National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Genetic/Familial High-Risk Assessment: Colorectal

Version 2.2015

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NCCN Guidelines Panel Disclosures

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

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

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

See NCCN Categories of Evidence and Consensus.

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Updates in Version 2.2015 of the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal from Version 1.2015 include:

MS-1

- **The discussion section was updated to reflect the changes in the algorithm.**

Updates in Version 1.2015 of the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal from Version 2.2014 include:

High-Risk Colorectal Cancer Syndromes

HRS-1

- **Last criterion was expanded by adding, "Individual with a desmoid tumor, *cribriform-morular variant of papillary thyroid cancer, or hepatoblastoma."***
- **Footnote was removed, "Referral to a specialized team is recommended."**

Lynch Syndrome

LS-1

- **Clinical Testing Criteria for Lynch Syndrome (based on personal and family history)**
  - **For risk status, no criteria met, the strategy was revised, "Individual management, ~~Colonoscopic monitoring~~ *CRC screening* based on individual risk assessment." (Also for LS-2)**
  - **For risk status, no known LS mutation with tumor available, the testing strategy was revised, "Tumor testing (See LS-A) ~~consider both~~ *with* IHC and/*or* MSI."**

LS-2

- **Routine Tumor Testing Criteria for Lynch Syndrome**
  - **For risk status, tumor available, the testing strategy was revised, "Tumor testing (See LS-A) ~~consider~~ *with* IHC and/*or* MSI."**

LS-3

- **The title "Lynch Syndrome Management" was added to the page. (Also for LS-4).**
- **Surveillance**
  - **Extracolonic, last bullet regarding breast cancer surveillance was revised, "There have been suggestions that there is an increased risk for breast cancer in LS patients; however, *there is not enough evidence to support increased screening above average-risk breast cancer screening recommendations* ~~due to limited data no screening recommendation is possible at this time~~."**

LS-4

- **Bullets regarding risks to relatives and reproductive options were added.**

Lynch Syndrome (continued)

LS-A 2 of 3

- **The table for "Tumor Testing Results and Additional Testing Strategies" was extensively revised.**

LS-A 3 of 3

- **Footnote "c" was revised by adding, "...*or additional features of hereditary cancer syndromes (multiple colon polyps) are* ~~is~~ present,..."**
- **Footnote "d" was extensively revised.**
- **Footnote "f" was added, "Germline LS genetic testing may include testing of the gene/s that are indicated (See 'Plausible Etiologies' for possibilities) by the abnormal tumor test results, or instead multi-gene testing that includes MLH1, MSH2, MSH6, PMS2, and EPCAM concurrently may be performed."**
- **Footnote "g" was added, "Evaluation for constitutional MLH1 epimutation involves MLH1 promoter hypermethylation studies on blood or other sources of normal tissue."**
- **Footnote "h" was added, "Somatic MMR genetic testing of the corresponding gene(s) (see "Plausible Etiologies" for possibilities) could be performed on tumor DNA to asses for somatic mutations that might explain the abnormal IHC and/or MSI results."**
- **Footnote "i" was added, "Absent MSH6 in rectal tumor tissue may be due to treatment effect (neoadjuvant chemoradiotherapy)."**

LS-C

- **The following text was removed from the title of the Amsterdam Criteria I and II definitions, "Minimum Criteria for Clinical Definition of LS."**

Continued on next page

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Updates in Version 2.2015 of the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal from Version 2.2014 include:

APC and *MUTYH* Genetic Testing Criteria

APC/MUTYH-1

- APC testing criteria was revised:
  - 1st bullet, "Personal history of ~~≥10~~ *20* adenomas."
  - 3rd bullet, "*Consider testing if a* personal history of a desmoid tumor, *hepatoblastoma, cribriform-morular variant of papillary thyroid cancer, or between 10–20 adenomas.*"
- *MUTYH* testing criteria was revised:
  - 1st bullet, "Personal history of ~~≥10~~ *20* adenomas."
  - 2nd bullet, "Known deleterious ~~biallelic~~ MUTYH mutation(s) in family."
  - 3rd bullet, "*Consider testing if personal history of between 10–20 adenomas or if* individual meets *criteria 1 or 3* for SPS (see SPS-1) with at least some adenomas."
- Footnote "a" is new, "Age of onset, family history, and/or presence of other features may influence whether genetic testing is offered in these situations."
- Footnote "b" the last sentence was revised, "~~Order of testing for APC and MUTYH is at the discretion of the clinician.~~ MUTYH genetic testing is not indicated based on a personal history of a desmoid tumor, *hepatoblastoma, or cribriform-morular variant of papillary thyroid cancer*.
- Footnote "c" was revised, "Siblings of a patient with MAP are recommended to have site-specific testing for the familial ~~biallelic~~ mutations. Full sequencing of MUTYH may be considered in an unaffected parent when the other parent has MAP. I*f the unaffected parent is found to not have a MUTYH mutation, genetic testing in the children is not necessary to determine MAP status. If the unaffected parent is not tested, comprehensive testing of MUTYH should be considered in the children. If the unaffected parent is found to have one MUTYH mutation, testing the children for the familial MUTYH mutations is indicated.*" (Also for MAP-3, footnote h)

Familial Adenomatous Polyposis

FAP-1

- Personal history of classical FAP, after surveillance for colon cancer, the option for surgery was revised, "Proctectomy *or colectomy* if dense polyposis or severe dysplasia." If cancer found, a link was added to "see appropriate NCCN Guidelines for Treatment of Cancer by Site."

FAP-2

- Surveillance
  - Extracolonic, first bullet was revised, "Duodenal or periampullary cancer: *Upper endoscopy* (including side-viewing examination) *starting at age 20–25 y. Consider* baseline upper endoscopy *earlier, if colectomy before age 20 y*."

FAP-2

- Surveillance
  - Extracolonic, second bullet was revised, "Gastric cancer: Examine stomach at time of ~~duodenoscopy~~ *upper endoscopy*.
    - ◊ Fundic gland polyps occur in a majority of FAP patients, and focal *low grade* dysplasia ~~is typical~~ *can occur* but is a~~lmost invariably~~ *typically* non-progressive. For this reason, special screening or surgery should only be considered in the presence of high-grade dysplasia."

FAP-A

- Surgical Options for Treating the Colon and Rectum in Patients with FAP
  - TAC/IRA,
    - ◊ Contraindications, sub-bullet was removed, "Curable cancer in rectum."
    - ◊ Advantages, last sub-bullet was revised, "Avoids the risks of sexual or bladder dysfunction and decreased fecundity that can occur following proctectomy."
    - ◊ Disadvantages, new sub-bullet was added, "Risk of metachronous cancer in the remaining rectum"

Attenuated Familial Adenomatous Polyposis

AFAP-1

- Surveillance
  - Extracolonic, third bullet was revised to, "Upper endoscopy (including sideviewing examination) starting at age 20–25 y. Consider baseline upper endoscopy earlier, if colectomy before age 20 y" from "Baseline upper endoscopy beginning at age 25–30 y."

MUTYH-Associated Polyposis

MAP-3

- Footnote "g" was revised, "An at-risk family member can be defined as a ~~first-degree relative~~ *sibling* 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~~. *Other individuals in a family may also be at risk of having MAP or a monoallelic MUTYH mutation."*

Additional High-Risk Syndromes Associated with Colorectal Cancer Risk

ADDIT-1

- This page was added to the Guidelines and Li-Fraumeni Syndrome and PTEN Hamartoma Tumor Syndrome/Cowden Syndrome were added as examples of other syndromes that have a risk for colon cancer.

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High-Risk Colorectal Cancer Syndromes

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CRITERIA FOR FURTHER RISK EVALUATION FOR HIGH-RISK SYNDROMES

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

or

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

or

>10 adenomas in same individual (See APC/MUTYH-1)

or

Individual with multiple GI hamartomatous polyps (See PJS-1 and JPS-1 and NCCN Guidelines for Cowden Syndrome) or serrated polyposis syndrome (See SPS-1)

or

Individual from a family with a known high-risk syndrome associated with colorectal cancer (CRC), with or without a known mutation (See appropriate high-risk syndrome)

or

Individual with a desmoid tumor, cribriform-morular variant of papillary thyroid cancer, or hepatoblastoma

→

RISK ASSESSMENT/ GENETIC COUNSELING[b,c]

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

→

HIGH-RISK SYNDROME

- **LS (See LS-1)**
- **Classical familial adenomatous polyposis (FAP)**
- **Attenuated FAP (AFAP)**
- ***MUTYH*-associated polyposis (MAP)**

→ **See *APC* and *MUTYH* Genetic Testing Criteria (APC/MUTYH-1)**

- **Peutz-Jeghers syndrome (PJS) (See PJS-1)**
- **Juvenile polyposis syndrome (JPS) (See JPS-1)**
- **Serrated polyposis syndrome (SPS) (See SPS-1)**
- **No syndromes, but familial risk present** → **See NCCN Guidelines for Colorectal Cancer Screening for Positive Family History or See Colonic Adenomatous Polyposis of Unknown Etiology (CPUE-1)**

[a]Endometrial cancer <50 y is not included in the revised Bethesda Guidelines; however recent evidence suggests that these individuals should be evaluated for LS.

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

[c]Genetic counseling is highly recommended when genetic testing is offered and after results are disclosed. A genetic counselor, medical geneticist, oncologist, gastroenterologist, surgeon, oncology nurse, or other health professional with expertise and experience in cancer genetics should be involved early in counseling patients who potentially meet criteria for an inherited 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.

OBTAINING A COMPREHENSIVE ASSESSMENT FOR HEREDITARY COLORECTAL CANCER

Family history of CRC and expanded pedigree

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

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

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

Detailed medical and surgical history

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

Directed examination for related manifestations

- Colonoscopy
- Esophagogastroduodenoscopy (EGD)
- 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.

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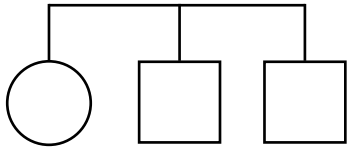
OBTAINING A COMPREHENSIVE ASSESSMENT FOR HEREDITARY COLORECTAL CANCER

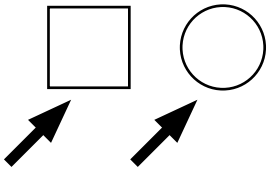
COMMON PEDIGREE SYMBOLS[2]

Male, Female

Mating

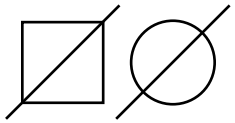


Sibship

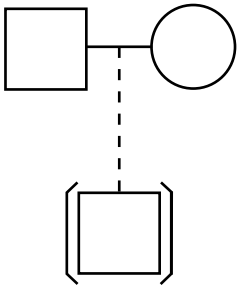


Proband (patient initiating genetic workup)

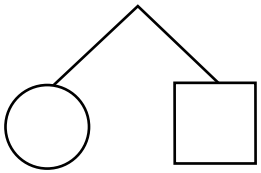
Affected with trait



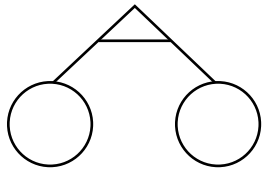
Deceased



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.

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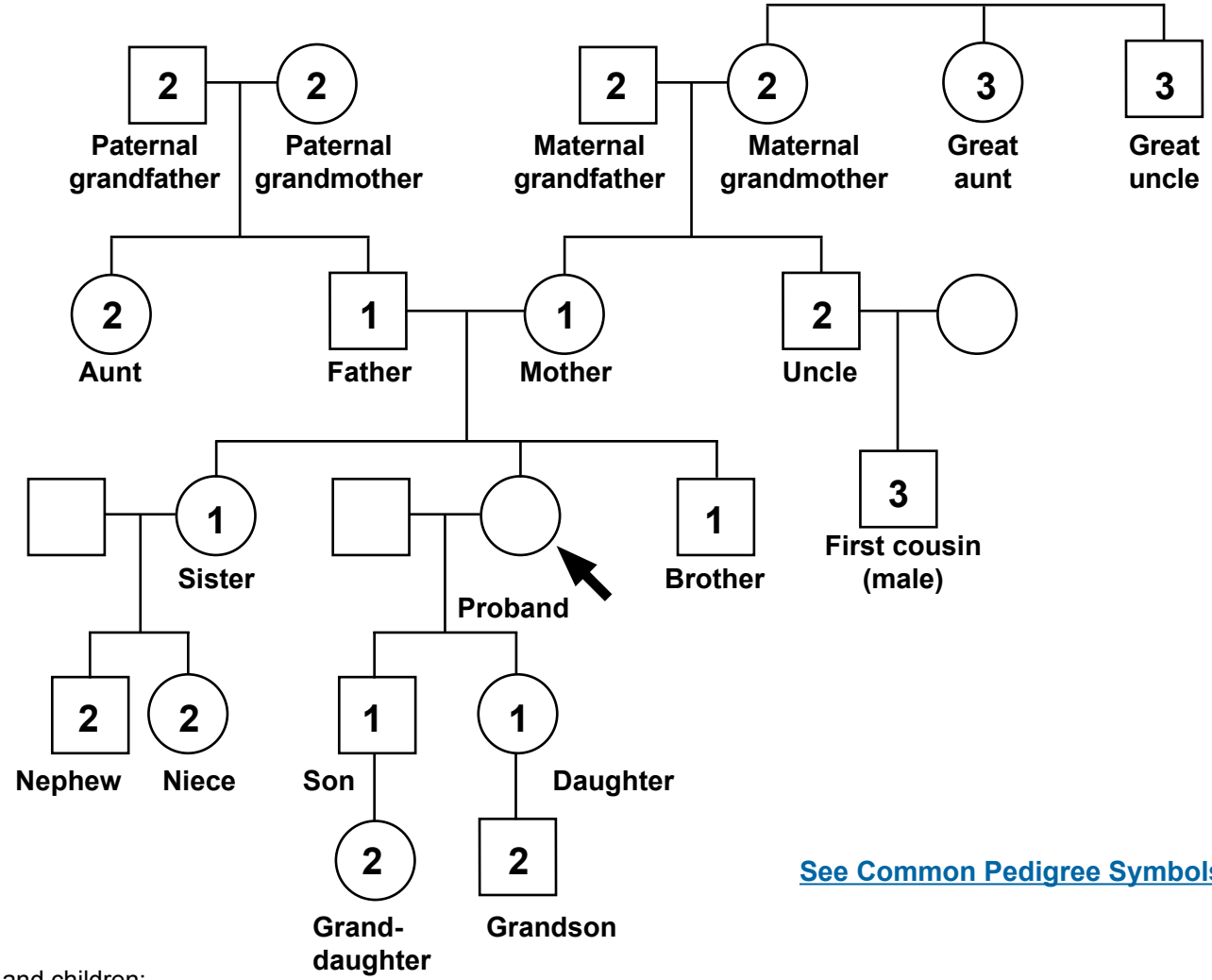
OBTAINING A COMPREHENSIVE ASSESSMENT FOR HEREDITARY COLORECTAL CANCER

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, grandchildren, and half-siblings;
Third-degree relatives: great-grandparents, great-aunts, great-uncles, great-grandchildren, and first cousins.

