National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology™

Colorectal Cancer Screening

V.1.2006

Continue

www.nccn.org

NCCN Colorectal Cancer Screening Panel Members

* Bernard Levin, MD/Chair ¤
The University of Texas M. D. Anderson Cancer Center

James S. Barthel, MD ¤ Þ
H. Lee Moffitt Cancer Center and Research Institute at the University of South Florida

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

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

James M. Ford, MD † Þ Δ
Stanford Hospital and Clinics

Francis M. Giardiello, MD, PhD ¤
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 Hamilton, MD ≠
The University of Texas M. D. Anderson Cancer Center

Wendy Kohlmann, MS, CGC Δ
University of Michigan Comprehensive Cancer Center

Kirk A. Ludwig, MD ¶
Duke Comprehensive Cancer Center

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

Christopher Marino, MD ¤
St. Jude Children's Research Hospital/University of Tennessee Cancer Institute

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

Robert J. Mayer, MD †
Dana-Farber/Partners CancerCare

Boris Pasche, MD, PhD Δ ‡ Þ
Robert H. Lurie Comprehensive Cancer Center of Northwestern University

Samuel J. Pirruccello, MD ≠
UNMC Eppley Cancer Center at The Nebraska Medical Center

Ashwani Rajput, MD ¶
Roswell Park 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 Comprehensive Cancer Center

David Weinberg, MD, MS ¤
Fox Chase Cancer Center

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

¤ Gastroenterology
Þ Internal medicine
Δ Cancer genetics
† Medical oncology
¶ Surgery/Surgical oncology
≠ Pathology
‡ Hematology/Hematology oncology
* Writing Committee member

Continue

Version 1.2006, 01/03/06 © 2006 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

Colorectal Cancer Screening

Table of Contents

NCCN Colorectal Cancer Screening Panel Members
Risk Assessment and Screening (CSCR-1)
- Average Risk (CSCR-2)
- Increased Risk: Personal History of Adenoma (CSCR-3)
- Increased Risk: Personal History of Colorectal Cancer (CSCR-4)
- Increased Risk: Personal History of Ovarian or Endometrial Cancer (CSCR-4)
- Increased Risk: Inflammatory Bowel Disease (CSCR-5)
- Increased Risk: Positive Family History (CSCR-6)

Hereditary Syndromes
- Inclusion Criteria, Assessment (CSCR-7)
- Hereditary Nonpolyposis Colorectal Cancer (HNPCC) (CSCR-8)
- Familial Adenomatous Polyposis Syndromes (CSCR-11)
- MYH-Associated Polyposis (CSCR-19)

Family History of Colorectal Cancer and Expanded Pedigree (CSCR-A)
Common Pedigree Symbols (CSCR-B)
First-, Second-, and Third-Degree Relatives of Proband (CSCR-C)
Primary Surgical Management of FAP (CSCR-D)
Revised Bethesda Guidelines for Testing of Colorectal Tumors for Microsatellite Instability (CSCR-E)
Minimum Criteria for Clinical Definition of HNPCC - Amsterdam Criteria I (CSCR-F)
Revised Minimum Criteria for Clinical Definition of HNPCC - Amsterdam Criteria II (CSCR-G)

For help using these documents, please click here

Guidelines Index

Print the Colorectal Screening Guideline

Manuscript

References

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

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

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

See NCCN Categories of Consensus

Summary of Guidelines Updates

These guidelines are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network makes no representations nor warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way. These guidelines are copyrighted by National Comprehensive Cancer Network. All rights reserved. These guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN. ©2006.

Colorectal Cancer Screening

RISK ASSESSMENT

Average risk:
- Age ≥ 50 y
- No history of adenoma
- No history of inflammatory bowel disease
- Negative family history[a]

→ See Screening and Evaluation (CSCR-2)

Increased risk:
- Personal history
  - Adenoma → See Follow-up of Clinical Findings: Adenoma (CSCR-3)
  - Colorectal cancer
  - Endometrial/Ovarian cancer < age 60 y

  → See Surveillance (CSCR-4)
  - Inflammatory bowel disease → See Screening and Follow-up (CSCR-5)
- Positive family history:
  - A first degree relative with colorectal cancer or two second degree relatives (related to each other) with colorectal cancer

  → See Screening (CSCR-6)
  - Clustering of colorectal cancer or HNPCC related cancers in the family (See CSCR-7)

Hereditary high risk (CSCR-5):
- Colorectal cancer at age < 50 y or clustering of colorectal cancer or HNPCC related cancers in the family, or personal or family history of polyposis.
- Polyposis syndromes
- HNPCC

→ See Hereditary Syndromes (CSCR-7)

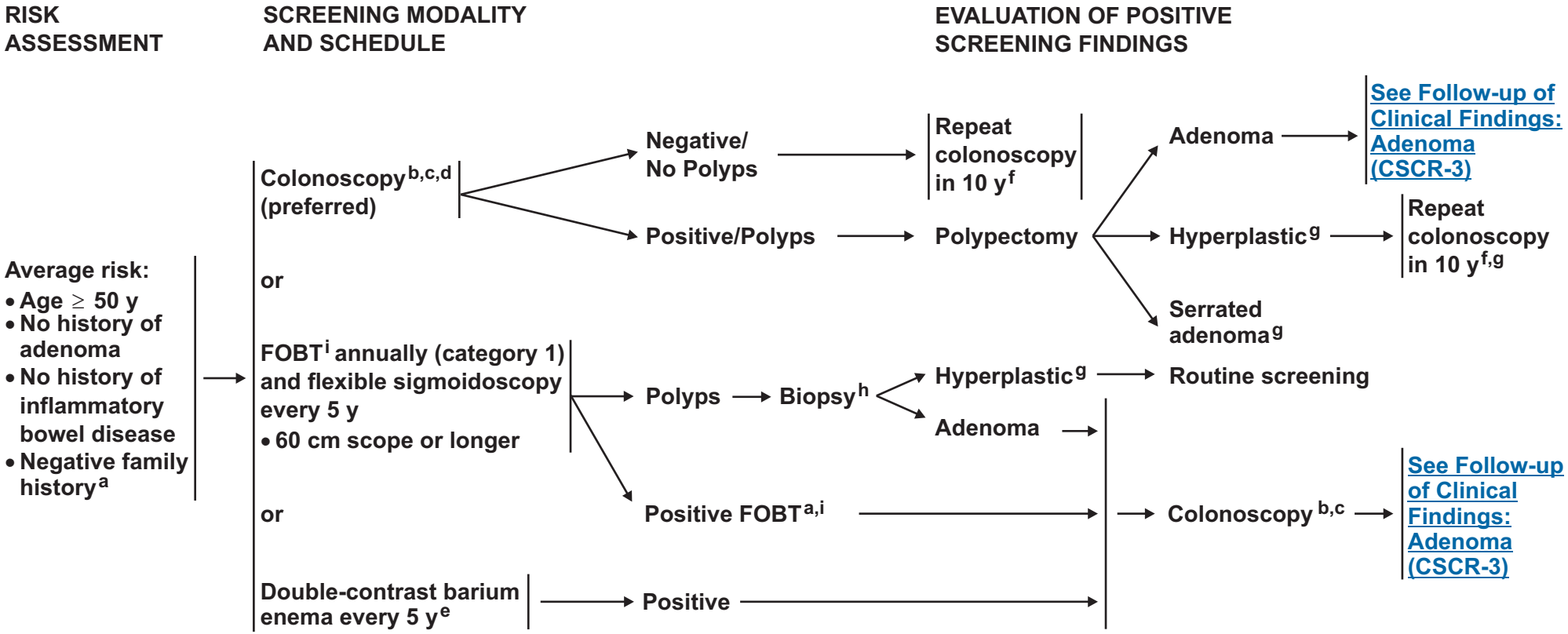
[a]Not having the following: A first degree relative or two second degree relatives with colorectal cancer, or clustering of HNPCC related cancers in the family.

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.

Version 1.2006, 01/03/06 © 2006 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

Colorectal Cancer Screening

Guidelines Index
Colorectal Screening TOC
MS, References



[a] Not having a first degree relative or two second degree relatives with colorectal cancer or clustering of HNPCC related cancers in the family.
[b] If FOBT positive and colonoscopy negative, proceed with additional workup.
[c] If colonoscopy incomplete, perform double-contrast barium enema at discretion of physician.
[d] Data regarding virtual colonoscopy are too premature to warrant its use in screening.
[e] Other screening options preferred over double contrast barium enema.
[f] If using 10 y interval, patient must have no identifiable risk factors except age and preparation must be adequate.
[g] Patients with large hyperplastic polyps (> 10 mm) or > 10 hyperplastic polyps, especially right-sided or with diffuse distribution, may need to be screened more frequently. Serrated adenomas, which may appear hyperplastic, have an association with adenocarcinoma, and patients with these lesions should also be screened more frequently.
[h] Lesions > 1 cm may not need biopsy because they are almost always adenomas.

[i] Fecal Occult Blood Test (FOBT)

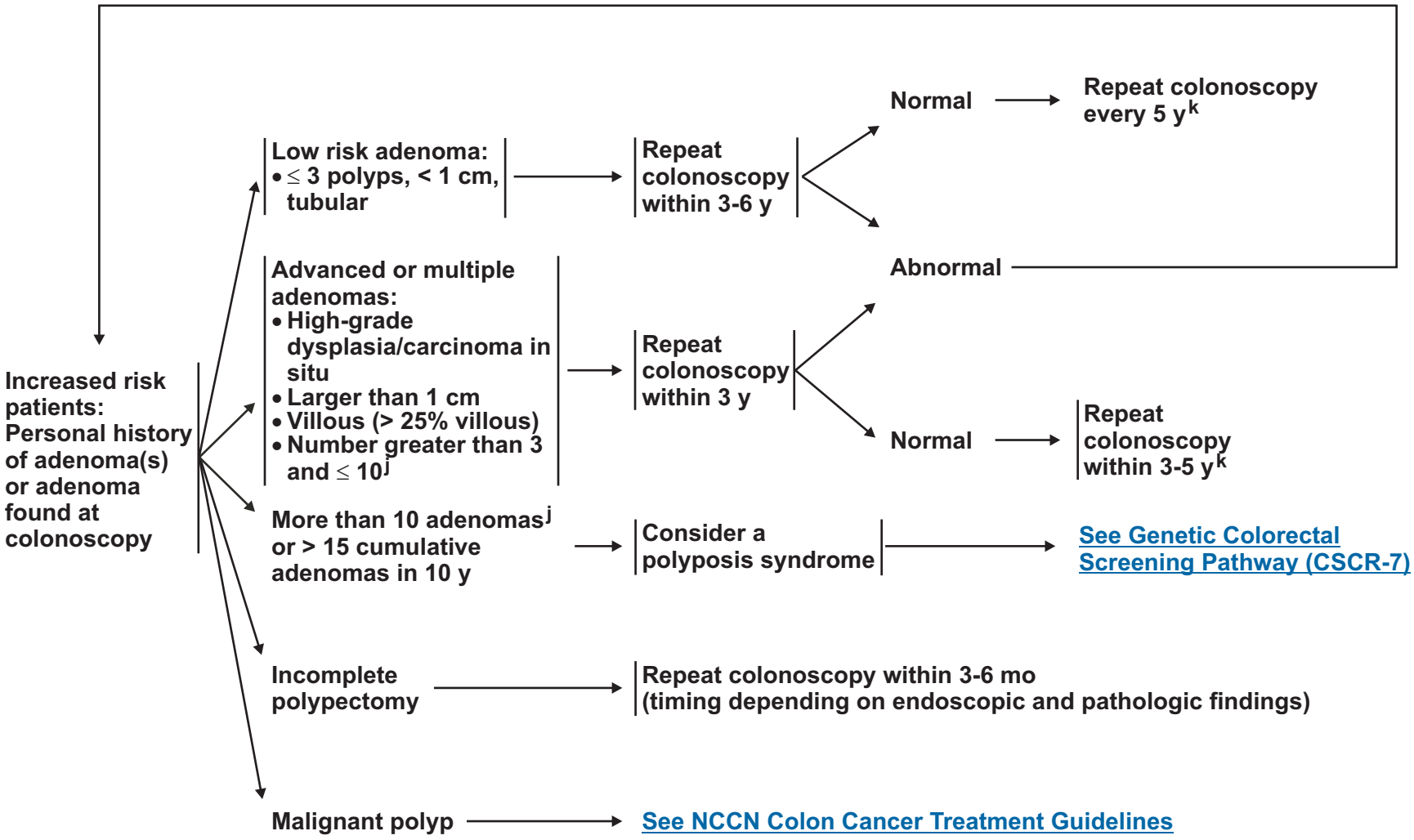
- **Any positive test requires evaluation**
- **3 successive stool specimens**
- **Prescribed diet**
- **Not via digital rectal examination**
- **Guaiac-based nonrehydrated**
- **Immunochemical techniques under investigation**
- **Coordinated by health care provider**
- **Annual FOBT need not be performed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

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.

Version 1.2006, 01/03/06 © 2006 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

Colorectal Cancer Screening

FOLLOW-UP OF CLINICAL FINDINGS: ADENOMA

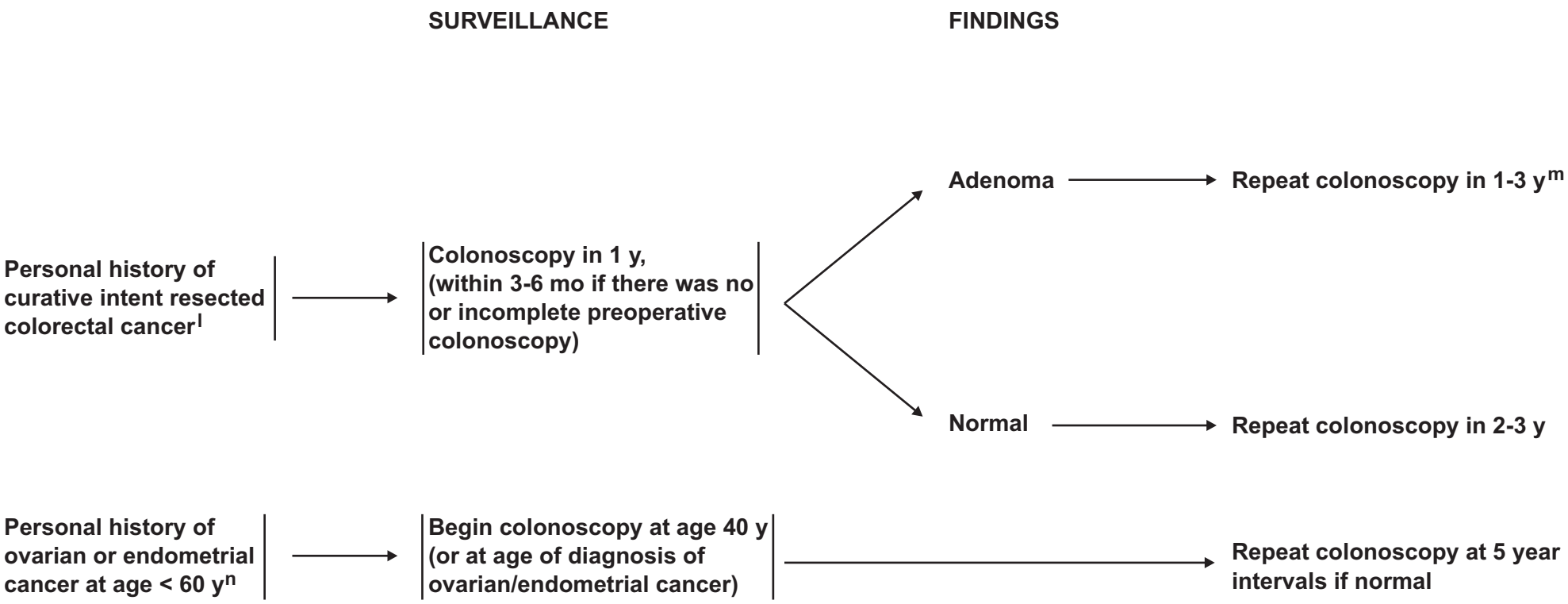


[j]Less than 10 polyps may sometimes be associated with an inherited polyposis syndrome.
[k]The number and characteristics of polyp may influence the judgment of frequencies of colonoscopy.

