Genetic Testing for Lynch Syndrome

LCD ID L35553

Jurisdiction
Tennessee

Original Effective Date
For services performed on or after 10/01/2015

LCD Title
Pathology and Laboratory: Genetic Testing for Lynch Syndrome

CMS National Coverage Policy

- Title XVIII of the Social Security Act, Section 1833 (e). This section states that no payment shall be made to any provider for any claims that lack the necessary information to process the claim.
- Title XVIII of the Social Security Act, Section 1861(s)(3). This section outlines coverage for clinical diagnostic laboratory tests.
- Title XVIII of the Social Security Act, Section 1862(a)(1)(A). This section allows coverage and payment for only those services that are considered to be reasonable and medically necessary, i.e., reasonable and necessary are those tests used in the diagnosis and management of illness or injury or to improve the function of a malformed body part.
- Title XVIII of the Social Security Act, section 1862 (a)(7). This section excludes routine physical evaluations.
- 42 CFR Section 410.32(a) indicates diagnostic tests are payable only when the physician who is treating the beneficiary for a specific medical problem uses the results in such treatment.
- 42 CFR 415(k)(1). Particular Services excluded from coverage.
- Medicare Benefit Policy Manual (Pub. 100-02), Chapter 15, Section 80.1. Clinical Laboratory Services.
- Medicare Program Integrity Manual (Pub. 100-08), Chapter 13. Local Coverage Determinations.

Coverage Guidance

Coverage Indications, Limitations, and/or Medical Necessity

Background

I. Lynch Syndrome (LS)

This policy limits Lynch syndrome (LS) genetic testing to a stepped approach for Microsatellite Instability and Immunohistochemistry (MSI/IHC) screening,*BRAF* gene mutation, *MLH1* gene promoter hypermethylation and targeted mismatch repair (MMR) germ-line gene testing to patients suspected of having LS.

Most colorectal cancer is caused by non hereditary somatic mutations. Individuals with LS (aka hereditary nonpolyposis colorectal cancer (HNPCC)) are predisposed to cancer due to having inherited or de novo germ-line mutations in DNA repair genes, that result in an accelerated accumulation of somatic mutations. LS, the most common hereditary cause of colorectal cancer, accounts for 2-3% of all colorectal cancers, followed by familial adenomatous polyposis (FAP) which accounts for <1% of colorectal malignancies and MUTYH-associated polyposis (MAP) whose frequency of occurrence is very rare.

LS is an autosomal dominant familial cancer syndrome caused by mutations in multiple susceptibility genes (e.g., *MLH1, MSH2, MSH6, PMS2, EPCAM*), and is associated with an increased lifetime risk for colorectal cancer (CRC) and other malignancies within the tumor spectrum including at least endometrial, ovarian, gastric, small bowel, urothelial, hepatobiliary tract, sebaceous and pancreatic cancers. Current literature suggests LS annually affects 28,000 individuals. In individuals with LS, the lifetime risk of colon cancer may be as high as 75% by the age of 70 years, with an average age onset of 45 years in *MLH1* and *MSH2* mutation carriers. While the incidence of adenomas in individuals with LS is similar to that in the general population, the high rate of colorectal cancer is due to an acceleration of the adenoma to carcinoma sequence.

Cancer risks associated with LS are largely derived from family studies. Mutations in *MLH1* and *MSH2* account for 70-90% of families with LS. The risk of colon and endometrial cancer is less in *MSH6* and *PMS2* mutation carriers, although the cancer risk may not be lower for *MSH6* carriers if one takes the data out to age 80. While individuals with a single *MLH1, MSH2, MSH6* and *PMS2* mutation develop cancers in mid-life, individuals with biallelic *MLH1, MSH2, MSH6* and *PMS2* mutations have a distinctive phenotype and tumor spectrum, and often develop cancer as early as the first decade of life.

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 an LS proband, testing of genetic carriers who are unaffected with a Lynch related cancer is not a Medicare benefit, and is statutorily excluded from coverage.

II. Testing Strategy for Patients with Personal History of Colorectal Cancer

Step 1: Patient selection

Patients with colorectal and/or endometrial cancer suspected of LS must undergo a comprehensive review of physical findings and a complete personal and family history.

In 1989, the Amsterdam criteria defined what is known as Hereditary Non-polyposis Colon Cancer Syndrome, and in 1999, the criteria were revised to include extra-colonic tumors (Table 1). Today we know there are two distinct groups comprising HNPCC: those with hereditary DNA mismatch repair germ-line mutations, known as Lynch Syndrome, and those with normal DNA mismatch repair, known as Familial Colorectal Cancer Type X.

