MEDICAL POLICY – 12.04.506
Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes

BCBSA Ref. Policy: 2.04.08

Effective Date: Dec. 1, 2018
Last Revised: Nov. 13, 2018
Replaces: N/A

RELATED MEDICAL POLICIES:
None

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Introduction

Five to ten percent of all cancers may be inherited. Several genes have been identified that are associated with colon cancer and are passed from parents to children. Genetic testing may help determine the risk of colon cancer in family members and guide the frequency of colon cancer screening tests. This policy describes when those tests are covered based on the latest scientific studies. Some of these tests need to be pre-approved by the health plan. See Coverage Criteria for more specific information.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria
<table>
<thead>
<tr>
<th>Testing</th>
<th>Medical Necessity</th>
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<tr>
<td><strong>Lynch Syndrome (Also known as hereditary non-polyposis colorectal cancer or HNPC)</strong></td>
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</table>
| **Initial screening** | Screening for Lynch syndrome as an initial evaluation of tumor tissue:  
- ALL cases of colorectal cancer, regardless of age screened for Lynch Syndrome using either microsatellite instability (MSI) or immunohistochemical (IHC), with or without BRAF/MLH1 promoter methylation testing, may be considered medically necessary as an initial evaluation of tumor tissue.  

**Note:** MSI/IHC testing prior to actual genetic testing for Lynch syndrome is recommended, but not required. |
| **MMR gene testing (Lynch syndrome) (eg, COLARIS® [Myriad])** | Genetic testing for mismatch repair (MMR) genes (MLH1, MSH2, MSH6, PMS2 sequence analysis) (Lynch syndrome) may be considered medically necessary when the member meets ANY ONE of the following criteria:  
- A colon cancer diagnosis with a positive result from MSI/IHC test (see Lynch syndrome initial screening, above)  
**OR**  
- Colorectal carcinoma (CRC) diagnosed in a patient who is less than 50 years old  
**OR**  
- Endometrial cancer diagnosed in a patient who is less than 50 years old  
**OR**  
- All of the Amsterdam II clinical criteria are met (see below)  
**OR**  
- One of the revised Bethesda guidelines are met (see below)  
**OR**  
- One first-degree or second-degree relative* with a Lynch syndrome mutation (genes MLH1, MSH2, MSH6, PMS2)  
**OR**  
- Personal history of endometrial cancer diagnosed at age 51-60 and one first-degree relative diagnosed with a Lynch-associated cancer.**|

*For the purposes of familial assessment, first- or second-degree relatives are blood relatives on the same side of the family (maternal or paternal). The maternal and paternal sides of the
Testing | Medical Necessity
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| | family should be considered independently for familial patterns of cancer.
| | *First-degree relatives are parents, siblings, and offspring. Second-degree relatives are aunts, uncles, grandparents, niece, nephews or half-siblings.
| | **Lynch-associated cancers include colorectal, endometrial, gastric, ovarian, pancreas, bladder, ureter and renal pelvis, brain (usually glioblastoma as seen in Turcot syndrome), and small intestinal cancers, as well as sebaceous gland adenomas and keratoacanthomas in Muir-Torre syndrome.

**Genetic testing for Lynch syndrome is considered investigational when the member has not met at least one of the criteria listed above.**

### Familial Adenomatous Polyposis (FAP) and Associated Variants

| **Adenosis polyposis coli (APC) testing (familial adenomatous polyposis)** (eg, Colaris AP® [Myriad]) | Genetic testing for adenosis polyposis coli (APC) gene variants may be considered medically necessary for ANY ONE of the following indications:
| | • Personal history of greater than 10 cumulative colonic adenomatous polyps
| | OR
| | • One first-degree relative diagnosed with familial adenomatous polyposis (FAP) or with a documented APC mutation.
| | o If feasible, the specific APC mutation should be identified in the affected first-degree relative with FAP prior to testing the member (see below).
| | o “Full sequence” APC genetic testing is considered medically necessary only when the affected family member is unavailable or unwilling to be tested.

**Note:** First-degree relatives are parents, siblings, and offspring.

**APC genetic testing is considered investigational when the member has not met at least one of the criteria listed above.**