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.

Version 1.2006, 01/03/06 © 2006 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

Colorectal Cancer Screening



[l] Identify colorectal patients who meet Bethesda criteria. Those patients may require genetic counseling or individualized management. See (CSCR-7, CSCR-8).

[m] The need for intensive screening immediately following resection is based mainly on a study of 3278 patients with resected stage II and III colorectal cancer, which found a high rate of recurrence in the first 4 years (Green et al, Annals of Internal Medicine. 2002;136:261-269). However, the study did not exclude patients with HNPCC.

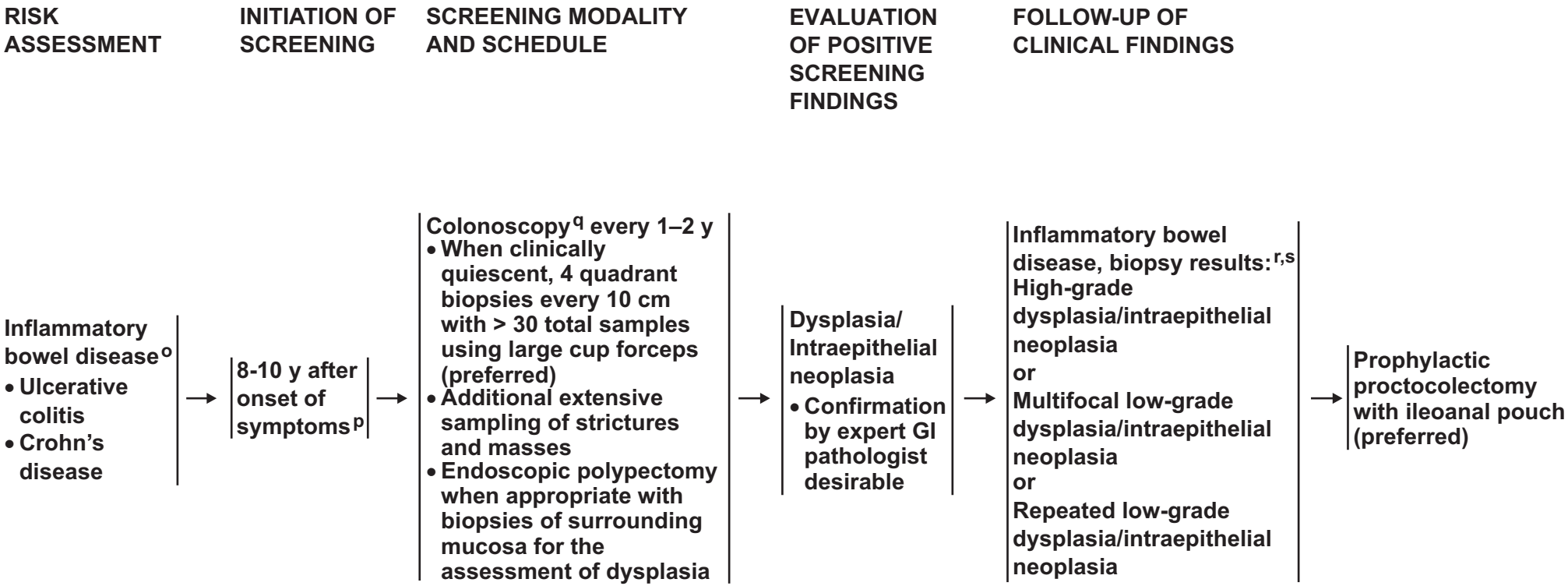
[n] Women with endometrial and ovarian cancer diagnosed prior to age 60 y are at mildly elevated risk for colorectal cancer. Risk is highest for women with the primary diagnosis prior to age 50 y. However, this observation is based on data that did not exclude patients with HNPCC who may account for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

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.

Version 1.2006, 01/03/06 © 2006 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

Colorectal Cancer Screening

Guidelines Index
Colorectal Screening TOC
MS, References



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

[p] Winawer S, Fletcher R, Rex D, et al. Colorectal cancer screening and surveillance: Clinical guidelines and rationale--update based on new evidence. Gastroenterology; 124:544-560, 2003. American Gastroenterological Association (www.gastro.org).

[q] Women diagnosed with endometrial cancer or ovarian cancer before the age of 50 are at increased risk of developing colon cancer. Early colonoscopy, at the time of gynecologic diagnosis, should be considered in these individuals.

[r] 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.

[s] 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.

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.

Version 1.2006, 01/03/06 © 2006 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

Colorectal Cancer Screening

INCREASED RISK

POSITIVE FAMILY HISTORY	SCREENING
• First degree relative with colorectal cancer < age 50 y, two first degree relatives with colorectal cancer at any age, or clustering of HNPCC related cancers, or polyposis in close relatives. See Evaluation for Genetic Screening (CSCR-7) and (CSCR-8)	If not meeting criteria for a defined syndrome, consider beginning screening colonoscopy at age 40 y or 10 y prior to earliest cancer in family → Repeat every 1-5 y
• First degree family member with colorectal cancer	Colonoscopy beginning at age 40 y or 10 y prior to earliest colorectal cancer in family → Repeat every 5 y
• Two related second degree relatives with colorectal cancer at any age	Risk equivalent to one affected first degree relative
• One second degree family member or any third degree family members	• Screen as average risk • Individualized evaluation, including a careful family history, is encouraged

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

Version 1.2006, 01/03/06 © 2006 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

Colorectal Cancer Screening

Guidelines Index
Colorectal Screening TOC
MS, References

INCLUSION CRITERIA

Early-age-onset colorectal cancer (< age 50)
or
Clustering of same or related cancer in close relative
- Colorectal
- Endometrial
- Ovarian
- Duodenal/small bowel
- Stomach
- Ureteral/renal pelvis
- Sebaceous adenomas or sebaceous carcinomas

or
Multiple colorectal carcinomas or >10 adenomas in same individual
or
Family with known hereditary syndrome associated with cancer with or without mutation (eg, polyposis)

→ Patient needs
+
Detailed family history[t]
+
Detailed medical and surgical history[u]
+
Directed examination for related manifestations[v]

HEREDITARY SYNDROME

- HNPCC criteria met (See CSCR-8) →
- Classical FAP criteria met (See CSCR-11) →
- Attenuated FAP criteria met (See CSCR-11) →
- MYH-associated polyposis criteria met (See CSCR-19)
- Peutz-Jeghers syndrome or juvenile polyposis criteria met →
- No syndromes, but familial risk (or HNPCC/FAP/MYH/PJS/JP) criteria not met →

RISK/GENETIC COUNSELING[w]

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

→ See HNPCC pathway (CSCR-8)
→ See Classical FAP pathway (CSCR-11)
→ See Attenuated FAP pathway (CSCR-11)
→ See MYH pathway (CSCR-19)

Referral to specialized team recommended

→ See Positive Family History (CSCR-6)

[t] Detailed Family History:
- Expanded pedigree to include first-, second-, and third-degree relatives (parents, children, siblings, half-siblings, aunts, uncles, grandparents, great-grandparents, cousins, nieces, nephews)
- Types of cancer
- Age at onset or diagnosis
- Medical record documentation of cancer strongly encouraged
- Ethnicity

See Family History of Colorectal Cancer and Expanded Pedigree (CSCR-A)

[u] Detailed Medical and Surgical History:
- Polyps
- Inflammatory bowel disease
- Other recognized syndromes:
  - Gardner's syndrome
  - HNPCC/Lynch syndrome
  - Turcot's syndrome
  - Muir-Torre syndrome
  - Peutz-Jeghers syndrome
  - Juvenile polyposis
  - Cowden syndrome and PTEN related syndromes
  - Bannayan-Riley-Ruvalcaba syndrome
  - MYH-associated polyposis
- Pathology verification strongly encouraged

[v] Directed examination for related manifestations:
- Colonoscopy
- Esophagogastroduodenoscopy
- Eye examination
- Skin, soft-tissue, and bone examination

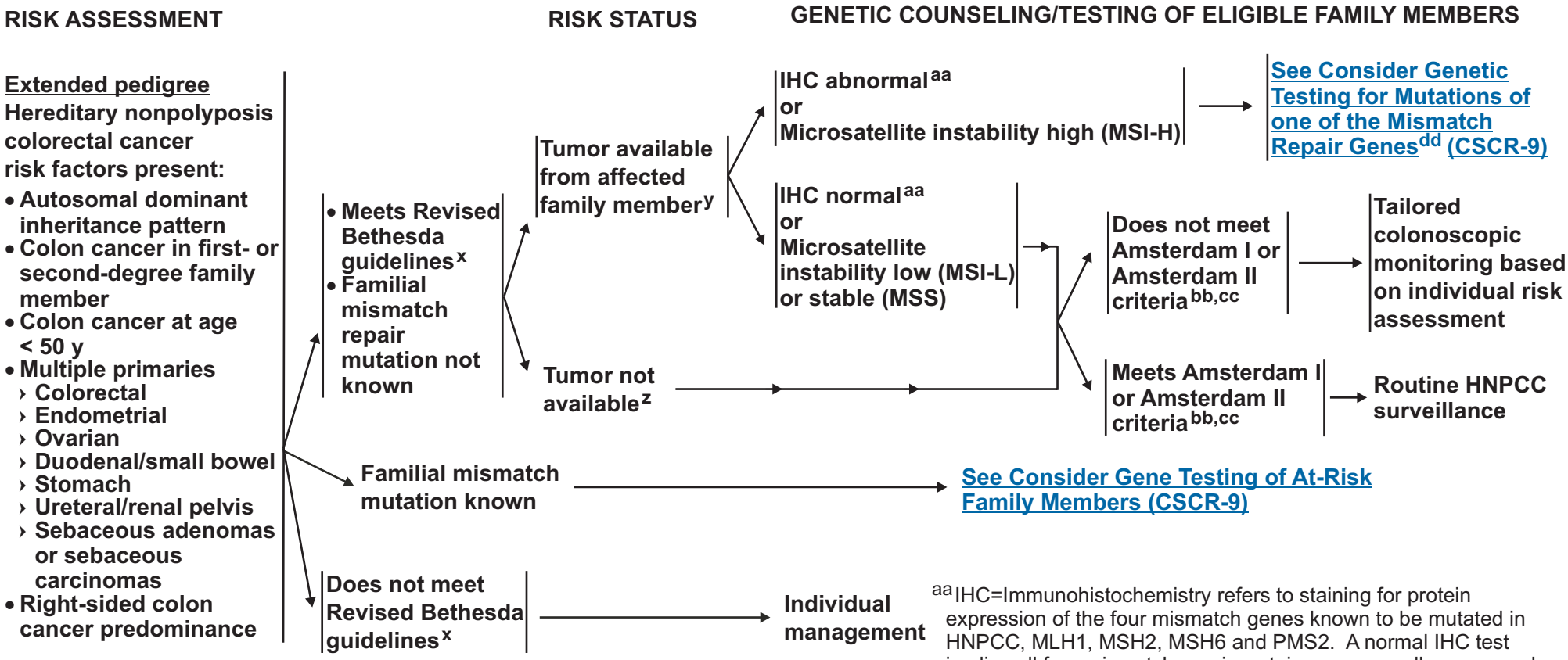
[w] A genetic counselor and/or medical geneticist should be involved early in counseling patients who (potentially) meet criteria for an inherited syndrome. Genetic counseling is advised when genetic testing is offered.

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.

Version 1.2006, 01/03/06 © 2006 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

Colorectal Cancer Screening

HEREDITARY PREDISPOSITION: SCREENING



[x] See Revised Bethesda Guidelines (CSCR-E).

[y] With informed consent as designated by local practice and IRB standards.

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

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

[bb] See Amsterdam I Criteria (CSCR-F).

[cc] See Amsterdam II Criteria (CSCR-G).

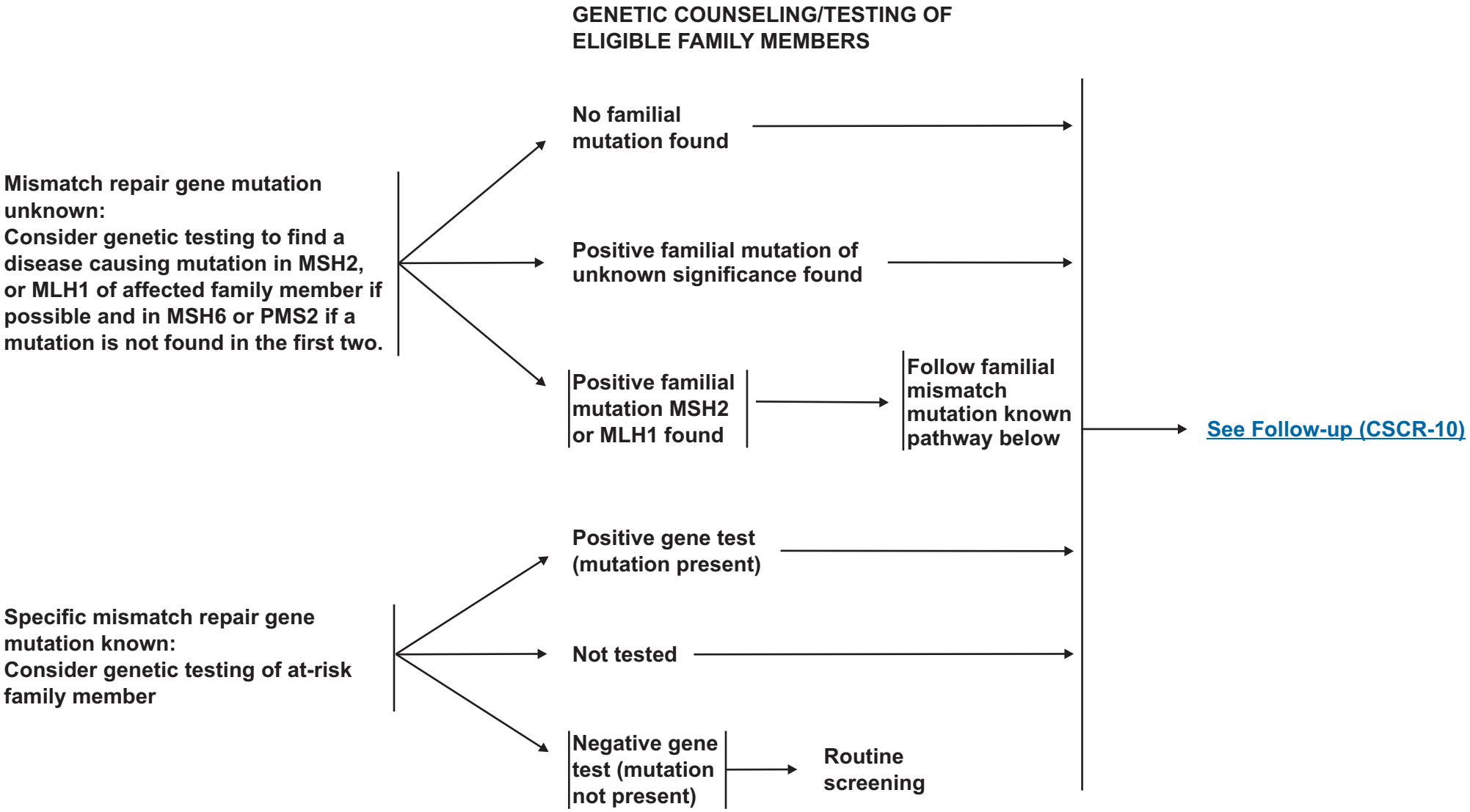
[dd] Loss of protein expression by immunohistochemistry (IHC) in any one of the mismatch repair genes guides genetic testing (mutation detection) to the gene where protein expression is not observed.

