**Genetic Testing for Lynch Syndrome**

**MPM 7.5**

**Disclaimer**

Refer to the member’s specific benefit plan and Schedule of Benefits to determine coverage. This may not be a benefit on all plans or the plan may have broader or more limited benefits than those listed in these criteria.

Prior Authorization is required. Please use the Prior Authorization/Benefit Certification Guide to determine when a prior authorization/benefit certification is required

https://ds.phs.org/preslogin/index.jsp

**Coverage Determination**

I. For Medicaid and Commercial members:

Presbyterian Health Plan follows the most recent NCCN Guideline Version for High-Risk Colorectal Cancer Syndromes (Criteria for the Evaluation of LS), for Commercial and Centennial Care members for Colaris Test.

For proprietary reasons, NCCN Guideline cannot be reproduced in this Medical Policy. Please contact Health Services for a copy of the NCCN Guidelines at (505) 923-5757 or 1-888-923-5757, Monday through Friday from 8:00 a.m. to 6:00 p.m.

II. For Medicare members:

**Colorectal cancer (CRC) genetic testing for Lynch Syndrome:**

PHP follows CMS LCD L36793 MolDX: Genetic Testing for Lynch Syndrome. **Note:** There are 3 different screening approaches to identify Lynch Syndrome outlined in this section for Medicare members. Select either **ONE** of the following population-based screening sub-set criteria **A, or B, or C.**

A. For IHC and/or MSI Testing

For coverage, the treating physician/pathologist is expected to follow the stepped approach (Step 1 thru Step 6) outlined below for LS screening and targeted MMR testing in this policy. Germ-line testing includes sequence and duplication-deletion analysis for a given gene.

Lynch Syndrome tumor screening with (IHC) or (MSI) is considered medically necessary and covered for members for the following indications:

- All individuals with colorectal cancer regardless of age
- individuals with endometrial cancer
- *Hereditary nonpolyposis colorectal cancer (HNPCC)-related tumors include colorectal, endometrial, gastric, ovarian, pancreas, ureter and renal pelvis, biliary tract, brain
(usually glioblastomas as seen in Turcot syndrome), small intestinal cancers, and sebaceous gland adenomas and keratoacanthomas as seen in Muir-Torre syndrome.

- For patients with unresectable or metastatic solid tumors, either MSI or IHC or a multigene NGS or other multi-analyte methodology panel inclusive of MSI microsatellite loci, and MLH1, MSH2, MSH6 and PMS2 genes is medically reasonable and necessary.

Step 1 thru Step 6 Testing Strategy for patients with personal history of colorectal or endometrial cancer (regardless of age):

There are two methods available to determine the presence of defective mismatch repair, i.e. microsatellite instability testing (MSI) and detection of loss of the protein product of the mismatch repair genes involved in DNA mismatch repair (MLH1, MSH2, MSH6 and PMS2) by immunohistochemistry (IHC). MSI testing and IHC are about equally sensitive (~95%) for detecting defective mismatch repair (MMR). Some authors advocate testing all tumors by both methods to ensure correct classification, while others prefer MSI testing if other biomarkers are being evaluated. The policy does not dictate the use of one method or another. However, if IHC is done first and is abnormal, MSI testing is not warranted. If IHC is normal, MSI is warranted.

For coverage, the treating physician/pathologist is expected to follow a stepped approach to meet the reasonable and necessary criteria. To progress to each subsequent step, refer to the indications detailed in the policy. See (A55135) that displays each subsequent steps.

Step 1 - Immunohistochemistry (IHC) testing for LS screening:

IHC test detects the loss of DNA mismatched repair (MMR) protein expression complements MSI to screen patients for defective MMR (dMMR), including both sporadic dMMR and LS dMMR. IHC allows detection of loss of protein expression for the MLH1, MSH2, MSH6 and PMS2 genes.

If IHC is done first and is abnormal, MSI testing is not warranted. Usually, IHC is done first because of its rapid turn-around and minimal amount of tissue required. If IHC demonstrates loss of protein expression for the MLH1, MSH2, MSH6 and PMS2 genes, the following test results direct further testing:
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- MLH1 loss by IHC, test for BRAF gene mutation (Step 3) or test for MLH1 promoter, (Step 4)
- MSH2/MS6 loss by IHC, perform MSH2 germ-line testing (Step 5)

If IHC test results are normal, there remains a small chance of high levels of microsatellite instability (MSI-H), so both IHC and MSI would be needed to rule out LS in a clinically suspicious setting.

