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ASCO SPECIAL ARTICLE

Hereditary Colorectal Cancer Syndromes: American Society of Clinical Oncology Clinical Practice Guideline Endorsement of the Familial Risk–Colorectal Cancer: European Society for Medical Oncology Clinical Practice Guidelines

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Editor's note: This American Society of Clinical Oncology clinical practice guideline endorsement provides recommendations based on the review and analyses of the relevant literature in the Familial Risk–Colorectal Cancer: European Society for Medical Oncology Clinical Practice Guidelines published in 2013 by Balmana et al on behalf of the European Society for Medical Oncology Guidelines Working Group in *Annals of Oncology*. Additional information, which includes Data Supplements, a Methodology Supplement, slide sets, and patient information, is available at www.asco.org/endorsements/HereditaryCRC.

Authors' disclosures of potential conflicts of interest are found in the article and online at www.jco.org. Author contributions are found at the end of this article.

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ABSTRACT

Purpose
To provide recommendations on prevention, screening, genetics, treatment, and management for people at risk for hereditary colorectal cancer (CRC) syndromes. The American Society of Clinical Oncology (ASCO) has a policy and set of procedures for endorsing clinical practice guidelines that have been developed by other professional organizations.

Methods
The Familial Risk–Colorectal Cancer: European Society for Medical Oncology Clinical Practice Guideline published in 2013 on behalf of the European Society for Medical Oncology (ESMO) Guidelines Working Group in *Annals of Oncology* was reviewed for developmental rigor by methodologists, with content and recommendations reviewed by an ASCO endorsement panel.

Results
The ASCO endorsement panel determined that the recommendations of the ESMO guidelines are clear, thorough, and based on the most relevant scientific evidence. The ASCO panel endorsed the ESMO guidelines and added a few qualifying statements.

Recommendations
Approximately 5% to 6% of patient cases of CRC are associated with germline mutations that confer an inherited predisposition for cancer. The possibility of a hereditary cancer syndrome should be assessed for every patient at the time of CRC diagnosis. A diagnosis of Lynch syndrome, familial adenomatous polyposis, or another genetic syndrome can influence clinical management for patients with CRC and their family members. Screening for hereditary cancer syndromes in patients with CRC should include review of personal and family histories and testing of tumors for DNA mismatch repair deficiency and/or microsatellite instability. Formal genetic evaluation is recommended for individuals who meet defined criteria.

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INTRODUCTION

Approximately 5% to 6% of all colorectal cancers (CRCs) are associated with germline mutations that confer an inherited predisposition to CRC. Timely identification of individuals at risk for hereditary CRC syndromes offers an opportunity to intervene to prevent the development of cancer. The purpose of this article is to endorse the European Society for Medical Oncology (ESMO) Guidelines Working Group clinical practice guideline on familial colorectal cancer published in 2013 by Balmana et al[1] on behalf of the ESMO Guidelines Working Group in *Annals of Oncology*, with the addition of a few qualifying statements by the American Society of Clinical Oncology (ASCO) endorsement panel. The issues addressed in the original guideline, as well as this endorsement, include prevention, screening, genetics, treatment, and management for individuals at risk for Lynch syndrome (LS), *APC*-associated familial adenomatous polyposis (FAP, also known as classic FAP), attenuated FAP (AFAP), *MUTYH*-associated polyposis (MAP), and familial CRC type X. Diagnosis and management of other rare hereditary syndromes (eg, Peutz-Jeghers syndrome, Cowden syndrome, and juvenile polyposis, among

THE BOTTOM LINE

ASCO Endorses the Familial Risk–Colorectal Cancer: ESMO Clinical Practice Guidelines, With Minor Qualifying Statements (in *bold italics)*

Guideline Question

What are the recommendations on prevention, screening, genetics, treatment, and management for people at risk for hereditary colorectal cancer (CRC) syndromes?

Target Population

People at risk for hereditary CRC syndromes.

Target Audience

Primary care providers, oncologists, gastroenterologists, gynecologists, surgeons, and other health care providers.

