LCD Database ID Number

L34912

Contractor Name

First Coast Service Options, Inc.

Contractor Number

09101 - Florida
09201 – PR/USVI
09102 – Florida
09202 – Puerto Rico
09302 – Virgin Islands

Contractor Type

MAC – Part A and B

LCD Title

Genetic Testing for Lynch Syndrome

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CMS National Coverage Policy

Language quoted from CMS National Coverage Determination (NCDs) and coverage provisions in interpretive manuals are italicized throughout the Local Coverage Determination (LCD). NCDs and coverage provisions in interpretive manuals are not subject to the LCD Review Process (42 CFR 405.860[b] and 42 CFR 426 [Subpart D]). In addition, an administrative law judge may not review an NCD. See §1869(f)(1)(A)(i) of the Social Security Act.

Unless otherwise specified, italicized text represents quotation from one or more of the following CMS sources:

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.
Genetic Testing for Lynch Syndrome AB

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.


**Primary Geographic Jurisdiction**

Florida
Puerto Rico/Virgin Islands

**Oversight Region**

Region I

**Original Determination Effective Date**

10/01/2015

**Original Determination Ending Date**

N/A

**Revision Effective Date**

6/28/2016

**Revision Ending Date**

06/27/2016

**Indications and Limitations of Coverage and/or Medical Necessity**

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

**I. Lynch Syndrome (LS)**

This local coverage determination 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 patients suspected of having LS.

Most colorectal cancer is caused by non hereditary somatic mutations. Individuals with LS (aka Hereditary nonpolyposis colorectal cancer (HNPCC) are predisposed to cancer due to having inherited or de novo germ-line mutations in DNA repair genes, that result in an accelerated accumulation of somatic mutations. LS, the most common hereditary cause of colorectal cancer, accounts for 2-3% of all colorectal cancers, followed by familial adenomatous polyposis (FAP) which accounts for <1% of colorectal malignancies and MUTYH-associated polyposis (MAP) whose frequency of occurrence is very rare.
LS is an autosomal dominant familial cancer syndrome caused by mutations in multiple susceptibility genes (e.g., MLH1, MSH2, MSH6, PMS2, EPCAM), and is associated with an increased lifetime risk for colorectal cancer (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 an LS proband, testing of genetic carriers who are unaffected with a Lynch related cancer is not a benefit, and is statutorily excluded from coverage.

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

Step 1: Patient selection

Patients with colorectal and/or endometrial cancer suspected of LS must undergo a comprehensive review of physical findings and a complete personal and family history.

In 1989, the Amsterdam criteria defined what is known as Hereditary Non-polyposis Colon Cancer Syndrome, and in 1999, the criteria were revised to include extra-colonic tumors (Table 1). Today we know there are two distinct groups comprising HNPCC: those with hereditary DNA mismatch repair germ-line mutations, known as Lynch Syndrome, and those with normal DNA mismatch repair, known as Familial Colorectal Cancer Type X.

<table>
<thead>
<tr>
<th>Table 1 - Amsterdam Criteria II (ACII)</th>
</tr>
</thead>
<tbody>
<tr>
<td>There should be at least three relatives with CRC or with a Lynch syndrome-associated cancer: endometrial, small bowel, ureter or renal pelvis cancer.</td>
</tr>
<tr>
<td>• One relative should be a 1st-degree relative of the other two,</td>
</tr>
<tr>
<td>• At least two successive generations should be affected,</td>
</tr>
<tr>
<td>• At least one tumor should be diagnosed before age 50 years,</td>
</tr>
<tr>
<td>• FAP should be excluded in the CRC case, if any,</td>
</tr>
<tr>
<td>• Tumors should be verified by histopathological exam</td>
</tr>
</tbody>
</table>

Approximately 50% of families meeting the ACII criteria have a mutation in an MMR gene. However, these criteria are very stringent and miss as many as 68% of patients with LS.

In 1997, the Bethesda guidelines were developed to identify individuals with CRC who should be tested for MSI. In 2002, the guidelines were revised (Table 2) to clarify selection criteria for microsatellite instability (MSI) testing and mismatch repair (MMR) protein expression by immunohistochemistry (IHC). Screening tumors of patients meeting the Bethesda guidelines for MSI was shown to be cost-effective with newly diagnosed CRC.
Table 2 - Revised Bethesda Guidelines

Meeting any of the following are sufficient for consideration of MSI/IHC testing:

- CRC diagnosed under age 50
- Presence of synchronous, or metachronous CRC or other Lynch-associated tumor, regardless of age
- CRC with MSI-H histology diagnosed in an individual who is < age 60
- CRC diagnosed with one or more 1st-degree relatives with a Lynch-related tumor, with one of the cancers diagnosed under age 50
- CRC diagnosed in two or more 1st- or 2nd-degree relatives with a Lynch-related tumor, regardless of age

If a patient meets standards for LS testing in Step 1 (i.e. meets ACII or Revised Bethesda guidelines), the physician should proceed to Step 2 and 3.