| **MUTYH (formerly known as MYH)-associated polyposis (MAP) testing** | Genetic testing for MUTYH gene variants (MUTYH-associated polyposis [MAP]) may be considered medically necessary for ANY ONE of the following indications:
| | • Personal history of 10 to 20 cumulative adenomatous polyps, with negative APC mutation testing and no family history of adenomatous polyposis
<table>
<thead>
<tr>
<th>Testing</th>
<th>Medical Necessity</th>
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<tbody>
<tr>
<td>OR</td>
<td>- Personal history of 10 to 20 cumulative adenomatous polyps in a member with a family history which is consistent with recessive inheritance (ie, family history is positive only for sibling[s])</td>
</tr>
<tr>
<td>OR</td>
<td>- Asymptomatic siblings of individuals with known MYH polyposis mutation</td>
</tr>
<tr>
<td>MUTYH-associated polyposis (MAP) genetic testing is considered investigational when the member has not met at least one of the criteria listed above.</td>
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</tr>
<tr>
<td>SMAD4 and BMPR1A testing (Juvenile polyposis syndrome)</td>
<td>Genetic testing for SMAD4 and BMPR1A gene variants may be considered medically necessary when any ONE of the following criteria is met:</td>
</tr>
<tr>
<td>- Patients with a clinical diagnosis of juvenile polyposis syndrome based on the presence of any one of the following:</td>
<td>- At least 3 to 5 juvenile polyps in the colon</td>
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<tr>
<td>- Multiple juvenile polyps in other parts of the gastrointestinal tract</td>
<td>- Any number of juvenile polyps in a person with a known family history of juvenile polyps</td>
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<tr>
<td>STK11 testing (Peutz-Jeghers syndrome)</td>
<td>Genetic testing for STK11 gene variants may be considered medically necessary when any ONE of the following criteria is met:</td>
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<tr>
<td>- Patients with a clinical diagnosis of Peutz-Jeghers syndrome based on the presence of any 2 of the following:</td>
<td>- Presence of 2 or more histologically confirmed Peutz-Jeghers polyps of the small intestine</td>
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<tr>
<td>- Characteristic mucocutaneous pigmentation of the mouth, lips, nose, eyes, genitalia, or fingers</td>
<td>- Family history of Peutz-Jeghers syndrome</td>
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<tr>
<td>Code</td>
<td>Description</td>
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<tr>
<td>81201</td>
<td>APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; full gene sequence</td>
</tr>
<tr>
<td>81202</td>
<td>APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; known familial variants</td>
</tr>
<tr>
<td>81203</td>
<td>APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; duplication/deletion variants</td>
</tr>
<tr>
<td>81210</td>
<td>BRAF (v-raf murine sarcoma viral oncogene homolog B1) (eg, colon cancer), gene analysis, V600E variant</td>
</tr>
<tr>
<td>81288</td>
<td>MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; promoter methylation analysis</td>
</tr>
<tr>
<td>81292</td>
<td>MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis</td>
</tr>
<tr>
<td>81293</td>
<td>MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants</td>
</tr>
<tr>
<td>81294</td>
<td>MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants</td>
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<tr>
<td>81295</td>
<td>MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis</td>
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<tr>
<td>81296</td>
<td>MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis, known familial variants</td>
</tr>
<tr>
<td>81297</td>
<td>MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis, duplication/deletion variants</td>
</tr>
<tr>
<td>81298</td>
<td>MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis, full sequence analysis</td>
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<tr>
<td>81299</td>
<td>MSH6 (mutS homolog 6 [e. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis, known familial variants</td>
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<tr>
<td>81300</td>
<td>MSH6 (mutS homolog 6 [e. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis, duplication/deletion variants</td>
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<tr>
<td>81301</td>
<td>Microsatellite instability analysis (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) of markers for mismatch repair deficiency (eg, BAT25, BAT26), includes comparison of neoplastic and normal tissue, if performed</td>
</tr>
<tr>
<td>81317</td>
<td>PMS2 (postmeiotic segregation increased 2 [ s. cerevisiae]) (eg, hereditary nonpolyposis colorectal cancer, Lynch syndrome) gene analysis, full sequence analysis</td>
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<tr>
<td>Code</td>
<td>Description</td>
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<tr>
<td>81318</td>
<td>PMS2 (postmeiotic segregation increased 2 [ s. cerevisiae]) (eg, hereditary nonpolyposis colorectal cancer, lynch syndrome) gene analysis, known familial variants</td>
</tr>
<tr>
<td>81319</td>
<td>PMS2 (postmeiotic segregation increased 2 [ s. cerevisiae]) (eg, hereditary nonpolyposis colorectal cancer, lynch syndrome) gene analysis, duplication/deletion variants</td>
</tr>
<tr>
<td>81404</td>
<td>Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)</td>
</tr>
<tr>
<td>81405</td>
<td>Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis).</td>
</tr>
<tr>
<td>81406</td>
<td>Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia)</td>
</tr>
<tr>
<td>81435</td>
<td>Hereditary colon cancer syndromes (eg, Lynch syndrome, familial adenomatosis polyposis); genomic sequence analysis panel, must include analysis of at least 7 genes, including APC, CHEK2, MLH1, MSH2, MSH6, MUTYH, and PMS2</td>
</tr>
<tr>
<td>81436</td>
<td>Hereditary colon cancer syndromes (eg, Lynch syndrome, familial adenomatosis polyposis); duplication/deletion gene analysis panel, must include analysis of at least 8 genes, including APC, MLH1, MSH2, MSH6, PMS2, EPCAM, CHEK2, and MUTYH</td>
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</tbody>
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**Note:** CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

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**Related Information**

**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 (see Table 1). 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 2 shows the recommended standard terminology—“pathogenic,” “likely pathogenic,” “uncertain significance,” “likely benign,” and “benign”—to describe variants identified that cause Mendelian disorders.

### Table 1. Nomenclature to Report on Variants Found in DNA

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

### Table 2. ACMG-AMP Standards and Guidelines for Variant Classification

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
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<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.
General Guidelines for Lynch and FAP Syndromes

1. Testing may be done to distinguish between a diagnosis of Lynch syndrome versus Familial Adenomatous Polyposis (FAP). Whether testing begins with the “MLH1, MSH2, MSH6, PMS2” mutations or the “APC” mutations depends upon the clinical presentation.

2. In ideal situations, initial genetic testing for FAP or Lynch syndrome is performed in an affected family member so that testing in unaffected family members can focus on the mutation found in the affected family member. When this was not done, the following guidelines apply.

Lynch-Specific Guidelines

1. For patients with colorectal cancer being evaluated for Lynch syndrome, it is recommended that either the microsatellite instability (MSI) test, or the immunohistochemistry (IHC) test, with or without BRAF gene mutation testing, be used as an initial evaluation of tumor tissue prior to MLH1, MSH2, MSH6, PMS2 sequence analysis. (Note that MSI/IHC testing may not be feasible if no tumor tissue is available.) Consideration of proceeding to MLH1, MSH2, MSH6, PMS2 sequencing would depend on the results of MSI or IHC testing. IHC testing in particular may help direct which Lynch syndrome gene likely contains a mutation, if any, and may also provide some additional information if Lynch syndrome genetic testing is inconclusive.

