Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes

Description

Genetic testing is available for those with various types of hereditary cancer. This review evaluates genetic testing for hereditary colorectal cancer (CRC) and polyposis syndromes, including familial adenomatous polyposis (FAP), Lynch syndrome (formerly known as hereditary nonpolyposis colorectal cancer), MUTYH-associated polyposis (MAP), Lynch syndrome-related endometrial cancer, juvenile polyposis syndrome (JPS), and Peutz-Jeghers syndrome (PJS).

OBJECTIVE

The objective of this evidence review is to assess whether the use of genetic testing improves the net health outcome in patients with Lynch syndrome and other inherited colon cancer syndromes. This review does not address individuals without a personal history of cancer, nor screening or presymptomatic use of genetic tests and services.
POLICY STATEMENT

APC Testing

Genetic testing for APC gene variants may be considered medically necessary in the following patients:

- Patients with a differential diagnosis of attenuated FAP vs MUTYH-associated polyposis (MAP) vs Lynch syndrome. Whether testing begins with APC variants or screening for mismatch repair (MMR) variants depends on clinical presentation.

Genetic testing for APC gene variants is not medically necessary for colorectal cancer patients with classical FAP for confirmation of the FAP diagnosis.

MUTYH Testing

Genetic testing for MUTYH gene variants may be considered medically necessary in the following patients:

- Patients with a differential diagnosis of attenuated FAP vs MAP vs Lynch syndrome and a negative result for APC gene variants. A family history of no parents or children with FAP is consistent with MAP (autosomal recessive).

MMR GENE Testing

Genetic testing for MMR genes (MLH1, MSH2, MSH6, PMS2) may be considered medically necessary in the following patients:

- Patients with colorectal cancer (CRC), for the diagnosis of Lynch syndrome (see Policy Guidelines section).
- Patients with endometrial cancer and a first-degree relative diagnosed with a Lynch-associated cancer (see Policy Guidelines section), for the diagnosis of Lynch syndrome.
- Patients with a differential diagnosis of attenuated FAP vs MAP vs Lynch syndrome. Whether testing begins with APC variants or screening for MMR genes depends on clinical presentation.

EPCAM Testing

Genetic testing for EPCAM gene variants may be considered medically necessary in the following patients:

- Patients with CRC, for the diagnosis of Lynch syndrome (see Policy Guidelines section) when:
  - Tumor tissue shows lack of MSH2 protein expression by immunohistochemistry and patient is negative for an MSH2 germline variant; OR
  - Tumor tissue shows a high level of microsatellite instability and patient is negative for a germline variant in MLH1, MSH2, MSH6, and PMS2

BRAF V600E or MLH1 promoter methylation

Genetic testing for BRAF V600E or MLH1 promoter methylation may be considered medically necessary to exclude a diagnosis of Lynch syndrome when the MLH1 protein is not expressed in a CRC tumor on immunohistochemical analysis.
**SMAD4 and BMPR1A Testing**

Genetic testing for SMAD4 and BMPR1A gene variants may be considered **medically necessary** in the following patients:

- Patients with a clinical diagnosis of juvenile polyposis syndrome based on the presence of any one of the following:
  - at least 3 to 5 juvenile polyps in the colon
  - multiple juvenile polyps in other parts of the gastrointestinal tract
  - any number of juvenile polyps in a person with a known family history of juvenile polyps.

**STK11 Testing**

Genetic testing for STK11 gene variants may be considered **medically necessary** in the following patients:

- Patients with a clinical diagnosis of Peutz-Jeghers syndrome based on the presence of any 2 of the following:
  - presence of 2 or more histologically confirmed Peutz-Jeghers polyps of the small intestine
  - characteristic mucocutaneous pigmentation of the mouth, lips, nose, eyes, genitalia, or fingers
  - family history of Peutz-Jeghers syndrome.

Genetic testing for all other gene variants for Lynch syndrome or CRC is considered **investigational**.