Table 1. Amsterdam Criteria II (ACII)

There should be at least three relatives with CRC or with a Lynch syndrome-associated cancer: endometrial, small bowel, ureter or renal pelvis cancer.

- One relative should be a 1st-degree relative of the other two,
- At least two successive generations should be affected,
- At least one tumor should be diagnosed before age 50 years,
- FAP should be excluded in the CRC case, if any,
- Tumors should be verified by histopathological exam

Approximately 50% of families meeting the ACII criteria have a mutation in an MMR gene. However, these criteria are very stringent and miss as many as 68% of patients with LS.

In 1997, the Bethesda guidelines were developed to identify individuals with CRC who should be tested for MSI. In 2002, the guidelines were revised (Table 2) to clarify selection criteria for microsatellite instability (MSI) testing and mismatch repair (MMR) protein expression by immunohistochemistry (IHC). Screening tumors of patients meeting the Bethesda guidelines for MSI was shown to be cost-effective with newly diagnosed CRC.

Table 2 - Revised Bethesda Guidelines

Meeting any of the following are sufficient for consideration of MSI/IHC testing

- CRC diagnosed under age 50
- Presence of synchronous, or metachronous CRC or other Lynch-associated tumor, regardless of age
- CRC with MSI-H histology diagnosed in an individual who is < age 60
- CRC diagnosed with one or more 1st-degree relatives with a Lynch-related tumor, with one of the cancers diagnosed under age 50
- CRC diagnosed in two or more 1st- or 2nd-degree relatives with a Lynch-related tumor, regardless of age

If a patient meets standards for LS testing in Step 1, (i.e., meets ACII or Revised Bethesda guidelines), the physician should proceed to Step 2 and 3.

Step 2: Immunohistochemistry (IHC) testing for LS Screening

The use of IHC to detect 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. Loss of MMR protein expression is detected by the absence of nuclear staining in the tumor cells and the presence of nuclear staining in lymphocytes and normal colon crypt epithelial cells.

The MMR proteins are present as heterodimers (*MLH1* pairs with *PMS2,* and *MSH2* pairs with *MSH6*). Knowledge of MMR protein expression loss patterns allows a logical and cost effective “directed” testing appropriate for germ-line mutation analysis. As a general rule, loss of expression of *MLH1* or *MSH2* is associated with loss of their partners. For example, mutation of the *MLH1* gene generally leads to loss of expression of both the *MLH1* and *PMS2* proteins. However, loss of *PMS2* or *MSH6* due to a germ-line mutation is associated only with loss of the mutated protein. For example, mutation of the *PMS2* gene

leads to loss of expression of only the *PMS2* protein.

If IHC is done first and is abnormal, MSI testing is not warranted. Often 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:

- *MLH1* loss by IHC, test for *BRAF* gene mutation (Step 4) or test for *MLH1* promoter, (Step 5)
- *MSH2/MS6* loss by IHC, perform *MSH2* germ-line testing (Step 6)

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.

Step 3: Microsatellite Instability (MSI) Analysis for LS Screening

MSI analysis for screening LS microsatellites are short repeated segments of DNA spread throughout the genome. Under normal conditions, the MMR gene complex *(MLH1, MSH2, MSH6* and *PMS2* genes) corrects mismatched base pairs that occur during the final stage of DNA replication. When the MMR complex is functioning normally, all cells show an identical pattern of microsatellite lengths. When the MMR complex is non-functioning, due to two hits of any type, random mutations accumulate in microsatellites, leading to differences in microsatellite lengths (microsatellite instability, MSI). Therefore, MSI indicates loss-of-function defects in a MMR protein, which may be due to somatic mutations, germ-line MMR gene mutations, allelic loss, or to epigenetic down-regulation. MSI is usually associated with absence of protein expression of one or more of the MMR proteins (*MLH1, MSH2, MSH6M* and *PMS2)*.

DNA from paraffin-embedded tumor tissue and normal tissue or peripheral blood is used for MSI analysis. A microsatellite is considered unstable if the distribution of the tumor fragments differs from that of the normal tissue. Noncancerous tissue in individuals with LS does not show MSI because normal tissue is heterozygous for the germ-line mutation.