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.

Version 1.2006, 01/03/06 © 2006 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

Colorectal Cancer Screening

HEREDITARY PREDISPOSITION: SCREENING



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

Version 1.2006, 01/03/06 © 2006 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

Colorectal Cancer Screening

Guidelines Index
Colorectal Screening TOC
MS, References

HEREDITARY PREDISPOSITION: HNPCC FOLLOW-UP (SURVEILLANCE)

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

Consider periodic evaluation for associated intra-abdominal malignancies

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

For women:

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

No pathologic findings → **Continued screening[ee]**
- **Consider prophylactic TAH/BSO**

Adenocarcinomas → **See NCCN Colon Cancer Treatment Guidelines**

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

Adenomas not amenable to endoscopic resection or high-grade dysplasia →
- **Total abdominal colectomy with ileorectal anastomosis[ff]**
- **Consider TAH/BSO at time of colon surgery if postmenopausal or family completed**

→ **Endoscopic rectal exam every 1-2 y**

[ee] May consider subtotal colectomy if patient is not a candidate for optimal screening.
[ff] The type of surgical procedure chosen should be based on individual considerations and discussion of risk.

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.

Version 1.2006, 01/03/06 © 2006 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

Colorectal Cancer Screening

HEREDITARY PREDISPOSITION: ADENOMATOUS POLYPOSIS SYNDROMES

INCLUSION CRITERIA

Classical familial adenomatous polyposis (FAP):

- Presence of ≥ 100 polyps (sufficient for clinical diagnosis)
- Autosomal dominant inheritance[gg] (except with *de novo* mutation)
- Associated additional findings
  - Congenital hypertrophy of retinal pigment epithelium (CHRPE)
  - Osteomas, supernumerary teeth, odontomas
  - Desmoids, epidermoid cysts
  - Duodenal and other small bowel adenomas
  - Gastric fundic gland polyps
- Increased risk of medulloblastoma, papillary carcinoma of the thyroid (<2%), hepatoblastoma (usually ≤ age 5 y)
- Pancreatic cancers (<2%)
- Gastric cancers (<1%)

Attenuated FAP

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

MYH associated polyposis

- Autosomal recessive (parents' phenotype negative)
- Usually fewer than 100 adenomas
- Adenomas and colorectal cancer at age older than FAP (median CRC age > 50 y)
- Duodenal adenomas occur uncommonly

RISK ASSESSMENT

- Personal history → See Genetic Screening (CSCR-12)
- No symptoms, positive family history
  - Family mutation known → See Genetic Screening (CSCR-13)
  - Family mutation unknown → See Genetic Screening (CSCR-14)
- Personal history → See Genetic Screening (CSCR-15)
- No symptoms (no adenomas), positive family history
  - Family mutation known → See Genetic Screening (CSCR-17)
  - Family mutation unknown → See Genetic Screening (CSCR-18)
- MYH associated polyposis
  - Personal history (known mutation)
  - Polyposis consistent with recessive inheritance
  - Attenuated polyposis with negative APC mutation
  → See MYH Associated Polyposis (CSCR-19)

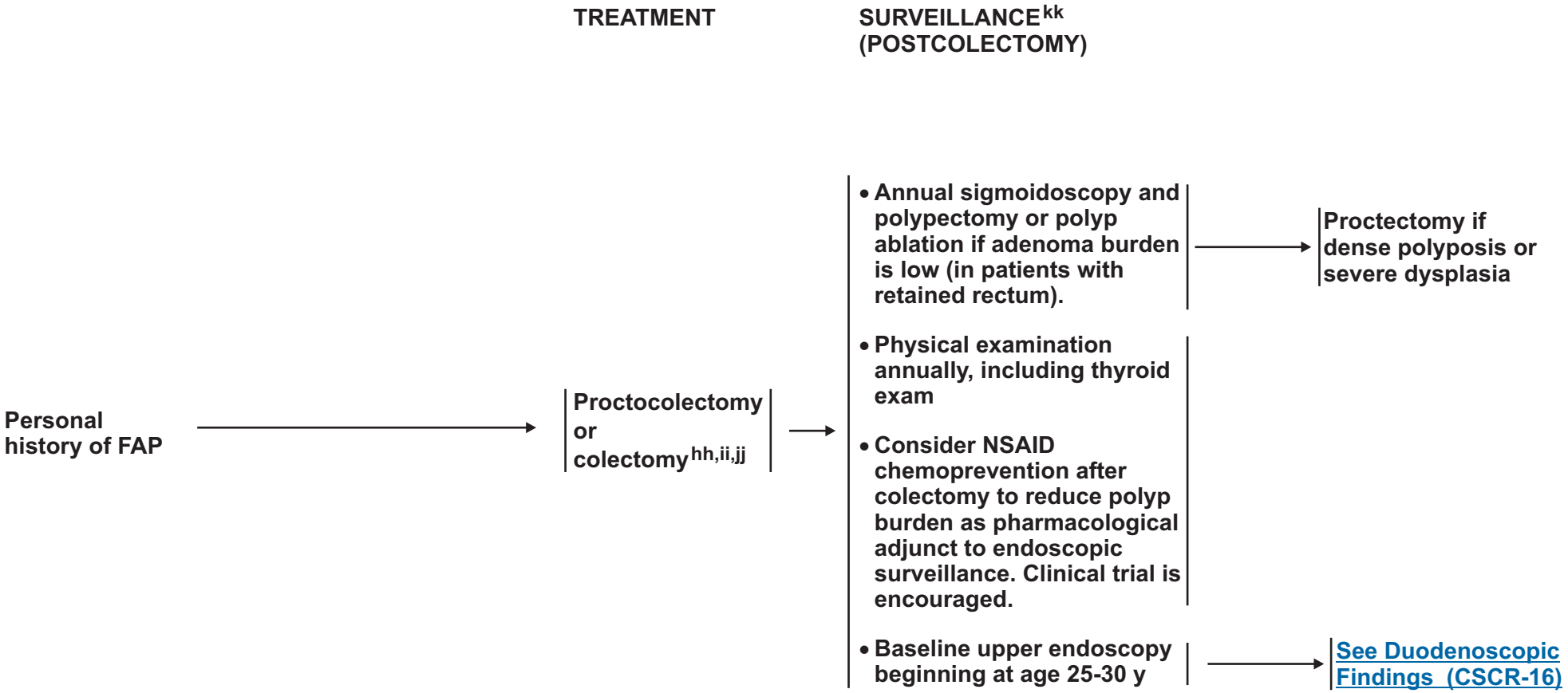
[gg] 30% spontaneous new mutation rate, thus familiy history may be negative. Especially noteworthy if onset < age 50 y.

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.

Version 1.2006, 01/03/06 © 2006 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

Colorectal Cancer Screening

HEREDITARY PREDISPOSITION: FAP MANAGEMENT AND SURVEILLANCE



[hh] APC testing may not change clinical management of affected individuals but is recommended for familial risk assessment.

[ii] See Primary Surgical Management of FAP (CSCR-D).

[jj] Timing of colectomy in patients under age 18 y is unresolved. In patients under 18 y with mild polyposis and without family history of early cancer or severe genotype, the timing of colectomy can be individualized. Colonoscopy if surgery is delayed.

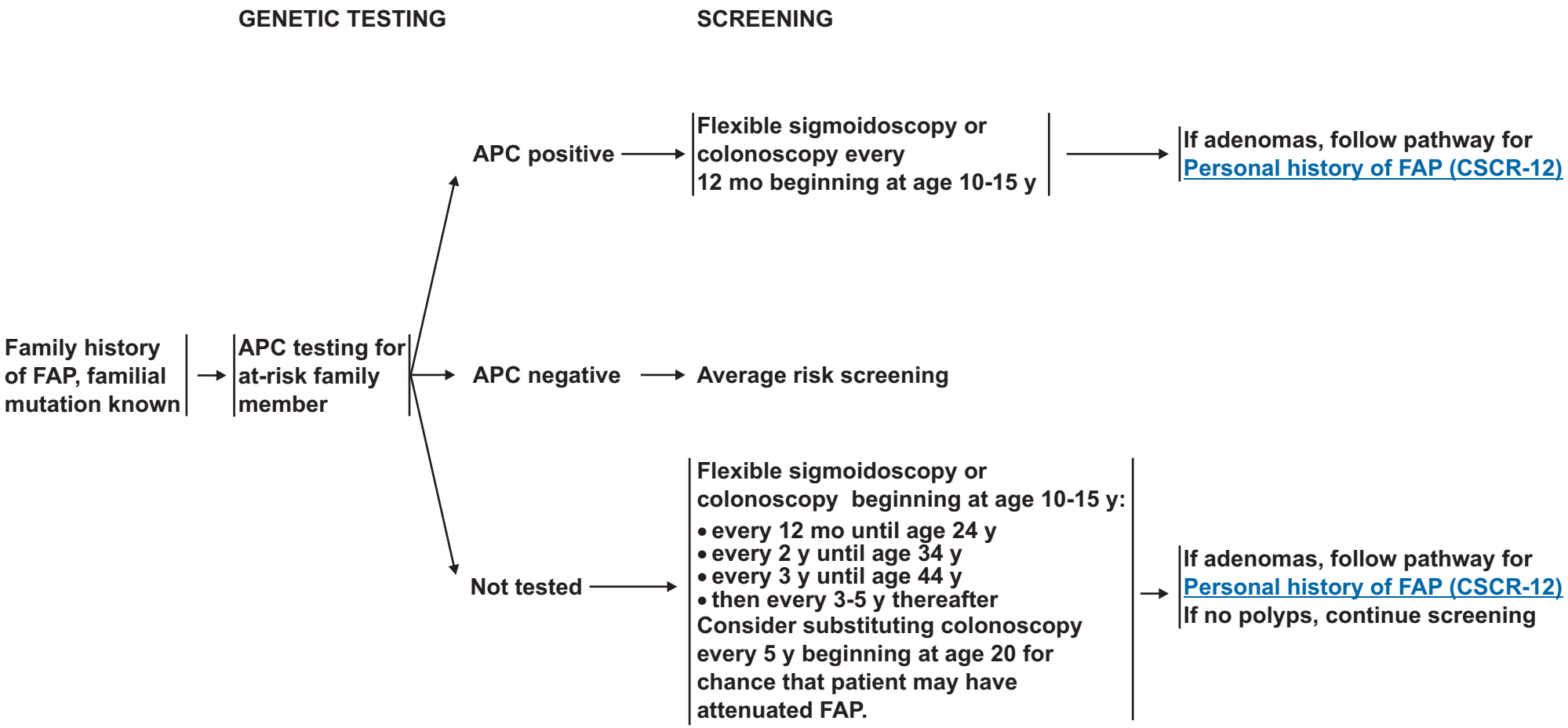
[kk] It is recommended that patients be managed by physicians or centers with expertise in FAP and that management would be individualized to account for genotype, phenotype and personal considerations.

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

Version 1.2006, 01/03/06 © 2006 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

Colorectal Cancer Screening

HEREDITARY PREDISPOSITION: FAP SCREENING

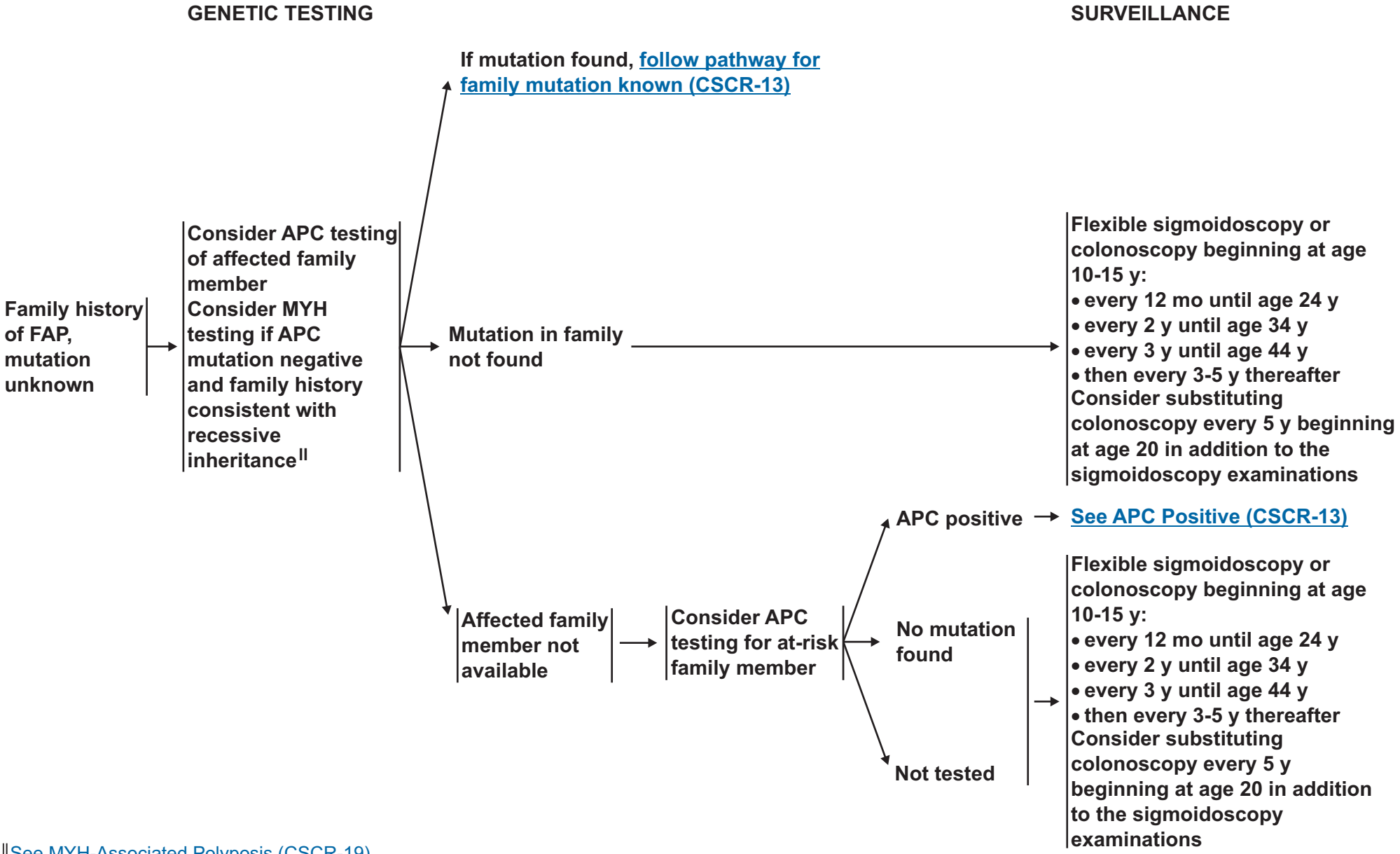


Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Version 1.2006, 01/03/06 © 2006 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