**POLICY GUIDELINES**

**Evaluation for Lynch Syndrome**

For patients with colorectal cancer (CRC) being evaluated for Lynch syndrome, either the microsatellite instability (MSI) test or the immunohistochemical (IHC) test with or without BRAF gene variant testing, should be used as an initial evaluation of tumor tissue before mismatch repair (MMR) gene analysis. Both tests are not necessary. Proceeding to MMR gene sequencing would depend on results of MSI or IHC testing. In particular, IHC testing may help direct which MMR gene likely contains a variant, if any, and may also provide additional information if MMR genetic testing is inconclusive.

When indicated, genetic sequencing for MMR gene variants should begin with MLH1 and MSH2 genes, unless otherwise directed by the results of IHC testing. Standard sequencing methods will not detect large deletions or duplications; when MMR gene variants are expected based on IHC or MSI studies, but none are found by standard sequencing, additional testing for large deletions or duplications is appropriate.

**Genetics Nomenclature Update**

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). The Society’s nomenclature is recommended by the Human Variome Project, the Human Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes,
panels, exomes, and genomes. Table PG2 shows the recommended standard terminology: "pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign" to describe variants identified that cause Mendelian disorders.

### Table PG1. Nomenclature to Report on Variants Found in DNA

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation</td>
<td>Disease-associated</td>
<td>Disease-associated change in the DNA sequence</td>
</tr>
<tr>
<td></td>
<td>variant</td>
<td></td>
</tr>
<tr>
<td>Variant</td>
<td>Change in the DNA</td>
<td>sequence</td>
</tr>
<tr>
<td></td>
<td>family</td>
<td></td>
</tr>
<tr>
<td>Familial variant</td>
<td>Disease-associated</td>
<td>variant identified in a proband for use in subsequent targeted genetic</td>
</tr>
<tr>
<td></td>
<td>variant</td>
<td>testing in first-degree relatives</td>
</tr>
</tbody>
</table>

### Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Likely pathogenic</td>
<td>Likely disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Variant of uncertain significance</td>
<td>Change in DNA sequence with uncertain effects on disease</td>
</tr>
<tr>
<td>Likely benign</td>
<td>Likely benign change in the DNA sequence</td>
</tr>
<tr>
<td>Benign</td>
<td>Benign change in the DNA sequence</td>
</tr>
</tbody>
</table>

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

### Genetic Counseling

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

### BENEFIT APPLICATION

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.
Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient’s existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

**FDA REGULATORY STATUS**

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Genetic tests reviewed in this evidence review are available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

Several Clinical Laboratory Improvement Amendments (CLIA)-licensed clinical laboratories offer MMR gene variant testing for Lynch syndrome. For example, the GeneTests website (available online at https://www.ncbi.nlm.nih.gov/gtr/all/?term=lynch+syndrome) lists laboratories that offer this service. In at least 1 laboratory, Lynch syndrome variant testing is packaged under a copyrighted name. The COLARIS test (Myriad Genetic Laboratories) includes sequence analysis of MLH1, MSH2, MSH6, and PMS2; large rearrangement analysis for MLH1, MSH2, PMS2, and MSH6 large deletions and duplications; and analysis for large deletions in the EPCAM gene near MSH2. Note that there are 2 versions of this test, the COLARIS (excludes PMS2 testing) and COLARIS Update (includes PMS2 testing). Individualized testing (eg, targeted testing for a family variant) can also be requested. The COLARIS PLUS test includes full sequence analysis of the MLH1, MSH2, MSH6, PMS2, and MYH genes and rearrangement analysis of MLH1, MSH2, MSH6, MYH, and EPCAM using microarray comparative genomic hybridization analysis, and of PMS2 using multiplex ligation-dependent probe amplification analysis.

Similarly, GeneTests lists U.S.-based CLIA-licensed clinical laboratories that provide APC variant testing and those that provide MUTYH variant testing. The COLARIS AP test (Myriad Genetic Laboratories) includes DNA sequencing analysis of the APC and MUTYH genes, as well as analysis of large rearrangements in the APC gene not detected by DNA sequencing.

