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

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Coverage Guidance

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.
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 MSH6 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 BRAF 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 germline 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 in 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, \textit{MLH1} and \textit{MSH2} testing should be performed first, since these two genes account for the majority of germ-line mutations. If no mutation is identified in \textit{MLH1} or \textit{MSH2}, testing of \textit{MSH6} is indicated. If no mutation is identified in \textit{MSH6}, testing of \textit{PMS2} may be considered.

\textbf{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.

\textbf{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.

\textbf{IV. Limitations}

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

\textbf{Proposed Process Information}

\textbf{Proposed}

\textbf{Documentation Requirement}

\textbf{Medical Documentation of Suspected Lynch Syndrome}

\textbf{Associated Information}

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.


**Open Meetings**

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**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**: XX000

**Revenue Codes**: Group 1: Paragraph Group 1: Codes
BRAF (V-RAF MURINE SARCOMA VIRAL ONCOGENE HOMOLOG B1) (EG, COLON CANCER), GENE ANALYSIS, V600E VARIANT

MLH1 (MUTL HOMOLOG 1, COLON CANCER, NONPOLYPOSIS TYPE 2) (EG, HEREDITARY NON-POLYPOSIS COLORECTAL CANCER, LYNCH SYNDROME) GENE ANALYSIS; PROMOTER METHYLATION ANALYSIS

MLH1 (MUTL HOMOLOG 1, COLON CANCER, NONPOLYPOSIS TYPE 2) (EG, HEREDITARY NON-POLYPOSIS COLORECTAL CANCER, LYNCH SYNDROME) GENE ANALYSIS; FULL SEQUENCE ANALYSIS

MLH1 (MUTL HOMOLOG 1, COLON CANCER, NONPOLYPOSIS TYPE 2) (EG, HEREDITARY NON-POLYPOSIS COLORECTAL CANCER, LYNCH SYNDROME) GENE ANALYSIS; KNOWN FAMILIAL VARIANTS

MLH1 (MUTL HOMOLOG 1, COLON CANCER, NONPOLYPOSIS TYPE 2) (EG, HEREDITARY NON-POLYPOSIS COLORECTAL CANCER, LYNCH SYNDROME) GENE ANALYSIS; DUPLICATION/DELETION VARIANTS

MSH2 (MUTS HOMOLOG 2, COLON CANCER, NONPOLYPOSIS TYPE 1) (EG, HEREDITARY NON-POLYPOSIS COLORECTAL CANCER, LYNCH SYNDROME) GENE ANALYSIS; FULL SEQUENCE ANALYSIS

MSH2 (MUTS HOMOLOG 2, COLON CANCER, NONPOLYPOSIS TYPE 1) (EG, HEREDITARY NON-POLYPOSIS COLORECTAL CANCER, LYNCH SYNDROME) GENE ANALYSIS; KNOWN FAMILIAL VARIANTS

MSH2 (MUTS HOMOLOG 2, COLON CANCER, NONPOLYPOSIS TYPE 1) (EG, HEREDITARY NON-POLYPOSIS COLORECTAL CANCER, LYNCH SYNDROME) GENE ANALYSIS; DUPLICATION/DELETION VARIANTS

MSH6 (MUTS HOMOLOG 6 [E. COLI]) (EG, HEREDITARY NON-POLYPOSIS COLORECTAL CANCER, LYNCH SYNDROME) GENE ANALYSIS; FULL SEQUENCE ANALYSIS

MSH6 (MUTS HOMOLOG 6 [E. COLI]) (EG, HEREDITARY NON-POLYPOSIS COLORECTAL CANCER, LYNCH SYNDROME) GENE ANALYSIS; KNOWN FAMILIAL VARIANTS
CANCER, LYNCH SYNDROME) GENE ANALYSIS; KNOWN FAMILIAL VARIANTS

MSH6 (MUTS HOMOLOG 6 [E. COLI]) (EG, HEREDITARY NON-POLYPOSIS COLORECTAL CANCER, LYNCH SYNDROME) GENE ANALYSIS; DUPLICATION/DELETION VARIANTS

