

Local Coverage Determination (LCD): MoIDX: Genetic Testing for Lynch Syndrome (L36374)

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Noridian Healthcare Solutions, LLC	A and B MAC	02101 - MAC A	J - F	Alaska
Noridian Healthcare Solutions, LLC	A and B MAC	02102 - MAC B	J - F	Alaska
Noridian Healthcare Solutions, LLC	A and B MAC	02201 - MAC A	J - F	Idaho
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LCD Information

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N/A

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CMS National Coverage Policy

Title XVIII of the Social Security Act, §1862(a)(1)(A) Allows coverage and payment for only those services that are considered to be reasonable and necessary.

42 CFR 410.32(a) Order diagnostic tests.

42 CFR 411.5(k)(1) Particular Services excluded from coverage.

Coverage Guidance

Coverage Indications, Limitations, and/or Medical Necessity

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 all patients with colorectal cancer and endometrial cancer regardless of age, or a multi-gene NGS or other multi-analyte methodology that is inclusive of MSI microsatellite loci, and MLH1, MSH2, MSH6 and PMS2 genes. MSI/MMR testing is also covered for adult and pediatric patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options, or colorectal cancer that has progressed following treatment with fluoropyrimidine, oxaliplatin, and irinotecan.

Summary of Evidence

I. Lynch Syndrome (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 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 colorectal cancer 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 Medicare benefit, and is statutorily excluded from coverage.

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

There are 2 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.

Step 1: 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 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.

Step 2: Microsatellite Instability (MSI) and/or Deficient Mismatch Repair (MMR) by IHC 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 2 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, MSH6 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 colorectal cancer 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 percentage 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 MSH6 germ-line mutations do not manifest the MSI-H phenotype. This finding supports the diagnostic strategy to screen suspected LS patients with colorectal cancer by both MSI and IHC. 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.

Definitive Molecular Testing for LS

1. Next generation sequencing (NGS "hotspot") testing platforms: Molecular testing for MLH1, MSH2, MSH6 and PMS2 genes by NGS is covered as medically acceptable for the identification of LS by this contractor. 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.
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:

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 BRAFM mutation and MLH1 PHM are very seldom seen in LS. BRAF mutation testing of the colorectal cancer 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 PHM 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 LS.

The following combinations of BRAF and MLH1 promoter methylation test results direct further testing in individuals with colorectal cancers 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 MLH1 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.

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 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 a 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 colorectal cancer 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: 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 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.

III. Indications of Coverage

IHC and/or MSI Testing

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

- All individuals with colorectal cancer regardless of age **OR**
- 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.

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 1 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 colorectal cancer or endometrial cancer.
- 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 4 MMR genes can be performed concurrently followed by testing for EPCAM, or per a testing strategy deemed appropriate by the physician.

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: 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.

IV. Limitations

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

Analysis of Evidence (Rationale for Determination)

Level of Evidence

Quality of Evidence – High

Strength of Evidence – High

Weight of Evidence - High

Based on the high level of scientific evidence to support Medicare coverage, MSI and/or IHC genetic testing for dMMR is reasonable and necessary for all patients with colorectal and endometrial cancer. Alternatively, a NGS panel inclusive of MSI, MLH1, MSH2, MSH6 and PMS2 genes is reasonable and necessary in lieu of MSI and/or dMMR by IHC.

General Information

Associated Information

Documentation Requirements

Medical Documentation of Suspected LS

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.

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, the contractor does not expect routine MMR germ-line mutation testing prior to appropriate screening (IHC/MSI).

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 1 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.

