Hereditary Colorectal Cancer Syndromes: American Society of Clinical Oncology Clinical Practice Guideline

Endorsement of the Familial Risk-Colorectal Cancer: European Society for Medical Oncology (ESMO) Clinical Practice Guidelines

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Introduction

Approximately 5% to 6% of patient cases of colorectal cancers (CRC) are associated with germline mutations that confer an inherited predisposition for cancer.

Timely identification of individuals at risk offers an opportunity to intervene to prevent the development of cancers.

A diagnosis of Lynch syndrome, familial adenomatous polyposis, or another genetic syndrome can influence clinical management for patients with CRC and their family members.
Lynch Syndrome
Lynch syndrome is the most common hereditary CRC syndrome and accounts for ~2% to 3% of all CRCs. The syndrome is characterized by an autosomal-dominant inheritance pattern and is associated with germline mutations in the mismatch repair (MMR) genes MLH1, MSH2, MSH6, PMS2, and EPCAM/TACSTD1.

APC–associated Familial Adenomatous Polyposis (FAP)
FAP is an autosomal dominant disorder characterized by the presence of tens to thousands of adenomas distributed in the colon and rectum. FAP is estimated to account for ≤1% of all CRC cases.

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Introduction

Attenuated Familial Adenomatous Polyposis (AFAP)
AFAP is suspected when a person has a history of $\geq 20$, but $\leq 100$ colorectal adenomas. Individuals with AFAP are at increased risk for developing CRC; however, the magnitude of risk depends on severity of the polyposis phenotype.

MUTYH-associated Polyposis (MAP)
MAP is characterized by multiple colorectal polyps characterized by an autosomal recessive pattern of inheritance.
Introduction

Familial CRC Type X

Study of families with Amsterdam criteria (three relatives with CRC, spanning two generations, with one case diagnosed at age < 50 years) positive-MMR mutation negative status, referred to commonly as Familial CRC Type X, confirms that these families are at increased risk for CRC, with no increase in risk for extracolonic cancers.

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The ASCO Clinical Practice Guidelines Committee (CPGC) endorsement review process includes:

• a methodological review by ASCO guidelines staff and experts
• a content review by an endorsement panel
• final endorsement approval by the ASCO CPGC.

The ASCO Endorsement’s Data and Methodology Supplements can be found at:
www.asco.org/endorsements/HereditaryCRC

The full original ESMO Guideline can be found at:
http://www.esmo.org/Guidelines-Practice/Clinical-Practice-Guidelines/Gastrointestinal-Cancers/Familial-Risk-Colorectal-Cancer

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Target Population and Audience

People at risk for hereditary CRC syndromes

Primary care providers, oncologists, gastroenterologists, gynecologists, surgeons and other health care providers
ASCO Summary of Recommendations

ESMO recommendations, with original language, are listed below with qualifying statements added by the ASCO Panel listed in **bold italics**:

- Tumor testing *for DNA mismatch repair (MMR) deficiency* with immunohistochemistry for MMR proteins and/or MSI should be *assessed* in all CRC patients. As an alternate strategy, tumor testing should be carried out in individuals with CRC younger than 70 years, or those older than 70 years who fulfill any of the revised *Bethesda guidelines*. 

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ASCO Summary of Recommendations

• If loss of MLH1/PMS2 **protein expression** is observed in the tumor, analysis of **BRAF** V600E mutation or analysis of methylation of the **MLH1** promoter should be carried out first to rule out a sporadic case. **If tumor is MMR deficient and somatic BRAF mutation is not detected or MLH1 promoter methylation is not identified, testing for germline mutations is indicated.**

• If loss of any of the other proteins (MSH2, MSH6, PMS2) is observed, germline genetic testing should be carried out **for the genes corresponding to the absent proteins (eg., MSH2, MSH6, EPCAM, PMS2, or MLH1).**
ASCO Summary of Recommendations

- Full germline genetic testing for Lynch Syndrome should include DNA sequencing and large rearrangement analysis.

- Follow-up recommendations in mutation carriers include colonoscopy every 1 to 2 years, and gynecological examination (with transvaginal ultrasound and aspiration biopsy) on a yearly basis. Prophylactic gynecological surgery might be an option in female carriers from age 35 and after childbearing is completed.

- Individuals with familial CRC X syndrome are recommended colonoscopy at 3 to 5 year intervals, starting 5 to 10 years earlier than the youngest case in the family.
ASCO Summary of Recommendations

• Patients with multiple colorectal adenomas (>10) should be considered for germline genetic testing of APC and/or MUTYH.

• Full germline genetic testing of APC should include DNA sequencing and large rearrangement analysis.

• Germline testing of MUTYH can be initiated by screening for the most common mutations (G396D, Y179C) in the Caucasian population followed by analysis of the entire gene in heterozygotes. Founder mutations among ethnic groups should be taken into account. For nonwhite individuals, full sequencing of MUTYH should be considered.

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ASCO Summary of Recommendations

• In families with classic-FAP, sigmoidoscopy (or colonoscopy) should be carried out every 1 to 2 years starting at the age of 10 to 11 years and continued lifelong in mutation carriers. Surgery is indicated if there are large numbers of adenomas including adenomas showing a high degree of dysplasia.

