Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes

BCBSA Ref. Policy: 2.04.08

Effective Date: Jan. 1, 2017
Last Revised: March 1, 2017
Replaces: N/A

Related Medical Policies: None

Select a hyperlink below to be directed to that section.

Policy Criteria | Coding | Related Information
Evidence Review | References | History

∞ Clicking this icon returns you to the hyperlinks menu above.

Introduction

Five to ten percent of all cancers may be inherited. For colon cancer, several genes have been identified that 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>Lynch Syndrome</th>
<th>Medical Necessity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Also known as hereditary non-polyposis colorectal cancer</td>
<td></td>
</tr>
</tbody>
</table>
or HNPC

| Initial screening | Screening for Lynch syndrome as an initial evaluation of tumor tissue:
|                   | • Screening 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 for ALL cases of colorectal cancer, regardless of age.

Note: MSI/IHC testing prior to actual genetic testing for Lynch syndrome is recommended, but not required.

| Genetic testing | Genetic testing for Lynch syndrome (MLH1, MSH2, MSH6, PMS2 sequence analysis) may be considered medically necessary when the member meets ANY ONE of the following criteria:
|                 | • A positive screening result from MSI/IHC (see Lynch syndrome initial screening, above)
|                 | • Amsterdam II criteria or revised Bethesda guidelines (see Related Information)
|                 | • One first-degree or second-degree relative with a Lynch syndrome mutation (genes MLH1, MSH2, MSH6, PMS2)
|                 | • Personal history of endometrial cancer diagnosed at 50 years of age or younger
|                 | • Personal history of endometrial cancer diagnosed at age 51-60 and one first-degree relative diagnosed with a Lynch-associated cancer.*

Notes: 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 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.

<table>
<thead>
<tr>
<th>Familial Adenomatous Polyposis (FAP) and Associated Variants</th>
<th>Coverage Criteria</th>
</tr>
</thead>
</table>
| **Adenosis polyposis coli (APC)**                           | Adenosis polyposis coli (APC) genetic testing is considered medically necessary for ANY ONE of the following indications:  
  - Personal history of greater than 10 cumulative colonic adenomatous polyps.  
  - One first-degree relative diagnosed with familial adenomatous polyposis (FAP) or with a documented APC mutation.  
    - If feasible, the specific APC mutation should be identified in the affected first-degree relative with FAP prior to testing the member see (Related Information).  
    - "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. |
| **MYH/MUTYH-Associated Polyposis (MAP)**                    | MYH/MUTYH-Associated Polyposis (MAP) Genetic Testing 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  
  - Personal history of 10 to 20 cumulative adenomatous polyps in a member with a family history which is consistent with recessive inheritance (i.e., family history is positive only for sibling[s])  
  - Asymptomatic siblings of individuals with known MYH polyposis mutation |
MYH/MUTYH-Associated Polyposis (MAP) genetic testing is considered investigational when the member has not met at least one of the criteria listed below.

### Coding

<table>
<thead>
<tr>
<th>CPT</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>81201</td>
<td>APC (adenomatous polyposis coli) (e.g., familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; full gene sequence</td>
</tr>
<tr>
<td>81202</td>
<td>APC (adenomatous polyposis coli) (e.g., familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; known familial variants</td>
</tr>
<tr>
<td>81203</td>
<td>APC (adenomatous polyposis coli) (e.g., 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) (e.g., colon cancer), gene analysis, V600E variant</td>
</tr>
<tr>
<td>81288</td>
<td>MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; promoter methylation analysis (new code effective 1/1/15)</td>
</tr>
<tr>
<td>81292</td>
<td>MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (e.g., 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) (e.g., 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) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants</td>
</tr>
<tr>
<td>81295</td>
<td>MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis</td>
</tr>
<tr>
<td>81296</td>
<td>MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (e.g., 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) (e.g., 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) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis</td>
</tr>
<tr>
<td>81299</td>
<td>MSH6 (mutS homolog 6 [e. coli]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis, known familial variants</td>
</tr>
</tbody>
</table>
### CPT

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>81300</td>
<td>MSH6 (muts homolog 6 [e. coli]) (e.g., hereditary non-polyposis colorectal cancer, lynch syndrome) gene analysis, duplication/deletion variants</td>
</tr>
<tr>
<td>81301</td>
<td>Microsatellite instability analysis (e.g., hereditary non-polyposis colorectal cancer, lynch syndrome) of markers for mismatch repair deficiency (e.g., 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]) (e.g., hereditary nonpolyposis colorectal cancer, lynch syndrome) gene analysis, full sequence analysis</td>
</tr>
<tr>
<td>81318</td>
<td>PMS2 (postmeiotic segregation increased 2 [s. cerevisiae]) (e.g., 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]) (e.g., hereditary nonpolyposis colorectal cancer, lynch syndrome) gene analysis, duplication/deletion variants</td>
</tr>
<tr>
<td>81406</td>
<td>Molecular pathology procedure, Level 7 (e.g., 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 (e.g., 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 (new code effective 1/1/15)</td>
</tr>
<tr>
<td>81436</td>
<td>Hereditary colon cancer syndromes (e.g., 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 (new code effective 1/1/15)</td>
</tr>
</tbody>
</table>

**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).

## Related Information

### General Guidelines for Lynch and FAP Syndromes

1. Testing may occur to resolve a differential diagnosis of Lynch syndrome versus Familial Adenomatous Polyposis. 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 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 (e.g., targeted testing for a family mutation) can also be requested.

3. Amsterdam II clinical criteria¹ are the most stringent criteria for defining families at high risk for Lynch syndrome. ALL criteria must be fulfilled:

   o 3 or more relatives with an associated cancer (colorectal cancer, or cancer of the endometrium, small intestine, ureter or renal pelvis)

   o 1 should be a first-degree relative of the other 2

   o 2 or more successive generations affected

   o 1 or more relatives 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\textsuperscript{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 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, 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 bland 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\textsuperscript{3}
FAP Guidelines

1. In many cases, genetic testing for MYH/MUTYH gene mutations should first target the specific mutations Y165C and G382D, which account 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.

Background

There are currently 2 well-defined types of hereditary colorectal cancer, familial adenomatous polyposis (FAP) and Lynch syndrome (formerly hereditary nonpolyposis colorectal cancer or HNPCC).

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 go on to develop colorectal cancer. The mean age of colon cancer diagnosis in untreated individuals is 39 years. FAP accounts for 1% of colorectal cancer 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 (CHRPE). FAP associated with these collective extra-intestinal manifestations is sometimes referred to as Gardener syndrome. FAP may also be associated with central nervous system (CNS) tumors, referred to as Turcot syndrome.

