMA 2006;295:2366-2373. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16720822.

32. Brenner H, Chang-Claude J, Seiler CM, et al. Does a negative screening colonoscopy ever need to be repeated? Gut 2006;55:1145-1150. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16469791.

33. Brenner H, Chang-Claude J, Seiler CM, Hoffmeister M. Long-term risk of colorectal cancer after negative colonoscopy. J Clin Oncol 2011;29:3761-3767. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21876077.

34. Newcomb PA, Norfleet RG, Storer BE, et al. Screening sigmoidoscopy and colorectal cancer mortality. J Natl Cancer Inst 1992;84:1572-1575. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1404450.

35. Atkin WS, Edwards R, Kralj-Hans I, et al. Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial. Lancet 2010;375:1624-1633. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20430429.

36. Segnan N, Armaroli P, Bonelli L, et al. Once-only sigmoidoscopy in colorectal cancer screening: follow-up findings of the Italian Randomized Controlled Trial--SCORE. J Natl Cancer Inst 2011;103:1310-1322. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21852264.

37. Hoff G, Grotmol T, Skovlund E, Bretthauer M. Risk of colorectal cancer seven years after flexible sigmoidoscopy screening: randomised controlled trial. BMJ 2009;338:b1846. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19483252.

38. Weissfeld JL, Schoen RE, Pinsky PF, et al. Flexible sigmoidoscopy in the PLCO cancer screening trial: results from the baseline screening examination of a randomized trial. J Natl Cancer Inst 2005;97:989-997. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15998952.

39. Weissfeld JL, Schoen RE, Pinsky PF, et al. Flexible sigmoidoscopy in the randomized prostate, lung, colorectal, and ovarian (PLCO) cancer screening trial: added yield from a second screening examination. J Natl Cancer Inst 2012;104:280-289. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22298838.

40. Schoen RE, Pinsky PF, Weissfeld JL, et al. Colorectal cancers not detected by screening flexible sigmoidoscopy in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. Gastrointest Endosc 2012;75:612-620. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22341106.

41. Kim DH, Pickhardt PJ, Taylor AJ, Menias CO. Imaging evaluation of complications at optical colonoscopy. Curr Probl Diagn Radiol 2008;37:165-177. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18502324.

42. Whitlock EP, Lin JS, Liles E, et al. Screening for colorectal cancer: a targeted, updated systematic review for the U.S. Preventive Services Task Force. Ann Intern Med 2008;149:638-658. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18838718.

43. Johnson CD, Chen MH, Toledano AY, et al. Accuracy of CT colonography for detection of large adenomas and cancers. N Engl J Med 2008;359:1207-1217. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18799557.

44. Johnson CD, Toledano AY, Herman BA, et al. Computerized tomographic colonography: performance evaluation in a retrospective multicenter setting. Gastroenterology 2003;125:688-695. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12949715.

45. Rockey DC, Paulson E, Niedzwiecki D, et al. Analysis of air contrast barium enema, computed tomographic colonography, and colonoscopy:

prospective comparison. Lancet 2005;365:305-311. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15664225.

46. Pickhardt PJ, Choi JR, Hwang I, et al. Computed tomographic virtual colonoscopy to screen for colorectal neoplasia in asymptomatic adults. N Engl J Med 2003;349:2191-2200. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14657426.

47. Kim DH, Pickhardt PJ, Taylor AJ, et al. CT colonography versus colonoscopy for the detection of advanced neoplasia. N Engl J Med 2007;357:1403-1412. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17914041.

48. Halligan S, Altman DG, Taylor SA, et al. CT colonography in the detection of colorectal polyps and cancer: systematic review, meta-analysis, and proposed minimum data set for study level reporting. Radiology 2005;237:893-904. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16304111.

49. Mulhall BP, Veerappan GR, Jackson JL. Meta-analysis: computed tomographic colonography. Ann Intern Med 2005;142:635-650. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15838071.

50. Pickhardt PJ, Hassan C, Halligan S, Marmo R. Colorectal cancer: CT colonography and colonoscopy for detection--systematic review and meta-analysis. Radiology 2011;259:393-405. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21415247.

51. de Haan MC, van Gelder RE, Graser A, et al. Diagnostic value of CT-colonography as compared to colonoscopy in an asymptomatic screening population: a meta-analysis. Eur Radiol 2011;21:1747-1763. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21455818.

52. Stoop EM, de Haan MC, de Wijkerslooth TR, et al. Participation and yield of colonoscopy versus non-cathartic CT colonography in population-based screening for colorectal cancer: a randomised controlled trial. Lancet Oncol 2012;13:55-64. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22088831.

53. Fletcher JG, Chen MH, Herman BA, et al. Can radiologist training and testing ensure high performance in CT colonography? Lessons From the National CT Colonography Trial. AJR Am J Roentgenol 2010;195:117-125. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20566804.

54. Lin OS. Computed tomographic colonography: hope or hype? World J Gastroenterol 2010;16:915-920. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20180228.

55. Berrington de Gonzalez A, Kim KP, Yee J. CT colonography: perforation rates and potential radiation risks. Gastrointest Endosc Clin N Am 2010;20:279-291. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20451817.

56. ACR Practice Guideline for the Performance of Coputed Tomography (CT) Colonography in Adults. 2009. Available at: http://www.acr.org/SecondaryMainMenuCategories/quality_safety/guidelines/dx/gastro/ct_colonography.aspx. Accessed June, 2011.

