Local Coverage Determination (LCD): Molecular Diagnostic Testing (L34762)

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Contractor Information

Contractor Name	Contract Type	Contract Number	Jurisdiction	State(s)
Wisconsin Physicians Service Insurance Corporation	MAC - Part A	05101 - MAC A	N/A	Iowa
Wisconsin Physicians Service Insurance Corporation	MAC - Part B	05102 - MAC B	N/A	Iowa
Wisconsin Physicians Service Insurance Corporation	MAC - Part A	05201 - MAC A	N/A	Kansas
Wisconsin Physicians Service Insurance Corporation	MAC - Part B	05202 - MAC B	N/A	Kansas
Wisconsin Physicians Service Insurance Corporation	MAC - Part A	05301 - MAC A	N/A	Missouri - Entire State
Wisconsin Physicians Service Insurance Corporation	MAC - Part B	05302 - MAC B	N/A	Missouri - Entire State
Wisconsin Physicians Service Insurance Corporation	MAC - Part A	05401 - MAC A	N/A	Nebraska
Wisconsin Physicians Service Insurance Corporation	MAC - Part B	05402 - MAC B	N/A	Nebraska
Wisconsin Physicians Service Insurance Corporation	MAC - Part A	05901 - MAC A	N/A	Alaska Alabama Arkansas Arizona Connecticut Florida Georgia Iowa Idaho Illinois Indiana Kansas Kentucky Louisiana Massachusetts Maine Michigan Minnesota Missouri - Entire State Mississippi Montana North Carolina North Dakota Nebraska New Hampshire New Jersey Ohio Oregon Rhode Island South Carolina South Dakota Tennessee Utah

Contractor Name	Contract Type	Contract Number	Jurisdiction	State(s)
				Virginia Virgin Islands Vermont Washington Wisconsin West Virginia Wyoming
Wisconsin Physicians Service Insurance Corporation	MAC - Part A	08101 - MAC A	N/A	Indiana
Wisconsin Physicians Service Insurance Corporation	MAC - Part B	08102 - MAC B	N/A	Indiana
Wisconsin Physicians Service Insurance Corporation	MAC - Part A	08201 - MAC A	N/A	Michigan
Wisconsin Physicians Service Insurance Corporation	MAC - Part B	08202 - MAC B	N/A	Michigan

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LCD Information

Document Information

LCD ID
L34762

Original ICD-9 LCD ID
L33219

LCD Title
Molecular Diagnostic Testing

Original Effective Date
For services performed on or after 10/01/2015

Revision Effective Date
For services performed on or after 01/01/2016

Revision Ending Date
N/A

Retirement Date
N/A

Notice Period Start Date
N/A

Notice Period End Date
N/A

CMS National Coverage Policy Title XVIII of the Social Security Act, Section 1862(a)(1)(A) states that no Medicare payment shall be made for items or services which are not reasonable and necessary for the diagnosis or treatment of illness or injury

Title XVIII of the Social Security Act, Section 1862(a)(1)(D) states that no Medicare payment may be made for any expenses incurred for items or services that are investigational or experimental.

42 Code of Federal Regulations (CFR) section 410.32(d)(3) indicates diagnostic tests are payable only when the physician who is treating the beneficiary for a specific medical problem and who uses the results in such treatment.

CMS Publication 100-02, Medicare Benefit Policy Manual, Chapter 15,
80- laboratory services must meet applicable requirements of CLIA.

CMS, Publication 100-03, National Coverage Decisions
90.1- Pharmacogenomic Testing to Predict Warfarin Responsiveness

CMS, Publication 100-08, Medicare Program Integrity Manual, Chapter 3, Sections:
3.4.1.3, Diagnosis Code Requirement.
3.6.2.3, Limitation of Liability Determinations.
3.2.3.3 - Third-party Additional Documentation Request
3.2.3.7 - Special Provisions for Lab Additional Documentation Requests

Change Request 8567 SUBJECT: Healthcare Common Procedure Coding System (HCPCS) Codes Subject to and Excluded from Clinical Laboratory Improvement Amendments (CLIA) Edits

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

General Coverage Rules
We are aware that there remain numerous potentially medically reasonable and necessary "therapy-directing" genetic tests, either currently available or in the development "pipeline" for emerging use in the coming months and years. Many questions remain, among them the lack of – and difficulty in establishing – good medical literature support of medical necessity; lack of standardized testing protocols; lack of good data for establishing patient-selection criteria; absence of test-specific CPT coding, which we believe to be essential for future development of this potentially monumental enhancement to patient care. Providers are reminded that we will allow payment for such tests, either those currently available or those to be brought into use in the future, based on applicable approval such as FDA labeling, if such exists, CLIA and appropriate Medicare regulations and its standards of medical reasonableness and necessity.