**RATIONALE**

**Summary of Evidence**

For individuals who are suspected of attenuated familial adenomatous polyposis (FAP), MUTYH-associated polyposis (MAP), and Lynch syndrome who receive genetic testing for APC, the evidence includes a TEC Assessment. The relevant outcomes are overall survival (OS), disease-specific survival, and test accuracy and validity. For patients with an APC variant, enhanced surveillance and/or prophylactic treatment will reduce the future incidence of colon cancer and improve health outcomes. A related familial polyposis syndrome, MAP syndrome, is associated with variants in the MUTYH gene. Testing for this genetic variant is necessary when the differential diagnosis includes both FAP and MAP because distinguishing between the two leads to different management strategies. Depending on the presentation, Lynch syndrome may be part of the same differential diagnosis. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who (1) are suspected of attenuated FAP, MAP, and Lynch syndrome, or (2) have colon cancer, or (3) have endometrial cancer and a first-degree relative diagnosed with a Lynch-associated cancer, who receive genetic testing for MMR genes, the evidence includes an Agency for Healthcare Research and Quality report, a supplemental assessment to that report by the Evaluation of Genomic Applications in Practice and Prevention Working Group, and an Evaluation of Genomic Applications in Practice and Prevention recommendation for genetic testing in CRC. The relevant outcomes are OS, disease-specific survival, and test accuracy and validity. A positive genetic test for an MMR variant can also lead to changes in the management of other Lynch syndrome malignancies. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who warrant Lynch testing, screen negative on MMR testing, but positive for microsatellite instability and lack MSH2 protein expression who receive genetic testing for EPCAM variants, the evidence includes variant prevalence studies and case series.

The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.
The relevant outcomes are OS, disease-specific survival, and test accuracy and validity. Identification of an EPCAM variant could lead to changes in management that improve health outcomes. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have CRC in whom MLH1 protein is not expressed on immunohistochemical analysis who receive genetic testing for BRAF V600E or MLH1 promoter methylation, the evidence includes case series. The relevant outcomes are OS, disease-specific survival, and test accuracy and validity. Studies have shown, with high sensitivity and specificity, an association between BRAF V600E variant and MLH1 promoter methylation with sporadic CRC. Therefore, this type of testing could eliminate the need for further genetic testing or counseling for Lynch syndrome. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who are suspected of juvenile polyposis syndrome (JPS) or Peutz-Jeghers syndrome (PJS) who receive genetic testing for SMAD4, BMPR1A, or STK11 genes, respectively, the evidence includes multiple observational studies. The relevant outcomes are OS, disease-specific survival, and test accuracy and validity. Studies have shown, with high sensitivity and specificity, an association between SMAD4 and BMPR1A and STK11 variants with JPS and PJS, respectively. Direct evidence of clinical utility for genetic testing of a JPS or PJS is not available. Genetic testing may have clinical utility by avoiding burdensome and invasive endoscopic examinations, release from intensified screening program resulting in psychological relief, and may improve health outcomes by identifying those who require intense surveillance or prophylactic colectomy. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

**SUPPLEMENTAL INFORMATION**

**Practice Guidelines and Position Statements**

**National Comprehensive Cancer Network**

The NCCN guidelines (v.2.2019) are summarized in Table 1.

Table 1. Criteria for Evaluation of Lynch Syndrome

<table>
<thead>
<tr>
<th>Criteria for the Evaluation of Lynch Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Known LS variant in the family</td>
</tr>
<tr>
<td>An individual with colorectal or endometrial cancer and any of the following:</td>
</tr>
<tr>
<td>• Diagnosed &lt;50 y</td>
</tr>
<tr>
<td>• Another synchronous or metachronous LS-related cancer(^a)</td>
</tr>
<tr>
<td>• (\geq 1) first-degree or second-degree relative with LS-related(^a) cancer diagnosed &lt;50 y</td>
</tr>
<tr>
<td>• (\geq 2) first-degree or second-degree relatives with LS-related(^a) cancers regardless of age</td>
</tr>
<tr>
<td>An individual with colorectal or endometrial cancer at any age with tumor showing evidence of MMR deficiency, either by MSI or loss of MMR protein expression(^b)</td>
</tr>
</tbody>
</table>