57. Sox HC. Office-based testing for fecal occult blood: do only in case of emergency. Ann Intern Med 2005;142:146-148. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15657163.

58. Collins JF, Lieberman DA, Durbin TE, Weiss DG. Accuracy of screening for fecal occult blood on a single stool sample obtained by digital rectal examination: a comparison with recommended sampling practice. Ann Intern Med 2005;142:81-85. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15657155.

59. Nadel MR, Berkowitz Z, Klabunde CN, et al. Fecal Occult Blood Testing Beliefs and Practices of U.S. Primary Care Physicians: Serious Deviations from Evidence-Based Recommendations. J Gen Intern Med 2010. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20383599.

60. Hardcastle JD, Chamberlain JO, Robinson MH, et al. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer.

Lancet 1996;348:1472-1477. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8942775.

61. Kronborg O, Fenger C, Olsen J, et al. Randomised study of screening for colorectal cancer with faecal-occult-blood test. Lancet 1996;348:1467-1471. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8942774.

62. Mandel JS, Bond JH, Church TR, et al. Reducing mortality from colorectal cancer by screening for fecal occult blood. Minnesota Colon Cancer Control Study. N Engl J Med 1993;328:1365-1371. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8474513.

63. Scholefield JH, Moss SM, Mangham CM, et al. Nottingham trial of faecal occult blood testing for colorectal cancer: a 20-year follow-up. Gut 2011. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22052062.

64. Hewitson P, Glasziou P, Watson E, et al. Cochrane systematic review of colorectal cancer screening using the fecal occult blood test (hemoccult): an update. Am J Gastroenterol 2008;103:1541-1549. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18479499.

65. Allison JE, Tekawa IS, Ransom LJ, Adrain AL. A comparison of fecal occult-blood tests for colorectal-cancer screening. N Engl J Med 1996;334:155-159. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8531970.

66. Lee TJ, Clifford GM, Rajasekhar P, et al. High yield of colorectal neoplasia detected by colonoscopy following a positive faecal occult blood test in the NHS Bowel Cancer Screening Programme. J Med Screen 2011;18:82-86. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21852700.

67. Hundt S, Haug U, Brenner H. Comparative evaluation of immunochemical fecal occult blood tests for colorectal adenoma detection. Ann Intern Med 2009;150:162-169. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19189905.

68. Park DI, Ryu S, Kim YH, et al. Comparison of guaiac-based and quantitative immunochemical fecal occult blood testing in a population at average risk undergoing colorectal cancer screening. Am J Gastroenterol 2010;105:2017-2025. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20502450.

69. Allison JE, Sakoda LC, Levin TR, et al. Screening for colorectal neoplasms with new fecal occult blood tests: update on performance characteristics. J Natl Cancer Inst 2007;99:1462-1470. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17895475.

70. Hol L, Van Leerdam ME, Van Ballegooijen M, et al. Screening For Colorectal Cancer; Randomised Trial Comparing Guaiac-Based And Immunochemical Faecal Occult Blood Testing And Flexible Sigmoidoscopy. Gut 2009. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19671542.

71. Rabeneck L, Rumble RB, Thompson F, et al. Fecal immunochemical tests compared with guaiac fecal occult blood tests for population-based colorectal cancer screening. Can J Gastroenterol 2012;26:131-147. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22408764.

72. Osborn NK, Ahlquist DA. Stool screening for colorectal cancer: molecular approaches. Gastroenterology 2005;128:192-206. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15633136.

73. Imperiale TF, Ransohoff DF, Itzkowitz SH, et al. Fecal DNA versus fecal occult blood for colorectal-cancer screening in an average-risk population. N Engl J Med 2004;351:2704-2714. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15616205.

74. Ahlquist DA, Sargent DJ, Loprinzi CL, et al. Stool DNA and occult blood testing for screen detection of colorectal neoplasia. Ann Intern Med 2008;149:441-450, W481. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18838724.

75. Ahlquist DA, Zou H, Domanico M, et al. Next-generation stool DNA test accurately detects colorectal cancer and large adenomas. Gastroenterology 2012;142:248-256; quiz e225-246. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22062357.

76. Ned RM, Melillo S, Marrone M. Fecal DNA testing for Colorectal Cancer Screening: the ColoSure test. PLoS Curr 2011;3:RRN1220. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21487548.

77. Friedenson B. BRCA1 and BRCA2 pathways and the risk of cancers other than breast or ovarian. MedGenMed 2005;7:60. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16369438.

78. Kadouri L, Hubert A, Rotenberg Y, et al. Cancer risks in carriers of the BRCA1/2 Ashkenazi founder mutations. J Med Genet 2007;44:467-471. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17307836.

79. Luo W, Cao Y, Liao C, Gao F. Diabetes mellitus and the incidence and mortality of colorectal cancer: A meta-analysis of twenty four cohort studies. Colorectal Dis 2011. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22053841.

80. Theuer CP, Wagner JL, Taylor TH, et al. Racial and ethnic colorectal cancer patterns affect the cost-effectiveness of colorectal cancer screening in the United States. Gastroenterology 2001;120:848-856. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11231939.

81. Agrawal S, Bhupinderjit A, Bhutani MS, et al. Colorectal cancer in African Americans. Am J Gastroenterol 2005;100:515-523; discussion 514. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15743345.

