National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™)

Colorectal Cancer Screening

Version 2.2011

NCCN.org

Continue

Version 2.2011, 10/22/10 © National Comprehensive Cancer Network, Inc. 2010, All rights reserved. **The NCCN Guidelines™ and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

National Comprehensive Cancer Network®

NCCN Guidelines™ Version 2.2011 Panel Members
Colorectal Cancer Screening

NCCN Guidelines Index
Colorectal Screening TOC
Discussion

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

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

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

Kelli Bullard Dunn, MD ¶
Roswell Park Cancer Institute

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

Dayna S. Early, MD ¤
City of Hope Comprehensive Cancer Center

James M. Ford, MD † Þ Δ
Stanford Comprehensive Cancer Center

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

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

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

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

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

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

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

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

Edward W. Martin, Jr, MD ¶
The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute

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

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

Dawn Provenzale, MD, MS ¤ Þ
Duke Comprehensive Cancer Center

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

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

Gideon Steinbach, MD, PhD ¤ Þ
Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance

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

David Weinberg, MD, MSc ¤
Fox Chase Cancer Center

NCCN
Mary Dwyer, MS
Maria Ho, PhD

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

Continue

NCCN Guidelines Panel Disclosures

Version 2.2011, 10/22/10 © National Comprehensive Cancer Network, Inc. 2010, All rights reserved. **The NCCN Guidelines™ and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

National Comprehensive Cancer Network®

NCCN Guidelines™ Version 2.2011 Panel Members
Colorectal Cancer Screening

NCCN Guidelines Index
Colorectal Screening TOC
Discussion

Sub-Committee Members

For Lynch Syndrome surveillance, Classical FAP surveillance, and Peutz-Jeghers Syndrome surveillance

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

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

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

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

Gideon Steinbach, MD, PhD ¤ Þ
Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance

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

Version 2.2011, 10/22/10 © National Comprehensive Cancer Network, Inc. 2010, All rights reserved. **The NCCN Guidelines™ and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

National Comprehensive Cancer Network®

NCCN Guidelines™ Version 2.2011 Table of Contents
Colorectal Cancer Screening

NCCN Guidelines Index
Colorectal Screening TOC
Discussion

NCCN Colorectal Cancer Screening Panel Members
Summary of the Guidelines Updates

Risk Assessment and Screening (CSCR-1)
Average Risk (CSCR-2)
Increased Risk
- Personal History of Adenoma/Sessile Serrated Polyp (CSCR-3)
- Personal History of Colorectal Cancer (CSCR-4)
- Personal History of Inflammatory Bowel Disease (CSCR-5)
- Based on Positive Family History (CSCR-6)

Screening Modality and Schedule (CSCR-A)
Definitions of Common Colorectal Resections (CSCR-B)

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

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

Polyposis Syndromes
- Familial Adenomatous Polyposis Syndromes (FAP-1)
- Surgical Management Options with FAP (FAP-A)
- MYH-Associated Polyposis (MAP-1)
- Peutz-Jeghers Syndrome (PJS-1)
- Juvenile Polyposis Syndrome (JPS-1)
- Hyperplastic Polyposis Syndrome (HPP-1)

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

See NCCN Categories of Evidence and Consensus

The NCCN Guidelines™ are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN 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® (NCCN®) makes no representations or warranties of any kind regarding their content, use or application and disclaims any responsibility for their application or use in any way. The NCCN Guidelines are copyrighted by National Comprehensive Cancer Network®. All rights reserved. The NCCN Guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN. ©2010.

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

National Comprehensive Cancer Network®

NCCN Guidelines™ Version 2.2011 Updates Colorectal Cancer Screening

NCCN Guidelines Index
Colorectal Screening TOC
Discussion

The 2.2011 version of the Colorectal Cancer Screening Guidelines represents the addition of the updated discussion section - MS-1.

Updates in Version 1.2011 of the Colorectal Cancer Screening Guidelines from Version 1.2010 include:

CSCR-1
- **Footnote a, was modified as, "*A negative family history* is not having a first-degree relative or two second-degree relatives with colorectal cancer *(advanced adenoma)* or multiple cases of Lynch syndrome/HNPCC -related cancers in the family".**

CSCR-2
- **Footnote 'g' was modified by removing "except in specific circumstances" from the statement, "At present, stool DNA is not considered a first line screening test".**

CSCR-5
- **After Crohn's disease, "especially if pancolitis" was added.**

CSCR-A 1 of 4
- **First bullet was modified by adding, "Colon cancer prevention *and early detection* should be the primary goal of colorectal cancer screening."**
- **References 2 through 4 were added to the page.**

CSCR-A 2 of 4
- **Subullets under "standardized colonoscopy reports that contain, at a minimum" were added or modified as follows:**
  - **Modified "Patient demographic, clinical factors, *adenoma and cancer history, GI family history*".**
  - **Modified "Endoscopic findings *including polyp number, size, location, method of excision*".**
  - **Added, "Written communication of the findings and plans to the patient and referring physician is encouraged".**

Continued on next page

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

Version 2.2011, 10/22/10 © National Comprehensive Cancer Network, Inc. 2010, All rights reserved. **The NCCN Guidelines™ and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

National Comprehensive Cancer Network®

NCCN Guidelines™ Version 2.2011 Updates Colorectal Cancer Screening

NCCN Guidelines Index
Colorectal Screening TOC
Discussion

Updates in Version 1.2011 of the Colorectal Cancer Screening Guidelines from Version 1.2010 include:

Lynch Syndrome

LS-1

- Lynch syndrome testing criteria has been specified as meeting revised Bethesda guidelines or Amsterdam criteria, endometrial cancer age < 50 y, and known LS in family.
- The testing strategy has been revised based on risk status of deleterious LS mutation known, no known LS mutation, and no criteria met.
- Footnotes 'a' through 'e' are new to the page.

LS-2

Surveillance:

- For colon cancer: bullet was modified as, "Colonoscopy at age 20-25 y *or 2-5 y prior to the earliest colon cancer if it is diagnosed under age 25 y* and repeat every 1-2 y" and removing "or 10 y prior to the youngest age at diagnosis in the family".
- For endometrial and ovarian cancer, the following bullets were added:
  - No clear evidence to support screening for endometrial cancer for LS. However, annual office endometrial sampling may be useful in select patients.
  - While there may be circumstances that clinicians find screening helpful, data does not support routine ovarian screening for LS. Transvaginal ultrasound for ovarian cancer and endometrial cancer may be considered at the clinicians discretion.
- For endometrial and ovarian cancer, the following bullet was removed:
  - Consider referral to gynecologist oncologist for screening for gynecologic tumors.
- For gastric and small bowel cancer, the following bullets were added:
  - Consider EGD, with extended duodenoscopy (to distal duodenum or into the jejunum) and polypectomy at 2-3 y intervals beginning at age 30 - 35.
    - Preliminary data suggests other screening may be considered as follows: Baseline gastric biopsies to evaluate for chronic inflammation, atrophic gastropathy, and intestinal metaplasia and consider shorter screening intervals in persons with extensive histological change and longer intervals in persons with normal histology. Evaluate for H. pylori on the biopsies and by serology and treat those with evidence of infection. Consider enteroscopy at the time of EGD to evaluate the distal duodenum and jejunum.
  - Consider capsule endoscopy for small bowel cancer at 2 - 3 y intervals beginning at age 30 - 35.
- For pancreatic cancer, bullet was modified by adding: "*Due to limited data,* no recommendation *is possible at this time*".

LS-A 1 of 2

- Principles of IHC and MSI testing for Lynch syndrome, last bullet, "This approach was recently endorsed for colon cancer by the Evaluation of Genomic Applications in Prevention and Practice group from the CDC and shown to be cost-effective" was added.

LS-A 2 of 2

- A table titled, "Tumor Testing Results and Additional Testing Strategies" is new to the guidelines.

Continued on next page

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

Version 2.2011, 10/22/10 © National Comprehensive Cancer Network, Inc. 2010, All rights reserved. The NCCN Guidelines™ and this illustration may not be reproduced in any form without the express written permission of NCCN®.

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

NCCN Guidelines™ Version 2.2011 Updates Colorectal Cancer Screening

NCCN Guidelines Index
Colorectal Screening TOC
Discussion

Updates in Version 1.2011 of the Colorectal Cancer Screening Guidelines from Version 1.2010 include:

Familial Adenomatous Polyposis

FAP-1

- For pancreatic cancers: the risk was changed from < 2% to < 1%.

FAP-2

- Colon cancer surveillance was modified by removing, "Annual sigmoidoscopy and polypectomy or polyp ablation if adenoma burden is low (in patients with retained rectum)" and adding the following bullets:
  - If patient had colectomy with ileorectal anastomosis, then endoscopic evaluation of rectum every 6 to 12 mo depending on polyp burden.
  - If patient had total proctocoelctomy with ileal pouch-anal anastomosis or ileostomy, then endoscopic evaluation of ileal pouch or ileostomy every 1-3 y depending on polyp burden. Surveillance frequency should be increased to every 6 mo for large flat polyps with villous histology and/or high-grade dysplasia.

FAP -3

- For gastric cancer: a new bullet "Examine stomach at time of duodenoscopy. Fundic gland polyps occur in a majority of FAP patients and focal dysplasia is typical but is almost invariably non-progressive. For this reason, special screening or surgery is not needed unless high grade dysplasia is present" was added.
- For thyroid cancer: "Annual ultrasound may be considered, though data to support this recommendation are lacking" was added.
- For CNS cancer: bullet was modified as "*Due to limited data,* no recommendation *is possible at this time*".
- For intra-abdominal desmoids: "If symptomatic desmoids in family, consider abdominal MRI or CT 1-3 y post-colectomy and then at 5 - 10 y intervals. Suggestive abdominal symptoms should prompt immediate abdominal imaging" replaced "after colectomy, consider abdominal and pelvic CT or MRI every 3 y, especially if family history of desmoids".
- For hepatoblastoma: bullet "No recommendations have been made for FAP; however there are other situations where the high risk of hepatoblastoma have been observed and the following recommendations have been considered" was added.
- For pancreatic cancer: bullet was modified as, "*Due to limited data,* no recommendation *is possible at this time*."

FAP-4

- Stage IV, surveillance bullet was modified as, "expert surveillance *at 3-6 mo intervals*" which replaced "every 6- 12 mo".

FAP-A

- For TAC/IRA, indications, "attenuated FAP with rectal sparing" was removed and "asymptomatic" was removed from "patients with few (< 20) rectal polyps..."
- For TPC/IPAA, contraindications, "incurable cancer" and "advanced low rectal cancer" were removed.
- For TPC/IPAA, disadvantages, "functional results can be unpredictable" was added.

Continued on next page

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

 © National Comprehensive Cancer Network, Inc. 2010, All rights reserved. **The NCCN Guidelines™ and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

National Comprehensive Cancer Network®

NCCN Guidelines™ Version 2.2011 Updates Colorectal Cancer Screening

NCCN Guidelines Index
Colorectal Screening TOC
Discussion

Updates in Version 1.2011 of the Colorectal Cancer Screening Guidelines from Version 1.2010 include:

Attenuated Familial Adenomatous Polyposis

AFAP-1

- **Adenoma/polyp burden: "≥ 21 with small adenoma burden" was modified as "≥ 21 - *40 y* with small adenoma burden".**
- **Surveillance was modified by removing, "If colectomy, annual endoscopic examination of the rectum" and adding the following bullet:**
  - **If patient had colectomy with ileorectal anastomosis, then endoscopic evaluation of rectum every 6- 12 mo depending on polyp burden.**
- **Footnote c was modified by adding "...especially if colonoscopy is difficult *and polyp control is uncertain*. Surgery *should be considered* when polyp burden is greater than 20 *at any individual examination, when polyps have been previously ablated..."***

Peutz Jeghers Syndrome

PJS-2

- **Stomach cancer surveillance with upper endoscopy every 2 - 3 y beginning in the late teens was added.**
- **Small intestine, surveillance recommendation was modified, "Small bowel visualization (CT enterography, small bowel enteroclysis) *baseline at 8-10 y with follow-up interval based on findings but at least by age 18, then every 2-3 y though this may be individualized,* or other symptoms".**
- **Pancreas, initiation of screening age was changed from "30 y" to "*25*-30 y."**
- **Footnote 1, "Although the absolute risk of adenocarcinoma of the ovary is elevated in Peutz-Jeghers syndrome, ovarian sex cord tumors are the most common ovarian pathology found in these patients" is new to the page.**

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

Version 2.2011, 10/22/10 © National Comprehensive Cancer Network, Inc. 2010, All rights reserved. **The NCCN Guidelines™ and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

National Comprehensive Cancer Network®

NCCN Guidelines™ Version 2.2011
Colorectal Cancer Screening

NCCN Guidelines Index
Colorectal Screening TOC
Discussion

RISK ASSESSMENT FOR COLON CANCER

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

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

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

High risk syndromes:
- Lynch Syndrome/Hereditary Nonpolyposis Colorectal Cancer (HNPCC) (LS-1)
- Polyposis syndromes
  - Classical Familial Adenomatous Polyposis (FAP-1)
  - Attenuated Familial Adenomatous Polyposis (AFAP-1)
  - MYH-associated Polyposis (MAP-1)
  - Peutz-Jeghers Syndrome (PJS-1)
  - Juvenile Polyposis syndrome (JPS-1)
  - Hyperplastic Polyposis Syndrome (HPP-1) (rarely inherited)

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

[a] A negative family history is not having a first-degree relative or two second-degree relatives with colorectal cancer (advanced adenoma) or multiple cases of Lynch syndrome/HNPCC -related cancers in the family.

[b] Sessile serrated polyp (SSP) is synonymous with sessile serrated adenoma but does not include classical hyperplastic polyp.

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

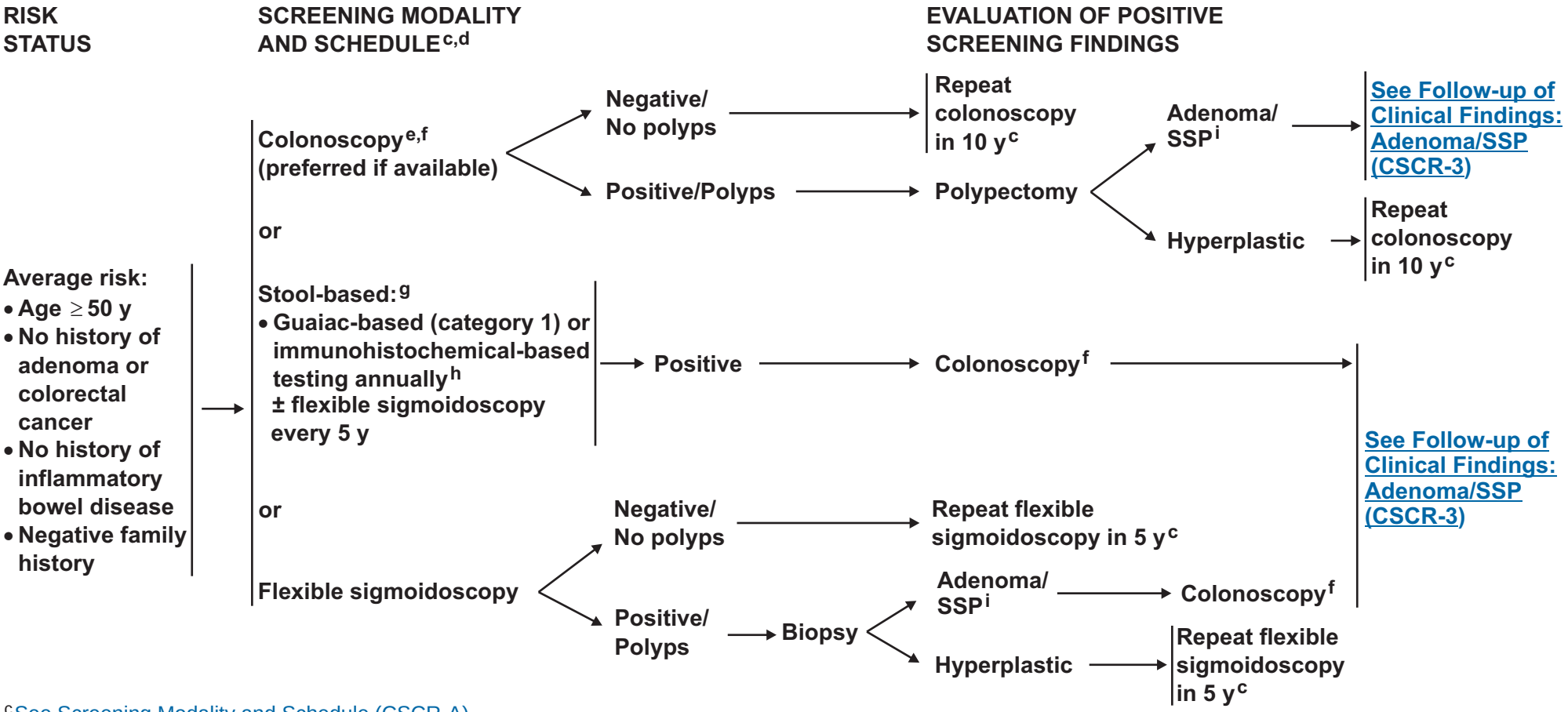
Version 2.2011, 10/22/10 © National Comprehensive Cancer Network, Inc. 2010, All rights reserved. **The NCCN Guidelines™ and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