Although there are still many unanswered questions regarding optimal clinical management of patients with inherited cancer-predisposing gene mutations, there is increasing data documenting potential benefits from increased surveillance, prophylactic surgery, hormonal manipulation, and changes in chemotherapy. Individuals who are carriers of a mutation, even if they have already been diagnosed and treated for a primary cancer, can be provided with additional information regarding their risk for further disease development and possible treatment and surveillance options.

For the covered syndromes noted below, those individuals who are determined not to be carriers may be prevented from undergoing unnecessary prophylactic surgery such as total versus partial colectomy, mastectomy, hysterectomy, and oophorectomy. Frequency of surveillance procedures (mammography, colonoscopy, etc.) may be affected depending on the presence or absence of a mutation.

1. Genetic tests for cancer are only a covered benefit for a **beneficiary with a personal history** of an illness, injury, or signs/symptoms thereof (i.e. clinically affected). A person with a personal history of a relevant cancer is a clinically affected person, even if the cancer is considered cured. Genetic testing is considered a non-covered screening test for patients unaffected by a relevant illness, injury, or signs/symptoms thereof.

2. Predictive or pre-symptomatic genetic tests and services, in the absence of past or present illness in the beneficiary, are **not** covered under national Medicare rules. For example, Medicare does not cover genetic tests based on family history alone.

3. A covered genetic test must be used to manage a patient. Medicare does not cover a genetic test for a clinically affected individual for purposes of medical research, family planning, disease risk assessment of other family members, when the treatment and surveillance of the beneficiary will not be affected or in any other circumstance that does not directly affect the diagnosis or treatment of the beneficiary.

4. The results of the genetic test should affect at least one of the management options considered by the referring physician in accordance with accepted standards of medical care (e.g. surgery, the extent of surgery, a change in surveillance, hormonal manipulation, or a change from standard therapeutic or adjuvant chemotherapy).

Genetic analysis must be provided through a laboratory which meets the following criteria:

1. The lab must meet appropriate Clinical Laboratory Improvement Amendment (CLIA) 1988 regulations;

2. Successful participation in the American College of Medical Genetics (ACMG)/College of American Pathologists (CAP) inspection and survey program;

3. Appropriate state licensing; and

4. the laboratory director must hold an earned doctoral degree in a chemical, physical, biological or clinical laboratory science from an accredited institution and be certified and continue to be certified by a board approved by HHS.

I. **Hereditary Breast and Ovarian Cancer Syndromes**

Families can be suspected of having hereditary breast or ovarian cancer based on occurrence at an early age, in multiple generations, often bilaterally, and in a pattern suggesting an autosomal dominant pattern of inheritance. The susceptibility may be transmitted through the maternal or paternal side of the family.

Germ-line alterations in two genes, BRCA1 and BRCA2, are associated with an increased risk of breast and ovarian cancer. Alterations in BRCA1 and BRCA2 explain many, but not all, of inherited forms of breast and ovarian cancer. With the identification of BRCA1 and BRCA2, it is now possible to test for abnormalities in the genes to provide information on the future risk of cancer and to make important treatment decisions in affected individuals.

Approximately five- to ten-percent of all breast cancers, and a similarly small percentage of ovarian cancers, are attributed to dominantly inherited susceptibility. Families at high risk of harboring a BRCA1 or BRCA2 mutation are those in which the incidence of breast or ovarian cancer suggests an autosomal dominant inheritance (50% chance of inheriting the disease causing mutation from an affected parent).

Men rarely develop breast cancer and, thus, there may not be an affected first-degree relative, and the size of the family may not permit analysis of possible autosomal dominant inheritance.

