Local Coverage Determination (LCD):
MolDX: Genetic Testing for Lynch Syndrome (L36370)

Links in PDF documents are not guaranteed to work. To follow a web link, please use the MCD Website.

Contractor Information

Contractor Name	Contract Type	Contract Number	Jurisdiction	State(s)
Noridian Healthcare Solutions, LLC	A and B MAC	01111 - MAC A	J - E	California - Entire State
Noridian Healthcare Solutions, LLC	A and B MAC	01112 - MAC B	J - E	California - Northern
Noridian Healthcare Solutions, LLC	A and B MAC	01182 - MAC B	J - E	California - Southern
Noridian Healthcare Solutions, LLC	A and B MAC	01211 - MAC A	J - E	American Samoa Guam Hawaii Northern Mariana Islands
Noridian Healthcare Solutions, LLC	A and B MAC	01212 - MAC B	J - E	American Samoa Guam Hawaii Northern Mariana Islands
Noridian Healthcare Solutions, LLC	A and B MAC	01311 - MAC A	J - E	Nevada
Noridian Healthcare Solutions, LLC	A and B MAC	01312 - MAC B	J - E	Nevada
Noridian Healthcare Solutions, LLC	A and B MAC	01911 - MAC A	J - E	American Samoa California - Entire State Guam Hawaii Nevada Northern Mariana Islands

Back to Top

LCD Information

Document Information

Original Effective Date
For services performed on or after 06/01/2016

LCD ID
L36370

Revision Effective Date
For services performed on or after 12/15/2016

LCD Title
MolDX: Genetic Testing for Lynch Syndrome

Revision Ending Date
N/A

Proposed LCD in Comment Period
N/A

Retirement Date
N/A

Source Proposed LCD
DL36370

Notice Period Start Date
04/14/2016

AMA CPT / ADA CDT / AHA NUBC Copyright Statement

Notice Period End Date
05/31/2016

CMS National Coverage Policy Title XVIII of the Social Security Act, §1833(e). Prohibits Medicare payment for any claim which lacks the necessary information to process the claim.

42 CFR 410.32(a). Order diagnostic tests.

42 CFR 415(k)(1). Particular Services excluded from coverage.

CMS On-Line Manual, Publication 100-02, *Medicare Benefit Policy Manual,* Chapter 15, §§80.0, 80.1.1, 80.2. Clinical Laboratory services.

Coverage Guidance
Coverage Indications, Limitations, and/or Medical Necessity

I. Lynch Syndrome (LS)

This policy limits Lynch Syndrome (LS) genetic testing to a stepped approach for Microsatellite Instability and Immunohistochemistry (MSI/IHC) testing, *BRAF* gene mutation, *MLH1* gene promoter hypermethylation and targeted mismatch repair (MMR) germ-line gene testing to all patients with colorectal cancer (CRC) and endometrial cancer regardless of age.

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 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 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.

Step 1: Use of Immunohistochemistry (IHC) 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) Analysis for LS Screening

MSI analysis for testing 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 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 test 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.

Definitive Molecular Testing for Lynch Syndrome

1. Next generation sequencing (NGS or "hotspot") testing platforms:

Molecular testing for *MLH1*, *MSH2*, *MSH6* and *PMS2* genes by NGS is covered as medically necessary 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 in a step-wise approach based:

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 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 LS.

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 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 preliminary 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 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 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: *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 testing with IHC or MSI is considered medically necessary and covered by Medicare for the following indications:

- All individuals with colorectal cancer diagnosed 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 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 from patient with CRC or endometrial cancer
- CRC or endometrial tumor diagnosis prior to Medicare eligibility **AND** tumor sample no longer available **AND** 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.

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.

Back to Top

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.

N/A
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.