The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.
Family history of any of the following:

- ≥1 first-degree relative with colorectal or endometrial cancer diagnosed <50 y
- ≥1 first-degree relative with colorectal or endometrial cancer and another synchronous or metachronous LS-related cancer\(^a\)
- ≥2 first-degree or second-degree relatives with LS-related cancer,\(^a\) including ≥1 diagnosed <50 y
- ≥3 first-degree or second-degree relatives with LS-related cancers,\(^a\) regardless of age

An individual with an LS-related cancer\(^a\) or unaffected individual with ≥5% risk\(^c\) of having an MMR gene variant based on predictive models (PREMM5, MMRpro, MMRpredict)

An individual with a colorectal tumor with MSI-high histology (ie, presence of tumor-infiltrating lymphocytes, Crohn’s-like lymphocytic reaction, mucinous/signet ring differentiation, or medullary growth pattern) diagnosed ≤60 y

LS: Lynch syndrome; MMR: mismatch repair; MSI: microsatellite instability.

\(^a\) LS-related cancers include colorectal, endometrial, gastric, ovarian, pancreas, ureter and renal pelvis, brain (usually glioblastoma), biliary tract, small intestinal cancers, as well as sebaceous carcinomas, and keratoacanthomas as seen in Muir-Torre syndrome.

\(^b\) Tumor screening for MMR deficiency is appropriate for all colorectal and endometrial cancers regardless of age at diagnosis, however, germline genetic testing is generally reserved for patients with early age at diagnosis; positive family history; or abnormal tumor testing results; MSI or loss of MMR protein expression.

\(^c\) There are recent data that resulted in a lower threshold of ≥2.5% for the PREMM5 predictive model risk for having an MMR gene variant. Based on these data, it is reasonable for testing to be done based on the ≥2.5% score result and clinical judgment. Of note, with the lower threshold, there is an increase in sensitivity, but a decrease in specificity. It is not known how this applies to the general population of unaffected individuals.

Additionally, the NCCN guidelines (v.2.2019) recommend screening for Lynch syndrome in all endometrial cancer patients younger than 50 years.\(^9\) Genetic testing is recommended for at-risk family members of patients with positive variants in MLH1, MSH2, MSH6, and PMS2. The NCCN guidelines also indicate BRAF V600E testing or MLH1 promoter methylation testing may be used when MLH1 is not expressed in the tumor on immunohistochemical analysis to exclude a diagnosis of Lynch syndrome. These guidelines also address familial adenomatous polyposis (classical and attenuated) and MUTYH-associated polyposis and are consistent with the information provided in this evidence review.

The NCCN guidelines for colon cancer (v.2.2019),\(^9\) and for CRC screening (v.3.2019),\(^10\) recommend CRC patients treated with curative-intent surgery undergo surveillance colonoscopy at 1 year post surgery and, if normal, again in 3 years, then every 5 years based on findings. However, because of the high likelihood of cancer, colonoscopy is recommended every one to two years throughout life for patients with Lynch syndrome before cancer diagnosis; and the high likelihood of a second primary cancer is based on a first cancer diagnosis.\(^8\) The NCCN guidelines on genetic/familial high-risk assessment for colorectal indicate for MLH1, MSH2, and EPCAM variant carriers that surveillance with colonoscopy should begin “at age 20 to 25 years or 2 to 5 years before the earliest colon cancer if it is diagnosed before age 25 years and repeat every 1 to 2 years.”\(^3\) MSH6 variant carriers should begin surveillance with colonoscopy at age 30 to 35 years, and PMS2 carriers should begin surveillance at age 35 to 40 years. However, screening may need to be initiated earlier in some families, depending on the ages of cancers observed in family members. This screening is recommended every 2 to 3 years until age 40 or 50 years for MSH6 and PMS2 variant carriers, respectively, at which time colonoscopy should be performed every 1 to 2 years. “If the patient is not a candidate for routine surveillance, subtotal colectomy may be considered.”