Methods

An ASCO endorsement panel was convened to consider endorsing the recommendation in the Familial Risk–Colorectal Cancer: ESMO Clinical Practice Guidelines published in 2013 by Balmana et al[1] on behalf of the ESMO Guidelines Working Group in *Annals of Oncology*. The ESMO recommendations were based on a thorough review of the medical literature. The ASCO expert ad hoc panel considered the ESMO methodology by reviewing the results from the AGREE II review instrument that assessed the actual guidelines and accompanying articles published by ESMO describing its consensus conference process. The ASCO panel carefully reviewed the ESMO clinical practice guidelines content to determine appropriateness for ASCO endorsement.

ASCO Summary of Recommendations: Hereditary Colorectal Cancer Syndromes

ESMO's recommendations, with original language, are listed here with qualifying statements added by the ASCO endorsement panel listed in ***bold italics*** (Data Supplement 1 provides the ESMO recommendations, reprinted with permission).

- 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 (Table 1).
- 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*).***
- 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 to have a colonoscopy at 3 to 5 year intervals, starting 5 to 10 years earlier than the youngest case in the family.
- 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 white 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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THE BOTTOM LINE (CONTINUED)

- 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.
- The decision on the type of colorectal surgery in FAP (total colectomy + ileorectal anastomosis [IRA] *v* proctocolectomy + ileal pouch anal anatomosis [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 to 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.
- 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 endorsement panel listed in ***bold italics*** (Data Supplement 2 provides the ESMO recommendations, reprinted with permission).

Lynch syndrome

- *Colon and rectum:* Colonoscopy every 1 to 2 years, starting at age 20 to 25 or 5 years before the youngest case in the family. No upper limit is established.
- *Endometrium and ovary:* Gynecological examination, pelvic ultrasound ***(not CA-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 GI 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.)***

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.

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THE BOTTOM LINE (CONTINUED)

- *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*).

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*).

Additional Resources

More information, including Data Supplements (with reprinted ESMO recommendations, diagnosis algorithms, and a glossary), a Methodology Supplement, slide sets, and clinical tools and resources, is available at www.asco.org/endorsements/HereditaryCRC. Patient information is available at www.cancer.net.

A link to the Familial Risk–Colorectal Cancer: ESMO Clinical Practice Guidelines published in 2013 by Balmana et al on behalf of the ESMO Guidelines Working Group in *Annals of Oncology* can also be found at http://www.esmo.org/Guidelines/Gastrointestinal-Cancers/Familial-Risk-Colorectal-Cancer.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care and that all patients should have the opportunity to participate.

Reprinted with permission.[1]

others) associated with increased risk for CRC are not addressed in the ESMO guidelines or the ASCO endorsement. A summary of all the ESMO recommendations, including surveillance recommendations, is found in Data Supplements 1 and 2 (reprinted with permission) and online at http://www.esmo.org/Guidelines/Gastrointestinal-Cancers/Familial-Risk-Colorectal-Cancer.

LS

LS is the most common hereditary CRC syndrome, and it accounts for approximately 2% to 3% of all CRCs.[2] 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* (ASCO addition). These alterations convey a predisposition to develop tumors with phenotypes of DNA microsatellite instability (MSI),[3] which often demonstrate loss of expression of the corresponding MMR protein detected by immunohistochemistry (IHC) techniques.[4,5]

Lifetime cancer risk for carriers of MMR gene mutations is highest for CRC (lifetime risk, 30% to 70%),[6-8] and accelerated neoplastic progression has been observed, with frequent reports of CRCs arising within 3 years of a clearing colonoscopy. Fortunately, longitudinal follow-up of patients undergoing colonoscopic surveillance has demonstrated that colonoscopy at 1- to 2-year intervals is effective in reducing CRC incidence and mortality.[9] Endometrial cancer is the second most common cancer affecting women with LS (lifetime risk, 30% to 60%).[2] Unlike CRC, data to support the effectiveness of transvaginal ultrasound and endometrial biopsy for gynecologic surveillance are lacking, and only surgical removal of the uterus and ovaries has been shown to reduce incidence of endometrial and ovarian cancers.[10] Individuals with LS also have an elevated risk of developing other cancers, specifically tumors of the urinary tract (lifetime risk, 5% to 12%), small intestine, ovary (lifetime risk, 4% to 12%), stomach (lifetime risk, 8% to 10%), pancreas (lifetime risk, 4%), biliary tract, brain, and skin.[11,12] Comparisons of phenotype according to MMR gene mutation have shown that *MLH1*-mutation carriers tend to develop CRC at younger ages, whereas *MSH2* carriers seem to be at higher risk for extracolonic cancers, and for women with *MSH6* mutations, the risk for endometrial cancer may surpass the lifetime CRC risk.[13-15] In contrast, the risks for CRC and endometrial cancer seem to be lower among individuals with mutations in *PMS2* (15% to 20%) compared with carriers of other MMR gene mutations.[16] An

