Local Coverage Determination (LCD):
MolDX: Genetic Testing for Lynch Syndrome (L35024)

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Contractor Information

Contractor Name	Contract Type	Contract Number	Jurisdiction	State(s)
Palmetto GBA	A and B and HHH MAC	11202 - MAC B	J - M	South Carolina
Palmetto GBA	A and B and HHH MAC	11302 - MAC B	J - M	Virginia
Palmetto GBA	A and B and HHH MAC	11402 - MAC B	J - M	West Virginia
Palmetto GBA	A and B and HHH MAC	11502 - MAC B	J - M	North Carolina

Back to Top

LCD Information

Document Information

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LCD Title
MolDX: Genetic Testing for Lynch Syndrome

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N/A

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N/A

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.

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) screening, *BRAF* gene mutation, *MLH1* gene promoter hypermethylation and targeted mismatch repair (MMR) germ-line gene testing to all patients with CRC diagnosed at ≤70 years of age, and those > 70 years who meet the revised Bethesda LS guidelines.

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: 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 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 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 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 *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 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 (eg., 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:

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

- All individuals with colorectal cancer diagnosed at ≤ 70 years of age, and those > 70 years of age who meet the revised Bethesda guidelines **OR**
- Individuals with endometrial cancer

  The revised Bethesda criteria are :
  - CRC diagnosed before age 50;
  - Presence of synchronous or metachronous CRC or other hereditary nonpolyposis CRC-related tumor*, regardless of age;
  - CRC in an individual younger than 60 years of age exhibiting MSI-H histology (tumor-infiltrating lymphocytes, Crohn's - like lymphocytic reaction, mucinous/signet ring differentiation, or medullary growth pattern):
  - CRC at any age, plus CRC or hereditary nonpolyposis CRC-related tumor diagnosed before the age of 50 years in at least one first-degree relative;
  - CRC at any age, plus CRC or hereditary nonpolyposis CRC-related tumor diagnosed before the age of 50 years in two or more first- or second-degree relatives

*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 if the individual fulfills the ACII or revised Bethesda guidelines.

- CRC or endometrial 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.

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)
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:

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
81436	HEREDITARY COLON CANCER DISORDERS (EG, LYNCH SYNDROME, PTEN HAMARTOMA SYNDROME, COWDEN SYNDROME, FAMILIAL ADENOMATOSIS POLYPOSIS); DUPLICATION/DELETION ANALYSIS PANEL, MUST INCLUDE ANALYSIS OF AT LEAST 5 GENES, INCLUDING MLH1, MSH2, EPCAM, SMAD4, AND STK11
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

ICD-10 Codes	Description
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
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

ICD-10 Codes	Description
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
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
Group 1 Paragraph: N/A

Group 1 Codes:

ICD-10 Codes	Description
C46.0	Kaposi's sarcoma of skin
C46.1	Kaposi's sarcoma of soft tissue
C46.2	Kaposi's sarcoma of palate
C46.3	Kaposi's sarcoma of lymph nodes
C46.4	Kaposi's sarcoma of gastrointestinal sites
C46.50	Kaposi's sarcoma of unspecified lung
C46.51	Kaposi's sarcoma of right lung
C46.52	Kaposi's sarcoma of left lung
C46.7	Kaposi's sarcoma of other sites
C46.9	Kaposi's sarcoma, unspecified
C50.019	Malignant neoplasm of nipple and areola, unspecified female breast
C50.119	Malignant neoplasm of central portion of unspecified female breast
C50.219	Malignant neoplasm of upper-inner quadrant of unspecified female breast
C50.319	Malignant neoplasm of lower-inner quadrant of unspecified female breast
C50.419	Malignant neoplasm of upper-outer quadrant of unspecified female breast
C50.519	Malignant neoplasm of lower-outer quadrant of unspecified female breast
C50.619	Malignant neoplasm of axillary tail of unspecified female breast
C50.819	Malignant neoplasm of overlapping sites of unspecified female breast
C50.919	Malignant neoplasm of unspecified site of unspecified female breast
C51.0	Malignant neoplasm of labium majus
C51.1	Malignant neoplasm of labium minus
C51.2	Malignant neoplasm of clitoris
C51.8	Malignant neoplasm of overlapping sites of vulva
C51.9	Malignant neoplasm of vulva, unspecified
C52	Malignant neoplasm of vagina
C53.0	Malignant neoplasm of endocervix
C53.1	Malignant neoplasm of exocervix
C53.8	Malignant neoplasm of overlapping sites of cervix uteri
C53.9	Malignant neoplasm of cervix uteri, unspecified
C57.7	Malignant neoplasm of other specified female genital organs
C57.8	Malignant neoplasm of overlapping sites of female genital organs
C57.9	Malignant neoplasm of female genital organ, unspecified
C60.0	Malignant neoplasm of prepuce
C60.1	Malignant neoplasm of glans penis
C60.2	Malignant neoplasm of body of penis
C60.8	Malignant neoplasm of overlapping sites of penis
C60.9	Malignant neoplasm of penis, unspecified
C62.00	Malignant neoplasm of unspecified undescended testis
C62.01	Malignant neoplasm of undescended right testis
C62.02	Malignant neoplasm of undescended left testis
C62.10	Malignant neoplasm of unspecified descended testis
C62.11	Malignant neoplasm of descended right testis
C62.12	Malignant neoplasm of descended left testis
C62.90	Malignant neoplasm of unspecified testis, unspecified whether descended or undescended
C62.91	Malignant neoplasm of right testis, unspecified whether descended or undescended
C62.92	Malignant neoplasm of left testis, unspecified whether descended or undescended
C63.00	Malignant neoplasm of unspecified epididymis
C63.01	Malignant neoplasm of right epididymis
C63.02	Malignant neoplasm of left epididymis
C63.10	Malignant neoplasm of unspecified spermatic cord
C63.11	Malignant neoplasm of right spermatic cord
C63.12	Malignant neoplasm of left spermatic cord
C63.2	Malignant neoplasm of scrotum
C63.7	Malignant neoplasm of other specified male genital organs
C63.8	Malignant neoplasm of overlapping sites of male genital organs