82. Heresbach D, Barrioz T, Lapalus MG, et al. Miss rate for colorectal neoplastic polyps: a prospective multicenter study of back-to-back video colonoscopies. Endoscopy 2008;40:284-290. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18389446.

83. Chow E, Lipton L, Lynch E, et al. Hyperplastic polyposis syndrome: phenotypic presentations and the role of MBD4 and MYH. Gastroenterology 2006;131:30-39. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16831587.

84. Rubio CA, Stemme S, Jaramillo E, Lindblom A. Hyperplastic polyposis coli syndrome and colorectal carcinoma. Endoscopy 2006;38:266-270. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16528654.

85. Yeoman A, Young J, Arnold J, et al. Hyperplastic polyposis in the New Zealand population: a condition associated with increased colorectal cancer risk and European ancestry. N Z Med J 2007;120:U2827. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18264196.

86. Ferrandez A, Samowitz W, DiSario JA, Burt RW. Phenotypic characteristics and risk of cancer development in hyperplastic polyposis: case series and literature review. Am J Gastroenterol 2004;99:2012-2018. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15447765.

87. Leggett BA, Devereaux B, Biden K, et al. Hyperplastic polyposis: association with colorectal cancer. Am J Surg Pathol 2001;25:177-184. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11176066.

88. Winawer SJ, Zauber AG, Fletcher RH, et al. Guidelines for colonoscopy surveillance after polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer and the American Cancer Society. CA Cancer J Clin 2006;56:143-159; quiz 184-145. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16737947.

89. Robertson DJ, Burke CA, Welch HG, et al. Using the results of a baseline and a surveillance colonoscopy to predict recurrent adenomas with high-risk characteristics. Ann Intern Med 2009;151:103-109. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19620162.

90. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2403953.

91. Golembeski C, McKenna B, Appelman HD. Advanced adenomas: Pathologists don't agree [abstract]. Modern Pathology 2007;20:115A. Available at: http://www.nature.com/modpathol/journal/v20/n2s/pdf/3800805a.pdf.

92. Walsh RM, Ackroyd FW, Shellito PC. Endoscopic resection of large sessile colorectal polyps. Gastrointest Endosc 1992;38:303-309. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1607080.

93. Rex DK, Kahi CJ, Levin B, et al. Guidelines for colonoscopy surveillance after cancer resection: a consensus update by the American Cancer Society and US Multi-Society Task Force on Colorectal Cancer. CA Cancer J Clin 2006;56:160-167; quiz 185-166. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16737948.

94. Rodriguez-Moranta F, Salo J, Arcusa A, et al. Postoperative surveillance in patients with colorectal cancer who have undergone curative resection: a prospective, multicenter, randomized, controlled trial. J Clin Oncol 2006;24:386-393. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16365182.

95. Sargent DJ, Wieand HS, Haller DG, et al. Disease-free survival versus overall survival as a primary end point for adjuvant colon cancer studies: individual patient data from 20,898 patients on 18 randomized trials. J Clin Oncol 2005;23:8664-8670. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16260700.

96. Shureiqi I, Cooksley CD, Morris J, et al. Effect of age on risk of second primary colorectal cancer. J Natl Cancer Inst 2001;93:1264-1266. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11504772.

97. Green RJ, Metlay JP, Propert K, et al. Surveillance for second primary colorectal cancer after adjuvant chemotherapy: an analysis of Intergroup 0089. Ann Intern Med 2002;136:261-269. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11848723.

98. Hoffman JP, Riley L, Carp NZ, Litwin S. Isolated locally recurrent rectal cancer: a review of incidence, presentation, and management. Semin Oncol 1993;20:506-519. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8211198.

99. Lowy AM, Rich TA, Skibber JM, et al. Preoperative infusional chemoradiation, selective intraoperative radiation, and resection for locally advanced pelvic recurrence of colorectal adenocarcinoma. Ann Surg 1996;223:177-185. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8597512.

100. Yu TK, Bhosale PR, Crane CH, et al. Patterns of locoregional recurrence after surgery and radiotherapy or chemoradiation for rectal cancer. Int J Radiat Oncol Biol Phys 2008;71:1175-1180. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18207667.

101. Pietra N, Sarli L, Costi R, et al. Role of follow-up in management of local recurrences of colorectal cancer: a prospective, randomized study. Dis Colon Rectum 1998;41:1127-1133. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9749496.

102. Secco GB, Fardelli R, Gianquinto D, et al. Efficacy and cost of risk-adapted follow-up in patients after colorectal cancer surgery: a prospective, randomized and controlled trial. Eur J Surg Oncol 2002;28:418-423. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12099653.

103. Desch CE, Benson AB, Somerfield MR, et al. Colorectal cancer surveillance: 2005 update of an American Society of Clinical Oncology practice guideline. J Clin Oncol 2005;23:8512-8519. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16260687.

104. Jeffery M, Hickey BE, Hider PN. Follow-up strategies for patients treated for non-metastatic colorectal cancer. Cochrane Database Syst Rev 2007. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17253476.

105. Renehan AG, Egger M, Saunders MP, O'Dwyer ST. Impact on survival of intensive follow up after curative resection for colorectal

cancer: systematic review and meta-analysis of randomised trials. BMJ 2002;324:813-813. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11934773.

106. Tepper JE, O'Connell M, Niedzwiecki D, et al. Adjuvant therapy in rectal cancer: analysis of stage, sex, and local control--final report of intergroup 0114. J Clin Oncol 2002;20:1744-1750. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11919230.