Germline mutations in the adenomatous polyposis coli (APC) gene, located on chromosome 5, are responsible for FAP and are inherited in an autosomal dominant manner. Mutations in the APC gene result in altered protein length in about 80% to 85% of cases of FAP. A specific APC
gene mutation (I1307K) has been found in subjects of Ashkenazi Jewish descent that may explain a portion of the familial colorectal cancer occurring in this population.

A subset of FAP patients may have attenuated FAP (AFAP), characterized by fewer than 100 cumulative colorectal adenomas occurring later in life than in classical FAP, colorectal cancer occurring at an average age of 50-55 years, but a high lifetime risk of colorectal cancer of about 70% by age 80 years. The risk of extra-intestinal cancer is lower compared to classical FAP but still high at an estimated cumulative lifetime risk of 38% compared to the general population.\(^4\) Only 30% or fewer of AFAP patients have APC mutations; some of these patients instead have mutations in the MUTYH (formerly MYH) gene and are then diagnosed with MUTYH-associated polyposis (MAP). MAP occurs with a frequency approximately equal to FAP, with some variability among prevalence estimates for both. While clinical features of MAP are similar to FAP or AFAP, a strong multigenerational family history of polyposis is absent. Bi-allelic MUTYH mutations are associated with a cumulative colorectal cancer risk of about 80% by age 70, whereas mono-allelic MUTYH mutation-associated risk of colorectal cancer appears to be relatively minimal, although still under debate.\(^5\) Thus, inheritance for high-risk colorectal cancer predisposition is autosomal recessive in contrast to FAP. When relatively few (i.e., 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 mutations, and screening for mutations associated with Lynch syndrome.

It is important to distinguish among classical FAP, attenuated FAP, and MAP (mono- or bi-allelic) by genetic analysis because recommendations for patient surveillance and cancer prevention vary according to the syndrome\(^6\).

**Lynch Syndrome**

Patients with Lynch syndrome have a predisposition to colorectal cancer and other malignancies as a result of an inherited mutation in a DNA mismatch repair (MMR) gene. Lynch syndrome includes those with an existing cancer and those who have not yet developed cancer. The term “HNPCC” originated prior to the discovery of explanatory MMR mutations for many of these patients, and now includes some who are negative for MMR mutations and likely have mutations in as-yet unidentified genes. For purposes of clarity and analysis, the use of Lynch syndrome in place of HNPCC has been recommended in several recent editorials and publications.

Lynch syndrome is estimated to account for 3% to 5% of colorectal cancer and is also associated with an increased risk of other cancers such as endometrial, ovarian, urinary tract, and biliary
tract cancer. Lynch syndrome is associated with a risk of developing colorectal cancer by age 70 years of approximately 27% to 45% for men, and 22% to 38% for women, after correction for ascertainment bias. Lynch syndrome patients who have colorectal cancer also have an estimated 16% risk of a second primary within 10 years.

Lynch syndrome is associated with any of a large number of possible mutations in 1 of several MMR genes, known as MLH1, MSH2, MSH6, PMS2, and rarely MLH3. Risk of all Lynch syndrome-related cancers is markedly lower for carriers of a mutation in the MSH6 and PMS2 genes, although for most cancers still significantly higher than that of the general population. Estimated cumulative risks of any associated cancer for a carrier of a mutation in any MMR gene do not begin to increase until after age 30 years.

Lynch syndrome mutations are heterozygous; that is, only one of the 2 gene alleles contains a mutation. In rare cases both alleles contain the mutation, i.e., biallelic MMR gene mutations. This unusual syndrome has been described in multiple families and is to a large extent the result of consanguinity. Children with biallelic MMR mutations may develop extra-colonic cancers in childhood, such as brain tumors, leukemias, or lymphomas. Those unaffected or surviving early malignancies are at high risk of later colorectal cancer (average age of colorectal cancer diagnosis 16.4 years). Family history may not suggest Lynch syndrome. Prior to cancer diagnosis, patients may have multiple adenomatous polyps and thus may have an initial differential diagnosis of attenuated FAP versus MUTYH-associated polyposis versus Lynch syndrome.

About 70% of Lynch syndrome patients have mutations in either MLH1 or MSH2. Testing for MMR gene mutations is often limited to MLH1 and MSH2 and, if negative, then MSH6 and PMS2 testing. Large gene sizes and the difficulty of detecting mutations in these genes make direct sequencing a time- and cost-consuming process. Thus, additional indirect screening methods are needed to determine which patients should proceed to direct sequencing for MMR gene mutations. Available screening methods are microsatellite instability (MSI) testing or immunohistochemical (IHC) testing. 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 slightly improve efficiency.

Mutations in MMR genes result in a failure of the mismatch repair system to repair errors that occur during the replication of DNA in tumor tissue. Such errors are characterized by the accumulation of alterations in the length of simple, repetitive microsatellite (2 to 5 base repeats) sequences that are distributed throughout the genome, termed microsatellite instability (MSI) and resulting in a MIS-high tumor phenotype. MSI testing was standardized subsequent to a 2004 National Cancer Institute (NCI) workshop. Methodologic studies have also shown the importance of laser microdissection of the tumor tissue, comparison of tumor and normal cells,
and a minimum proportion of tumor in relation to the quality of the test results. While the sensitivity of MSI testing is high, the specificity is low because approximately 10% of sporadic colorectal carcinoma (CRC) is MSI-positive due to somatic hypermethylation of the MLH1 promoter. Additionally, some tumors positive for MSH6 mutations are associated with the MSI-low phenotype rather than MSI-high; thus MSI-low should not be a criterion against proceeding to MMR mutation testing.\textsuperscript{9,10}

Absent or reduced protein expression may be a consequence of an MMR gene mutation. IHC assays for the expression of MLH1, MSH2, MSH6, and PMS2 can be used to detect loss of expression of these genes and to focus sequencing efforts on a single gene. It is also possible for IHC assays to show loss of expression, and thus indicate the presence of a mutation, when sequencing is negative for a mutation. In such cases, mutations may be in unknown regulatory elements and cannot be detected by sequencing of the protein coding regions. Thus IHC may add additional information.

The BRAF gene is often mutated in colorectal cancer; when a particular BRAF mutation (V600E, a change from valine to glutamic acid at amino acid position 600 in the BRAF protein) is present; to date no MLH1 gene mutations have been reported.\textsuperscript{9} Therefore, patients negative for MLH1 protein expression by IHC, and therefore potentially positive for an MLH1 mutation, could first be screened for a BRAF mutation. BRAF-positive samples need not be further tested by MLH1 sequencing. MLH1 gene methylation correlates with the presence of BRAF-V600E and in combination with BRAF testing can accurately separate Lynch from sporadic colorectal cancer in IHC MLH1-negative cases.\textsuperscript{12}

Various attempts have been made to identify which patients with colon cancer should undergo testing for MMR mutations, based primarily on family history and related characteristics using criteria such as the Amsterdam II criteria (low sensitivity but high specificity) and the Bethesda guidelines (better sensitivity but poorer specificity). 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. The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group recommends testing all patients with colorectal cancer for Lynch syndrome, using a screening strategy based on MSI or IHC (+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 mutation; family members would be tested only for the family mutation; those testing positive would benefit from early and increased surveillance to prevent future colorectal cancer.
• Patients with a differential diagnosis of Lynch syndrome vs. attenuated FAP vs. MUTYH-associated polyposis.