2. Several Clinical Laboratory Improvement Amendments (CLIA)–licensed clinical laboratories offer gene mutation testing for Lynch syndrome. The GeneTests website (available online at: http://www.ncbi.nlm.nih.gov/sites/GeneTests/lab/clinical_disease_id/2622?db=genetests) lists 21 U.S.-located laboratories that offer this service. Lynch syndrome mutation testing is packaged under a copyrighted name by at least one of these. The COLARIS® test from Myriad Genetic Laboratories includes sequence analysis of MLH1, MSH2, MSH6, and PMS2; large rearrangement analysis for MLH1, MSH2, PMS2, and MSH6 large deletions/duplications; and analysis for large deletions in the EPCAM gene near MSH2. Two versions of this test, the COLARIS (excludes PMS2 testing) and COLARIS Update (includes PMS2 testing) are available. Testing is likely done in stages, beginning with the most common types of mutations. Individualized testing (eg, targeted testing for a family mutation) can also be requested.
3. Amsterdam II clinical criteria\(^1\) are the most stringent criteria for defining families at high risk for Lynch syndrome. **ALL** of the following criteria must be fulfilled:

- 3 or more relatives have been diagnosed with an associated cancer (colorectal cancer, or cancer of the endometrium, small intestine, ureter or renal pelvis)
- 1 of the 3 should be a first-degree relative of the other 2
- 2 or more successive generations are affected
- 1 or more relatives were diagnosed before the age of 50 years
- Familial adenomatous polyposis (FAP) should be excluded in cases of colorectal carcinoma
- Tumors should be verified by pathologic examination
- Modifications:
  - **EITHER:** very small families, which cannot be further expanded, can be considered to have HNPCC with only 2 colorectal cancers in first-degree relatives if at least 2 generations have the cancer and at least 1 case of colorectal cancer was diagnosed by the age of 55 years;
  - **OR**
    - In families with 2 first-degree relatives affected by colorectal cancer, the presence of a third relative with an unusual early-onset neoplasm or endometrial cancer is sufficient.

4. The revised Bethesda guidelines\(^2\) are less strict than the Amsterdam criteria and are intended to increase the sensitivity of identifying at-risk families. The Bethesda guidelines are also felt to be more useful in identifying which patients with colorectal cancer should have their tumors tested for microsatellite instability and/or immunohistochemistry. Fulfillment of **any** of the following criterion meets guidelines:

- Colorectal carcinoma (CRC) diagnosed in a patient who is less than 50 years old
- Presence of synchronous (at the same time) or metachronous (at another time, i.e., a recurrence of) CRC or other Lynch syndrome–associated tumors, regardless of age
- CRC with high microsatellite instability histology diagnosed in a patient less than 60 years old
 CRC diagnosed in 1 or more first-degree relatives with a Lynch syndrome-associated tumor, (colorectal, endometrial, gastric, ovarian, pancreas, bladder, ureter and renal pelvis, brain (usually glioblastoma as seen in Turcot syndrome), and small intestinal cancers, as well as sebaceous gland adenomas and keratoacanthomas in Muir-Torre syndrome) with one of the cancers being diagnosed at younger than 50 years of age

 CRC diagnosed with 1 or more first-degree relatives with an HNPCC-related tumor (colorectal, endometrial, stomach, ovarian, pancreas, bladder, ureter and renal pelvis, biliary tract, brain [usually glioblastoma as seen in Turcot syndrome], sebaceous gland adenomas and keratoacanthomas in Muir-Torre syndrome, and carcinoma of the small bowel), with one of the cancers being diagnosed at younger than age 50 years, OR CRC diagnosed in 2 or more first- or second-degree relatives with HNPCC-related tumor, regardless of age.

Multiple risk prediction models that provide quantitative estimates of the likelihood of an MMR variant are available such MMRpro, PREMM5 (Kastrinos et al [2017]), or MMRpredict. National Comprehensive Cancer Network guidelines recommend (category 2A) testing for Lynch syndrome in individuals with a 5% or higher predicted risk of the syndrome on these risk prediction models.

**MUTYH Gene Guidelines**

1. In many cases, genetic testing for MYH/MUTYH gene mutations should first target the specific mutations Y165C and G382D, which account for more than 80% of mutations in Caucasian populations, and subsequently proceed to sequencing only as necessary. In other ethnic populations, however, proceeding directly to sequencing is appropriate.

2. GeneTests lists 15 U.S.-based CLIA-licensed clinical laboratories that provide APC mutation testing and 14 that provide MYH/MUTYH mutation testing. The COLARIS® AP test from Myriad Genetic Laboratories includes DNA sequencing analysis of the APC and MYH/MUTYH genes, as well as analysis of large rearrangements in the APC gene that are not detected by DNA sequencing.

**Benefit Application**

It is recommended that, when possible, initial genetic testing for familial adenomatous polyposis or Lynch syndrome be performed in an affected family member so that testing in unaffected
family members can focus on the variant found in the affected family member. However, coverage for testing of the affected index case (proband) depends on contract benefit language when there is no conclusive evidence of clinical benefit to the index case from testing.

Specific contract language must be reviewed and considered when determining coverage for testing. In some cases, coverage for testing the index case may be available on the contract that covers the unaffected individual who will benefit from knowing the results of the genetic test.