Colorectal Cancer Screening

HEREDITARY PREDISPOSITION GENETIC TESTING AND SURVEILLANCE: FAMILY HISTORY OF FAP



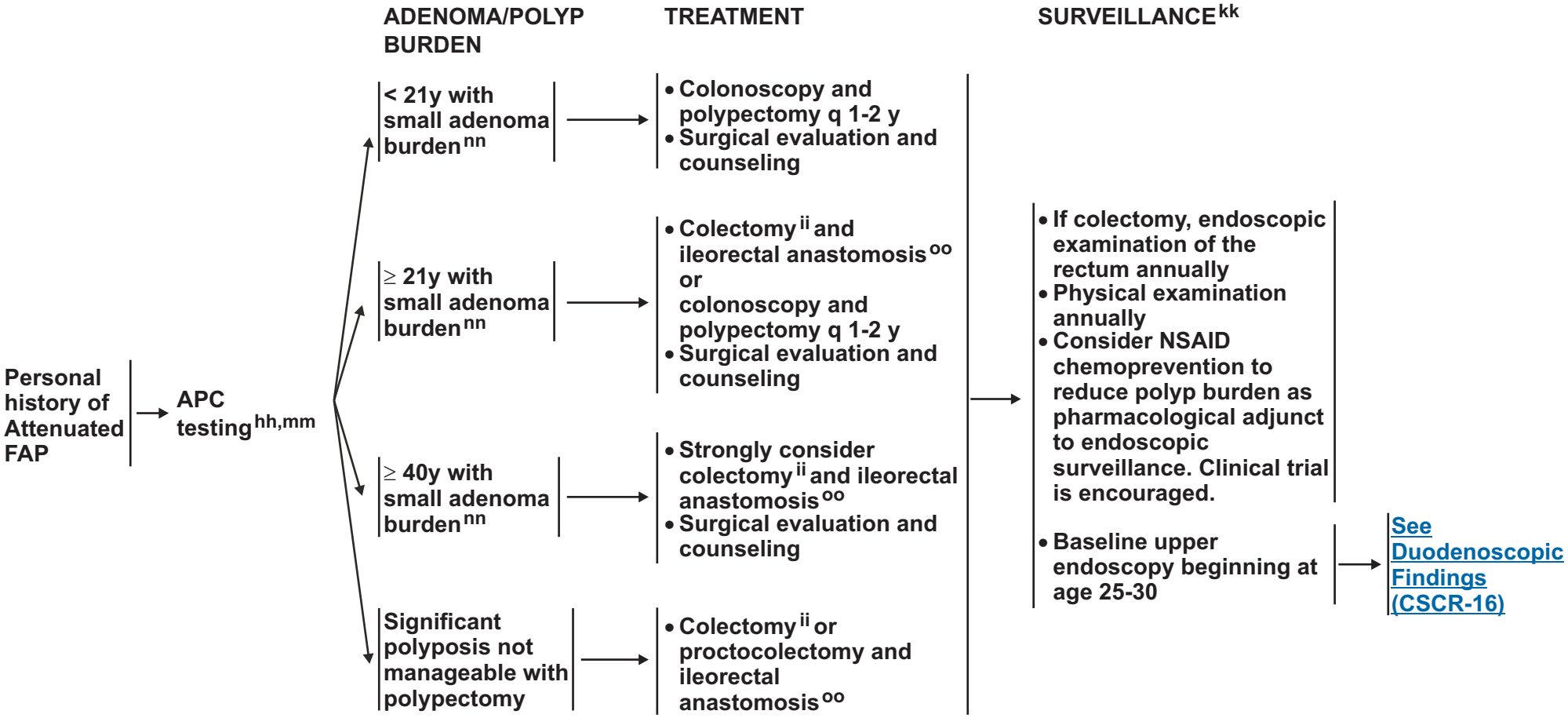
‖See MYH-Associated Polyposis (CSCR-19).

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

Version 1.2006, 01/03/06 © 2006 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

Colorectal Cancer Screening

HEREDITARY PREDISPOSITION MANAGEMENT AND SURVEILLANCE: ATTENUATED FAP



hh APC testing may not change clinical management of affected individuals but is recommended for familial risk assessment.

ii See Primary Surgical Management of FAP (CSCR-D).

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

mm Consider MYH testing if APC mutation not found, and family consistent with recessive inheritance (See CSCR-19).

nn Small adenoma burden is defined (somewhat arbitrarily) as fewer than 20 adenomas, all < 1 cm in diameter and none with advanced histology, so that colonoscopy with polypectomy can be used to effectively eliminate the polyps. Colectomy may be indicated before this level of polyp profusion, especially if colonoscopy is difficult. Surgery is strongly advised when polyp burden is greater than 20, some polyps have reached a size > 1 cm, or advanced histology is encountered in any polyp.

oo Earlier surgical intervention should be considered in patients with family history of cancer under age 40 or noncompliant 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.

Version 1.2006, 01/03/06 © 2006 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

Colorectal Cancer Screening

DUODENOSCOPIC FINDINGS[pp]	SURVEILLANCE[kk]
Stage 0, no polyposis	Repeat endoscopy q 4 y
Stage I, minimal polyposis, (1-4 tubular adenomas, size 1-4 mm)	Repeat endoscopy q 2-3 y[qq]
Stage II, mild polyposis, (5-19 tubular adenomas, size 5-9 mm)	Repeat endoscopy q 1-3 y[qq]
Stage III, moderate polyposis, (≥ 20 lesions, or size 1 cm)	Repeat endoscopy q 6-12 mo
Stage IV, Dense polyposis or severe dysplasia	Surgery[rr] is recommended for severe dysplasia. Current management of dense polyposis includes surgical evaluation and/or expert surveillance q 6-12 mo.

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

[pp] Recommend examination with side-viewing endoscope, use of Spigelman's or other standardized staging, extensive biopsy of dense lesions, endoscopic treatment of large or villous adenomas, more intensive surveillance and/or treatment of periampullary lesions and at age > 50. (Spigelman AD, Williams CB, Talbot IC et al. Upper gastrointestinal cancer in patients with familial adenomatous polyposis. Lancet 1989;2(8666): 783-785.

[qq] Endoscopy interval depends on individual phenotype as well as on the treatment plan. Management that includes prophylactic polypectomies or ablation may require shorter intervals.

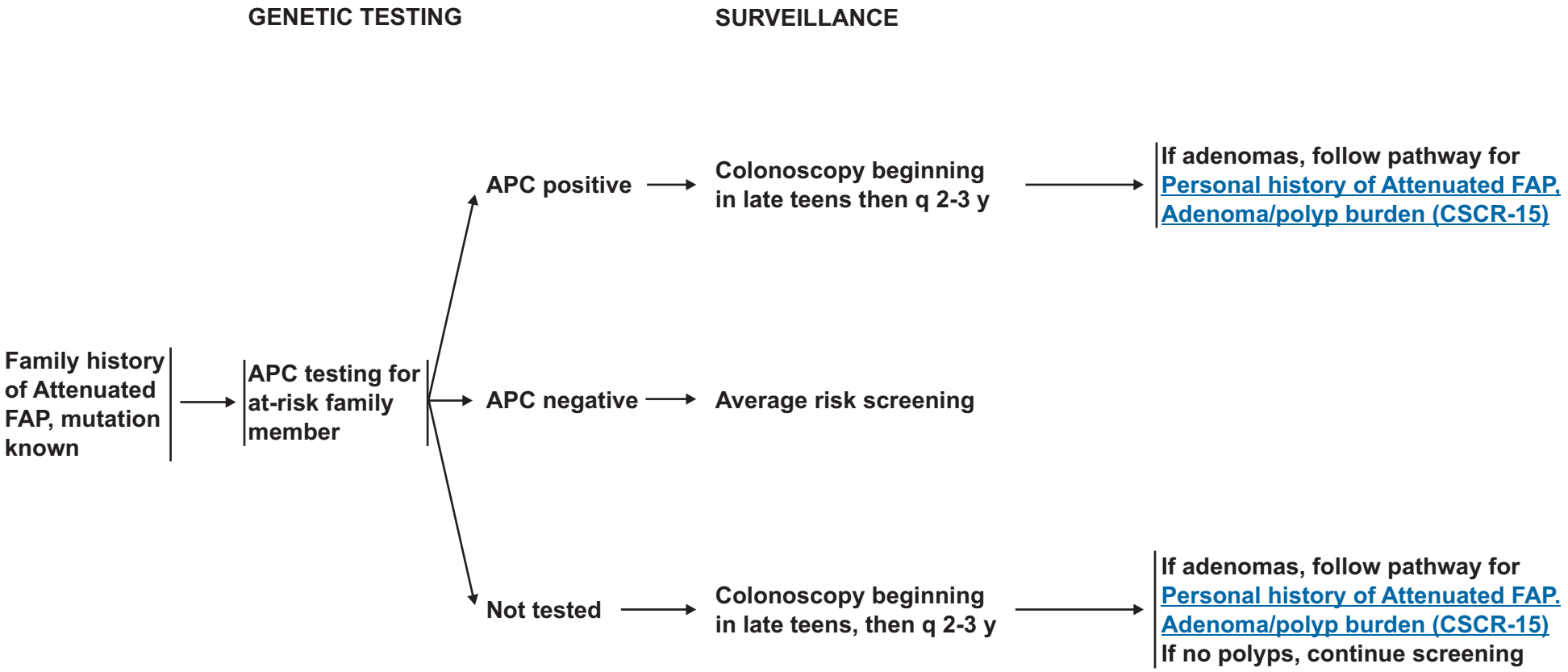
[rr] For severe polyposis not manageable by endoscopic polypectomy, or for severe dysplasia, pancreaticoduodenectomy is recommended.

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.

Version 1.2006, 01/03/06 © 2006 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

Colorectal Cancer Screening

HEREDITARY PREDISPOSITION TESTING AND SURVEILLANCE: FAMILY HISTORY OF AFAP

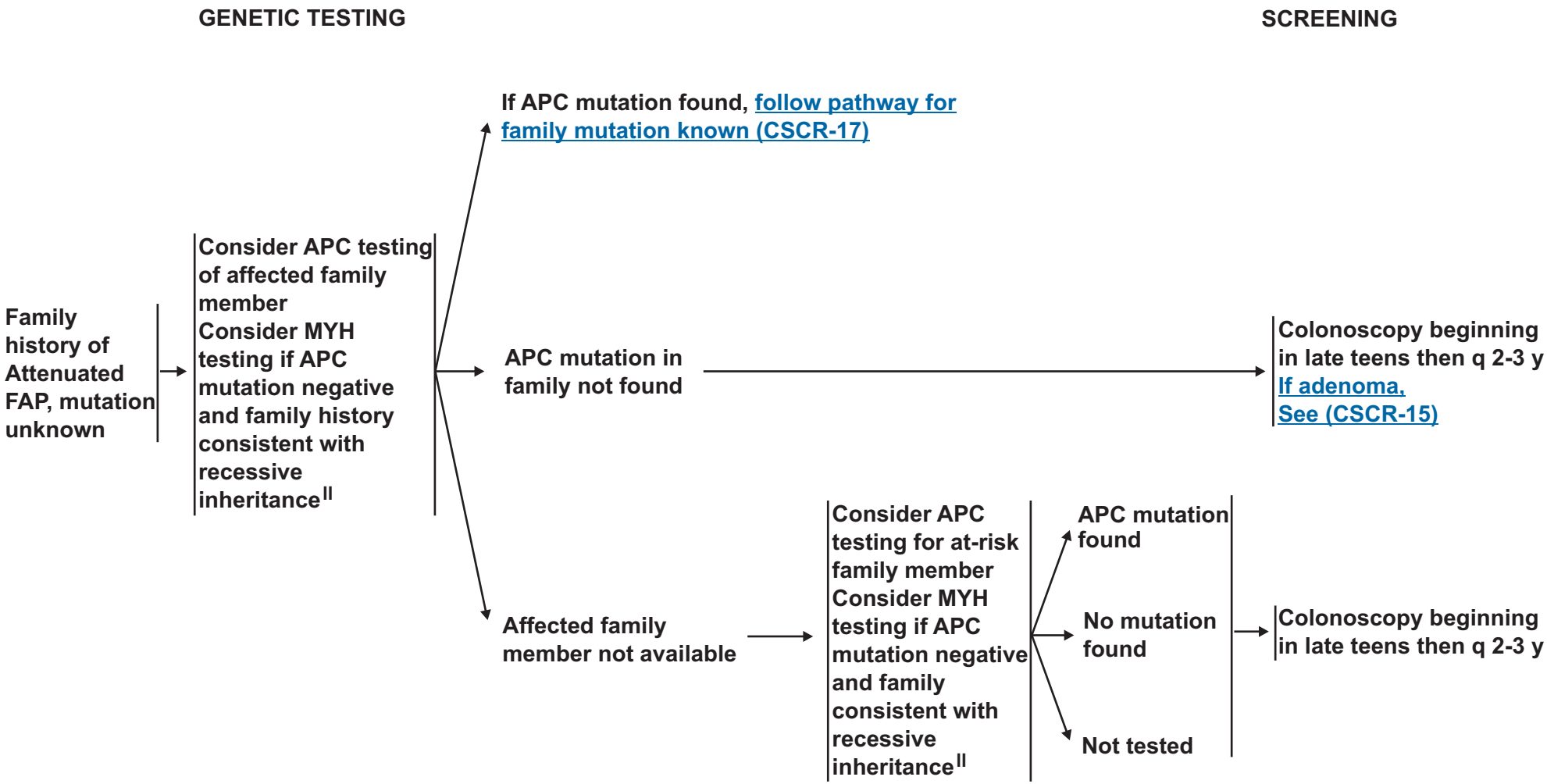


Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Version 1.2006, 01/03/06 © 2006 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

Colorectal Cancer Screening

HEREDITARY PRE-DISPOSITION: FAMILY HISTORY OF ATTENUATED FAP



[II] See MYH-Associated Polyposis (CSCR-19).