In other words, to detect the presence of a defective mismatch pair may be performed by **ONE or both** of the following methods:

**Method 1:** (IHC) for **MLH1, MLH2, MSH6, and PMS2**, (CPT 88342/88341x3), if normal do MSI test too.

**Method 2:** (MSI) (CPT:81301). MSI not recommended if IHC is abnormal.

**If results from methods 1 or 2 are abnormal, proceed to step 2.**

**Step 2 – MSI and/or Deficient Mismatch Repair (MMR) by (IHC) Analysis for LS Screening:**

As indicated above, MSI testing is not necessary if IHC demonstrates loss of protein expression for the **MLH1, MLH2, MSH6 and PMS2** genes. If IHC test results are normal, there remains a small chance of high levels of microsatellite instability (MSI-H), so both IHC and MSI should be performed to rule out LS in a clinically suspicious setting such as meeting a Revised Bethesda guideline. Additionally, some individuals with MSH6 germ-line mutations do not manifest the MSI-H phenotype. This finding supports the diagnostic strategy to screen suspected LS patients with CRC by both MSI and IHC. Immunohistochemistry (IHC) can be used to identify whether the protein products of **MLH1, MLH2, MSH6 and PMS2** genes are present or absent. Individuals with tumors that display high levels of MSI or loss of expression of MMR proteins by IHC are then referred for targeted germ-line mutation.

Definitive Molecular Testing for Lynch Syndrome may be performed by **ONE** of the following methods.

**Method 1:** Next generation sequencing (NGS "hotspot") testing platforms:

Molecular testing for **MLH1, MLH2, MSH6 and PMS2** genes by NGS is covered as medically acceptable for the identification of LS. BRAF V600E and MLH1 promoter
methylation may not be included in NGS panel hereditary colon cancer panels. If MLH1 is abnormal for MMR by IHC, BRAF codon 600 reflex testing may be performed. If BRAF is negative, reflex MLH1 promoter methylation may be performed. Reflex EpCAM testing is indicated when EpCAM is not included in a hereditary colon cancer panel by NGS and IHC shows a loss of MSH2.

OR

Method 2: Non-NGS testing platforms:

Molecular testing for MLH1, MSH2, MSH6 and PMS2 genes by non-NGS must be based upon IHC and/or MSI preliminary test results according to the following stepped approach:

Note: For Non-NGS testing (Step 2-6, Method 2), you may ONLY progress to the subsequent genetic test IF additional information is necessary to rule out or diagnose LS.

Steps 3 and/or 4 apply only for tumors that are negative for MLH1 protein expression by IHC.

Step 3 – BRAF V600E (BRAF Mutation Testing):

BRAF mutation testing and MLH1 promoter methylation studies distinguish between sporadic dMMR and LS dMMR. This is because BRAF mutation and MLH1 PHM are very seldom seen in LS. BRAF mutation testing of the CRC tumor is associated with the presence of an epigenetic alteration (i.e., hypermethylation of MLH1) and either finding excludes germ-line MMR gene mutation (e.g. LS).

Step 4: MLH1 Promoter Hypermethylation (MLH1 PHM)

The combination of MLH1 PHM and a BRAF mutation in tumors rules out LS and no further molecular analysis is warranted.

Tumors with MLH1 PMH identify dMMR which will most often be sporadic, but its presence does not fully rule out LS. However, there have been rare reports of MLH1 hypermethylation as a second hit in LS and there are new reports of constitutional MLH1 methylation. As a rule, discovery of MLH1 PHM indicates the tumor is not due to Lynch syndrome.

The following combinations of BRAF and MLH1 promoter methylation test results direct further testing in individuals with CRCs with loss of IHC expression of MLH1/PMS2:
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- If BRAF mutation is present, no further testing is medically necessary; LS is ruled out.

- If BRAF mutation is absent, MLH1 promoter methylation testing is indicated and directs the following testing:
  - If MKH1 is hypermethylated, germline MLH1 is not medically necessary.
  - If the MLH1 promoter is hypermethylated and modified Amsterdam Criteria ACII is fulfilled, germ-line MLH1 may still be considered (2nd hit scenario).
  - If the MLH1 promoter is normally methylated, and BRAF is negative for mutation then germ-line MLH1 testing is medically indicated.

  **Note:** There is variability in laboratory preference for BRAF and MLH1 promoter testing sequence. Although BRAF is generally cheaper and faster, some labs test MLH1 PHM first because it is more sensitive for detection of sporadic dMMR.