• Lynch syndrome patients. Genetic testing of the proband with colorectal cancer 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 mutation.

Recently, novel deletions have been reported to affect the expression of the MSH2 MMR gene in the absence of a MSH2 gene mutation, 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 mutation is found by sequencing. (Note: This policy does not address EPCAM testing.)

Separately from patients with EPCAM deletions, rare Lynch syndrome patients have been reported without detectable germline MMR mutations although IHC testing demonstrates a loss of expression of one of the MMR proteins. In at least some of these cases, research has identified germline "epimutations," i.e., methylation of promoter regions that control the expression of the MMR genes.\textsuperscript{13-15} Such methylation may be isolated or in conjunction with a linked genetic alteration near the affected MMR gene. The germline epimutations may arise de novo or may be heritable in either Mendelian or non-Mendelian fashion. This is distinct from some cases of MSI-high sporadic colorectal cancer wherein the tumor tissue may show MLH1 promoter methylation and IHC non-expression, but the same is not true of germline cells. Clinical testing for Lynch syndrome-related germline epimutations is not routine but may be helpful in exceptional cases. Epimutations as a cause of Lynch syndrome are described only for informational purposes; no policy statement is made regarding this testing.

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 mutationsMLH1, MSH2, MSH6, and PMS2 have an estimated 40-62\% lifetime risk of developing endometrial cancer, as well as a 4 to 12\% lifetime risk of ovarian cancer.

**Benefit Application**

It is recommended that, when possible, 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 possible, the microsatellite instability (MSI) test or the immunohistochemistry (IHC) test, as an initial evaluation for Lynch syndrome, should be performed as part of the routine pathological evaluation of the CRC specimen. Thus, this policy primarily addresses testing for genetic mutations. Consideration of proceeding to DNA mismatch repair (MMR) gene sequencing would depend on results of MSI and IHC testing. The MSI and IHC testing may also provide some additional information when Lynch syndrome genetic testing is inconclusive.

**Evidence Review**

This policy was originally created in 1998 and was regularly updated with searches of the MEDLINE database. The most recent literature search was performed through October 2014. The following is a summary of the key findings to date.

**Familial Adenomatous Polyposis (FAP) Genetic Testing**

The policy for FAP genetic testing was based on a 1998 TEC Assessment, which offered the following conclusions:

- Genetic testing for familial adenomatous polyposis (FAP) may improve health outcomes by identifying which currently unaffected at-risk family members require intense surveillance or prophylactic colectomy.
- At-risk subjects are considered to be those with greater than 10 colon polyps; or close relatives of patients with clinically diagnosed FAP of patients with identified APC mutation.
- The optimal testing strategy is to define the specific genetic mutation in an affected family member and then test the unaffected family members to see if they have inherited the same mutation.

The additional policy information on attenuated FAP and on MYH-associated polyposis diagnostic criteria and genetic testing is based on information from GeneReviews and from several publications that build on prior, cited research. In addition, GeneReviews summarizes clinical FAP genotype-phenotype correlations that could be used to determine different patient management strategies. The authors of the review conclude, however, that there is not yet agreement about using such correlations to direct management choices.
Lynch Syndrome Genetic Testing

An evidence report was published by the Agency for Healthcare Research and Quality (AHRQ),\textsuperscript{22} a supplemental assessment to that report contracted by the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group,\textsuperscript{11} which resulted in an EGAPP recommendation for genetic testing in colorectal cancer (CRC).\textsuperscript{23} Based on the AHRQ report and supplemental assessment, the EGAPP recommendation came to the following conclusions regarding genetic testing for MMR mutations in patients already diagnosed with colorectal cancer:

- Family history, while important information to elicit and consider in each case, has poor sensitivity and specificity as a screening test to determine who should be considered for MMR mutation testing and should not be used as a sole determinant or screening test.

- Microsatellite instability (MSI) and Immunohistochemical (IHC) screening tests for MMR mutations have similar sensitivity and specificity. MSI screening has a sensitivity of about 89% for MLH1 and MSH2 and 77% for MSH6, and a specificity of about 90% for all. It is likely that, using high quality MSI testing methods, these parameters can be improved. IHC screening has a sensitivity for MLH1, MSH2, and MSH6 of about 83% and a specificity of about 90% for all.

- Optional BRAF testing can be used to reduce the number of patients, who are negative for MLH1 expression by IHC, needing MLH1 gene sequencing, thus improving efficiency without reducing sensitivity for MMR mutations.

- A chain of indirect evidence can be constructed for the clinical utility of testing all patients with colorectal cancer for MMR mutations.
  
  1. The chain of indirect evidence from well-designed experimental nonrandomized studies (as noted below) 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 MMR mutation.

  2. Seven studies examined how counseling affected testing and surveillance choices among unaffected family members of Lynch syndrome patients. About half of relatives received counseling, and 95% of these chose MMR gene mutation testing. Among those positive for MMR gene mutations, uptake of colonoscopic surveillance beginning at age 20–25 years was high at 53–100%.
- One long-term, nonrandomized controlled study and one cohort study of Lynch syndrome family members found significant reductions in colorectal cancer among those who followed recommended colonic surveillance vs. those who did not.

- Surveillance, prevention for other Lynch syndrome cancers (for detail, refer to last outline bullet)

3. The chain of evidence from descriptive studies and expert opinion (as noted below) is inadequate (inconclusive) to demonstrate the clinical utility of testing the probands with Lynch syndrome (i.e., cancer index patient).

- Subtotal colectomy is recommended as an alternative to segmental resection, but has not been shown superior in follow-up studies

- Although a small body of evidence suggests that MSI-positive tumors are resistant to 5-fluorouracil and more sensitive to irinotecan than MSI-negative tumors, no alteration in therapy according to MSI status has yet been recommended.