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Lynch Syndrome

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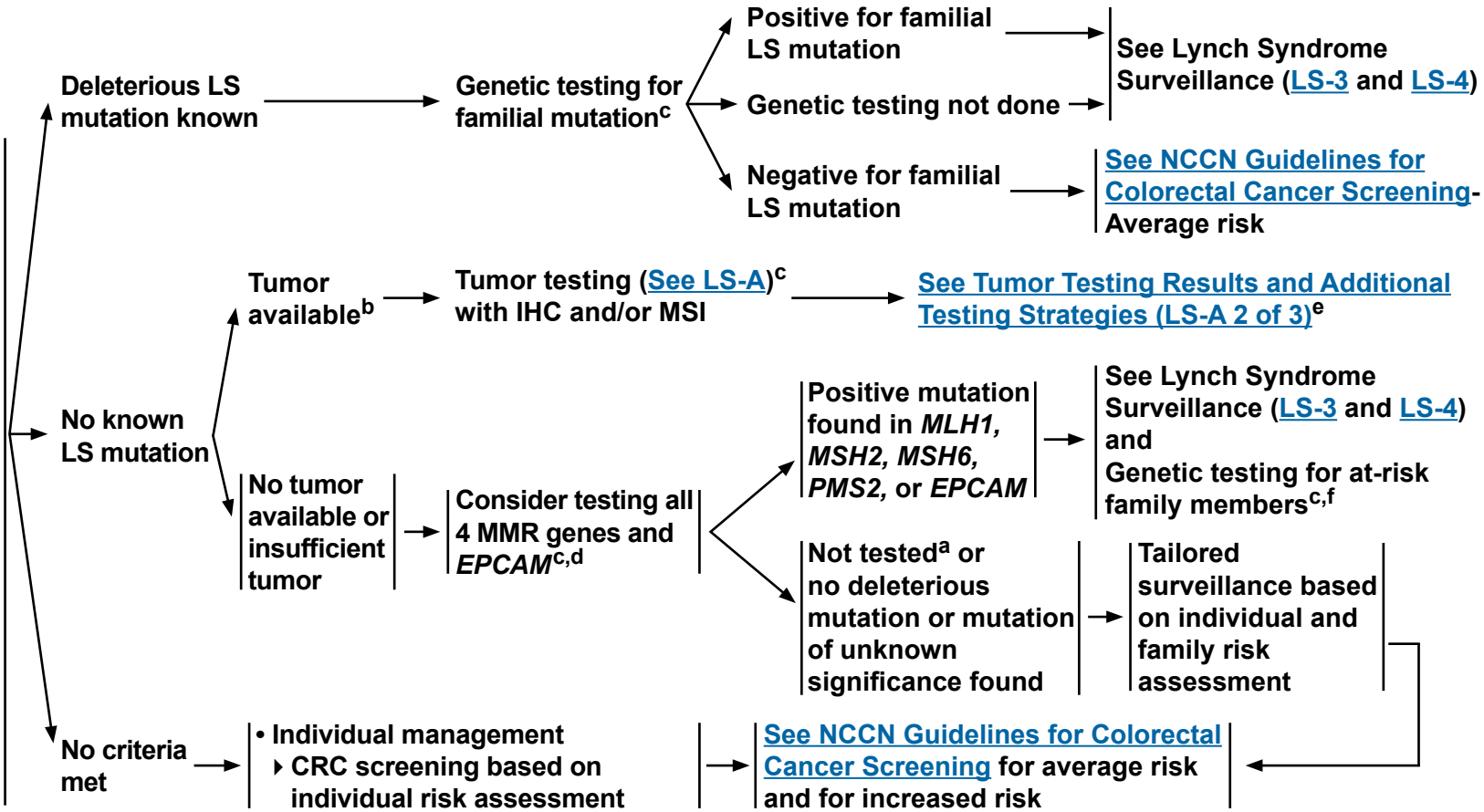
CLINICAL TESTING CRITERIA FOR LYNCH SYNDROME (based on personal and family history)

Meets revised Bethesda Guidelines (See LS-B) or Amsterdam criteria (See LS-C)
or
Endometrial cancer at age <50 y
or
Known LS in family
or
Consider testing individuals with ≥5% risk of LS on one of the following mutation prediction models: MMRpro, PREMM[1,2,6], or MMRpredict. Testing affected individuals in the family with an LS cancer (See LS-B) is preferred.



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

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

[c]Proper pretest counseling should be done by an individual with expertise in genetics.

[d]The decision to test all 4 MMR genes and *EPCAM* concurrently versus sequentially (stepwise) is left to the discretion of the clinician.

[e]For individuals found to have a deleterious LS mutation, see LS surveillance recommendations (LS-3 and LS-4).

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

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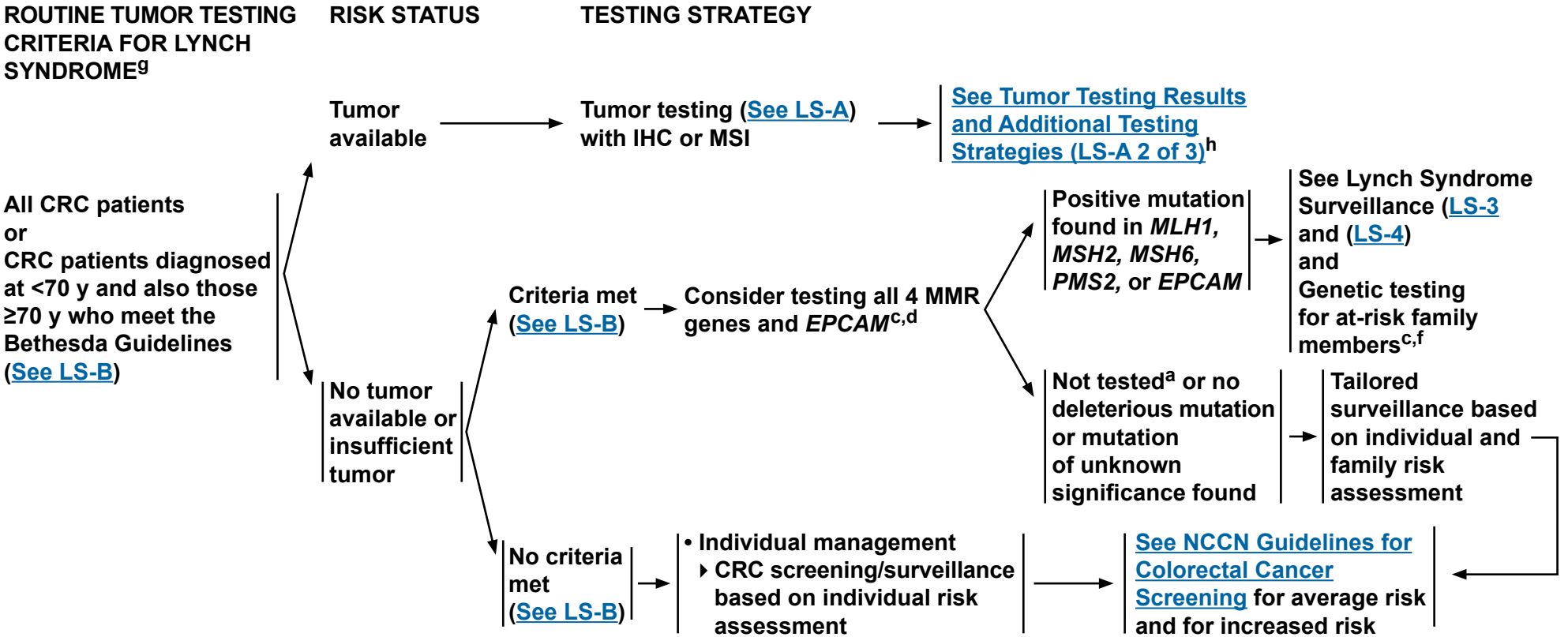

[a]Testing of unaffected family members when no affected member is available should be considered. Significant limitations of interpreting test results should be discussed.

[c]Proper pretest counseling should be done by an individual with expertise in genetics.

[d]The decision to test all 4 MMR genes and *EPCAM* concurrently versus sequentially (stepwise) is left to the discretion of the clinician.

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

[g]IHC and/or MSI screening of all colorectal and endometrial cancers (usually from surgical resection but may be performed on biopsies), regardless of age at diagnosis or family history, has been implemented at some centers to identify individuals at risk for LS. This approach was recently endorsed for colorectal cancer by the Evaluation of Genomic Applications in Practice and Prevention Working Group from the CDC and shown to be cost-effective (EGAPP Recommendation Statement. Genet Med 2009;11:35-41). Counseling by an individual with expertise in genetics is not required prior to *routine* tumor testing. An infrastructure needs to be in place to handle the screening results.

[h]For individuals found to have a deleterious LS mutation, see LS surveillance recommendations (LS-3 and LS-4).

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LYNCH SYNDROME MANAGEMENT

Surveillance for *MLH1*, *MSH2*, and *EPCAM* Mutation Carriers[i,j]

Colon cancer:

- **Colonoscopy at age 20–25 y or 2–5 y prior to the earliest colon cancer if it is diagnosed before age 25 y and repeat every 1–2 y.**
- **There are data to suggest that aspirin may decrease the risk of colon cancer in LS; however, at this time the data are not sufficiently robust to make a recommendation for its standard use.**

Extracolonic:

- **Endometrial and ovarian cancer:**
  - **Prophylactic hysterectomy and bilateral salpingo-oophorectomy (BSO) is a risk-reducing option that should be considered by women who have completed childbearing.**
  - **Patients must be aware that dysfunctional uterine bleeding warrants evaluation.**
  - **There is no clear evidence to support screening for endometrial cancer for LS. However, annual office endometrial sampling is an option.**
  - **While there may be circumstances where clinicians find screening helpful, data do not support routine ovarian screening for LS. Transvaginal ultrasound for ovarian and endometrial cancer has not been shown to be sufficiently sensitive or specific as to support a positive recommendation, but may be considered at the clinician's discretion. Serum CA-125 is an additional ovarian screening test with caveats similar to transvaginal ultrasound.**
- **Gastric and small bowel cancer: There is no clear evidence to support screening for gastric, duodenal, and small bowel cancer for LS. Selected individuals or families or those of Asian descent[k] may consider EGD with extended duodenoscopy (to distal duodenum or into the jejunum) every 3–5 y beginning at age 30–35 y.**
- **Urothelial cancer: Consider annual urinalysis starting at 25–30 y.**
- **Central nervous system (CNS) cancer: Annual physical/neurologic examination starting at 25–30 y; no additional screening recommendations have been made.**
- **Pancreatic cancer: Despite data indicating an increased risk for pancreatic cancer, no effective screening techniques have been identified; therefore, no screening recommendation is possible at this time.**
- **Breast cancer: There have been suggestions that there is an increased risk for breast cancer in LS patients; however, there is not enough evidence to support increased screening above average-risk breast cancer screening recommendations.**

→ See Follow-up of Surveillance Findings (LS-5)

See Surveillance for MSH6 and PMS2 Mutation Carriers (LS-4)

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

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

[k] Vasen HF, Blanco I, Aktan-Collan K, et al. Revised guidelines for the clinical management of Lynch syndrome (HNPCC): Recommendations by a group of European experts. Gut 2013;62:812-823.

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.

LYNCH SYNDROME MANAGEMENT

Surveillance for *MSH6* and *PMS2* Mutation Carriers[l]

- **Colon cancer:**
  - **Colonoscopy[l] at age 25–30 y or 2–5 y prior to the earliest colon cancer if it is diagnosed before age 30 y and repeat every 1–2 y**

- **Extracolonic:**
  - **For endometrial and ovarian cancer, see surveillance for *MLH1*, *MSH2*, and *EPCAM* mutation carriers (See LS-3).**
  - **The risk of other LS-related cancers is reportedly low;[i] however, due to limited data no screening recommendation is possible at this time.**

→ See Follow-up of Surveillance Findings (LS-5)

Risk to Relatives

- **Advise relatives about possible inherited cancer risk, options for risk assessment, and management.**
- **Recommend genetic counseling and consideration of genetic testing for at-risk relatives.**

Reproductive Options

- **For patients of reproductive age, advise about options for prenatal diagnosis and assisted reproduction including pre-implantation genetic diagnosis. Discussion should include known risks, limitations, and benefits of these technologies.**
- **For patients of reproductive age, advise about the risk of a rare recessive syndrome (constitutional mismatch repair deficiency [CMMRD syndrome][m]) if both partners are a carrier of a mutation/s in the same MMR gene or *EPCAM* (example, both partners carry a mutation in the *PMS2* gene, then their future offspring have a risk for CMMRD syndrome).**

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

[l] There are limited data to suggest definitive recommendations for when to initiate screening. Current data suggest that *MSH6* and *PMS2* mutation carriers have significantly lower risks for colorectal and certain extracolonic cancers compared to *MLH1*, *MSH2*, and *EPCAM* mutation carriers. However, given the limited data and variability in the ages of onset and penetrance among *MSH6* and *PMS2* carriers, colonoscopies starting at younger or later ages may be considered in some families.

[m] Wimmer K, Kratz CP, Vasen HF, et al. EU-Consortium Care for CMMRD (C4CMMRD). Diagnostic criteria for constitutional mismatch repair deficiency syndrome: suggestions of the European consortium 'care for CMMRD' (C4CMMRD). J Med Genet 2014;51:355-365.

Note: All recommendations are category 2A unless otherwise indicated.
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SURVEILLANCE FINDINGS	FOLLOW-UP
No pathologic findings	• Continued surveillance[n] • Consider prophylactic hysterectomy/BSO if postmenopausal or childbearing completed
Adenocarcinomas	See appropriate NCCN Guidelines for Treatment of Cancer by Site
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[o] → Endoscopic rectal exam every 1–2 y • Consider prophylactic hysterectomy/BSO at time of colon surgery if postmenopausal or family completed

[n]May consider subtotal colectomy if patient is not a candidate for optimal surveillance.
[o]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) in the NCCN Guidelines for Colorectal Cancer Screening.

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PRINCIPLES OF IHC AND MSI TESTING FOR LYNCH SYNDROME

General

- **IHC and MSI analyses are screening tests (either by themselves or in conjunction) that are typically done on colon and endometrial cancer tissue to identify individuals at risk for LS. Greater than 90% of LS tumors are MSI-H (microsatellite instability-high) and/or lack expression of at least one of the mismatch repair (MMR) proteins by IHC. Ten percent to 15% of sporadic colon cancers exhibit abnormal IHC and are MSI-H due to abnormal methylation of the MLH1 gene promoter, rather than due to LS (an inherited mutation of one of the MMR genes or *EPCAM*). Thus, the presence of an abnormal MLH1 IHC test increases the possibility of LS but does not make a definitive diagnosis. Those with a germline mutation are then identified as LS patients.**
- **The Bethesda criteria (See LS-B) are intended to help identify CRC patients whose tumors should be tested for MMR defects, by MSI and/or IHC analysis, thereby identifying patients with a greater chance of having LS. Although more sensitive than the Amsterdam criteria (See LS-C), up to 50% of patients with LS fail to meet even the revised Bethesda Guidelines.**

IHC

- **IHC refers to staining tumor tissue for protein expression of the 4 MMR genes known to be mutated in LS: *MLH1*, *MSH2*, *MSH6*, and *PMS2*. A normal IHC test implies all 4 MMR proteins are normally expressed, and thus it is unlikely that an underlying MMR gene mutation is present. An abnormal test means that at least one of the proteins is not expressed and an inherited mutation may be present in the related gene. Loss of protein expression by IHC in any one of the MMR genes guides genetic testing (mutation detection) to the gene(s) where protein expression is not observed or to the corresponding protein dimer.**
- **Abnormal MLH1 IHC should be followed by tumor testing for presence of *BRAF* V600E mutation (or with IHC for *BRAF*) or hypermethylation of the MLH1 promoter, which are associated with sporadic colorectal tumors, and subsequently by genetic testing if the latter are negative (See LS-A 2 of 3). Those with a germline mutation are then identified as LS patients.**
- **There is a 5%–10% false-negative rate with IHC testing.**

MSI

- **MSI-H in tumors refers to changes in 2 or more of the 5 microsatellite markers. 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.**

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TUMOR TESTING RESULTS AND ADDITIONAL TESTING STRATEGIES

Tumor Testing[a]							Plausible Etiologies	Additional Testing[d,e]
IHC				MSI	*BRAF* V600E[b]	MLH1 Promoter Methylation		
MLH1	*MSH2*	*MSH6*	*PMS2*					
+	+	+	+	MSS/MSI-Low	N/A	N/A	1) Sporadic cancer 2) Other (not Lynch syndrome) hereditary CRC syndrome	1) None[c]
+	+	+	+	MSI- High	N/A	N/A	1) Germline mutation in any LS gene 2) Sporadic cancer	1) Germline LS genetic testing[f] 2) If germline testing negative, consider somatic MMR genetic testing[h]
N/A	N/A	N/A	N/A	MSI- High	N/A	N/A	1) Sporadic cancer 2) Germline mutation in any of the LS genes	1) Consider IHC analysis and additional testing depending on IHC results 2) If IHC not performed, consider germline LS genetic testing[f]
--	+	+	--	N/A	N/A	N/A	1) Sporadic cancer 2) Germline mutation *MLH1* or rarely *PMS2*	1) Consider *BRAF*[b]/methylation studies 2) Germline LS genetic testing[f]
--	+	+	--	N/A	Positive	N/A	1) Sporadic cancer 2) Rarely germline *MLH1* mutation or constitutional *MLH1* epimutation	1) None, unless young age of onset or significant family history; then consider constitutional *MLH1* epimutation testing[g] and/or germline LS genetic testing[f]
--	+	+	--	N/A	Negative	Positive	1) Sporadic cancer 2) Rarely germline *MLH1* mutation or constitutional *MLH1* epimutation	
--	+	+	--	N/A	Negative	Negative	1) Germline mutation *MLH1* or rarely *PMS2* 2) Sporadic cancer	1) Germline LS genetic testing[f] 2) If germline testing negative, consider somatic MMR genetic testing[h]
+	--	--	+	N/A	N/A	N/A	1) Germline mutation *MSH2*/*EPCAM*; rarely germline mutation in *MSH6* 2) Sporadic cancer	
+	+	+	--	N/A	N/A	N/A	1) Germline mutation *PMS2* 2) Germline mutation *MLH1*	
+	--	+	+	N/A	N/A	N/A	1) Germline mutation *MSH2/EPCAM* 2) Sporadic cancer	
+	+	--	+	N/A	N/A	N/A	1) Germline mutation *MSH6* 2) Germline mutation *MSH2* 3) Sporadic cancer/Treatment effect[i]	1) Germline LS genetic testing[f] 2) If applicable, consider MSI analysis or repeat IHC testing on nontreated tumor[i] 3) If germline testing negative, consider somatic MMR genetic testing[h]
–	+	+	+	N/A	N/A	N/A	1) Germline mutation *MLH1*; possibly sporadic cancer or *PMS2* mutation	1) Germline LS genetic testing[f] 2) If germline testing of *MLH1* negative, consider *BRAF*[b]/methylation studies 3) If germline testing negative, consider somatic MMR genetic testing[h]
–	–	–	–	N/A	N/A	N/A	1) Germline mutation in *any* LS gene 2) Sporadic cancer	

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

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See Footnotes on LS-A 3 of 3

TUMOR TESTING RESULTS AND ADDITIONAL TESTING STRATEGIES

Footnotes from LS-A 2 of 3

[a]Tumor testing strategies apply to colorectal and endometrial cancers. Limited data exist 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) or additional features of hereditary cancer syndromes (multiple colon polyps) are 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.
[d]Individuals with abnormal MSI and/or IHC tumor results and no germline mutation detected in the corresponding gene(s) may still have undetected Lynch syndrome. At this time, no consensus has been reached as to whether these patients should be managed as LS (See LS-3 and LS-4) or managed based on personal/family history (See NCCN Guidelines for Colorectal Cancer Screening- for average risk and for increased risk). Growing evidence suggests that the majority of these individuals with abnormal tumor results and no germline mutation found have double somatic mutations/changes in the mismatch repair (MMR) genes. Although the efficacy has not yet been proven, genetic testing of the corresponding gene(s) could be performed on tumor DNA to assess for somatic mutations. Individuals found to have double somatic mutations/changes in the mismatch repair (MMR) genes likely do not have LS and management should be based on personal/family history.
[e]Prior to germline genetic testing, proper pre-test counseling should be done by an individual with expertise in genetics.
[f]Germline LS genetic testing may include testing of the gene/s that are indicated (see “Plausible Etiologies” for possibilities) by the abnormal tumor test results, or instead, multi-gene testing that includes *MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM* concurrently may be performed.
[g]Evaluation for constitutional *MLH1* epimutation involves *MLH1* promoter hypermethylation studies on blood or other sources of normal tissue.
[h]Somatic MMR genetic testing of the corresponding gene(s) (see “Plausible Etiologies” for possibilities) could be performed on tumor DNA to asses for somatic mutations that might explain the abnormal IHC and/or MSI results.
[i]Absent MSH6 in rectal umor tissue may be due to treatment effect (neoadjuvant chemoradiotherapy).