algorithm for molecular diagnosis of LS presented in the ESMO guidelines is provided in Data Supplement 3 (reprinted with permission). The utility of screening CRC tumors for LS using MSI and IHC has been well established, and it is worth mentioning that some have recommended applying similar universal screening strategies to endometrial cancer[17]; however, this is not addressed in the ESMO guidelines.

CLASSIC FAP

FAP is an autosomal-dominant disorder characterized by the presence of tens to thousands of adenomas distributed in the colon and rectum.[2] FAP is estimated to account for $\leq$ 1% of all CRC cases. FAP is associated with germline mutations in the *APC* tumor suppressor gene. *APC*-mutation carriers often develop polyps as adolescents or young adults. Without surgical colectomy, the heavy colonic burden associated with classic FAP (hundreds to thousands of colorectal adenomas) is associated with a lifetime risk for CRC of $>$ 90%. Individuals with FAP frequently exhibit extracolonic manifestations of the disease, particularly gastric and duodenal polyps, desmoid tumors, thyroid and brain tumors, congenital hypertrophy of the retinal pigmented epithelium, supernumerary teeth, osteomas, and epidermoid cysts, among others.[18] Duodenal and ampullary adenocarcinomas follow CRC as a major cause of cancer death among individuals with FAP; consequently, lifelong endoscopic surveillance of the upper GI tract is required even after colectomy.

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 the severity of the polyposis phenotype. Although some individuals with AFAP carry mutations in *APC* or *MUTYH*, in the majority of cases, a genetic basis cannot be identified. In contrast to classic FAP, in which polyps develop in adolescence, individuals with AFAP tend to develop polyps later in life. The clinical course of AFAP can be variable. Although the colorectal polyp burden may require colectomy, some individuals are managed endoscopically. Although phenotypes vary, families with AFAP seem to be at lower risk for developing extracolonic neoplasms or desmoid tumors.[19]

MAP

MAP is characterized by multiple colorectal polyps with an autosomal-recessive pattern of inheritance.[20] Clinically, MAP may resemble classic FAP or AFAP, with an average age of onset in approximately the mid-50s, often with $<$ 100 adenomas. Management is similar to that of classic FAP or AFAP, with surgical colectomy and/or endoscopic surveillance depending on the colorectal polyp burden. Of note, up to one third of biallelic *MUTYH*-mutation carriers identified in population-based CRC studies developed CRC in the absence of colorectal polyposis.[21,22] An algorithm for genetic diagnosis in polyposis syndromes is provided in Data Supplement 4 (reprinted with permission).

FAMILIAL CRC TYPE X

Although the Amsterdam criteria (three relatives with CRC, spanning two generations, with one patient diagnosed at age $<$ 50 years) were originally devised to identify families with CRC at risk for LS, it is important to note that fewer than half of MMR gene–mutation carriers meet Amsterdam criteria, and approximately 40% of individuals who do meet Amsterdam criteria do not exhibit MMR-deficient tumors or have identifiable germline mutations in any of the MMR genes.[23] The study of families with Amsterdam criteria–positive, MMR mutation–negative status, referred to commonly as familial CRC type X, has confirmed that such families are at increased risk for CRC, with no increase in risk for extracolonic cancers. The lack of a unifying genetic explanation for these patient cases raises the possibility that familial CRC type X may not represent a single disease but possibly different diseases with multifactorial causal factors.