XX000
N/A
CPT/HCPCS Codes
Group 1 Paragraph: N/A

Group 1 Codes:

81210	BRAF (B-RAF PROTO-ONCOGENE, SERINE/THREONINE KINASE) (EG, COLON CANCER, MELANOMA), GENE ANALYSIS, V600 VARIANT(S)
81288	MLH1 (MUTL HOMOLOG 1, COLON CANCER, NONPOLYPOSIS TYPE 2) (EG, HEREDITARY NON-POLYPOSIS COLORECTAL CANCER, LYNCH SYNDROME) GENE ANALYSIS; PROMOTER METHYLATION ANALYSIS
81292	MLH1 (MUTL HOMOLOG 1, COLON CANCER, NONPOLYPOSIS TYPE 2) (EG, HEREDITARY NON-POLYPOSIS COLORECTAL CANCER, LYNCH SYNDROME) GENE ANALYSIS; FULL SEQUENCE ANALYSIS
81293	MLH1 (MUTL HOMOLOG 1, COLON CANCER, NONPOLYPOSIS TYPE 2) (EG, HEREDITARY NON-POLYPOSIS COLORECTAL CANCER, LYNCH SYNDROME) GENE ANALYSIS; KNOWN FAMILIAL VARIANTS
81294	MLH1 (MUTL HOMOLOG 1, COLON CANCER, NONPOLYPOSIS TYPE 2) (EG, HEREDITARY NON-POLYPOSIS COLORECTAL CANCER, LYNCH SYNDROME) GENE ANALYSIS; DUPLICATION/DELETION VARIANTS
81295	MSH2 (MUTS HOMOLOG 2, COLON CANCER, NONPOLYPOSIS TYPE 1) (EG, HEREDITARY NON-POLYPOSIS COLORECTAL CANCER, LYNCH SYNDROME) GENE ANALYSIS; FULL SEQUENCE ANALYSIS
81296	MSH2 (MUTS HOMOLOG 2, COLON CANCER, NONPOLYPOSIS TYPE 1) (EG, HEREDITARY NON-POLYPOSIS COLORECTAL CANCER, LYNCH SYNDROME) GENE ANALYSIS; KNOWN FAMILIAL VARIANTS
81297	MSH2 (MUTS HOMOLOG 2, COLON CANCER, NONPOLYPOSIS TYPE 1) (EG, HEREDITARY NON-POLYPOSIS COLORECTAL CANCER, LYNCH SYNDROME) GENE ANALYSIS; DUPLICATION/DELETION VARIANTS
81298	MSH6 (MUTS HOMOLOG 6 [E. COLI]) (EG, HEREDITARY NON-POLYPOSIS COLORECTAL CANCER, LYNCH SYNDROME) GENE ANALYSIS; FULL SEQUENCE ANALYSIS
81299	MSH6 (MUTS HOMOLOG 6 [E. COLI]) (EG, HEREDITARY NON-POLYPOSIS COLORECTAL CANCER, LYNCH SYNDROME) GENE ANALYSIS; KNOWN FAMILIAL VARIANTS
81300	MSH6 (MUTS HOMOLOG 6 [E. COLI]) (EG, HEREDITARY NON-POLYPOSIS COLORECTAL CANCER, LYNCH SYNDROME) GENE ANALYSIS; DUPLICATION/DELETION VARIANTS
81301	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
81317	PMS2 (POSTMEIOTIC SEGREGATION INCREASED 2 [S. CEREVISIAE]) (EG, HEREDITARY NON-POLYPOSIS COLORECTAL CANCER, LYNCH SYNDROME) GENE ANALYSIS; FULL SEQUENCE ANALYSIS
81318	PMS2 (POSTMEIOTIC SEGREGATION INCREASED 2 [S. CEREVISIAE]) (EG, HEREDITARY NON-POLYPOSIS COLORECTAL CANCER, LYNCH SYNDROME) GENE ANALYSIS; KNOWN FAMILIAL VARIANTS
81319	PMS2 (POSTMEIOTIC SEGREGATION INCREASED 2 [S. CEREVISIAE]) (EG, HEREDITARY NON-POLYPOSIS COLORECTAL CANCER, LYNCH SYNDROME) GENE ANALYSIS; DUPLICATION/DELETION VARIANTS
81403	MOLECULAR PATHOLOGY PROCEDURE, LEVEL 4 (EG, ANALYSIS OF SINGLE EXON BY DNA SEQUENCE ANALYSIS, ANALYSIS OF >10 AMPLICONS USING MULTIPLEX PCR IN 2 OR MORE INDEPENDENT REACTIONS, MUTATION SCANNING OR DUPLICATION/DELETION VARIANTS OF 2-5 EXONS)
81435	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
81479	UNLISTED MOLECULAR PATHOLOGY PROCEDURE