In patients with breast or ovarian cancer who are from high-risk families without a known BRCA1 or BRCA2 gene, the entirety of both genes must be analyzed to identify possible mutations. In those families with a known BRCA1 or BRCA2 gene mutation, only a single mutation site sequence is required. In the case of individuals with Ashkenazi Jewish ancestry, testing for 3 mutations common in this population may be warranted even after a single mutation has been identified in their family member. Then if negative, one should consider comprehensive ("Reflex") testing based on assessment of individual and family history as if the individual is of non-Ashkenazi Jewish descent.

Testing of unaffected family members or other individuals - not diagnosed with cancer - is considered by Medicare to be screening and is not payable under the Medicare program.

Invasive and ductal carcinoma in situ (DCIS) breast cancers are included. Comprehensive genetic testing of BRCA1 and BRCA2 includes full sequencing and detection of large genomic rearrangements.

BRCA1 and BRCA2 genetic testing is covered for a beneficiary who has or has had:

1. Breast cancer.

2. Epithelial ovarian/fallopian tube/primary peritoneal cancer.

II. **Hereditary Colorectal and Endometrial Cancer Syndromes**

Hereditary nonpolyposis colorectal cancer (HNPCC) or Lynch Syndrome is an autosomal dominant syndrome that accounts for about 3-5% of colorectal cancer cases. HNPCC syndrome mutations occur in the following genes: hMLH1, hMSH2, hMSH6, PMS2 and EPCAM. Colorectal cancers associated with Lynch syndrome occur at a younger age (average age of onset between 44-61 years of age) compared with the more common colorectal cancers typically found during the seventh decade of life.

Other Lynch syndrome-associated cancers include endometrial, ovarian, gastric, pancreas, ureter and renal pelvis, biliary tract, brain (usually glioblastoma, and small intestine cancers, as well as sebaceous gland adenomas/carcinomas and keratoacanthomas (AKs). Female carriers of a specific Lynch gene mutation have up to a 71% risk of endometrial cancer and 12% risk of ovarian cancer, in addition to the other Lynch syndrome cancer risks. Furthermore, gynecologic cancers may precede colorectal cancer in as many as 50% of female gene mutation carriers.

Inherited mutations in MLH1 and MSH2 account for the majority (~70%) of mutations detected with MSH6 and PMS2 found in the remainder of mutation positive cases. MSH6 mutations are responsible for approximately 15% of Lynch syndrome cases. Recent reports confirm that PMS2 mutations are a significant contributor to Lynch syndrome. Estimates of the proportion of Lynch syndrome cases due to PMS2 vary and are as high as 15%.

Familial Adenomatous Polyposis (FAP) is an autosomal dominant syndrome caused by a germ-line mutation of the APC gene. Characteristically, affected patients develop multiple adenomas diffusely throughout the colon beginning in their teens. Colorectal cancer is inevitable in patients with FAP if colectomy is not performed. The average age at symptomatic diagnosis ranges from 34 to 45 years of age. However, the average age of colonic adenoma appearance is 16 years and of cancer diagnosis is 39 years. The FAP gene mutation occurs in approximately 1/10,000 - 1/30,000 live births in the United States, affects both sexes equally, and accounts for up to 1% of colorectal cancers.

MYH-associated polyposis (MAP) is an autosomal recessive syndrome linked to germ-line mutations of the MYH gene. The full clinical picture of MYH-associated polyposis (MAP) is incompletely understood at this time. Current evidence suggests it is associated with about 0.4-1.0% of colorectal cancers.

hMLH1, hMSH2, hMSH6 and PMS2 gene tests are covered to diagnose Lynch syndrome. hMLH1, hMSH2 and hMSH6 gene testing must be negative before a test for the less common PMS2 gene mutations is considered reasonable and necessary.

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 (see below). 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.

Amsterdam Criteria II (ACII)

There should be at least three relatives with CRC or with a Lynch syndrome-associated cancer: endometrial, small bowel, ureter or renal pelvis cancer.

- One relative should be a 1st-degree relative of the other two,
- At least two successive generations should be affected,
- At least one tumor should be diagnosed before age 50 years,
- FAP should be excluded in the CRC case, if any,
- Tumors should be verified by histopathological exam

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 (see below) 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.

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, MSH6M* and *PMS2*).