Step 2: 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 4) or test for MLH1 promoter, (Step 5)
- MSH2/MS6 loss by IHC, perform MSH2 germ-line testing (Step 6)

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 3: 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, MSH6).
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 % level of MSI-H is less consistent and is inadequately studied.

As indicated above, MSI testing is not necessary if IHC demonstrates loss of protein expression for the *MLH1, MSH2, MSH6 and PMS2* genes. If IHC test results are normal, there remains a small chance of high levels of microsatellite instability (MSI-H), so both IHC and MSI should be performed to rule out LS in a clinically suspicious setting such as meeting a Revised Bethesda guideline. Additionally, some individuals with MSH6 germ-line mutations do not manifest the MSI-H phenotype. This finding supports the diagnostic strategy to screen suspected LS patients with 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 4 and/or 5 apply only for tumors that are negative for *MLH1* protein expression by IHC.

**Step 4: BRAF V600E (BRAF) Mutation Testing**

*BRAF* mutation testing and *MLH1* promoter methylation studies distinguish between sporadic dMMR and LS dMMR. This is because *BRAF* mutation and *MLH1 PHM* are very seldom seen in LS. *BRAF* mutation testing of the CRC tumor is associated with the presence of an epigenetic alteration (i.e., hypermethylation of *MLH1*) and either finding excludes germ-line MMR gene mutation (e.g., LS).

**Step 5: MLH1 Promoter Hypermethylation (MLH1 PHM)**

The combination of *MLH1 PHM* and a *BRAF* mutation in tumors rules out LS and no further molecular analysis is warranted. Tumors with *MLH1 PHM* identify dMMR which will most often be sporadic, but its presence does not fully rule out LS. However, there have been rare reports of *MLH1* hypermethylation as a second hit in LS and there are new reports of constitutional *MLH1* methylation. As a rule, discovery of *MLH1 PHM* indicates the tumor is not due to 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 *MLH1* is hypermethylated, germline *MLH1* is not medically necessary.
  - If the *MLH1* promoter is hypermethylated and ACII if 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 6: Targeted MMR (MLH1, MSH2, MSH6 and PMS2 gene) Germ-line and EpCAM Testing

Step 6A: 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 germ-line is positively identified, then LS is diagnosed and further testing of the patient is not medically necessary.

Step 6B: 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 6C: 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 6D: 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 7: 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 on colorectal and/or endometrial tumors is considered medically necessary and covered for the following indications:

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

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 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 if the individual fulfills the ACII or revised Bethesda guidelines.
- CRC tumor diagnosis prior to 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 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

Universal Testing for CRC and Endometrial Cancer

Universal testing of CRC and endometrial cancers by MSI/MMR protein expression by IHC is not a benefit. The NCCN colorectal cancer screening guidelines (V2.2013) recommends that “risk assessment be individualized and include a careful family history … and if a patient meets the criteria for an inherited colorectal syndrome, further risk evaluation and counseling, as outlined in the guidelines, is required. The guidelines indicates that “when any one of the revised Bethesda criteria are met, the possibility of LS is suggested, and IHC staining for the four MMR proteins and/or MSI testing on the colon tumor of the youngest affected family member is warranted.”

The NCCN colon cancer treatment guidelines (V3.2013) “recommend that MMR protein testing be performed for
all patients younger than 50 years with colon cancer, based on an increased likelihood of LS in this population. MMR testing should also be considered in all patients with stage II disease, because stage II MSI-H patients may have a good prognosis and stage II MSI-H patients do not benefit from 5-FU adjuvant therapy.”

Similarly, although the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group found sufficient evidence in 2009 to recommendation offering genetic testing for LS to individuals with newly diagnosed CRC to reduce morbidity and mortality in relatives, molecular testing for LS for identify carrier status or family studies is not a benefit.

**Type of Bill Code**

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.