OVERVIEW OF ASCO GUIDELINE ENDORSEMENT PROCESS

ASCO has policies and procedures for endorsing practice guidelines that have been developed by other professional organizations. The goal of guideline endorsement is to increase the number of high-quality, ASCO-vetted guidelines available to the ASCO members. The ASCO endorsement process involves an assessment by ASCO staff of candidate guidelines for methodologic quality and content using the Rigour of Development subscale of the Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument and a content review conducted using the ASCO Guideline Endorsement Content Review Form. An endorsement panel is then formed, with members conducting additional reviews and deliberation (more detail provided in Methodology Supplement).

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The clinical practice guidelines and other guidance published herein are provided by ASCO to assist providers in clinical decision making. The information herein should not be relied on as being complete or accurate, nor should it be considered as inclusive of all proper treatments or methods of care or as a statement of the standard of care. With the rapid development of scientific knowledge, new evidence may emerge between the time information is developed and when it is published or read. The information is not continually updated and may not reflect the most recent evidence. The information addresses only the topics specifically identified herein and is not applicable to other interventions, diseases, or stages of diseases. This information does not mandate any particular course of medical care. Furthermore, the information is not intended to substitute for the independent professional judgment of the treating provider, because the information does not account for individual variation among patients. Recommendations reflect high, moderate, or low confidence that the recommendations reflect the net effect of a given course of action. The use of words like "must," "must not," "should," and "should not" indicate that a course of action is recommended or not recommended for either most or many patients, but there is latitude for the treating physician to select other courses of action in individual cases. In all cases, the selected course of action should be considered by the treating provider in the context of treating the individual patient. Use of the information is voluntary. ASCO provides this information

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Guideline and Conflicts of Interest

The endorsement panel was assembled in accordance with the ASCO Conflicts of Interest Management Procedures for Clinical Practice Guidelines (summarized at www.asco.org/rwc). Members of the panel completed the ASCO disclosure form, which requires disclosure of financial and other interests that are relevant to the subject matter of the guideline, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as the result of promulgation of the guideline. Categories for disclosure include employment relationships, consulting arrangements, stock ownership, honoraria, research funding, and expert testimony. In accordance with these procedures, the majority of the members of the panel did not disclose any such relationships (see Author Disclosures of Potential Conflicts of Interest section at the end of the article).

CLINICAL QUESTIONS AND TARGET POPULATION

The ESMO guidelines addressed clinical questions on prevention, screening, genetics, treatment, and management for people at risk for LS, *APC*-associated FAP, AFAP, MAP, and familial CRC type X.

SUMMARY OF ESMO GUIDELINES DEVELOPMENT METHODOLOGY

The methodology was not fully described in detail in the actual guidelines, but approaches used in developing other ESMO guidelines have been published previously[24,25] (Data Supplement 4; reprinted with permission). ESMO consensus conferences are organized under the auspices of ESMO, Conticanet, the Multinational Association of Supportive Care in Cancer, the Swiss Cancer League, Eurobonet, and the San Salvatore Foundation. The number of panel members ranges from 23 to 66, and the number of participating countries ranges from five to 22. All guidelines are published.

Briefly, the methodology is as follows: ESMO appoints chairs, forms expert panels, collects conflicts of interest information, defines the topic, assigns staff, prepares evidence-based reviews of the literature, convenes discussions with experts, drafts a manuscript, revises, gets final sign off by the consensus conference, and submits the manuscript for approval and publication (Data Supplement 5; reprinted with permission).

RESULTS OF ASCO METHODOLOGIC REVIEW

The ASCO methodologic review of the EMSO guidelines was completed independently by three ASCO guideline staff members using the Rigour of Development subscale from the AGREE II instrument. Detailed results of the scoring for this guideline are available on request to guidelines@asco.org. Overall, the ESMO guidelines scored 60%, because the methodology was not described in detail in the actual guidelines manuscript. The preliminary ASCO content reviewers of the ESMO guidelines, as well as the ASCO endorsement panel, found the recommendations well supported in the original guidelines. Each section, including the introduction, information on diagnosis, referral for genetic testing, screening, risk reduction (where appropriate), treatment, and surveillance, was clear and well referenced.