- Surveillance, prevention for other Lynch syndrome cancers:
  a. While invasive and not recommended, women may choose hysterectomy with salpingo-oophorectomy to prevent gynecologic cancer. In one retrospective study, women who chose this option had no gynecologic cancer over 10 years whereas about one-third of women who did not have surgery developed endometrial cancer, and 5.5% developed ovarian cancer.

  b. In one study, surveillance endometrial biopsy detected endometrial cancer and potentially precancerous conditions at earlier stages in those with Lynch syndrome but results were not statistically significant and a survival benefit has yet to be shown. Transvaginal ultrasound (TVUS) is not a highly effective surveillance mechanism for endometrial cancer in patients with Lynch syndrome; however, TVUS in conjunction with endometrial biopsy has been recommended for surveillance.

  c. Gastroduodenoscopy for gastric cancer surveillance and urine cytology for urinary tract cancer surveillance are recommended based on expert opinion only, in the absence of adequate supportive evidence.

Based on an indirect chain of evidence with adequate evidence of benefit to unaffected family members found to have Lynch syndrome, the EGAPP working group recommended testing all patients with colorectal cancer for MMR gene mutations. Further support for universal testing of colorectal cancer patients for MMR gene mutations was reported by Moreira and colleagues in
2013 in a comparison of universal testing of colorectal cancer patients to alternate screening approaches.\textsuperscript{24} The alternate screening approaches included using the Bethesda guidelines, the Jerusalem recommendations and a selective strategy including only those diagnosed with colorectal cancer before age 70, or after age 70 if meeting the Bethesda guidelines. In the analysis of 10,206 newly diagnosed colorectal cancer patients from 4 large cohort studies, MSI testing was used in 2150 patients and immunostaining was used in 2278 patients while both MSI and immunostaining were used in 5591 patients. MMR gene mutations were found in 312 (3.1%) patients overall.

The universal screening approach was found to be superior to the other screening approaches in the population-based cohorts (n=3671 probands) with a sensitivity of 100% (95% confidence interval [CI], 99.3 to 100%), specificity of 93% (95% CI: 92.0 to 93.7%) and diagnostic yield of 2.2% (95% CI: 1.7 to 2.7%). The Bethesda guidelines screening sensitivity was 87.8% (95% CI: 78.9 to 93.2%) with a specificity of 97.5% (95% CI: 96.9 to 98.0%) and a diagnostic yield of 2.0% (95% CI: 1.5 to 2.4%; p<0.001). The screening sensitivity with the Jerusalem recommendations was 85.4% (95% CI: 77.1 to 93.6%) with a specificity of 96.7% (95% CI: 96.0 to 97.2%) and a diagnostic yield of 1.9% (95% CI: 1.4 to 2.3%; p<0.001). The selective strategy had a sensitivity of 95.1% (95% CI: 89.8 to 99.0%) with a specificity of 95.5% (95% CI: 94.7 to 96.1%) and a diagnostic yield of 2.1% (95% CI: 1.6 to 2.6%; p<0.001). However, the diagnostic yield differences between the screening approaches were small, and the false-positive yield was 2.5% with universal screening. Whereas, in the selective strategy, 34.8% fewer patients required tumor MMR testing and 28.6% fewer analyses of MMR mutations resulting in 4.9% missed Lynch syndrome cases.

In addition to DNA mismatch repair (MMR) gene mutation testing, evidence now supports testing for EPCAM deletions in particular cases where all MMR gene mutation testing is negative, but tumor MSH2 IHC indicates lack of expression, and tumor MSI testing shows a high level of instability. 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 result 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 mutation 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 mutations with Lynch-like disease in families.\textsuperscript{15,25-29} Because studies differ slightly in how patients were selected, prevalence of these EPCAM mutations is difficult to estimate but may be in the range of 20% to 40% of
patients/families who meet Lynch syndrome criteria, do not have an MMR mutation, but have MSI-high tumor tissue. Kempers et al reported that carriers of an EPCAM deletion had a 75% (95% CI, 65 to 85) cumulative risk of CRC by age 70 years, not significantly different from that of carriers of an MSH2 deletion (77%; 95% CI, 64 to 90); mean age at diagnosis was 43 years. However, the cumulative risk of endometrial cancer was low at 12% (95% CI, 0 to 27) by age 70, compared with carriers of a mutation in MSH2 (51%; 95% CI, 33 to 69; p<0.001).30

Grandval et al selected 25 patients with tumors exhibiting complete loss of MSH2 protein but without a point mutation or genomic rearrangement of the MSH2 gene and found 7 cases of a deletion of the 3 prime exon of EPCAM. Genetic testing was subsequently performed on 25 adult first-degree relatives of the 7 cases, and 12 relatives were found to be deletion carriers. Six additional relatives had deceased from Lynch-associated tumors, and 5 were obligate carriers. In summary, the risk to develop CRC was high, 93.1% (27/29) in deletion carriers older than 30 years of age.31

Although MMR gene sequencing of all patients is the most sensitive strategy, it is highly inefficient and cost-ineffective and not recommended. Rather, a screening strategy of MSI or IHC testing (with or without optional BRAF testing) is recommended and retains a relatively high sensitivity. Some evidence suggests that IHC requires particular training and experience.32 Although a particular strategy was not recommended by the EGAPP Working Group, several are potentially effective; efficiency and cost-effectiveness may depend upon local factors.

In 2010, Bouzourene and colleagues analyzed MLH1 protein abnormalities in 11 patients with sporadic colorectal carcinoma (CRC) and 16 patients with Lynch syndrome.10 BRAF mutation was not found in any of the Lynch syndrome patients. MLH1 promoter methylation was only present in 1 Lynch syndrome patient. However, 8 of the 11 sporadic CRC patients had the BRAF mutation, and all 11 patients were MLH1 methylated, suggesting patients with BRAF mutations could be excluded from germline testing for Lynch syndrome. In 2013, Jin et al. evaluated MMR proteins in 412 newly diagnosed CRC patients.33 MLH1 and PMS2 protein stains were absent in 65 (72%) patients who were subsequently tested for BRAF mutation. Thirty-six (55%) patients were found to have the BRAF V600E mutation, thus eliminating the need for further genetic testing or counseling for Lynch syndrome.

In 2013, Capper et al. reported on a technique of VE1 IHC testing for BRAF mutations on a series of 91 MSI-H CRC patients.34 The authors detected BRAF-mutated CRC with 100% sensitivity and 98.8% specificity. VE1 positive lesions were detected in 21% of MLH1-negative CRC patients who could be excluded from MMR germline testing for Lynch syndrome. Therefore, VE1 IHC testing for BRAF could be an alternative to MLH1 promoter methylation analysis.
Section Summary

To summarize, BRAF mutation V 600E or MLH1 promoter methylation testing are optional screening methods that may be used when IHC testing shows a loss of MLH protein expression by IHC testing for MLH1. The presence of BRAF V600E or absence of MLH1 protein expression due to MLH1 promoter methylation rarely occurs in Lynch syndrome and would eliminate the need for further germline mutation analysis for a Lynch syndrome diagnosis.\textsuperscript{35}

Previous recommendations have used family history as an initial screen to determine who should proceed further to MMR laboratory testing. Family history is important for counseling families, but based on this and similar evidence, it is not recommended as an initial screening tool to make decisions about testing patients who already have CRC. Recent studies have shown that limiting laboratory testing to patients who met even the more sensitive Revised Bethesda criteria (ie, compared with the Amsterdam II criteria) would miss as much as 28% of Lynch syndrome cases.\textsuperscript{36,37} However, as noted in the policy statement, the Amsterdam II or Revised Bethesda criteria may be used in identifying those without colorectal cancer who might be tested.