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

Version 1.2006, 01/03/06 © 2006 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

Colorectal Cancer Screening

MYH-ASSOCIATED POLYPOSIS[ss]

TREATMENT/SURVEILLANCE

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

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

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

Consider upper endoscopy and side viewing duodenoscopy at age 30-35 y and every 3-5 y
Patients with duodenal adenomas are treated as FAP (See Duodenoscopic Findings FAP CSCR-16)

Personal history of adenomatous polyposis (> 10 adenomas, or > 15 cumulative adenomas in 10 y) either consistent with recessive inheritance or with adenomatous polyposis with negative APC mutation testing[tt]

→ **Counseling and testing for MYH mutations**

→ **Biallelic MYH mutation negative**

→ **Manage individually as multiple adenomatous polyps (CSCR-7)**

→
- **Colonoscopy and polypectomy q 1-2 y[uu]**
- **Consider upper endoscopy and side viewing duodenoscopy beginning at age 30-35 y and every 3-5 y**
  Patients with duodenal adenomas are treated as FAP. (See Duodenoscopic Findings FAP CSCR-16)

→ **Biallelic MYH mutation positive**

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

→
- **Colonoscopy and polypectomy q 1-2 y[uu]**
- **Consider upper endoscopy and side viewing duodenoscopy beginning at age 30-35 y and every 3-5 y**
  Patients with duodenal adenomas are treated as FAP. (See Duodenoscopic Findings FAP CSCR-16)

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

→
- **Counseling regarding surgical options**
- **Subtotal colectomy or proctocolectomy depending on adenoma density and distribution[ss,uu]**
- **Upper endoscopy and side viewing duodenoscopy at age 30-35 y and every 3-5 y**
  Patients with duodenal adenomas are treated as FAP. (See Duodenoscopic Findings FAP CSCR-16)

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

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

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

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.

Version 1.2006, 01/03/06 © 2006 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

FAMILY HISTORY OF COLORECTAL CANCER AND EXPANDED PEDIGREE

- It is essential to obtain a detailed family history, including:
  - parents
  - children
  - siblings/half-siblings
  - aunts and uncles
  - grandparents
  - great-grandparents
  - cousins
  - nieces and nephews

- Minimal data set on each relative:
  - Current age and age at diagnosis of cancer (medical record documentation of cancer strongly encouraged)
  - Age/availability of tumor sample and cause of death
  - Type of cancer (note multiple primaries)
  - Ethnicity/country of origin
  - Suspected colon cancer syndromes and additional syndrome-specific features (eg, Muir-Torre, Turcot, Peutz-Jeghers, juvenile polyposis)[1]
  - All other inherited conditions and birth defects

Forward to common pedigree symbols (CSCR-B)

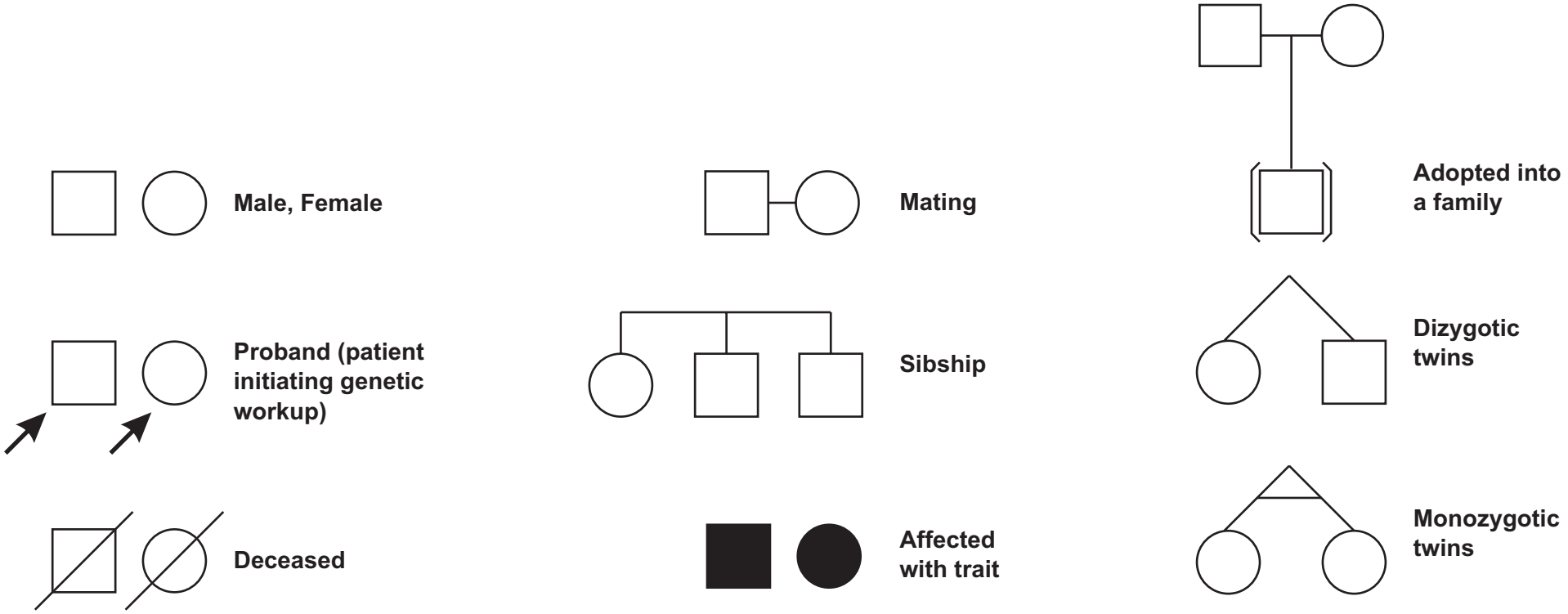
[1]Burt R and Neklason DW. Genetic testing for inherited colon cancer. Gastroenterology 2005;128:1696-1716.

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.

Version 1.2006, 01/03/06 © 2006 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

Colorectal Cancer Screening

COMMON PEDIGREE SYMBOLS[1]



[1] Bennet RL, Steinhuas KA, Urich SB, et al. Recommendations for standardized human pedigree nomenclature. American Journal of Human Genetics 1995a;56:745-752.

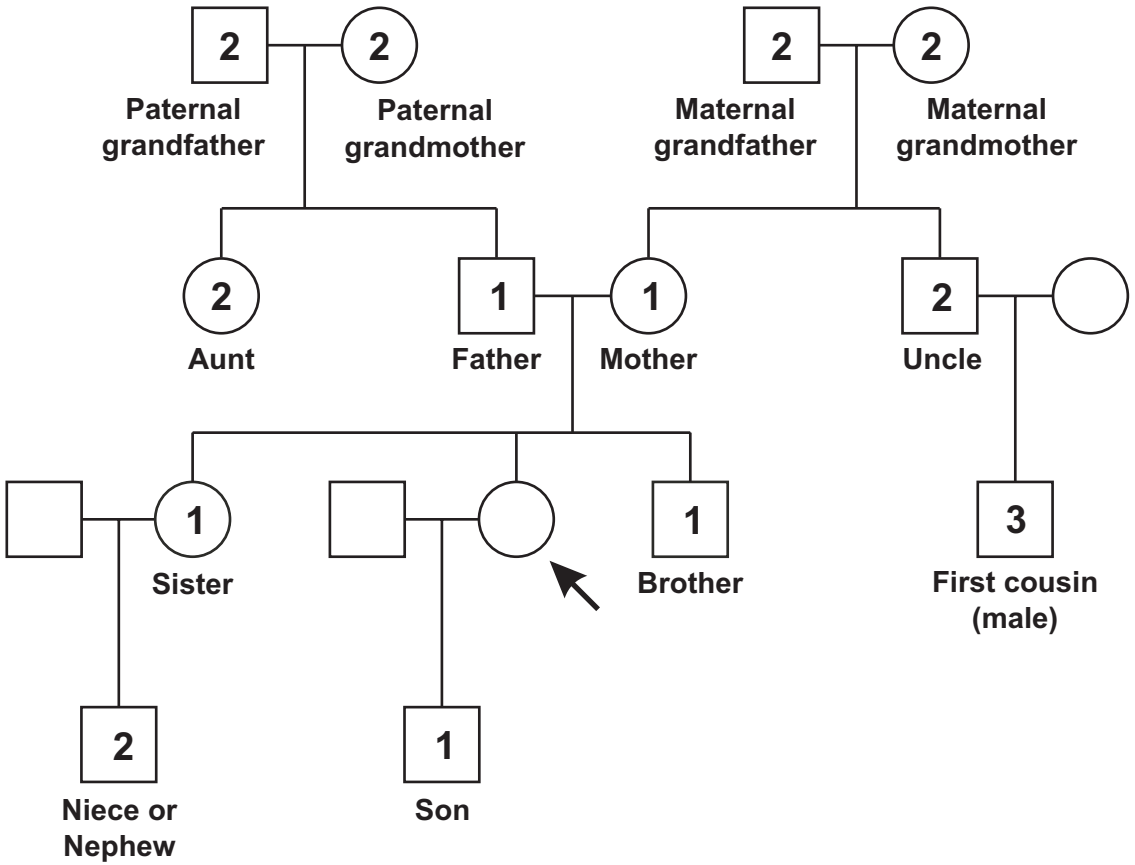
Forward to First, Second and Third-Degree Relatives (CSCR-C)

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.

Version 1.2006, 01/03/06 © 2006 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

Colorectal Cancer Screening

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



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

Version 1.2006, 01/03/06 © 2006 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

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

TOTAL ABDOMINAL COLECTOMY WITH ILEORECTAL ANASTOMOSIS (TAC/IRA)

Indications:
- Young, asymptomatic patient with few (<20) rectal polyps and mild colonic disease (<1000) polyps
- Attenuated FAP with rectal sparing

Contraindications:
- Curable cancer in colon or rectum
- Severe rectal or colon disease (size or number of polyps)
- Patient not reliable for follow-up surveillance of retained rectum

Advantages:
- Technically straightforward
- Relatively low complication rate
- Good function outcome
- No permanent or temporary stoma
- Avoids risk of proctectomy (sexual or bladder dysfunction).

TOTAL PROCTOCOLECTOMY WITH END ILEOSTOMY (TPC/EI)

Indications:
- Very low, advanced rectal cancer
- Inability to perform IPAA
- Patient with IPAA with unacceptable function
- Patient with contraindication to IPAA

Advantages:
- Removes risk of colorectal cancer
- One operation

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

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

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

Contraindications:
- Incurable cancer
- Intra-abdominal desmoid
- Advanced low rectal cancer
- Patient not a candidate for IPAA (ie, concomitant Crohn's disease, anal sphincter dysfunction, etc)

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

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

TOTAL PROCTOCOLECTOMY WITH CONTINENT ILEOSTOMY (TPC/CI)

Indications:
- Patient with poorly functioning IPAA or end ileostomy who is motivated to avoid an end ileostomy
- Patient who is not an IPAA candidate who is motivated to avoid an end ileostomy

Advantages:
- No need to wear an external appliance

Disadvantages:
- Complex operation with a not insignificant risk for re-operation.

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.

Version 1.2006, 01/03/06 © 2006 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

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

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

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

- **Colorectal cancer diagnosed in a patient who is less than 50 years of age.**
- **Presence of synchronous, or metachronous HNPCC-associated tumors,[2] regardless of age.**
- **Colorectal cancer with the MSI-H[3] histology[4] diagnosed in a patient who is less than 60 years of age.[5]**
- **Colorectal cancer diagnosed in a patient with one or more first-degree relatives with an HNPCC-related cancer, with one of the cancers being diagnosed under age 50 years.**
- **Colorectal cancer diagnosed in a patient with two or more first- or second-degree relatives with HNPCC-related cancers, regardless of age.**

[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(4)261-268 and Ahnen DJ and Axell L. Clinical features and diagnosis of HNPCC. www.uptodate.com. Accessed 10/05.

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

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

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

[5] There was no consensus among the Workshop participants on whether to include the age criteria in guideline 3 above; participants voted to keep less than 60 years of age in the guidelines.

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.

Version 1.2006, 01/03/06 © 2006 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

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

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

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

[1] From Vasen HFA. Clinical diagnosis and management of hereditary colorectal cancer syndromes. J Clin Onc 2000;18(21):81-92.

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.

Version 1.2006, 01/03/06 © 2006 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

REVISED MINIMUM CRITERIA FOR CLINICAL DEFINITION OF HNPCC (AMSTERDAM CRITERIA II)[1]

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

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

[1] From Vasen HFA. Clinical diagnosis and management of hereditary colorectal cancer syndromes. J Clin Onc 2000;18(21):81-92.

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.

Version 1.2006, 01/03/06 © 2006 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

Summary of the Guidelines updates

Highlights of major changes in the 2006 version of the Colorectal Cancer Screening guidelines from the 1.2005 version include:

- **The panel added the following new pages:**
  - **Risk Assessment for "Average risk", "Increased risk", and "Hereditary high risk" (CSCR-1)**
  - **Personal history of colorectal and endometrial/ovarian cancer surveillance (CSCR-4)**
  - **Positive family history screening (CSCR-6)**
  - **MYH-Associated Polyposis"(CSCR-19)**
- **MYH-associated polyposis, Peutz-Jeghers syndrome, juvenile polyposis, and familial risk were added under "Hereditary Syndrome" (CSCR-7).**
- **New footnotes regarding "immunohistochemistry (IHC)" were added to page (CSCR-8).**
- **Under HNPCC Follow-up: Surveillance, new screening recommendations for women were added (CSCR-10).**
- **Under "Adenomatous polyposis syndromes" a new MYH-associated polyposis pathway was added (CSCR-11).**

Version 1.2006, 01/03/06 © 2006 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

Manuscript

NCCN Categories of Consensus

Category 1: There is uniform NCCN consensus, based on high-level evidence, that the recommendation is appropriate.

Category 2A: There is uniform NCCN consensus, based on lower-level evidence including clinical experience, that the recommendation is appropriate.

Category 2B: There is non-uniform NCCN consensus (but no major disagreement), based on lower-level evidence including clinical experience, that the recommendation is appropriate.

Category 3: There is major NCCN disagreement that the recommendation is appropriate.

All recommendations are category 2A unless otherwise noted.

Overview

Colorectal cancer is the third most frequently diagnosed cancer in men and women in the United States. In 2005, an estimated 104,950 new cases of colon cancer and 40,340 new cases of rectal cancer will occur in the United States. During the same year, it is estimated that 56,290 people will die from colon and rectal cancer.[1] Fecal occult blood screening has been demonstrated to be an effective screening tool to reduce mortality associated with colorectal cancer by 33%.[2] Other options for screening are colonoscopy, combined fecal occult blood test (FOBT) and sigmoidoscopy, sigmoidoscopy alone or double-contrast barium enema.[3] Patients with localized colon cancer have 90% five-year survival rate.[3-6] Thus, screening is a critical and particularly effective procedure for colorectal cancer prevention because of colonoscopic polypectomy.

Risk Assessment (CSCR-1)

The Colorectal Screening panel members suggest to initially stratifying patients for risk of getting colorectal cancer into two groups: 1) average risk group and 2) increased risk. Patients with a positive family history and the hereditary high risk group are considered for different screening options. The individuals at average risk of getting colorectal cancer are those older than 50 years of age with no history of adenoma and inflammatory bowel disease and negative family history. Individuals with personal history of any of the following: adenomas, colorectal cancer, endometrial/ovarian cancer before 60 years of age, or inflammatory bowel disease are considered at increased risk for getting colorectal cancer.

Individuals at Average Risk

Colorectal cancer risk assessment in persons without known family history is advisable by age 40 years to determine the appropriate age for initiating screening. Individuals with a negative family history for colorectal neoplasia and associated hereditary syndromes, and a negative personal history of colorectal neoplasia, HNPCC associated cancers, and inflammatory bowel disease, represent the group at average risk for development of colorectal cancer.[3] It is recommended that average risk screening begin at age 50 after discussion of the available options.