107. Guyot F, Faivre J, Manfredi S, et al. Time trends in the treatment and survival of recurrences from colorectal cancer. Ann Oncol 2005;16:756-761. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15790673.

108. Li Destri G, Di Cataldo A, Puleo S. Colorectal cancer follow-up: useful or useless? Surg Oncol 2006;15:1-12. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16891116.

109. Pfister DG, Benson AB, 3rd, Somerfield MR. Clinical practice. Surveillance strategies after curative treatment of colorectal cancer. N Engl J Med 2004;350:2375-2382. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15175439.

110. Neumann H, Vieth M, Langner C, et al. Cancer risk in IBD: how to diagnose and how to manage DALM and ALM. World J Gastroenterol 2011;17:3184-3191. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21912466.

111. Umar A, Boland CR, Terdiman JP, et al. Revised Bethesda Guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. J Natl Cancer Inst 2004;96:261-268. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14970275.

112. Taylor DP, Burt RW, Williams MS, et al. Population-based family history-specific risks for colorectal cancer: a constellation approach. Gastroenterology 2010;138:877-885. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19932107.

113. Aaltonen LA, Salovaara R, Kristo P, et al. Incidence of hereditary nonpolyposis colorectal cancer and the feasibility of molecular screening for the disease. N Engl J Med 1998;338:1481-1487. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9593786.

114. Hampel H, Frankel WL, Martin E, et al. Screening for the Lynch syndrome (hereditary nonpolyposis colorectal cancer). N Engl J Med 2005;352:1851-1860. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15872200.

115. Hampel H, Frankel WL, Martin E, et al. Feasibility of screening for Lynch syndrome among patients with colorectal cancer. J Clin Oncol 2008;26:5783-5788. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18809606.

116. Lynch HT, de la Chapelle A. Hereditary colorectal cancer. N Engl J Med 2003;348:919-932. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12621137.

117. Boland CR, Goel A. Microsatellite instability in colorectal cancer. Gastroenterology 2010;138:2073-2087 e2073. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20420947.

118. Kempers MJ, Kuiper RP, Ockeloen CW, et al. Risk of colorectal and endometrial cancers in EPCAM deletion-positive Lynch syndrome: a cohort study. Lancet Oncol 2011;12:49-55. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21145788.

119. Rumilla K, Schowalter KV, Lindor NM, et al. Frequency of deletions of EPCAM (TACSTD1) in MSH2-associated Lynch syndrome cases. J Mol Diagn 2011;13:93-99. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21227399.

120. Vasen HF, Wijnen JT, Menko FH, et al. Cancer risk in families with hereditary nonpolyposis colorectal cancer diagnosed by mutation analysis. Gastroenterology 1996;110:1020-1027. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8612988.

121. Aaltonen LA, Peltomaki P, Mecklin JP, et al. Replication errors in benign and malignant tumors from hereditary nonpolyposis colorectal cancer patients. Cancer Res 1994;54:1645-1648. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8137274.

122. Moslein G, Tester DJ, Lindor NM, et al. Microsatellite instability and mutation analysis of hMSH2 and hMLH1 in patients with sporadic, familial and hereditary colorectal cancer. Hum Mol Genet 1996;5:1245-1252. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8872463.

123. Jarvinen HJ, Mecklin JP, Sistonen P. Screening reduces colorectal cancer rate in families with hereditary nonpolyposis colorectal cancer. Gastroenterology 1995;108:1405-1411. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7729632.

124. Lindor NM, Petersen GM, Hadley DW, et al. Recommendations for the care of individuals with an inherited predisposition to Lynch syndrome: a systematic review. JAMA 2006;296:1507-1517. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17003399.

125. Vasen HF, Watson P, Mecklin JP, Lynch HT. New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative group on HNPCC. Gastroenterology 1999;116:1453-1456. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10348829.

126. Vasen HF. Clinical diagnosis and management of hereditary colorectal cancer syndromes. J Clin Oncol 2000;18:81S-92S. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11060333.

127. Barnetson RA, Tenesa A, Farrington SM, et al. Identification and survival of carriers of mutations in DNA mismatch-repair genes in colon cancer. N Engl J Med 2006;354:2751-2763. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16807412.

128. Rodriguez-Bigas MA, Boland CR, Hamilton SR, et al. A National Cancer Institute Workshop on Hereditary Nonpolyposis Colorectal Cancer Syndrome: meeting highlights and Bethesda guidelines. J Natl Cancer Inst 1997;89:1758-1762. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9392616.

129. Raedle J, Trojan J, Brieger A, et al. Bethesda guidelines: relation to microsatellite instability and MLH1 promoter methylation in patients with colorectal cancer. Ann Intern Med 2001;135:566-576. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11601928.

130. Pinol V, Castells A, Andreu M, et al. Accuracy of revised Bethesda guidelines, microsatellite instability, and immunohistochemistry for the identification of patients with hereditary nonpolyposis colorectal cancer. JAMA 2005;293:1986-1994. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15855432.

131. Ramsey SD, Clarke L, Etzioni R, et al. Cost-effectiveness of microsatellite instability screening as a method for detecting hereditary nonpolyposis colorectal cancer. Ann Intern Med 2001;135:577-588. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11601929.

132. Balmana J, Stockwell DH, Steyerberg EW, et al. Prediction of MLH1 and MSH2 mutations in Lynch syndrome. JAMA 2006;296:1469-1478. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17003395.