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REVISED BETHESDA GUIDELINES FOR TESTING CRC FOR LYNCH SYNDROME BY IHC AND/OR MSI[1]

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

- **CRC[2] diagnosed in a patient who is younger than 50 years of age.**
- **Presence of synchronous, or metachronous, colorectal, or other LS-related tumors,[3] regardless of age.**
- **CRC with the MSI-H histology[4] diagnosed in a patient who is younger than 60 years of age.**
- **CRC diagnosed in a patient with one or more first-degree relatives with an LS-related cancer,[3] with one of the cancers being diagnosed before age 50 years.**
- **CRC 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 LS.
[3]LS-related cancers include colorectal, endometrial, gastric, ovarian, pancreas, ureter and renal pelvis, biliary tract, brain (usually glioblastoma as seen in Turcot syndrome), and small intestinal cancers, as well as sebaceous gland adenomas and keratoacanthomas as seen in Muir-Torre syndrome.
[4]Presence of tumor-infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern.

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AMSTERDAM CRITERIA I[1,2]

At least three relatives with 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 CRC must have received the diagnosis before the age of 50 years;**
- **FAP should be excluded;**
- **Tumors should be verified by pathologic examination.**

AMSTERDAM CRITERIA II[1,2]

At least three relatives must have a cancer associated with LS (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 relative with cancer associated with LS should be diagnosed before age 50 years;**
- **FAP should be excluded in the CRC case(s) (if any);**
- **Tumors should be verified whenever possible.**

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

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Cancer Risk Up to Age 70 Years in Individuals with Lynch Syndrome Compared to the General Population

Cancer	General Population Risk[1]	*MLH1* or *MSH2*[1,2]		*MSH6*[2]		*PMS2*[3]	
		Risk	Mean Age of Onset	Risk	Mean Age of Onset	Risk	Mean Age of Onset
Colon	5.5%	40%–80%	44–61 years	10%–22%	54 years	15%–20%	61–66 years
Endometrium	2.7%	25%–60%	48–62 years	16%–26%	55 years	15%	49 years
Stomach	<1%	1%–13%	56 years	≤3%	63 years	†	70–78 years
Ovary	1.6%	4%–24%[5]	42.5 years	1%–11%	46 years	†	42 years
Hepatobiliary tract	<1%	1.4%–4%	50–57 years	Not reported	Not reported	†	Not reported
Urinary tract	<1%	1%–4%	54–60 years	<1%	65 years	†	Not reported
Small bowel	<1%	3%–6%	47–49 years	Not reported	54 years	†	59 years
Brain/CNS	<1%	1%–3%	~50 years	Not reported	Not reported	†	45 years
Sebaceous neoplasms	<1%	1%–9%	Not reported	Not reported	Not reported	Not reported	Not reported
Pancreas[4]	<1%	1%–6%	Not reported	Not reported	Not reported	Not reported	Not reported

[1]Adapted from Kohlmann W, Gruber SB (Updated September 20, 2012) Lynch Syndrome. In: GeneReviews at GeneTests: Medical Genetics Information Resource (database online). Copyright, University of Washington, Seattle. 1993-2014. Available at http://www.genetests.org. Accessed February 21, 2014.
[2]Bonadona V, Bonaïti B, Olschwang S, et al. French Cancer Genetics Network. Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome. JAMA 2011;305:2304-2310.
[3]Senter L, Clendenning M, Sotamaa K, et al. The clinical phenotype of Lynch syndrome due to germ-line PMS2 mutations. Gastroenterology 2008;135:419-428.
[4]Kastrinos F, Mukherjee B, Tayob N, et al. Risk of pancreatic cancer in families with Lynch syndrome. JAMA 2009;302:1790-1795.
[5]The 24% risk reported in Bonadona V et al. (JAMA 2011;305:2304-2310) included wide confidence intervals (1%–65% for MLH1; 3%–52% for MSH2).
†The combined risk for renal pelvic, stomach, ovary, small bowel, ureter, and brain is 6% to age 70 (Senter L, et al. Gastroenterology 2008;135:419-428).

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APC and *MUTYH* Genetic Testing Criteria

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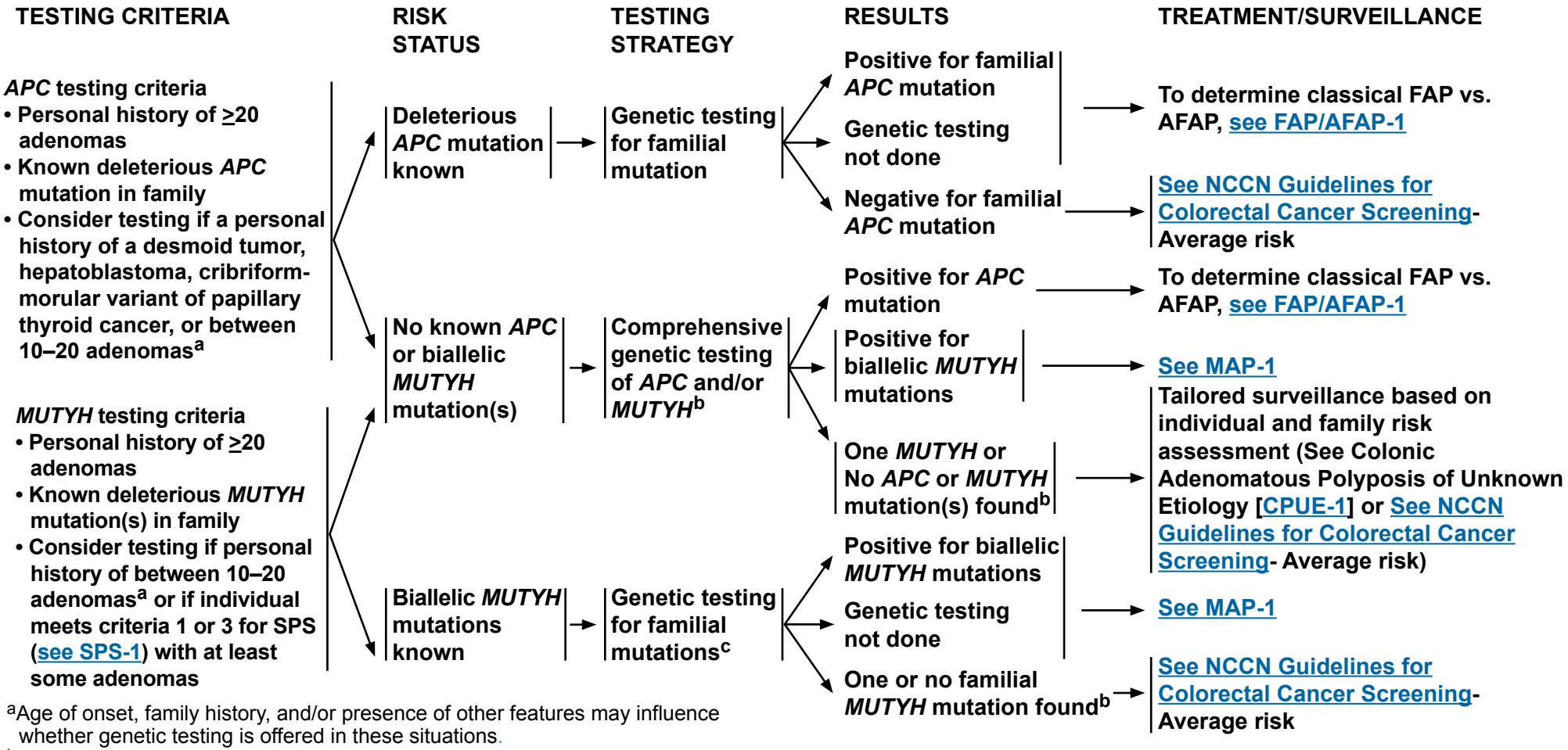

[a]Age of onset, family history, and/or presence of other features may influence whether genetic testing is offered in these situations.

[b]When colonic polyposis is present in a single person with a negative family history, consider testing for a *de novo APC* mutation; if negative, follow with testing of *MUTYH* (targeted testing for the two common northern European founder mutations c.536A>G and c.1187G>A may be considered first followed by full sequencing if biallelic mutations are not found). When colonic polyposis is present only in siblings, consider recessive inheritance and test for *MUTYH* first. Order of testing for *APC* and *MUTYH* is at the discretion of the clinician. *MUTYH* genetic testing is not indicated based on a personal history of a desmoid tumor, hepatoblastoma, or cribriform-morular variant of papillary thyroid cancer.

[c]Siblings of a patient with MAP are recommended to have site-specific testing for the familial mutations. Full sequencing of *MUTYH* may be considered in an unaffected parent when the other parent has MAP. If the unaffected parent is found to not have a *MUTYH* mutation, genetic testing in the children is not necessary to determine MAP status. If the unaffected parent is not tested, comprehensive testing of *MUTYH* should be considered in the children. If the unaffected parent is found to have one *MUTYH* mutation, testing the children for the familial *MUTYH* mutations is indicated.

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Familial Adenomatous Polyposis/AFAP

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PHENOTYPE

Classical FAP:[a]
- Germline *APC* mutation
- Presence of ≥100 polyps[b] (sufficient for clinical diagnosis) or fewer polyps at younger ages, especially in a family known to have FAP
- Autosomal dominant inheritance[c] (except with de novo mutation)
- Possible associated additional findings
  - Congenital hypertrophy of retinal pigment epithelium (CHRPE)
  - Osteomas, supernumerary teeth, odontomas
  - Desmoids, epidermoid cysts
  - Duodenal and other small bowel adenomas
  - Gastric fundic gland polyps
- Increased risk for medulloblastoma, papillary carcinoma of the thyroid (<2%), hepatoblastoma (1%–2%, usually age ≤5 y)
- Pancreatic cancers (<1%)
- Gastric cancers (<1%)
- Duodenal cancers (4%–12%)

RISK STATUS

- Personal history of classical FAP → See Treatment and Surveillance (FAP-1)
- Family history of classical FAP, unaffected (no symptoms, findings, adenomas), family mutation known → See Genetic Testing and Surveillance (FAP-4)

AFAP[d]
- Germline *APC* mutation
- Presence of 10–<100 adenomas (average of 30 polyps)
- Frequent right-sided distribution of polyps
- Adenomas and cancers at age older than classical FAP (mean age of cancer diagnosis >50 y)
- Upper GI findings, thyroid and duodenal cancer risks are similar to classical FAP
- Other extraintestinal manifestations, including CHRPE and desmoids, are unusual

- Personal history of AFAP → See Treatment and Surveillance (AFAP-1)
- Family history of AFAP, unaffected (no symptoms, findings, adenomas), family mutation known → See Genetic Testing and Surveillance (AFAP-2)

[a]A clinical diagnosis of FAP is made when >100 polyps are present at a young age; however, genetic testing of *APC* and *MUTYH* is important to differentiate FAP from MAP or colonic polyposis of unknown etiology. Identification of a germline *APC* mutation confirms the diagnosis of FAP.
[b]Individuals with >100 polyps occurring at older ages (35–40 years or older) may be found to have AFAP.
[c]There is a 30% spontaneous new mutation rate; thus, family history may be negative. This is especially noteworthy if onset age <50 y.
[d]There is currently no consensus on what constitutes a clinical diagnosis of AFAP. AFAP is considered when >10–<100 adenomas are present and is confirmed when an *APC* mutation is identified. Genetic testing of *APC* and *MUTYH* is important to differentiate AFAP from MAP or colonic polyposis of unknown etiology.

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CLASSICAL FAP TREATMENT AND SURVEILLANCE: PERSONAL HISTORY

	TREATMENT	SURVEILLANCE[d,e] (POSTCOLECTOMY)	
Personal history of classical FAP	→ **Proctocolectomy or colectomy[a,b,c]**	→ **Colon cancer:** • **If patient had colectomy with ileorectal anastomosis, then endoscopic evaluation of the rectum every 6–12 mo depending on polyp burden.** • **If patient had total proctocolectomy (TPC) with ileal pouch-anal anastomosis (IPAA) or ileostomy, then endoscopic evaluation of the ileal pouch or ileostomy every 1–3 y depending on polyp burden. Surveillance frequency should be increased to every 6 mo for large, flat polyps with villous histology and/or high-grade dysplasia.** • **The use of chemoprevention is to facilitate management of the remaining rectum post-surgery. There are no FDA-approved medications for this indication at present. While there are data to suggest that sulindac is the most potent polyp regression medication, it is not known if the decrease in polyp burden decreases cancer risk.** **Extracolonic Surveillance (See FAP-2)**	→ **Proctectomy or colectomy if dense polyposis or severe dysplasia** **If cancer found, see appropriate NCCN Guidelines for Treatment of Cancer by Site**

[a]*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.
[b]See Surgical Options for Treating the Colon and Rectum in Patients with FAP (FAP-A).
[c]Timing of colectomy in patients <18 y of age is not established. In patients <18 y with mild polyposis and without family history of early cancer or severe genotype, the timing of colectomy can be individualized. An annual colonoscopy if surgery is delayed.
[d]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.
[e]Other than colon cancer, screening recommendations are expert opinion rather than evidence-based.