ICD-10 Codes	Description
C63.9	Malignant neoplasm of male genital organ, unspecified
C67.0	Malignant neoplasm of trigone of bladder
C67.1	Malignant neoplasm of dome of bladder
C67.2	Malignant neoplasm of lateral wall of bladder
C67.3	Malignant neoplasm of anterior wall of bladder
C67.4	Malignant neoplasm of posterior wall of bladder
C67.5	Malignant neoplasm of bladder neck
C67.6	Malignant neoplasm of ureteric orifice
C67.7	Malignant neoplasm of urachus
C67.8	Malignant neoplasm of overlapping sites of bladder
C67.9	Malignant neoplasm of bladder, unspecified
C68.0	Malignant neoplasm of urethra
C68.1	Malignant neoplasm of paraurethral glands
C68.9	Malignant neoplasm of urinary organ, unspecified
Z85.3	Personal history of malignant neoplasm of breast

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 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, 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". The documentation is expected if Palmetto GBA or another Medicare contractor upon request.

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.

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Back to Top

Revision History Information

Please note: Most Revision History entries effective on or before 01/24/2013 display with a Revision History Number of "R1" at the bottom of this table. However, there may be LCDs where these entries will display as a separate and distinct row.

Revision History Date	Revision History Number	Revision History Explanation	Reason(s) for Change
12/24/2015	R8	Revision due to reconsideration request	• Reconsideration Request
10/01/2015	R7	typographical error correction for the less than or equal to symbol	• Typographical Error
10/01/2015	R6	Corrected typographical errors and removed ICD-10 codes C21.0 and C21.1 from Does NOT Support Medical Necessity" section. It was erroneously in both "Supports" and "Does NOT Support" fields.	• Typographical Error
10/01/2015	R5	Addition of MolDX to LCD title.	• Other (per request of MAC's using MolDX service)
10/01/2015	R4	Under ICD-10 Codes That Support Medical Necessity added ICD-10 codes inadvertently omitted from the LCD: C18.9 C21.0 C57.00 C57.10 C57.20 C57.4 C64.9 C65.9 C66.9	• Request for Coverage by a Practitioner (Part B)
10/01/2015	R3	Added additional cross walked ICD-10 codes from ICD-9 codes currently in the policy.	• Revisions Due To ICD-10-CM Code Changes
10/01/2015	R2	Added CPT 81288 as limited coverage. The following CPT codes were added as non-covered: 81435 81436 81445 81455 The following CPT/HCPCS codes were deleted: G0461 was deleted from Group 1 G0462 was deleted from Group 1 This revision is due to CR 8975 HCPCS Annual Update published 10/24/14.	• Revisions Due To CPT/HCPCS Code Changes
10/01/2015	R1	Combined HCPCS and ICD-10 codes to one group. Updated policy according to new science. Added resources.	• New/Updated Technology

Back to Top

Associated Documents

Attachments N/A

Related Local Coverage Documents N/A

Related National Coverage Documents N/A

Public Version(s) Updated on 12/22/2015 with effective dates 12/24/2015 - N/A Updated on 10/09/2015 with effective dates 10/01/2015 - 12/23/2015 Updated on 07/21/2015 with effective dates 10/01/2015 - N/A Updated on 07/01/2015 with effective dates 10/01/2015 - N/A Updated on 06/02/2015 with effective dates 10/01/2015 - N/A Updated on 05/20/2015 with effective dates 10/01/2015 - N/A Updated on 12/16/2014 with effective dates 10/01/2015 - N/A Updated on 09/05/2014 with effective dates 10/01/2015 - N/A Updated on 03/14/2014 with effective dates 10/01/2015 - N/A Back to Top

Keywords

- LS
- Lynch Syndrome

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