DNA from paraffin-embedded tumor tissue and normal tissue or peripheral blood is used for MSI analysis. A microsatellite is considered unstable if the distribution of the tumor fragments differs from that of the normal tissue. Noncancerous tissue in individuals with LS does not show MSI because normal tissue is heterozygous for the germ-line mutation.

Levels of MSI in colon tumors are classified as:
- MSI-H> - 30% or more of a tumor's markers are unstable;

- MSI-L - > one but < 30% of a tumor's markers are unstable;

- MSS - no loci are unstable.

MSI-L and MSS indicates the MMR mechanism is functioning adequately. Virtually all CRC tumors from individuals with LS demonstrate MSI-H. However, MSI-H is NOT diagnostic of LS as MSI-H can be observed in roughly 15% of sporadic colorectal cancers. In other Lynch tumors, the % 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 BRAFM mutation and MLH1 PHM are very seldom seen in LS. BRAF mutation testing of the CRC tumor is associated with the presence of an epigenetic alteration (i.e., hypermethylation of MLH1) and either finding excludes germ-line MMR gene mutation (eg., LS).

Step 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 PMH identify dMMR which will most often be sporadic, but its presence does not fully rule out LS. However, there have been rare reports of MLH1 hypermethylation as a second hit in LS and there are new reports of constitutional MLH1 methylation. As a rule, discovery of MLH1 PHM indicates the tumor is not due to Lynch syndrome.

The following combinations of BRAF and MLH1 promoter methylation test results direct further testing in individuals with CRCs with loss of IHC expression of MLH1/PMS2:
- If BRAF mutation is present, no further testing is medically necessary; LS is ruled out.

- If BRAF mutation is absent, MLH1 promoter methylation testing is indicated and directs the following testing:

- If MKH1 is hypermethylated, germline MLH1 is not medically necessary.

- If the MLH1 promoter is hypermethylated and 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 prescreening 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: PMS2Testing
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.

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 by Medicare for the following indications:

- Individual with colorectal or endometrial cancer whose family meets the ACII or revised Bethesda guidelines, OR

- Individual with endometrial cancer diagnosed before age 50.
  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 Germ-line Gene Mutation Testing Exception
If a lab is unable to perform the stepped testing approach outlined in this LCD, multiple germ-line gene testing will be covered by Medicare only for one or more of the following findings:

- MSI/IHC testing yields normal IHC and MSI-H, suggesting LS

- If tumor is not available or determined by a pathologist to be inadequate to assess DNA MMR deficiency by MSI or IHC, then MMR germ-line testing can be conducted on blood 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 LS.

Note: This LCD does not imply that testing family members of a known familial variant is not medically warranted. The scope of the Medicare benefit requires the beneficiary to have signs and symptoms of disease. Coverage of molecular testing for LS for carrier status or family studies is considered screening and is statutorily excluded from coverage.

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 Medicare 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 Medicare benefit.

III. **Familial Adenomatous Polyposis (FAP)**
APC and MYH gene testing for Familial Adenomatous Polyposis (FAP), Attenuated FAP (AFAP), or MYH associated polyposis (MAP) is covered for the following individuals:

1. A beneficiary with ≥ 10 cumulative colorectal adenomas over a lifetime.

2. Testing for APC gene mutations should precede testing for the less common MYH mutation

IV. **Chronic Myeloproliferative Disorder**
JAK2 testing is appropriate in patients with signs or symptoms suggesting an underlying chronic myeloproliferative disorder, including increased red-cell mass, increased platelets, unexplained persistent peripheral cytopenia or cytosis, unexplained peripheral or hepatic vein thrombosis (Budd- Chiari Syndrome) or bone marrow examination showing features of a chronic myeloproliferative disorder. Documentation must also indicate that the provider anticipates that the test result is likely to be of use in management of the condition.

V. **Hematologic Disorders**
The **BCR/ABL fusion** gene is the classic mutation seen in Chronic Myelogenous Leukemia (CML). It could also be seen in Acute Lymphocytic Leukemia (ALL), Lymphoma and certain other hematologic diseases.

VI. **Therapy Directing Treatment**

KRAS Testing
Literature supports coverage for KRAS testing use in patients with metastatic colorectal cancer for whom either cetuximab (Erbitux) or panitumumab (Vectibix) therapy is contemplated as being appropriate.