National Comprehensive Cancer Network®

NCCN Guidelines™ Version 1.2011
Colorectal Cancer Screening

NCCN Guidelines Index
Colorectal Screening TOC
Discussion



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

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

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

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

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

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

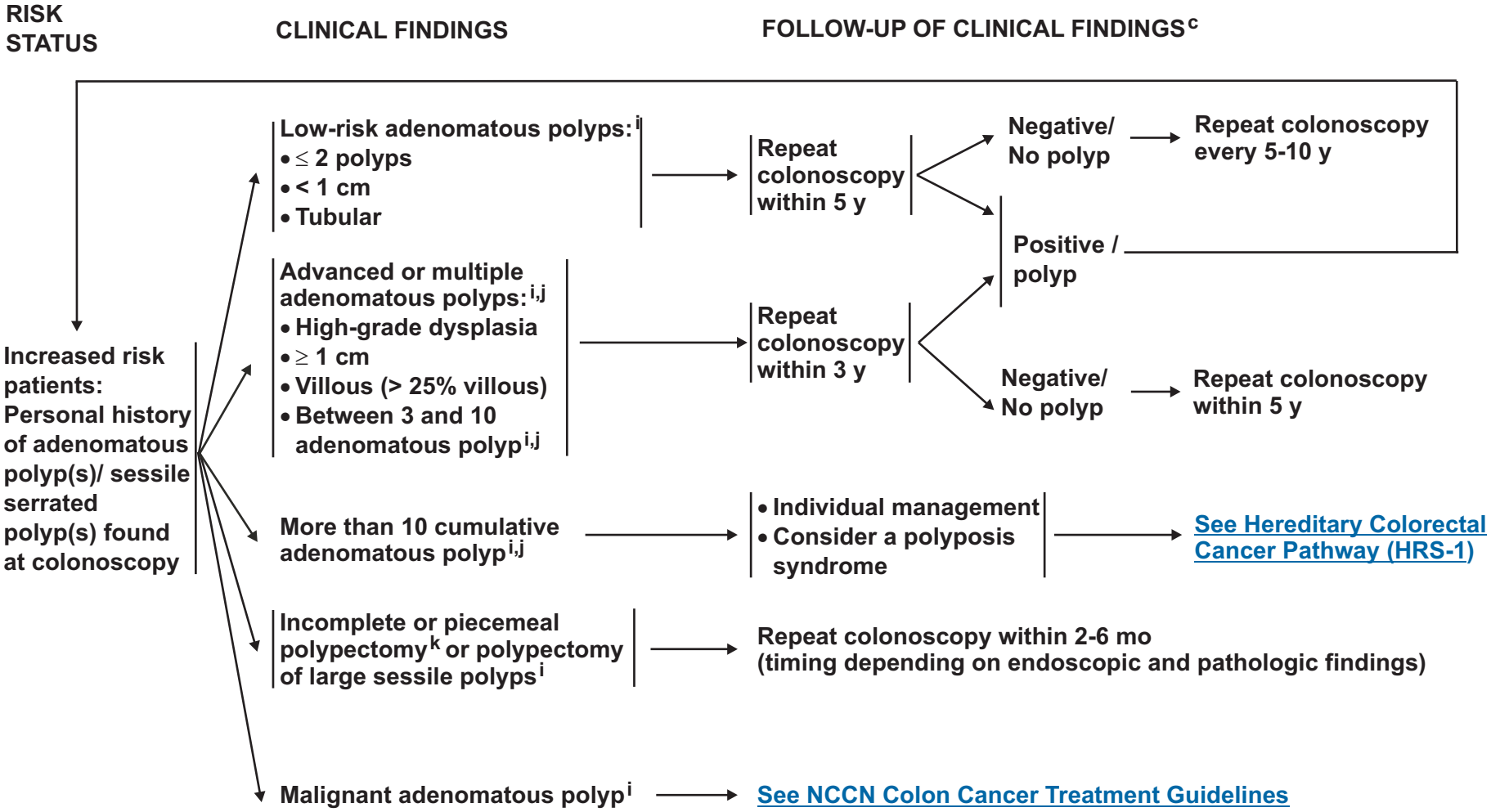
[i] Sessile serrate polyps are managed the same as adenomas.

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 2.2011, 10/22/10 © National Comprehensive Cancer Network, Inc. 2010, All rights reserved. **The NCCN Guidelines™ and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

INCREASED RISK BASED ON PERSONAL HISTORY OF ADENOMATOUS POLYP/SESSILE SERRATED POLYP (SSP)[i]



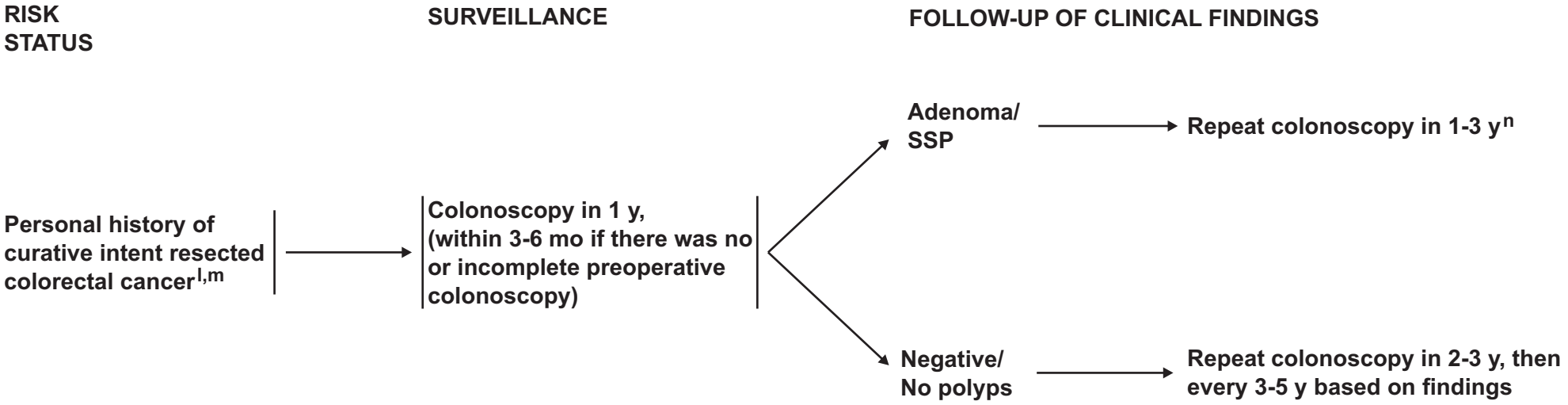
[c] See Screening Modality and Schedule (CSCR-A).
[i] Sessile serrate polyps are managed the same as adenomas.
[j] 10 polyps or fewer in the setting of a strong family history or younger age (< 40 y) may sometimes be associated with an inherited polyposis syndrome.
[k] Ink lesion for later identification.

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 2.2011, 10/22/10 © National Comprehensive Cancer Network, Inc. 2010, All rights reserved. **The NCCN Guidelines™ and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

INCREASED RISK BASED ON PERSONAL HISTORY OF COLORECTAL CANCER



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

[m] In addition to the colonoscopy, patients with rectal cancer should also undergo periodic limited endoscopic evaluation of the rectal anastamosis to identify local recurrence. Optimal timing for surveillance is not known. Expert opinion supports repeat evaluation every 3-6 months for the first 2-3 years of surveillance. No specific data clearly support rigid versus flexible sigmoidoscopy. The utility of routine endoscopic ultrasound for early surveillance is not defined. See surveillance section of NCCN Rectal Cancer Guidelines.

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

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

Version 2.2011, 10/22/10 © National Comprehensive Cancer Network, Inc. 2010, All rights reserved. **The NCCN Guidelines™ and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

INCREASED RISK BASED ON PERSONAL HISTORY OF INFLAMMATORY BOWEL DISEASE

RISK STATUS	INITIATION OF SCREENING	SCREENING MODALITY AND SCHEDULE	EVALUATION OF POSITIVE SCREENING FINDINGS	FOLLOW-UP OF CLINICAL FINDINGS[q,r]
Personal history of inflammatory bowel disease[o] • Ulcerative colitis • Crohn's disease, especially if pancolitis	→ 8-10 y after onset of symptoms[p]	→ Colonoscopy every 1–2 y • When clinically quiescent, 4 quadrant biopsies every 10 cm with > 30 total samples (preferred) • Additional extensive sampling of strictures and masses • Endoscopic polypectomy when appropriate with biopsies of surrounding mucosa for the assessment of dysplasia	→ Dysplasia/intraepithelial neoplasia • Confirmation by expert GI pathologist desirable	→ Surgical consultation for resection[s]

[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 2003;124:544-560.

[q] 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.

[r] 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.

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

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

Version 2.2011, 10/22/10 © National Comprehensive Cancer Network, Inc. 2010, All rights reserved. **The NCCN Guidelines™ and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

INCREASED RISK BASED ON POSITIVE FAMILY HISTORY

FAMILY HISTORY CRITERIA[t]	SCREENING	
First-degree relative with colorectal cancer age 50-60 y[u]	Colonoscopy beginning at age 40 y	Repeat every 5 y[w]
First-degree relative with colorectal cancer < age 50 y[u,v]	Colonoscopy beginning at age 40 y or 10 y before earliest diagnosis of colorectal cancer	Repeat every 3-5 y depending on other family history
First-degree relative with colorectal cancer at age ≥ 60 y[u]	Colonoscopy beginning at age 50 y	Repeat every 5 y
Two related first-degree relatives with colorectal cancer at any age[v]	Colonoscopy beginning at age 40 y or 10 y before earliest diagnosis of colorectal cancer	Repeat every 3-5 y depending on other family history
Two related second-degree relatives with colorectal at any age	Colonoscopy beginning at age 50 y	Repeat every 5 y
One second-degree relative or any third-degree relative(s) with colorectal cancer or First-degree relative with non-advanced adenoma(s)	• Treat as average risk patients • Colonoscopy is preferred screening	

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

[u] First-degree relatives with advanced adenoma may confer some risk as in first-degree relatives with colorectal cancer, and any adenoma under age 40 y may confer a similar risk to colorectal cancer under age 50 y.

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

[w] Shorter intervals may be needed depending upon the family history.

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 2.2011, 10/22/10 © National Comprehensive Cancer Network, Inc. 2010, All rights reserved. **The NCCN Guidelines™ and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

SCREENING MODALITY AND SCHEDULE (1 of 4)

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

Screening Modalities that Detect Adenomatous Polyps and Cancer[1,2,3,4]

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

Screening Modalities that Primarily Detect Cancer[2,3,4,6]

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

Continued on next page

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

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

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

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

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

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

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

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

Version 2.2011, 10/22/10 © National Comprehensive Cancer Network, Inc. 2010, All rights reserved. **The NCCN Guidelines™ and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

SCREENING MODALITY AND SCHEDULE (2 of 4)

Colonoscopy

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

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

Continued on next page

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

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

SCREENING MODALITY AND SCHEDULE (3 of 4)

Flexible sigmoidoscopy

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

Stool based screening

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

Continued on next page

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

Version 2.2011, 10/22/10 © National Comprehensive Cancer Network, Inc. 2010, All rights reserved. The NCCN Guidelines™ and this illustration may not be reproduced in any form without the express written permission of NCCN®.

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

SCREENING MODALITY AND SCHEDULE (4 of 4)

Radiographic

CT colonography (CTC)[9,10,11]

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

[9] See American Gastroenterological Association CT Colonography Standards.

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

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

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

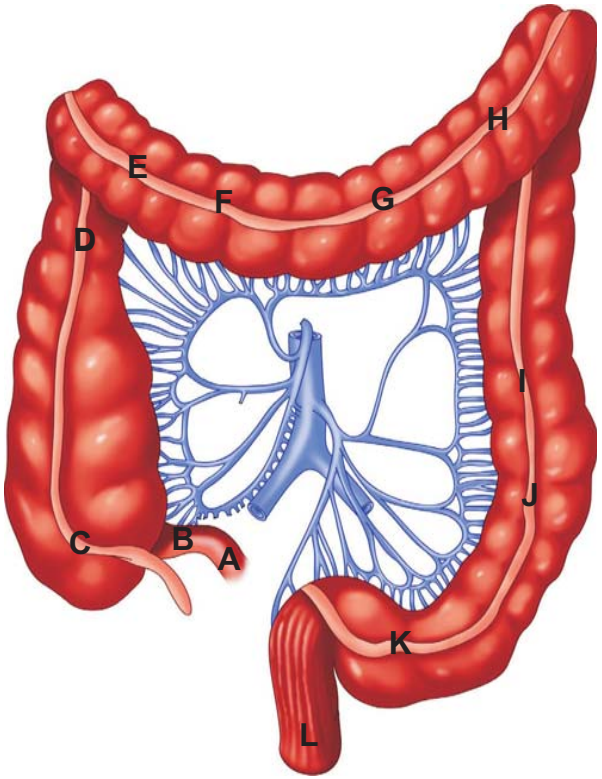
Version 2.2011, 10/22/10 © National Comprehensive Cancer Network, Inc. 2010, All rights reserved. **The NCCN Guidelines™ and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

DEFINITIONS OF COMMON COLORECTAL RESECTIONS

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

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



A through C Ileocecetomy

A through D Ascending colectomy

A through F Right hemicolectomy

A through G Extended right hemicolecotmy

E through H Transverse colectomy

G through I Left hemicolectomy

F through I Extended left hemicolectomy

J through K Sigmoid colectomy

A through J Subtotal colectomy

A through K Total colectomy

K through L Low Anterior Resection with sphincter preservation

K through L Abdominoperineal resection without sphincter preservation

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

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

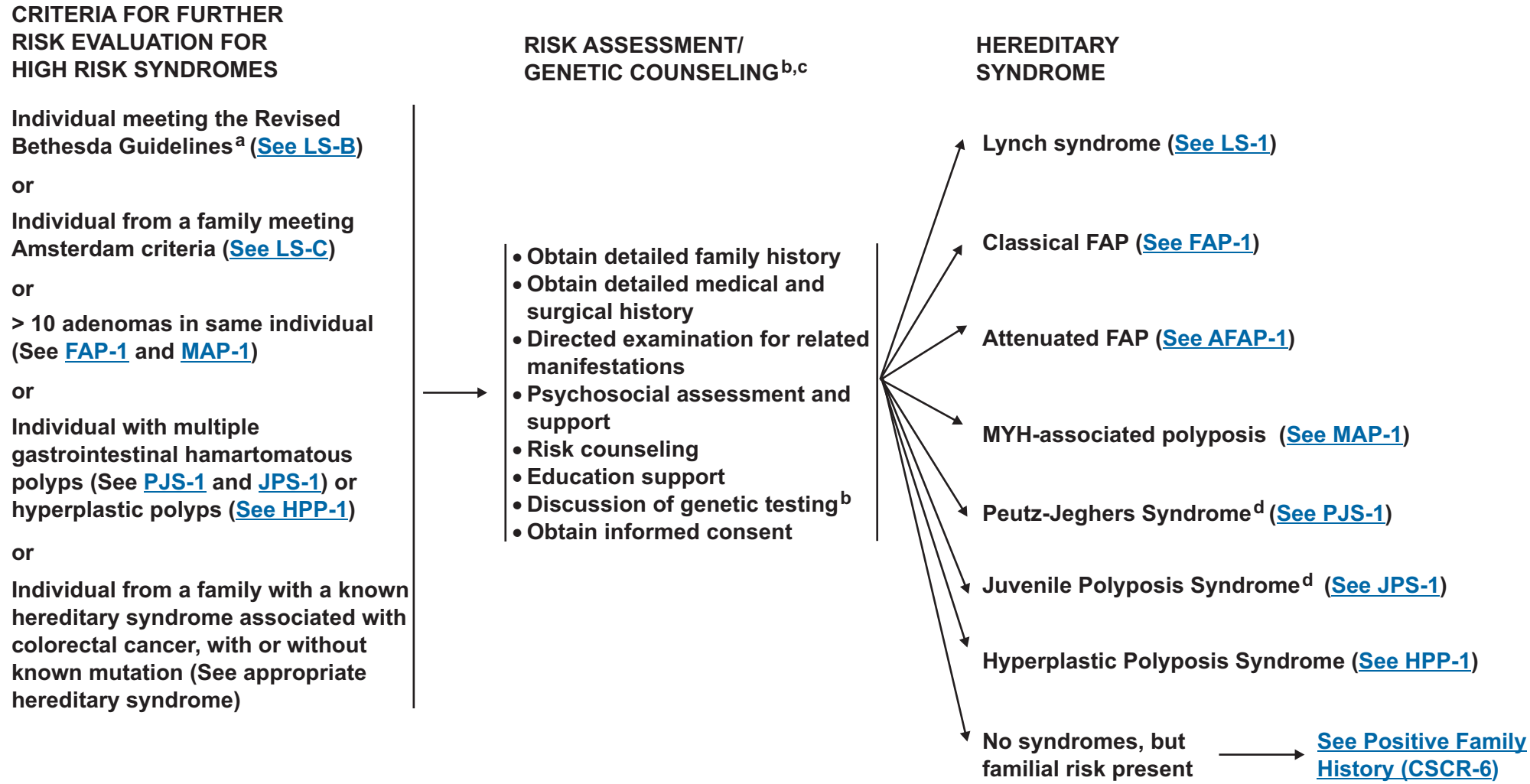
Version 2.2011, 10/22/10 © National Comprehensive Cancer Network, Inc. 2010, All rights reserved. **The NCCN Guidelines™ and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

National Comprehensive Cancer Network®

NCCN Guidelines™ Version 2.2011
High Risk Syndromes

NCCN Guidelines Index
Colorectal Screening TOC
Discussion



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

[b] See Obtaining a Comprehensive Risk Assessment for Hereditary Colorectal Cancer (HRS-A).