**Step 5: Targeted MMR (MLH1, MSH2, MSH6 and PMS2 gene) Germ-line and EpCAM Testing:**

**Step 5A: MLH1 Testing**

When IHC shows loss of both MLH1 and PMS2, further genetic testing of PMS2 is not indicated, as no cases have been reported of a PMS2 germ-line mutation when IHC showed a loss of both MLH1 and PMS2. PMS2 mutations have only been detected when IHC shows a loss of PMS2 only. If MLH1 gene mutation is positively identified, then LS is diagnosed and further testing of the patient is not medically necessary.

**Step 5B: MSH2 Testing**

When IHC shows loss of MSH2 and MSH6, genetic testing should start with analysis of the MSH2 gene, given its frequency of germ-line mutation in LS. If MSH2 germ-line mutation is identified, then LS is diagnosed, and further testing of the patient is not medically necessary.

However, if genetic testing for germ-line mutations in MSH2 is negative, analysis for deletion in the EpCAM gene should be performed (Step 6). If EpCAM is also negative, genetic testing of MSH6 should be performed (Step 5C). The presence of MSI and the loss of MSH2/MSH6 strongly indicate an MMR germ-line defect.

**Step 5C: MSH6 Testing**
When IHC shows loss of just MSH6, it suggests a germ-line mutation in MSH6 and genetic testing of that gene is indicated. As previously noted, MSH6 CRC tumors can be MSI-H, MSI-L or MSS. This pitfall illustrates the utility of IHC for MMR protein expression. If MSH6 germ-line mutation is identified, then LS is diagnosed, and further testing of the patient is not medically necessary.

**Step 5D: PMS2Testing**

If IHC shows PMS2 loss only, germ-line testing for PMS2 mutations is indicated. No cases of a PMS2 germ-line mutation have been identified after IHC showed a loss of both MLH1 and PMS2. If PMS2 germ-line mutation is identified, then LS is diagnosed, and further testing of the patient is not medically necessary.

**Step 6: EpCAM Testing**

Recently, deletions in a portion of the EpCAM gene were found in a subset of families with LS with a loss of MSH2 by IHC. A common deletion in the 3’ region of EpCAM causes somatic hypermethylation of MSH2, as the 2 genes are adjacent to one another on chromosome 2. Approximately 20% of patients with absence of MSH2 and MSH6 protein expression by IHC, but without MSH2 or MSH6 mutation, will have germ-line deletions in EpCAM. Early estimates suggest that germ-line mutations in EpCAM may account for approximately 6% of LS cases and possibly as high as 30% when IHC shows a loss of MSH2.

**Note:** Many labs incorporate EpCAM detection their MSH2 dup/deletion analysis.

The following criteria (B & C) are performed only when criteria (A), with the stepped approach, outlined above is unable to be performed. In this case, select either ONE of the following population-based sub-set criteria B, or C for Medicare members.

**B. MMR Germline Gene Mutation Testing Exception**

If a lab is unable to perform the stepped testing mentioned above, multiple germ-line gene testing will be covered by PHP only for one or more of the following findings:

- MSI/IHC testing yields normal IHC and MSI-H, suggesting LS
- If tumor is not available or determined by a pathologist to be inadequate to assess DNA MMR deficiency by MSI or IHC, then MMR germ-line testing can be conducted on blood from patient with CRC or endometriual cancer.
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- Diagnosis of any Lynch-associated cancer prior to Medicare eligibility **AND** tumor sample no longer available **AND** meets either Revised Bethesda guidelines or has at least a personal 5% estimated likelihood to be mutation positive, as calculated by an established available risk model (e.g., PREMM, MMRpredict, MMRpro).

  If targeted gene testing is not possible, testing of the four MMR genes can be performed concurrently followed by testing for EpCAM, or per a testing strategy deemed appropriate by the physician.

C. Testing for Known Familial Variant

Testing for a specific known familial variant is considered medically necessary and covered only when the individual being tested has signs and symptoms of a Lynch-associated cancer **AND** has a blood relative with the specific disease-causing mutation for LS.

**Note:** The LCD does not imply that testing family members of a known familial variant is not medically warranted. The scope of the benefit requires the member to have signs and symptoms of disease. Coverage of molecular testing for LS for carrier status or family studies is considered screening and is excluded from coverage.

**Exclusion(s)**

- First-degree relatives of mutation carriers have a 50% probability of having the same germ-line mutation. Despite the high penetrance of CRC and endometrial cancer and recommendations of consideration for screening unaffected first-degree relatives following diagnosis of a LS proband, testing of genetic carriers who are unaffected with a Lynch related cancer is not a benefit, and is excluded from coverage.

  Molecular testing for LS to identify carrier status or family studies is not a covered benefit.

**Coding**

The coding listed in this medical policy is for reference only. Covered and non-covered codes are within this list.