133. Chen S, Wang W, Lee S, et al. Prediction of germline mutations and cancer risk in the Lynch syndrome. JAMA 2006;296:1479-1487. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17003396.

134. Kastrinos F, Steyerberg EW, Mercado R, et al. The PREMM(1,2,6) model predicts risk of MLH1, MSH2, and MSH6 germline mutations based on cancer history. Gastroenterology 2011;140:73-81. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20727894.

135. Beamer LC, Grant ML, Espenschied CR, et al. Reflex Immunohistochemistry and Microsatellite Instability Testing of Colorectal Tumors for Lynch Syndrome Among US Cancer Programs and Follow-Up of Abnormal Results. J Clin Oncol 2012;30:1058-1063. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22355048.

136. Burt RW. Who should have genetic testing for the lynch syndrome? Ann Intern Med 2011;155:127-128. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21768586.

137. Recommendations from the EGAPP Working Group: genetic testing strategies in newly diagnosed individuals with colorectal cancer aimed at reducing morbidity and mortality from Lynch syndrome in relatives. Genet Med 2009;11:35-41. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19125126.

138. Ladabaum U, Wang G, Terdiman J, et al. Strategies to identify the Lynch syndrome among patients with colorectal cancer: a cost-effectiveness analysis. Ann Intern Med 2011;155:69-79. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21768580.

139. Palomaki GE, McClain MR, Melillo S, et al. EGAPP supplementary evidence review: DNA testing strategies aimed at reducing morbidity and mortality from Lynch syndrome. Genet Med 2009;11:42-65. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19125127.

140. Hendriks YM, de Jong AE, Morreau H, et al. Diagnostic approach and management of Lynch syndrome (hereditary nonpolyposis colorectal carcinoma): a guide for clinicians. CA Cancer J Clin 2006;56:213-225. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16870997.

141. Caldes T, Godino J, Sanchez A, et al. Immunohistochemistry and microsatellite instability testing for selecting MLH1, MSH2 and MSH6 mutation carriers in hereditary non-polyposis colorectal cancer. Oncol Rep 2004;12:621-629. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15289847.

142. Vasen HF, Hendriks Y, de Jong AE, et al. Identification of HNPCC by molecular analysis of colorectal and endometrial tumors. Dis Markers 2004;20:207-213. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15528786.

143. Hampel H, Frankel W, Panescu J, et al. Screening for Lynch syndrome (hereditary nonpolyposis colorectal cancer) among endometrial cancer patients. Cancer Res 2006;66:7810-7817. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16885385.

144. Lindor NM, Burgart LJ, Leontovich O, et al. Immunohistochemistry versus microsatellite instability testing in phenotyping colorectal tumors. J Clin Oncol 2002;20:1043-1048. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11844828.

145. Reyes CM, Allen BA, Terdiman JP, Wilson LS. Comparison of selection strategies for genetic testing of patients with hereditary nonpolyposis colorectal carcinoma: effectiveness and cost-effectiveness. Cancer 2002;95:1848-1856. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12404277.

146. Shia J, Klimstra DS, Nafa K, et al. Value of immunohistochemical detection of DNA mismatch repair proteins in predicting germline mutation in hereditary colorectal neoplasms. Am J Surg Pathol 2005;29:96-104. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15613860.

147. Pino MS, Chung DC. Application of molecular diagnostics for the detection of Lynch syndrome. Expert Rev Mol Diagn 2010;10:651-665. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20629513.

148. Lagerstedt Robinson K, Liu T, Vandrovcova J, et al. Lynch syndrome (hereditary nonpolyposis colorectal cancer) diagnostics. J Natl Cancer Inst 2007;99:291-299. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17312306.

149. Yurgelun MB, Goel A, Hornick JL, et al. Microsatellite instability and DNA mismatch repair protein deficiency in lynch syndrome colorectal polyps. Cancer Prev Res (Phila) 2012;5:574-582. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22262812.

150. Burt RW. Diagnosing lynch syndrome: more light at the end of the tunnel. Cancer Prev Res (Phila) 2012;5:507-510. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22491516.

151. Dinh TA, Rosner BI, Atwood JC, et al. Health benefits and cost-effectiveness of primary genetic screening for Lynch syndrome in the general population. Cancer Prev Res (Phila) 2011;4:9-22. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21088223.

152. Bonadona V, Bonaiti B, Olschwang S, et al. Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome. JAMA 2011;305:2304-2310. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21642682.

153. Kohlmann W, Gruber S. Lynch Syndrome. GeneReviews at GeneTests: Medical Genetics Information Resource 2011. Available at: http://www.ncbi.nlm.nih.gov/books/NBK1211/.

154. Kastrinos F, Mukherjee B, Tayob N, et al. Risk of pancreatic cancer in families with Lynch syndrome. JAMA 2009;302:1790-1795. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19861671.

155. Watson P, Vasen HF, Mecklin JP, et al. The risk of extra-colonic, extra-endometrial cancer in the Lynch syndrome. Int J Cancer 2008;123:444-449. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18398828.

156. Win AK, Young JP, Lindor NM, et al. Colorectal and other cancer risks for carriers and noncarriers from families with a DNA mismatch repair gene mutation: a prospective cohort study. J Clin Oncol 2012;30:958-964. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22331944.

157. Senter L, Clendenning M, Sotamaa K, et al. The clinical phenotype of Lynch syndrome due to germ-line PMS2 mutations. Gastroenterology 2008;135:419-428. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18602922.