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

[d] Referral to a specialized team is recommended.

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

Version 2.2011, 10/22/10 © National Comprehensive Cancer Network, Inc. 2010, All rights reserved. **The NCCN Guidelines™ and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

OBTAINING A COMPREHENSIVE ASSESSMENT FOR HEREDITARY COLORECTAL CANCER

Family History of Colorectal Cancer and Expanded Pedigree

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

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

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

Detailed Medical and Surgical History

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

Directed examination for related manifestations

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

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

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

Version 2.2011, 10/22/10 © National Comprehensive Cancer Network, Inc. 2010, All rights reserved. **The NCCN Guidelines™ and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

OBTAINING A COMPREHENSIVE ASSESSMENT FOR HEREDITARY COLORECTAL CANCER

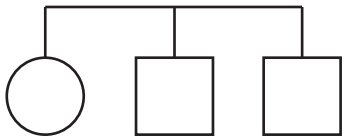
COMMON PEDIGREE SYMBOLS[2]



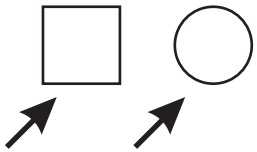
Male, Female



Mating



Sibship



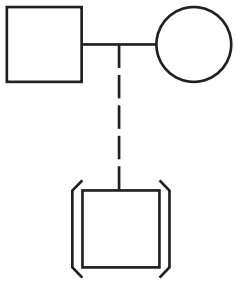
Proband
(patient initiating genetic workup)



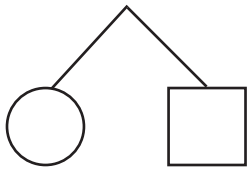
Affected with trait



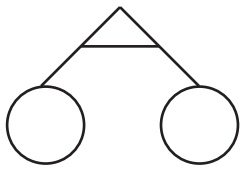
Deceased



Adopted into a family



Dizygotic twins



Monozygotic twins

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

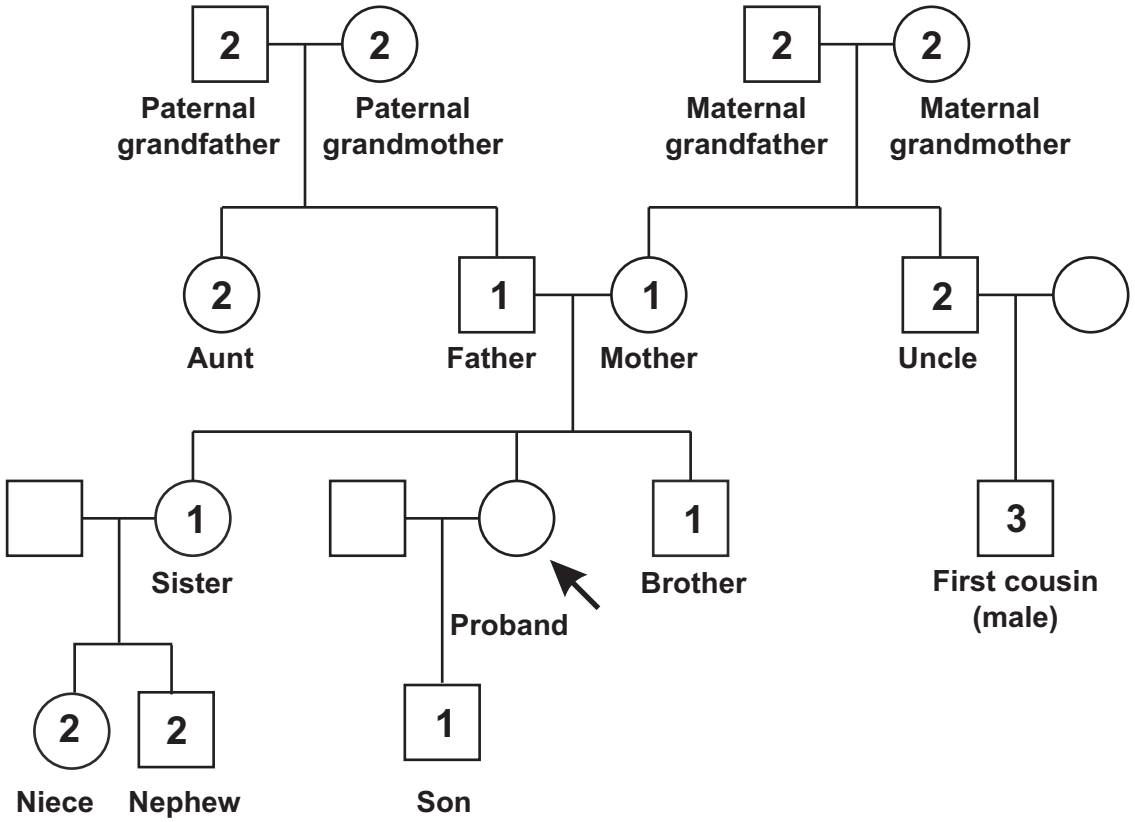
[2]Bennett RL, Steinhaus KA, Uhrich SB, et al. Recommendations for standardized human pedigree nomenclature. Am J Hum Genet 1995;56:745-752.

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

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

OBTAINING A COMPREHENSIVE ASSESSMENT FOR HEREDITARY COLORECTAL CANCER

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



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

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

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

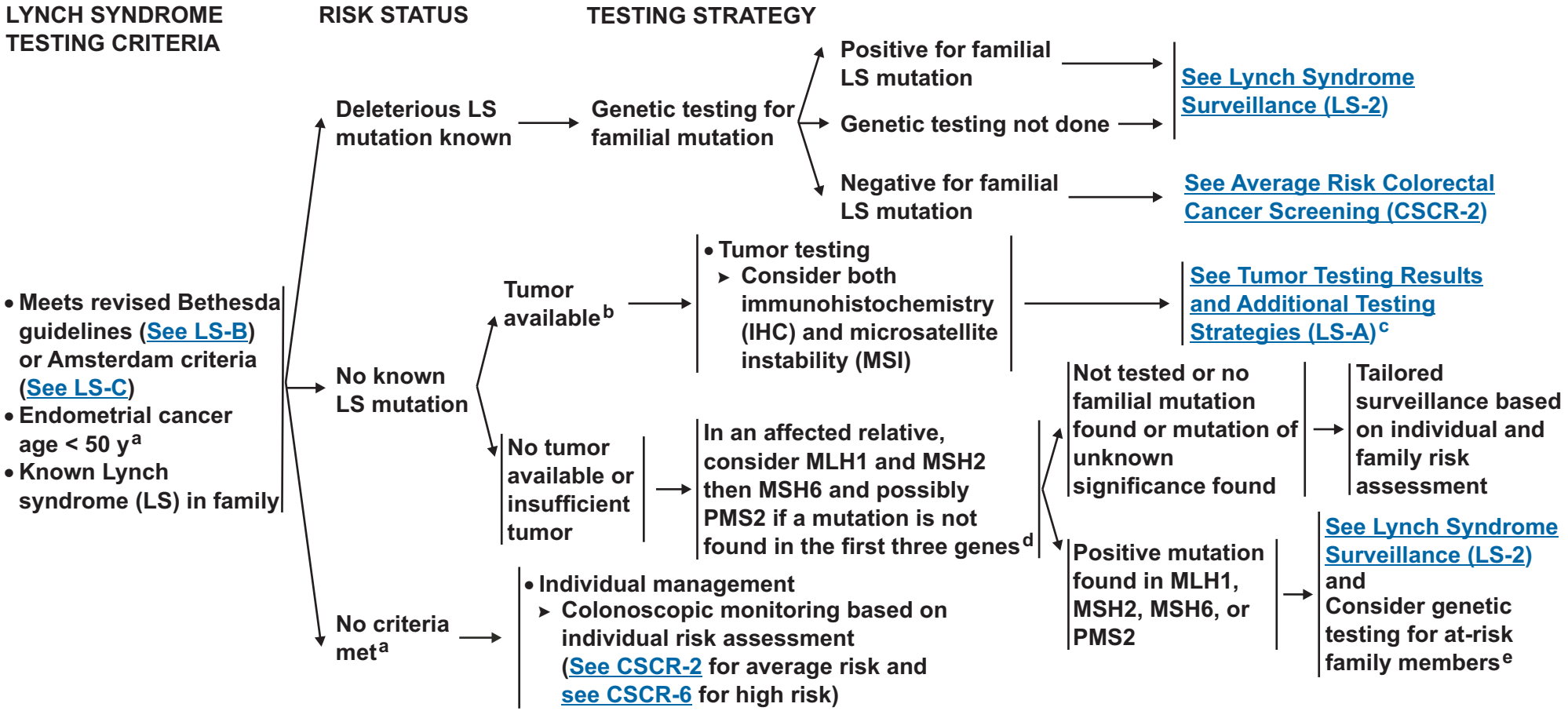
Version 2.2011, 10/22/10 © National Comprehensive Cancer Network, Inc. 2010, All rights reserved. **The NCCN Guidelines™ and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

National Comprehensive Cancer Network®

NCCN Guidelines™ Version 2.2011
Lynch Syndrome

NCCN Guidelines Index
Colorectal Screening TOC
Discussion



[a] Recently, IHC and/or MSI screening of all colorectal and endometrial cancers regardless of age at diagnosis or family history, has been implemented at some centers to identify individuals at risk for LS. This approach was recently endorsed for colorectal cancer by the Evaluation of Genomic Applications in Prevention and Practice group from the CDC and shown to be cost-effective (EGAPP Recommendation Statment. Genetics in Medicine 2009;1135-1141.)

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

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

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

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

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

Version 2.2011, 10/22/10 © National Comprehensive Cancer Network, Inc. 2010, All rights reserved. **The NCCN Guidelines™ and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

SURVEILLANCE[g,h]

Colon cancer:

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

Extra-colonic:

- **Endometrial and ovarian cancer:**
  - **Prophylactic hysterectomy and bilateral salpingo-oophorectomy is a risk reducing option for women who have completed childbearing that should be considered.**
  - **Perform patient education which would include recommending prompt response to endometrial cancer symptoms.**
  - **No clear evidence to support screening for endometrial cancer for LS. However, annual office endometrial sampling may be useful in select patients.**
  - **While there may be circumstances that clinicians find screening helpful, data does not support routine ovarian screening for LS. Transvaginal ultrasound for ovarian cancer and endometrial cancer may be considered at the clinicians discretion.**
- **Gastric and small bowel cancer:**
  - **Consider EGD, with extended duodenoscopy (to distal duodenum or into the jejunum) and polypectomy at 2-3 y intervals beginning at age 30 - 35.**
    - **Preliminary data suggests other screening may be considered as follows: Baseline gastric biopsies to evaluate for chronic inflammation, atrophic gastropathy, and intestinal metaplasia and consider shorter screening intervals in persons with extensive histological change and longer intervals in persons with normal histology. Evaluate for H. pylori on the biopsies and by serology and treat those with evidence of infection. Consider enteroscopy at the time of EGD to evaluate the distal duodenum and jejunum.**
  - **Consider capsule endoscopy for small bowel cancer at 2 - 3 y intervals beginning at age 30 - 35.**
- **Urothelial cancer: Consider annual urinalysis.**
- **CNS cancer: Annual physical examination; no additional screening recommendations have been made.**
- **Pancreatic cancer: Due to limited data, no recommendation is possible at this time.**

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

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

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

[i] Given the later average age of onset for MSH6 or PMS2 mutation carriers, consider starting colonoscopy at the age of 30-35 y or 10 y prior to the youngest age of diagnosis in the family, whichever comes first.

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 2.2011, 10/22/10 © National Comprehensive Cancer Network, Inc. 2010, All rights reserved. **The NCCN Guidelines™ and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

NCCN Guidelines™ Version 2.2011
Lynch Syndrome

NCCN Guidelines Index
Colorectal Screening TOC
Discussion

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

[j] May consider subtotal colectomy if patient is not a candidate for optimal surveillance.

[k] The type of surgical procedure chosen should be based on individual considerations and discussion of risk. Surgical management is evolving. See Definitions of Common Colorectal Resections (CSCR-B).

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

Version 2.2011, 10/22/10 © National Comprehensive Cancer Network, Inc. 2010, All rights reserved. **The NCCN Guidelines™ and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

PRINCIPLES OF IHC AND MSI TESTING FOR LYNCH SYNDROME

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

Immunohistochemistry

- **IHC refers to staining tumor tissue for protein expression of the four mismatch genes known to be mutated in Lynch syndrome: MLH1, MSH2, MSH6, and PMS2. A normal IHC test implies all four mismatch repair proteins are normally expressed and thus no underlying mismatch repair gene mutation is present. An abnormal test means that one of the proteins is not expressed and an inherited mutation may be present in the related gene. Loss of protein expression by IHC in any one of the mismatch repair genes guides genetic testing (mutation detection) to the gene where protein expression is not observed.**
- **Ten to 15% of sporadic colon cancers exhibit abnormal IHC, often due to abnormal methylation of the MLH1 gene promoter, but occasionally due to an inherited mutation of one of the mismatch repair genes. Thus the presence of an abnormal IHC test increases the possibility of Lynch syndrome but does not make a definitive diagnosis. Genetic testing of peripheral blood DNA to find a disease causing mutation of one of the mismatch repair genes should then be done. Most patients will be found to have sporadic colon cancer and not a germline mutation. Those with a germline mutation are then identified as Lynch syndrome patients.**
- **There is a 5-10% false negative rate with IHC testing.**

Microsatellite instability

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

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

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

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

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

Version 2.2011, 10/22/10 © National Comprehensive Cancer Network, Inc. 2010, All rights reserved. **The NCCN Guidelines™ and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

National Comprehensive Cancer Network®

NCCN Guidelines™ Version 2.2011
Lynch Syndrome

NCCN Guidelines Index
Colorectal Screening TOC
Discussion

TUMOR TESTING RESULTS AND ADDITIONAL TESTING STRATEGIES

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

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

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

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

Version 2.2011, 10/22/10 © National Comprehensive Cancer Network, Inc. 2010, All rights reserved. **The NCCN Guidelines™ and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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

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

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

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

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

Version 2.2011, 10/22/10 © National Comprehensive Cancer Network, Inc. 2010, All rights reserved. **The NCCN Guidelines™ and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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

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

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

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

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

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

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

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

Version 2.2011, 10/22/10 © National Comprehensive Cancer Network, Inc. 2010, All rights reserved. **The NCCN Guidelines™ and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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

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

[1]Kohlmann W, Gruber SB (Updated November 29, 2006). Hereditary Non-Polyposis Colon Cancer. In: GeneReviews at GeneTests: Medical Genetics Information Resource (database online). Copyright, University of Washington, Seattle. 1997-2009. Available at http://www.genetests.org. Accessed September 23, 2010.