Group 2 Paragraph: The following CPT codes do not represent the stepped approach for Lynch Syndrome testing outlined in this policy, and therefore have been determined as non-covered.

Group 2 Codes:

81445	TARGETED GENOMIC SEQUENCE ANALYSIS PANEL, SOLID ORGAN NEOPLASM, DNA ANALYSIS, AND RNA ANALYSIS WHEN PERFORMED, 5-50 GENES (EG, ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, NRAS, MET, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), INTERROGATION FOR SEQUENCE VARIANTS AND COPY NUMBER VARIANTS OR REARRANGEMENTS, IF PERFORMED
81455	TARGETED GENOMIC SEQUENCE ANALYSIS PANEL, SOLID ORGAN OR HEMATOLYMPHOID NEOPLASM, DNA ANALYSIS, AND RNA ANALYSIS WHEN PERFORMED, 51 OR GREATER GENES (EG, ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MLL, NPM1, NRAS, MET, NOTCH1, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), INTERROGATION FOR SEQUENCE VARIANTS AND COPY NUMBER VARIANTS OR REARRANGEMENTS, IF PERFORMED

ICD-10 Codes that Support Medical Necessity

Group 1 Paragraph: The correct use of an ICD-10 code listed below does not assure coverage of a service. The service must be reasonable and necessary in the specific case and must meet the criteria specified in this determination.

These are the only ICD-10 codes that Support Medical Necessity for CPT Codes in Group 1.

Group 1 Codes:

ICD-10 Codes	Description
C16.0	Malignant neoplasm of cardia
C16.1	Malignant neoplasm of fundus of stomach
C16.2	Malignant neoplasm of body of stomach
C16.3	Malignant neoplasm of pyloric antrum
C16.4	Malignant neoplasm of pylorus
C16.5	Malignant neoplasm of lesser curvature of stomach, unspecified
C16.6	Malignant neoplasm of greater curvature of stomach, unspecified
C16.8	Malignant neoplasm of overlapping sites of stomach
C16.9	Malignant neoplasm of stomach, unspecified
C17.0	Malignant neoplasm of duodenum
C17.1	Malignant neoplasm of jejunum
C17.2	Malignant neoplasm of ileum
C17.3	Meckel's diverticulum, malignant
C17.8	Malignant neoplasm of overlapping sites of small intestine
C17.9	Malignant neoplasm of small intestine, unspecified
C18.0	Malignant neoplasm of cecum
C18.1	Malignant neoplasm of appendix
C18.2	Malignant neoplasm of ascending colon
C18.3	Malignant neoplasm of hepatic flexure
C18.4	Malignant neoplasm of transverse colon
C18.5	Malignant neoplasm of splenic flexure
C18.6	Malignant neoplasm of descending colon
C18.7	Malignant neoplasm of sigmoid colon
C18.8	Malignant neoplasm of overlapping sites of colon
C18.9	Malignant neoplasm of colon, unspecified
C19	Malignant neoplasm of rectosigmoid junction
C20	Malignant neoplasm of rectum
C21.0	Malignant neoplasm of anus, unspecified
C21.1	Malignant neoplasm of anal canal
C21.2	Malignant neoplasm of cloacogenic zone
C21.8	Malignant neoplasm of overlapping sites of rectum, anus and anal canal
C22.0	Liver cell carcinoma
C22.1	Intrahepatic bile duct carcinoma
C22.2	Hepatoblastoma
C22.3	Angiosarcoma of liver
C22.4	Other sarcomas of liver
C22.7	Other specified carcinomas of liver
C22.8	Malignant neoplasm of liver, primary, unspecified as to type
C22.9	Malignant neoplasm of liver, not specified as primary or secondary
C24.0	Malignant neoplasm of extrahepatic bile duct
C24.9	Malignant neoplasm of biliary tract, unspecified
C25.0	Malignant neoplasm of head of pancreas
C25.1	Malignant neoplasm of body of pancreas
C25.2	Malignant neoplasm of tail of pancreas
C25.3	Malignant neoplasm of pancreatic duct
C25.4	Malignant neoplasm of endocrine pancreas
C25.7	Malignant neoplasm of other parts of pancreas
C25.8	Malignant neoplasm of overlapping sites of pancreas
C25.9	Malignant neoplasm of pancreas, unspecified
C45.1	Mesothelioma of peritoneum
C48.1	Malignant neoplasm of specified parts of peritoneum