Levels of MSI in colon tumors are classified as:

- **MSI-H>** - 30% or more of a tumor's markers are unstable;
- **MSI-L** - > one but < 30% of a tumor's markers are unstable;
- **MSS** - no loci are unstable.

MSI-L and MSS indicates the MMR mechanism is functioning adequately. Virtually all CRC tumors from individuals with LS demonstrate MSI-H. However, MSI-H is NOT diagnostic of LS as MSI-H can be observed in roughly 15% of sporadic colorectal cancers. In other Lynch tumors, the % level of MSI-H is less consistent and is inadequately studied.

As indicated above, MSI testing is not necessary if IHC demonstrates loss of protein expression for the *MLH1, MSH2, 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 *MSH*6 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, MSH2, 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.

Steps 4 and/or 5 apply only for tumors that are negative for *MLH1* protein expression by IHC.

Step 4: *BRAF V600E (BRAF)* Mutation Testing

BRAF mutation testing and *MLH1* promoter methylation studies distinguish between sporadic dMMR and

LS dMMR. This is because *BRAFM* 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 (eg., LS).

Step 5: *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:

- 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 ACII if 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.

In a study by Gausachs (2012), when *MLH1* PHM testing is used in conjunction with *BRAF* mutation testing, the cost per additional mutation detected when using hypermethylation analysis was lower than that of *BRAF* and germinal *MLH1* mutation analysis. Somatic hypermethylation of *MLH1* is an accurate and cost-effective pre-screening method in the selection of patients that are candidates for *MLH1* germ-line analysis when LS is suspected and *MLH1* protein expression is absent.

Step 6: Targeted MMR (*MLH1, MSH2, MSH6* and *PMS2* gene) Germ-line and *EpCAM*Testing

Step 6A: *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 mutationgeme-line is positively identified, then LS is diagnosed and further testing of the patient is not medically necessary.

Step 6B: *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 7). If *EpCAM*is also negative, genetic testing of MSH6 should be performed (Step 6C). The presence of MSI and the loss of *MSH2/MSH6* strongly indicate a MMR germ-line defect.

Step 6C: *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 6D: *PMS2*Testing

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 7: *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.

Indications

IHC and/or MSI Testing

LS tumor screening with IHC or MSI on colorectal and/or endometrial tumors is considered medically necessary and covered by Medicare for the following indications:

- Individual with colorectal or endometrial cancer whose family meets the ACII or revised Bethesda guidelines**, **OR**
- Individual with endometrial cancer diagnosed before age 50.

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

MMR Germline Gene Mutation Testing Exception

If a lab is unable to perform the stepped testing approach outlined in this LCD, multiple germ-line gene testing will be covered by Medicare 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 if the individual fulfills the ACII or revised Bethesda guidelines.
- CRC tumor diagnosis prior to Medicare eligibility **AND** tumor sample no longer available **AND** individual meets ACII or revised Bethesda guidelines or was diagnosed with endometrial cancer before 50

If targeted gene testing is not possible, *MLH1* and *MSH2* testing should be performed first, since these two genes account for the majority of germ-line mutations. If no mutation is identified in *MLH1* or *MSH2,* testing of *MSH6* is indicated. If no mutation is identified in *MSH6*, testing of *PMS2* may be considered.

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.

Limitations

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

2. Universal testing of CRC and endometrial cancers by MSI/MMR protein expression by IHC is not a Medicare benefit.

CODING INFORMATION

Bill Type Codes:
Contractors may specify Bill Types to help providers identify those Bill Types typically used to report this service. Absence of a Bill Type does not guarantee that the policy does not apply to that Bill Type. Complete absence of all Bill Types indicates that coverage is not influenced by Bill Type and the policy should be assumed to apply equally to all claims.

999x	Not Applicable

Revenue Codes:
Contractors may specify Revenue Codes to help providers identify those Revenue Codes typically used to report this service. In most instances Revenue Codes are purely advisory; unless specified in the policy services reported under other Revenue Codes are equally subject to this coverage determination. Complete absence of all Revenue Codes indicates that coverage is not influenced by Revenue Code and the policy should be assumed to apply equally to all Revenue Codes.

CPT/HCPCS Codes

Group 1 Paragraph: N/A

Group 1 Codes:

81210	Braf gene
81292 - 81300	Mlh1 gene full seq - Msh6 gene dup/delete variant
81317 - 81319	Pms2 gene full seq analysis - Pms2 gene dup/delet variants
81403	Mopath procedure level 4

Group 2 Paragraph: N/A

Group 2 Codes:

81301	Microsatellite instability
88341	Immunohisto antibody slide
88342	Immunohisto antibody stain
88344	Immunohisto antibody slide

ICD-10 Codes that Support Medical Necessity

1. Coverage of molecular testing for LS for carrier status or family studies is considered screening and is statutorily excluded from coverage.