Limiting testing for Lynch syndrome on the basis of age (eg, test only patients <50 years) is also not recommended. For example, Hampel et al found that among 18 Lynch syndrome patients discovered among 500 unselected CRC patients, only 8 (44%) patients were diagnosed at age younger than 50 years.\textsuperscript{36} Similarly, Canard et al reported that restricting screening to patients younger than 50 years would have missed about half of patients eventually found to have Lynch syndrome.\textsuperscript{37} Another group screened CRC patients who were younger than age 60 and identified 98 likely (MSI-positive, BRAF-negative) Lynch syndrome cases; of these, 47% were between 50 and 60 years of age.\textsuperscript{38} A large study of Lynch syndrome family studies found that the cumulative risk of CRC in MMR mutation carriers was only 13% (95% CI, 9 to 19) by age 50, but 35% (95% CI, 25 to 49) by age 70.\textsuperscript{7} For MSH6 mutation carriers, however, CRC risks do not appear to increase until after age 60.

The estimated risk of stomach cancer in a large study of Lynch syndrome families was 6% (95% CI: 0.2-17%) for carriers of MLH1 mutations and warrants further study to address the utility of gastric surveillance.\textsuperscript{7}

As the EGAPP recommendations noted, the evidence to date is limited to clearly support benefit from genetic testing to the index patient with colorectal cancer if found to have Lynch syndrome. However, professional societies have reviewed the evidence and concluded that genetic testing likely has direct benefits for at least some patients with colorectal cancer and Lynch syndrome on the basis of differing recommendations for post-surgical surveillance, and
for those who choose prophylactic surgical treatment instead of surveillance. This policy is based on the evidence and professional society recommendations reviewed below.

In the absence of preventive surgery, heightened surveillance is recommended. The National Comprehensive Cancer Network (NCCN) guidelines for colon cancer\textsuperscript{39} and for colorectal cancer screening\textsuperscript{40} recommend post-surgical colonoscopy at 1 year and, if normal, again in 3 years, then every 5 years based on findings. However, for Lynch syndrome patients, colonoscopy is recommended every 1 to 2 years throughout life based on the high likelihood of cancer for patients diagnosed with Lynch syndrome prior to a cancer diagnosis, and on the high likelihood of a second primary cancer in those diagnosed with Lynch syndrome based on a first cancer diagnosis.\textsuperscript{41} NCCN guidelines on Genetic/Familial High-Risk Assessment: Colorectal\textsuperscript{42} indicate for MLH1, MSH2 and EPCAM mutation carriers surveillance with colonoscopy should begin “at age 20-25 years or 2 to 5 years prior to the earliest colon cancer if it is diagnosed before age 25 years and repeat every 1 to 2 years.” MSH6-mutation carriers should begin surveillance with colonoscopy “at age 30-35 years and PMS2 mutation carriers should begin surveillance with colonoscopy “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 PMS3 mutation 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.\textsuperscript{42}

Early documentation of the natural history of colorectal cancer in highly selected families with a strong history of hereditary colorectal cancer indicated risks of synchronous and metachronous cancers as high as 18% and 24%, respectively,\textsuperscript{43} in patients who already had colorectal cancer. As a result, in 1996, the Cancer Genetic Studies Consortium, a temporary NIH-appointed body, recommended that if colorectal cancer is diagnosed in patients with an identified mutation or a strong family history, a subtotal colectomy with ileorectal anastomosis (IRA) should be considered in preference to segmental resection.\textsuperscript{44} Although the average risk of a second primary is now estimated to be somewhat lower overall in patients with Lynch syndrome and colorectal cancer, effective prevention measures remain imperative. One study suggested that subtotal colectomy with IRA markedly reduced the incidence of second surgery for metachronous cancer from 28% to 6% but could not rule out the impact of surveillance.\textsuperscript{45} A mathematical model comparing total colectomy and IRA to hemicolec)
options of total proctocolectomy with ileal pouch anal anastomosis or anterior proctosigmoidectomy with primary reconstruction. The rationale for total proctocolectomy is the 17% to 45% rate of metachronous colon cancer in the remaining colon after an index rectal cancer in Lynch syndrome patients.

Lynch Syndrome and Endometrial Cancer Genetic Testing

Recently, several groups have recommended screening endometrial cancer patients for Lynch syndrome. At the 2010 Jerusalem Workshop on Lynch Syndrome,\textsuperscript{48} it was proposed that all incident case of endometrial cancer be screened for Lynch syndrome using mismatch repair-immunohistochemical (MMR-IHC) testing. Clarke and Cooper\textsuperscript{49} note that Sloan-Kettering Cancer Center screens all patients younger than 50 years of age with endometrial cancer using MMR-IHC; as well as patients older than 50 years with suggestive tumor morphology, lower uterine segment (LUS) location, personal/family history, or synchronous cell carcinoma of the ovary. Kwon et al.\textsuperscript{50} recommended MMR-IHC screening of women with endometrial cancer at any age with at least one first-degree relative with a Lynch syndrome-associated cancer.

The risk of endometrial cancer in MMR mutation carriers has been estimated at 34% (95% CI: 17-60%) by age 70, and of ovarian cancer 8% (95% CI: 2-39%) by age 70.\textsuperscript{7} Risks do not appear to appreciably increase until after age 40.

In a recent prospective study, 179 consecutive endometrial cancer patients \(\leq 70\) years of age were analyzed for microsatellite instability (MSI), by IHC for expression of 4 MMR proteins, MMR gene methylation status and BRAF mutations. Results are presented in Table 1 below; 92% of patients were older than 50 years of age.\textsuperscript{51}

### Table 1. Testing Unselected Endometrial Cancer Patients for Lynch Syndrome

<table>
<thead>
<tr>
<th>Result</th>
<th>N</th>
<th>% (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable MMS and normal protein staining</td>
<td>137</td>
<td>76%</td>
</tr>
<tr>
<td>MSI-H and MLH1 absent</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Sporadic MSI-H</td>
<td>31</td>
<td>17% (13-24%)</td>
</tr>
<tr>
<td>Likely to have Lynch syndrome</td>
<td>11</td>
<td>6% (3-11%)</td>
</tr>
<tr>
<td>Mutation-positive</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Result</td>
<td>N</td>
<td>% (95% CI)</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>---</td>
<td>------------</td>
</tr>
<tr>
<td>No mutation found</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Refuses further DNA testing</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Another study examined 625 endometrial cancer patients who underwent hysterectomy; endometrial cancer was classified as LUS in 9 patients. Twenty-seven randomly chosen patients from the non-LUS group were compared to the LUS group, and no statistically significant differences were found between groups with regard to MSI status or IHC findings. The incidence of Lynch syndrome in the LUS group was 1 in 9.