This policy also assumes that the microsatellite instability test or the immunohistochemistry test as an initial evaluation for Lynch syndrome is performed as part of the routine pathological evaluation of the colorectal or endometrial cancer specimen. Thus, this policy deals only with testing for genetic variants.

Proceeding to DNA mismatch repair gene sequencing would depend on results of microsatellite instability and immunohistochemical testing. Microsatellite instability and immunohistochemical testing may also provide additional information when genetic testing for nonpolyposis colorectal cancer is inconclusive.

The complex patient selection criteria requiring a detailed family history are not readily available on claim forms. Also, genetic testing is a multistep procedure that is currently coded using a series of nonspecific CPT codes. For these reasons, the most efficient application of this policy may be its use as a tool for prospective or retrospective review.

Consideration of Age

The ages stated in this policy for which genetic testing for Lynch syndrome is considered medically necessary are based on scientific evidence, professional society recommendations and current guidelines from the National Comprehensive Cancer Network.

Evidence Review

Description

Genetic testing is available for both those with and those at risk for various types of hereditary cancer. This policy evaluates genetic testing for hereditary colorectal cancer and polyposis syndromes, including familial adenomatous polyposis (FAP), Lynch syndrome (formerly known as

Background

**Hereditary Colorectal Cancers**

Currently, 2 types of hereditary colorectal cancers (CRC) are well-defined: familial adenomatous polyposis (FAP) and Lynch syndrome (formerly hereditary nonpolyposis CRC). Lynch syndrome has been implicated in some endometrial cancers as well.

**Familial Adenomatous Polyposis FAP and Associated Variants**

FAP typically develops by age 16 years and can be identified by the appearance of hundreds to thousands of characteristic, precancerous colon polyps. If left untreated, all affected individuals will develop CRC. Mean age of colon cancer diagnosis in untreated individuals is 39 years. FAP accounts for 1% of CRC and may also be associated with osteomas of the jaw, skull, and limbs; sebaceous cysts; and pigmented spots on the retina referred to as congenital hypertrophy of the retinal pigment epithelium. FAP associated with these collective extra-intestinal manifestations is sometimes referred to as Gardner syndrome. FAP may also be related to central nervous system tumors, referred to as Turcot syndrome.

Germline variants in the adenomatous polyposis coli (APC) gene, located on chromosome 5, are responsible for FAP and are inherited in an autosomal dominant manner. Variants in the APC gene result in altered protein length in about 80% to 85% of cases of FAP. A specific APC gene variant (I1307K) has been found in Ashkenazi Jewish descendants, which may explain a portion of the familial CRC occurring in this population.

A subset of FAP patients may have an attenuated form of FAP, typically characterized by fewer than 100 cumulative colorectal adenomas occurring later in life than in classical FAP. In the attenuated form of FAP, CRC occurs later in life (at an average age of 50-55 years) but lifetime risk of CRC remains high (~70% by age 80 years). The risk of extra-intestinal cancer is also lower but cumulative lifetime risk remains high (~38%) compared to the general population.¹ Only 30% or fewer of attenuated FAP patients have APC variants; some of these patients have variants in the MUTYH (formerly MYH) gene, and this form of the condition is called MUTYH-associated polyposis (MAP). MAP occurs with a frequency similar to FAP, with some variability among
prevalence estimates for both. While clinical features of MAP are similar to FAP or attenuated FAP, a strong multigenerational family history of polyposis is absent. Biallelic MUTYH variants are associated with a cumulative CRC risk of about 80% by age 70, whereas the monoallelic MUTYH variant-associated risk of CRC appears to be relatively minimal, although still under debate. Thus, inheritance for high-risk CRC predisposition is autosomal recessive in contrast to FAP. When relatively few (ie, between 10 and 99) adenomas are present and family history is unavailable, the differential diagnosis may include both MAP and Lynch syndrome; genetic testing in this situation could include APC, MUTYH if APC is negative for variants, and screening for variants associated with Lynch syndrome.

It is important to distinguish among classical FAP, attenuated FAP, and MAP (mono- or biallelic) by genetic analysis because recommendations for patient surveillance and cancer prevention vary by syndrome.

Testing

Genetic testing for APC variants may be considered in the following situations:

- Patients at high risk such as those with a family member who tested positive for FAP and have a known APC variant.
- Patients undergoing differential diagnosis of attenuated FAP vs MAP vs Lynch syndrome. These patients do not meet the clinical diagnostic criteria for classical FAP and have few adenomatous colonic polyps.
- To confirm FAP in patients with colon cancer with a clinical picture or family history consistent with classical FAP.

Lynch Syndrome

Lynch syndrome is an inherited disorder that results in a higher predisposition to CRC and other malignancies including endometrial and gastric cancer. Lynch syndrome is estimated to account for 3% to 5% of CRC. Lynch syndrome is estimated to account for 3% to 5% of all CRC. People with Lynch syndrome have a 70% to 80% lifetime risk of developing any type of cancer. However the risk varies by genotype. It occurs as a result of germline variant in the mismatch repair (MMR) genes that include MLH1, MSH2, MSH6, and PMS2. In approximately 80% of cases, the variants are located in the MLH1 and MSH2 genes, while 10% to 12% of variants are located in the MSH6 gene and 2% to 3% in the PMS2 gene. Additionally, variants in 3 additional genes
(MLH3, PMS1, EX01) have been implicated with Lynch Syndrome. Notably, in individuals meeting the various clinical criteria for Lynch syndrome, 50% of individuals have a variant in the MLH1, MSH2, MSH6, and PMS2 genes. The lifetime risk of CRC is nearly 80% in individuals carrying a variant in one of these genes.