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 2.2011, 10/22/10 © National Comprehensive Cancer Network, Inc. 2010, All rights reserved. **The NCCN Guidelines™ and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

National Comprehensive Cancer Network®

NCCN Guidelines™ Version 2.2011
Familial Adenomatous Polyposis

NCCN Guidelines Index
Colorectal Screening TOC
Discussion

PHENOTYPE

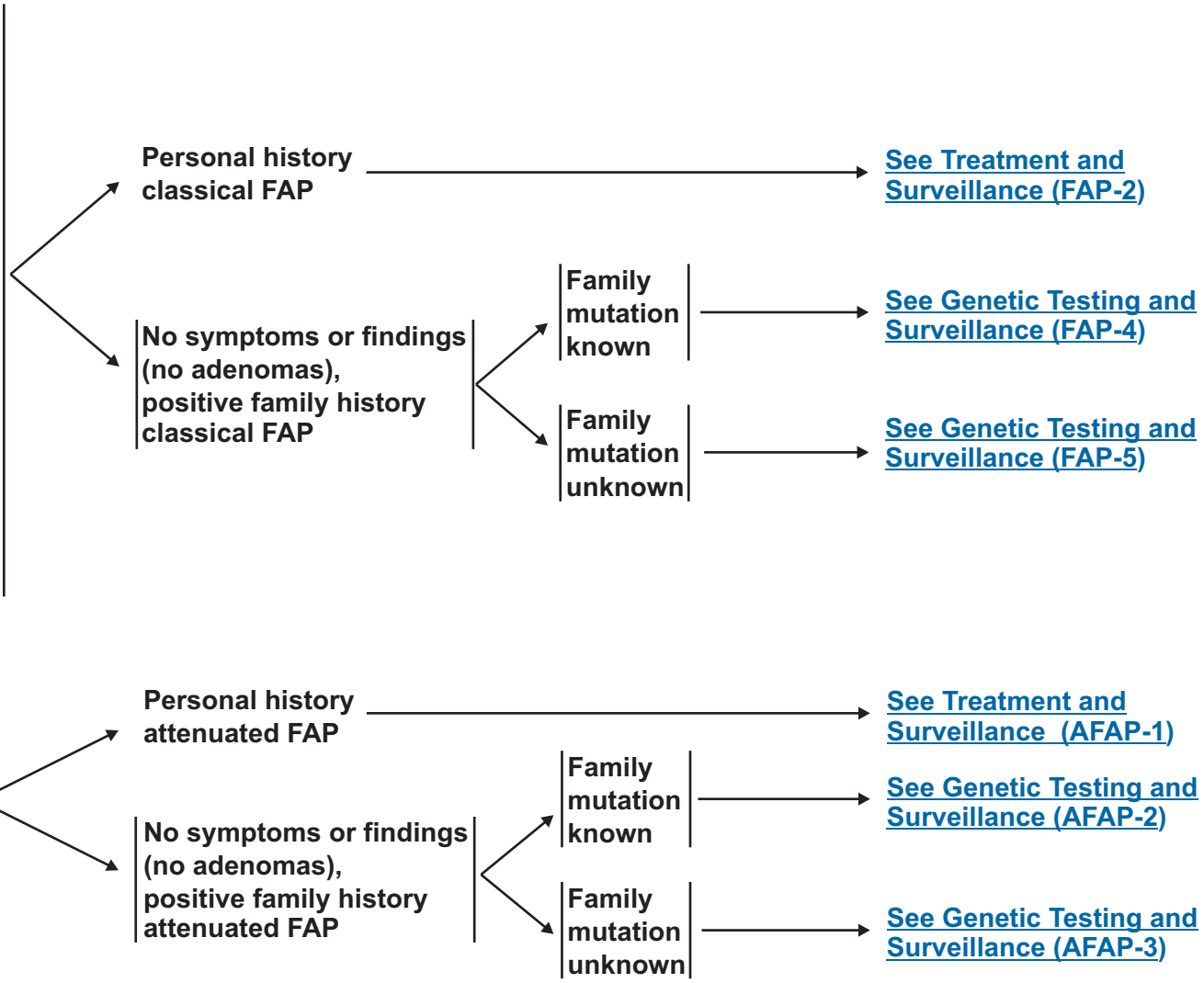
Classical familial adenomatous polyposis (FAP):

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

Attenuated FAP

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

RISK ASSESSMENT



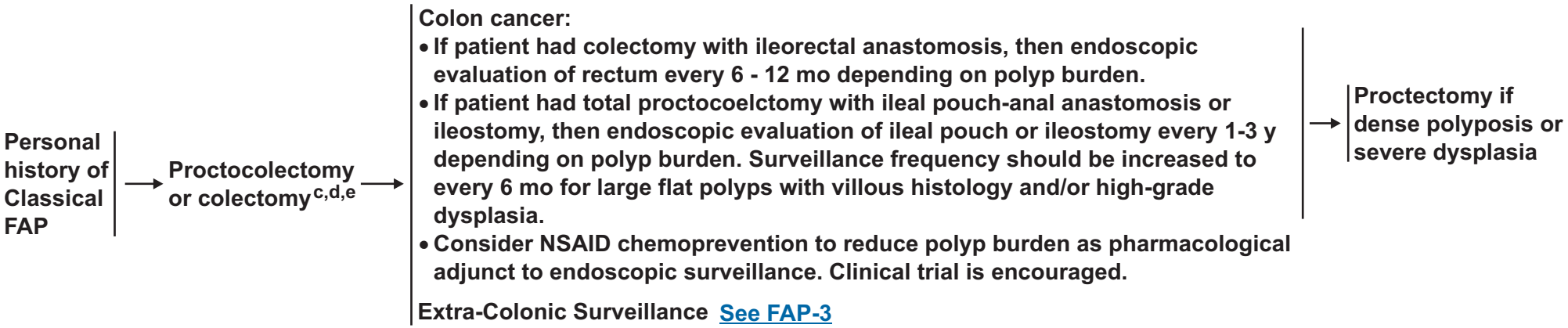
[a] Individuals with 100 or more polyps occurring at older ages (35 to 40 years or older) may be found to have attenuated FAP.
[b] Thirty percent spontaneous new mutation rate, thus family history may be negative. Especially noteworthy if onset < age 50 y.

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

Version 2.2011, 10/22/10 © National Comprehensive Cancer Network, Inc. 2010, All rights reserved. **The NCCN Guidelines™ and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

CLASSICAL FAP TREATMENT AND SURVEILLANCE: PERSONAL HISTORY



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

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

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

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

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

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

Version 2.2011, 10/22/10 © National Comprehensive Cancer Network, Inc. 2010, All rights reserved. **The NCCN Guidelines™ and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

CLASSICAL FAP SURVEILLANCE: PERSONAL HISTORY

SURVEILLANCE[f,g] (POSTCOLECTOMY)

Extra-colonic:

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

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.

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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

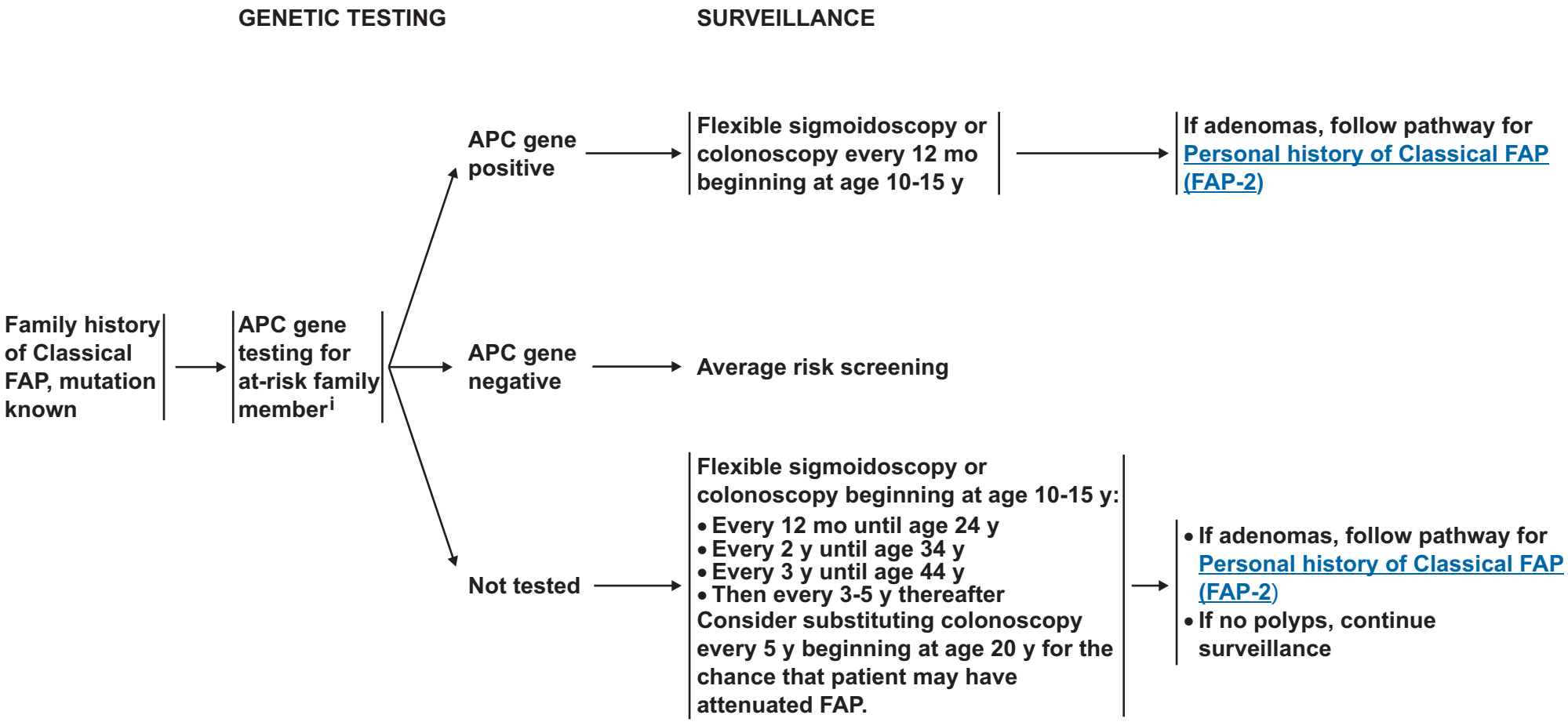
[h] Duodenal Surveillance:

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

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

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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



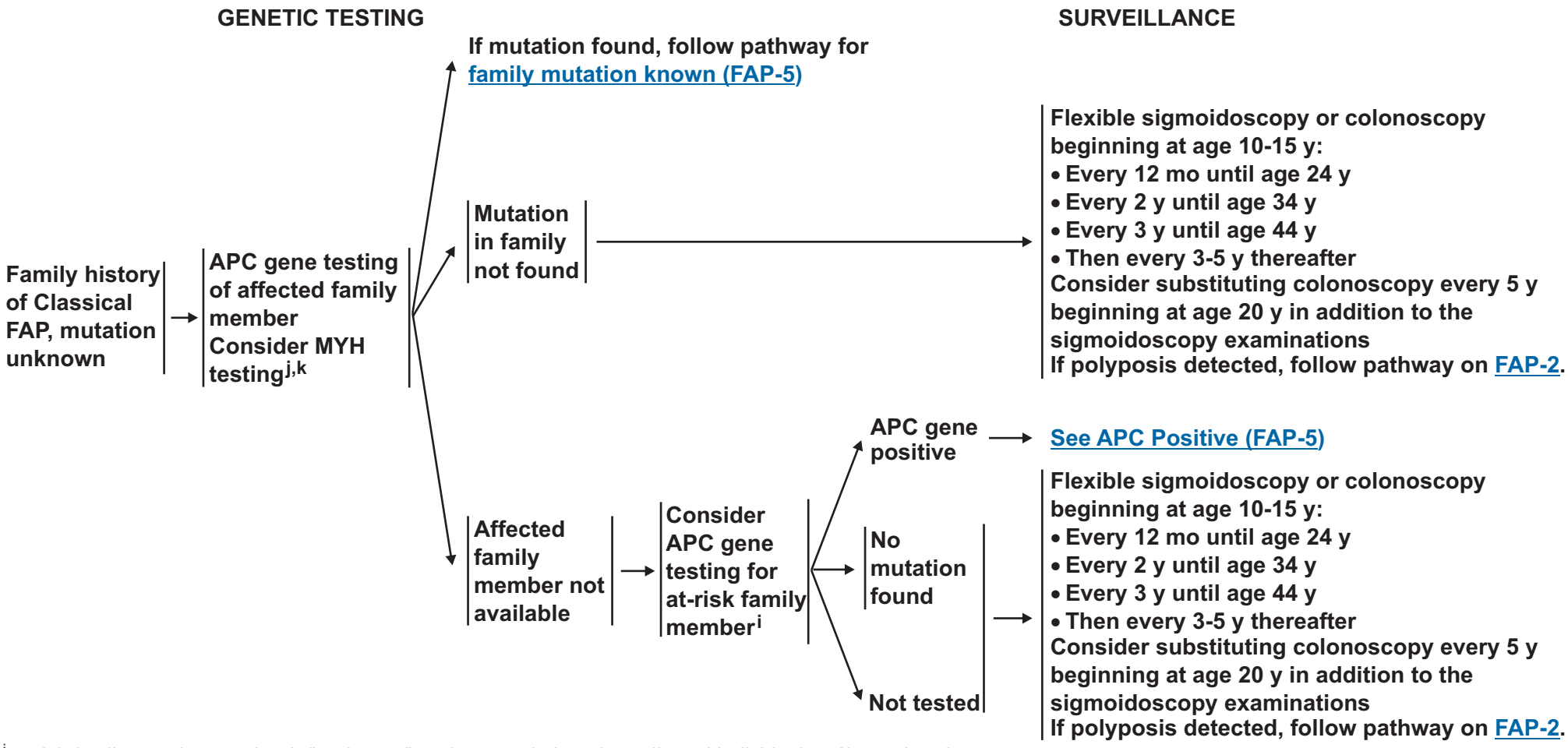
[i] At-risk family member can be defined as a first-degree relative of an affected individual and/or proband. If a first-degree relative is unavailable or unwilling to be tested, more distant relatives should be offered testing for the known mutation in the family.

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

Version 2.2011, 10/22/10 © National Comprehensive Cancer Network, Inc. 2010, All rights reserved. **The NCCN Guidelines™ and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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



[i] At-risk family member can be defined as a first-degree relative of an affected individual and/or proband.

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

[k] When polyposis is present in a single person with negative family history, consider testing for a *de novo* APC mutation; if negative, follow with testing for 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.

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.

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

NCCN Guidelines™ Version 2.2011
Familial Adenomatous Polyposis

NCCN Guidelines Index
Colorectal Screening TOC
Discussion

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

TOTAL ABDOMINAL COLECTOMY WITH ILEORECTAL ANASTOMOSIS (TAC/IRA)

- Indications:
  - Patients with few (<20) rectal polyps and mild colonic disease (<100) polyps
- Contraindications:
  - Curable cancer in colon or rectum
  - Severe rectal or colon disease (size or number of polyps)
  - Patient not reliable for follow-up surveillance of retained rectum
- Advantages:
  - Technically straightforward
  - Relatively low complication rate
  - Good functional outcome
  - No permanent or temporary stoma
  - Avoids 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:
  - Severe disease in colon and/or rectum
  - After TAC/IRA with unstable rectum
  - Curable colon or rectal cancer
  - Patient unreliable for follow-up after TAC/IRA
- Contraindications:
  - Intra-abdominal desmoid that would interfere with completion of surgery
  - Patient not a candidate for IPAA (ie, concomitant Crohn's disease, anal sphincter dysfunction, etc)
- Advantages:
  - Minimal 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

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 2.2011, 10/22/10 © National Comprehensive Cancer Network, Inc. 2010, All rights reserved. **The NCCN Guidelines™ and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

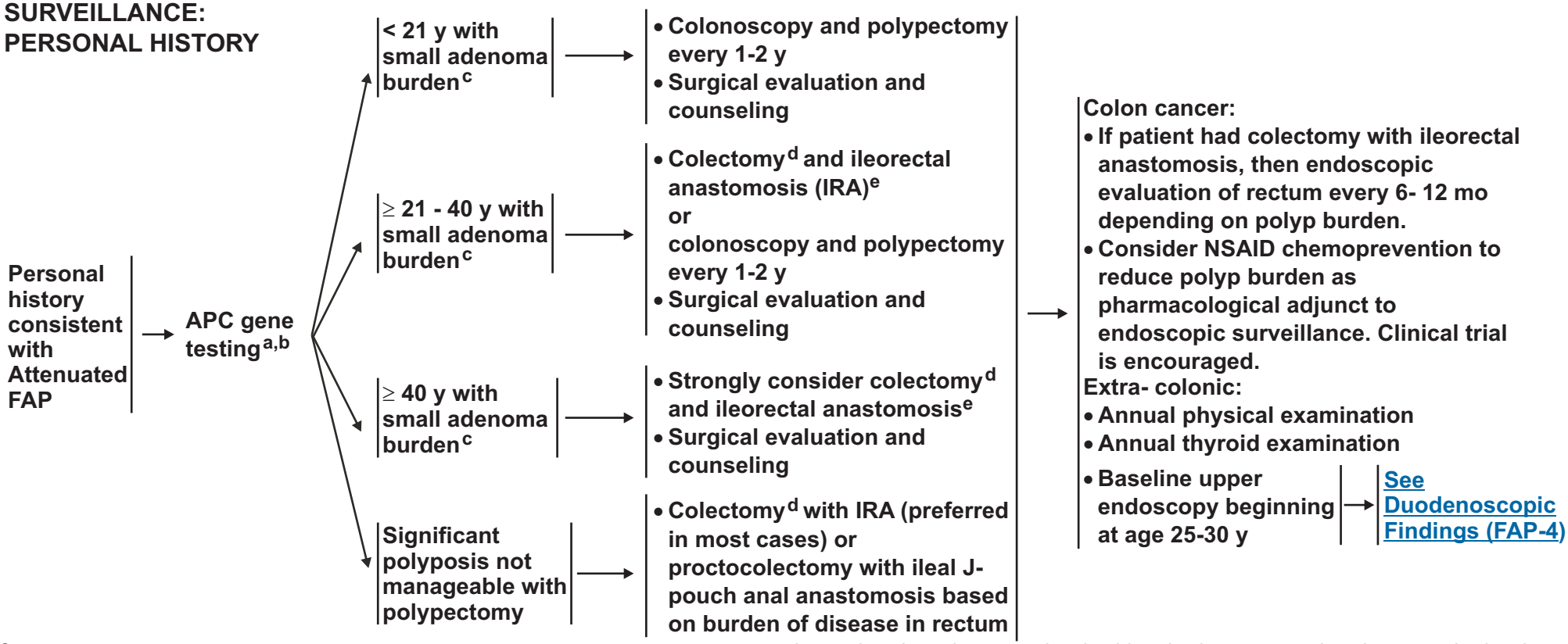
Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

National Comprehensive Cancer Network®

NCCN Guidelines™ Version 2.2011
Attenuated Familial Adenomatous Polyposis

NCCN Guidelines Index
Colorectal Screening TOC
Discussion

ATTENUATED FAP TREATMENT AND SURVEILLANCE: PERSONAL HISTORY



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

[b] MYH testing if APC mutation not found (See MAP-1).