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CLASSICAL FAP SURVEILLANCE: PERSONAL HISTORY

SURVEILLANCE[d,e] (POSTCOLECTOMY)

Extracolonic:

- **Duodenal or periampullary cancer: Upper endoscopy (including side-viewing examination) starting at age 20–25 y. Consider baseline upper endoscopy earlier, if colectomy before age 20 y.** → See Duodenoscopic Findings (FAP-3)
- **Gastric cancer: Examine stomach at time of upper endoscopy.**
  - **Fundic gland polyps occur in a majority of FAP patients, and focal low grade dysplasia can occur but is typically non-progressive. For this reason, special screening or surgery should only be considered in the presence of high-grade dysplasia.**
  - **Non-fundic gland polyps should be managed endoscopically if possible. Patients with polyps that cannot be removed endoscopically but with high-grade dysplasia or invasive cancer detected on biopsy should be referred for gastrectomy.**
- **Thyroid cancer: Annual thyroid examination, starting in late teenage years. Annual thyroid ultrasound may be considered, though data to support this recommendation are lacking.**
- **CNS cancer: An annual physical examination; due to limited data, no additional screening recommendation is possible at this time.**
- **Intra-abdominal desmoids: Annual abdominal palpation. If family history of symptomatic desmoids, consider abdominal MRI or CT 1–3 y post-colectomy and then every 5–10 y. Suggestive abdominal symptoms should prompt immediate abdominal imaging.**
- **Small bowel polyps and cancer: Consider adding small bowel visualization to CT or MRI for desmoids as outlined above, especially if duodenal polyposis is advanced.**
- **Hepatoblastoma: No recommendations have been made for FAP; however, there are other situations where the high risk for hepatoblastoma has been observed and the following recommendations have been considered:**
  - **Liver palpation, abdominal ultrasound, and measurement of AFP~~,~~ every 3–6 mo~~,~~ during the first 5 y of life. Screening in a clinical trial is preferred.**
- **Pancreatic cancer: Due to limited data, no screening recommendation is possible at this time.**

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

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

[f]Duodenal Surveillance:

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

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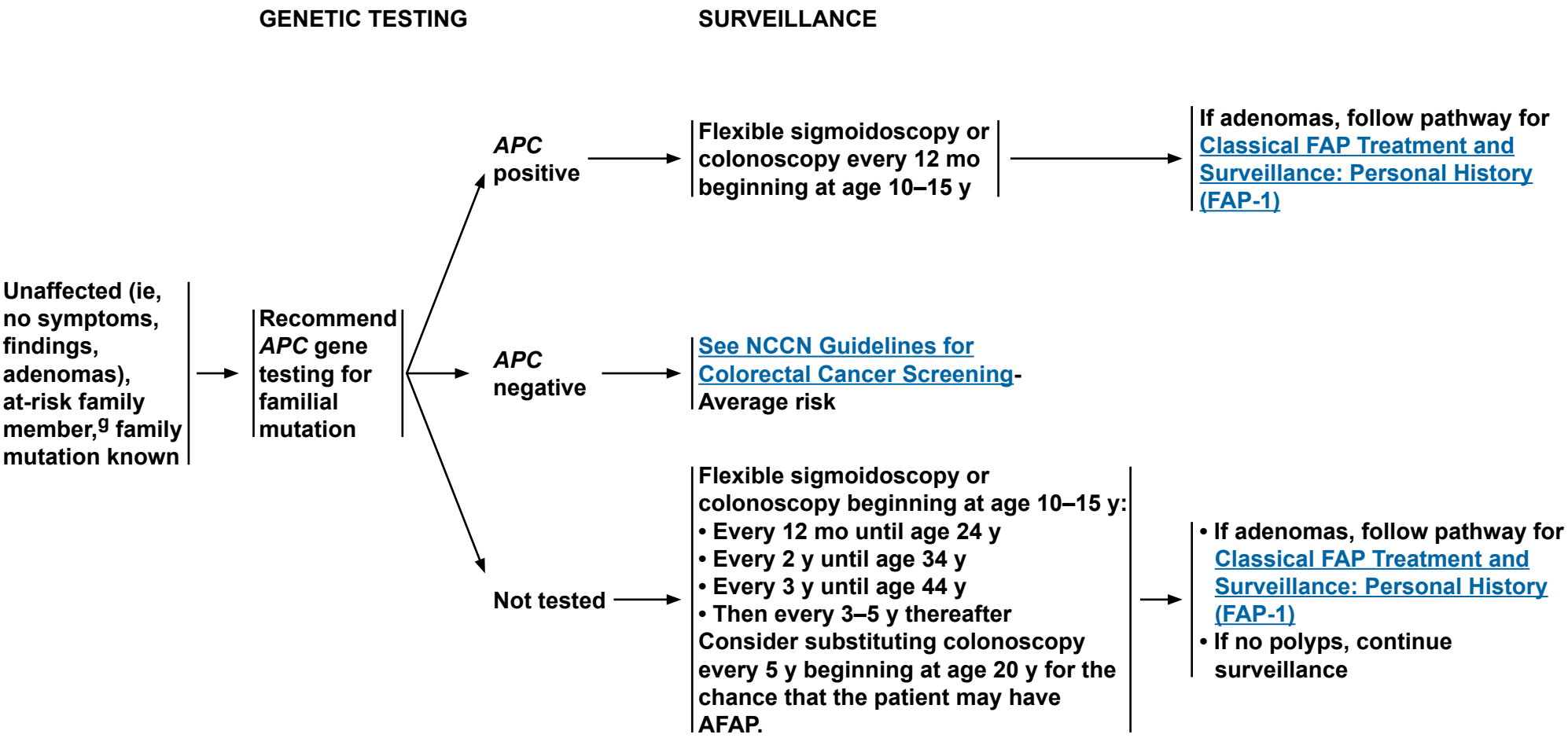
CLASSICAL FAP GENETIC TESTING AND SURVEILLANCE: FAMILY HISTORY OF CLASSICAL FAP MUTATION KNOWN



gAn 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.

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

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

TOTAL ABDOMINAL COLECTOMY WITH ILEORECTAL ANASTOMOSIS (TAC/IRA)

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

TOTAL PROCTOCOLECTOMY WITH END ILEOSTOMY (TPC/EI)

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

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

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

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

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Attenuated Familial Adenomatous Polyposis

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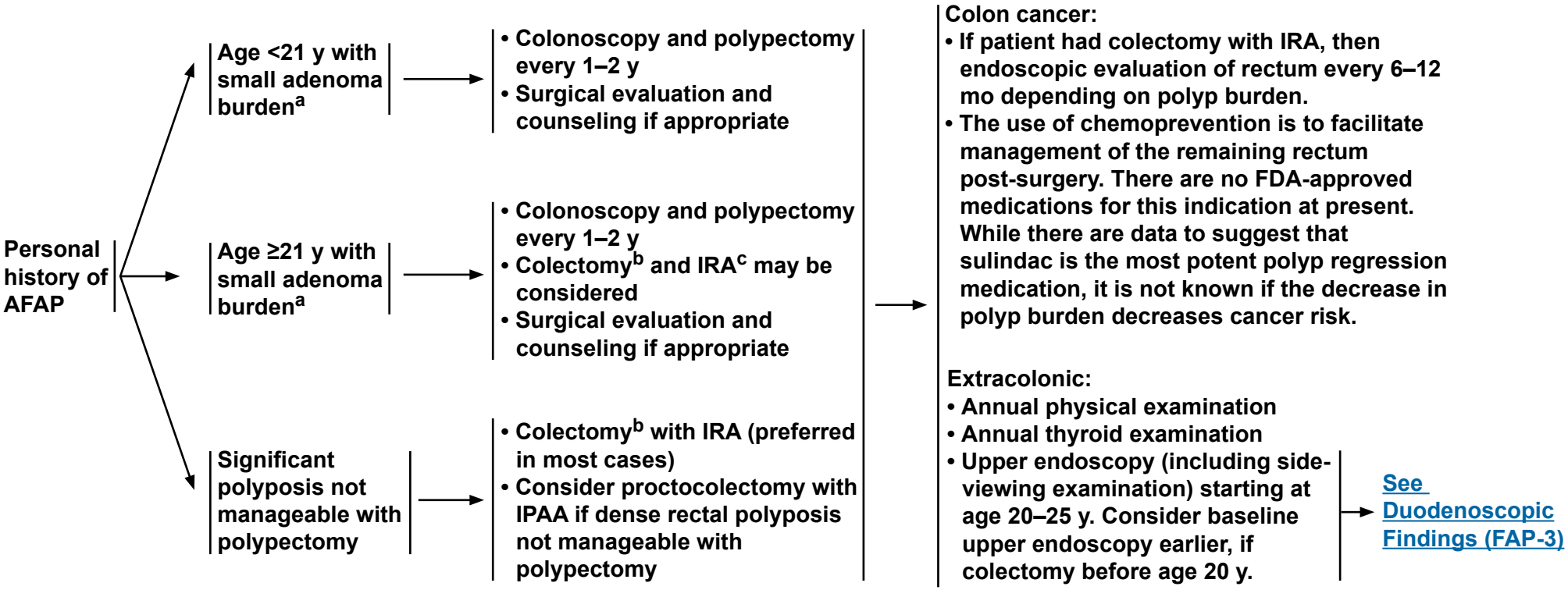
ATTENUATED FAP TREATMENT AND SURVEILLANCE: PERSONAL HISTORY



[a]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 >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.

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

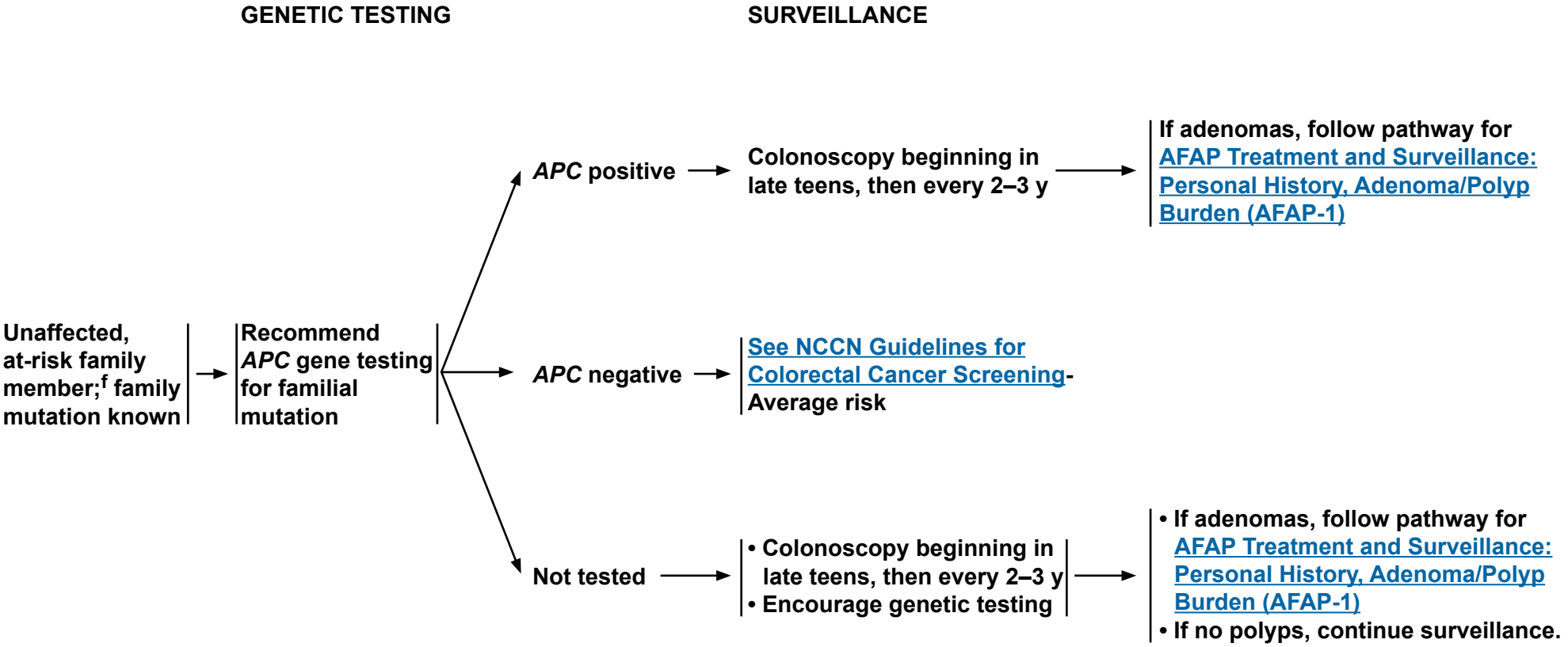
[c]Earlier surgical intervention should be considered in noncompliant patients.

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

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

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

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



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

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

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MUTYH-Associated Polyposis

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PHENOTYPE

- **Biallelic *MUTYH* mutations**
- **Polyposis or colon cancers consistent with autosomal recessive inheritance (ie, parents unaffected, siblings affected)**
- **Consanguinity**
- **Fewer than 100 adenomas[a] (range 0–100s and uncommonly >1000)**
- **Adenomas and CRC at age older than classical FAP (median CRC age >50 y)**
- **Duodenal cancer (5%)**
- **Duodenal polyps**
- **Gastric polyposis is uncommon**

RISK STATUS

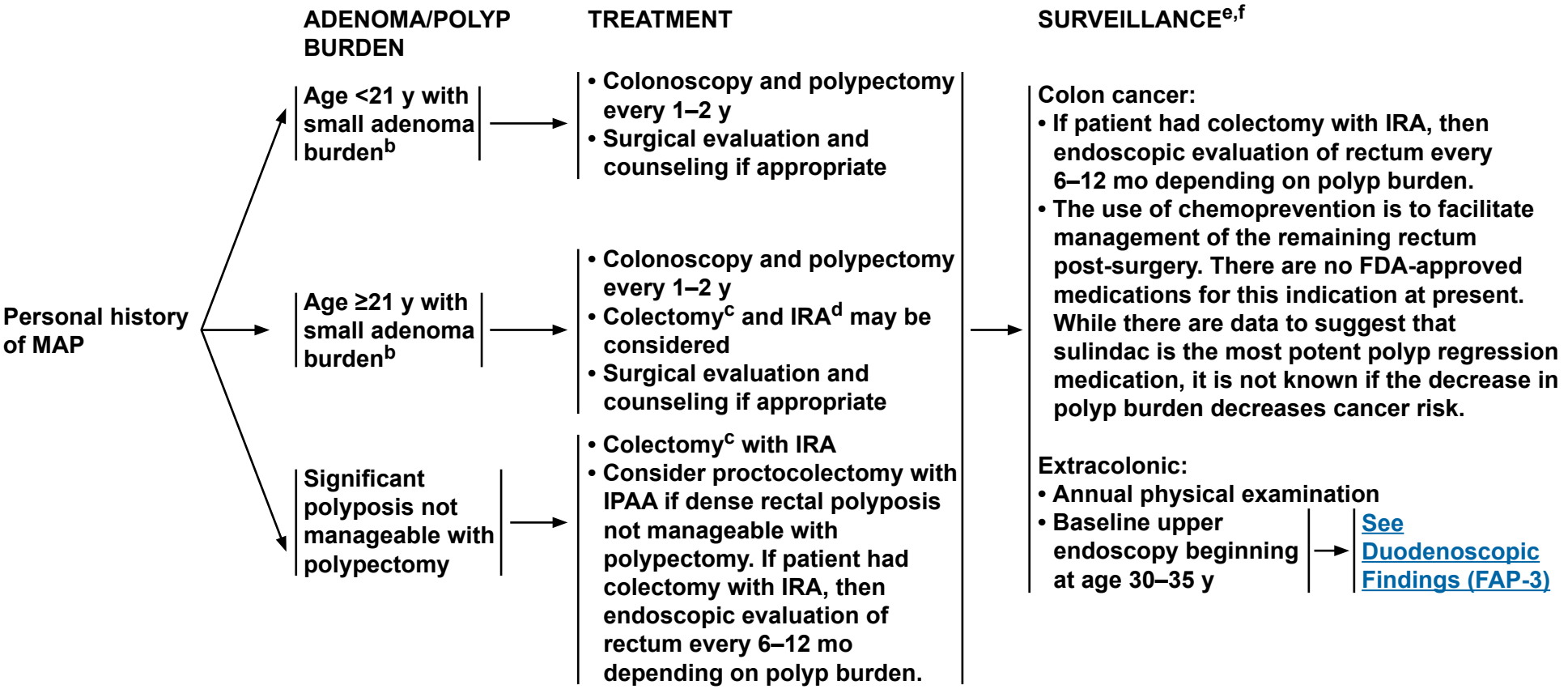
Personal history of MAP → **See Treatment and Surveillance (MAP-2)**

Unaffected, at-risk family member; family mutation known → **See Genetic Testing and Surveillance (MAP-3)**

[a]Multiple serrated polyps (hyperplastic polyps, sessile serrated polyps, and traditional serrated adenomas) may also be seen in patients with MAP polyposis. Patient with MAP may also meet criteria for serrated 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.

MAP TREATMENT AND SURVEILLANCE: PERSONAL HISTORY



[b]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 >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.

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

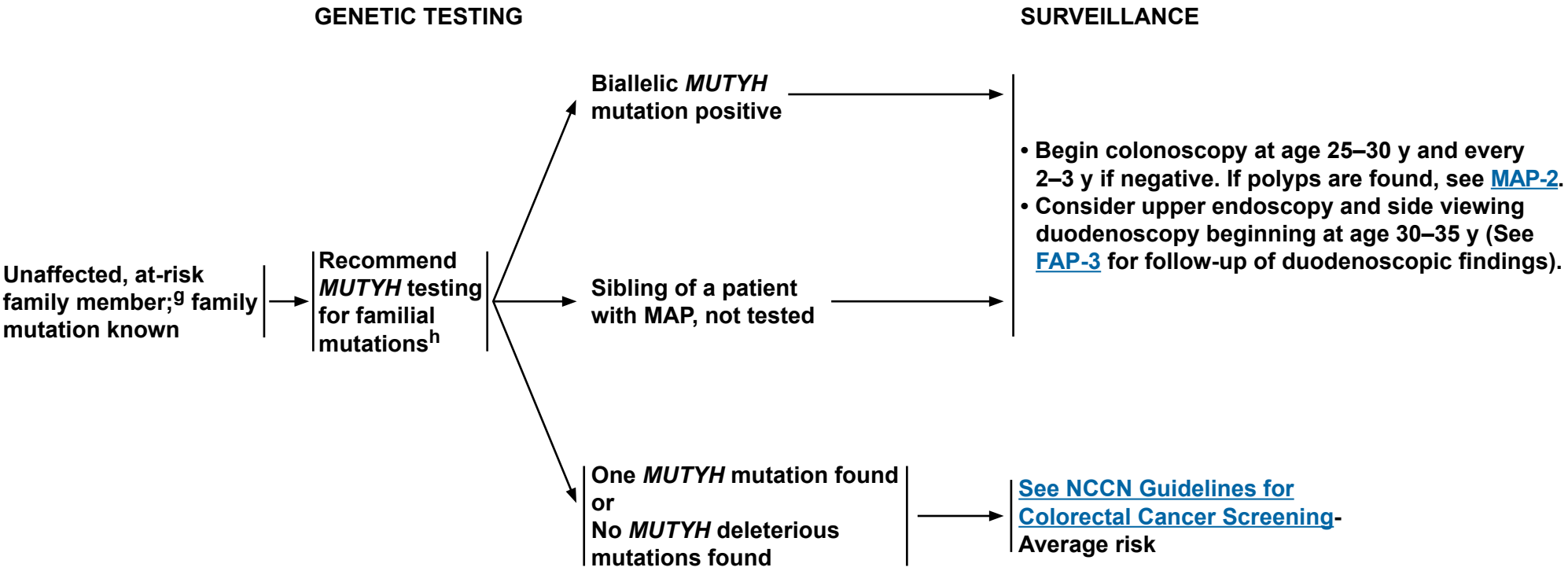
[d]Earlier surgical intervention should be considered in noncompliant patients.