ICD-10 Codes	Description
C48.2	Malignant neoplasm of peritoneum, unspecified
C48.8	Malignant neoplasm of overlapping sites of retroperitoneum and peritoneum
C54.0	Malignant neoplasm of isthmus uteri
C54.1	Malignant neoplasm of endometrium
C54.2	Malignant neoplasm of myometrium
C54.3	Malignant neoplasm of fundus uteri
C54.8	Malignant neoplasm of overlapping sites of corpus uteri
C54.9	Malignant neoplasm of corpus uteri, unspecified
C55	Malignant neoplasm of uterus, part unspecified
C56.1	Malignant neoplasm of right ovary
C56.2	Malignant neoplasm of left ovary
C56.9	Malignant neoplasm of unspecified ovary
C57.00	Malignant neoplasm of unspecified fallopian tube
C57.01	Malignant neoplasm of right fallopian tube
C57.02	Malignant neoplasm of left fallopian tube
C57.10	Malignant neoplasm of unspecified broad ligament
C57.11	Malignant neoplasm of right broad ligament
C57.12	Malignant neoplasm of left broad ligament
C57.20	Malignant neoplasm of unspecified round ligament
C57.21	Malignant neoplasm of right round ligament
C57.22	Malignant neoplasm of left round ligament
C57.3	Malignant neoplasm of parametrium
C57.4	Malignant neoplasm of uterine adnexa, unspecified
C64.1	Malignant neoplasm of right kidney, except renal pelvis
C64.2	Malignant neoplasm of left kidney, except renal pelvis
C64.9	Malignant neoplasm of unspecified kidney, except renal pelvis
C65.1	Malignant neoplasm of right renal pelvis
C65.2	Malignant neoplasm of left renal pelvis
C65.9	Malignant neoplasm of unspecified renal pelvis
C66.1	Malignant neoplasm of right ureter
C66.2	Malignant neoplasm of left ureter
C66.9	Malignant neoplasm of unspecified ureter
C68.8	Malignant neoplasm of overlapping sites of urinary organs
C71.0	Malignant neoplasm of cerebrum, except lobes and ventricles
C71.1	Malignant neoplasm of frontal lobe
C71.2	Malignant neoplasm of temporal lobe
C71.3	Malignant neoplasm of parietal lobe
C71.4	Malignant neoplasm of occipital lobe
C71.5	Malignant neoplasm of cerebral ventricle
C71.6	Malignant neoplasm of cerebellum
C71.7	Malignant neoplasm of brain stem
C71.8	Malignant neoplasm of overlapping sites of brain
C71.9	Malignant neoplasm of brain, unspecified
C78.5	Secondary malignant neoplasm of large intestine and rectum
D12.0	Benign neoplasm of cecum
D12.1	Benign neoplasm of appendix
D12.2	Benign neoplasm of ascending colon
D12.3	Benign neoplasm of transverse colon
D12.4	Benign neoplasm of descending colon
D12.5	Benign neoplasm of sigmoid colon
D12.6	Benign neoplasm of colon, unspecified
K63.5	Polyp of colon
L85.3	Xerosis cutis
Z15.04	Genetic susceptibility to malignant neoplasm of endometrium
Z15.09	Genetic susceptibility to other malignant neoplasm
Z80.0	Family history of malignant neoplasm of digestive organs
Z85.00	Personal history of malignant neoplasm of unspecified digestive organ
Z85.038	Personal history of other malignant neoplasm of large intestine

