MolDX: Genetic Testing for Lynch Syndrome

Noridian Healthcare Solutions, LLC

Please Note: This is a Proposed LCD.
Proposed LCDs are works in progress and not necessarily a reflection of the current policies or practices. Proposed LCDs in an approval status display on the CMS MCD for public review.

Contractor Information

Contractor Name	Noridian Healthcare Solutions, LLC
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Contract Type	A and B MAC
Associated Contract Numbers	(A and B MAC - 01182 - J - E) Noridian Healthcare Solutions, LLC, (A and B MAC - 01212 - J - E) Noridian Healthcare Solutions, LLC, (A and B MAC - 01312 - J - E) Noridian Healthcare Solutions, LLC

Proposed LCD Information

Source LCD ID	N/A
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Proposed LCD Title	MolDX: Genetic Testing for Lynch Syndrome

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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. 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.
Jurisdiction	California - Northern
Super MAC Jurisdiction	J - E

Coverage Guidance

Coverage Indications,	**I. Lynch Syndrome** This policy limits Lynch Syndrome genetic testing to a stepped approach

Limitations and/or Medical Necessity

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 CRC diagnosed at age ≤70 years of age, and those > 70 years who meet the revised Bethesda Lynch Syndrome guidelines.

Most colorectal cancer is caused by non-hereditary somatic mutations. Individuals with Lynch Syndrome (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. Lynch Syndrome, 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.

Lynch Syndrome 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 Lynch Syndrome annually affects 28,000 individuals. In individuals with Lynch Syndrome, 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 Lynch Syndrome 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 Lynch Syndrome are largely derived from family studies. Mutations in *MLH1* and *MSH2* account for 70-90% of families with Lynch Syndrome. 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 Lynch Syndrome 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 Lynch Syndrome Testing

The use of IHC to detect loss of DNA mismatched repair (MMR) protein expression complements MSI to test patients for defective MMR (dMMR), including both sporadic dMMR and Lynch Syndrome 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 Lynch Syndrome in a clinically suspicious setting.

Step 2: Microsatellite Instability (MSI) Analysis for Lynch Syndrome Testing

MSI analysis for testing Lynch Syndrome 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 Lynch Syndrome 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 Lynch Syndrome demonstrate MSI-H. However, MSI-H is NOT diagnostic of Lynch Syndrome 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 Lynch Syndrome 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 test suspected Lynch Syndrome 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 Lynch Syndrome dMMR. This is because *BRAFM* mutation and *MLH1* PHM are very seldom seen in Lynch Syndrome. *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., Lynch Syndrome).

Step 4: *MLH1* Promoter Hypermethylation (*MLH1* PHM)

The combination of *MLH1* PHM and a *BRAF* mutation in tumors rules out Lynch Syndrome 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 Lynch Syndrome. However, there have been rare reports of *MLH1* hypermethylation as a second hit in Lynch Syndrome 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; Lynch Syndrome 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 Lynch Syndrome 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 Lynch Syndrome 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 Lynch Syndrome. If MSH2 germ-line mutation is identified, then Lynch

Syndrome 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 Lynch Syndrome 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 Lynch Syndrome 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 Lynch Syndrome 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 Lynch Syndrome 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

Lynch Syndrome tumor testing 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 tumor-infiltrating lymphocytes;
- 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

For coverage, the treating physician/pathologist is expected to follow the stepped approach outlined for Lynch Syndrome testing 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 Lynch Syndrome
- If tumor is not available or determined by a pathologist to be inadequate to assess DNA MMR deficiency by MSI or IHC, then MMR germ-line testing can be conducted on blood if the individual fulfills the ACII or revised Bethesda guidelines.
- CRC tumor diagnosis prior to Medicare eligibility **AND** tumor sample no longer available **AND** individual meets

ACII or revised Bethesda guidelines or was diagnosed with endometrial cancer before 50

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

Testing for Known Familial Variant

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

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 Lynch Syndrome for carrier status or family studies is considered screening and is statutorily excluded from coverage.

IV. Limitations

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

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Proposed Process Information

Documentation Requirement

Associated Information

<u>Medical Documentation of Suspected Lynch Syndrome</u>

Noridian 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.