158. Chen LM, Yang KY, Little SE, et al. Gynecologic cancer prevention in Lynch syndrome/hereditary nonpolyposis colorectal cancer families. Obstet Gynecol 2007;110:18-25. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17601891.

159. Schmeler KM, Lynch HT, Chen LM, et al. Prophylactic surgery to reduce the risk of gynecologic cancers in the Lynch syndrome. N Engl J Med 2006;354:261-269. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16421367.

160. Auranen A, Joutsiniemi T. A systematic review of gynecological cancer surveillance in women belonging to hereditary nonpolyposis colorectal cancer (Lynch syndrome) families. Acta Obstet Gynecol Scand 2011;90:437-444. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21306348.

161. Jarvinen HJ, Renkonen-Sinisalo L, Aktan-Collan K, et al. Ten years after mutation testing for Lynch syndrome: cancer incidence and outcome in mutation-positive and mutation-negative family members. J Clin Oncol 2009;27:4793-4797. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19720893.

162. Renkonen-Sinisalo L, Butzow R, Leminen A, et al. Surveillance for endometrial cancer in hereditary nonpolyposis colorectal cancer syndrome. Int J Cancer 2007;120:821-824. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17096354.

163. Rijcken FE, Mourits MJ, Kleibeuker JH, et al. Gynecologic screening in hereditary nonpolyposis colorectal cancer. Gynecol Oncol 2003;91:74-80. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14529665.

164. Dove-Edwin I, Boks D, Goff S, et al. The outcome of endometrial carcinoma surveillance by ultrasound scan in women at risk of hereditary nonpolyposis colorectal carcinoma and familial colorectal carcinoma. Cancer 2002;94:1708-1712. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11920532.

165. Capelle LG, Van Grieken NC, Lingsma HF, et al. Risk and epidemiological time trends of gastric cancer in Lynch syndrome carriers in the Netherlands. Gastroenterology 2010;138:487-492. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19900449.

166. Renkonen-Sinisalo L, Sipponen P, Aarnio M, et al. No support for endoscopic surveillance for gastric cancer in hereditary non-polyposis colorectal cancer. Scand J Gastroenterol 2002;37:574-577. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12059060.

167. Schulmann K, Engel C, Propping P, Schmiegel W. Small bowel cancer risk in Lynch syndrome. Gut 2008;57:1629-1630. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18941010.

168. ten Kate GL, Kleibeuker JH, Nagengast FM, et al. Is surveillance of the small bowel indicated for Lynch syndrome families? Gut 2007;56:1198-1201. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17409122.

169. Koornstra JJ, Kleibeuker JH, Vasen HF. Small-bowel cancer in Lynch syndrome: is it time for surveillance? Lancet Oncol 2008;9:901-905. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18760246.

170. Burn J, Gerdes AM, Macrae F, et al. Long-term effect of aspirin on cancer risk in carriers of hereditary colorectal cancer: an analysis from the CAPP2 randomised controlled trial. Lancet 2011;378:2081-2087. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22036019.

171. Galiatsatos P, Foulkes WD. Familial adenomatous polyposis. Am J Gastroenterol 2006;101:385-398. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16454848.

172. Half E, Bercovich D, Rozen P. Familial adenomatous polyposis. Orphanet J Rare Dis 2009;4:22. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19822006.

173. Ballhausen WG. Genetic testing for familial adenomatous polyposis. Ann N Y Acad Sci 2000;910:36-47; discussion 47-39. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10911904.

174. Mihalatos M, Apessos A, Papadopoulou E, et al. Genetic alterations of the APC gene in familial adenomatous polyposis patients of the hellenic group for the study of colorectal cancer. Anticancer Res 2003;23:2191-2193. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12894596.

175. Gryfe R, Di Nicola N, Lal G, et al. Inherited colorectal polyposis and cancer risk of the APC I1307K polymorphism. Am J Hum Genet 1999;64:378-384. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9973276.

176. Locker GY, Kaul K, Weinberg DS, et al. The I1307K APC polymorphism in Ashkenazi Jews with colorectal cancer: clinical and pathologic features. Cancer Genet Cytogenet 2006;169:33-38. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16875934.

177. Nieuwenhuis MH, Vasen HF. Correlations between mutation site in APC and phenotype of familial adenomatous polyposis (FAP): a review of the literature. Crit Rev Oncol Hematol 2007;61:153-161. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17064931.

178. Sturt NJ, Gallagher MC, Bassett P, et al. Evidence for genetic predisposition to desmoid tumours in familial adenomatous polyposis independent of the germline APC mutation. Gut 2004;53:1832-1836. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15542524.

179. Burt RW, Leppert MF, Slattery ML, et al. Genetic testing and phenotype in a large kindred with attenuated familial adenomatous polyposis. Gastroenterology 2004;127:444-451. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15300576.

180. Knudsen AL, Bulow S, Tomlinson I, et al. Attenuated familial adenomatous polyposis: results from an international collaborative

study. Colorectal Dis 2010;12:e243-249. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20105204.

181. Hegde MR, Roa BB. Detecting mutations in the APC gene in familial adenomatous polyposis (FAP). Curr Protoc Hum Genet 2006;Chapter 10:Unit 10 18. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18428386.

182. Giardiello FM, Brensinger JD, Petersen GM, et al. The use and interpretation of commercial APC gene testing for familial adenomatous polyposis. N Engl J Med 1997;336:823-827. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9062090.