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

[f]Surveillance for upper GI findings for MAP 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.

MAP TREATMENT AND SURVEILLANCE: FAMILY HISTORY OF MAP MUTATION KNOWN



[g]An at-risk family member can be defined as a sibling of an affected individual and/or proband. Other individuals in a family may also be at risk of having MAP or a monoallelic *MUTYH* mutation.

[h]Siblings of a patient with MAP are recommended to have site-specific testing for the familial mutations. Full sequencing of *MUTYH* may be considered in an unaffected parent when the other parent has MAP. If the unaffected parent is found to not have a *MUTYH* mutation, genetic testing in the children is not necessary to determine MAP status. If the unaffected parent is not tested, comprehensive testing of *MUTYH* should be considered in the children. If the unaffected parent is found to have one *MUTYH* mutation, testing the children for the familial *MUTYH* mutations is indicated.

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

NCCN Guidelines Version 2.2015
Peutz-Jeghers Syndrome

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PJS definition:[a,b]

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

Surveillance considerations:

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

See Cancer Risk and Surveillance Guidelines (PJS-2)

[a]Tomlinson IP, Houlston RS. Peutz-Jeghers syndrome. J Med Genet 1997;34:1007-1011.
[b]Due to the rarity of the syndrome and complexities of diagnosing and managing individuals with Peutz-Jeghers syndrome, referral to a specialized team is recommended.

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

Peutz-Jeghers Syndrome: Cancer Risk and Surveillance Guidelines

Site	% Lifetime Risk	Screening Procedure and Interval	Initiation Age (y)
Breast	45%–50%	• Mammogram and breast MRI annually[c] • 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
Small intestine	13%	• Small bowel visualization (CT or MRI enterography 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
Pancreas	11%–36%	• Magnetic resonance cholangiopancreatography or endoscopic ultrasound every 1–2 years	~ 30–35 y
Ovary[c] Cervix Uterus	18%–21% 10% 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	

[c]See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast/Ovarian (HBOC-A) for further breast screening recommendations regarding mammogram and breast MRI screening. High-quality breast MRI limitations include having: a need for a dedicated breast coil, the ability to perform biopsy under MRI guidance, experienced radiologists in breast MRI, and regional availability. Breast MRI performed preferably days 7–15 of menstrual cycle for premenopausal women. The appropriateness of imaging modalities and scheduling is still under study. Lowry KP, et al. Annual screening strategies in *BRCA1* and *BRCA2* gene mutation carriers: a comparative effectiveness analysis. Cancer 2012; 118:2021-2030.

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.

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NCCN Guidelines Version 2.2015
Juvenile Polyposis Syndrome

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JPS definition:[a]

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

Genetic testing:

- **Clinical genetic testing is recommended with approximately 50% of JPS cases occurring due to mutations in the *BMPR1A* and *SMAD4*[b] genes. If known *SMAD4* mutation in family, genetic testing should be performed within the first 6 months of life due to hereditary hemorrhagic telangiectasia (HHT) risk.**

Surveillance considerations:

- **Referral to a specialized team is recommended and participation in clinical trials is especially encouraged.**
- **Surveillance should begin at the approximate ages listed below, if symptoms have not already occurred. Any early symptoms should be evaluated thoroughly.**
- **The following surveillance guidelines for the multiple organs at risk for cancer may be considered. Limited data exist regarding the efficacy of various screening modalities in JPS.**

Juvenile Polyposis Syndrome: Risk and Surveillance Guidelines

Site	% Lifetime Risk	Screening/Surveillance Procedure and Interval	Initiation Age (y)
Colon	40%–50%	Colonoscopy: repeat annually if polyps are found and if no polyps, repeat every 2–3 years	~ 15 y
Stomach	21% if multiple polyps	Upper endoscopy: repeat annually if polyps are found and if no polyps, repeat every 2–3 years	~ 15 y
Small intestine	Rare, undefined	No recommendations have been made	
Pancreas	Rare, undefined	No recommendations have been made	
HHT	Undefined	In individuals with *SMAD4* mutations, screen for vascular lesions associated with HHT[b]	Within first 6 mo of life

[a]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.

[b]Faughnan ME, Palda VA, Garcia-Tsao G, et al. R; HHT Foundation International - Guidelines Working Group. International guidelines for the diagnosis and management of hereditary haemorrhagic telangiectasia. J Med Genet 2011;48:73-87.

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.

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NCCN Guidelines Version 2.2015
Serrated Polyposis Syndrome

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Serrated polyposis syndrome (previously known as hyperplastic polyposis) definition:[a,b,c]

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

Surveillance recommendations for individuals with serrated polyposis:

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

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

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

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

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

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

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

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

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

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

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

COLONIC ADENOMATOUS POLYPOSIS OF UNKNOWN ETIOLOGY

The following are surveillance/management recommendations for colonic adenomatous polyposis without known *APC* or biallelic *MUTYH* mutations.

Phenotype	Management/Surveillance
Personal history of ≥100 adenomas	Manage as FAP (See FAP-1)
Personal history of >10–<100 adenomas: Small adenoma burden manageable by colonoscopy and polypectomy	• Colonoscopy and polypectomy every 1–2 years ‣ Clearing of all polyps is recommended. Repeat at short interval if residual polyps are present.
Personal history of >10–<100 adenomas: Dense polyposis or large polyps not manageable by polypectomy	• Subtotal colectomy • Consider proctocolectomy if there is dense rectal polyposis not manageable by polypectomy.
Family history of ≥100 adenomas diagnosed at age <40 y in a first-degree relative[a,b]	• Consider colonoscopy beginning at age 10–15 y ‣ then every 1 y until age 24 y, ‣ every 2 y from 24–34 y, ‣ every 3 y from 34–44 y, ‣ then every 3–5 y thereafter • If polyposis is detected, follow pathway for Classical FAP Treatment and Surveillance: Personal History (See FAP-1).
Family history of >10–<100 adenomas in a first-degree relative[a,b]	Consider colonoscopy and polypectomy every 3–5 y[c] starting at the same age as the youngest diagnosis of polyposis in the family if uncomplicated by cancer or by age 40, whichever is earliest
Family history of >100 adenomas diagnosed at age ≥40 in a first-degree relative[a,b]	Consider colonoscopy and polypectomy every 2–3 y[c] starting at age 40 y if uncomplicated by cancer

[a]Consider genetic testing (See APC/MUTYH-1) in family member affected with polyposis.
[b]There are limited data to suggest definitive recommendations for when to initiate screening or the interval of screening.
[c]If multiple polyps are found, then colonoscopy every 1–3 years depending on type, number, and size of polyps.

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

ADDITIONAL HIGH-RISK SYNDROMES ASSOCIATED WITH COLORECTAL CANCER RISK

Li-Fraumeni Syndrome (See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian)
- ***TP53* gene**
- **Colon cancer risk: The lifetime risk for CRC is likely increased, especially at younger ages.**
- **Extracolonic cancer risks: Soft-tissue sarcomas, osteosarcomas, breast cancer, leukemia, adrenal cortical carcinomas, brain tumors, and a number of other cancers.**

***PTEN* Hamartoma Tumor Syndrome/Cowden Syndrome (See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian)**
- ***PTEN* gene**
- **Colon cancer risk: Up to 92% of patients with Cowden syndrome have colon polyps and recent estimates suggest a 9%–18% prevalence of CRC[1]**
- **Extracolonic cancer risks: Breast, endometrial, thyroid, and renal cancer**

[1]Stanich PP, Pilarski R, Rock J, Frankel WL, El-Dika S, Meyer MM. Colonic manifestations of PTEN hamartoma tumor syndrome: Case series and systematic review. World J Gastroenterol. 2014;20:1833-1838.

Discussion

NCCN Categories of Evidence and Consensus

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

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

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

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

All recommendations are category 2A unless otherwise noted.

Table of Contents

Overview

Colorectal cancer (CRC) is the fourth most frequently diagnosed cancer in the United States. In 2014, an estimated 93,090 new cases of colon cancer and 39,610 new cases of rectal cancer will occur in the United States. During the same year, it is estimated that 49,700 people will die from colon and rectal cancer.[1] Importantly, the incidence of colon and rectal cancers per 100,000 decreased from 60.5 in 1976 to 46.4 in 2005.[2] The incidence of CRC continued to trend downward, with an average annual percentage change of -2.7% in men and -2.1% in women from 2004 to 2008.[3] In addition, mortality from CRC decreased by almost 35% from 1990 to 2007,[4] and in 2011 was down by 47% from peak mortality rates.[1] These improvements in incidence of and mortality from CRC are thought to be a result of cancer prevention and earlier diagnosis through screening and better treatment modalities. Currently, patients with localized CRC have a 90.3% relative 5-year survival rate, whereas rates for those with regional and distant disease are 70.4% and 12.5%.[5]

CRC often occurs sporadically, but familial cancer syndromes are also common in this disease. 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 MutY human homolog (MUTYH)-associated polyposis (MAP). Other entities include Muir-Torre, Turcot, Gardner, Cowden, Bannayan-Riley-Ruvalcaba, Peutz-Jeghers, juvenile polyposis, and serrated polyposis syndromes (SPS).[6-8]

These NCCN Guidelines for Colorectal Cancer Screening provide recommendations for the management of patients with high-risk syndromes, including Lynch syndrome, FAP, MAP, Peutz-Jeghers syndrome, juvenile polyposis syndrome, SPS, and other high risk syndromes associated with CRC risk (Li-Fraumeni syndrome and Cowden syndrome/PTEN hamartoma tumor syndrome).

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines for Genetics/Familial High-Risk Assessment: Colon, an electronic search of the PubMed database was performed to obtain key literature in the field of high-risk colorectal cancer published between October 15, 2013 and October 15, 2014, using the following search terms: (lynch syndrome) or (hereditary nonpolyposis colorectal cancer) or (familial adenomatous polyposis) or (MUTYH-associated polyposis) or (Peutz-Jeghers syndrome) or (polyposis syndrome) or (familial colon cancer) or (familial rectal cancer) or (familial colorectal cancer) or (hereditary colon cancer) or (hereditary rectal cancer) or (hereditary colorectal cancer). The PubMed database was chosen because it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.[9]

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Practice Guidelines; Randomized Controlled Trials; Meta-Analysis; Systematic Reviews; and Validation Studies.

The PubMed search resulted in 45 citations, and their potential relevance was examined. The data from key PubMed articles and articles from additional sources deemed as relevant to these Guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Recommendations for which high-level evidence is lacking

are based on the panel's review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available on the NCCN website (available at www.NCCN.org).

Inherited Colon Cancer

Genetic susceptibility to CRC includes well-defined inherited syndromes such as Lynch syndrome (HNPCC), FAP, MAP, and other less common syndromes. Understanding the potential genetic basis for cancer in the family is critical in inherited syndromes. If there is a concern about the presence of a hereditary syndrome, the guidelines recommend referring patients to a genetic service or genetic counselor. In addition, genetic counseling is highly recommended whenever genetic testing is offered and after results are disclosed. A genetic counselor, medical geneticist, oncologist, gastroenterologist, surgeon, oncology nurse, or other health care professional with expertise and experience in cancer genetics should be involved early in counseling patients who potentially meet criteria for an inherited syndrome.

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 SPS are outlined in the algorithm. Individuals with a familial risk and no syndrome should be managed as described for those with a positive family history in the NCCN Guidelines for Colorectal Cancer Screening (available at www.NCCN.org) or following the recommendations for *Colonic Adenomatous Polyposis of Unknown Etiology,* in these guidelines.

Lynch Syndrome (Hereditary Nonpolyposis Colorectal Cancer)

Lynch syndrome is the most common form of genetically determined colon cancer predisposition, accounting for 2% to 4% of all CRC cases.[10-13] This hereditary syndrome usually results from a germline mutation in 1 of 4 DNA MMR genes (*MLH1*, *MSH2*, *MSH6*, or *PMS2*), although possible associations with three other genes (*MLH3*, *PMS1*, and *EXO1*) have also been found.[14] Evidence has shown that 3 deletions in the *EPCAM* gene, which lead to hypermethylation of the *MSH2* promoter and subsequent *MSH2* silencing, are an additional cause of Lynch syndrome.[15,16] *EPCAM* deletions likely account for 20% to 25% of cases in which *MSH2* protein is not detected by IHC (see below) but germline *MSH2* mutations are not found.[16] MMR mutations are detected in more than half of persons meeting the clinical criteria of Lynch syndrome, and the lifetime risk for CRC approaches 80% in affected individuals carrying a mutation in one of these genes.[17] MSI occurs in 80% to 90% of resulting colorectal tumors.[18,19]

Surveillance in patients with Lynch syndrome has been shown to reduce the risk for CRC and may be of benefit in the early diagnosis of endometrial cancer, which is also common in these patients.[20,21] Site-specific evaluation and heightened attention to symptoms is also advised for other cancers that occur with increased frequency in affected persons, including gastric, ovarian, pancreatic, urethral, brain (glioblastoma), and small intestinal cancers, as well as sebaceous gland adenomatous polyps and keratoacanthomas. However, efficacy of surveillance for these sites has not been clearly demonstrated (reviewed by Lindor et al[21]).

Risk factors for the presence of Lynch syndrome related to the extended family history in an individual are listed in the guidelines. Due to the high risk for CRC in a person with the syndrome, intensive

screening is essential, though the optimal interval has not been fully established in clinical trials. The recommendations in this area are based on the best evidence available to date, but more data are still needed.

Molecular Workup and Genetic Testing for Lynch Syndrome

When a familial mutation is known, genetic testing for that mutation should be done (see *Definitive Testing*, below). In the absence of a known familial mutation, criteria for testing can be based on family and personal history (see *Clinical Testing Criteria for Lynch Syndrome Based on Family and Personal History*, below). In addition, patients with CRC and no known familial mutation can undergo testing as discussed below (see *Routine Tumor Testing Criteria for Lynch Syndrome*, below). While identifying a germline mutation in an MMR gene (*MLH1*, *MSH2*, *MSH6*, and *PMS2*) or *EPCAM* by sequencing is definitive for Lynch syndrome, patients with CRC and no known familial mutation can be screened for Lynch syndrome by having initial tests on tumor tissue (see *Initial Tumor Testing Methodologies*, below).

Definitive Testing in the Setting of Known Lynch Syndrome Mutation

When a known MMR or *EPCAM* mutation exists in the family, the individual should be tested for the familial mutation. If tested positive or if testing is not performed for any reason, the individual should follow surveillance for Lynch syndrome outlined below. Individuals who test negative for the familial mutation are considered to be at average risk, not zero risk, for CRC and should follow the corresponding screening pathway.

Definitive Testing in the Setting where Lynch Syndrome Status in Family is Unknown

Initial tests in individuals without a known mutation do not necessarily indicate that a patient has Lynch syndrome. Abnormal results can occur in patients with sporadic CRC due to abnormal methylation of the *MLH1* gene promoter. A recent study estimated that 7.1% (95% CI, 2.8% to 18.2%) of patients with CRC with defective MMR have germline mutations associated with Lynch syndrome.[22] Therefore, all individuals with abnormal IHC or MSI results should be referred for proper pretest counseling by an individual with expertise in genetics so that the appropriate follow-up testing can be offered. Such tests might include one for abnormal *MLH1* promoter methylation and/or germline genetic testing of one or more of the MMR genes or *EPCAM*. If a mutation is not found by sequencing, testing for large rearrangements and deletions of MMR genes may also be performed. Most patients will be found to have sporadic CRC; those with a germline alteration are identified as having Lynch syndrome and should undergo surveillance for Lynch syndrome as described below.

If no deleterious familial mutation is identified, surveillance should be tailored based on individual and family risk assessment. Individuals with abnormal MSI and/or IHC tumor results and no germline mutation detected in the corresponding gene(s) may still have undetected Lynch syndrome. At this time, no consensus has been reached as to whether these patients should be managed as Lynch syndrome or managed based on personal/family history. Growing evidence suggests a subset of these individuals may have double somatic mutations/changes in the MMR genes.[23] Although the efficacy of the approach has not yet been proven, genetic testing of the corresponding gene(s) could be performed on tumor DNA to assess for somatic mutations. Individuals found to have double somatic mutations/changes in the MMR genes likely do not have Lynch syndrome, and management should be based on personal/family history. Germline testing may be normal despite a strong family history (ie, Amsterdam criteria) or additional features of hereditary cancer syndromes (multiple colon polyps) being present. In

these cases, additional testing may be warranted in the proband, or tumor testing in an affected family member could be considered due to the possibility of a phenocopy.

