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

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Effective Date: Dec. 1, 2017
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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.
# Testing

## Medical Necessity

### Lynch Syndrome (Also known as hereditary non-polyposis colorectal cancer or HNPC)

<table>
<thead>
<tr>
<th>Initial screening</th>
<th>Screening for Lynch syndrome as an initial evaluation of tumor tissue:</th>
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<tbody>
<tr>
<td></td>
<td>• 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.</td>
</tr>
</tbody>
</table>

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

### Genetic testing (eg, COLARIS® (Myriad))

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 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.**

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*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) (eg, Colaris AP® (Myriad)) | 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  
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 (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.

| 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  
OR  

Testing

- 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])

OR

- 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 above.**

Coding

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>CPT</td>
<td>Description</td>
</tr>
<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>
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<tr>
<td>81288</td>
<td>MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (e.g., hereditary nonpolyposis colorectal cancer, Lynch syndrome) gene analysis; promoter methylation analysis</td>
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<tr>
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<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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<td>MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis, known familial variants</td>
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<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>
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<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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<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>
</tr>
<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>
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<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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<td>81319</td>
<td>PMS2 (postmeiotic segregation increased 2 [s. cerevisiae]) (eg, hereditary nonpolyposis colorectal cancer, Lynch syndrome) gene analysis, duplication/deletion variants</td>
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<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>
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<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>
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<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>
</tr>
</tbody>
</table>

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Genetic Counseling

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. 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 клиническая_дisease_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 criteria 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\(^3\)

**FAP Guidelines**

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

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 affected individuals and those at risk for various types of hereditary cancer. This review evaluates genetic testing for hereditary colorectal cancer and polyposis syndromes, including familial adenomatous polyposis, Lynch syndrome (formerly known as hereditary nonpolyposis colorectal cancer), MUTYH-associated polyposis, and Lynch syndrome–related endometrial cancer.
Background

**Hereditary Colorectal Cancers**

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 Gardner 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. In AFAP, colorectal cancer occurs at an average age of 50-55 years, but there is a high lifetime risk of colorectal cancer of about 70% by age 80 years. The risk of extra-intestinal cancer is lower in AFAP compared to classical FAP, but it is still high at an estimated cumulative lifetime risk of 38% compared to the general population. Only 30% or fewer of AFAP patients have APC mutations. Instead, some of these patients 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 it is still under debate.\textsuperscript{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\textsuperscript{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 an increased risk of developing colorectal cancer by age 70. After correction for ascertainment bias, the risk is approximately 27% to 45% for men, and 22% to 38% for women.\textsuperscript{7} 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 it is still significantly higher than that of the general population.\textsuperscript{6,7} 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. 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 rather than the MSI-high phenotype; thus MSI-low should not be a criterion against proceeding to MMR mutation testing.

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.
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.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 mutations MLH1, 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.

**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, it was proposed that all incident cases of endometrial cancer be screened for Lynch syndrome using mismatch repair-immunohistochemical (MMR-IHC) testing. Clarke and Cooper 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. 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. Risks do not appear to appreciably increase until after age 40.

Female patients with Lynch syndrome who choose risk-reducing surgery are also encouraged to consider oophorexy 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.\textsuperscript{30,31,57} 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.\textsuperscript{31} 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.\textsuperscript{58} Surveillance in Lynch syndrome populations for ovarian cancer has not yet been demonstrated to be successful at improving survival.\textsuperscript{58}

**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.

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 1.

Table 1. 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>Ongoing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01447199</td>
<td>The Molecular Predisposition to Hereditary Nonpolyposis Colon Cancer (HNPCC)</td>
<td>2000</td>
<td>Sep 2017</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</td>
</tr>
<tr>
<td>Unpublished</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>
</tr>
</tbody>
</table>

NCT: national clinical trial

Practice Guidelines and Position Statements

National Comprehensive 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.47

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, the FDA does not require regulatory review of these tests.


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


### History

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>05/19/98</td>
<td>Add to Medicine Section - New Policy.</td>
</tr>
<tr>
<td>09/01/98</td>
<td>Replace Policy - References to TEC assessments added to rationale section; policy unchanged.</td>
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<tr>
<td>01/07/99</td>
<td>Replace Policy - 1999 CPT Coding Release.</td>
</tr>
<tr>
<td>01/18/01</td>
<td>Replace Policy - Updated information on microsatellite instability; remainder unchanged.</td>
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<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>
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<tr>
<td>02/06/06</td>
<td>Codes Updated - No other changes.</td>
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<tr>
<td>06/30/06</td>
<td>Update Scope and Disclaimer - No other changes</td>
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<tr>
<td>03/21/07</td>
<td>Codes Updated - No other changes.</td>
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<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</td>
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<tr>
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<tr>
<td>12/29/11</td>
<td>Codes 81296 – 81319 added.</td>
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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>
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<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>
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<td>11/15/12</td>
<td>Reviewed and recommended by OAP, November 2012.</td>
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<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>
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<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>
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<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>
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<tr>
<td>07/24/14</td>
<td>Update Related Policies. Remove 12.04.91.</td>
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<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>
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<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</td>
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</tbody>
</table>
### Date | Comments
--- | ---
 | 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.
01/12/16 | Annual Review. Policy updated with literature review through October 26, 2014. References 42 added. Policy statement unchanged
08/31/16 | Policy moved into new format; no change to policy statements.
01/01/17 | 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.
03/01/17 | Updated Related Policies, removed 2.04.29 as it was archived.
12/01/17 | Annual Review, approved November 9, 2017. Policy updated with literature review. No references added, no changes to policy statements.

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Email AppealsDepartmentInquiries@Premera.com

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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)
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Premera Blue Cross

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TTY: 800-842-5357

Web Site:
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