<table>
<thead>
<tr>
<th>CPT CODES</th>
<th>Descriptions</th>
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</thead>
<tbody>
<tr>
<td>81210</td>
<td>BRAF (B-RAF proto-oncogene, serine/threonine kinase) (eg, colon cancer, melanoma), gene analysis, V600 variant(s).</td>
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<tr>
<td>81288</td>
<td>MLH1 (MUTL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; promoter methylation analysis</td>
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<table>
<thead>
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<th>CPT CODES</th>
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<tbody>
<tr>
<td>81292</td>
<td>MLH1 (MUTL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, lynch syndrome) gene analysis; full sequence analysis</td>
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<tr>
<td>81293</td>
<td>MLH1 (MUTL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, lynch syndrome) gene analysis; known familial variants</td>
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<td>81294</td>
<td>MLH1 (MUTL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, lynch syndrome) gene analysis; duplication/deletion variants</td>
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<td>81295</td>
<td>MSH2 (MUTS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, lynch syndrome) gene analysis; full sequence analysis</td>
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<tr>
<td>81298</td>
<td>MSH6 (MUTS homolog 6 [E. Coli]) (eg, hereditary non-polyposis colorectal cancer, lynch syndrome) gene analysis; full sequence analysis</td>
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<td>81299</td>
<td>MSH6 (MUTS homolog 6 [E. Coli]) (eg, hereditary non-polyposis colorectal cancer, lynch syndrome) gene analysis; known familial variants</td>
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<td>MSH6 (MUTS homolog 6 [E. Coli]) (eg, hereditary non-polyposis colorectal cancer, lynch syndrome) gene analysis; duplication/deletion variants</td>
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<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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<td>81317</td>
<td>PMS2 (postmeiotic segregation increased 2 [S. Cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, lynch syndrome) gene analysis; full sequence analysis</td>
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<td>81318</td>
<td>PMS2 (postmeiotic segregation increased 2 [S. Cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, lynch syndrome) gene analysis; known familial variants</td>
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<tr>
<td>81319</td>
<td>PMS2 (postmeiotic segregation increased 2 [S. Cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, lynch syndrome) gene analysis; duplication/deletion variants</td>
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<td>81403</td>
<td>Molecular pathology procedure, level 4 (eg, analysis of single exon by DNA sequence analysis, analysis of &gt;10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)</td>
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<td>81435</td>
<td>Hereditary colon cancer disorders (eg, lynch syndrome, PTEN hamartoma syndrome, cowden syndrome, familial adenomatosis polyposis); genomic sequence analysis panel, must include sequencing of at least 10 genes, including APC, BMPR1A, CDH1, MLH1, MSH2, MSH6, MUTYH, PTEN, SMAD4, and STK11</td>
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<tr>
<td>81479</td>
<td>Unlisted molecular pathology procedure</td>
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**ICD-10 Diagnosis Codes**

| ICD10 Codes | Access LCD L36793 for the ICD-10 codes that support Medical Necessity for CPT Codes listed above. |

**References**

1. LCD, MolDX: Genetic Testing for Lynch Syndrome LCD L36793, Effective Date 02/16/2017, Revision date

Not every Presbyterian health plan contains the same benefits. Please refer to the member’s specific benefit plan and Schedule of Benefits to determine coverage. [MPMPPC051001]
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01/01/2019, R4. [Cited 08/21/2019]


Approval Signatures
Clinical Quality Utilization Mgmt. Committee: Howard Epstein MD
Medical Director: Norman White MD

Approval Date
September 25, 2019

Publications History
09-25-19 Creation of MPM 7.5 to moved Lynch Syndrome from MPM 7.1. Reviewed and approved by Medical Directors to use LCD L36793 for Medicare members only and for Commercial and Medicaid use NCCN criteria.

This Medical Policy is intended to represent clinical guidelines describing medical appropriateness and is developed to assist Presbyterian Health Plan and Presbyterian Insurance Company, Inc. (Presbyterian) Health Services staff and Presbyterian medical directors in determination of coverage. The Medical Policy is not a treatment guide and should not be used as such.

For those instances where a member does not meet the criteria described in these guidelines, additional information supporting medical necessity is welcome and may be utilized by the medical director in reviewing the case. Please note that all Presbyterian Medical Policies are available online at: Click here for Medical Policies

Web links:
At any time during your visit to this policy and find the source material web links has been updated, retired or superseded, PHP is not responsible for the continued viability of websites listed in this policy.

When PHP follows a particular guidelines such as LCDs, NCDs, MCG, NCCN etc., for the purposes of determining coverage; it is expected providers maintain or have access to appropriate documentation when requested to support coverage. See the References section to view the source materials used to develop this resource document.