Clinical Testing Criteria for Lynch Syndrome Based on Family and Personal History

Several different sets of criteria have been developed to identify patients who should be tested for possible Lynch syndrome based on family and personal history. The first version of the minimum criteria for clinical definition of Lynch syndrome (Amsterdam criteria) was introduced in 1991, and these criteria were modified (Amsterdam II criteria) in 1999.[24] Approximately 50% of families meeting the Amsterdam II criteria have a mutation in an MMR gene.[25] These criteria are very stringent, however, and miss as many as 68% of patients with Lynch syndrome.[26]

The classical Bethesda guidelines were later developed to provide broader criteria for testing colorectal tumors for MSI.[27] The National Cancer Institute introduced the revised Bethesda guidelines in 2002 to clarify selection criteria for MSI testing.[28] One study reported that *MLH1* and *MSH2* mutations were detected in 65% of patients with MSI of colon cancer tissue who met the Bethesda criteria.[29] Another study reported on the accuracy of the revised Bethesda criteria, concluding that the guidelines were useful for identifying patients who should undergo further testing.[30] Patients fulfilling the revised Bethesda criteria had an odds ratio for carrying a germline mutation in *MLH1* or *MSH2* of 33.3 (95% CI, 4.3–250; P = .001). Still, a considerable number of patients with Lynch syndrome fail to meet even the revised Bethesda guidelines. [12]

The panel recommends testing for Lynch syndrome for individuals who 1) meet the revised Bethesda guidelines or Amsterdam criteria; 2) are diagnosed with endometrial cancer before age 50 years; 3) have known Lynch syndrome in the family. Screening tumors of patients meeting the Bethesda criteria for MSI was shown to be cost-effective not only for patients with newly diagnosed CRC but also when considering benefit for the siblings and children of mutation carriers.[31]

Some newer models have also been developed to assess the likelihood that a patient carries a mutation in a MMR gene.[26,32-34] These computer programs give probabilities of mutations and/or of the development of future cancers based on family and personal history. The PREMM[1,2,6] model can be used online at http://premm.dfci.harvard.edu/ and the MMR predict model is available for online use at http://hnpccpredict.hgu.mrc.ac.uk/. MMRpro is available for free download at http://www4.utsouthwestern.edu/breasthealth/cagene/. These models may be particularly useful when there is no tumor or insufficient tumor available for IHC or MSI testing, and the panel recommends that definitive testing be considered for individuals with ≥5% risk of LS on MMRpro, PREMM[1,2,6], or MMRpredict.

The testing that follows when clinical criteria are met in the absence of a known familial mutation depends on whether sufficient tumor is available from an affected individual. If so, IHC and/or MSI testing should be considered (see *Initial Testing Methodologies*, below). If not, germline testing of all 4 MMR genes and *EPCAM* should be considered in unaffected family members. This testing can be performed either concurrently or sequentially at the discretion of the clinician, and the significant limitations of interpreting test results in this situation should be discussed.

Routine Tumor Testing Criteria for Lynch Syndrome

Many NCCN Member Institutions and other comprehensive cancer centers now perform IHC and sometimes MSI testing on all newly diagnosed colorectal and endometrial cancers regardless of family history to determine which patients should have genetic testing for Lynch syndrome.[35,36] The cost effectiveness of this approach, referred to as universal or reflex testing, has been confirmed for CRC, and this approach has been endorsed by the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) working group at the CDC, the US Multi-Society Task Force on Colorectal Cancer and the European Society of Medical Oncology.[37-41] The Cleveland Clinic recently reported on their experiences implementing such a screening approach.[42]

An alternative approach is to test all patients with CRC diagnosed prior to age 70 years plus patients diagnosed at older ages who meet the Bethesda guidelines.[43] This approach gave a sensitivity of 95.1% (95% CI, 89.8%–99.0%) and a specificity of 95.5% (95% CI, 94.7%–96.1%). This level of sensitivity was better than that of both the revised Bethesda and Jerusalem (testing all patients diagnosed with CRC at age <70[44]) recommendations. Whereas this new selective strategy failed to identify 4.9% of Lynch syndrome cases, it resulted in approximately 35% fewer tumors undergoing MMR testing.[43]

The NCCN Panel recommends that institutions use either this selective approach (testing all patients with CRC diagnosed <70 years plus patients diagnosed at older ages who meet the Bethesda guidelines) or the universal testing approach to select patients with CRC for initial Lynch syndrome testing (see *Initial Tumor Testing Methodologies*, below), consistent with recommendations from the US Multi-Society Task Force and the European Society of Medical Oncology.[40,41] An infrastructure needs to be in place to handle the screening results in either case, but counseling by an individual with expertise in genetics is not required prior to routine tumor testing.

Initial Tumor Testing Methodologies

There are 2 main initial tests performed on CRC specimens to identify individuals who might have Lynch syndrome: 1) IHC analysis for MMR protein expression, which is often diminished in the setting of MMR mutation; and 2) analysis for MSI, which results from MMR deficiency.[45] Greater than 90% of Lynch syndrome tumors are MSI-H and/or lack expression of at least one of the mismatch repair proteins by IHC.

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.[39,46,47] However, conclusive data are not yet available that establish which strategy is optimal.[14,30,48-51] A review showed that the sensitivities of MSI and IHC testing are 77% to 89% and 83%, respectively; specificities are 90% and 89%, respectively.[39] An analysis of 5,591 unrelated CRC probands undergoing both MSI and IHC testing showed a concordance rate of 97.5%.[43] Some experts advocate for using both methods when possible.[52] However, the panel recommends using only one test initially. If normal results are found and Lynch syndrome is strongly suspected, then the other test should be carried out.

MSI testing is particularly helpful when the family history is not strongly suggestive of Lynch syndrome. Families that meet the minimal criteria for consideration (diagnosis before the age of 50, but no other criteria) may not represent the disorder. A microsatellite stable tumor arising within a young onset patient without a strong family history of colorectal/endometrial cancer is very unlikely to represent the disorder.[53] Proceeding with genetic testing in this setting is unlikely to yield an informative result. On the other hand, among patients who met

the Amsterdam criteria with MSI-negative tumors, 29% were found to have germline MMR gene mutations. MMR gene mutations were found in 88% of patients with MSI-positive tumors who met the Amsterdam criteria.[53]

IHC analysis is especially useful for family members who meet the Amsterdam criteria I or II, since there is a 50% to 92% chance of identifying a mutation in an MMR gene in these individuals.[45] IHC analysis has the advantage of predicting which gene is most likely mutated (the gene for the affected protein or its corresponding dimer partner) and thus the first candidate(s) for germline sequencing.[45]

If abnormal results are found for IHC and/or MSI, then germline Lynch syndrome genetic testing may include testing of the genes that are indicated by the abnormal tumor test results, or instead, multi-gene testing that includes *MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM* concurrently may be performed.

In sporadic colon cancers, 10% to 15% exhibit abnormal IHC and are MSI-H because of abnormal methylation of the *MLH1* promoter, rather than due to an inherited mutation. Thus, the presence of an abnormal *MLH1* IHC test increases the possibility of Lynch syndrome but does not make a definitive diagnosis. Testing the *BRAF* gene for mutation, with IHC for BRAF, or for hypermethylation of the *MLH1* promoter is thus indicated when *MLH1* expression is absent in the tumor by IHC analysis.[41] Alterations in BRAF or hypermethylation indicate that *MLH1* expression is down-regulated by somatic methylation of the promoter region of the gene and not by a germline mutation.[45]

Additional testing strategies and a table of IHC and MSI testing results are included in the algorithm section of these guidelines.

Often, a patient presents with a strong family history of Lynch syndrome-associated cancer, but no tumor sample is available for testing. One study showed that large (≥ 10 mm) adenomatous colorectal polyps in patients with Lynch syndrome display a loss of MMR protein expression by IHC and are MSI-positive.[54] These results indicate that MSI and/or IHC testing of large polyps when a tumor sample is not available is justified in high-risk families.[55] Importantly, a negative result would not rule out Lynch syndrome. An alternative approach is to go directly to germline sequencing in patients determined to have ≥5% risk for Lynch syndrome when a tumor sample is not readily available,[56] 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.

Newly Identified Lynch Syndrome

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

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

Surveillance for Patients with Lynch Syndrome

The NCCN Panel has had extensive discussions on the surveillance schemes for individuals with Lynch syndrome. These patients are at an

increased lifetime risk compared to the general population for CRC (10%–80% vs. 5.5%), endometrial cancer (16%–60% vs. 2.7%), and other cancers including of the stomach and ovary.[57-62] For the 2013 version of the guidelines, the panel devised separate cancer screening recommendations for patients with mutations in *MLH1*/*MSH2*/*EPCAM*, versus *MSH6*/*PMS2*. This decision was based on emerging data that show a smaller risk for cancer in the latter group.[57,60,63] For example, individuals with *MSH6* and *PMS2* mutations have a 10% to 22% risk for colon cancer up to age 70, while those with *MLH1* and *MSH2* mutations have a 40% to 80% risk.

Existing screening data in the literature are mainly on colon and endometrial cancers. More data are needed to evaluate the risk and benefits of extracolonic and extra-endometrial cancer screening, and recommendations are based mainly on expert opinion.

Colon Cancer Surveillance

If Lynch syndrome with *MLH1, MSH2,* or *EPCAM* mutation is confirmed, colonoscopy is advised to start between the ages of 20 to 25 or 2 to 5 years younger than the youngest diagnosis age in the family, whichever comes first, to be repeated every 1 to 2 years. This recommendation is based upon a systematic review of data between 1996 and 2006 on the reduction in cancer incidence and mortality by colonoscopy [21] and is consistent with recommendations made by the US Multi-Society Task Force on Colorectal Cancer, as well as the European Society of Medical Oncology.[40,41]

Because the average age of colon cancer onset for *MSH6* or *PMS2* mutation carriers is somewhat older than for *MLH1, MSH2*, and *EPCAM* mutation carriers,[57,63] the start of colon screening may be delayed. *MSH6* and *PMS2* carriers should begin colonoscopic surveillance at age 25 to 30 years or 2-5 y prior to the earliest colorectal cancer in the family if it is diagnosed before age 30 years*PMS2*. This screening is recommended every 1 to 2 years. However, colonoscopies may be started at younger or later ages in some families, given the limited data suggesting definitive recommendations for when to initiate screening and the variability in the ages of onset and penetrance among *MSH6* and *PMS2* carriers.

Endometrial and Ovarian Cancer Surveillance

Women with Lynch syndrome are at heightened risk for endometrial and ovarian cancers (up to 60% and 24%, respectively).[21,57,59,61] Education that enhances recognition of relevant symptoms (ie, dysfunctional uterine bleeding) is advised. Total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH/BSO) is an option that should be considered for risk reduction in women who have completed child-bearing and carry a *MLH1*, *MSH2*, *EPCAM*, *PMS2*, or *MSH6* mutation.[64-66] There is no clear evidence to support routine screening for gynecologic cancers. Annual endometrial sampling is an option for all mutation.[64,67-70] Routine transvaginal ultrasound and serum CA-125 testing are not endorsed because they have not been shown to be sufficiently sensitive or specific,[64,67-71] but the panel recognized that there may be circumstances where the clinician may find these tests helpful.

Surveillance for Other Cancers

The lifetime risk for gastric cancer varies widely between individuals with Lynch syndrome in different populations, from 2% to 4% in the Netherlands to 30% in Korea.[21,72] Most cases occur after age 40, and males have a stronger predisposition. Lynch syndrome is also associated with a 3% to 6% risk for small bowel cancer.[57,60,63,73-75] There is no clear evidence to support screening for gastric, duodenal, and small bowel cancer in patients with Lynch syndrome.[76] For selected individuals or families or those of Asian descent with *MLH1*, *MSH2*, or

EPCAM mutations, physicians may consider upper esophagogastroduodenoscopy (EGD) extended to the distal duodenum or into the jejunum every 3 to 5 years starting at age 30 to 35.[77]

Annual urinalysis starting at age 25 to 30 years should also be considered to screen for urothelial cancers in carriers of *MLH1*, *MSH2*, or *EPCAM* mutations, giving the relative ease and low cost compared to other tests. There is an increased risk for pancreatic and brain cancer in these individuals.[59-62] However, no effective screening techniques have been identified for pancreatic cancer; therefore, no screening recommendation is possible at this time. Annual physical and neurological examination starting at age 25 to 30 years is appropriate for CNS cancer.

In addition, there have been suggestions of an increased risk for breast cancer in the Lynch syndrome population[78,79]; however, there is not enough evidence to support increased screening above average risk breast cancer screening recommendations. A study of 188 men with Lynch syndrome also showed a 5-fold increase in risk of prostate cancer.[80] However, there is not enough evidence to support prostate cancer screening among males with Lynch syndrome.

Lynch Syndrome 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 (available at www.NCCN.org).

For patients with adenomatous polyps, recommendations include endoscopic polypectomy with a follow-up colonoscopy every 1 to 2 years. This option depends on the location and characteristics of the polyp, the surgical risk, and patient preference. If the adenomatous polyps identified cannot be endoscopically resected or high-grade dysplasia is identified, total abdominal colectomy (TAC) with an ileorectal anastomosis (IRA) is recommended. These patients should be followed with endoscopic rectal exams every 1 to 2 years. Because surgical management is evolving, the option of segmental or extended segmental colectomy is based on individual considerations and discussion of risks. For example, the US Multi-Society Task Force on Colorectal Cancer recommends that surgery in those older than 60-65 years and those with underlying sphincter dysfunction should potentially be less extensive.[41]

Blood relatives should be advised about possible inherited cancer risk, options for risk assessment, and management. Genetic counseling and consideration of genetic testing should be recommended for at-risk relatives.

Reproductive Options

Patients of reproductive age should be advised regarding their options for prenatal diagnosis and assisted reproduction, including pre-implantation genetic diagnosis. This discussion should include known risks, limitations, and benefits of these technologies. If both partners are a carrier of a mutation(s) in the same MMR gene or *EPCAM* (eg, if both partners carry a mutation in the *PMS2* gene), then they should also be advised about the risk of constitutional mismatch repair deficiency syndrome (CMMRD syndrome), a rare recessive syndrome.[81]

Chemoprevention in Lynch Syndrome

In the recent randomized CAPP2 trial, 861 participants with Lynch syndrome took either daily aspirin (600 mg) or placebo for up to 4 years; the primary endpoint was the development of CRC.[82] After a mean follow-up of 55.7 months, participants taking daily aspirin for at least 2 years had a 63% reduction in the incidence of CRC (IRR, 0.37; 95% CI, 0.18–0.78; *P* = .008). These participants also saw protection from all Lynch syndrome cancers (IRR, 0.42; 95% CI, 0.25–0.72; *P* = .001). Risk of colorectal neoplasia was unaffected, and there was no protection seen for participants who completed <2 years of the intervention. Criticisms of this trial have been published.[83,84] At this time, the panel believes that the data are not sufficiently robust to recommend standard use of aspirin as chemoprevention in Lynch syndrome.

Familial Adenomatous Polyposis

Classical FAP and attenuated FAP (AFAP) are autosomal dominant conditions characterized by a germline mutation in the *APC* gene, located on chromosome 5q21.[85,86] Truncating mutation of the *APC* gene is detectable in about 80% of patients with FAP using protein-truncating tests.[87,88] Although FAP accounts for less than 1% of all CRC, it has been recognized as a paradigm for treating individuals at increased risk for cancer.

The I1307K polymorphism in the *APC* gene, found people of Ashkenazi Jewish decent, predisposes carriers to CRC.[89-91] Testing for I1307K can be considered if available, although very little evidence to date indicates what kind of screening should be offered to individuals with this mutation.

Diagnosis: Classical vs. Attenuated FAP

A clinical diagnosis of classical FAP is based on the presence of ≥100 polyps or fewer polyps at younger ages, especially in a patient with a family history of FAP.[85] When fully developed, patients exhibit hundreds to thousands of colonic adenomatous polyps. The lifetime risk for cancer in individuals with classic FAP approaches 100% by the age of 50. Most of the resulting cancers occur in the left colon. Individuals with FAP also have an increased risk for other cancers, including duodenal cancer (4%–12%), hepatoblastoma (1%–2%, usually by age 5 years), and thyroid cancer (<2%). FAP is associated with increased malignancy risk in cribriform-morular variant, a rare form of papillary thyroid carcinoma[92]. Other possible associated findings of patients with FAP include desmoid tumors, which occur more frequently in patients with distal *APC* mutations, and congenital hypertrophy of retinal pigment epithelium (CHRPE), which occurs in patients with mutations in the central portion of the gene.[93,94 95] 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.[96]

AFAP is a recognized variant of FAP characterized by a later onset of disease and fewer adenomatous polyps, typically 10 to <100.[85,86] These adenomatous polyps are more prone to occur in the right colon and may take the form of diminutive sessile adenomatous polyps.[97] Phenotypic expression is often variable within families. The onset of CRC is typically delayed compared to patients with FAP,[98] but the incidence of cancer rises sharply after the age of 40 and approaches 70% by age 80. Upper gastrointestinal findings and thyroid and duodenal cancer risks are similar to that in classical FAP.