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

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

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

[f] 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.

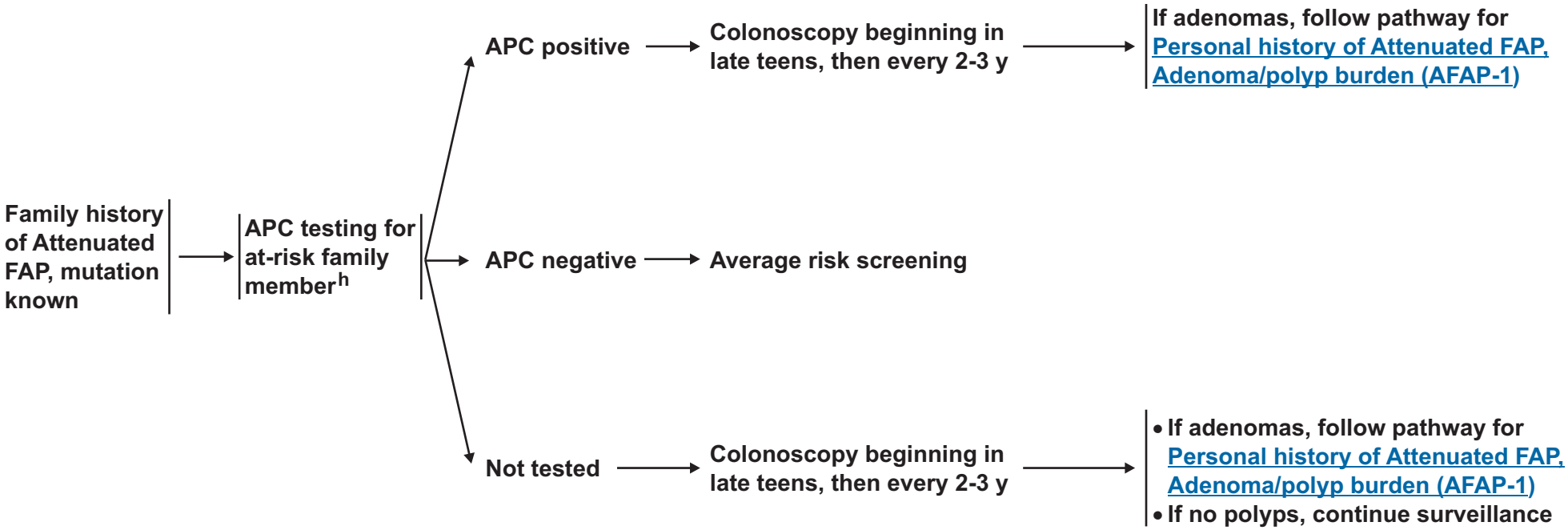
[g] Surveillance for upper GI findings for attenuated FAP is similar to classical FAP.

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

Version 2.2011, 10/22/10 © National Comprehensive Cancer Network, Inc. 2010, All rights reserved. **The NCCN Guidelines™ and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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



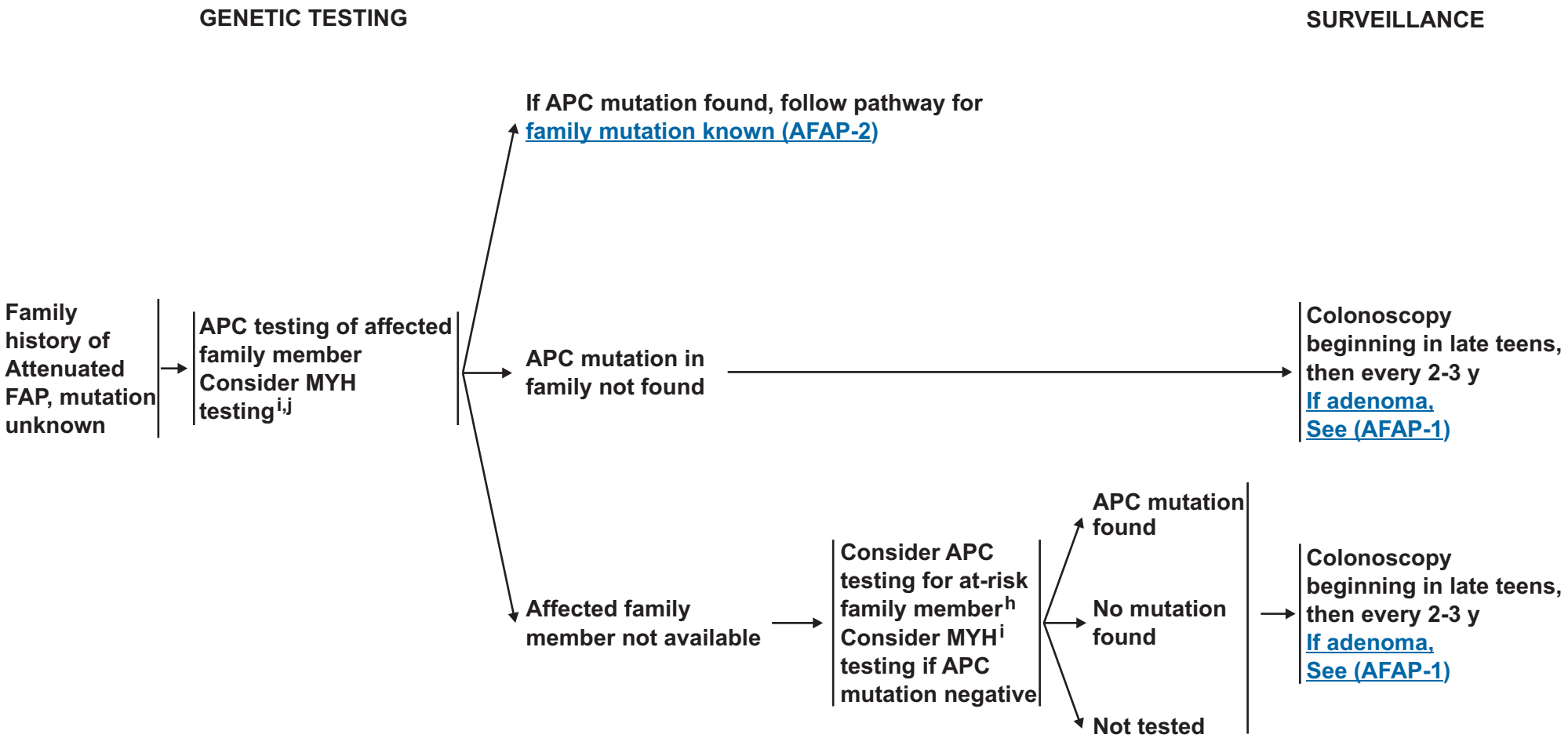
[h] At-risk family member can be defined as a first-degree relative of an affected individual and/or proband. If a first-degree relative is unavailable or unwilling to be tested, more distant relatives should be offered testing for the known mutation in the family.

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 2.2011, 10/22/10 © National Comprehensive Cancer Network, Inc. 2010, All rights reserved. **The NCCN Guidelines™ and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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



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

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

[j] When polyposis is present in a single person with negative family history, consider testing for a *de novo* APC mutation; if negative, follow with testing for MYH. When family history is positive only for a sibling, 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.

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 2.2011, 10/22/10 © National Comprehensive Cancer Network, Inc. 2010, All rights reserved. **The NCCN Guidelines™ and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

National Comprehensive Cancer Network®

NCCN Guidelines™ Version 2.2011
MYH-associated Polyposis

PHENOTYPE

MYH -associated polyposis (MAP)

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

RISK ASSESSMENT

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

See MYH-Associated Polyposis (MAP-2)

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

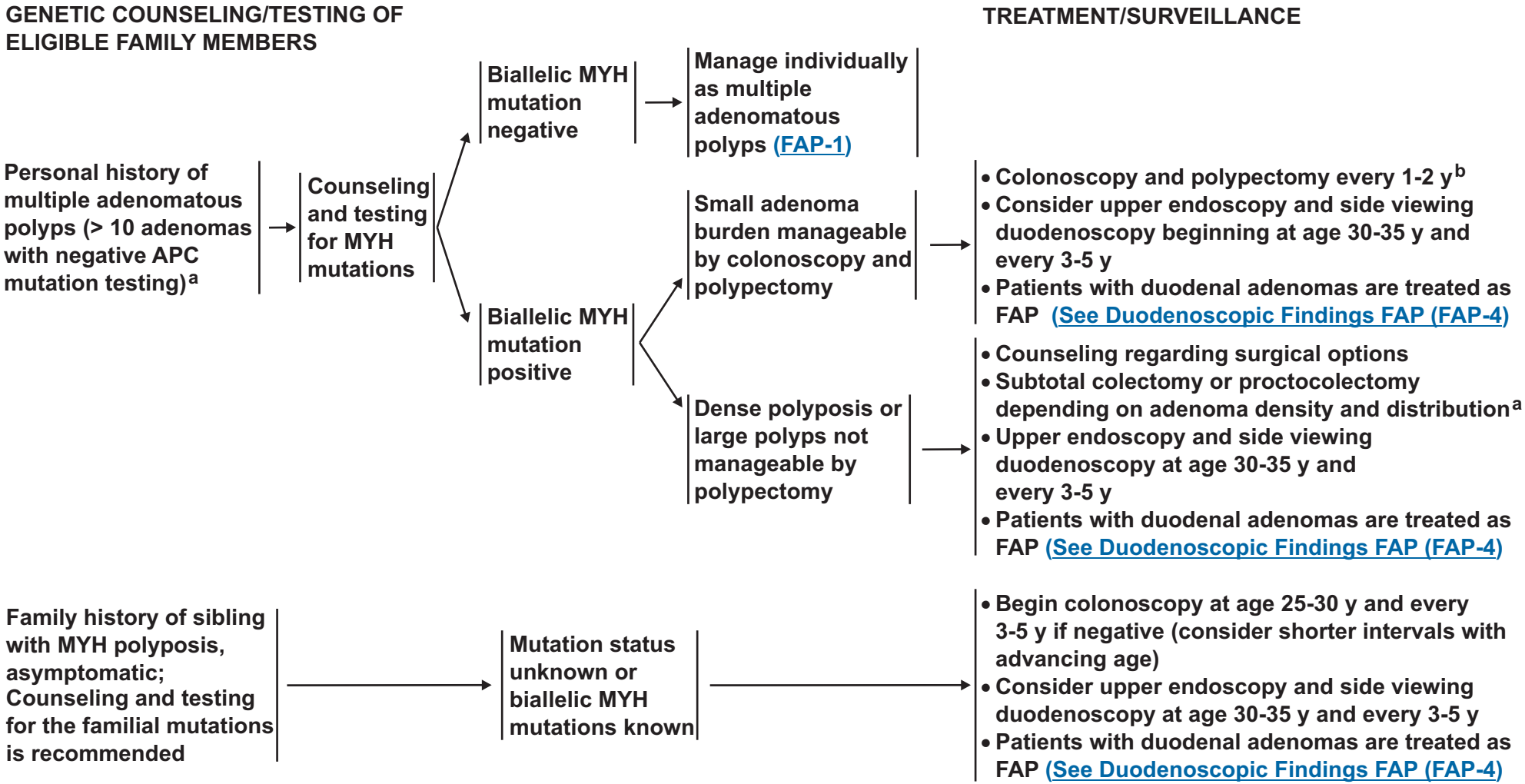
Version 2.2011, 10/22/10 © National Comprehensive Cancer Network, Inc. 2010, All rights reserved. **The NCCN Guidelines™ and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

National Comprehensive Cancer Network®

NCCN Guidelines™ Version 2.2011
MYH-associated Polyposis

NCCN Guidelines Index
Colorectal Screening TOC
Discussion



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

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

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 2.2011, 10/22/10 © National Comprehensive Cancer Network, Inc. 2010, All rights reserved. **The NCCN Guidelines™ and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

Peutz-Jeghers syndrome (PJS) Definition:[1,2]

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

Surveillance considerations:

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

See Cancer Risk and Surveillance Guidelines (PJS-2)

[1] Tomlinson IP, Houlston RS: Peutz-Jeghers syndrome. J Med Genet 1997; 34(12):1007-1011.

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

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

Version 2.2011, 10/22/10 © National Comprehensive Cancer Network, Inc. 2010, All rights reserved. **The NCCN Guidelines™ and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

Peutz-Jeghers Syndrome: Cancer Risk and Surveillance Guidelines

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

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

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

Version 2.2011, 10/22/10 © National Comprehensive Cancer Network, Inc. 2010, All rights reserved. **The NCCN Guidelines™ and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

NCCN Guidelines™ Version 2.2011
Juvenile Polyposis Syndrome

NCCN Guidelines Index
Colorectal Screening TOC
Discussion

Juvenile Polyposis Syndrome (JPS) Definition:[1]

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

Surveillance considerations:

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

Juvenile Polyposis Syndrome: Cancer Risk and Surveillance Guidelines

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

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

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 2.2011, 10/22/10 © National Comprehensive Cancer Network, Inc. 2010, All rights reserved. **The NCCN Guidelines™ and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

NCCN Guidelines™ Version 2.2011
Hyperplastic Polyposis Syndrome

NCCN Guidelines Index
Colorectal Screening TOC
Discussion

Hyperplastic Polyposis Syndrome Definition:[1]

- **A clinical diagnosis of hyperplastic polyposis is considered in an individual who meets at least one of the following criteria:**
  - **> 20-30**[2] **cumulative hyperplastic polyps distributed throughout the colon**[3]
  - **> 5 hyperplastic polyps proximal to the sigmoid colon with 2 > 1 cm**
  - **> 1 hyperplastic polyp proximal to the sigmoid colon and a first degree relative with hyperplastic polyposis**
- **HPS is rarely inherited**

Surveillance recommendations for individuals with hyperplastic polyposis:

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

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

- **The risk of colorectal cancer in relatives of individuals with hyperplastic polyposis is still unclear.**
- **First-degree relatives should be encouraged to undergo average risk screening colonoscopy. Increased screening may be warranted for individuals with a family history of multiple adenomas and/or colorectal cancer.**

[1] Sessile serrated polyps, traditional serrated polyps and/or mixed adenomas can be substituted for hyperplastic polyps in all parts of the definition.
[2] The total number of polyps necessary to make a diagnosis of hyperplastic polyposis is unclear. A lower threshold of polyps (> 20) has also been used to make a diagnosis of hyperplastic polyposis.
[3] Multiple hyperplastic polyps localized to the rectal sigmoid is unlikely to be hyperplastic polyposis syndrome.

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

Version 2.2011, 10/22/10 © National Comprehensive Cancer Network, Inc. 2010, All rights reserved. **The NCCN Guidelines™ and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

Discussion

NCCN Categories of Evidence and Consensus

Category 1: The recommendation is based on high-level evidence (e.g. randomized controlled trials) and there is uniform NCCN consensus.

Category 2A: The recommendation is based on lower-level evidence and there is uniform NCCN consensus.

Category 2B: The recommendation is based on lower-level evidence and there is nonuniform NCCN consensus (but no major disagreement).

Category 3: The recommendation is based on any level of evidence but reflects major disagreement.

All recommendations are category 2A unless otherwise noted.