**Testing**

Testing approach to identify patients with Lynch syndrome is summarized next. Preliminary screening of tumor tissue does not identify MMR gene variants but is used to guide subsequent diagnostic testing via DNA analysis for specific variants. Genetic testing or DNA analysis (gene sequencing, deletion and duplication testing) for the MMR genes involves assessment for MLH1, MSH2, MSH6, and PMS2 variants. The following are 3 testing strategies.

1. **Microsatellite instability (MSI) testing (phenotype):** Individuals with high MSI either proceed to genetic testing for MLH1, MSH2, MSH6, and PMS2 or to immunohistochemical (IHC) testing.

2. **IHC testing (phenotype):** Individuals with negative staining would proceed to genetic testing for MLH1, MSH2, MSH6, and PMS2.

3. **Modification strategy:** Tumor tissue of patients with negative staining for MLH1 on IHC is tested for the BRAF V600E variant to determine methylation status. If the BRAF variant is not detected, the individual receives MLH1 DNA analysis.

The phenotype tests used to identify individuals who may be at a high-risk of Lynch syndrome are explained next. The first screening test measures MSI. As a result of variance in the MMR gene family, the MMR protein is either absent or deficient, resulting in an inability to correct DNA replication errors causing MSI. Approximately 80% to 90% of Lynch syndrome CRC tumors have MSI. The National Cancer Institute has recommended screening for 5 markers to detect MSI (Bethesda markers). MSI detection in 2 of these markers is considered a positive result or “high probability of MSI”.

The second phenotype screening test is IHC, which involves the staining of tumor tissue for the presence of 4 MMR proteins (MLH1, MSH2, MSH6, PMS2). The absence of one or more of these proteins is considered abnormal.

BRAF testing is an optional screening method that may be used in conjunction with IHC testing for MLH1 to improve efficiency. A methylation analysis of the MLH1 gene can largely substitute for BRAF testing, or be used in combination to improve efficiency slightly.
Both MSI and IHC have a 5% to 10% false-negative rate. MSI testing performance depends on the specific MMR variant. MSI screening has a sensitivity of about 89% for MLH1 and MSH2 and 77% for MSH6 and a specificity of about 90% for each. The specificity of MSI testing is low because approximately 10% of sporadic CRCs are MSI-positive due to somatic hypermethylation of the MLH1 promoter. Additionally, some tumors positive for MSH6 variants are associated with the MSI-low phenotype rather than MSI-high; thus MSI-low should not be a criterion against proceeding to MMR variant testing.\(^7,8\) IHC screening has sensitivity for MLH1, MSH2, and MSH6 of about 83% and a specificity of about 90% for each.

Screening of tumor tissue from patients enables genetic testing for a definitive diagnosis of Lynch syndrome and leads to counseling, cancer surveillance (eg, through frequent colonoscopic or endometrial screening examinations), and prophylaxis (eg, risk-reducing colorectal or gynecologic surgeries) for CRC patients, as well as for their family members.

Genetic testing for an MMR gene variant is often limited to MLH1 and MSH2 and, if negative, then MSH6 and PMS2. The BRAF gene is often mutated in CRC when a particular BRAF variant (V600E, a change from valine to glutamic acid at amino acid position 600 in the BRAF protein) is present; to date, no MLH1 gene variants have been reported.\(^9\) Therefore, patients negative for MLH1 protein expression by IHC, and therefore potentially positive for an MLH1 variant, could first be screened for a BRAF variant. BRAF-positive samples need not be further tested by MLH1 sequencing. MLH1 gene methylation largely correlates with the presence of BRAF V600E and in combination with BRAF testing can accurately separate Lynch from sporadic CRC in IHC MLH1-negative cases.\(^10\)

Recently, novel deletions have been reported to affect the expression of the MSH2 gene in the absence of a MSH2 gene variant, and thereby cause Lynch syndrome. In these cases, deletions in EPCAM, the gene for the epithelial cell adhesion molecule, are responsible. EPCAM testing has been added to many Lynch syndrome profiles and is conducted only when tumor tissue screening results are MSI-high, and/or IHC shows a lack of MSH2 expression, but no MSH2 variant is found by sequencing. EPCAM is found just upstream, in a transcriptional sense, of MSH2. Deletions of EPCAM that encompass the last 2 exons of the EPCAM gene, including the polyadenylation signal that normally ends transcription of DNA into messenger RNA, results in transcriptional “read-through” and subsequent hypermethylation of the nearby and downstream MSH2 promoter. This hypermethylation prevents normal MSH2 protein expression and leads to Lynch syndrome in a fashion similar to Lynch cases in which an MSH2 variant prevents MSH2 gene expression. Several studies have characterized such EPCAM deletions, established their correlation with the presence of EPCAM-MSH2 fusion messenger RNAs (apparently nonfunctional) and with the presence of MSH2 promoter hypermethylation, and, most
importantly, have shown the cosegregation of these EPCAM variants with Lynch-like disease in families.\textsuperscript{11-16}

Distinct from patients with EPCAM deletions, rare cases of Lynch syndrome have been reported without detectable germline MMR variants, although IHC testing demonstrated a loss of expression of one of the MMR proteins. In at least some of these cases, research has identified germline “epivariants,” ie, methylation of promoter regions that control the expression of the MMR genes.\textsuperscript{11,17,18} Such methylation may be isolated or be in conjunction with a linked genetic alteration near the affected MMR gene. The germline epivariants may arise de novo or may be heritable in Mendelian or non-Mendelian fashion. This is distinct from some cases of MSI-high sporadic CRC wherein the tumor tissue may show MLH1 promoter methylation and IHC nonexpression, but the same is not true of germline cells. Clinical testing for Lynch syndrome-related germline epivariants is not routine but may help in exceptional cases.