Colorectal Cancer Screening for Persons at Average Risk

Currently recommended options include annual fecal occult blood test (FOBT) (category 1) and flexible sigmoidoscopy every 5 years

Version 1.2006, 01/03/06 © 2006 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

using a 60 cm or longer scope, or colonoscopy every 10 years. The NCCN panelists prefer colonoscopy as a screening modality for individuals at average risk). Double-contrast barium enema every 5 years is an alternative option.

The data underpinning these recommendations include three randomized, controlled trials of FOBT conducted in the United States and Europe [2,4,7] and two case-control studies of flexible sigmoidoscopy.[8,9] Flexible sigmoidoscopy followed by colonoscopic polypectomy has been used as the screening method and demonstrated a 45%-79% of mortality reduction in case-control studies. Randomized, controlled trials of flexible sigmoidoscopy are still in progress in the United States and in the United Kingdom.[10,11] It is recommended that polyps identified at sigmoidoscopy be biopsied by trained personnel to determine if polyps are hyperplastic or adenomatous. If hyperplastic polyps are found, routine screening should be continued.

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

Fecal Occult Blood Test

Two methods are currently available to determine the presence of fecal occult blood: 1) guaiac and 2) immunochemical. Fecal occult blood testing should be performed on 3 successive stool specimens obtained while the patient adheres to a prescribed diet. At present, guaiac-based, non-rehydrated technology is used (CSCR-2). Previously in the United States, Hemoccult test slides were rehydrated (ie, a drop of distilled water was added before adding the developer). However, this technique contributes significantly to a high incidence of false-positive results and is not recommended by the manufacturer.

Hemoccult II SENSA is the guaiac technique currently recommended. It appears to be as sensitive as the original Hemoccult test and is more “reader friendly.” In the future, however, physicians will probably switch to immunochemical techniques, which are currently being investigated on a larger scale than in the past. To ensure adequate follow-up, a health care professional should coordinate this testing, so that the patient who has a positive FOBT result enters the health care system in a responsible way.[12] Digital rectal examination (DRE) is not a proven method for colorectal screening and it has been shown that DRE is not associated with reduction in mortality from distal rectal cancer. Fecal occult blood testing of a specimen obtained at digital rectal examination is not recommended.[13]

Alternative Screening Options

If the colonoscopy is incomplete or the preparation is inadequate, the addition of a double-contrast barium enema would be an alternative screening option. Although a double-contrast barium enema is relatively sensitive and specific for detecting large neoplasms, its availability is limited. Experience with this procedure is decreasing, because radiologists in training receive minimum exposure to this technique. The new technique, such as CT colonography (virtual colonoscopy), appears to be a very promising tool for colorectal cancer screening.[5] Some studies have demonstrated that virtual colonoscopy is accurate in detecting large polyps in individuals at average risk of developing colorectal cancer.[14] However, studies

Version 1.2006, 01/03/06 © 2006 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

using older technology are relatively disappointing.[15,16] The technique continues to evolve. Molecular techniques for the detection of DNA or protein abnormalities in the stool or blood are also under development, and one test has received FDA approval for use.

Individuals at Increased Risk

Family History of Colorectal Cancer

Persons who have a first degree family member or two related second degree family members with colorectal cancer are at increased risk for colorectal cancer. The risk is inversely related to the age of cancer onset. The guideline for this group is to begin screening colonoscopy at age 40 or 10 years before the earliest date of colorectal cancer onset in the family (whichever date is earlier). Screening is continued at 5 year intervals if colonoscopy is negative for neoplasia. In families with late onset cancer (after age 65 y) it may be reasonable to begin screening by age 50.

Persons with a family history of early onset colorectal cancer or of clustering of HNPCC-related tumors, especially those meeting Bethesda guidelines), may be at relatively high risk and require individualized assessment that includes drawing of an extended pedigree (see below).

Persons who have one second degree, or one or more third degree family members with colorectal cancer are screened as average risk individuals. However, it is recommended that risk assessment be individualized and include a careful family history to determine whether a familial clustering of cancers is present in the extended family.

Personal History of Neoplasia

Individuals with adenomas are at increased risk for recurrent adenomas and colorectal cancer and are recommended surveillance colonoscopy and complete polypectomy. For patients with a completely resected adenomatous polyp, the surveillance schedule depends on the risk of recurrence, which is related to adenoma number, size and histology. Number greater than 3, size equal or greater than 10 mm, villous histology (> 25% villous), and presence of high grade dysplasia or carcinoma in situ, have been associated with increased risk. Because studies have used 1 cm as the standard measure, data is lacking on the relative significance of intermediate size adenomas (size 5-10 mm).

Low risk adenomas are tubular, 3 or fewer, and less than 1 cm. In this group, colonoscopy should be performed within 3 to 6 years. Emerging data suggest that the longer intervals are usually appropriate If this examination is normal, colonoscopy should be performed every 5 years (CSCR-3).

Individuals with high risk adenomas are recommended repeat colonoscopy within 3 years. Subsequent surveillance colonoscopies are recommended within 3-5 years, depending on colonoscopic findings. The longer intervals are recommended for persons with normal follow-up colonoscopies. It is appropriate to reassess risk, including contributing medical and personal factors, at each interval, prior to and following procedures.

Individuals with more than 10 adenomas or more than 15 cumulative adenomas in 10 years are recommended to undergo evaluation for a polyposis syndrome (see below, CSCR-19), though only a small fraction of those with no family history and low adenoma burden will have a defined hereditary syndrome (CSCR-3 and CSCR-5).

Individuals with serrated adenomas are at similar risk to those with tubular adenomas and are surveilled following the same guidelines.

Version 1.2006, 01/03/06 © 2006 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

Polypectomy of large sessile polyps is associated with a high rate of recurrence, attributed to the presence of residual adenoma tissue at the time of polypectomy. Hence, follow up colonoscopy, within 3-6 months is appropriate in this setting, or when polypectomy is incomplete due to other factors.[17]

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

Individuals with a personal history of colorectal cancer who had undergone colonic resection with intent to cure are at increased risk for recurrent adenomas and cancer. A study of 3278 patients with resected stage II and III colorectal cancer, found that recurrence rate is especially high in the immediate 4 years following surgery, suggesting that intense screening be considered during that period. However, the study did not exclude patients with HNPCC who are at greater than 30% risk for synchronous and metachronous cancers.[18] The guidelines recommend a complete colonoscopy preoperatively as well as at 1 year following surgery (within 3-6 months if preoperative colonoscopy was incomplete). If this examination is normal, colonoscopy should be performed in 2-3 years. Shorter intervals are considered if adenomas are found. Subsequent colonoscopic intervals are individualized and generally should not exceed 5 years (CSCR-4).

Women with a personal history of endometrial or ovarian cancer prior to age 60 y are considered to be at mildly increased risk for colorectal cancer, though this data is derived from populations that include persons with HNPCC who may account for some of the observed risk.[19] Screening colonoscopy is recommended in this group at 5 year intervals beginning at age 40 y.

Hyperplastic polyps

A large body of literature indicates that hyperplastic polyps are not associated with significantly increased risk of colorectal cancer, and supports the recommendation that persons with hyperplastic polyps be screened as average risk. Recent literature, however, suggests that a small and poorly defined subset of persons with numerous large, right sided hyperplastic polyps may be at increased risk for colorectal cancer. This observation is based on two main lines of evidence. First, a few small series of patients with hyperplastic polyposis have been reported in whom high risk for cancer was observed. The majority, however, had concomitant adenomas or serrated adenomas.[20] Secondly, there is accumulating literature suggesting that some cancers with extensive DNA methylation and microsatellite instability might derive from hyperplastic polyps.[21] Based on these observations, it is recommended that colonoscopic polypectomy and surveillance be considered in patients with multiple right sided hyperplastic polyps that include size over 10 mm. There is insufficient data regarding appropriate colonoscopic intervals.

Inflammatory Bowel Disease (CSCR-5)

It is well recognized that individuals with symptoms of pancolitis for 8 or more years are at an increased risk for colorectal cancer. Colonoscopic surveillance biopsies are recommended for these individuals. An endoscopist, who is familiar with the appearance of chronic inflammatory bowel disease (ulcerative colitis, Crohn's disease), should perform screening. When the disease is clinically quiescent, multiple four-quadrant biopsies (every 10 cm with 30 or more samples) should be taken for histologic examination using large cup forceps (CSCR-5). Strictures that are suggestive (particularly in ulcerative colitis) should be evaluated thoroughly

Version 1.2006, 01/03/06 © 2006 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

using biopsy and brush cytology. Any masses, including so-called dysplasia-associated lesions, are, of course, of extreme concern. Endoscopic polypectomy should be performed when appropriate with biopsies of surrounding mucosa for the assessment of dysplasia.

Interpretation of dysplasia/intraepithelial neoplasia can be difficult. A pathologist, experienced in interpreting inflammatory bowel disease lesions, should evaluate biopsies. In most findings of high-grade dysplasia or multifocal low-grade dysplasia place the ulcerative colitis patient at high-risk for developing carcinoma and prophylactic surgery, such as a protocolectomy with ileonal anastomosis (preferred).

Inherited Colon Cancer

Genetic susceptibility to colorectal cancer includes defined inherited syndromes, such as familial adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal cancer (HNPCC), as well as nonsyndromic familial colorectal cancer. Familial adenomatous polyposis is an autosomal dominant condition characterized by hundreds to thousands of polyps that carpet the colon. Although FAP accounts for approximately 1% of all colorectal cancers, its importance has been recognized as a paradigm for treating individuals at increased risk of cancer.[22] The lifetime risk of cancer in individuals with classic FAP approaches 100% by the age of 50. Management includes early screening and colectomy or proctocolectomy after the onset of polyposis. Because FAP is related to mutations of the gene for adenomatous polyposis coli (APC), located on 5q21 chromosome, genetic testing can be used to help manage cancer risk in patients and their family members.[23]

The second major form of a genetically determined colon cancer predisposition is hereditary nonpolyposis colon cancer (HNPCC), sometimes called Lynch syndrome, is characterized by the familial aggregation of a spectrum of cancer arising at an early age. The syndrome is the result of deficiencies in mismatch repair genes (hMSH2, hMLH1, PMS1, PMS2, and hMSH6). The lifetime risk of colorectal cancer approaches 80% in individuals carrying a mutation in an HNPCC gene. Hereditary nonpolyposis colorectal cancer is relatively common, accounting for 2% to 3% of all colorectal cancer cases.[22] Surveillance has been shown to reduce the risk of colorectal cancer [24] and may be of benefit in the early diagnosis of endometrial cancer. Site-specific evaluation and heightened attention to symptoms is also advised for other cancers that occur with increased frequency in HNPCC, such as ovarian, gastric, and ureteral cancers, though efficacy of surveillance of these sites has not been demonstrated.

Evaluation for Inherited colorectal cancer

A detailed family history, including ethnicity, as well as a detailed medical and surgical history and physical examination, is paramount in screening for inherited colorectal cancer syndromes. The history should include questions about colon cancer syndromes or syndrome-specific features such as, juvenile polyposis, Muir-Torre, Turcot, Peutz-Jeghers, and Cowden.[25-27] A directed examination for extracolonic manifestations should include an eye examination, esophagogastroduodenoscopy, skin and soft tissue examination, and a thyroid examination. Certain physical features that may be helpful in the recognition of FAP include congenital hypertrophy of retinal pigment epithelium (CHRPE), osteomas, odontomas, supernumerary teeth, epidermoid cysts, desmoids, and duodenal and other small-bowel adenomas.

Version 1.2006, 01/03/06 © 2006 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

Family History

When taking a family history of cancer (CSCR-A), it is important to include first-degree relatives (parents, siblings, and offspring), second-degree relatives (aunts, uncles, grandparents, great-grandparents, and half-siblings), and additional relatives with cancer (nieces and nephews). Sometimes, a great deal of information can be obtained by looking at first cousins as well. Grandchildren are often not old enough to manifest any of the clinical phenotypes of cancer syndromes.

Individuals who have first degree relative with a colorectal cancer who are younger than 50 years of age, or two first degree relatives with colorectal cancer at any age, or either clustering of HNPCC-related tumors or polyposis in close relatives should proceed for hereditary evaluation and screening pathways (CSCR-7 and CSCR-8). Those, not meeting criteria for a defined syndrome or with a first degree family member who has a colorectal cancer, screening colonoscopy beginning at the age of 40 years old or 10 years prior to earliest cancer in family is recommended and be repeated every 5 years (CSCR-6).

Minimal data are needed on each of the relatives. For instance, current age and age at diagnosis of any cancer - as well as a date, age, cause of death, and availability of a tumor sample - are very important for discerning whether relatives were at risk of developing cancer, how long they were at risk, and what type of cancer they had. It is particularly important to note the occurrence of multiple primary tumors. Other inherited conditions and birth defects should be included in this family history. Ethnicity and country of origin are also important. The newly developed test for I1307K, a mutation found among Ashkenazi Jews that predisposes them to colorectal cancer, has been intentionally excluded from the guidelines because there is very little evidence to date indicating what kinds of screening guidelines should be offered to individuals with this mutation.

Other entities that are important to recognize include suspected colon cancer syndromes, such as Muir-Torre, Turcot, and Peutz-Jeghers syndromes, and juvenile polyposis.[28] These syndromes are also fairly critical to understanding what could be the potential genetic basis for cancer in the family.[26,27] 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.

Familial Adenomatous Polyposis (FAP)

Patients with a Personal History of FAP

The clinical diagnosis of classical FAP is based on the presence of over 100 adenomas in a newly diagnosed proband, or on the documentation of early onset adenomas in a patient with a family history of FAP.[29] Increasingly, family members are diagnosed at adolescence through genetic testing for their specific familial mutation or through sigmoidoscopic screening in the second decade of life. Because cancer incidence rises dramatically early in the third decade, prophylactic proctocolectomy is indicated in the second decade. Current practice is to perform surgery either at the onset of polyposis or by age 19, depending on the severity of the familial phenotype and genotype, the extent of polyposis at diagnosis, individual considerations and local practices and expertise (CSCR-12).

The prime factors when choosing an operation for FAP are: 1) the personal and familial phenotype, including the rectal polyp burden and 2) whether colon or rectal cancer is present at diagnosis. In patients with the classical FAP phenotype proctocolectomy, if

Version 1.2006, 01/03/06 © 2006 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

possible, is the procedure of choice, since it prevents both colon and rectal cancer.

Three surgeries are in use to treat the colon and rectum in FAP patients: 1) total proctocolectomy with end ileostomy, 2) total abdominal colectomy with ileorectal anastomosis, and 3) total proctocolectomy with ileal pouch anal anastomosis with or without temporary loop ileostomy. A total proctocolectomy with end ileostomy is rarely indicated as a prophylactic procedure because good options are available that do not involve a permanent stoma, which has implications for the patient and 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 the proctectomy 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).