This is the most recent information as of the publication date. For updates and the most recent information, please visit www.asco.org/guidelines/HereditaryCRC and the ASCO Guidelines Wiki (www.asco.org/guidelineswiki).

METHODS AND RESULTS OF ASCO UPDATED LITERATURE REVIEW

ASCO guideline staff updated the literature search. MEDLINE was searched from June 2013 to December 2013. The search was restricted to new studies and guidelines published in English on familial risk–CRC. The updated search yielded a recently published guideline,[26] and the recommendations are consistent with those in this ASCO endorsement (of special interest, this consensus statement by US Multi-Society Task Force on Colorectal Cancer endorsed testing all people with CRC age $\leq$ 70 years and testing people age $>$ 70 years who have relevant family history).

RESULTS OF ASCO CONTENT REVIEW

The ASCO endorsement panel reviewed the ESMO guidelines (Summary of Recommendations and Surveillance Recommendations in the bottom line box) and concurs that the recommendations are clear, thorough, based on the most relevant scientific evidence in this content area, and present options that will be acceptable to patients. Overall, the ASCO endorsement panel agrees with the recommendations as stated in the ESMO guidelines, with the minor qualifications (highlighted in bold and italics) discussed in detail as follows.

DISCUSSION

The ASCO endorsement panel wants to highlight, offer clarification, and qualify some of the statements from the ESMO guidelines.

Chemoprevention

No chemoprevention recommendations were included in the ESMO guidelines Summary of Recommendations Table (Data Supplement 1; reprinted with permission); however, there was an extensive discussion of chemoprevention in the body of the guidelines. A synopsis is presented here.

Chemoprevention in LS. Recent data from the Colorectal Adenoma/Carcinoma Prevention Program have shown in a randomized, placebo-controlled trial a significant 60% reduction in the incidence of CRC and other LS-associated cancers among those using 600 mg of aspirin per day for at least 2 years.[27] The adverse event rate among patients taking aspirin or placebo did not differ. This study, along with earlier data, supports the potential of aspirin for prevention of advanced colorectal neoplasia in patients with LS; however, as noted by the study authors, the optimal dose and duration of aspirin use require further evaluation. The ASCO

Table 1. Revised Bethesda Guidelines for Testing Colorectal Tumors for MSI

Tumors from individuals should be tested for MSI in the following situations:
Colorectal cancer diagnosed in a patient who is < 50 years of age
Presence of synchronous, metachronous colorectal or other Lynch-associated tumors,* regardless of age
Colorectal cancer with the MSI-H histology† diagnosed in a patient who is < 60 years of age‡
Colorectal cancer diagnosed in one or more first-degree relatives with a Lynch-related tumor, with one of the cancers being diagnosed under age 50 years
Colorectal cancer diagnosed in two or more first- or second-degree relatives with Lynch-related tumors, regardless of age

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Abbreviations: MSI, microsatellite instability; MSI-H, high-frequency microsatellite instability.
*Lynch syndrome–related tumors include colorectal, endometrial, stomach, ovarian, pancreatic, ureter and renal pelvic, biliary tract, and brain (usually glioblastoma, as seen in Turcot syndrome) tumors; sebaceous gland adenomas and keratoacanthomas in Muir-Torre syndrome, and carcinomas of the small bowel.
†Presence of tumor-infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern.
‡There was no consensus among workshop participants on whether to include age criterion of < 60 years of age; participants voted to keep < 60 years of age in guideline.

endorsement panel agrees with the ESMO guidelines that the use of aspirin may be considered for cancer prevention; however, because existing data on the effectiveness of aspirin for cancer prevention in LS are derived from a single clinical trial, there are insufficient data to make strong recommendations in favor of or against the use of aspirin for chemoprevention in LS.