We will cover KRAS testing (variants exon 2) **or** a KRAS additional variant(s) test. It is not medically necessary to perform both of these tests. Only one of these tests will be allowed.

EGFR Testing
Epidermal growth factor receptor (EGFR) mutation testing is indicated for patients with NSCLC who are being considered for first-line therapy with an EGFR tyrosine kinase inhibitor (TKI), i.e., for patients who have not previously received chemotherapy or an EGFR TKI, should have their tumor tested for EGFR mutations to determine whether an EGFR TKI or chemotherapy is the appropriate first-line therapy.

HLA-B57:01 Testing
The Department of Health and Human Services (DHHS) Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) is a working group of the Office of AIDS Research Advisory Council (OARAC). The Panel recommends HLA-B5701 testing prior to initiating abacavir therapy to reduce the risk of hypersensitivity reaction. HLA-B:57:01-positive patients should not be prescribed abacavir, and the positive status should be recorded as an abacavir allergy in the patient's medical record (All). Based on this recommendation, this testing is included in the list of covered Genetic Tests under this LCD.

HLA-B57:01 testing is covered prior to initiating abacavir therapy in patients with either Human Immunodeficiency Virus (HIV) disease or Asymptomatic Human Immunodeficiency virus (HIV) infection.

Cyp2d6 Testing- is covered to guide treatment and /or dosing for individuals for whom initial therapy is planned with Amitriptyline or nortriptyline for treatment of depressive disorders, and Tetrabenazine for doses greater than 50- mg per day, or re-initiation of therapy with doses greater than 50 mg per day.

There is insufficient evidence that this gene impacts clinical outcomes for antidepressants other than those listed above, antipsychotics, codeine, donepezil, galantamine and tamoxifen, and testing is considered investigational at this time.

BRAF V600 Testing
Testing is covered for unresectable or metastatic melanoma and plan on using vemurafenib, dabrafenib and trametinib.

Limitations
As noted in each major section below providers are once again reminded:
The clinical information preceding this statement notwithstanding, testing of unaffected family members or other individuals is considered by Medicare to be screening and is not payable under the Medicare program.

Compliance with the provisions in this policy is subject to monitoring by post payment data analysis and subsequent medical review. Title XVIII of the Social Security Act, Section 1862(a)(1)(A) states " ...no Medicare payment shall be made for items or services which are not reasonable and necessary for the diagnosis and treatment of illness or injury...".

It has been longstanding CMS policy that "tests that are performed in the absence of signs, symptoms, complaints, or personal history of disease or injury are not covered unless explicitly authorized by statute". **Screening services**, such as pre-symptomatic genetic tests and services, are those used to detect an undiagnosed disease or disease predisposition, and as such are not a Medicare benefit and not covered by Medicare. Tests for Quality Control/Quality Assurance (QA/QC), i.e., tests performed to ensure a tissue specimen matches the patient are not covered.

Medicare may not reimburse the costs of tests/examinations that assess the risk for and/or of a condition unless the risk assessment clearly and directly effects the management of the patient.

Medicare does cover a broad range of legislatively mandated **preventive services** to prevent disease, detect disease early when it is most treatable and curable, and manage disease so that complications can be avoided. These services can be found on the CMS website. Any preventive services and tests not listed on the CMS Preventive Services webpage are considered non-covered screening (preventive) tests or services which are not a benefit of the Medicare program.

Testing in the absence of symptoms or disease is considered screening and is not payable.
See our Billing and Coding Guidelines for tests currently considered to be screening and are not covered.

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Coding Information

Bill Type Codes:

Contractors may specify Bill Types to help providers identify those Bill Types typically used to report this service. Absence of a Bill Type does not guarantee that the policy does not apply to that Bill Type. Complete absence of all Bill Types indicates that coverage is not influenced by Bill Type and the policy should be assumed to apply equally to all claims.

N/A
Revenue Codes:

Contractors may specify Revenue Codes to help providers identify those Revenue Codes typically used to report this service. In most instances Revenue Codes are purely advisory. Unless specified in the policy, services reported under other Revenue Codes are equally subject to this coverage determination. Complete absence of all Revenue Codes indicates that coverage is not influenced by Revenue Code and the policy should be assumed to apply equally to all Revenue Codes.