The NCCN guidelines for colon cancer recommend that patients 70 years or younger plus those older than 70 years of age who meet the Bethesda guidelines be tested for the mismatch repair (MMR) protein for possible Lynch syndrome.\(^9\) These guidelines also

The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.
indicate all colon cancer patients should be questioned about family history and considered for risk assessment as per the NCCN colorectal screening guidelines. The NCCN guidelines for uterine neoplasm also recommend universal screening for MMR genes.

There are limited data on the efficacy of various screening modalities in juvenile polyposis syndrome and Peutz-Jeghers syndrome. The NCCN cancer risk and surveillance 2 category 2A recommendations for these indications are summarized in Tables 2 and 3.

Table 2. Risk and Surveillance Guidelines for Peutz-Jeghers Syndrome

<table>
<thead>
<tr>
<th>Site</th>
<th>Lifetime Risk, %</th>
<th>Screening Procedure and Interval</th>
<th>Initiation Age, y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>45-50</td>
<td>• Mammogram and breast MRI annually</td>
<td>25 y</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Clinical breast exam every 6 mo</td>
<td></td>
</tr>
<tr>
<td>Colon</td>
<td>39</td>
<td>Colonoscopy every 2-3 y</td>
<td>Late teens</td>
</tr>
<tr>
<td>Stomach</td>
<td>29</td>
<td>Upper endoscopy every 2-3 y</td>
<td>Late teens</td>
</tr>
<tr>
<td>Small intestine</td>
<td>13</td>
<td>Small bowel visualization (CT or MRI enterography or video capsule endoscopy 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)</td>
<td>8 to 10 y</td>
</tr>
<tr>
<td>Pancreas</td>
<td>11-36</td>
<td>Magnetic resonance choangiopancreatography with contrast or endoscopic ultrasound every 1-2 h</td>
<td>30 to 35 y</td>
</tr>
<tr>
<td>Ovary (typically benign sex cord/Sertoli cell tumors)</td>
<td>18-21</td>
<td>• Pelvic examination and Pap smear annually</td>
<td>18 to 20 y</td>
</tr>
<tr>
<td>Cervix (typically cervical adenoma malignum)</td>
<td>10</td>
<td>• Consider transvaginal ultrasound</td>
<td></td>
</tr>
<tr>
<td>Uterus</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Testes (typically sex cord/Sertoli cell tumors)</td>
<td></td>
<td>Annual testicular exam and observation for feminizing changes</td>
<td>10 y</td>
</tr>
<tr>
<td>Lung</td>
<td>15-17</td>
<td>• Provide education about symptoms and smoking cessation</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• No other specific recommendations have been made</td>
<td></td>
</tr>
</tbody>
</table>

CT: computed tomography; MRI: magnetic resonance imaging.

The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.
Table 3. Risk and Surveillance Guidelines for Juvenile Polyposis Syndrome

<table>
<thead>
<tr>
<th>Site</th>
<th>Lifetime Risk, %</th>
<th>Screening Procedure and Interval</th>
<th>Initiation Age, y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>40-50</td>
<td>Colonoscopy every year if polyps are found and every 2-3 y if no polyps are found&lt;sup&gt;a&lt;/sup&gt;</td>
<td>15 y</td>
</tr>
<tr>
<td>Stomach</td>
<td>21 if multiple polyps</td>
<td>Upper endoscopy annually if polyps are found and every 2-3 y if no polyps are found&lt;sup&gt;a&lt;/sup&gt;</td>
<td>15 y</td>
</tr>
<tr>
<td>Small intestine</td>
<td>Rare, undefined</td>
<td>No recommendations made</td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td>Rare, undefined</td>
<td>No recommendations made</td>
<td></td>
</tr>
<tr>
<td>HHT</td>
<td>Undefined</td>
<td>In individuals with SMAD4 variants, screen for vascular lesions associated with HHT</td>
<td>Within first 6 mo of age</td>
</tr>
</tbody>
</table>

HHT: hereditary hemorrhagic telangiectasia.