Overview

Colorectal cancer (CRC) is the third most frequently diagnosed cancer in men and women in the United States. In 2010, an estimated 102,900 new cases of colon cancer and 39,670 new cases of rectal cancer will occur in the United States. During the same year, it is estimated that 51,370 people will die from colon and rectal cancer.[1, 2] Patients with localized colon cancer have a 90% five-year survival rate.

CRC mortality can be reduced both by early diagnosis and by cancer prevention through polypectomy.[3-5] Hence the goal of CRC screening is to detect cancer at an early, curable stage as well as detecting and removing adenomatous polyps. Screening tests that can detect both early cancer and adenomatous polyps are encouraged, although the panel recognized that patient preference and resource accessibility play a large role in test selection. According to the Centers for Disease Control and Prevention (CDC), the screening rate among U.S. adults aged 50-75 years has increased from 52% in 2002 to 63% in 2008.[6]

Current technology falls into two broad categories: structural tests and stool/fecal-based tests.[7] While some techniques are better established than others, panelists agreed that any screening is better than none.

Structural Screening Tests

Structural tests are able to detect both early cancer and adenomatous polyps using endoscopic or radiologic imaging. These have several limitations including their relative invasiveness, the need for dietary preparation and bowel cleansing, and the time dedicated to the examination (typically a day). Endoscopic exams require informed consent as well as the need for sedation and related risks including perforation and bleeding. Recently, a large cohort study of 53,220 Medicare patients between age 66 to 95 years showed that the risks of adverse events after colonoscopy increase with age.[8]

Colonoscopy

Colonoscopy is the most complete screening procedure, allowing examination of the entire large bowel as well as removal of polyps in one session. It is currently the preferred screening method and also the required procedure for confirmation of positive findings from other tests. Colonoscopy is also considered the current “gold standard” for assessment of the efficacy of other screening methods. Although there are no randomized controlled trials that directly demonstrate mortality reduction by colonoscopy, findings from case-control and cohort studies show significant impact of colonoscopy and polypectomy - estimated over 50% reduction – on CRC incidence.[9-11] Rabeneck and colleagues

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

recently reported an inverse correlation between colonoscopy use and death from CRC from a large population study involving close to 2.5 million Canadians.[12] For every 1% increase in colonoscopy rate, the risk of death decreased by 3%.

Interestingly, in a Canadian case-control study that matched each of 10,292 individuals who died of CRC to 5 controls, colonoscopy was associated with lower mortality from left-sided CRC (adjusted conditional OR = 0.33, 95% CI, 0.28-0.39) but not right-sided CRC (OR = 0.99, CI, 0.86-1.14).[13] Part of this finding may be related to significant variation in the quality of this widely-used procedure in the community which can lead to variable effectiveness.[14, 15] Recommendations made by the panel are based on the premise of complete, high quality colonoscopies as reflected by: colonoscopy to cecum, rectal retro-flexion, excellent preparation or endoscopic clearing of residual stool, sufficient distention and full 360 degree view of front and back side of all folds, withdrawal time over 10 minutes, and complete excision polyps (may require extra snare/biopsy or cautery following initial polypectomy). A recent European report on a screening program involving over 45,000 subjects confirmed the endoscopist's rate of adenoma detection as an important predictor of the risk of interval CRC (P=0.008), highlighting the need for meticulous inspection of the large intestinal tract.[16] The study did not demonstrate statistical significance with cecal intubation rate, another widely recognized quality indicator; one explanation is that the importance of this factor is restricted to the right colon, which gives rise to a small number of cancer cases. In an effort to enhance screening quality, the Quality Assurance Task Group of the National Colorectal Cancer Roundtable developed a standardized reporting system for colonoscopy.[17] The algorithm lists the common quality indicators of colonoscopy and minimum requirements of a colonoscopy report.

An optimal screening protocol should have an interval during which there is a low likelihood of developing cancer and is cost effective based on the duration of risk reduction following an initial negative colonoscopy. The general consensus is that a 10 year interval is appropriate for most individuals (average risk), although shorter intervals may be indicated depending on the completeness and quality of the colonoscopy. The panel emphasized the importance of family history in the screening scheme. Individual risk factors, the number or characteristics of polyps found, and physician judgment should also be included in the interval determination. An 1996 study reported that twenty-seven percent of individuals had adenomatous polyps identified on repeat colonoscopy a mean of 66 months after an initial negative colonoscopy.[18] Only one of 154 individuals had a polyp $\geq$ 1cm. These results suggest that an interval of repeat colonoscopy after an initial negative colonoscopy beyond 5 years is safe. Imperiale et al.[19] reported on 2436 individuals with no adenomatous polyps at baseline colonoscopy. No cancers were found at rescreening at a mean of 5.3 years later. Adenomatous polyps were identified in 16% and only 1.3% had advanced adenomatous polyps. The authors recommended a rescreening interval of 5 years or longer. Lieberman and colleagues[20] reported that advanced adenomatous polyps were found in only 2.4% of individuals on repeat colonoscopy within 5.5 years after a baseline normal colonoscopy. In this study, individuals with adenomatous polyps <1cm at baseline also had a low rate of developing advanced neoplasia.

Further studies have evaluated the durability of risk reduction 10 years after an endoscopic evaluation. An early study evaluating the value of rigid sigmoidoscopy for CRC screening compared individuals who received rigid sigmoidoscopy during the 10 years before diagnosis of colon cancer to a cohort of matched controls.[21] The negative

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

association was 0.41 risk reduction (95% CI, 0.25-0.69) in the proctosigmoidoscopy group. Singh et al.[22] also assessed the time that risk reduction persists after colonoscopy. This study was a population-based retrospective analysis utilizing a physician billing claims database of individuals who had a screening colonoscopy. Patients in the surveillance cohort were compared to the general population regarding incidence of CRC. A negative colonoscopy was associated with a standardized incidence ratio of 0.28 (95% CI, 0.09-0.65) at 10 years. A similar study calculated the adjusted relative risk of CRC among subjects with a previous negative colonoscopy.[23] The adjusted odds ratio was 0.26 (95% CI, 0.16-0.40). The low risk was seen even if the colonoscopy had been performed up to 20 or more years previously. Recently, Robertson et al reported on a study of 564 participants that combining results of two prior colonoscopies can help predict the likelihood of high-risk findings (advanced adenomatous polyps or cancers) on the third screen.[24]

Flexible sigmoidoscopy

Flexible sigmoidoscopy followed by colonoscopic polypectomy significantly reduced mortality risk in earlier case-control studies.[11, 25] A recent British report on a randomized population screening study of over 110,000 individuals attributed a 33% and 43% reduction in CRC incidence and mortality, respectively, to flexible sigmoidoscopy offered once between ages 55 and 64 compared to no screening.[26] Currently, three other randomized studies are ongoing in the United States and Europe.[27-29] Compared to colonoscopy, this technique requires no sedation and less bowel preparation, but is limited to examination of the lower half of the colon tract. Flexible sigmoidoscopy should be performed using a scope 60 cm or longer. Polyps identified should be biopsied by trained personnel to determine if they are hyperplastic, adenomatous, or sessile serrated (flat adenomatous polyps are unusual and may be missed during colonoscopy). Patients with lesions larger than 1 cm should be referred directly to colonoscopy, since they are almost always adenomatous polyps associated with a risk of proximal colonic neoplasms.

Double-contrast barium enema

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

Computed tomographic colonography

Computed tomographic (CT) colonography, also known as virtual colonoscopy, is evolving as a promising technique for CRC screening. CTC has the advantages of being non-invasive and not requiring sedation. The risk of test-related complications is also very low. However, a positive finding requires a colonoscopy, and extra colonic findings which are present in up to 16% of patients pose a dilemma.[30, 31] These findings require further investigations and have a potential for benefit as well as harm. At the present time there are no sufficient data to determine the clinical impact of these findings.

The accuracy of CT colonography in detecting polyps or cancers measuring 10 mm or more was assessed in the recently completed National CT Colonography Trial (ACRIN 6664) organized by the American College of Radiology.[32] There were 128 large adenomatous polyps or carcinomas in 109 of the 2531 patients participating in the study. CT colonography detected 90% of patients who had lesions measuring 10 mm or above found by colonoscopy. There were 18 lesions found on CT colonography, but not colonoscopy for which a subsequent colonoscopy was performed. Five of the 18 lesions were confirmed: 4 adenomatous polyps and 1 inflammatory polyp. The CT

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

colonography performance in this study was better than that reported from earlier studies[33, 34] and similar to what was reported by Pickhardt.[35]

In 2005, two meta-analysis reviewed the performance of CT colonography in the detection of colorectal polyps.[36, 37] In one meta-analysis, CT colonography showed high average sensitivity (93%) and specificity (97%), both of which decreased to 86% when medium polyps were included in the analysis. The sensitivity of CT colonography was heterogenous but improved as the polyps size increased in another meta-analysis (48% for polyps less than 6 mm, 70% for 6 to 9mm polyps and 85% for polyps larger than 9 mm. The specificity was uniform (92%) for the detection of all the polyps. Kim et al compared CT colonography with colonoscopy for the detection of advanced neoplasia.[38] Although this study was not randomized, the detection rates were comparable between the two groups (3.2% for CT colonography and 3.4% for colonoscopy).

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

The issue of radiation exposure also requires consideration. The reported dose of radiation exposure during CT colonography is about 10 mSv. The precise risk from life-long screening cannot be estimated, but it has been suggested that 1 additional person in 1000 would develop cancer in a lifetime after being exposed to radiation at the dose used for CT colonography.[39]

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

Fecal-based Screening Tests

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

Fecal occult blood test

Two fecal occult blood tests (FOBT) are currently available: guaiac-based and immunochemical. These may be used alone annually or in combination with flexible sigmoidoscopy. Based on the pseudoperoxidase activity of heme in human blood, guaiac FOBT is the most common stool test in use for CRC screening. A meta-analysis on four randomized controlled trials involving over 320,000 participants showed a 16% reduction in relative risk for CRC death with guaiac FOBT screening (95% CI, 0.78-0.90).[40] The sensitivity of different guaiac FOBT for cancer detection ranges from 37% to 79% in a study of about 8,000 candidates by Allison and colleagues.[41] The technique currently recommended is Hemoccult™ II SENSA, which is the most sensitive and “reader-friendly.” One major disadvantage for guaiac

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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

Fecal Immunochemical test (FIT), approved by the FDA in 2001, directly detects human globin within hemoglobin. Unlike guaiac FOBT, FIT does not require dietary restrictions, and a single testing sample is sufficient. However, sensitivity (25-72%) and specificity (59-97%) also vary widely for FIT as illustrated by a recent German study that assessed six different FIT methods on 1,319 participants.[42] Comparative studies generally show that FIT is on par with, if not superior to, guaiac FOBT depending on the test used. For example, in the study by Allison et al, FIT had a sensitivity of 69% for cancer, between that for Hemoccult™ II Sensa and Hemoccult™ II.[41] An update study by the same group demonstrated a higher sensitivity for cancer by a newer FIT compared to Hemoccult™ Sensa (82% vs. 64%). A Dutch randomized study also demonstrated higher detection rates of advanced neoplasia by FIT (2.4%) than guaiac FOBT (1.1%), although both were less reliable than flexible sigmoidoscopy (8.0%).[43]

To ensure adequate follow-up, a healthcare professional should coordinate FOBT testing, so that the patient who has a positive result enters the health care system in a responsible way. FOBT of a single specimen obtained at digital rectal examination is not recommended due to exceptionally low sensitivity.[44, 45] Unfortunately, a recent survey of over 1,000 primary care physicians revealed that inappropriate in-office testing is still widely used (25% used in-office testing only and 53% used both in-office and home testing), suggesting the need for strengthened education.[46]

Stool DNA Test

Stool DNA test is an emerging screening tool for CRC. It detects the presence of known DNA alterations during colorectal carcinogenesis in tumor cells sloughed into stool. Early proof-of-principle tests involving single-target marker such as K-ras produced less than 40% sensitivity.[47] In an effort to improve sensitivity, newer tests with multi-panel markers were developed. In a large multicenter study of 4404 patients, eligible subjects submitted one stool specimen for DNA analysis, underwent standard Hemoccult™ II testing, and then a colonoscopy.[48] In a subgroup analysis, the multi-target DNA assay SDT-1 (21 mutations) detected 52% of CRC compared with 13% by Hemoccult™ at specificities of 94% and 95%, respectively. The SDT-1 assay did not perform as well in another large multicenter, prospective, triple-blinded trial that also assessed a second-generation combination test SDT-2 (*APC*, *K-ras*, and vimentin methylation).[49] A total of 3,764 average-risk healthy adults underwent screening colonoscopy, Hemoccult™, Hemoccult™ Sensa, SDT-1, and SDT-2. The sensitivity of SDT-1 and Hemoccult™ Sensa was very similar for screen-relevant neoplasms (20% and 21%, respectively), whereas the sensitivity of SDT-2 was 40%.

For those unwilling or unable to have screening colonoscopy, there is increasing evidence that a stool DNA test may provide a valuable noninvasive option. However, stool DNA has not yet been approved by the FDA, and is currently not considered a first-line screening tool. More research is also necessary to determine the optimal testing interval.

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

Risk Assessment

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

Average Risk

Individuals at average risk of developing CRC are those 50 years or older with no history of adenoma, CRC, or inflammatory bowel disease, as well as negative family history, defined as not having a first-degree relative or two second-degree relatives with CRC (advanced adenoma) or multiple cases of Lynch syndrome-related cancers in the family.

Increased Risk

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

High Risk Syndromes

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

Individuals at Average Risk

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

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

If available, colonoscopy is the preferred screening modality for individuals at average risk. If the colonoscopy is incomplete, other screening methods (including double-contrast barium enema) or repeat colonoscopy should be considered based on physician judgment.

Interpretation of Findings

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

Adenoma/adenomatous polyps

Adenomatous polyps or adenomatous polyps (most often found to be tubular), the most common form of polyps, are associated with an increased risk of CRC (see following section on “Individuals at

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

Increased Risk"). Villous adenomatous polyps have a greater risk of harboring cancer and finding adenomatous polyps or cancer on follow-up.

Sessile serrated polyps and flat adenoma

Sessile serrated polyps (SSP), also known as sessile serrated adenomatous polyps, are rare forms of polyps that have been associated with adenocarcinoma. The pathologic classification is currently controversial and guidelines for screening such polyps are not clearly established. Patients with SSP may need more frequent screening than those with hyperplastic polyps. Pending additional data, individuals with SSP should be treated following the same guidelines for those with adenomatous polyps.

Flat adenomatous polyps are unusual and can be easily missed during colonoscopy because they are not protruding from the colon wall.[50] More prospective studies are required to clarify their role in CRC risk. In the meantime, all flat adenomatous polyps should be removed upon identification with routine post-adenoma follow-up.

Hyperplastic polyps

A large body of literature indicates that hyperplastic polyps are not associated with significantly increased risk of CRC, and supports the recommendation that persons with hyperplastic polyps be screened as average risk. Recent literature, however, suggests that a small subset of persons with multiple or large hyperplastic polyps – the hyperplastic polyposis syndrome (HPP) - have a 26% to 70% risk of CRC.[51-53] The majority of these had concomitant adenomatous polyps or SSP.[54] Additionally, there is evidence suggesting that some cancers with extensive DNA methylation and microsatellite instability might derive from hyperplastic polyps.[55] Based on these observations, all hyperplastic polyps larger than 5 mm should be removed during the initial colonoscopy and polypectomy session, followed by colonoscopy every 1 to 3 years. Ideally, all detected polyps should be removed, but this is not always possible. Removed polyps should also be examined for degree of dysplasia, as well as for histological features of SSP. HPP is rarely reported to be inherited, and the CRC risk of individuals with affected relatives remains unclear.

Individuals at Increased Risk

Personal History of Adenoma/SSP

Individuals with adenomatous polyps are at increased risk for recurrent adenomatous polyps and CRC. To minimize the risk of developing CRC, a surveillance program is recommended for patients with adenomatous polyps following screening colonoscopy and complete polypectomy.[56] For patients with a completely resected adenomatous polyp, the surveillance schedule depends on the risk of recurrence, which in turn is related to the number of adenomatous polyps, their size and histology.

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

Advanced or multiple adenomatous polyps (3-10 polyps, 10 mm or larger with greater than 25% villous histology or high-grade dysplasia) have been associated with increased risk. High-grade dysplasia is defined as an adenoma that shows features of severe dysplasia (marked reduction of interglandular stromas with complex irregularity of glands, papillary infolding and cytogenetic abnormalities) or carcinoma in situ (severe architectural disturbance of glands along with cytological

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

features of dysplasia).[57] Carcinoma in situ is a term previously used by pathologist to describe colon polyps and cancer and is currently being replaced by the term high-grade dysplasia. A study by Golembeski and colleagues has shown that the identification of villous architecture and high-grade dysplasia is associated with poor reproducibility among pathologists.[58]

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

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

Polypectomy of large sessile polyps is associated with a high rate of recurrence, attributed to the presence of residual adenoma tissue at the time of polypectomy.[59] Hence, follow-up colonoscopy, within 2 to 6 months is appropriate in this setting, or when polypectomy is incomplete or involves removal of large sessile polyps.