Chemoprevention in FAP. Primary chemoprevention has not been demonstrated in randomized controlled trials to delay the appearance of clinically significant polyposis in FAP. Chemoprevention with the use of nonsteroidal anti-inflammatory drugs has been shown to reduce the number and extent of colorectal adenomas and, less reliably, duodenal adenomas. Accordingly, sulindac and celecoxib can be considered as adjuvant treatments when adenoma recurrence is detected in individuals who have undergone colectomy. Because cardiovascular adverse effects have been reported in patients receiving nonsteroidal anti-inflammatory drugs (including COX-2 inhibitors), caution is warranted.[28,29]

Chemoprevention in MAP. To date, no studies have demonstrated that any primary or secondary chemoprevention strategies are effective in this setting.

CRC Tumor Screening for MMR Deficiency (LS)

For any person with CRC diagnosed at age < 70 years and those ≥ 70 years who meet the revised Bethesda guidelines. Screening CRC tumors for LS through testing for MMR deficiency is cost effective.[30] Existing data suggest that sensitivity of MSI and that of IHC testing are equivalent; however, an IHC test may offer an advantage in that identifying loss of expression of a specific MMR protein may help target DNA sequencing toward the MMR gene most likely to be mutated. A recent pooled-data analysis of four large population-based cohorts of individuals with CRC demonstrated that a strategy of universal screening of CRC tumors for MMR deficiency was more sensitive than use of the revised Bethesda guidelines (Table 1[3]) for identifying MMR-mutation carriers (100% *v* 87.8%).[31] However, increased prevalence of MMR-deficient CRCs among individuals diagnosed at older ages results in reduced specificity for LS.

As an alternative to screening all patients with CRC, the strategy of selective universal screening (screening all tumors of patients with CRC diagnosed at age < 70 years and selective screening of tumors diagnosed in patients age ≥ 70 years who fulfill revised Bethesda guidelines) missed only 4.9% of patient cases of LS, resulting in 34.8% fewer cases of MMR tumor testing and 28.6% fewer cases requiring germline genetic testing when compared with unselected universal screening. Because the diagnostic yields of selective and universal tumor screening were similar (MMR mutations identified in 2.1% *v* 2.2% of unselected patients with CRC), the selective screening approach seems reasonable; however, it will be important to evaluate the feasibility and effectiveness of this strategy in clinical practice. The ASCO endorsement panel notes that the Evaluation of Genomic Applications in Practice and Prevention Working Group and the National Society of Genetic Counselors and Collaborative Group of the Americas on Inherited Colorectal Cancer (CGA) joint practice guideline recommends all CRC tumors be screened for MMR deficiency and does not specify an age limit.[32,33]

Germline Genetic Testing for LS

Screening should include DNA sequencing and testing for large rearrangements of MMR genes, the proteins of which are noted to be absent on tumor IHC. Furthermore, for cases of absent expression of MSH2 and MSH6, genetic testing for mutations and large deletions in *EPCAM* should be considered. Germline deletions in the *EPCAM* gene (also known as *TACSTD1*) have been identified in a subset of individuals whose CRCs exhibit loss of MSH2 protein expression without detectable germline mutations in the *MSH2* gene. Deletions in the 3′ end of *EPCAM* have been demonstrated to result in promoter hypermethylation and epigenetic silencing of the neighboring *MSH2* gene. Mutations in *EPCAM* may account for up to 6.3% of all patient cases of LS.[34-36] Although *EPCAM* is not a DNA MMR gene, it is important to include *EPCAM* mutations among the genetic alterations associated with LS.

Cancer Surveillance for Individuals With LS

Colonoscopy every 1 to 2 years beginning at age 20 to 25 years has proven effective for early detection and prevention of LS-associated CRC; however, the clinical utility of screening for extracolonic cancers associated with LS remains unclear. Regarding early detection and/or prevention of endometrial cancer, the effectiveness of screening remains unproven, and the optimal strategy for managing endometrial cancer risks in women with germline mutations in DNA MMR genes has yet to be determined. The ESMO guidelines recommends gynecologic examination, cancer antigen 125, pelvic ultrasound, and endometrial aspirate annually beginning at age 30 to 35 years. The ASCO endorsement panel notes that data regarding routine surveillance for endometrial and ovarian cancers is limited. Prospective cohort studies

have demonstrated that annual endometrial aspirate identifies asymptomatic women with endometrial precancer (complex atypical hyperplasia) and early endometrial cancer. However, attention to symptoms including irregular vaginal bleeding also may identify those women with early endometrial cancer. Annual transvaginal ultrasound can be considered to evaluate the ovaries, although data on efficacy are limited. There are no data to support the annual use of CA-125 in screening. The ASCO endorsement panel concurs with the ESMO recommendations that prophylactic removal of the uterus and ovaries might be an option in female carriers from age 35 years and after childbearing is completed.