A total abdominal colectomy with ileorectal anastomosis (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 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 to 12 months). A recent review of 659 patients in the Dutch-Scandinavian collaborative registries who underwent colectomy with ileoanal anastomosis found a high rate of advanced and fatal rectal cancers even though 88% of the patients underwent an undiagnostic proctoscopy within 18 months of presentation. It was estimated that 12.5% of patients undergoing this procedure would die of rectal cancer by age 65 even if compliant with endoscopic screening. The authors concluded that proctocolectomy is the preferred procedure for most patients with the classical FAP phenotype, though some controversy remains regarding this choice. They and others also observed that patients could not be reliably selected for colectomy based on genotype alone. On the other hand, ileo-rectal anastomosis is the surgery of choice for the majority of patients with attenuated FAP who either have rectal sparing or endoscopically manageable rectal polyposis. It is not recommended for patients with curable colon or rectal cancer or those with extensive rectal or colonic polyposis. It is not recommended for patients with curable colon or rectal cancer or those with extensive rectal or colonic polyposis. Patients and families must be absolutely reliable for follow-up endoscopic examinations. The risk to the rectal stump rises considerably after the age of 50,[30] and if the rectum becomes unstable, a proctectomy with either an ileal pouch anal anastomosis or end ileostomy is recommended. Prophylactic treatment of the rectal stump with COX-2 inhibitors or sulindac may be beneficial, though long-term efficacy in reducing rectal cancer incidence has not been studied.[31,32]

The third operative option is a total proctocolectomy with ileal pouch anal anastomosis (IPAA), usually with a temporary loop ileostomy. The advantages of this operation are that the risks of developing rectal cancer are negligible (but not 0, because of the imperfect nature of mucosectomy) and a permanent stoma is not needed. The

Version 1.2006, 01/03/06 © 2006 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

disadvantages are that it is a complex operation, a temporary stoma is usually needed, and it carries a small risk of bladder and sexual dysfunction after proctectomy. Bowel function, although usually reasonable, is also somewhat unpredictable. The ileal pouch requires surveillance, and the area of the ileal pouch anal anastomosis should still be examined due to the imperfect nature of mucosectomy. This procedure is offered to patients with classical FAP, patient with attenuated FAP with severe phenotypes resulting in carpeting of the rectum, patients with curable colon or rectal cancer complicating the polyposis, and patients who underwent ileorectal anastomosis and now have an unstable rectum in terms of polyp number, size, or histology. The operation is generally not offered to patients with incurable cancer, those with an intra-abdominal desmoid or low rectal cancer, or patients who have an anatomic, physiologic, or pathologic contraindication to an ileal pouch anal anastomosis.

The remaining controversy over the choice of total abdominal colectomy with ileorectal anastomosis versus total proctocolectomy with ileal pouch anal anastomosis centers on the issues of the relative quality of life.[33-40] A modest reduction in life expectancy is expected in patients with classical FAP with rectal preservation.[41-47] Proctoscopic examination of a retained rectum is indicated annually.

The major surveillance in patients after colectomy relates to the upper gastrointestinal tract. Duodenal adenomas occur in over 90% of patients and have a predilection for the ampulla and periampullary duodenum. The cumulative lifetime risk of duodenal cancer is 5-15%, with a mean age in the late 50's. The accuracy of this estimate is limited by the paucity of cohorts over age 50 years who have been followed post colectomy. Duodenal cancer risk is uncommon under age 40 years, and rare under age 30 years. Hence, surveillance with side viewing duodenoscopy is recommended starting at age 25 to 30, though efficacy of surveillance of these sites has not been demonstrated. The appropriate period for follow-up endoscopy relates to the burden of polyps, varying from every 4 years if no polyps are found to every 6 to 12 months for Spigelman's stage IV polyposis (CSCR-16). Surgical evaluation is indicated in the presence of high-grade dysplasia or dense polyposis that cannot be managed with surveillance endoscopy. The cumulative risk of developing severe duodenal polyposis (stage IV) has been estimated to be around 40% by age 60-70. The risk of duodenal cancer increases dramatically with stage IV disease

Fundic gland polyps (FGP) occur in the majority of FAP patients, classical and attenuated, and often are too numerous to count. In FAP, FGPs usually have biallelic inactivation of the *APC* gene, and often display foci of dysplasia or microadenomas of the foveolar epithelium. However, malignant progression in FGPs is uncommon and the lifetime risk of gastric cancer in patients with FAP in Western countries is reported to be in the range of 0.5-1%. Endoscopic biopsies of FGP are not routinely recommended. However, the recommendation is to observe carefully for polyps that stand out because they appear irregular in shape or texture or large suggesting adenomas. It is also recommended that polyps in the antrum or immediate pre-antrum should be removed if possible. These are less common and are often adenomas.[28]

Patients with FAP are at risk for thyroid cancer with a lifetime risk of fewer than 2%, and female predominance (95%). Peak incidence is in the third decade of life with a mean age of 30 years. Yearly thyroid physical examination is recommended and is considered adequate for timely diagnosis and treatment.

Version 1.2006, 01/03/06 © 2006 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

For patients with retained rectums, NSAID chemoprevention treatment has been shown to induce polyp regression in the short term, although the neoplastic process is not completely suppressed. This modality may be used to reduce the rectal polyp burden. Long-term follow-up is needed to more precisely determine the role of this type of therapy, and studies with agents of lesser toxicity are also ongoing.[31,48]

Patients with a Personal History of Attenuated FAP

Attenuated FAP is a recently recognized variant of FAP characterized by a later onset of disease and fewer adenomas, typically less than 100. These adenomas are more prone to occur in the right colon and may take the form of diminutive sessile adenomas. Phenotypic expression is often variable within families. The onset of colorectal cancer is typically delayed, but the incidence of cancer rises sharply after the age of 40 and is greater than 50%.[48] Treating patients with a personal history of attenuated FAP varies depending on the patient's age and adenoma burden. For patients aged 21 and younger with a small adenoma burden; colonoscopy and polypectomy are recommended every 1 to 2 years with appropriate surgical evaluation and counseling. Young adults with small adenomas may be treated with polypectomy or surgery. For patients over the age of 40 years and those who have significant polyposis that is not manageable with polypectomy, a colectomy and ileorectal anastomosis is recommended (CSCR-15). Attenuated FAP patients with severe phenotype are treated similarly to classical FAP.

Individuals with a Family History of FAP (CSCR-13)

It is important to note the distinction between patients with a personal history of FAP and individuals who are considered at high risk based on a family history of FAP. This distinction makes an important difference in clinical management.

For those who have a family history of familial polyposis, there are two possible situations: 1) the specific mutation that has caused familial polyposis in that family is known, or 2) the familial mutation is not known, but that family has a history of familial polyposis.

When the mutation responsible for FAP within a family is known, screening can be appropriately directed to those at highest risk, and APC testing can be considered for at-risk family members. This does not mean telling those individuals that they must have APC testing. Rather, it means providing them with genetic counseling so that they are able to make informed decisions about the implications involved in genetic testing, as well as the implications for their own management.

Genetic Counseling: When people are asked to consider APC testing for at-risk family members, three outcomes may result from this type of genetic counseling. The first outcome is that an individual at risk undergoes testing and is found to carry an APC mutation. If he or she does have an APC mutation, there is over 90% probability that the individual will develop familial polyposis.[22,49] Truncating mutation of the APC gene is detectable in about 80% of FAP patients using protein-truncating tests.[50,51] Gene testing individuals with familial polyposis should be considered before or at the age of screening. The information obtained can help guide whether these patients need to undergo flexible sigmoidoscopy or colonoscopy every 12 months, beginning between the ages of 10 and 15. The age for beginning screening should be based on the patient's symptoms, family phenotype and other individual considerations. Fatal colorectal cancer is rare before the age of 18 years.

Version 1.2006, 01/03/06 © 2006 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

The second outcome following genetic counseling is that an individual at risk undergoes testing and is found not to carry the APC mutation responsible for familial polyposis in the family. For such individuals, screening as an average risk patient is recommended. Some people who undergo genetic counseling decide, for one reason or another, not to undergo genetic testing, which influences how their screening is managed. These individuals are considered to be potentially at risk and are offered the same screening recommendation that is proposed for those who are known to carry the mutation; namely, flexible sigmoidoscopy or colonoscopy every 12 months, beginning at age 10-15 until the age of 24. Then screening is scaled down to every 2 years until age 34, every 3 years until age 44, and every 3 to 5 years thereafter (CSCR-13). One should also consider substituting colonoscopy every 5 years beginning at age 20 for a chance that a patient may have attenuated FAP.

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

Unknown APC Mutations: Not all families with FAP carry known APC mutations. In some families, a mutation cannot be found with available testing technology, recognizing that the sensitivity to identify APC mutations is currently only about 80%. In other families, affected individuals have died or are not immediately available for testing due to other circumstances. Evaluating presymptomatic individuals at risk in these families presents a difficult problem, since the mutation responsible for FAP within the family is not known. By far the best approach in this situation is to attempt to identify the mutation in an affected family member, even if the available person is not a first-degree relative. If a mutation is found, then the management of that family follows the algorithm for “family mutation known.” Without this information, genetic testing offers less precision in estimating a person's risk.

If the mutation responsible for FAP within a family is not found or is not available, it is important to remember the limitations of interpreting a gene test in a presymptomatic individual. Certainly, a positive test in a presymptomatic person is informative even when the familial mutation has not been previously identified. But interpreting a test in which “no mutation is found” in a presymptomatic person is not the same as a “negative test.” The NCCN Colorectal screening panel members also recommend consider MYH testing if APC mutation is negative and family is consistent with a recessive inheritance. Gene testing excludes FAP in a person at risk only when no mutation is found in that person and a mutation has been identified in an affected family member. Physicians have recognized this particular issue as a source of confusion and misinterpretation. Thus, it is critical that patients

Version 1.2006, 01/03/06 © 2006 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

receive appropriate genetic counseling to avoid false-negative interpretations of test results.[25]

Surveillance: The surveillance of at-risk individuals who do not undergo testing is identical to that of individuals for whom no mutation is found (and the family mutation is not known). Substituting with colonoscopy is recommended beginning at age 20 then every 5 years while following sigmoidoscopy recommendations (CSCR-14).

Individuals with Family History of Attenuated FAP (CSCR-17)

The same surveillance considerations discussed previously for patients with a classical FAP family history apply to patients with a family history of attenuated FAP, except for the endoscopy approach. 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. The recommended endoscopic schedule is colonoscopy beginning at age 13 to 15, with repeat examinations every 2-3 years. Thus, the late onset and right colon involvement is accommodated in contrast to classical FAP. These recommendations apply to patients who have known gene familial mutations, those not tested, and those in which a familial mutation is not known. Families with severe phenotype are managed similarly to patients with classical FAP (CSCR-12, CSCR-13).

Hereditary Nonpolyposis Colorectal Cancer (HNPCC)

Hereditary nonpolyposis colorectal syndrome is autosomal dominant and comprises between 2%-3% of all cases of colorectal cancer. Mutation in mismatch repair (MMR) genes is the high risk factor for development of colorectal, endometrial, and ovarian cancer.[52] Genetic testing for HNPCC is somewhat more complicated than testing for FAP because several different genes contribute to the development of HNPCC. A screening test that examines tumors for microsatellite instability (an imperfect, but helpful, molecular "fingerprint" of HNPCC) is often useful in guiding choices about whether further genetic testing is needed.

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

Clinical clues that can alert a physician to the presence of HNPCC in a patient include 1) colon cancer in a first- or second-degree family member; 2) colon cancer diagnosed under the age of 50 years; 3) multiple generations affected; 4) multiple primary cancers, including endometrial, ureteral/renal pelvis, small bowel, and stomach cancers; 5) the predominance of right-sided colon cancer; and 6) ovarian cancer (CSCR-8).

Breast cancer is not included in the guidelines as a risk factor and remains a fairly controversial aspect of what constitutes the clinical phenotype of HNPCC.[53]

Molecular Workup

It is clear that individuals with a potential history of HNPCC should receive a molecular diagnostic workup, but it is unclear which tests are preferable.[54] Several different levels of tests can be performed to help provide clues about whether HNPCC is present. One of those tests, the "replication error phenotype," (is also known as the microsatellite

Version 1.2006, 01/03/06 © 2006 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

instability test [MSI]), is very sensitive but less specific.[55,56] Microsatellite instability occurs in 85%-90% of HNPCC patients.[56] The classical Bethesda guidelines [57] provide several criteria for testing colorectal tumors for microsatellite instability (CSCR-E). The National Cancer Institute introduced revised Bethesda guidelines in 2002 to further clarify selection criteria for the MSI testing.[58] Only one Bethesda criterion is required to fulfill the requirements for MSI testing.[59]

A second molecular technique is genetic testing for three mismatch repair genes (MMR) - hMSH2, hMLH1, and MSH6 - that account for about 60% of all HNPCC cases. Testing for mutations of hMSH2 and hMLH1 is not perfectly sensitive, and this type of genetic sequencing remains expensive.[60,61] Some studies show that HNPCC associated with MSH6 gene mutations may actually reveal age of onset and recommend to include MSH6 testing in screening recommendations.[62] Identification of the MSH6 mutation provide valuable information for HNPCC prevention, treatment, clinical management, and prognosis.[63,64]

The MSI test is particularly helpful when the family history is not strongly suggestive of HNPCC. Families that meet the minimal criteria for consideration - such as diagnosis before the age of 50, but no other criteria - may not represent HNPCC. A microsatellite-stable tumor arising within a young-onset patient is very unlikely to represent HNPCC. Proceeding with genetic testing in this setting is unlikely to yield an informative result. If a patient's MSI is determined to be low or stable, additional monitoring with a colonoscopy regimen tailored to the patient's individual risk assessment is indicated. In contrast, almost all tumors arising within the context of HNPCC are microsatellite unstable. If a patient is determined to have high MSI, genetic testing for hMSH2, hMLH1, and MSH-6 in affected member is recommended.

Rationale for HNPCC Testing

With the current strategy for the molecular workup of suspected HNPCC, an analysis of the tumor block for MSI provides diagnostic information, as well as guidance regarding the likelihood of informative predictive testing. Genetic screening for MSI is cost-effective for patients with newly diagnosed colon cancer as well as for the siblings and children of mutation carriers.[55] If a tumor from an affected family member is MSI negative, the diagnosis of HNPCC should be reevaluated, and one should consider individualized management. In those who are MSI positive, or who meet the more stringent Amsterdam criteria, predictive testing by sequencing hMSH2 and hMLH1 may be warranted. The first version of the minimum criteria for clinical definition of HNPCC (Amsterdam criteria) was introduced in 1991 (CSCR-F), and the revised (Amsterdam II criteria) version was introduced in 1999 (CSCR-G).

A question may be raised concerning the value of performing MSI testing if it will only lead to a diagnostic test, such as direct genetic mutational analysis. Data are not yet available that establish which test is the most cost-effective screening mechanism in HNPCC. Mixed strategy (MSI testing for all colorectal cancer patients with the following MSH2 and MLH1 testing of MSI-H tumors) has been shown as the most cost-effective approach for HNPCC screening.[54] Because testing for MSI is much less expensive than DNA sequencing for specific gene mutations, a negative MSI test may save cost to the patient.

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 gene testing of at-risk family members when the family mutation is known. A directed examination for extracolonic

Version 1.2006, 01/03/06 © 2006 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

manifestations in HNPCC patients includes: colonoscopy, transvaginal ultrasound, endometrial sampling, and gynecologic examination.