Female patients with Lynch syndrome have a predisposition to endometrial cancer. Lynch syndrome is estimated to account for 2\% of all endometrial cancers in women and 10\% of endometrial cancers in women younger than 50 years of age. Female carriers of the germline variants MLH1, MSH2, MSH6, and PMS2 have an estimated 40 to 62\% lifetime risk of developing endometrial cancer, as well as a 4\% to 12\% lifetime risk of ovarian cancer.

**Population Selection**

Various attempts have been made to identify which patients with colon cancer should undergo testing for MMR variants, based primarily on family history and related characteristics using criteria such as the Amsterdam II criteria\textsuperscript{19} (low sensitivity but high specificity), Revised Bethesda guidelines\textsuperscript{20} (better sensitivity but poorer specificity), and risk prediction models (eg, MMRpro; PREMM5; MMRpredict).\textsuperscript{21} While family history is an important risk factor and should not be discounted in counseling families, it has poor sensitivity and specificity for identifying Lynch syndrome. Based on this and other evidence, the Evaluation of Genomic Applications in Practice and Prevention Working Group recommended testing all newly diagnosed CRC patients for Lynch syndrome, using a screening strategy based on MSI or IHC (with or without BRAF) followed by sequencing in screen-positive patients. This recommendation includes genetic testing for the following types of patients:

- Family members of Lynch syndrome patients with a known MMR variant; family members would be tested only for the family variant; those testing positive would benefit from early and increased surveillance to prevent future CRC.

- Patients with a differential diagnosis of Lynch syndrome vs attenuated FAP vs MAP.
For Lynch syndrome patients, genetic testing of the proband with CRC likely benefits the proband where Lynch syndrome is identified, and appropriate surveillance for associated malignancies can be initiated and maintained and benefits family members by identifying the family variant.

**Juvenile Polyposis Syndrome**

Juvenile polyposis syndrome (JPS) is an autosomal dominant genetic disorder characterized by the presence of multiple hamartomatous (benign) polyps in the digestive tract. It is rare, with an estimated incidence of 1 in 100,000 to 160,000. Generalized juvenile polyposis refers to polyps in the upper and lower gastrointestinal tract, and juvenile polyposis coli refers to polyps of the colon and rectum. Those with JPS are at a higher risk for colorectal and gastric cancer. Approximately 60% of patients with JPS have a germline variant in the BMPR1A gene or the SMAD4 gene. Approximately 25% of patients have de novo variants. In most cases, polyps appear in the first decade of life and most patients are symptomatic by age 20 years. Rectal bleeding is the most common presenting symptom, occurring in more than half of patients. Other presenting symptoms include prolapsing polyp, melena, pain, iron deficiency anemia, and diarrhea.

As noted, individuals with JPS are at increased risk for colorectal and gastric cancer. By 35 years of age, the cumulative risk of CRC is 17% to 22%, which increases to 68% by age 60 years. The estimated lifetime risk of gastric cancer is 20% to 30%, with a mean age at diagnosis of 58 years. JPS may also be associated with hereditary hemorrhagic telangiectasia. The most common clinical manifestations of hereditary hemorrhagic telangiectasia are telangiectasias of the skin and buccal mucosa, epistaxis, and iron deficiency anemia from bleeding.

**Diagnosis**

A clinical diagnosis of JPS is made on the basis of the presence of any one of the following: at least 3 to 5 juvenile polyps in the colon or multiple juvenile polyps in other parts of the gastrointestinal tract or any number of juvenile polyps in a person with a known family history of juvenile polyps. It is recommended that individuals who meet clinical criteria for JPS undergo genetic testing for a germline variant in the BMPR1A and SMAD4 genes for a confirmatory diagnosis of JPS and to counsel at-risk family members.
Peutz-Jeghers Syndrome

Peutz-Jeghers syndrome (PJS) is also an autosomal dominant genetic disorder, similar to JPS, and characterized by the presence of multiple hamartomatous (benign) polyps in the digestive tract, mucocutaneous pigmentation, and an increased risk of gastrointestinal and nongastrointestinal cancers. It is rare, with an estimated incidence of 1 in 8000 to 200,000. In most cases, a germline variant in the STK11 (LKB1) gene is responsible for PJS, which has a high penetrance of over 90% by the age of 30 years. However, 10% to 20% of individuals with PJS have no family history and are presumed to have PJS due to de novo variants. A variant in STK11 is detected in only 50% to 80% of families with PJS, suggesting that there is a second PJS gene locus.

The reported lifetime risk for any cancer is between 37% and 93% among those diagnosed with PJS with an average age of cancer diagnosis at 42 years. The most common sites for malignancy are colon and rectum, followed by breast, stomach, small bowel, and pancreas. The estimated lifetime risk of gastrointestinal cancer ranges from 38% to 66%. Lifetime cancer risk stratified by organ site is colon and rectum (39%), stomach (29%), small bowel (13%), and pancreas (11%-36%).

Diagnosis

A clinical diagnosis of PJS is made if an individual meets two or more of the following criteria: presence of two or more histologically confirmed PJ polyps of the small intestine or characteristic mucocutaneous pigmentation of the mouth, lips, nose, eyes, genitalia, fingers, or family history of PJS. Individuals who meet clinical criteria for PJS should undergo genetic testing for a germline variant in the STK11 gene for a confirmatory diagnosis of PJS and counseling at-risk family members. In addition, if there is a known SMAD4 variant in the family, genetic testing should be performed within the first 6 months of life due to hereditary hemorrhagic telangiectasia risk.