<sup>a</sup> In families without an identified genetic variants, consider substituting endoscopy every 5 y beginning at age 20 and every 10 y beginning at age 40 y in patients in whom no polyps are found.

American College of Gastroenterology

The American College of Gastroenterology (2015) issued practice guidelines for the management of patients with hereditary gastrointestinal cancer syndromes.<sup>26</sup>

For Lynch syndrome, the College recommended:

*All newly diagnosed colorectal cancers (CRCs) should be evaluated for mismatch repair deficiency.*

Analysis may be done by immunohistochemical testing for the MLH1/MSH2/MSH6/PMS2 proteins and/or testing for microsatellite instability. Tumors that demonstrate loss of MLH1 should undergo BRAF testing or analysis for MLH1 promoter hypermethylation.

Individuals who have a personal history of a tumor showing evidence of mismatch repair deficiency (and no demonstrated BRAF variant or hypermethylation of MLH1), a known family variant associated with LS [Lynch syndrome], or a risk of ≥5% chance of LS based on risk prediction models should undergo genetic evaluation for LS.<sup>101</sup>

Genetic testing of patients with suspected LS should include germline variant genetic testing for the MLH1, MSH2, MSH6, PMS2, and/or EPCAM genes or the altered gene(s) indicated by IHC testing.*

*Familial adenomatous polyposis syndromes, the College recommended:

*Familial adenomatous polyposis (FAP)/MUTYH-associated polyposis/attenuated polyposis*

Individuals who have a personal history of >10 cumulative colorectal adenomas, a family history of one of the adenomatous polyposis syndromes, or a history of adenomas and FAP-type extracolonic manifestations (duodenal/ampullary adenomas, desmoid tumors, papillary thyroid cancer, congenital hypertrophy of the retinal pigment epithelium, epidermal cysts, osteomas) should undergo assessment for the adenomatous polyposis syndromes.

The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.
Genetic testing of patients with suspected adenomatous polyposis syndromes should include \textit{APC} and \textit{MUTYH} gene variant analysis."

\textit{For juvenile polyposis syndrome}, the College recommended:

"Genetic evaluation of a patient with possible JPS [juvenile polyposis syndrome] should include testing for \textit{SMAD4} and \textit{BMPR1A} mutations"

"Surveillance of the gastrointestinal (GI) tract in affected or at-risk JPS patients should include screening for colon, stomach, and small bowel cancers (strong recommendation, very low quality of evidence).

Coelectomy and ileorectal anastomosis or proctocolectomy and ileal pouch-anal anastomosis is indicated for polyp-related symptoms, or when the polyps cannot be managed endoscopically (strong recommendation, low quality of evidence).

Cardiovascular examination for and evaluation for hereditary hemorrhagic telangiectasia should be considered for \textit{SMAD4} mutation carriers (conditional recommendation, very low quality of evidence)."

\textit{For Peutz-Jeghers syndrome}, the College recommended:

"Genetic evaluation of a patient with possible PJS [Peutz-Jeghers syndrome] should include testing for \textit{STK11} mutations."

"Surveillance in affected or at-risk PJS patients should include monitoring for colon, stomach, small bowel, pancreas, breast, ovary, uterus, cervix, and testes cancers. Risk for lung cancer is increased, but no specific screening has been recommended. It would seem wise to consider annual chest radiograph or chest computed tomography (CT) in smokers (conditional recommendation, low quality of evidence)."

\begin{table}
\caption{American Society of Clinical Oncology and Society of Surgical Oncology}
\end{table}

The American Society of Clinical Oncology (2015) concluded the European Society for Medical Oncology clinical guidelines published in 2013 were based on the most relevant scientific evidence and therefore endorsed them with minor qualifying statements (in bold italics).\textsuperscript{102} The recommendations as related to genetic testing hereditary CRC syndromes are summarized below:

\begin{itemize}
\item "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.