Screening, Follow-up Surveillance, and Treatment Options

If HNPCC can be confirmed, colonoscopy is advised between the ages of 20 to 25 or 10 years younger than the youngest age at diagnosis in the family, whichever comes first, to be repeated every 1 to 2 years. This recommendation is based upon empiric data from a European trial of 251 patients that looked at the frequency and timing of colon cancer among individuals who carried known mutations for HNPCC or who did not carry mutations but were from HNPCC-like families.[24] For women, an annual transvaginal ultrasound or endometrial aspirate, beginning at ages 25 to 35 years, should be considered. However, there are no definitive data to support the use of transvaginal ultrasound or endometrial biopsy to reduce the risk of cancer. Most of these individuals present with spotting or dysfunctional uterine bleeding, so that endometrial cancer can often be diagnosed relatively early.[65]

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

When no familial mutation is found, follow-up includes colonoscopy at ages 20 to 25 or 10 years younger than the youngest age at diagnosis in the family, whichever comes first. Colonoscopy should be repeated every 1 to 2 years. Periodic evaluation (every 3-5 years) should be considered for associated intra-abdominal malignancies. Annual urinalysis with cytology and imaging of the renal collecting system are also should be considered. For female patients, follow up should also include annual endometrial sampling aspiration beginning at ages 25 30 to 35 or 5-10 years earlier than the earliest age of first diagnosis of these cancers in the family, and a transvaginal ultrasound (preferably on day 1-10 of cycle for premenopausal women) with or without CA-125 testing every 6-12 months should be considered.

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

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

If adenomas are not amenable to endoscopic resection or high-grade dysplasia is identified, total abdominal colectomy with an ileorectal anastomosis is recommended. The option of segmental or extended segmental colectomy is based on individual considerations and discussion of risks. Total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH/BSO) are not routinely recommended for HNPCC, although it is reasonable to discuss this option. If rectal cancer is involved, an appropriate

Version 1.2006, 01/03/06 © 2006 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

surgical resection is recommended, with consideration of TAH/BSO at the time of rectal surgery. The guidelines also include endoscopic polypectomy with a follow-up colonoscopy every 1 to 2 years as a treatment option for patients with adenomas. This option depends on the location and character of the tumor, the surgical risk, and the patient's preference (CSCR-10).

Nonsyndromic Hereditary Colon Cancer

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

Individuals with a MYH-associated polyposis (CSCR-19)

MYH-associated polyposis is a recently described autosomal recessive hereditary syndrome that predisposes to attenuated adenomatous polyposis and colorectal cancer.[66,67] It is caused by biallelic germline mutations in the *MYH* gene, reported in approximately 0.4% of colorectal cancer patients. MYH is an excision repair protein responsible for excising adenine nucleotides mismatched with 8-oxo-guanine, a product of oxidative damage to DNA. Dysfunctional MYH protein can thus result in G:C to T:A transversions during DNA replication. Adenomatous polyposis is thought to result from such transversions occurring within the *APC* gene.

Most patients with MYH-associated polyposis are reported to present with less than 100 colorectal adenomas or with colorectal cancer. The mean and median colorectal cancer ages are in the late 5th or early 6th decade, with approximately 15% of cases presenting in the 4th decade. Duodenal polyposis is reported less frequently than in FAP, and the magnitude of risk of duodenal cancer is not yet defined.

Guidelines for screening and surveillance are based on limited retrospective data. Genetic counseling and testing for germline *MYH* mutations is recommended for siblings of affected patients, as well as for patients with adenomatous polyposis (more than 10 adenomas or more than 15 cumulative adenomas in 10 y) whose family history is consistent with recessive inheritance. Testing for *APC* mutations usually precedes testing for *MYH* mutations, except in families in which only siblings are affected (suggesting recessive inheritance rather than *de novo* mutations).

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

Upper endoscopy for affected patients, as well as for persons at risk, is recommended starting at age 30-35 years and every 3-5 years. Patients with duodenal adenomas are managed similarly to patients with FAP (see above, CSCR-16).

Version 1.2006, 01/03/06 © 2006 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

Disclosures for the NCCN Colorectal Cancer Screening Guidelines Panel

At the beginning of each panel meeting to develop NCCN guidelines, panel members disclosed financial support they have received in the form of research support, advisory committee membership, or speakers' bureau participation. Members of the panel indicated that they have received support from the following: Breast Cancer Research Program, Bristol-Myers Squibb, Exact Sciences, Department of Defense, Enterix, Genentech, Komen Foundation, Merck, Myriad Genetics, NCI, NIH, Pfizer, U.S. Surgical and V Foundation.

Some panel members do not accept any support from industry. The panel did not regard any potential conflicts of interest as sufficient reason to disallow participation in panel deliberations by any member.

Version 1.2006, 01/03/06 © 2006 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

References

1. Jemal A, Murray T, Ward E et al. Cancer Statistics, 2005. CA Cancer J Clin. 2005;55(1):10-30.

2. 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.

3. Anderson FW, Guyton KZ, Hiatt RA et al. Colorectal Screening for persons at average risk. J Natl Cancer Inst 2002;94(15):1126-1133.

4. Hardcastle JD, Chamberlain JO, Robinson MH et al. Randomized controlled trial of faecal-occult-blood screening for colorectal cancer. Lancet 1996;348:1472-1477.

5. Levin B, Brooks D, Smith RA, Stone A. Emerging Technologies in Screening for Colorectal cancer: CT Colonography, Immunochemical Fecal Occult Blood Tests, and Stool Screening Using Molecular Markers. CA Cancer J Clin 2003;53:44-55.

6. Winawer SJ, Fletcher RH, Rex D et al. Colorectal cancer screening and surveillance: Clinical guidelines and rationale - Update Based on New Evidence. Gastroenterology 2003;124:544-560.

7. Kronborg O, Fenger C, Olsen J et al. Randomized study of screening for colorectal cancer with faecal-occult-blood test. Lancet 1996;348:1467-1471.

8. Newcomb PA, Norfleet RG, Storer BE et al. Screening sigmoidoscopy and colorectal cancer mortality. J Natl Cancer Inst 1992;84:1572-1575.

9. Selby JV, Friedman GD, Quesenberry CP Jr, Weiss NS. A case-control study of screening sigmoidoscopy and mortality from colorectal cancer. N Engl J Med 1992;326:653-657.

10. Atkin WS, Edwards R, Wardle J et al. Design of a multicentre randomized trial to evaluate flexible sigmoidoscopy in colorectal cancer screening. J Med Screen 2001;8:137-144.

11. O'Brien B, Nichaman L, Browne JE et al. Coordination and management of a large multicenter screening trial: The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. Control Clin Trials 2000;21[suppl 6]:310S-328S.

12. Smith RA, Cokkinides V, von Eschenbach AC et al. American Cancer Society guidelines for the early detection of cancer. CA Cancer J Clin 2002;52:8-22.

13. Sox HC. Office-based testing for fecal occult blood: do only in case of emergency. Ann Intern Med. 2005;142(2):146-8.

14. Pickhardt PJ, Choi R, Hwang I et al. Computed Tomographic Virtual Colonoscopy to screen for colorectal neoplasia in asymptomatic adults. New Engl J Med 2003;349(23):2191-200.

15. Van Gelder RE, Nio CY, Florie J et al. Computed tomographic colonography compared with colonoscopy in patients at increased risk for colorectal cancer. Gastroenterology 2004;127(1):41-8.

16. Cotton PB, Durkalski VL, Pineau BC et al. Computed tomographic colonography (Virtual Colonoscopy). A multicenter comparison with standard colonoscopy for detection of colorectal neoplasia. JAMA 2004;291:1713-1719.

17. Brooker JC, Saunders BP, Shah SG et al. Total colonic dye-spray increases the detection of diminutive adenomas during routine colonoscopy: a randomized controlled trial. Gastrointest Endosc 2002;56(3):333-8.

Version 1.2006, 01/03/06 © 2006 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

18. 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(4):261-9.

19. Weinberg DS, Newschaffer CJ, Topham A. Risk for colorectal cancer after gynecologic cancer. Ann Intern Med 1999;131(3):189-93.

20. 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(10):2012-8.

21. Leggett BA, Devereaux B, Biden K et al. Hyperplastic polyposis: association with colorectal cancer. Am J Surg Pathol 2001;25(2):177-84.

22. Petersen GM, Brensinger JD, Johnson KA, Giardiello FM. Genetic testing and counseling for hereditary forms of colorectal cancer. Cancer 1999;86:2540-50.

23. Lynch HT, Smyrk T, McGinn T et al. Attenuated familial adenomatous polyposis (AFAP): A phenotypically and genotypically distinctive variant of FAP. Cancer 1995;76:2427-2433.

24. Jarvinen HJ, Mecklin JP, Sistonen P. Screening reduces colorectal cancer rate in families with hereditary nonpolyposis colorectal cancer. Gastroenterology 1995;108:1405-1411.

25. 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.

26. Hamilton SR, Liu B, Parsons RE et al. The molecular basis of Turcot's syndrome. N Engl J Med 1995;332:839-847.

27. Giardiello FM, Offerhaus JG. Phenotype and cancer risk of various polyposis syndromes. Eur J Cancer 1995;31:1085-1087.

28. Burt R, Neklason DW. Genetic testing for inherited colon cancer. Gastroenterology 2005;128(6):1696-716.

29. Bussey HJR. Familial polyposis coli: Family studies, histopathology, differential diagnosis and results of treatment. Baltimore: Johns Hopkins University Press, 1975.

30. Nugent KP, Phillips RKS. 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.

31. Steinbach G, Lynch PM, Phillips RKS et al. The effect of celecoxib, a cyclooxygenase-2 inhibitor, in familial adenomatous polyposis. New Eng J Med 2000;342:1946-1952.

32. Cruz-Correa M, Hylind LM, Romans KE. Long-term treatment with sulindac in familial adenomatous polyposis: a prospective cohort study. Gastroenterology 2002;122(3):641-5.

33. Ziv Y, Church JM, Oakley JR et al. Surgery for the teenager with familial adenomatous polyposis: Ileorectal anastomosis or restorative proctocolectomy? Int J Colorectal Dis 1995;10:6-9.

34. Bulow C, Vasen H, Jarvinen H et al. Ileorectal anastomosis is appropriate for a subset of patients with familial adenomatous polyposis. Gastroenterology 2000;119:1454-1460.

35. 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.

Version 1.2006, 01/03/06 © 2006 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

36. 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.

37. 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.

38. Setti-Carraro P, Nicholls RJ. Choice of prophylactic surgery for the large bowel component of familial adenomatous polyposis. Br J Surg 1996;83:885-892.

39. Madden MV, Neale KF, Nicholls RJ et al. Comparison morbidity and function after colectomy and ileorectal anastomosis or restorative proctocolectomy for familial adenomatous polyposis. Br J Surg 1991;78:789-792.

40. Ambroze WL, Dozois RR, Pemberton JH et al. Familial adenomatous polyposis: Results following ileal pouch anal anastomosis and ileorectostomy. Dis Colon Rectum 1992;35:12.

41. 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.

42. 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.

43. Bussey HJ, Eyers AA, Ritchie SM, Thompson JP. The rectum in adenomatous polyposis: The St. Mark's policy. Br J Surg 1985;72:S29-31.

44. Sarre RG, Jagelman DG, Beck DJ et al. Colectomy with ileorectal anastomosis for familial adenomatous polyposis: The risk of rectal cancer. Surgery 1987;101-20.

45. Decosse JJ, Bulow S, Neale K et al. Rectal cancer risk in patients treated for familial adenomatous polyposis. Br J Surg 1992;79:1372.

46. Moertel CG, Hill JR, Adson MA. Surgical management of multiple polyposis: The problem of cancer in the retained bowel segment. Arch Surg 1970;100:521-526.

47. Bess MA, Adson MA, Elveback IR et al. Rectal cancer following colectomy for polyposis. Arch Surg 1980;115:460-467.

48. Giardiello FM, Hamilton SR, Krush AJ et al. Treatment of colonic and rectal adenomas with sulindac in familial adenomatous polyposis. N Engl J Med 1993;328:1313-1316.

49. Petersen GM. Genetic testing and counseling for in familial adenomatous polyposis. Oncology 1996;10(1):89-94.

50. Ballhausen WG. Genetic testing for familial adenomatous polyposis. Ann NY Acad Sci 2000;910:36-47.

51. 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(3A):2191-2193.

52. Lynch HT, Smyrk TC, Watson P et al. Genetics, natural history, tumour spectrum, and pathology of hereditary nonpolyposis colorectal cancer: an updated review. Gastroenterology 1993;104:1535-1549.

Version 1.2006, 01/03/06 © 2006 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

53. Muller A, Edmonston TB, Corao DA et al. Exclusion of breast cancer as an integral tumor of hereditary nonpolyposis colorectal cancer. Cancer Res 2002;62:1014-1019.

54. Reyes CM, Allen BA, Terdiman JP, Wilson LS. Comparison of selection strategies for genetic testing of patients with hereditary nonpolyposis colorectal carcinoma. Cancer 2002;95:1848-56.

55. 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.

56. Loukola A, Eklin K, Laiho P et al. Microsatellite marker analysis in screening for hereditary nonpolyposis colorectal cancer (HNPCC). Cancer Research 2001;61:4545-4549.

57. Rodriguez-Bigas MA, Boland CR, Hamilton SR. A National Cancer Institute Workshop on Hereditary Nonpolyposis Colorectal Cancer Syndrome: Meeting highlights and Bethesda guidelines. J Natl Cancer Inst 1997;89:1758-1762.

58. 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(4)261-268.

59. 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.

60. 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(3):621-9.

61. Vasen HF, Hendriks Y, de Jong AE et al. Identification of HNPCC by molecular analysis of colorectal and endometrial tumors. Dis Markers 2004;20(4-5):207-13.

62. Kunstmann E, Vieland J, Brasch FE et al. HNPCC: six new pathogenic mutations. BMC Med Genetics 2004;5(1):16.

63. Offit K. MSH6 mutations in hereditary nonpolyposis colon cancer: another slice of the pie. J Clin Oncol 2004;22(22):4449-51.

64. Yang G, Scherer SJ, Shell SS et al. Dominant effects of an Msh6 missense mutation on DNA repair and cancer susceptibility. Cancer Cell 2004;6(2):139-50.

65. Rijcken FE, Mourits MJ, Kleibeuker JH et al. Gynecologic screening in hereditary nonpolyposis colorectal cancer. Gynecologic Oncology 2003;91;74-80.

66. 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(2):227-32.

67. 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(23):2961-7.

Recommended Reading

Bellacosa A, Genuardi M, Anti M. Hereditary nonpolyposis colorectal cancer: Review of clinical, molecular genetics, and counseling aspects. Am J Med Genet 1996;62:353-364.

Version 1.2006, 01/03/06 © 2006 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

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

Byers T, Levin B, Rothenberger D et al. American Cancer Society guidelines for screening and surveillance for early detection of colorectal polyps and cancer: Update 1997. CA Cancer J Clin 1997;47:154-160.

Syngal S, Fox E, Li C. Interpretation of genetic test results for hereditary nonpolyposis colorectal cancer: Implications for clinical predisposition testing. JAMA 1999;282:247-253.

Young GP, Macrae FA, St John DJ. Clinical methods for early detection: Basis, use and evaluation. In: Young GP, Rozen P, Levin B, eds. Prevention and Early Detection of Colorectal Cancer. London: WB Saunders 1996:241-270.

Goldstein N, Bhanot P, Odish E et al. Hyperplastic-like colon polyps that preceded microsatellite-unstable adenocarcinomas. American Journal of Clinical pathology 2003;119(6):778-796.

Version 1.2006, 01/03/06 © 2006 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**