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

Personal History of Colorectal Cancer

Individuals with a personal history of CRC who had undergone colonic resection with a curative intent are at increased risk for recurrent adenomatous polyps and cancer. The recommendation for intensive surveillance immediately following resection is based on studies that found a high recurrence rate in the 4 to 5 years following CRC resections.[60-63]

An analysis of 3278 patients with resected stage II and III CRC found that recurrence rate is especially high in the immediate 5 years following surgery, suggesting that intense surveillance be considered during that period (Intergroup 0089 study).[60] However, the studies did not exclude patients with Lynch syndrome who are at greater than 30% risk for synchronous and metachronous cancers. The guidelines recommend a complete colonoscopy preoperatively as well as at 1 year following surgery (within 3 to 6 months if preoperative colonoscopy was incomplete). If this examination is normal, colonoscopy should be repeated in 2 to 3 years. Shorter intervals (1 to 3 years) are recommended if adenomatous polyps or SSP are found. Subsequent colonoscopic intervals are individualized and generally should not exceed 5 years.

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

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

Inflammatory Bowel Disease

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

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

Family History

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

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

Positive Family History

Individuals with one or more first-degree relative (FDR) diagnosed with CRC are at increased risk for the malignancy. Colonoscopy every 5 years beginning at age 40 is recommended for persons with an FDR diagnosed with CRC between age 50 to 60. If the diagnosis was made at age 60 or over, screening should begin at age 50 and repeated every 5 years. The same screening schedule is recommended if there are two second-degree relatives diagnosed with CRC at any age.

For individuals with an FDR diagnosed with CRC before age 50 or two FDRs diagnosed with CRC at any age, screening colonoscopy beginning at age 40 or 10 years prior to earliest CRC in family, whichever is earlier, is recommended. Screening interval will depend on other family history but should be between every 3 to 5 years. Additionally, such a family history (or if any of the revised Bethesda criteria are met) suggests the possibility of Lynch syndrome and IHC/MSI testing on the colon tumor of the youngest affected family member is warranted.

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

Individuals who have FDR with advanced adenoma(s) may confer some CRC risk as in FDR with CRC. Similarly, having an FDR with early-onset adenoma(s) (under age 40) may confer similar CRC risk as having an FDR with early-onset CRC (under age 50).

Persons who have a second-degree or any number of third-degree relative(s) with CRC or individuals with FDR with non-advanced adenoma(s) are screened as average-risk individuals, with colonoscopy as the preferred method. 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.

In all cases, further risk evaluation and counseling as outlined on HRS-1 is required for patients who meet the criteria for an inherited CRC syndrome.

Inherited Colon Cancer

Genetic susceptibility to CRC includes well-defined inherited syndromes such as Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer, or HNPCC), familial adenomatous polyposis (FAP), and MYH-associated polyposis (MAP).

Other entities that are important to recognize include suspected colon cancer syndromes, such as Muir-Torre, Turcot, Gardner, Cowden, Bannayan-Riley-Ruvalcaba, Peutz-Jeghers syndromes, juvenile polyposis, and HPP.[64-66] Although increasing genetic research has rendered some of these terms obsolete, the panel recognized that they are still being widely used in the community. Inherited syndromes are critical to understanding what could be the potential genetic basis for cancer in the family. If there is a concern about the presence of a hereditary syndrome, the guidelines recommend referring the patient to a genetic service or genetic counselor.

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

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

Lynch Syndrome (Hereditary Nonpolyposis Colorectal Cancer)

Lynch syndrome is the most common form of a genetically determined colon cancer predisposition, accounting for 2% to 3% of all CRC cases.[67, 68] This hereditary syndrome results from germline mutations in DNA mismatch repair (MMR) genes (MLH1, MSH2, MSH6 and PMS2), although associations with three other genes (MLH3, PMS1, EXO1) have also been found. MMR mutations are detected in more than half of persons meeting the clinical criteria of Lynch syndrome, and the lifetime risk of CRC approaches 80% in affected individuals carrying a mutation in one of these genes.[69] Microsatellite instability (MSI) occurs in 85% to 90% of resulting CRCs. [70] Surveillance has been shown to reduce the risk of CRC and may be of benefit in the early diagnosis of endometrial cancer.[71, 72] Site-specific evaluation and heightened

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

attention to symptoms is also advised for other cancers that occur with increased frequency in affected persons, including gastric, ovarian, pancreas, urethral, brain (glioblastoma), and small intestinal cancers, as well as sebaceous gland adenomatous polyps and keratoacanthomas, though efficacy of surveillance for these sites has not been clearly demonstrated (reviewed by Lindor et al[72]).

Risk factors for the presence of Lynch syndrome related to the extended family history in an individual are listed on LS-1. Due to the high risk for CRC in a person with the syndrome, intensive screening is essential, though the exact interval has not been fully established in clinical trials. The recommendations in this area are based on the best evidence available to date, but more data are still needed.

Molecular Work-up and Genetic Testing

Molecular testing for Lynch syndrome is somewhat complicated because several different genes contribute to its development. MSI and immunohistochemical (IHC) analysis done on CRC specimens are frequently first used to identify individuals who might have Lynch syndrome.[73] IHC analysis is used to detect the protein expression of the four MMR genes in tumor tissue. If one of the genes is not expressed, then underlying dysfunction of that gene is indicated. Both MSI and IHC have false negative rates of 5% to 10%. Some studies have shown that both IHC and MSI are cost-effective and useful for selecting high-risk patients who may have MLH1, MSH2 and MSH6 germline mutations.[74, 75] However, conclusive data are not yet available that establishes which strategy is optimal.[76-80]

MSI analysis of colon cancer tissue is very sensitive but less specific than IHC testing. The classical Bethesda guidelines provide several criteria for testing colorectal tumors for microsatellite instability.[81] The National Cancer Institute introduced the revised Bethesda guidelines in 2002 to clarify selection criteria for the MSI testing.[82] Bethesda guidelines are useful for the detection of which individuals should have MSI testing, leading to subsequent identification of MLH1 and MSH2 germline mutations. One study reported that MLH1 and MSH2 mutations were detected in 65% of the patients with MSI of the colon cancer tissue who met the Bethesda criteria.[83]

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

IHC analysis is usually performed for family members that meet the Amsterdam criteria I or II, since there is a 50% to 92% chance of identifying a mutation in one of the four MMR genes in these individuals.[73] The first version of the minimum criteria for clinical definition of HNPCC (Amsterdam criteria) was introduced in 1991, and these criteria were modified (Amsterdam II criteria) in 1999.[84] MMR gene mutations are found in 88% of patients with MSI-positive tumors and who meet the Amsterdam criteria.[85] Among patients with MSI-negative tumors, only 29% were found to have germline MMR gene mutations. Some centers now perform IHC (and sometimes MSI) testing on all CRCs and endometrial cancers to determine which patients should have genetic testing for Lynch syndrome. The cost effectiveness of this approach has been confirmed for CRC and this approach was endorsed by the Evaluation of Genomic Applications in Prevention and Practice (EGAPP) working group at the CDC.[86] If Lynch syndrome is suspected based on the extended pedigree, an analysis of the tumor block for MSI provides diagnostic information, as well as

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

guidance regarding the likelihood of informative predictive testing. Screening for MSI is cost-effective for patients with newly diagnosed CRC as well as for the siblings and children of mutation carriers.[87]

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

[88-90]There are many other issues involved in the genetic counseling process of individuals for presymptomatic testing for cancer susceptibility. A fair number of individuals elect not to undergo testing, and it is important to counsel these individuals so they continue with increased surveillance.

Testing Criteria and Strategy

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

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

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

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

Surveillance

The NCCN panel had an extensive discussion on the surveillance schemes for individuals with Lynch syndrome. These patients are at an increased lifetime risk compared to the general population for CRC (80% vs. 6% respectively), endometrial cancer (20-60% vs. 3% respectively), and other cancers.[91, 92] Existing screening study data in the literature is mainly on colon and endometrial cancers. More data are needed to evaluate the risk and benefits of extracolonic cancer screening and recommendations are based on expert opinion.

If Lynch syndrome can be confirmed, colonoscopy is advised to start between the ages of 20 to 25 or 2 to 5 years younger than the youngest diagnosis age in the family, whichever comes first, to be repeated every

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

1 to 2 years. This recommendation is based upon a systematic review of data between 1996 and 2006 on the reduction in cancer incidence and mortality by colonoscopy.[72] Women with Lynch syndrome are at heightened risk for endometrial and ovarian cancers (about 60% and 7%, respectively).[72, 92] Education that enhances alert to relevant symptoms is advised. Total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH/BSO) is an option that should be considered for risk reduction for women who have completed child-bearing. Strong evidence is lacking to support routine screening for gynecological cancers. Annual endometrial sampling is a strategy that may be useful at the clinician's discretion. Routine transvaginal ultrasound is not endorsed, but the panel recognized that there may be circumstances where the clinician may find it helpful.

The lifetime risk for gastric cancer varies widely with the population, from under 10% to 30%.[72, 93] Most cases occur after age 40, and males have a stronger predisposition. Starting at age 30 to 35, consider upper gastrointestinal endoscopy extended to the distal duodenum and jejunum plus polypectomy as required every 2 to 3 years. Some additional measures that may be considered include: baseline gastric biopsies and adjustment of surveillance intervals based on histological findings, H. pylori evaluation and treatment if positive, and enteroscopy at the time of endoscopy. Lynch syndrome is also associated with a 4% risk for small bowel cancer.[94-96] Non-invasive capsule endoscopy to screen for this cancer should also be considered at a similar interval as for gastric cancer.[96]

Annual urinalysis should also be considered to screen for urothelial cancers, giving the relative ease and low cost compared to other tests. Due to the current lack of data, annual history and physical examination is appropriate for other cancers (eg, brain and pancreatic).

Surveillance Findings and Follow-up

If there are no pathologic findings, continued surveillance is recommended. If the patient is not a candidate for routine surveillance, subtotal colectomy may be considered. This important feature comes up clinically often because some people cannot undergo a colonoscopy or decline to have one on a regular basis.

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

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

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

Familial Adenomatous Polyposis

FAP is an autosomal dominant condition characterized by a germline mutation in the APC gene, located on chromosome 5q21.[97] Although FAP accounts for less than 1% of all CRC, its importance has been

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

recognized as a paradigm for treating individuals at increased risk of cancer.

Diagnosis: Classical vs Attenuated FAP

Diagnosis of classical FAP is based on the presence of over 100 polyps or fewer polyps at younger ages especially in a patient with a family history of FAP.[97] When fully developed, patients exhibit hundreds to thousands of colonic adenomatous polyps. The lifetime risk of cancer in individuals with classic FAP approaches 100% by the age of 50. Most of the resulting cancers occur in the left colon. 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 usually indicated in the second decade.

Attenuated FAP is a recognized variant of FAP characterized by a later onset of disease and fewer adenomatous polyps, typically less than 100.[97] These adenomatous polyps are more prone to occur in the right colon and may take the form of diminutive sessile adenomatous polyps.[98] Phenotypic expression is often variable within families. The onset of CRC is typically delayed, but the incidence of cancer rises sharply after the age of 40 and approaches 70% by age 80.

Management of FAP includes early screening and colectomy or proctocolectomy after the onset of polyposis. Genetic testing can guide management of cancer risk in patients and their family members. It is important to note the distinction between individuals with a personal history of FAP and individuals who are considered at high risk based on a family history of FAP (but no symptoms or findings). This distinction makes a significant difference in clinical management. Again, at-risk family member can be defined as an FDR of an affected individual and/or proband. If an FDR is unavailable or unwilling to be tested, more distant relatives should be offered testing for the known family mutation.

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 bi-allelic inactivation of the APC gene, and often display foci of dysplasia or microadenomatous polyps of the foveolar epithelium.[99] 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 adenomatous polyps. It is also recommended that polyps in the antrum or immediate pre-antrum should be removed if possible. These are less common and are often adenomatous polyps.

Surgical Options

Three different surgical options are available for individuals with classical and attenuated FAP.[100] The prime factors when choosing an operation for FAP are the personal and familial phenotype, including the rectal polyp burden and whether colon or rectal cancer is present at diagnosis. In patients presenting with the classical FAP phenotype, proctocolectomy, if possible, is the procedure of choice, since it prevents both colon and rectal cancer.

Total proctocolectomy with ileal pouch anal anastomosis (IPAA)

Total proctocolectomy with ileal pouch anal anastomosis (IPAA), usually with a temporary loop ileostomy, is offered to patients with classical FAP, patient with attenuated FAP with severe phenotypes resulting in carpeting of the rectum, patients with curable colon or rectal cancer complicating the polyposis, and patients who underwent

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

ileorectal anastomosis and now have an unstable rectum in terms of polyp number, size, or histology. The operation is generally not offered to patients with incurable cancer, those with an intra-abdominal desmoid that may interfere with the completion of surgery, or patients who have an anatomic, physiologic, or pathologic contraindication to an ileal pouch anal anastomosis. The advantages of this operation are that the risks of developing rectal cancer are negligible and a permanent stoma is not needed. The disadvantages are that it is a complex operation, a temporary stoma is usually needed, and it carries a small risk of bladder and sexual dysfunction after proctectomy. Functional results can be unpredictable. Bowel function, although usually reasonable, is also somewhat unpredictable. The ileal pouch requires surveillance, and the area of the ileal pouch anal anastomosis should still be examined due to the imperfect nature of mucosectomy. The remaining controversy over the choice of total abdominal colectomy with ileorectal anastomosis versus total proctocolectomy with IPAA centers on the issues of the relative quality of life.[101-106] A modest reduction in life expectancy is expected in patients with classical FAP with rectal preservation.[107, 108] Proctoscopic examination of a retained rectum is indicated annually.

Total abdominal colectomy with ileorectal anastomosis (IRA)

A total abdominal colectomy with ileorectal anastomosis is a fairly quick, straightforward operation with an overall low morbidity rate. It generally results in good bowel function. Most patients have 3 to 4 bowel movements per day, and the risk of urgency, seepage, or fecal incontinence is low. Without proctectomy, there should be no risk of bladder or sexual function problems, and even a temporary stoma is obviated. The major disadvantages of total abdominal colectomy with IRA are the high risk of rectal cancer development and associated morbidity and mortality, the frequent need to undergo subsequent proctectomy because of severe rectal polyposis, and the real need for regular endoscopic surveillance of the retained rectum (every 6-12 months). Review of 659 patients in the Dutch-Scandinavian collaborative national polyposis registries who underwent colectomy with IRA found a high rate of advanced and fatal rectal cancers even though 88% of the patients underwent a diagnostic proctoscopy within 18 months of presentation. It was estimated that 12.5% of patients undergoing this procedure would die of rectal cancer by age 65 even if compliant with endoscopic screening.[109] The authors concluded that proctocolectomy is the preferred procedure for most patients with the classical FAP phenotype, though some controversy remains regarding this choice. They and others also observed that patients could not be reliably selected for colectomy based on genotype alone. However, studies have reported that the risk of rectal cancer associated with total abdominal colectomy and IRA has declined since the 1980s when IPAA first became available for high-risk patients with severe polyposis.[110, 111]

On the other hand, ileorectal 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. Patients and families must be absolutely reliable for follow-up endoscopic examinations. The risk to the rectal stump rises considerably after the age of 50 and if the rectum becomes unstable, a proctectomy with either an IPAA or end ileostomy is recommended.[112]

Total proctocolectomy with ileostomy (TPC)

A total proctocolectomy with end ileostomy is rarely indicated as a prophylactic procedure because good options are available that do not involve a permanent stoma, which has implications for the patient and the family. Fear of a permanent stoma may make family members reluctant to undergo screening. The operation removes all risk of colon

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

and rectal cancer, but is associated with the risk of bladder or sexual function disorders. This operation may be offered to patients with a low, locally advanced rectal cancer, patients who cannot have an ileal pouch due to a desmoid tumor, patients with a poorly functioning ileal pouch, and patients who have a contraindication for an ileal pouch anal anastomosis (eg, concomitant Crohn's disease, poor sphincter function).

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

Surveillance following surgery

It is recommended that physicians or centers with expertise in FAP should manage patients and the management should be individualized based on genotype, phenotype and other personal considerations. The surveillance interval should be adjusted according to the actual polyp burden. Patients with retained rectum should undergo endoscopic rectal examination every 6 to 12 months. If all of the colorectal tract has been removed, the ileal pouch or ileostomy should be evaluated endoscopically every 1 to 3 years; this should be increased to every 6 months if large flat polyps with villous histology and/or high-grade dysplasia are found. Chemoprevention may be considered (see section below).