To confirm the diagnosis of FAP or AFAP, a germline mutation in *APC* must be identified (see *Genetic Testing for FAP, AFAP, and MAP*, below).

Management of FAP and AFAP

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

Preoperative surveillance schedules, surgical options, and surveillance following resection are discussed in more detail below.

Preoperative Surveillance for Individuals with a Family History of Classical FAP

Management of individuals with a family history of FAP depends on whether the familial mutation is known or unknown (also see *Genetic Testing for FAP, AFAP, and MAP*, below). When the mutation is unknown, an affected family member should have genetic counseling and testing, followed by counseling and testing of at-risk family members. If affected family members are unavailable, testing of at-risk individuals can be considered. When the familial mutation is known, genetic counseling and testing of at-risk family members is indicated.

Preoperative surveillance for at-risk individuals with a family history of FAP depends on genetic testing results, as described below.

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

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

No genetic testing: Some people who undergo genetic counseling decide, for one reason or another, not to undergo genetic testing, which influences how their screening is managed. These individuals are considered to be potentially at risk and should be offered annual flexible sigmoidoscopy or colonoscopy beginning at age 10 to15 years 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 AFAP.

There are several reasons why screening is recommended so often for these individuals. First, adenomatous polyps may begin to develop in adolescence. Most people with classic FAP present with polyps before the age of 25, so annual screening with sigmoidoscopy will detect the majority of patients with FAP. Less often, people with FAP will not develop polyps until a later age. The probability of FAP in a person without any polyps on annual screening begins to decrease with age around this time, so that screening does not need to be as frequent between the ages of 24 and 34, and can be even less frequent between

the ages of 34 and 44. However, even this recommended schedule is more rigorous than screening guidelines for the general population, because serial negative examinations up to age 35 do not exclude the diagnosis of FAP. It is important to recognize that individuals with attenuated polyposis may not present until a later age and may have fewer polyps than those with classic FAP; yet enhanced screening is still warranted in these individuals.

No familial mutation found: In some families, mutations cannot be found with available testing technology. The sensitivity to identify *APC* gene mutations is currently only about 70% to 90%.[99] Evaluating presymptomatic individuals at risk in these families presents a difficult problem. By far the best approach in this situation is additional attempts to identify the *APC* or *MUTYH* mutation in an affected family member, even if the available person is not a first-degree relative. If a mutation is found, then the at-risk individual should be managed similarly to those with known familial mutations. FAP can be excluded in a person at risk whose genetic testing results indicate no mutation is found when a mutation has been previously identified in an affected family member (a "true negative" test result).

If, however, a familial mutation is still not identified, genetic testing of at-risk individuals can be considered. Certainly, a positive test in a presymptomatic person is informative even when the familial mutation has not been previously identified. However, interpreting a test in which "no mutation is found" in a presymptomatic person is not the same as a "negative test." This particular issue is often a source of confusion and misinterpretation. Thus, it is critical that patients receive appropriate genetic counseling to avoid false-negative interpretations of test results.[100] Surveillance for these at-risk individuals for whom no mutation is found is identical to that for untested individuals with known familial mutation (see section above). Again, if polyposis is detected, they should be managed in the same way as those with a personal history of classical FAP.

Preoperative Surveillance for Individuals with a Family History of AFAP

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

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

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

Preoperative Surveillance for Individuals with a Personal History of AFAP

Treating patients with a personal history consistent with AFAP varies depending on the patient's age and adenoma burden. For young patients under age 21 with a small adenoma burden, colonoscopy and polypectomy are recommended every 1 to 2 years with surgical

evaluation and counseling if appropriate. In patients aged 21 years and older with small adenomatous polyp burden, colectomy and IRA are alternative treatment options to colonoscopy and polypectomy that may be considered. Patients with what appears to be an endoscopically manageable adenoma burden may choose to defer colectomy.

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

Surgical Options in FAP and AFAP

Three different surgical options are available for individuals with classical FAP and AFAP: total proctocolectomy with ileal pouch anal anastomosis (TPC/IPAA), TAC with IRA (TAC/IRA), and TPC with permanent end ileostomy (TPC/EI).[101] The prime factors to consider when choosing an operation for FAP and AFAP are the personal and familial phenotype, including the rectal polyp burden, and whether colon or rectal cancer is present at diagnosis. In patients presenting with the classical FAP phenotype, TPC/IPAA is generally recommended, because it prevents both colon and rectal cancers. For patients with AFAP, TAC/IRA is generally recommended; TPC/IPAA can also be considered in cases of dense rectal polyposis not manageable with polypectomy. Surgery is performed either at the onset of polyposis or later, depending on the severity of the familial phenotype and genotype, the extent of polyposis at diagnosis, individual considerations, and local practices and expertise. Proper post-surgical surveillance should be followed as outlined in sections below. In patients who are younger than 18 years with mild polyposis and without a family history of early cancers or genetic disposition, timing of colectomy can be individualized, but annual colonoscopy is essential.

Total Proctocolectomy with Ileal Pouch Anal Anastomosis: TPC/IPAA, usually with a temporary loop ileostomy, is offered to patients with classical FAP, patients with AFAP with severe phenotypes resulting in carpeting of the rectum, patients with curable rectal cancer complicating the polyposis, and patients who underwent IRA and now have an unstable rectum in terms of polyp number, size, or histology. The operation is generally not offered to patients with incurable cancer, those with an intra-abdominal desmoid that may interfere with the completion of surgery, or patients who have an anatomic, physiologic, or pathologic contraindication to an IPAA. The advantages of this operation are that the risks of developing rectal cancer are negligible and a permanent stoma is not needed. The disadvantages are that it is a complex operation, a temporary stoma is usually needed, and it carries a small risk of bladder and sexual dysfunction after proctectomy. Functional results are variable. Bowel function, although usually reasonable, is also somewhat unpredictable. The ileal pouch requires surveillance, and the area of the IPAA should still be examined due to the imperfect nature of mucosectomy.

Total Abdominal Colectomy with Ileorectal Anastomosis: A TAC/IRA is a fairly quick, straightforward operation with an overall low morbidity rate. It generally results in good bowel function. Most patients have 3 to 4 bowel movements per day, and the risk of urgency or fecal incontinence is low. Without proctectomy, there should be no risk of problems with bladder or sexual function, or decreased fertility, and even a temporary stoma is obviated. The major disadvantages of TAC with IRA are the high risk for metachronous 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).

A 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.[102] 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 reliably be selected for colectomy based on genotype alone. However, studies have reported that the risk for rectal cancer associated with TAC and IRA has declined since the 1980s when IPAA first became available for high-risk patients with severe polyposis.[103,104]

The choice of TAC with IRA versus TPC with IPAA centers on the issues of the relative quality of life.[105-110] A modest reduction in life expectancy is expected in patients with classical FAP with rectal preservation.[111,112] The decision to remove the rectum is dependent on whether the polyps are amenable to endoscopic surveillance and resection. Proctoscopic examination of a retained rectum is indicated annually. IRA is the surgery of choice for the majority of patients with AFAP who either have rectal sparing or endoscopically manageable rectal polyposis. It is not recommended for patients with extensive rectal 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 EI is recommended.[113]

Total Proctocolectomy with Permanent End Ileostomy: A TPC/EI 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 for colon and rectal cancer, but is associated with the risk of bladder or sexual function disorders. This operation may be offered to patients with a low, locally advanced rectal cancer, patients who cannot have an ileal pouch due to a desmoid tumor, patients with a poorly functioning ileal pouch, and patients who have a contraindication for an IPAA (eg, concomitant Crohn's disease, poor sphincter function).

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

Surveillance Following Surgery for FAP

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

Duodenal or Periampullary Cancer: A major component of surveillance in patients with a personal history of FAP or AFAP after surgery relates to the upper gastrointestinal tract. Duodenal adenomatous polyps develop in over 90% of patients with FAP. These adenomatous polyps are classified into stages 0 to IV, as defined by Spigelman based on macroscopic and histologic criteria.[114] Duodenal

cancer is uncommon before age 40 years, and rare before age 30 years. The cumulative lifetime risk of developing severe duodenal polyposis (stage IV) has been estimated to be around 35% (95% CI, 25% to 45%).[115] The risk for duodenal cancer increases dramatically with stage IV disease.

Surveillance following colectomy should be done with upper endoscopy (including side-viewing duodenoscopy examination). Use of Spigelman's or other standardized staging system, and extensive biopsy of dense lesions to evaluate advanced histology is recommended, though efficacy of surveillance of these sites has not been demonstrated. More intensive surveillance and/or treatment are required in patients older than 50 years with large or villous adenomatous polyps. The panel recommends that surveillance begin between 20 and 25 years of age. If colectomy was done before age 20, then an earlier baseline upper endoscopy could be considered.

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

Other Cancers: Fundic gland polyps (FGP) of the stomach also occur in the majority of patients with FAP and AFAP 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.[116] However, malignant progression in FGPs is uncommon and the lifetime risk for gastric cancer in patients with FAP in Western countries is reported to be in the range of 0.5% to 1%. The upper endoscopy for duodenal surveillance is adequate surveillance for gastric cancers. The recommendation is to observe carefully for gastric polyps that stand out because they appear irregular in shape or texture or are large, suggesting adenomatous polyps. It is also recommended that polyps in the antrum or immediate pre-antrum should be removed if possible. These are less common and are often adenomatous polyps. Special screening or surgery should only be considered in the presence of high-grade dysplasia. Non-FGPs should be managed endoscopically if possible. Patients with polyps that cannot be removed endoscopically, but with high-grade dysplasia or invasive cancer detected on biopsy, should be referred for gastrectomy.

Patients with classical FAP also have elevated risk for developing other extracolonic cancers that warrants attention during surveillance.[117] In the absence of rigorous data, there was extensive discussion among panelists on this area. Patients are at heightened risk for thyroid cancer with a lifetime risk of approximately 2% to 6% and female predominance (95%).[117,118] In a study of 192 patients with FAP who were screened for thyroid cancer, 38% had thyroid nodules.[119] Peak incidence is in the third decade of life with a mean age of around 30 years. Yearly thyroid physical examination starting in the late teenage years is recommended and is considered adequate for timely diagnosis and treatment. Annual thyroid ultrasound may be considered to supplement physical examination, although supportive data are lacking.

There is also an increased risk for intra-abdominal desmoid tumors, the majority of which present within 5 years of colectomy. Since significant morbidity and mortality are associated with advanced desmoid tumors, early diagnosis is likely of benefit.[120] Annual abdominal palpation during

physical examination is advised. If family history of symptomatic desmoids is present, consider abdominal CT or MRI 1 to 3 years post-colectomy and then at 5- to 10-year intervals. Immediate abdominal imaging is warranted if suggestive abdominal symptoms are present.

Data on screening for small bowel polyps and cancer are lacking, but adding small bowel visualization to CT or MRI for desmoids can be considered especially if duodenal polyposis is advanced. The risk for hepatoblastoma is much higher in young children with FAP.[95] 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 patients with FAP, predominantly in females younger than age 20.[121] The incidence of pancreatic cancer in FAP is not well defined and is likely very low. Giardiello and colleagues reported 4 retrospective cases (histology not documented) out of 1,391 FAP-related subjects.[122] More studies are needed to elucidate the risk and benefit of screening for brain and pancreatic cancers, and no additional screening recommendation other than annual physical exam is made.

Surveillance After Surgery for AFAP

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

Chemoprevention in FAP and AFAP

Nonsteroidal anti-inflammatory drug (NSAID) aspirin has been shown to reduce the incidence and recurrence of colorectal adenomatous polyps in the general population.[123-128]

Cyclooxygenase-2 (COX-2) has been shown to be overexpressed in colorectal adenomatous polyps and cancers. The COX-2 inhibitor celecoxib is another NSAID that has been studied for its role in the chemoprevention of colorectal adenomatous polyps in the general population.[125,127,129-132] Results from the Prevention of Colorectal Sporadic Adenomatous Polyps (PreSAP) trial showed that the use of celecoxib significantly reduced the occurrence of colorectal adenomatous polyps within three years after polypectomy.[129] Similarly, the Adenoma Prevention with Celecoxib trial (*APC* trial) showed that in patients at high risk for CRC who had their polyps removed, celecoxib significantly lowered the formation of adenomatous polyps during a 3-year period.[132] Five-year safety and efficacy results of the *APC* trial showed that compared to placebo, the reduction in the incidence of advanced adenomatous polyps over 5 years was 41% for those who received the lower dose of celecoxib and 26% in patients who received the higher dose compared to the control arm (both $P < .0001$).[133] However, due to the increased risk of cardiovascular events associated with their use, COX-2 inhibitors are not recommended routinely for sporadic adenomatous polyps.[134,135]

NSAIDs have also been studied for their role in chemoprevention in patients with FAP and AFAP. In a randomized, double-blind, placebo-controlled study, the NSAID sulindac did not prevent the development of adenomatous polyps in persons with FAP prior to surgical intervention.[136] In addition, a randomized controlled trial failed to show a strong benefit to chemoprevention with aspirin in young patients with FAP prior to surgical intervention, despite non-significant

trends to reduced polyp size and number.[137] Thus, NSAIDs do not seem to be as effective as primary treatment of FAP.

Chemoprevention with NSAIDs has also been studied following initial prophylactic surgery for both classical FAP and AFAP as an adjunct to endoscopic surveillance and to reduce the rectal polyp burden. In a randomized, double-blind, placebo-controlled study of 77 patients with FAP who had not had their entire colon and rectum removed, patients treated twice daily with 400 mg of celecoxib for 6 months had a 28% reduction in polyp number (P = .003) and a 31% decrease in sum of polyp diameters (P = .001), whereas patients receiving placebo had 4.5% and 4.9% reductions in those parameters, respectively.[138] Long-term use of sulindac also seems to be effective in polyp regression and preventing recurrence of higher-grade adenomatous polyps in the retained rectal segment of patients with FAP.[139] It should be noted, however, that the FDA indication for use of celecoxib in FAP was removed in 2011 due to the lack of phase IV (follow-up) data.

A randomized, double-blind, placebo-controlled trial looked at a possible similar postoperative chemopreventive role in FAP and AFAP for the omega-3 polyunsaturated fatty acid eicosapentaenoic acid (EPA).[140] Patients receiving EPA demonstrated a significant 22.4% decrease in polyp number and a significant 29.8% decrease in sum polyp diameter after 6 months of treatment, while patients in the placebo arm saw a worsening of global polyp burden during this time.

Overall, the panel notes that there are no FDA-approved medications for chemoprevention to facilitate management of the remaining rectum after surgery. While data suggest that sulindac is the most potent polyp-regression medication,[136] it is not known if the decrease in polyp burden decreases cancer risk.

MUTYH-Associated Polyposis

MAP is an autosomal recessive hereditary syndrome that predisposes individuals to attenuated adenomatous polyposis and CRC.[141-143] It is caused by biallelic germline mutations in the *MUTYH* gene. *MUTYH* encodes the A/G-specific adenine DNA glycosylase excision repair protein (also called hMYH), which is responsible for excising adenine nucleotides mismatched with 8-oxo-guanine, a product of oxidative damage to DNA. Dysfunctional hMYH protein can thus result in G:C to T:A transversions during DNA replication. Adenomatous polyposis is thought to result from such transversions occurring within the *APC* gene. Individuals with MAP also have an increased risk for extracolonic tumors including duodenal cancer.[144]

Monoallelic carriers of *MUTYH* mutations may also be at increased risk of CRC, though study results are conflicting. A study of 2,332 relatives of patients with CRC with monoallelic *MUTYH* mutations showed that carriers have an estimated 2.5-fold increased risk of CRC, relative to the general population.[145] Another study of 852 monoallelic *MUTYH* mutation carriers who were relatives of patients with CRC showed an increase in risk of CRC, relative to the general population (SIR, 2.04, 95% CI, 1.56—2.70, P < .001).[146] In contrast, a population-based analysis of 198 monoallelic *MUTYH* mutation carriers showed that a monoallelic *MUTYH* mutation does not significantly increase CRC risk (OR, 1.07, 95% CI, 0.87—1.31, P = 0.55).[147] It is currently unclear whether monoallelic carriers of *MUTYH* should receive specialized surveillance for colorectal cancer.

Most individuals with MAP generally have fewer than 100 polyps, although a minority can present with over 1,000. Hyperplastic polyps, SSPs, and traditional serrated adenomas may also be seen in this setting. In fact, patients with MAP may also meet the criteria for SPS.

The life-time risk for CRC for patients with MAP may be very high.[148] The median age of presentation is approximately 45 to 59 years. While duodenal polyposis is reported less frequently in MAP than in FAP, duodenal cancer occurs in about 5% of patients with MAP. Gastric polyposis is uncommon. In addition, individuals with MAP generally require colectomy at a later age than those with FAP.