N/A
CPT/HCPCS Codes
Group 1 Paragraph: Note: Tier 2 and above can be used for testing of many different genes as a result these claims are subject to review and are not limited to the dx codes listed below.

Group 1 Codes:
81162 Brca1&2 seq & full dup/del
81201 Apc gene full sequence
81202 Apc gene known fam variants
81203 Apc gene dup/delet variants
81206 Bcr/abl1 gene major bp

81207 Bcr/abl1 gene minor bp
81208 Bcr/abl1 gene other bp
81210 Braf gene
81211 Brca1&2 seq & com dup/del
81212 Brca1&2 185&5385&6174 var
81213 Brca1&2 uncom dup/del var
81214 Brca1 full seq & com dup/del
81215 Brca1 gene known fam variant
81217 Brca2 gene known fam variant
81226 Cyp2d6 gene com variants
81235 Egfr gene com variants
81270 Jak2 gene
81275 Kras gene variants exon 2
81276 Kras gene addl variants
81292 Mlh1 gene full seq
81293 Mlh1 gene known variants
81294 Mlh1 gene dup/delete variant
81295 Msh2 gene full seq
81296 Msh2 gene known variants
81297 Msh2 gene dup/delete variant
81298 Msh6 gene full seq
81299 Msh6 gene known variants
81300 Msh6 gene dup/delete variant
81301 Microsatellite instability
81317 Pms2 gene full seq analysis
81318 Pms2 known familial variants
81319 Pms2 gene dup/delet variants
81381 Hla i typing 1 allele hr
81403 Mopath procedure level 4
81405 Mopath procedure level 6
81406 Mopath procedure level 7
88341 Immunohisto antb addl slide
88342 Immunohisto antb 1st stain
88363 Xm archive tissue molec anal

ICD-10 Codes that Support Medical Necessity
Group 1 Paragraph: CPT codes 81201, 81202, 81203 81210, 81292, 81293, 81294, 81295, 81296, 81297, 81298, 81299, 81300, 81317, 81318, 81319, and 81403, 81405, 81406 (that meet coverage criteria as indications for testing for lynch syndrome).

Z86.010 should be used to denote any of the polyposis conditions as described under Indications and Limitations section.

81210 will also be covered for (C43.0, C43.11, C43.12, C43.21, C43.22, C43.31, C43.39, C43.4, C43.51, C43.52, C43.59, C43.61, C43.62, C43.71, C43.72, C43.8, D03.0, D03.11, D03.12, D03.21, D03.22, D03.39, D03.4, D03.51, D03.52, D03.59, D03.61, D03.62, D03.71, D03.72, D03.8).

Group 1 Codes:

ICD-10 Codes	Description
C16.0	Malignant neoplasm of cardia
C16.1	Malignant neoplasm of fundus of stomach
C16.2	Malignant neoplasm of body of stomach
C16.3	Malignant neoplasm of pyloric antrum
C16.4	Malignant neoplasm of pylorus
C16.5	Malignant neoplasm of lesser curvature of stomach, unspecified
C16.6	Malignant neoplasm of greater curvature of stomach, unspecified
C16.8	Malignant neoplasm of overlapping sites of stomach

ICD-10 Codes	Description
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
C43.0*	Malignant melanoma of lip
C43.11*	Malignant melanoma of right eyelid, including canthus
C43.12*	Malignant melanoma of left eyelid, including canthus
C43.21*	Malignant melanoma of right ear and external auricular canal
C43.22*	Malignant melanoma of left ear and external auricular canal
C43.31*	Malignant melanoma of nose
C43.39*	Malignant melanoma of other parts of face
C43.4*	Malignant melanoma of scalp and neck
C43.51*	Malignant melanoma of anal skin
C43.52*	Malignant melanoma of skin of breast
C43.59*	Malignant melanoma of other part of trunk
C43.61*	Malignant melanoma of right upper limb, including shoulder
C43.62*	Malignant melanoma of left upper limb, including shoulder
C43.71*	Malignant melanoma of right lower limb, including hip
C43.72*	Malignant melanoma of left lower limb, including hip
C43.8*	Malignant melanoma of overlapping sites of skin
C45.1	Mesothelioma of peritoneum