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

\item If loss of any of the other proteins (MSH2, MSH6, PMS2) is observed, germline genetic testing should be carried out \textit{for the genes corresponding to the absent proteins} (eg, MSH2, MSH6, EPCAM, PMS2, or MLH1).

\item Full germline genetic testing for Lynch syndrome should include DNA sequencing and large rearrangement analysis...

\item Patients with multiple colorectal adenomas should be considered for full germline genetic testing of \textit{APC} and/or \textit{MUTYH}.

\item Germline testing of \textit{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. \textit{For nonwhite individuals, full sequencing of MUTYH should be considered."

\begin{table}
\caption{U.S. Preventive Services Task Force Recommendations}
\end{table}

No U.S. Preventive Services Task Force recommendations for genetic testing of Lynch syndrome and other inherited colon cancer syndromes have been identified.

\begin{table}
\caption{The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.}
\end{table}
Medicare National Coverage

Under Medicare, genetic tests for cancer are a covered benefit only for a beneficiary with a personal history of an illness, injury, or signs/symptoms thereof (i.e., clinically affected). A person with a personal history of a relevant cancer is a clinically affected person, even if the cancer is considered cured. Predictive or presymptomatic genetic tests and services, in the absence of past or present illness in the beneficiary, are not covered under national Medicare rules. The Centers for Medicare & Medicaid Services recognizes Lynch syndrome as "an autosomal dominant syndrome that accounts for about 3% to 5% of colorectal cancer cases. [Lynch] syndrome variants occur in the following genes: hMLH1, hMSH2, hMSH6, PMS2, and EPCAM." The Centers for Medicare & Medicaid Services also recognize for familial adenomatous polyposis and MUTYH-associated polyposis syndromes and their associated variants.

REFERENCES


The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.


The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.


The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.


The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.

POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>March 2012</td>
<td>New policy</td>
<td>Policy updated with name change and literature review; References 15, 30, 43-49, 52, 53 added. Additional medically necessary indication added for patients with endometrial cancer and one first-degree relative diagnosed with a Lynch-associated cancer.</td>
</tr>
<tr>
<td>March 2013</td>
<td>Replace policy</td>
<td>Updated with literature review through September 2013. References 24, 33-35 and 58 added. References 39-40 updated. Policy Statement added that BRAF V600E or MLH1 promoter methylation may be considered medically necessary when MLH1 is not expressed in the tumor on IHC analysis.</td>
</tr>
<tr>
<td>March 2014</td>
<td>Replace policy</td>
<td>Policy updated with literature review through December 29, 2015; references 59-60 added. Policy statements unchanged.</td>
</tr>
<tr>
<td>December 2016</td>
<td>Replace policy</td>
<td>Policy updated with literature review through July 21, 2017; references 4-6, 28-33, 35-39, 41, 51-57, 64-65, 67-70, 83 added.</td>
</tr>
</tbody>
</table>

The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.
<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>December 2018</td>
<td>Replace policy</td>
<td>Policy updated with literature review through July 9, 2018; references 22-36 and 92-99 added. Policy section revised to add policy statements indicating that genetic testing for SMAD4, BMPR1A, or STK11 gene variants may be considered medically necessary for juvenile polyposis syndrome and Peutz-Jeghers syndrome. Information related to “at-risk relatives” deleted due to benefit considerations.</td>
</tr>
<tr>
<td>December 2019</td>
<td>Replace policy</td>
<td>Policy updated with literature review through August 6, 2019; references on NCCN updated. Clarification added to objective statement “This review does not address individuals without a personal history of cancer, nor screening or presymptomatic use of genetic tests and services.”</td>
</tr>
</tbody>
</table>