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

PMS2 (POSTMEIOTIC SEGREGATION INCREASED 2 [S. CEREVISIAE]) (EG, HEREDITARY NON-POLYPOSIS COLORECTAL CANCER, LYNCH SYNDROME) GENE ANALYSIS; FULL SEQUENCE ANALYSIS

PMS2 (POSTMEIOTIC SEGREGATION INCREASED 2 [S. CEREVISIAE]) (EG, HEREDITARY NON-POLYPOSIS COLORECTAL CANCER, LYNCH SYNDROME) GENE ANALYSIS; KNOWN FAMILIAL VARIANTS

PMS2 (POSTMEIOTIC SEGREGATION INCREASED 2 [S. CEREVISIAE]) (EG, HEREDITARY NON-POLYPOSIS COLORECTAL CANCER, LYNCH SYNDROME) GENE ANALYSIS; DUPLICATION/DELETION VARIANTS

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)

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

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

HEREDITARY COLON CANCER SYNDROMES (EG, LYNCH SYNDROME, FAMILIAL ADENOMATOUS POLYPOSIOS); DUPLICATION/DELETION GENE ANALYSIS PANEL, MUST INCLUDE ANALYSIS OF AT LEAST 8 GENES, INCLUDING APC, MLH1, MSH2, MSH6, PMS2, EPCAM, CHEK2, AND MUTYH

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

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

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.

ICD-10 Codes that Support Medical Necessity
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
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<tr>
<td>C18.9</td>
<td>Malignant neoplasm of colon, unspecified</td>
</tr>
<tr>
<td>C19</td>
<td>Malignant neoplasm of rectosigmoid junction</td>
</tr>
<tr>
<td>C20</td>
<td>Malignant neoplasm of rectum</td>
</tr>
<tr>
<td>C21.0</td>
<td>Malignant neoplasm of anus, unspecified</td>
</tr>
<tr>
<td>C21.1</td>
<td>Malignant neoplasm of anal canal</td>
</tr>
<tr>
<td>C21.2</td>
<td>Malignant neoplasm of cloacogenic zone</td>
</tr>
<tr>
<td>C21.8</td>
<td>Malignant neoplasm of overlapping sites of rectum, anus and anal canal</td>
</tr>
<tr>
<td>C22.0</td>
<td>Liver cell carcinoma</td>
</tr>
<tr>
<td>C22.1</td>
<td>Intrahepatic bile duct carcinoma</td>
</tr>
<tr>
<td>C22.2</td>
<td>Hepatoblastoma</td>
</tr>
<tr>
<td>C22.3</td>
<td>Angiosarcoma of liver</td>
</tr>
<tr>
<td>C22.4</td>
<td>Other sarcomas of liver</td>
</tr>
<tr>
<td>C22.7</td>
<td>Other specified carcinomas of liver</td>
</tr>
<tr>
<td>C22.8</td>
<td>Malignant neoplasm of liver, primary, unspecified as to type</td>
</tr>
</tbody>
</table>
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
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
<table>
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<tr>
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<td>Malignant neoplasm of left spermatic cord</td>
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<td>C63.2</td>
<td>Malignant neoplasm of scrotum</td>
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<tr>
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<td>Malignant neoplasm of other specified male genital organs</td>
</tr>
<tr>
<td>C63.8</td>
<td>Malignant neoplasm of overlapping sites of male genital organs</td>
</tr>
<tr>
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<td>Malignant neoplasm of male genital organ, unspecified</td>
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<td>C67.0</td>
<td>Malignant neoplasm of trigone of bladder</td>
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<td>C67.1</td>
<td>Malignant neoplasm of dome of bladder</td>
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<td>Malignant neoplasm of lateral wall of bladder</td>
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<td>C67.5</td>
<td>Malignant neoplasm of bladder neck</td>
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<td>Malignant neoplasm of ureteric orifice</td>
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<td>Malignant neoplasm of urachus</td>
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<td>Malignant neoplasm of paraurethral glands</td>
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<tr>
<td>Z85.3</td>
<td>Personal history of malignant neoplasm of breast</td>
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**Additional ICD-10 Information**

**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.

**Attachments**

There are no attachments for this LCD.

**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