• In families with attenuated-FAP, colonoscopy should be carried out every 2 years starting at the age of 18 to 20 years and continued lifelong in mutation carriers. Surgery is indicated if there are large numbers of adenomas, including adenomas showing a high degree of dysplasia. Some patients with AFAP can be conservatively managed with a colonoscopy every 1 to 2 years and polypectomy.
ASCO Summary of Recommendations

• The decision on the type of colorectal surgery in FAP (total colectomy + (ileorectal anastomosis (IRA) vs proctocolectomy + ileal pouch anal anastomosis (IPAA) depends on the age of the patient, the severity of rectal polyposis, the wish to have children, the risk of developing desmoids and possibly the site of the mutation in the APC gene.

• After colorectal surgery, surveillance of the rectum or pouch should be carried out every 6 -12 months if rectal tissue remains and every 6 months to 5 years if ileoanal pouch, depending on polyp burden. Surveillance of the gastroduodenum should be performed every 6 months to 5 years depending on the polyp burden.
ASCO Summary of Recommendations

• In both classic and attenuated FAP, screening for extracolonic manifestations (gastroduodenal polyposis, thyroid cancer, desmoid tumors) should be considered when colorectal polyposis is diagnosed or at the age of 25 to 30 years, whichever comes first.

• The suggested surveillance protocol for MAP patients is similar to that for patients with AFAP.
ASCO Surveillance Recommendations

ESMO recommendations, with original language, are listed below with qualifying statements added by the ASCO panel listed in **bold italics:**

**Lynch syndrome**

- **Colon and rectum:** Colonoscopy every 1 to 2 years, starting at age 20–25 or 5 years before the youngest case in the family. No upper limit is established.
- **Endometrium and ovary:** Gynecological examination, pelvic ultrasound, *(not cancer antigen 125)* and aspiration biopsy every year, from age 30 to 35 years. Consider prophylactic hysterectomy and salpingoophorectomy when childbearing is completed.
- **Gastric cancer:** For gastric cancer, the search for the presence of Helicobacter pylori and subsequent eradication is recommended in mutation carriers. In case of a high incidence of gastric cancer in some populations, some experts recommend upper gastrointestinal endoscopy every 1 to 3 years.
- **Other Lynch-associated cancers:** Surveillance is not recommended due to the low sensitivity and specificity. *(Although there are insufficient data supporting surveillance for other target organs, it may be considered in the context of family history.)*

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ASCO Surveillance Recommendations

Classic Familial Adenomatous Polyposis:

- **Colon and rectum:** Sigmoidoscopy (or colonoscopy) every 1 to 2 years, starting at age 10 to 11 years and continued lifelong in mutation carriers. Once adenomas are detected, annual colonoscopy should be carried out until colectomy is planned. **Surgery is indicated if there are large numbers of adenomas, including adenomas showing a high degree of dysplasia.**

- **Gastroduodenal adenomas:** Gastroduodenal endoscopy using both front and side-view scopes starting when colorectal polyposis is diagnosed or at age 25 to 30 years, whichever comes first. Surveillance intervals are based on the Spigelman stage.

- **Thyroid cancer:** Annual cervical ultrasonography may be considered starting at age 25 to 30 years.

- **Desmoid tumors:** A baseline computed tomography (CT) or magnetic resonance imaging (MRI) scan, should be considered if risk factors (positive family history for desmoids and site of the mutation in APC).

ASCO Surveillance Recommendations

**Attenuated Familial Adenomatous Polyposis:**

- **Colon and rectum:** Colonoscopy every 1 to 2 years, starting at age 18 to 20 years and continued lifelong in mutation carriers. Once adenomas are detected, colonoscopy should be carried out annually.
- **Gastroduodenal adenomas:** Gastroduodenal endoscopy using both front and side-view scopes starting when colorectal polyposis is diagnosed or at age 25 to 30 years, whichever comes first. Surveillance intervals are based on the Spigelman stage.
- **Thyroid cancer:** Annual cervical ultrasonography *may be considered* starting at age 25 to 30 years.
- **Desmoid tumors:** A baseline CT scan or MRI *should be considered* if risk factors (positive family history for desmoids and site of the mutation in APC).
Bethesda Guidelines

Colorectal tumors from individuals should be tested for microsatellite instability in the following situations:

• CRC diagnosed in a patient who is <50 years of age.
• Presence of synchronous, metachronous colorectal or other Lynch-associated tumors, regardless of age.
• CRC with the MSI-H histology diagnosed in a patient who is <60 years of age.
• CRC diagnosed in one or more first-degree relatives with a Lynch-related tumor, with one of the cancers being diagnosed under age 50 years.
• CRC diagnosed in two or more first- or second-degree relatives with Lynch-related tumors, regardless of age.

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Endorsement Recommendation


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Additional Resources

More information, including an Endorsement Data Supplement, Methodology Supplement, slide sets, and clinical tools and resources, is available at

www.asco.org/endorsements/HereditaryCRC.

All original ESMO recommendations, including surveillance recommendations, can be found at: http://www.esmo.org/Guidelines-Practice/Clinical-Practice-Guidelines/Gastrointestinal-Cancers/Familial-Risk-Colorectal-Cancer

Patient information is available at www.cancer.net
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