<table>
<thead>
<tr>
<th>Bill Type</th>
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<tbody>
<tr>
<td>012x Hospital Inpatient (Medicare Part B only)</td>
</tr>
<tr>
<td>013x Hospital Outpatient</td>
</tr>
<tr>
<td>014x Hospital - Laboratory Services Provided to Non-patients</td>
</tr>
<tr>
<td>018x Hospital - Swing Beds</td>
</tr>
<tr>
<td>021x Skilled Nursing - Inpatient (Including Medicare Part A)</td>
</tr>
<tr>
<td>022x Skilled Nursing - Inpatient (Medicare Part B only)</td>
</tr>
<tr>
<td>023x Skilled Nursing - Outpatient</td>
</tr>
<tr>
<td>071x Clinic - Rural Health</td>
</tr>
<tr>
<td>072x Clinic - Hospital Based or Independent Renal Dialysis Center</td>
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<tr>
<td>073x Clinic - Freestanding</td>
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<tr>
<td>075x Clinic - Comprehensive Outpatient Rehabilitation Facility (CORF)</td>
</tr>
<tr>
<td>077x Clinic - Federally Qualified Health Center (FQHC)</td>
</tr>
<tr>
<td>083x Ambulatory Surgery Center</td>
</tr>
<tr>
<td>085x Critical Access Hospital</td>
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</tbody>
</table>

**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.

<table>
<thead>
<tr>
<th>Revenue Code</th>
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<tbody>
<tr>
<td>030X Laboratory - General Classification</td>
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<tr>
<td>031X Laboratory Pathology - General Classification</td>
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</tbody>
</table>

**CPT/HCPCS Codes**
### Group 1 codes:

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>81288</td>
<td>MLH1 (MUTL HOMOLOG 1, COLON CANCER, NONPOLYPOSIS TYPE 2) (EG, HEREDITARY NON-POLYPOSIS COLORECTAL CANCER, LYNCH SYNDROME) GENE ANALYSIS; PROMOTER METHYLATION ANALYSIS</td>
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<tr>
<td>81293</td>
<td>MLH1 (MUTL HOMOLOG 1, COLON CANCER, NONPOLYPOSIS TYPE 2) (EG, HEREDITARY NON-POLYPOSIS COLORECTAL CANCER, LYNCH SYNDROME) GENE ANALYSIS; KNOWN FAMILIAL VARIANTS</td>
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<tr>
<td>81294</td>
<td>MLH1 (MUTL HOMOLOG 1, COLON CANCER, NONPOLYPOSIS TYPE 2) (EG, HEREDITARY NON-POLYPOSIS COLORECTAL CANCER, LYNCH SYNDROME) GENE ANALYSIS; DUPLICATION/DELETION VARIANTS</td>
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<td>81295</td>
<td>MSH2 (MUTS HOMOLOG 2, COLON CANCER, NONPOLYPOSIS TYPE 1) (EG, HEREDITARY NON-POLYPOSIS COLORECTAL CANCER, LYNCH SYNDROME) GENE ANALYSIS; FULL SEQUENCE ANALYSIS</td>
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<td>81296</td>
<td>MSH2 (MUTS HOMOLOG 2, COLON CANCER, NONPOLYPOSIS TYPE 1) (EG, HEREDITARY NON-POLYPOSIS COLORECTAL CANCER, LYNCH SYNDROME) GENE ANALYSIS; KNOWN FAMILIAL VARIANTS</td>
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<td>MSH2 (MUTS HOMOLOG 2, COLON CANCER, NONPOLYPOSIS TYPE 1) (EG, HEREDITARY NON-POLYPOSIS COLORECTAL CANCER, LYNCH SYNDROME) GENE ANALYSIS; DUPLICATION/DELETION VARIANTS</td>
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</tr>
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### Group 2 codes:
81210  BRAF (B-RAF Proto-Oncogene, Serine/Threonine Kinase) (EG, Colon Cancer, Melanoma), Gene Analysis, V600 Variant(s)

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

81403  Molecular Pathology Procedure, Level 4 (EG, Analysis of Single Exon by DNA Sequence Analysis, Analysis of >10 Amplicons Using Multiplex PCR in 2 or More Independent Reactions, Mutation Scanning or Duplication/Deletion Variants of 2-5 Exons)

81435  Hereditary Colon Cancer Disorders (EG, Lynch Syndrome, PTEN Hamartoma Syndrome, Cowden Syndrome, Familial Adenomatosis Polyposis); Genomic Sequence Analysis Panel, Must Include Sequencing of at Least 10 Genes, Including APC, BMPR1A, CDH1, MLH1, MSH2, MSH6, MUTYH, PTEN, SMAD4, and STK11

81479  Unlisted Molecular Pathology Procedure

88341  Immunohistochemistry or Immunocytochemistry, Per Specimen; Each Additional Single Antibody Stain Procedure (List Separately in Addition to Code for Primary Procedure)

88342  Immunohistochemistry or Immunocytochemistry, Per Specimen; Initial Single Antibody Stain Procedure

88344  Immunohistochemistry or Immunocytochemistry, Per Specimen; Each Multiplex Antibody Stain Procedure

ICD-10 Codes that Support Medical Necessity

It is the responsibility of the physician/provider to code to the highest level specified in the ICD-10-CM (e.g., to the fourth or fifth digit). The correct use of an ICD-10-CM 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 I.