Sources of Information

N/A

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Revision History Information

REVISION HISTORY DATE	REVISION HISTORY NUMBER	REVISION HISTORY EXPLANATION	REASON(S) FOR CHANGE
01/07/2021	R6	<p>Under Associated Information, the verbiage "When MSI/IHC testing cannot be performed or is contradictory, claims for MMR germ-line testing exemptions will require 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". Documentation must be provided upon request." has been removed and is included in the related Billing and Coding: MolDX: Genetic Testing for Lynch Syndrome.</p> <p>Under Bibliography changes were made to citations to reflect AMA citation guidelines. Formatting, punctuation and typographical errors were corrected throughout the LCD. Acronyms were defined and inserted where appropriate throughout the LCD.</p> <p><i>At this time 21st Century Cures Act will apply to new and revised LCDs that restrict coverage which requires comment and notice. This revision is not a restriction to the coverage determination; and, therefore not all the fields included on the LCD are applicable as noted in this policy.</i></p>	<ul style="list-style-type: none"> Provider Education/Guidance
11/01/2019	R5	<p>The LCD is revised to remove CPT/HCPCS codes in the Keyword Section of the LCD.</p> <p><i>At this time 21st Century Cures Act will apply to new and revised LCDs that restrict coverage which requires</i></p>	<ul style="list-style-type: none"> Other (The LCD is revised to remove CPT/HCPCS codes in the Keyword Section of the LCD.)

REVISION HISTORY DATE	REVISION HISTORY NUMBER	REVISION HISTORY EXPLANATION	REASON(S) FOR CHANGE
		comment and notice. This revision is not a restriction to the coverage determination; and, therefore not all the fields included on the LCD are applicable as noted in this policy.	
11/01/2019	R4	<p>CMS references were revised. TOB 028x was not transferred to the coding article. 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.</p> <p>At this time 21st Century Cures Act will apply to new and revised LCDs that restrict coverage which requires comment and notice. This revision is not a restriction to the coverage determination; and, therefore not all the fields included on the LCD are applicable as noted in this policy</p>	<ul style="list-style-type: none"> • Creation of Uniform LCDs With Other MAC Jurisdiction
11/01/2019	R3	<p>As required by CR 10901, all billing and coding information has been moved to the companion article, this article is linked to the LCD.</p> <p>At this time 21st Century Cures Act will apply to new and revised LCDs that restrict coverage which requires comment and notice. This revision is not a restriction to the coverage determination; and, therefore not all the fields included on the LCD are applicable as noted in this policy.</p>	<ul style="list-style-type: none"> • Revisions Due To Code Removal
04/16/2019	R2	This LCD version was created as a result of DL36374 being released to a Final LCD.	<ul style="list-style-type: none"> • Creation of Uniform LCDs With Other MAC Jurisdiction
12/15/2016	R1	<p>Added "endometrial cancer" to the end of the first paragraph under Coverage Indications, Limitations and/or Medical Necessity.</p> <p>Redefined age limitation of patient, added more clarity for NGS "hotspot", updated reference numbers 13, 14, and added new references.</p>	<ul style="list-style-type: none"> • Creation of Uniform LCDs With Other MAC Jurisdiction

Associated Documents

Attachments

N/A

Related Local Coverage Documents

Article(s)

A54996 - Billing and Coding: MoIDX: Genetic Testing for Lynch Syndrome

A56104 - Billing and Coding: MoIDX: Microsatellite Instability-High (MSI-H) and Mismatch Repair Deficient (dMMR)

Biomarker Billing and Coding Guidelines for Patients with Unresectable or Metastatic Solid Tumors

A56362 - Response to Comments: MoIDX: Genetic Testing for Lynch Syndrome

LCD(s)

DL36374

- (MCD Archive Site)

Related National Coverage Documents

N/A

Public Version(s)

Updated on 12/22/2020 with effective dates 01/07/2021 - N/A

Updated on 01/29/2020 with effective dates 11/01/2019 - 01/06/2021

Updated on 01/06/2020 with effective dates 11/01/2019 - N/A

Updated on 10/31/2019 with effective dates 11/01/2019 - N/A

Some older versions have been archived. Please visit the MCD Archive Site to retrieve them.

Keywords

N/A