183. Guillem JG, Wood WC, Moley JF, et al. ASCO/SSO review of current role of risk-reducing surgery in common hereditary cancer syndromes. J Clin Oncol 2006;24:4642-4660. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17008706.

184. Vasen HF, van Duijvendijk P, Buskens E, et al. Decision analysis in the surgical treatment of patients with familial adenomatous polyposis: a Dutch-Scandinavian collaborative study including 659 patients. Gut 2001;49:231-235. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11454800.

185. Bulow S, Bulow C, Vasen H, et al. Colectomy and ileorectal anastomosis is still an option for selected patients with familial adenomatous polyposis. Dis Colon Rectum 2008;51:1318-1323. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18523824.

186. Church J, Burke C, McGannon E, et al. Risk of rectal cancer in patients after colectomy and ileorectal anastomosis for familial adenomatous polyposis: a function of available surgical options. Dis Colon Rectum 2003;46:1175-1181. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12972960.

187. Ambroze WL, Jr., Dozois RR, Pemberton JH, et al. Familial adenomatous polyposis: results following ileal pouch-anal anastomosis and ileorectostomy. Dis Colon Rectum 1992;35:12-15. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1310269.

188. Madden MV, Neale KF, Nicholls RJ, et al. Comparison of morbidity and function after colectomy with ileorectal anastomosis or restorative proctocolectomy for familial adenomatous polyposis. Br J Surg 1991;78:789-792. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1651799.

189. Soravia C, Klein L, Berk T, et al. Comparison of ileal pouch-anal anastomosis and ileorectal anastomosis in patients with familial adenomatous polyposis. Dis Colon Rectum 1999;42:1028-1033; discussion 1033-1024. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10458126.

190. Van Duijvendijk P, Slors JF, Taat CW, et al. Quality of life after total colectomy with ileorectal anastomosis or proctocolectomy and ileal pouch-anal anastomosis for familial adenomatous polyposis. Br J Surg 2000;87:590-596. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10792315.

191. van Duijvendijk P, Slors JF, Taat CW, et al. Functional outcome after colectomy and ileorectal anastomosis compared with proctocolectomy and ileal pouch-anal anastomosis in familial adenomatous polyposis. Ann Surg 1999;230:648-654. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10561088.

192. Ziv Y, Church JM, Oakley JR, et al. Surgery for the teenager with familial adenomatous polyposis: ileo-rectal anastomosis or restorative proctocolectomy? Int J Colorectal Dis 1995;10:6-9. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7745328.

193. Bjork JA, Akerbrant HI, Iselius LE, Hultcrantz RW. Risk factors for rectal cancer morbidity and mortality in patients with familial adenomatous polyposis after colectomy and ileorectal anastomosis. Dis Colon Rectum 2000;43:1719-1725. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11156457.

194. De Cosse JJ, Bulow S, Neale K, et al. Rectal cancer risk in patients treated for familial adenomatous polyposis. The Leeds Castle Polyposis Group. Br J Surg 1992;79:1372-1375. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1336702.

195. Nugent KP, Phillips RK. Rectal cancer risk in older patients with familial adenomatous polyposis and an ileorectal anastomosis: a cause for concern. Br J Surg 1992;79:1204-1206. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1334761.

196. Spigelman AD, Williams CB, Talbot IC, et al. Upper gastrointestinal cancer in patients with familial adenomatous polyposis. Lancet 1989;2:783-785. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2571019.

197. Saurin JC, Gutknecht C, Napoleon B, et al. Surveillance of duodenal adenomas in familial adenomatous polyposis reveals high cumulative risk of advanced disease. J Clin Oncol 2004;22:493-498. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14752072.

198. Abraham SC, Nobukawa B, Giardiello FM, et al. Fundic gland polyps in familial adenomatous polyposis: neoplasms with frequent somatic adenomatous polyposis coli gene alterations. Am J Pathol 2000;157:747-754. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10980114.

199. Groen EJ, Roos A, Muntinghe FL, et al. Extra-intestinal manifestations of familial adenomatous polyposis. Ann Surg Oncol 2008;15:2439-2450. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18612695.

200. Steinhagen E, Guillem JG, Chang G, et al. The Prevalence of Thyroid Cancer and Benign Thyroid Disease in Patients With Familial Adenomatous Polyposis May Be Higher Than Previously Recognized. Clin Colorectal Cancer 2012. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22425061.

201. Church J, Lynch C, Neary P, et al. A desmoid tumor-staging system separates patients with intra-abdominal, familial adenomatous polyposis-associated desmoid disease by behavior and prognosis. Dis Colon Rectum 2008;51:897-901. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18322756.

202. Aretz S, Koch A, Uhlhaas S, et al. Should children at risk for familial adenomatous polyposis be screened for hepatoblastoma and children with apparently sporadic hepatoblastoma be screened for APC germline mutations? Pediatr Blood Cancer 2006;47:811-818. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16317745.

203. Attard TM, Giglio P, Koppula S, et al. Brain tumors in individuals with familial adenomatous polyposis: a cancer registry experience and pooled case report analysis. Cancer 2007;109:761-766. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17238184.

204. Giardiello FM, Offerhaus GJ, Lee DH, et al. Increased risk of thyroid and pancreatic carcinoma in familial adenomatous polyposis. Gut 1993;34:1394-1396. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8244108.