ICD-10 Codes	Description
Z85.048	Personal history of other malignant neoplasm of rectum, rectosigmoid junction, and anus
Z85.42	Personal history of malignant neoplasm of other parts of uterus
Z85.43	Personal history of malignant neoplasm of ovary
Z85.53	Personal history of malignant neoplasm of renal pelvis
Z85.54	Personal history of malignant neoplasm of ureter
Z85.59	Personal history of malignant neoplasm of other urinary tract organ
Z85.841	Personal history of malignant neoplasm of brain
Z86.010	Personal history of colonic polyps

ICD-10 Codes that DO NOT Support Medical Necessity N/A
ICD-10 Additional Information Back to Top

General Information

Associated Information
Documentation Requirement

Medical Documentation of Suspected LS

Palmetto GBA 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.

Palmetto GBA recognizes 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, Palmetto GBA 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". This documentation is expected upon request by Palmetto GBA or another Medicare Contractor.

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.

This final LCD, effective 6/1/2016, combines JEA DL36331 into the JEB LCD so that both JEA and JEB contract numbers will have the same final MCD LCD number.

Sources of Information and Basis for Decision
References

1. Bagletto L, Lindor NM, Douty JG, et al. Risks of Lynch Syndrome Cancers for MSH6 Mutation Carriers. *J Natl Cancer Inst.* 2010;102:193-201.

2. Boland CR. Evolution of the Nomenclature for the Hereditary Colorectal Cancer Syndromes. *Fam Cancer.* 2005;4(3):211-8.

3. Bouzourene H, Hutter P, Losi L, Martin P, Behattar J. Selection of patients with germline MLH1 mutated Lynch syndrome by determination of MLH1 methylation and BRAF mutation. Fam Cancer. 2010;9(2);167-72. doi: 10.1007/s10689-009-9302-4.

4. Center for Disease Control and Prevention. Genetic Testing. Health Professionals: More about Genetic Testing for Lynch Syndrome. (2011, April 26). Available at: http://www.cdc.gov/genomics/gtesting/EGAPP/recommend/lynch_more.htm. Accessed 06/19/2013.

5. Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group. Recommentations from EGAPP Working Group: genetic testing strategies in newly diagnosed individuals with colorectal cancer aimed at reducing morbidit and mortality from Lynch syndromes in relatives. Genetic in Med. Jan 2009;11(1):35-41.

6. Gausachs M, Mur P, Corral J,et al. MLH1 promoter hypermethylation in the analytical algorithm of Lynch syndrome: A cost-effectiveness study. *European Journal of Human Genetics.* 2012;20:762-8.

7. Giardiello FM, Allen JI, Axilbund JE, et al. Guidelines on Genetic Evaluation and Management of Lynch Syndrome: A Consensus Statement by the U.S. Multi-Society Task Force on Colorectal Cancer. Am J Gastroenterol, 2014 Aug; 109(8):1159-79.

8. Grover S, Stoffel EM, Mercado RC, Ford BM, Kohlman WK, Shannon KM, et al. Colorectal cancer risk perception on the basis of genetic test results in individuals at risk for Lynch syndrome. *J Clin Oncol.* 27(24):3981-6.

9. Hegde M, Ferber M, Mao R, et al. ACMG technical standards and guidelines for genetic testing for inherited colorectal cancer (Lynch syndrome, familial adenomatous polyposis, and MYH-associated polyposis). Genetics in Med. Jan 2014;16(1):101-16.

10. Ligtenberg MJ, Kuiper RP, Chan TL, Goossens M, Hebeda KM, Voorendt M, et al. Heritable Somatic Methylation and Inactivation of MSH2 in Families with Lynch Syndrome due to Deletion of the 3' exons of TACSTD1. *Nat Genet.* Jan 2009;41:112-7.