Preoperative and Surgical Management of MAP

Genetic counseling and testing is recommended for individuals with a family history of MAP and known *MUTYH* mutations (see *Genetic Testing for FAP, AFAP, and MAP*, below). With positive genetic testing (biallelic *MUTYH* mutations) or no testing in such individuals, surveillance colonoscopy should begin at age 25 to 30 years, repeated every 2 to 3 years if negative. If polyps are found, these patients should be managed as those with a personal history of MAP (see below). Upper endoscopy and side-viewing duodenoscopy can also be considered beginning at age 30 to 35 years, with follow-up as described above for patients with FAP.

With one or no mutations found in individuals with a family history of MAP and known *MUTYH* mutations, individuals should be screened as those at average risk.

Genetic counseling and testing is recommended for patients with multiple adenomatous polyps (see *Genetic Testing for FAP, AFAP, and MAP*, below). Such individuals who have a negative test for *MUTYH* mutation should be managed individually as patients with FAP.

Individuals younger than 21 years of age with confirmed biallelic *MUTYH* mutations and a small adenoma burden are followed with colonoscopy and complete polypectomy every 1 to 2 years. Surgical evaluation and counseling is also recommended if appropriate.

Colectomy and IRA may be considered as the patient gets older. Surgery in the form of colectomy with IRA is recommended in most cases of significant polyposis not manageable by polypectomy. Proctocolectomy with IPAA can be considered in cases of dense rectal polyposis not manageable by polypectomy.

Postoperative Surveillance in MAP

After colectomy with IRA, endoscopic evaluation of the rectum every 6 to 12 months is recommended, depending on polyp burden. The use of chemoprevention can facilitate management of the remaining rectum postsurgery, although there are no FDA-approved medications for this indication at the present time. While there are data suggesting that sulindac is the most potent polyp-regression medication,[136] it is not known if the decrease in polyp burden decreases cancer risk.

In addition to evaluation of the rectum, annual physical exam is recommended, with baseline upper endoscopy beginning at age 30 to 35 years. Follow-up of duodenoscopic findings is as described for patients with FAP, above.

Genetic Testing for FAP, AFAP, and MAP

Genetic testing of *APC* and/or *MUTYH* is important to differentiate between FAP/AFAP from MAP and colonic polyposis of unknown etiology. A cross-sectional study of >7000 individuals found that the prevalence of pathogenic *APC* mutations was 80%, 56%, 10%, and 5% for those with ≥1000 adenomas, 100 to 999 adenomas, 20 to 99 adenomas, and 10 to 19 adenomas, respectively.[149] For the same groups, the prevalence of biallelic *MUTYH* mutations was 2%, 7%, 7%, and 4%. Notably, these prevalence estimates may be over-estimates since data from this study were taken from a convenience sample of individuals referred for genetic testing to a testing provider, and not from consecutive patients with multiple adenomas.

When a patient with a known deleterious *APC* familial mutation presents with a history of >19 adenomas, then comprehensive genetic testing of *APC* is recommended. Testing may be considered if there is a personal history of a desmoid tumor, hepatoblastoma,[95] cribriform-morular variant of papillary thyroid cancer,[92,150] or between 10 and 19 adenomas. Age of onset, family history, and/or presence of other features may influence whether genetic testing is offered in these situations.

As with *APC*, when a patient with a known deleterious *MUTYH* familial mutation presents with a history of > 19 adenomas, the panel recommends comprehensive genetic testing. In addition, testing may be considered if there is a personal history of 10 to 19 adenomas, with age of onset, family history, and/or presence of other features influencing whether testing may be offered. Testing may also be considered if the patient meets the following criteria for serrated polyposis syndrome with the presence of at least some adenomas: at least 5 serrated polyps proximal to the sigmoid colon, with 2 or more of these being > 10 mm; or, greater than 20 serrated polyps of any size, but distributed throughout the colon.

MAP follows a recessive pattern of inheritance, so *MUTYH* testing can be performed prior to *APC* testing if a recessive pattern is apparent in the pedigree (eg, when family history is positive only for a sibling). If, on the other hand, a clear autosomal dominant inheritance pattern is observed, *MUTYH* testing is unlikely to be informative. In addition, *MUTYH* testing is not indicated based only on a personal history of a desmoid tumor, hepatoblastoma, or cribriform-morular variant of papillary thyroid cancer. These guidelines recommend genetic counseling and testing for germline *MUTYH* mutations for asymptomatic siblings of patients with known *MUTYH* mutations, as well as for patients who are *APC* mutation-negative with more than 10 cumulative adenomatous polyps.

Genetic testing confirms the diagnosis and allows mutation-specific testing in other family members to clarify their risks. Additionally, identifying the location of an *APC* mutation can be useful in predicting the general severity of colonic polyposis and the severity of rectal involvement (for FAP) and risks of extracolonic cancers in affected patients. If a mutation in *APC* is not found by sequencing, testing for large rearrangements and deletions of the *APC* gene may also be performed.

When a familial mutation is known (ie, deleterious *APC* mutation or biallelic *MUTYH* mutations), genetic testing can be considered for at-risk family members. An at-risk family member can be defined as a sibling of an affected individual and/or proband. Siblings of a patient with MAP are recommended to have site-specific testing for the familial mutations. Other individuals in a family may also be at risk of having MAP or a monoallelic *MUTYH* mutation. Full sequencing of *MUTYH* may be considered in an unaffected parent when the other parent has MAP. If the unaffected parent is found to not have a *MUTYH* mutation, then genetic testing in the children is not necessary to determine MAP status. If the unaffected parent is not tested, then comprehensive testing of *MUTYH* should be considered in the children. If the unaffected parent is found to have one *MUTYH* mutation, then testing the children for the familial *MUTYH* mutations is indicated.

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

familial polyposis in the family, screening as an average-risk individual is recommended. If the familial mutation(s) is found, there is virtually a 100% probability that the individual will eventually develop familial polyposis.

It is important to note that *de novo* mutations can occur in *APC* or *MUTYH*. Thus, when colonic polyposis is present in an individual with a negative family history, consideration should be given to genetic testing of *APC*, followed by testing of *MUTYH* if no *APC* mutation is found.

Surveillance and treatment recommendations depend on the performance and findings of genetic testing, as outlined above.

Peutz-Jeghers Syndrome

Peutz-Jeghers syndrome (PJS) is an autosomal dominant condition mainly characterized by hamartomatous gastrointestinal polyps.[151] Though PJS polyps tend to be fewer than in FAP, they tend to be larger and pedunculated. Medical treatment if often sought due to complications that arise from the polyps (eg, obstruction, bleeding). PJS polyps tend to be accompanied with freckling or hyperpigmentation on the lips, buccal mucosa, vulva, fingers, and toes, which appears early in life but tends to fade during adulthood.[151] Besides being associated with an increased risk of CRC, PJS is also associated with increased risk of cancers of the breast, pancreas, ovary, and gallbladder.[152-155] A study of 33 patients with PJS in the UK showed that the risk of developing any cancer by age 65 is 37% (95% CI: 21-61%).[156] In a study of 72 patients with PJS, 12.5% had a GI malignancy.[155]The majority of PJS cases occur due to mutations in the *STK11 (LKB1)* gene.[157,158] However, other genetic mutations may be involved, as an estimated half of patients with PJS do not have detectable *STK11/LKB1* mutations.[156]

A PJS clinical diagnosis is made when an individual presents with at least two of the following: two or more PJS-type polyps of the small intestine; hyperpigmentation of the mouth, lips, nose, eyes, genitalia, or fingers; family history of PJS. Since PJS is rare, referral to a specialized team is recommended.

Management of Peutz-Jeghers Syndrome

As there is limited data regarding the efficacy of various screening modalities in PJS, panel recommendations were made while taking into consideration cancer risk in PJS and the known utility of the specific screening modalities. Individuals with PJS should receive a colonoscopy every 2-3 years, beginning in the late teens.[159] To screen for breast cancer, a mammography and breast MRI should be done annually with a clinical breast exam conducted every six months, beginning at around age 25. For cancer of the stomach and small intestine, upper endoscopy should be done every 2-3 years beginning in the late teens, and small bowel visualization every 2-3 years, or based on individual findings, beginning around ages 8-10. To monitor for cancer of the pancreas, magnetic resonance cholangiopancreatography or endoscopic ultrasound should be done every 1-2 years beginning in one's early 30's. To monitor for gynecologic cancer, a pelvic exam and Pap smear should be done annually, beginning around ages 18-20. Transvaginal ultrasound may also be considered. In males, annual testicular exam and observation for feminizing changes should be done beginning around age 10. No specific screening recommendations have been made for lung cancer; education should be provided about symptoms and smoking cessation, if necessary.

Juvenile Polyposis Syndrome

Juvenile Polyposis Syndrome (JPS) is an autosomally dominant condition that is characterized by multiple hamartomatous polyps of the

colon and rectum that usually manifests during childhood. Colonic polyps tend to be right-sided,[160] and 90% of patients present with bleeding and/or anemia.[161] Though patients with JPS are usually diagnosed during adolescence, it is a heterogeneous condition in that symptom intensity and age of diagnosis vary across patients.[162]About 50-64% of JPS cases occur due to mutations in the genes *BMPR1A* and *SMAD4*. [159,160] If there is a known *SMAD4* mutation in the family, then genetic testing should be done within the first six months of life, due to risk of hereditary hemorrhagic telangiectasia.[163] In a retrospective review of 44 patients with JPS from a polyposis registry in the UK, 9% had telangiectasia or vascular abnormalities.[160] Family history of juvenile polyposis is present in about half of patients with JPS.[161] Though lifetime risk of CRC has been difficult to estimate, a review of a large JPS kindred (117 members) provided an estimate of a 50% risk of gastrointestinal malignancy.[164] That polyps tend to be numerous increases the risk of malignancy.[161] In a separate review of 218 patient with juvenile polyposis, malignancy developed in 17% of patients.[161] The mean age of cancer diagnosis in this sample was 33.5. Out of the 36 malignancies that developed, 4 were not resectable, 7 were poorly differentiated, and 4 were metastatic.

A clinical diagnosis is made if at least one of three criteria is met: at least three to five juvenile polyps of the colon; multiple juvenile polyps found throughout the GI tract; at least one polyp in an individual with a family history of JPS.[165]

Management of Juvenile Polyposis Syndrome

Since JPS is rare, referral to a specialized team is recommended. Further, there is limited data regarding the efficacy of various screening modalities in JPS, so panel recommendations were made while taking into consideration cancer risk in JPS and the known utility of the specific screening modalities.

CRC screening via colonoscopy should begin around age 15, since the mean age of a juvenile polyp undergoing adenomatous changes is 18.6.[161] If polyps are found, colonoscopy should be repeated annually. If no polyps are found, then colonoscopy would only need to be done every 2-3 years. Screening for stomach cancer should also begin at age 15. An upper endoscopy screening schedule should match that of the colonoscopy screening schedule (ie, annually if polyps are found, every 2-3 years if no polyps found). The panel has made no recommendations regarding surveillance of the small intestine and the pancreas, since cancer of these organs in patients with JPS is rare and/or undefined.

Serrated Polyposis Syndrome

Serrated polyps include hyperplastic polyps, sessile serrated adenomas/polyps, and traditional serrated adenomas.[166] SSPs are flat or slightly raised and usually occur on the right side, while traditional serrated adenomas are generally polyploid.[167] Serrated polyps are more difficult to detect during colonoscopy and account for a disproportionate amount of interval cancers.[168] These polyps are considered premalignant, may account for as many as a third of CRCs, and should be managed similarly to adenomas.[168] Serrated polyps are thought to progress to cancer via pathways that are different from those in adenomas and to have an unfavorable prognosis.[167,169-171]

A clinical diagnosis of serrated polyposis (previously known as hyperplastic polyposis) is considered in an individual with serrated polyps and/or a family history of SPS following the criteria outlined in the guidelines above. Individuals with serrated polyposis have an increased risk for colon cancer, though data on patients with SPS are limited.[172,173] One retrospective study found that 35% of patients developed CRC during a mean follow-up period of 5.6 years (0.5–26.6 years).[172] In fact, in 6% of the patients, CRC was found during

surveillance in diminutive polyps (4–16 mm) after a median interval of 11 months. In a retrospective cohort study examining 52 individuals who met criteria for serrated polyposis, 82% had colorectal adenomas, 16% had a personal history of CRC, and 37% had a family history of CRC.[174] Another retrospective analysis of 64 patients with serrated polyposis showed a standard incidence ratio of 18.72 (95% CI, 6.87—40.74) for CRC.[175] Although SPS is clearly inherited in some cases, no causative gene has yet been identified. Epigenetic and environmental factors are also thought to play a role in the syndrome.

Management of Serrated Polyposis

Based on available data and on expert consensus opinion, the panel outlined surveillance recommendations for individuals with serrated polyposis in the guidelines above. Colonoscopic surveillance with consideration of surgical referral is recommended if colonoscopic treatment and/or surveillance are inadequate or if high-grade dysplasia occurs.

Management of First-Degree Relatives

The risk for CRC in relatives of individuals with SPS is still unclear, although several studies have found a significantly increased risk.[176] One study that compared CRC incidence in 347 first-degree relatives of patients with SPS to that in the general population (Eindhoven Cancer Registry) found 27 cases compared to an expected 5 cases (RR, 5.4; 95% CI, 3.7–7.8; $P < .001$).[177] In addition, this study found that 4 first-degree relatives satisfied the criteria for serrated polyposis (projected RR, 39; 95% CI, 13–121), suggesting a hereditary basis in some cases. Another multinational retrospective study found a similar increase in risk for CRC in both first- and second-degree relatives of patients with SPS.[178] In addition, an increased risk for pancreatic cancer was observed. In a recent prospective study, 76% of first-degree relatives of patients with SPS were found to have SPS upon colonographic screening.[179]

Pending further data, the panel believes it is reasonable to screen first-degree relatives at the youngest age of onset of SPS diagnosis, 10 years earlier than earliest diagnosis of CRC in the family, or by age 40 years, whichever is earliest. Subsequent screening is per colonoscopic findings or every 5 years if no polyps are found.

Colonic Adenomatous Polyposis of Unknown Etiology

When comprehensive genetic testing in an individual with polyposis reveals no *APC* and one or no *MUTYH* mutations, surveillance should be tailored based on individual and family risk assessment, as outlined in the guidelines.

Additional High Risk Syndromes Associated with CRC Risk

Li-Fraumeni Syndrome

Li-Fraumeni syndrome (LFS) is a rare hereditary cancer syndrome associated with germline *TP53* gene mutations.[180] LFS is associated with a high life-time risk of cancer and is characterized by a wide spectrum of neoplasms occurring at a young age. It is associated with soft-tissue sarcomas, osteosarcomas, premenopausal breast cancer, acute leukemia, colon cancer, adrenocortical carcinoma, and brain tumors.[180-188] Sarcoma, breast cancer, adrenocortical tumors, and certain brain tumors have been referred to as the “core” cancers of LFS, since they account for the majority of cancers observed in individuals with germline mutations in the *TP53* gene. The lifetime risk of CRC associated with LFS is not currently known, but is likely increased, especially at young ages.

For information about how Li-Fraumeni syndrome relates to breast and ovarian cancer, see the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian (available at www.NCCN.org).

Cowden Syndrome/PTEN Hamartoma Tumor Syndrome

Cowden syndrome is an autosomal dominant disorder associated with germline mutations in the *PTEN* tumor suppressor gene located on chromosome 10q23. The estimated penetrance of *PTEN* mutation is high, at approximately 80%.[189] Cowden syndrome is associated with multiple hamartomatous and/or cancerous lesions in various organs and tissues, such as the skin, mucous membranes, breast, thyroid, endometrium, and brain.[190,191] Hamartomas, a common manifestation of these syndromes, are benign tumors resulting from an overgrowth of normal tissue.

In a study of patients meeting diagnostic criteria for Cowden syndrome (N = 211; identified from published literature and records from a single institution), *PTEN* mutations had been identified in 97 of 105 patients (92%) who underwent testing.[192] The cumulative lifetime risk for CRC for all evaluable patients (n = 210) was 16%. In a prospective study that evaluated genotype-phenotype associations between *PTEN* mutations and cancer risk, a large number of patients meeting modified (relaxed) International Cowden Consortium criteria (N = 3,399) were enrolled and tested for *PTEN* mutations.[193] Deleterious germline mutations in *PTEN* were identified in 368 patients (11%). Calculation of age-adjusted standardized incidence ratios (SIRs) using cancer incidence data from the SEER database showed elevated SIRs among individuals with *PTEN* mutations for CRC (10). Further, the estimated cumulative lifetime CRC risk was 9%. A systematic review of published case series (N = 102) regarding gastrointestinal manifestations in PHTS and component syndromes showed that 92.5% of these patients had polyps, with 64% having 50 or more.[194] Histologies were described as: hyperplastic (44%), adenomatous (40%), hamartomatous (38%), ganglioneuroma (33%), and inflammatory (24.5%). CRC was found in 11% of the cohort.

For information about how Cowden syndrome relates to breast and ovarian cancer, see the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian (available at www.NCCN.org).

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