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

A major surveillance in patients with a personal history of FAP or attenuated FAP after surgery relates to the upper gastrointestinal tract. Most classical and attenuated FAP patients will develop duodenal adenomatous polyps that can become cancerous (see section below on duodenoscopic findings). On the other hand, fundic gland polyps commonly arising in the stomach of FAP patients rarely progress. High-grade dysplasia that may warrant special screening is also uncommon on these gastric polyps. Baseline upper endoscopy including side-viewing, repeated every 1 to 3 years, is adequate surveillance for both duodenal and gastric cancers.

Patients with classical FAP also have elevated risk for developing other extra-colonic cancers that warrants attention during surveillance.[113] In the absence of rigorous data, there was extensive discussion among panelists on this area, as in the case of Lynch syndrome. Patients are at heightened risk for thyroid cancer with a lifetime risk of approximately 2% and female predominance (95%).[113] Peak incidence is in the third decade of life with a mean age of around 30 years. Yearly thyroid physical examination is recommended and is considered adequate for timely diagnosis and treatment. Annual thyroid ultrasound may be considered to supplement physical examination, although supportive data is lacking. There is also an increased risk of intra-abdominal desmoid tumors, the majority of which present within 5 years of colectomy. Since significant morbidity and mortality are associated with advanced tumors, early diagnosis is likely of benefit.[114] Annual abdominal palpation during physical examination is advised. If family history of symptomatic desmoids is present, consider abdominal CT or MRI every 1 to 3 years post-colectomy and immediately if suggestive

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

abdominal symptoms are present. Data on screening for small bowel polyps and cancer is lacking but adding small bowel visualization to CT or MRI for desmoids can be considered. The risk of hepatoblastoma is much higher in young children predisposed to FAP.[115] Although the absolute risk is about 1.5%, given the lethality of the disease (25% mortality), active screening by liver palpation, ultrasound and AFP measurements every 3 to 6 months during the first five years of life may be considered. The optimal approach would be to do this screening in a clinical trial.

Medulloblastoma accounts for most of the brain tumors found in FAP patients, predominantly in females under age 20.[116] The incidence of pancreatic cancer in FAP is not well defined and likely very low. Giardiello reported 4 retrospective cases (histology not documented) out of 1391 FAP–related subjects.[117] More studies are needed to elucidate the risk and benefit of screening for brain and pancreatic cancers and no specific recommendation other than annual physical exam is made.

Duodenoscopic findings

Duodenal adenomatous polyps develop in over 90% of patients with FAP. These adenomatous polyps are classified into stages 0 to IV, as defined by Spigelman[118] based on macroscopic and histologic criteria. Duodenal cancer risk is uncommon under age 40 years, and rare under age 30 years. The cumulative risk of developing severe duodenal polyposis (stage IV) has been estimated to be around 40% by age 60.[119] The risk of duodenal cancer increases dramatically with stage IV disease.

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

Endoscopic treatment options include endoscopic papillectomy in addition to excision or ablation of resectable large or villous adenomatous polyps as well as mucosectomy of resectable advanced lesions to potentially avert surgery. The appropriate period for follow-up endoscopy relates to the burden of polyps, varying from every 4 years if no polyps are found to every 3 to 6 months for Spigelman's stage IV polyposis. Surgical evaluation and expert surveillance every 6 to 12 months is recommended for Stage IV polyps, invasive carcinoma as well as high-grade dysplasia or dense polyposis that cannot be managed endoscopically. Surgical counseling is also advisable for those with stage IV polyposis.

Chemoprevention

Nonsteroidal anti-inflammatory drugs (NSAID) have been shown to reduce the incidence and recurrence of colorectal adenomatous polyps.[120-122] Long-term follow-up is needed to more precisely determine the role of this type of therapy. Long-term use of sulindac seems to be effective in polyp regression and preventing recurrence of higher-grade adenomatous polyps in the retained rectal segment of FAP patients.[123] However, in a randomized, double-blinded placebo-controlled study, sulindac did not prevent the development of adenomatous polyps in persons with FAP.[124] NSAIDs are not effective as primary treatment of familial adenomatous polyposis. Prophylactic colectomy remains the treatment of choice to prevent CRC in patients with FAP. Chemoprevention with NSAIDs can be considered following initial prophylactic surgery for both classical and attenuated FAP, as an adjunct to endoscopic surveillance, to reduce the rectal polyp burden.

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

Cyclooxygenase-2 (COX-2) inhibitors are a form of NSAID that have been shown to be overexpressed in colorectal adenomatous polyps and cancers. International multicenter studies have been conducted to study the effect of these agents in the chemoprevention of colorectal adenomatous polyps.[125-128] Results from the Prevention of Colorectal Sporadic Adenomatous Polyps (PreSAP) trial showed that the use of celecoxib, a COX-2 inhibitor, significantly reduced the occurrence of colorectal adenomatous polyps within three years after polypectomy.[125] The Adenoma Prevention with Celecoxib trial (APC trial) showed that in patients at high risk of CRC who had their polyps removed, celecoxib significantly lowered the formation of adenomatous polyps during a three-year period.[127] Five-year safety and efficacy results showed that compared to placebo, the reduction in the incidence of advanced adenomatous polyps over 5 years was 41% for those who received lower dose of celecoxib compared to 26% in patients who received the higher dose (both $P<0.0001$).[129] However, due to the increased risk of cardiovascular events associated with their use, COX-2 inhibitors are not recommended routinely for sporadic adenomatous polyps.[130, 131]

Personal History of Classical FAP

Prophylactic surgery (proctocolectomy or colectomy) remains the primary treatment of choice for this group of individuals. Surgery is performed either at the onset of polyposis or later, depending on the severity of the familial phenotype and genotype, the extent of polyposis at diagnosis, individual considerations and local practices and expertise. Proper post-surgical surveillance should be followed as outlined in above sections. In patients who are less than 18 years with mild polyposis and without family history of early cancers or genetic disposition, timing colectomy can be individualized, but annual colonoscopy is essential.

Personal History of Attenuated FAP

Treating patients with a personal history consistent with attenuated FAP varies depending on the patient's age and adenoma burden. For young patients under age 21 with a small adenoma burden, colonoscopy and polypectomy are recommended every 1 to 2 years with appropriate surgical evaluation and counseling. In patients aged 21 and older up to 40 years with small adenomatous polyps, colectomy and IRA are alternative treatment options to colonoscopy and polypectomy. Patients over the age of 40 years should strongly consider colectomy and IRA. Even over age 40, subjects with what appears to be an endoscopically manageable adenoma burden, particularly if responsive to a chemo-preventative agent such as sulindac or celecoxib, may choose to defer consideration of colectomy. For those who have significant polyposis that is not manageable with polypectomy, colectomy with IRA is preferred, but IPAA is an option. Proctocolectomy is rarely indicated for attenuated FAP. After surgery, annual physical and thyroid examinations are recommended, and NSAID may be considered as chemoprevention. Surveillance of the rectum and upper gastrointestinal tract is similar to that for classical FAP.

Family History of Classical FAP

Management of individuals with a family history of FAP depends on whether the familial mutation is known or unknown. For those who have a family history of FAP, there are two possible situations: known specific mutation that has caused familial polyposis, or family has a history of polyposis without a known familial mutation.

Familial Mutation Known

Genetic Counseling

When the mutation responsible for FAP within a family is known, screening can be appropriately directed to those at highest risk, and

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

APC testing can be considered for at-risk family members. For those at-risk individuals, it means providing 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 Testing

Genetic testing for the APC gene in individuals with familial polyposis should be considered before or at the age of screening. The age for beginning screening should be based on the patient's symptoms, family phenotype and other individual considerations. Fatal CRC is rare before the age of 18 years.

If an APC gene mutation is found, there is virtually a 100% probability that the individual will eventually develop familial polyposis. Truncating mutation of the APC gene is detectable in about 80% of FAP patients using protein-truncating tests.[132, 133] These patients need to undergo flexible sigmoidoscopy or colonoscopy every 12 months, beginning at 10 to15 years of age.

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

No Genetic Testing

Some people who undergo genetic counseling decide, for one reason or another, not to undergo genetic testing, which influences how their screening is managed. These individuals are considered to be potentially at risk and should be offered annual flexible sigmoidoscopy or colonoscopy beginning at age 10 to15 until the age of 24. Then if results continue to be negative, screening is scaled down to every 2 years until age 34, every 3 years until age 44, and every 3 to 5 years thereafter. One should also consider substituting colonoscopy every 5 years beginning at age 20 for a chance that a patient may have attenuated FAP. There are several reasons why screening is recommended so often for these individuals. First, adenomatous polyps may begin to develop in adolescence. Most people with classic FAP present with polyps before the age of 25, so annual screening with sigmoidoscopy will detect the majority of patients with FAP. Less often, people with FAP will not develop polyps until a later age. The probability of FAP in a person without any polyps on annual screening begins to decrease with age around this time, so that screening does not need to be as frequent between the ages of 24 and 34, and can be even less frequent between the ages of 34 and 44. However, even this recommended schedule is more rigorous than screening guidelines for the general population, because serial negative examinations up to age 35 do not exclude the diagnosis of FAP. It is important to recognize that individuals with attenuated polyposis may not present until a later age and may have fewer polyps than those with classic FAP; yet enhanced screening is still warranted in these people.

Familial Mutation Unknown

In some families, mutations cannot be found with available testing technology, recognizing that the sensitivity to identify APC gene mutations is currently only about 80%. In other families, affected individuals have died or are not immediately available. Under these circumstances, APC testing should be considered for at-risk family member. If the mutation responsible for FAP within a family is not found, it is important to remember the limitations of interpreting a gene test in a presymptomatic individual. Evaluating presymptomatic individuals at risk in these families presents a difficult problem, since the mutation responsible for FAP within the family is not known. Certainly, a positive test in a presymptomatic person is informative even when the familial mutation has not been previously identified. But

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

interpreting a test in which “no mutation is found” in a presymptomatic person is not the same as a “negative test.”

By far the best approach in this situation is to attempt to identify the APC mutation in an affected family member, even if the available person is not a first-degree relative. Without this information, genetic testing in an unaffected individual offers less precision in estimating a person’s risk. If a mutation is found, then they should be managed similar to those with known familial mutations. FAP is only excluded in a person at risk whose genetic testing results indicate no mutation is found when a mutation has been previously identified in an affected family member (a “true negative” test result). Physicians have recognized this particular issue as a source of confusion and misinterpretation. Thus, it is critical that patients receive appropriate genetic counseling to avoid false-negative interpretations of test results.[134] MYH testing should be considered if APC gene mutation is negative and family is consistent with a recessive inheritance.

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

Family History of Attenuated FAP

The same genetic counseling, testing and surveillance considerations discussed previously for patients with a classical FAP family history apply to patients with a family history of attenuated FAP, except for the endoscopy approach. 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 in late teens, with repeat examinations every 2 to 3 years. Thus, the late onset and right colon involvement is accommodated in contrast to classical FAP. These recommendations apply to patients who have known gene familial mutations, those not tested, and those in which a familial mutation is not known. Individuals should continue with screening until adenomatous polyps are found, at which point they should be managed as patients with personal history of attenuated FAP.

MYH-associated Polyposis

MAP is an autosomal recessive hereditary syndrome that predisposes some individuals to attenuated adenomatous polyposis and CRC.[135, 136] It is caused by bi-allelic germline mutations in the MutY human homolog (MYH) gene. MYH is an excision repair protein responsible for excising adenine nucleotides mismatched with 8-oxo-guanine, a product of oxidative damage to DNA. Dysfunctional MYH protein can thus result in G:C to T:A transversions during DNA replication. Adenomatous polyposis is thought to result from such transversions occurring within the APC gene.

Most individuals with MAP generally have fewer than 100 polyps, although a minority can present with over 1,000. The median age of presentation is in the mid 40s to late 50s. Duodenal polyposis is reported less frequently than in FAP, and the magnitude of risk of duodenal cancer is not yet defined. Individuals with MYH mutations also require colectomy at a later age than those with FAP.

Guidelines for screening and surveillance are based on limited retrospective data.[137, 138] Balaguer et al recently reported that patients with CRC and more than 15 synchronous colorectal adenomatous polyps or those younger than 50 years might benefit from MYH genetic testing.[139]

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

NCCN guidelines recommend genetic counseling and testing for germline MYH mutations for siblings of affected patients, as well as for APC mutation-negative patients with more than 10 cumulative adenomatous polyps. Genetic testing for MYH mutations may precede APC gene testing for families in which only siblings are affected (suggesting recessive inheritance).

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

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

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

References

1. Jemal A, Siegel R, Xu J, Ward E. Cancer Statistics, 2010. CA Cancer J Clin 2010. Available at: http://caonline.amcancersoc.org/cgi/content/abstract/caac.20073v1.

2. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2009. CA Cancer J Clin 2009;59:225-249. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19474385.

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

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

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

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

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

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

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

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

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

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

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

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

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

Version 2.2011, 10/22/10 © National Comprehensive Cancer Network, Inc. 2010, All rights reserved. **The NCCN Guidelines™ and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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

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

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

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

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

21. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1736103.

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

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

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

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

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

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

28. Segnan N, Senore C, Andreoni B, et al. Baseline findings of the Italian multicenter randomized controlled trial of "once-only sigmoidoscopy"--SCORE. J Natl Cancer Inst 2002;94:1763-1772. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12464648.

29. Gondal G, Grotmol T, Hofstad B, et al. The Norwegian Colorectal Cancer Prevention (NORCCAP) screening study: baseline findings and implementations for clinical work-up in age groups 50-64 years. Scand J Gastroenterol 2003;38:635-642. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12825872.

30. Kim DH, Pickhardt PJ, Taylor AJ, Menias CO. Imaging evaluation of complications at optical colonoscopy. Curr Probl Diagn Radiol

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

2008;37:165-177. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18502324.

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

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

33. Johnson CD, Harmsen WS, Wilson LA, et al. Prospective blinded evaluation of computed tomographic colonography for screen detection of colorectal polyps. Gastroenterology 2003;125:311-319. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12891530.

34. Rockey DC, Paulson E, Niedzwiecki D, et al. Analysis of air contrast barium enema, computed tomographic colonography, and colonoscopy: prospective comparison. Lancet 2005;365:305-311. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15664225.

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

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

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

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

39. Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation BoRER, Division on Earth and Life Sciences, and National Research Council of the National Academies. Health risks from exposure to low levels of ionizing radiation: BEIR VII, Phase 2. Available at: http://www.nap.edu/catalog.php?record_id=11340. Washington, DC: The National Academies Press; 2006.

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

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

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

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

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

Version 2.2011, 10/22/10 © National Comprehensive Cancer Network, Inc. 2010, All rights reserved. **The NCCN Guidelines™ and this illustration may not be reproduced in any form without the express written permission of NCCN®.**

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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

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

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

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

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

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

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

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

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

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

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

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

57. O'Brien MJ, Winawer SJ, Zauber AG, et al. The National Polyp Study. Patient and polyp characteristics associated with high-grade dysplasia in colorectal adenomas. Gastroenterology 1990;98:371-379. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2403953.

58. Golembeski C, McKenna B, Appelman HD. Advanced adenomas: Pathologists don't agree. Modern Pathology 2007;20:115A. Available at:

59. 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

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

2002;56:333-338. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12196768.

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

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

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

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

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

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

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

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

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

69. Chung DC, Rustgi AK. The hereditary nonpolyposis colorectal cancer syndrome: genetics and clinical implications. Ann Intern Med 2003;138:560-570. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12667026.

70. Loukola A, Eklin K, Laiho P, et al. Microsatellite marker analysis in screening for hereditary nonpolyposis colorectal cancer (HNPCC). Cancer Res 2001;61:4545-4549. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11389088.

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

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

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

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

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

89. Barnetson RA, Tenesa A, Farrington SM, et al. Identification and survival of carriers of mutations in DNA mismatch-repair genes in colon

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

cancer. N Engl J Med 2006;354:2751-2763. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16807412.

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

91. Kohlmann W, Gruber S. Hereditary Non-Polyposis Colon Cancer. GeneReviews at GeneTests: Medical Genetics Information Resource 2004-2006. Available at: http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=hnpcc.

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

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

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

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

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

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

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

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

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

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

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

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

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

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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

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

121. Chan AT, Giovannucci EL, Meyerhardt JA, et al. Long-term use of aspirin and nonsteroidal anti-inflammatory drugs and risk of colorectal cancer. JAMA 2005;294:914-923. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16118381.

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

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

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

125. Arber N, Eagle CJ, Spicak J, et al. Celecoxib for the prevention of colorectal adenomatous polyps. N Engl J Med 2006;355:885-895. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1310269.

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

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

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

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

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

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

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

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

134. Giardiello FM, Brensinger JD, Petersen GM, et al. The use and interpretation of commercial APC gene testing for familial adenomatous

Printed by Jorge Garc?a on 12/30/2010 8:47:10 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

polyposis. N Engl J Med 1997;336:823-827. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9062090.

135. Al-Tassan N, Chmiel NH, Maynard J, et al. Inherited variants of MYH associated with somatic G:C-->T:A mutations in colorectal tumors. Nat Genet 2002;30:227-232. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11818965.

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

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

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

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