Kwon et al. developed a Markov Monte Carlo simulation model to compare 6 strategies for Lynch syndrome testing in women with endometrial cancer. Overall, the results suggested that IHC triage at any age, in women with at least one first-degree relative (FDR) with a Lynch-associated cancer, was the most cost-effective strategy (incremental cost-effectiveness ratio [ICER]= $9126) for identifying Lynch syndrome and subsequent colorectal carcinoma (CRC) cases. The model used published prevalence estimates of Lynch syndrome in all endometrial cancer patients of 2% (range 1-3%), and of 17% (range 15-20%) in endometrial cancer patients with at least one FDR with a Lynch-associated cancer. Results are presented in Table 2.

Table 2. Modeling of Endometrial Cancer Patient Screening Strategies for Detecting Lynch Syndrome

<table>
<thead>
<tr>
<th>Testing Strategy</th>
<th>No. cases subject to IHC triage</th>
<th>No. identified with Lynch syndrome</th>
<th>No. subsequent CRC cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amsterdam II criteria</td>
<td>NA</td>
<td>539</td>
<td>2582</td>
</tr>
<tr>
<td>Age &lt;50, and at least 1 FDR (Lynch-associated cancer)</td>
<td>NA</td>
<td>530</td>
<td>2470</td>
</tr>
<tr>
<td>IHC triage &lt; age 50</td>
<td>6285</td>
<td>520</td>
<td>2442</td>
</tr>
<tr>
<td>IHC triage &lt; age 60</td>
<td>16226</td>
<td>548</td>
<td>2450</td>
</tr>
<tr>
<td>IHC triage at any age; at least 1 FDR with Lynch-associated cancer</td>
<td>5786</td>
<td>755</td>
<td>2442</td>
</tr>
<tr>
<td>IHC triage all endometrial cancers</td>
<td>45000</td>
<td>827</td>
<td>2413</td>
</tr>
</tbody>
</table>

FDR: first degree relative; IHC: immunohistochemical; NA: not available
Female patients with Lynch syndrome who choose risk-reducing surgery are also encouraged to consider oophorectomy because of the risk of ovarian cancer in Lynch syndrome. As already noted, in one retrospective study, women who chose this option had no gynecologic cancer over 10 years, whereas about one-third of women who did not have surgery developed endometrial cancer, and 5.5% developed ovarian cancer. In another retrospective cohort study, hysterectomy improved survival among female colon cancer survivors with Lynch syndrome. This study also estimated that for every 100 women diagnosed with Lynch syndrome-associated colorectal cancer, about 23 will be diagnosed with endometrial cancer within 10 years absent a hysterectomy. Recent data on mutation-specific risks suggest that prophylactic gynecological surgery benefits for carriers of MSH6 mutations may offer less obvious benefits compared to harms as lifetime risk of endometrial cancer is lower than for carriers of MLH1 or MSH2 mutations, and lifetime risk of ovarian cancer is similar to the risk for the general population.

However, in the case of EPCAM deletion carriers, 3 recent studies found 3 cases of endometrial cancer in 103 female carriers who did not undergo preventative hysterectomy. Women with EPCAM deletions consequently have a lifetime risk of developing endometrial cancer decreased by 10-fold when compared with MMR gene-mutation carriers. This might support a clinical management scenario rather than prophylactic surgery. An alternative to prophylactic surgery is surveillance for endometrial cancer using TVUS and endometrial biopsy. Evidence indicates that such surveillance significantly reduces the risk of interval cancers, but no evidence as yet indicates surveillance reduces mortality due to endometrial cancer. Surveillance in Lynch syndrome populations for ovarian cancer has not yet been demonstrated to be successful at improving survival.

### Ongoing and Unpublished Clinical Trials

A search of ClinicalTrials.gov on October, 2014 identified the following studies on genetic testing for Lynch syndrome. Results are presented 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>
<tbody>
<tr>
<td>NCT01447199</td>
<td>The Molecular Predisposition to Hereditary</td>
<td>2000</td>
<td>September 2017</td>
</tr>
<tr>
<td>NCT No.</td>
<td>Trial Name</td>
<td>Planned Enrollment</td>
<td>Completion Date</td>
</tr>
<tr>
<td>------------</td>
<td>----------------------------------------------------------------</td>
<td>-------------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td></td>
<td>Nonpolyposis Colon Cancer (HNPCC)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01646112</td>
<td>Uncertain Genetic Test Results for Lynch Syndrome</td>
<td>40</td>
<td>Completion date unavailable</td>
</tr>
<tr>
<td>NCT01850654</td>
<td>Ohio Colorectal Cancer Prevention Initiative</td>
<td>4000</td>
<td>September 2017</td>
</tr>
</tbody>
</table>

NCT: national clinical trial

Summary of Evidence

Results of testing for the adenomatous polyposis coli (APC) mutation in individuals with a family history of familial adenomatous polyposis (FAP), or a known APC mutation in the family, lead to changes in surveillance and prophylactic treatment. For patients with a positive result, enhanced surveillance and/or prophylactic treatment will reduce the future incidence of colon cancer and improve health outcomes. Therefore APC testing is medically necessary for patients with a family history of FAP or a known APC mutation in the family. A related familial polyposis syndrome, MUTYH-associated polyposis (MAP) syndrome, is associated with mutations in the MUTYH gene. Testing for this genetic mutation is medically necessary when the differential diagnosis includes both FAP and MAP, since distinguishing between the two leads to different management strategies. In some cases, Lynch syndrome may be part of the same differential diagnosis, depending on presentation.

A substantial portion of patients with colorectal cancer will be found to have Lynch syndrome, which is associated with mutations in the mismatch repair (MMR) gene. A positive genetic test for the MMR mutation can lead to enhanced surveillance, changes in recommendations about treatment options, and possible prophylactic treatment for other Lynch syndrome malignancies. Therefore, testing patients at high risk for Lynch syndrome, defined by meeting the clinical criteria listed in the policy statement, is considered medically necessary. Additionally, immunohistochemical (IHC) testing for BRAF V600E or MLH1 promoter methylation may be considered medically necessary to exclude a diagnosis of Lynch syndrome when MLH1 is not expressed in the colorectal tumor.