Summary of Evidence

For individuals who are suspected of attenuated FAP, MAP, and Lynch syndrome who receive genetic testing for APC, or are at-risk relatives of patients with FAP who receive genetic testing for MUTYH after a negative APC test result, the evidence includes a TEC Assessment. Relevant
outcomes are overall survival, 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 2 leads to different management strategies. Depending on 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, or (4) are at-risk relatives of patients with Lynch syndrome, or (5) are without colon cancer but with a family history meeting the Amsterdam or Revised Bethesda criteria 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. Relevant outcomes are overall survival, disease-specific survival, and test accuracy and validity. A chain of evidence from well-designed experimental nonrandomized studies is adequate to demonstrate the clinical utility of testing unaffected (without cancer) first- and second-degree relatives of patients with Lynch syndrome who have a known variant in an MMR gene, in that counseling has been shown to influence testing and surveillance choices among unaffected family members of Lynch syndrome patients. One long-term, nonrandomized controlled study and a cohort study of Lynch syndrome family members found significant reductions in CRC among those who followed recommended colonic surveillance. 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. Relevant outcomes are overall survival, disease-specific survival, and test accuracy and validity. Studies have shown an association between EPCAM variants and Lynch-like disease in families, and the cumulative risk for CRC is similar to carriers of an MSH2 variant. 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. Relevant outcomes are overall survival, 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 (1) are suspected of JPS or PJS or (2) are at-risk relatives of patients suspected of or diagnosed with JPS or PJS who receive genetic testing for SMAD4, BMPR1A, or STK11 genes, respectively, the evidence includes multiple observational studies. Relevant outcomes are overall survival, 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 currently unaffected at-risk family members 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.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 3.

Table 3. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
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<tr>
<td><strong>Ongoing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01646112</td>
<td>Living in Lynch Syndrome Limbo: Exploring the Meaning of Uncertain Genetic Test Results</td>
<td>34</td>
<td>Feb 2016 (completed)</td>
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<tr>
<td>NCT01850654</td>
<td>Ohio Colorectal Cancer Prevention Initiative: Universal Screening for Lynch Syndrome</td>
<td>4000</td>
<td>Sep 2017 (completed)</td>
</tr>
</tbody>
</table>

NCT: national clinical trial
**Clinical Input From Physician Specialty Societies And Academic Medical Centers**

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received from 3 physician specialty societies and 3 academic medical centers while this policy was under review in 2009. In general, those providing input agreed with the overall approach described in this policy.

**Practice Guidelines and Position Statements**

**National Comprehensive Cancer Network**

National Comprehensive Cancer Network (NCCN) guidelines (v.1.2018) for genetic/familial high-risk assessment of colorectal cancer (CRC) recommend 2 approaches to Lynch syndrome variant screening:

- All newly diagnosed CRC
- All CRC patients diagnosed before age 70 plus those diagnosed at ages 70 and older who meet Bethesda guidelines

Additionally, NCCN guidelines (v.2.2018) recommend screening for Lynch syndrome in all endometrial cancer patients younger than 50 years. Genetic testing is recommended for at-risk family members of patients with positive variants in MLH1, MSH2, MSH6, or PMS2. 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 policy.

NCCN guidelines for colon cancer (v.3.2018) and for CRC screening (v.3.2018) recommend CRC patients treated with curative-intent surgery undergo surveillance colonoscopy at 1 year postsurgery 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 1 to 2 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. NCCN guidelines on genetic/familial high-risk assessment for colorectal cancer 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.” 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 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.”

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. These guidelines also indicate all colon cancer patients should be questioned about family history and considered for risk assessment as per NCCN colorectal screening guidelines. 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. NCCN cancer risk and surveillance guidelines for these 2 indications are summarized in Tables 4 and 5.

Table 4. Risk and Surveillance Guidelines for Peutz-Jeghers Syndrome (Category 2A Recommendations)

<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,</td>
<td>≈8 to 10 y</td>
</tr>
<tr>
<td>Site</td>
<td>Lifetime Risk, %</td>
<td>Screening Procedure and Interval</td>
<td>Initiation Age, y</td>
</tr>
<tr>
<td>------------------------------</td>
<td>------------------</td>
<td>---------------------------------------------------------------------------------------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Pancreas</td>
<td>11-36</td>
<td>Magnetic resonance cholangiopancreatography 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>Pelvic examination and Pap smear annually</td>
<td></td>
</tr>
<tr>
<td>Testes (typically sex cord / Sertoli cell tumors)</td>
<td>Annual testicular exam and observation for feminizing changes</td>
<td>≈10 y</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>15-17</td>
<td>Provide education about symptoms and smoking cessation</td>
<td></td>
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</tbody>
</table>

CT: computed tomography; MRI: magnetic resonance imaging.

Table 5. Risk and Surveillance Guidelines for Juvenile Polyposis Syndrome (Category 2A Recommendations)

<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 56 mo of age</td>
</tr>
</tbody>
</table>

HHT: hereditary hemorrhagic telangiectasia.
<sup>a</sup> In families without an identified genetic variant, 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.26

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.103

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.

For 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.

Genetic testing of patients with suspected adenomatous polyposis syndromes should include APC and MUTYH gene variant analysis.

For juvenile polyposis syndrome, the College recommended:

Genetic evaluation of a patient with possible JPS [juvenile polyposis syndrome] should include testing for SMAD4 and 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).

Colectomy 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 SMAD4 mutation carriers (conditional recommendation, very low quality of evidence).