205. Algra AM, Rothwell PM. Effects of regular aspirin on long-term cancer incidence and metastasis: a systematic comparison of evidence from observational studies versus randomised trials. Lancet Oncol 2012. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22440112.

206. Baron JA, Cole BF, Sandler RS, et al. A randomized trial of aspirin to prevent colorectal adenomas. N Engl J Med 2003;348:891-899. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12621133.

207. Brasky TM, Potter JD, Kristal AR, et al. Non-steroidal anti-inflammatory drugs and cancer incidence by sex in the VITamins And Lifestyle (VITAL) cohort. Cancer Causes Control 2012;23:431-444. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22212612.

208. Chan AT, Giovannucci EL, Meyerhardt JA, et al. Long-term use of aspirin and nonsteroidal anti-inflammatory drugs and risk of colorectal

cancer. JAMA 2005;294:914-923. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16118381.

209. Ruder EH, Laiyemo AO, Graubard BI, et al. Non-steroidal anti-inflammatory drugs and colorectal cancer risk in a large, prospective cohort. Am J Gastroenterol 2011;106:1340-1350. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21407185.

210. Sandler RS, Halabi S, Baron JA, et al. A randomized trial of aspirin to prevent colorectal adenomas in patients with previous colorectal cancer. N Engl J Med 2003;348:883-890. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12621132.

211. Arber N, Eagle CJ, Spicak J, et al. Celecoxib for the prevention of colorectal adenomatous polyps. N Engl J Med 2006;355:885-895. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16943401.

212. Arber N, Spicak J, Racz I, et al. Five-year analysis of the prevention of colorectal sporadic adenomatous polyps trial. Am J Gastroenterol 2011;106:1135-1146. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21503000.

213. Baron JA, Sandler RS, Bresalier RS, et al. A randomized trial of rofecoxib for the chemoprevention of colorectal adenomas. Gastroenterology 2006;131:1674-1682. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17087947.

214. Bertagnolli MM, Eagle CJ, Zauber AG, et al. Celecoxib for the prevention of sporadic colorectal adenomas. N Engl J Med 2006;355:873-884. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16943400.

215. Bertagnolli MM, Eagle CJ, Zauber AG, et al. Five-year efficacy and safety analysis of the Adenoma Prevention with Celecoxib Trial. Cancer Prev Res (Phila Pa) 2009;2:310-321. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19336730.

216. Bresalier RS, Sandler RS, Quan H, et al. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. N Engl J Med 2005;352:1092-1102. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15713943.

217. Solomon SD, McMurray JJ, Pfeffer MA, et al. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. N Engl J Med 2005;352:1071-1080. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15713944.

218. Giardiello FM, Yang VW, Hylind LM, et al. Primary chemoprevention of familial adenomatous polyposis with sulindac. N Engl J Med 2002;346:1054-1059. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11932472.

219. Burn J, Bishop DT, Chapman PD, et al. A randomized placebo-controlled prevention trial of aspirin and/or resistant starch in young people with familial adenomatous polyposis. Cancer Prev Res (Phila) 2011;4:655-665. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21543343.

220. Steinbach G, Lynch PM, Phillips RK, et al. The effect of celecoxib, a cyclooxygenase-2 inhibitor, in familial adenomatous polyposis. N Engl J Med 2000;342:1946-1952. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10874062.

221. Cruz-Correa M, Hylind LM, Romans KE, et al. Long-term treatment with sulindac in familial adenomatous polyposis: a prospective cohort study. Gastroenterology 2002;122:641-645. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11874996.

222. West NJ, Clark SK, Phillips RK, et al. Eicosapentaenoic acid reduces rectal polyp number and size in familial adenomatous polyposis. Gut 2010;59:918-925. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20348368.

223. Al-Tassan N, Chmiel NH, Maynard J, et al. Inherited variants of MYH associated with somatic G:C-->T:A mutations in colorectal

tumors. Nat Genet 2002;30:227-232. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11818965.

224. Jones S, Emmerson P, Maynard J, et al. Biallelic germline mutations in MYH predispose to multiple colorectal adenoma and somatic G:C-->T:A mutations. Hum Mol Genet 2002;11:2961-2967. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12393807.

225. Theodoratou E, Campbell H, Tenesa A, et al. A large-scale meta-analysis to refine colorectal cancer risk estimates associated with MUTYH variants. Br J Cancer 2010;103:1875-1884. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21063410.

226. Vogt S, Jones N, Christian D, et al. Expanded extracolonic tumor spectrum in MUTYH-associated polyposis. Gastroenterology 2009;137:1976-1985 e1971-1910. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19732775.

227. Nieuwenhuis MH, Vogt S, Jones N, et al. Evidence for accelerated colorectal adenoma-carcinoma progression in MUTYH-associated polyposis? Gut 2011. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21846783.

228. Jo WS, Bandipalliam P, Shannon KM, et al. Correlation of polyp number and family history of colon cancer with germline MYH mutations. Clin Gastroenterol Hepatol 2005;3:1022-1028. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16234049.

229. Wang L, Baudhuin LM, Boardman LA, et al. MYH mutations in patients with attenuated and classic polyposis and with young-onset colorectal cancer without polyps. Gastroenterology 2004;127:9-16. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15236166.

230. Balaguer F, Castellvi-Bel S, Castells A, et al. Identification of MYH mutation carriers in colorectal cancer: a multicenter, case-control, population-based study. Clin Gastroenterol Hepatol 2007;5:379-387. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17368238.