Women with endometrial cancer are also at risk for Lynch syndrome, at a low prevalence; the prevalence is increased substantially when the population is limited to those aged 50 and younger and those age 51-60 with a first-degree relative diagnosed with a Lynch-associated cancer. Those found to have a MMR mutation will also benefit from enhanced colorectal cancer surveillance and prophylactic treatments. Therefore, testing for Lynch syndrome in patients with
newly diagnosed endometrial cancer age 51-60 who also have a first-degree relative diagnosed with a Lynch-associated cancer may be considered medically necessary. In addition, testing for Lynch syndrome in patients age 50 or younger with newly diagnosed endometrial cancer but no additional family history may be considered medically necessary.

**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. See evidence review section.

**Practice Guidelines and Position Statements**

*Cancer Network (NCCN)*

The NCCN guidelines for Genetic/Familial High-Risk Assessment: Colorectal cancer screening recommend 2 approaches to Lynch syndrome mutation screening of either:

- All colorectal cancers, or
- Colorectal cancer patients diagnosed before age 70 and those ages 70 and older when meeting Bethesda guidelines

Additionally, the colorectal cancer screening guidelines also recommend screening for Lynch syndrome for all endometrial cancer patients younger than 50 years. These guidelines note immunohistochemistry (IHC) and sometimes microsatellite instability (MSI) testing may be performed at some centers on all newly diagnosed colorectal and endometrial cancer patients to determine need for genetic testing for Lynch syndrome mutations regardless of family history. The guidelines note “evidence has shown 3 deletions in the EPCAM gene that lead to hypermethylation of the MSH2 promoter and subsequent MSH2 silencing, are an additional cause of Lynch syndrome.” The guidelines indicate that individuals with loss of MSH2 and/or MSH6 protein expression by immunohistochemistry, regardless of germline MMR mutation status, should be followed as though they have Lynch syndrome. Genetic testing is recommended for at-risk family members of patients with positive mutations in MLH1, MSH2, MSH6, or PMS2. The NCCN colon cancer screening guidelines also indicate BRAF V600E testing or MLH1 promoter methylation testing may be used when MLH1 is not expressed in the tumor.
on immunohistochemical (IHC) analysis to exclude a diagnosis of Lynch syndrome. As noted in the NCCN guidelines, “the presence of a BRAF mutation indicates MLH1 expression is down regulated by somatic methylation of the promoter region of the gene and not by germline mutation.” These guidelines also address familial adenomatous polyposis (classical and attenuated), and MUTYH-associated polyposis (MAP), consistent with the information in this policy.

NCCN guidelines for colon cancer recommend colon cancer patients younger than 50 years of age be tested for the MMR protein for possible Lynch syndrome. The colon cancer guidelines also 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 on uterine neoplasms indicate all endometrial cancer patients, especially those younger than 55 years, should be considered for testing for genetic mutations such as Lynch syndrome.

**European Society for Medical Oncology (ESMO)**

The ESMO published clinical practice guidelines for familial colorectal cancer risk in 2010. These guidelines addressed Lynch syndrome, familial adenomatous polyposis, and MUTYH-associated polyposis. No specific recommendations were made regarding how to initially identify Lynch syndrome cases; several methods, including clinical criteria and universal screening of all CRC cases, were mentioned.

**American Society of Clinical Oncology (ASCO) and the Society of Surgical Oncology (SSO)**

ASCO and (SSO recommends offering prophylactic total abdominal hysterectomy to female patients with colorectal cancer who have completed childbearing or to women undergoing abdominal surgery for other conditions, especially when there is a family history of endometrial cancer. This recommendation is based on the high rate of endometrial cancer in mutation-positive individuals and the lack of efficacy of screening.

**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 pre-symptomatic genetic tests and services, in the absence of past or present illness in the beneficiary, are not covered under national Medicare rules. CMS recognizes Lynch syndrome as “an autosomal dominant syndrome that accounts for about 3-5% of colorectal cancer cases. [Lynch] syndrome mutations occur in the following genes: hMLH1, hMSH2, hMSH6, PMS2 and EPCAM.” CMS also recognizes FAP and MAP syndromes and their associated mutations.

**Regulatory Status**

None of the tests reviewed in this policy are approved by the U.S. Food and Drug Administration (FDA). Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of CLIA.

Genetic tests reviewed in this policy are available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing.

To date, FDA does not require regulatory review of these tests.

**References**


27. Kovacs ME, Papp J, Szentirmay Z et al. Deletions removing the last exon of TACSTD1 constitute a distinct class of mutations predisposing to Lynch syndrome. Hum Mutat 2009; 30(2):197-203. PMID 19177550


<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>03/11/03</td>
<td>Replace Policy - Policy revised; testing for microsatellite instability considered medically necessary in certain patients.</td>
</tr>
<tr>
<td>05/11/04</td>
<td>Replace Policy - Policy reviewed; 2004 HCPC codes added; no criteria changes.</td>
</tr>
<tr>
<td>07/13/04</td>
<td>Replace Policy - Policy revised with literature updates; policy statements reflect newly revised guidelines.</td>
</tr>
<tr>
<td>07/12/05</td>
<td>Replace Policy - Policy updated with literature search; no change in policy statement; no further scheduled review. Status changed from BC to AR.</td>
</tr>
<tr>
<td>02/06/06</td>
<td>Codes Updated - No other changes.</td>
</tr>
<tr>
<td>06/30/06</td>
<td>Update Scope and Disclaimer - No other changes</td>
</tr>
<tr>
<td>03/21/07</td>
<td>Codes Updated - No other changes.</td>
</tr>
<tr>
<td>04/10/07</td>
<td>Replace Policy - Policy updated with literature review; codes updated. No change in policy statement.</td>
</tr>
<tr>
<td>06/10/08</td>
<td>Replace Policy - Policy updated with literature search; no change to the policy statement. Code added. Status changed from AR to PR.</td>
</tr>
<tr>
<td>06/13/11</td>
<td>Replace Policy - Policy updated with literature review. Clinical input reviewed. Policy description and rationale extensively rewritten; reference list completely revised. Policy statement clarified to indicate that testing the index patient with APC is considered medically necessary. Intent of other policy statements generally unchanged, although requirement for positive family history no longer required for testing. ICD-10 codes added to policy.</td>
</tr>
<tr>
<td>12/29/11</td>
<td>Codes 81296 – 81319 added.</td>
</tr>
<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>
</tbody>
</table>
| 06/10/13   | Replace policy. Policy updated with literature review. References added. Additional medically necessary indication added for patients with endometrial cancer and one first-degree relative diagnosed with a Lynch-associated cancer. CPT coding updated. Policy title revised to “Genetic Testing for Lynch Syndrome and Other Inherited Colon...
<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<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>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>
</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). ©2017 Premera All Rights Reserved.