For Peutz-Jeghers syndrome, the College recommended:

- Genetic evaluation of a patient with possible PJS [Peutz-Jeghers syndrome] should include testing for 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).

American Society of Clinical Oncology and Society of Surgical Oncology

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). The recommendations as related to genetic testing hereditary CRC syndromes are summarized below:

- 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.
- 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...

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

• 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.

U.S. Preventive Services Task Force Recommendations

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

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 (ie 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.
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 policy are available under the auspices of Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by 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.

References


**History**

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<tr>
<td>01/26/12</td>
<td>CPT Codes 81292 – 81295 added.</td>
</tr>
<tr>
<td>05/08/12</td>
<td>Replace policy. Policy updated with literature review. Extensive rewrite of rationale and background. Additional medically necessary indication added for testing for EPCAM mutations in patients with colorectal cancer and negative MMR mutations. References added.</td>
</tr>
<tr>
<td>05/24/12</td>
<td>Policy renumbered to 12.04.506 (previously 2.04.506) and reassigned to new Genetic Testing category.</td>
</tr>
<tr>
<td>11/15/12</td>
<td>Reviewed and recommended by OAP, November 2012.</td>
</tr>
<tr>
<td>01/14/13</td>
<td>Coding update. CPT codes 83890 – 83913 deleted as of 12/31/12; CPT codes 81201 – 81203 and 81599, effective 1/1/13, are added to the policy.</td>
</tr>
<tr>
<td>09/09/13</td>
<td>Clarification. Amsterdam Criteria II of policy statement clarified: “Tumors should be verified by pathologic examination whenever possible”.</td>
</tr>
<tr>
<td>Date</td>
<td>Comments</td>
</tr>
<tr>
<td>------------</td>
<td>---------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>01/13/14</td>
<td>Replace policy. Policy 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. Added policy statement indicating testing for all other gene mutations for Lynch syndrome or colorectal cancer is considered investigational. CPT codes 81599 removed; there are specific codes for this testing; deleted codes 83890-83914 removed; deleted (4/12) HCPCS codes S3828-S3832 removed and notation made on S3833-S3834 that codes are deleted as of 1/1/14. All ICD-9 diagnosis codes removed from the policy; adjudication not diagnosis dependent. CPT codes 81210 (specific to BRAF) and 81406 (molecular pathology) added to the policy.</td>
</tr>
<tr>
<td>07/24/14</td>
<td>Update Related Policies. Remove 12.04.91.</td>
</tr>
<tr>
<td>08/13/14</td>
<td>Update Related Policies. Add 12.04.93.</td>
</tr>
<tr>
<td>01/12/15</td>
<td>Coding update. New CPT code 81288, 81435 &amp; 81436, effective 1/1/15, added to policy.</td>
</tr>
<tr>
<td>01/23/15</td>
<td>Update Related Policies. Add 2.04.29.</td>
</tr>
<tr>
<td>09/16/15</td>
<td>Annual Review. Policy statement reformatted primarily by syndrome rather than mutation. Major criteria revisions: Second qualifying criterion of endometrial cancer added, medically necessary statement for testing of affected family member added, list of Lynch-associated cancers expanded, MSI/IHC/BRAF/MLH1 combined in policy statement as initial tests, more criteria detail added for APC/MYH testing, EPCAM statement deleted. Rationale updated. References added. CPT code 96040 removed; it does not relate to the policy.</td>
</tr>
<tr>
<td>01/12/16</td>
<td>Annual Review. Policy updated with literature review through October 26, 2014. References 42 added. Policy statement unchanged</td>
</tr>
<tr>
<td>08/31/16</td>
<td>Policy moved into new format; no change to policy statements.</td>
</tr>
<tr>
<td>01/01/17</td>
<td>Interim Review, approved December 13, 2016. Language added to indicate that application of this policy based on age criteria is supported by scientific evidence, professional society recommendations and current guidelines from the National Comprehensive Cancer Network. Note added to Lynch syndrome testing: Maternal and paternal sides of the family should be considered independently for familial patterns of cancer.</td>
</tr>
<tr>
<td>03/01/17</td>
<td>Updated Related Policies, removed 2.04.29 as it was archived.</td>
</tr>
<tr>
<td>12/01/17</td>
<td>Annual Review, approved November 9, 2017. Policy updated with literature review. No references added, no changes to policy statements.</td>
</tr>
<tr>
<td>12/01/18</td>
<td>Annual Review, approved November 13, 2018. Policy updated with literature review through July 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</td>
</tr>
<tr>
<td>Date</td>
<td>Comments</td>
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<td>------</td>
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</tr>
<tr>
<td></td>
<td>Peutz-Jeghers syndrome. Added codes 81404 and 81405.</td>
</tr>
</tbody>
</table>

**Disclaimer:** This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2018 Premera All Rights Reserved.

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  - Qualified sign language interpreters
  - Written information in other formats (large print, audio, accessible electronic formats, other formats)
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  - Qualified interpreters
  - Information written in other languages

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Civil Rights Coordinator - Complaints and Appeals
PO Box 91102, Seattle, WA 98111
Toll free 855-332-4535, Fax 425-918-5592, TTY 800-842-5357
Email AppealsDepartmentInquiries@Premera.com

You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:

Office for Civil Rights Complaint Portal, available at
200 Independence Avenue SW, Room 509F, HHH Building
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This Notice has Important Information. This notice may have important information about your application or coverage through Premera Blue Cross. There may be key dates in this notice. You may need to take action by certain deadlines to keep your health coverage or help with costs. You have the right to get this information and help in your language at no cost. Call 800-722-1471 (TTY: 800-842-5357).

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