**Group 1 Codes 81288, 81292-81300 and 81317-81319:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<td>Malignant neoplasms of digestive organs</td>
</tr>
<tr>
<td>C21.2-C22.9</td>
<td>Malignant neoplasms of digestive organs</td>
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<tr>
<td>C24.0</td>
<td>Malignant neoplasm of extrahepatic bile duct</td>
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<tr>
<td>C24.9</td>
<td>Malignant neoplasm of biliary tract, unspecified</td>
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<td>C25.0-C25.9</td>
<td>Malignant neoplasm of pancreas</td>
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<tr>
<td>C55</td>
<td>Malignant neoplasm of uterus, part unspecified</td>
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<td>Malignant neoplasms of urinary tract</td>
</tr>
<tr>
<td>C68.8</td>
<td>Malignant neoplasm of overlapping sites of urinary organs</td>
</tr>
<tr>
<td>C71.0-C71.9</td>
<td>Malignant neoplasm of brain</td>
</tr>
<tr>
<td>D12.0-D12.6</td>
<td>Benign neoplasm of colon, rectum, anus and anal canal</td>
</tr>
<tr>
<td>K63.5</td>
<td>Polyp of colon</td>
</tr>
<tr>
<td>L85.3</td>
<td>Xerosis cutis</td>
</tr>
<tr>
<td>*Z85.00</td>
<td>Personal history of malignant neoplasm of unspecified digestive organ</td>
</tr>
<tr>
<td>*Z85.038</td>
<td>Personal history of other malignant neoplasm of large intestine</td>
</tr>
<tr>
<td>*Z85.048</td>
<td>Personal history of other malignant neoplasm of rectum, rectosigmoid junction, and anus</td>
</tr>
<tr>
<td>*Z85.42-Z85.43</td>
<td>Personal history of malignant neoplasm of genital organs</td>
</tr>
</tbody>
</table>
Genetic Testing for Lynch Syndrome AB

<table>
<thead>
<tr>
<th>Diagnosis Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Z85.53-Z85.59</td>
<td>Personal history of malignant neoplasm of urinary tract</td>
</tr>
<tr>
<td>Z85.841</td>
<td>Personal history of malignant neoplasm of brain</td>
</tr>
<tr>
<td>Z86.010</td>
<td>Personal history of colonic polyps</td>
</tr>
</tbody>
</table>

* Diagnosis codes Z85.00, Z85.038, Z85.048, Z85.42-Z85.43, Z85.53-Z85.59, Z85.841 and Z86.010 should not be billed as the primary diagnosis.

**Diagnoses that Support Medical Necessity**

N/A

**ICD-10 Codes that DO NOT Support Medical Necessity**

N/A

**Diagnoses that DO NOT Support Medical Necessity**

N/A

**Associated Information**

**Documentation Requirements**

**Medical Documentation of Suspected LS**

The ordering/treating physician or pathologist is expected 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 has been 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, Routine MMR germ-line mutation testing is not expected 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.” Documentation is expected to be available 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.

**Utilization Guidelines**

N/A

**Sources of Information and Basis for Decision**

FCSO reference LCD number(s) – L34483
Genetic Testing for Lynch Syndrome AB


**Start Date of Comment Period**

N/A

**End Date of Comment Period**

N/A

**Start Date of Notice Period**

04/01/2014

**Revision History**

**Revision History Number: R3**

**Revision Number:** 3  
Publication: July 2016 Connection  
LCR A/B2016-075

Explanation of Revision: This LCD was revised to add CPT code 81435 to the “CPT/HCPCS Codes” section of the LCD under Group 2 codes. The effective date of this revision is based on date of service.

**Revision History Number: R2**

**Revision Number:** 2  
Publication: March 2016 Connection  
LCR A/B2016-052
Explanation of Revision: Verbiage for Lynch Syndrome tumor screening was revised to match the ‘Indications of Coverage’ section in the Special Histochemical Stains and Immunohistochemical Stains LCD (#L36234). The effective date of this revision is based on date of service.

Revision History Number: R1

Revision Number: 1
Publication: December 2015 Connection
LCR A/B2016-008

Explanation of Revision: Annual 2016 HCPCS Update. Descriptor revised for CPT code 81210. The effective date of this revision is based on date of service.

Revision History Number: Original

This LCD replaces all previous LCD versions (refer to “Sources of Information and Basis for Decision” section of the LCD) and publications on this subject to comply with ICD-10-CM based on Change Request 8112. The effective date of this LCD is based on date of service.

Related Documents

N/A

LCD Attachments

N/A