Regarding screening and surveillance for rare extracolonic cancers, there is no evidence that routine screening of other target organs (eg, small bowel or urinary) changes outcomes, but there may be a role for specialized surveillance to be considered on a case-by-case basis depending on family history.

Clinical Management of Individuals With Classic FAP, AFAP, and MAP

Sigmoidoscopy or colonoscopy in families with classic FAP. Although the ESMO guidelines specifies that carriers of *APC* mutations (or those at risk) should undergo sigmoidoscopy every 2 years, starting at the age of 12 to 14 years, the ASCO endorsement panel notes that its members and other experts recommend initiating colorectal screening at age 10 to 11 years[37] and also suggests that the surveillance interval be dependent on findings and may be as frequent as every year. Given the variability in polyposis phenotypes, colonoscopy may be the preferred test for diagnosis and management of clinically significant neoplasia. Although surgery remains the preferred management option for individuals with large numbers of polyps and/or advanced adenomas, close endoscopic follow-up with colonoscopy and polypectomy at frequent intervals (eg, every 6 to 24 months) may be considered for interim management of individuals with moderate to low polyp burden.

For at-risk individuals in families with AFAP. The results of genetic testing may help guide management. *APC*-mutation carriers should be managed as described in the previous paragraph. Individuals without identified germline mutations should begin colonoscopy at the age of 18 to 20 years, with surveillance every 2 years or more frequently, depending on polyp burden. Surgery is the preferred management option if there are large numbers of adenomas, including adenomas showing a high degree of dysplasia. Some patients with AFAP can be conservatively managed with colonoscopy and polypectomy every 1 to 2 years.

Surveillance of the rectum or pouch after colorectal surgery. Surveillance of the rectum or pouch should be continued even after colectomy. For individuals with residual rectum, careful surveillance at 6- to 12-month intervals is recommended. For individuals with ileal pouch anal anastomosis, surveillance may be performed at 1- to 5-year intervals, depending on polyp burden. The expert opinion of the ASCO endorsement panel is that 5-year surveillance intervals may be too infrequent for effective surveillance. Surveillance intervals should be determined on a case-by-case basis and may even be shorter than 1 year for some individuals.

Screening for desmoid tumors and thyroid cancer in classic FAP and AFAP. Development of desmoid tumors is unpredictable; however, the risk for desmoid disease may be influenced by family history and abdominal surgery. For individuals considered to be at high risk for desmoid disease, a regular physical examination and baseline imaging (abdominal computed tomography or magnetic resonance imaging) should be considered if high risk factors are identified (ie, strong family history of desmoid tumors). Thyroid screening may be considered, although data to support its effectiveness are lacking.

Germline genetic testing for mutations in MUTYH*—full sequencing for nonwhite individuals.* The ESMO guidelines recommends that testing begin with screening for the most common mutations (*G396D*, *Y179C*) identified in white populations, followed by analysis of the entire gene in heterozygotes. Because there are other founder mutations in other ethnic groups, full sequencing of *MUTYH* should be considered for individuals of non-European, nonwhite ancestry with multiple adenomas.

ENDORSEMENT RECOMMENDATION

ASCO endorses the Familial Risk–Colorectal Cancer: ESMO Clinical Practice Guidelines published in 2013 by Balmana et al[1] on behalf of the ESMO Guidelines Working Group in *Annals of Oncology*, with minor qualifying statements.

ADDITIONAL RESOURCES

More information, including Data Supplements with a reprint of all ESMO recommendations, a Methodology Supplement, slide sets, and clinical tools and resources, is available at www.asco.org/endorsements/HereditaryCRC. Patient information is available at www.cancer.net.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Appendix

Table A1. Members of Familial Risk–Colorectal Cancer Endorsement Panel

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