2. Universal testing of CRC and endometrial cancers by MSI/MMR protein expression by IHC **is not a Medicare benefit.**

General Information

Associated Information
Documentation Requirements

1. All 'Indications' must be clearly documented in the patient's medical record and made available to Medicare upon request.

2. This Contractor expects the ordering/treating physician or pathologist to obtain sufficient clinical and family history to warrant first-line testing (IHC/MSI), and subsequent targeted MMR germ-line testing or for germ-line mutation exceptions (as above). The clinical/family data to support IHC/MSI testing should be documented in the test interpretation/report and the information should be available to the lab performing targeted testing to assist the lab in the appropriate selection of target genes. Labs performing MMR germ-line panels without appropriate selection of targeted genes based on patient data, screening test (MSI/IHC) results, or exceptions are not reasonable and necessary.

3. This Contractor recognized that there is some variation in the order of testing based on tissue availability, prevalence, patient history, test availability, testing turn-around time and patient treatment schedule. However, this Contractor does not expect routine MMR germ-line mutation testing prior to appropriate screening (IHC/MSI). When MSI/IHC testing cannot be performed or is contradictory, claims

for MMR germ-line testing exemptions will requires the addition of the KX modifier with the billing CPT code. The KX modifier specifies that the “Requirements specified in the medical policy have been met. Documentation on file”. The documentation is expected if this Contractor or another Medicare contractor upon request.

4. At the current time, there is insufficient data to warrant MMR testing for prostate cancer, even though preliminary studies suggest that prostate cancer in MMR gene mutation carriers share a molecular profile and at least one pathological feature in common with other LS-associated tumors. Similarly the clinical significance of MMR testing in other malignancies is not known. Therefore, molecular testing for malignancies other than those specifically cited in this LCD is non-covered.

5. Documentation must support CMS 'signature requirements' as described in the Medicare Program Integrity Manual (Pub. 100-08), Chapter 3.

Sources of Information and Basis for Decision

- Baglietto L, Lindor NM, Douty JG, et al. Risks of Lynch Syndrome Cancers for MSH6 Mutation Carriers. *J Natl Cancer Inst.* 2010;102:193-201.
- Center for Disease Control and Prevention. Genetic Testing. Health Professionals: More about Genetic Testing for Lynch Syndrome. (2011, April 26). Available at: Genetic Testing for Lynch Syndrome. Accessed 06/19/2013.
- Consultations with the representatives to the Carrier Advisory Committee and other Medicare Contractors.
- Lynch HT, Lynch PM, Lanspa SJ, Synder CL, Lynch JF, Boland CR. Review of the Lynch Syndrome: History, Molecular Genetics, Screening, Differential Diagnosis, and Medicolegal Ramifications. *Clin Genet.* 2009;76:1-18.
- Other Medicare Contractor’s Local Coverage Determinations.
- Rumilla K, Schowalter KV, Lindor NM, Thomas BC, Mensink KA, Gallinger S, et al. Frequency of Deletions of EPCAM (TACSTD1) in MSH2-Associated Lynch Syndrome Cases. *J Mol Diagn.* Jan 2011;13(1):93-9.
- Strafford JC. Genetic testing for lynch syndrome, an inherited cancer of the bowel, endometrium, and ovary. *Rev Obstet Gynecol.* 2012;5(1):42-9.
- Umar A, Boland CR, Terdiman JP, Syngal S, de la Chapelle A, Ruschoff J, et al. Revised Bethesda Guidelines for Hereditary Nonpolyposis Colorectal Cancer (Lynch Syndrome) and Microsatellite Instability. *J Natl Cancer Inst.* 2004;96:261-8.
- Vasen HF, Moslein G, Alonso A. Guidelines for the Clinical Management of Lynch Syndrome (hereditary non-polyposis cancer) *J Med Genet.*2007;44:353-62.

Please Note: This Local Coverage Determination (LCD) is the result of collaboration among the Medicare Administrative Contractors, and the template or model is being accepted by Cahaba as part of the effort to implement more uniform LCD’s across contractors.

Local Coverage Determination (LCD) Disclaimer