It is 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, Noridian does not expect routine MMR germ-line mutation testing prior to appropriate preliminary (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." Documentation to support the MMR germ line mutation testing shall be made available upon request to Noridian or other Medicare entity.

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 Lynch Syndrome-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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	Meeting Date	Meeting Information	State
Open Meetings	10/01/2015	The open public meeting will be held at the following location: Embassy Suites Flamingo	American Samoa, California - Entire State, Guam, Hawaii, Nevada, Northern Mariana

		Ballroom 4315 Swenson St. Las Vegas, NV 89119	Islands, California - Northern, California - Southern
	Meeting Date	**Meeting Information**	**State**
Part B MAC Contractor Advisory Committee (CAC) Meetings	10/09/2015	The Pacific Club Card Room 1451 Queen Emma St Honolulu, HI 96813	American Samoa, Guam, Hawaii, Northern Mariana Islands
	10/21/2015	DoubleTree by Hilton San Francisco Airport Tiburon/Sausalito Room 835 Airport Boulevard Burlingame, CA 94010	California - Entire State, California - Northern, California - Southern
	10/22/2015	Clark County Medical Association/NV State Medical Association 2590 E Russell Rd Las Vegas, NV 89120	Nevada
Comment Period Start Date	10/01/2015		
Comment Period End Date	12/07/2015		
Released to Final LCD Date	Not yet released.		
Reason for Proposed LCD	Creation of Uniform LCDs... Creation of Uniform LCDs With Other MAC Jurisdiction		
Proposed LCD Contact	Noridian Healthcare Solutions, LLC JE Part B Contractor Medical Director(s) Attention: Draft LCD Comments PO Box 6783 Fargo, North Dakota 58108-6783 policyb.drafts@noridian.com		

Coding Information

Bill Type Codes

Revenue Codes	XX000
CPT/HCPCS Codes	**Group 1: Paragraph** **Group 1: Codes**

81210	BRAF (V-RAF MURINE SARCOMA VIRAL ONCOGENE HOMOLOG B1) (EG, COLON CANCER), GENE ANALYSIS, V600E VARIANT
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 SYNDROMES (EG, LYNCH SYNDROME, FAMILIAL ADENOMATOSIS POLYPOSIS); GENOMIC SEQUENCE ANALYSIS

		PANEL, MUST INCLUDE ANALYSIS OF AT LEAST 7 GENES, INCLUDING APC, CHEK2, MLH1, MSH2, MSH6, MUTYH, AND PMS2
	81436	HEREDITARY COLON CANCER SYNDROMES (EG, LYNCH SYNDROME, FAMILIAL ADENOMATOSIS POLYPOSIS); DUPLICATION/DELETION GENE ANALYSIS PANEL, MUST INCLUDE ANALYSIS OF AT LEAST 8 GENES, INCLUDING APC, MLH1, MSH2, MSH6, PMS2, EPCAM, CHEK2, AND MUTYH
	81445	TARGETED GENOMIC SEQUENCE ANALYSIS PANEL, SOLID ORGAN NEOPLASM, DNA ANALYSIS, 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 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

Does the CPT 30% Coding Rule Apply? No

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.

Note: Performance is optimized by using code ranges.

Group 1: Codes

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
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
	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
	Group 1: Paragraph	
	Group 1: Codes	
ICD-10 Codes that DO NOT Support Medical Necessity **Note: Performance is optimized by using code ranges.**	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
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

Additional ICD-10 Information

Associated Documents

Attachments	There are no attachments for this LCD.
Related Local Coverage Documents	This LCD version has no Related Local Coverage Documents.
Related National Coverage Documents	This LCD version has no Related National Coverage Documents.
All Versions	**Version 4 - Updated on 08/12/2015 17:08:08, by Christine.Burnside@noridian.com, with effective dates N/A - N/A (Approved).** Version 3 - Updated on 08/12/2015 14:49:41, by Cheryl.Ryan@noridian.com, with effective dates N/A - N/A. Version 2 - Updated on 08/10/2015 15:19:33, by

Cheryl.Ryan@noridian.com, with effective dates N/A - N/A.
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