11. Lynch HT, de la Chapelle A. Hereditary colorectal cancer. *N Engl J Med*, 2003;348(10):919-2.

12. 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.

13. National Comprehensive Cancer Network®. NCCN Guidelines Colorectal Cancer Screening. Version 2.2016 Available at: http://www.nccn.org/professionals/physician_gls/pdf/colorectal_screening.pdf. Accessed 10/03/2016.

14. National Comprehensive Cancer Network®. NCCN Guidelines Colon Cancer. Version 1,2016. Available at: http://www.nccn.org/professionals/physician_gls/pdf/colon.pdf Accessed 10/3/2016.

15. Quehenberger F, Vasen HFA, van Houwelingen HC. Risk of colorectal and endometrial cancer for carriers of mutations of the hMLH1 and hMSH2 gene: correction for ascertainment. *J Med Genet.* 2005;42:491-496.

16. Ribic CM, Sargent DJ, Moore MJ, Thibodeau SN, French AJ, Goldberg RM, et al. Tumor Microsatellite-Instability Status as a Predictor of Benefit from Fluorouracil-Based Adjuvant Chemotherapy for Colon Cancer. *NEJM.* Jul 2003;349:247-57. Available at: http://www.nejm.org/doi/pdf/10.1056/NEJMoa022289. Accessed 6/19/13.

17. Rubenstein JH, Enns R, Heidelbaugh J, et al. American Gastroenterological Association Institute Guideline on the Diagnosis and Management of Lynch Syndrome. Gastroenterology 2015;149(3):777 - 782

18. 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.

19. Senter L, Clendenning M, Sotamaa K, Hampel H, Green J, Potter JD,et al. The Clinical Phenotype of Lynch Syndrome Due to Germline PMS2 Mutations. *Gastroenterology.* 2008;135:419-28.

20. Strafford JC. Genetic testing for lynch syndrome, an inherited cancer of the bowel, endometrium, and ovary. Rev Obstet Gynecol. 2012;5(1):42-9.

21. Thomas BC,Ferber MJ, Lindor NM. DNA Mismatch Repair and Lynch Syndrome. In: Potter JD, Lindor NM, eds. Genetics of Colorectal Cancer. New York, NY:Springer Science; 2009.

22. 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.

23. US Preventive Services Task Force. Screening for Colorectal Cancer: US Preventive Services Task Force Recommendation Statement. JAMA. 2016;315(23):2564-2575.

24. Vasen HF, Mecklin JP, Khan PM, Lynch HT. The International Collaborative Group on Hereditary Non-Polyposis Colorectal Cancer (ICG-HNPCC). *Dis Colon Rectum.* May 1991;34(5):424-5.

25. 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.

26. Vasen HF, Watson P, Mecklin JP, et al. New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative Group on HNPCC. *Gastroenterology.* 1999;116:1453-6. Back to Top

Revision History Information

Revision History Date	Revision History Number	Revision History Explanation	Reason(s) for Change
12/15/2016	R1	Added "endometrial cancer" to the end of the first paragraph under Coverage Indications, Limitations and/or Medical Necessity. Redefined age limitation of patient, added more clarity for NGS "hotspot" and updated reference numbers 13, 14, and add new references.	• Creation of Uniform LCDs With Other MAC Jurisdiction

Back to Top

Associated Documents

Attachments N/A

Related Local Coverage Documents Article(s) A54995 - MolDX: Billing and Coding for Lynch Syndrome Testing Services A54964 - Response to Comments: MolDX: Genetic Testing for Lynch Syndrome LCD(s) DL36331 - (MCD Archive Site) DL36370 - (MCD Archive Site)

Related National Coverage Documents N/A

Public Version(s) Updated on 01/24/2017 with effective dates 12/15/2016 - N/A Updated on 04/01/2016 with effective dates 06/01/2016 - N/A Back to Top

Keywords

- MolDX
- LS
- Lynch Syndrome
- genetic
- testing
- IHC
- MSI
- MMR
- gene

Read the **LCD Disclaimer** Back to Top