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.
Discrimination is Against the Law

Premera Blue Cross complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex. Premera does not exclude people or treat them differently because of race, color, national origin, age, disability or sex.

Premera:
- Provides free aids and services to people with disabilities to communicate effectively with us, such as:
  - Qualified sign language interpreters
  - Written information in other formats (large print, audio, accessible electronic formats, other formats)
- Provides free language services to people whose primary language is not English, such as:
  - Qualified interpreters
  - Information written in other languages

If you need these services, contact the Civil Rights Coordinator.

If you believe that Premera has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, you can file a grievance with:
Civil Rights Coordinator - Complaints and Appeals
PO Box 9110, 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:
U.S. Department of Health and Human Services
200 Independence Avenue SW, Room S09F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)
Complaint forms are available at:

Getting Help in Other Languages

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 before 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).

中文 (Chinese):
本通知有重要的訊息。本通知可能有關於您透過 Premera Blue Cross 提交的申請或保險的重要訊息。本通知可能有重要的日期。您可能需要在截止日期之前採取行動，以保留您們的健康保險或費用補貼。您有權利免費以您的母語得到本訊息和幫助。請接電話 800-722-1471 (TTY: 800-842-5357).

Oromo (Cushite):

Deutsche (German):

Italiano (Italian):
Este Aviso contiene información importante. Es posible que este aviso contenga información importante acerca de su solicitud de cobertura a través de Premera Blue Cross. Es posible que haya fechas claves en este aviso. Es posible que deba tomar alguna medida antes de determinadas fechas para mantener su cobertura médica o ayuda con los costos. Usted tiene derecho a recibir esta información y ayuda en su idioma sin costo alguno. Llame al 800-722-1471 (TTY: 800-842-5357).

Tagalog (Tagalog):
Ang Paunawa na ito ay naglalaman ng mahalagang impormasyon. Ang paunawa na ito ay naglalaman ng mahalagang impormasyon tungkol sa iyong aplikasyon o pagkakautsak sa Premera Blue Cross. Ang paunawa na ito ay maaaring naglalaman ng mahalagang informasyon.

ไทย (Thai):
ประกาศนี้มีข้อความสำคัญเกี่ยวกับการขอรับบริการสุขภาพของคุณผ่าน Premera Blue Cross และมีข้อความที่สำคัญเกี่ยวกับการอนุญาตให้ขอรับบริการสุขภาพเพิ่มเติมหรือดำเนินการตามที่กำหนดไว้ หากคุณต้องการข้อมูลเพิ่มเติม โปรดติดต่อที่ 800-722-1471 (TTY: 800-842-5357).

українською (Ukrainian):
Це повідомлення містить важливу інформацію. Це повідомлення може містити важливу інформацію про Ваше звернення щодо страхування через Premera Blue Cross. Зверніть увагу на ключові дати, які можуть бути вказані у цьому повідомленні. Існує імовірність того, що Вам буде здобутися нової кривої в конкретні кінцеві строки для того, щоб зберегти Ваше медичне страхування або отримати фінансову допомогу. У Вас є право на отримання цієї інформації та допомоги безкоштовно на Ваший рідний мові. Дозвоніться за номером телефону 800-722-1471 (TTY: 800-842-5357).

Tiếng Việt (Vietnamese):

Русский (Russian):
Настоящее уведомление содержит важную информацию. Это уведомление может содержать важную информацию о вашем заявлении или страховом покрытии через Premera Blue Cross. В настоящем уведомлении могут быть указаны ключевые даты. Вам, возможно, потребуется принять меры к определенным предельным срокам для сохранения страхового покрытия или помощи с расходами. Вы имеете право на бесплатное получение этой информации и помощь на вашем языке. Звоните по телефону 800-722-1471 (TTY: 800-842-5357).

Español (Spanish):
Este Aviso contiene información importante. Es posible que este aviso contenga información importante acerca de su solicitud o cobertura a través de Premera Blue Cross. Es posible que haya fechas claves en este aviso. Es posible que deba tomar alguna medida antes de determinadas fechas para mantener su cobertura médica o ayuda con los costos. Usted tiene derecho a recibir esta información y ayuda en su idioma sin costo alguno. Llame al 800-722-1471 (TTY: 800-842-5357).

日本語 (Japanese):
この通知には重要な情報が含まれています。この通知には、Premera Blue Crossの申請または補償範囲に関する重要な情報が含まれている場合があります。この通知には記載されている可能性がある重要な日目をご確認ください。健康保険や無料サポートを維持するには、特定の期限までに行動を取らなければならない場合があります。自信の言語による情報とサポートが無料で提供されます。800-722-1471 (TTY: 800-842-5357)までお電話ください。

한국어 (Korean):
본 통지서에는 중요한 정보가 들어 있습니다. 즉 이 통지서는 귀하의 신청에 관하여 그리고 Premera Blue Cross를 통한 커버지에 관한 정보를 포함하고 있습니다. 본 통지서에는 특별이 되는 날짜들이 있을 수 있습니다. 귀하는 귀하의 건강 커버지를 계속 유지하거나 비용을 절약하기 위해서 일정한 마감일까지 조치를 취해야 할 필요가 있을 수 있습니다. 귀하의 이러한 정보는 귀하의 안전과 비용 부담없이 익을 수 있는 권리가 있습니다. 800-722-1471 (TTY: 800-842-5357)로 전화하십시오.

 práctico. Este aviso puede contener importantes informaciones privilegiadas de manera que no sea posible acceder a ellas a menos que se cumplan determinadas condiciones. Deberá tener en cuenta el número gratuito 800-722-1471 (TTY: 800-842-5357) para obtener información y ayuda.

Polski (Polish):
To ogłoszenie może zawierać ważne informacje. To ogłoszenie może zawierać ważne informacje odnośnie płatności przez Premera Blue Cross. Prosimy zwrócić uwagę na kluczowe daty, które mogą być zawarte w tym ogłoszeniu aby nie przekroczyć terminów w przypadku utraty polisy ubezpieczenia lub pomocy związanej z kosztami. Macie prawo do bezpłatnej informacji we własnym języku. Zadzwoń pod numer 800-722-1471 (TTY: 800-842-5357).

Português (Portuguese):
Este aviso contém informações importantes. Este aviso poderá conter informações importantes a respeito de sua aplicação ou cobertura por meio do Premera Blue Cross. Poderão existir datas importantes neste aviso. Talvez seja necessário que você tome providências dentro de determinados prazos para manter sua cobertura de saúde e cuidado. Você tem o direito de obter esta informação e ajuda em seu idioma e sem custos. Ligue para 800-722-1471 (TTY: 800-842-5357).