ICD-10 Codes	Description
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
D03.0*	Melanoma in situ of lip
D03.11*	Melanoma in situ of right eyelid, including canthus
D03.12*	Melanoma in situ of left eyelid, including canthus
D03.21*	Melanoma in situ of right ear and external auricular canal
D03.22*	Melanoma in situ of left ear and external auricular canal
D03.39*	Melanoma in situ of other parts of face
D03.4*	Melanoma in situ of scalp and neck
D03.51*	Melanoma in situ of anal skin
D03.52*	Melanoma in situ of breast (skin) (soft tissue)
D03.59*	Melanoma in situ of other part of trunk
D03.61*	Melanoma in situ of right upper limb, including shoulder
D03.62*	Melanoma in situ of left upper limb, including shoulder
D03.71*	Melanoma in situ of right lower limb, including hip

ICD-10 Codes	Description
D03.72*	Melanoma in situ of left lower limb, including hip
D03.8*	Melanoma in situ of other sites
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 Medical Necessity ICD-10 Codes Asterisk Explanation: ***C43.0, C43.11, C43.12, C43.21, C43.22, C43.31, C43.39, C43.4, C43.51, C43.52, C43.59, C43.61, C43.62, C43.71, C43.72, C43.8, D03.0, D03.11, D03.12, D03.21, D03.22, D03.39, D03.4, D03.51, D03.52, D03.59, D03.61, D03.62, D03.71, D03.72, D03.8 are only covered for 81210

Group 2 Paragraph: 81301

Group 2 Codes:

ICD-10 Codes	Description
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
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

Group 3 Paragraph: CPT codes CPT codes 81162, 81211, 81212, 81213, 81214, 81215 and 81217 and meet the coverage criteria for BRCA1 and BRCA2 gene mutation testing.

Group 3 Codes:

ICD-10 Codes	Description
C45.1	Mesothelioma of peritoneum
C48.0	Malignant neoplasm of retroperitoneum
C48.1	Malignant neoplasm of specified parts of peritoneum
C48.8	Malignant neoplasm of overlapping sites of retroperitoneum and peritoneum
C50.011	Malignant neoplasm of nipple and areola, right female breast
C50.012	Malignant neoplasm of nipple and areola, left female breast
C50.021	Malignant neoplasm of nipple and areola, right male breast
C50.022	Malignant neoplasm of nipple and areola, left male breast
C50.111	Malignant neoplasm of central portion of right female breast
C50.112	Malignant neoplasm of central portion of left female breast
C50.121	Malignant neoplasm of central portion of right male breast
C50.122	Malignant neoplasm of central portion of left male breast
C50.211	Malignant neoplasm of upper-inner quadrant of right female breast
C50.212	Malignant neoplasm of upper-inner quadrant of left female breast
C50.221	Malignant neoplasm of upper-inner quadrant of right male breast
C50.222	Malignant neoplasm of upper-inner quadrant of left male breast
C50.311	Malignant neoplasm of lower-inner quadrant of right female breast
C50.312	Malignant neoplasm of lower-inner quadrant of left female breast
C50.321	Malignant neoplasm of lower-inner quadrant of right male breast

ICD-10 Codes	Description
C50.322	Malignant neoplasm of lower-inner quadrant of left male breast
C50.411	Malignant neoplasm of upper-outer quadrant of right female breast
C50.412	Malignant neoplasm of upper-outer quadrant of left female breast
C50.421	Malignant neoplasm of upper-outer quadrant of right male breast
C50.422	Malignant neoplasm of upper-outer quadrant of left male breast
C50.511	Malignant neoplasm of lower-outer quadrant of right female breast
C50.512	Malignant neoplasm of lower-outer quadrant of left female breast
C50.521	Malignant neoplasm of lower-outer quadrant of right male breast
C50.522	Malignant neoplasm of lower-outer quadrant of left male breast
C50.611	Malignant neoplasm of axillary tail of right female breast
C50.612	Malignant neoplasm of axillary tail of left female breast
C50.621	Malignant neoplasm of axillary tail of right male breast
C50.622	Malignant neoplasm of axillary tail of left male breast
C50.811	Malignant neoplasm of overlapping sites of right female breast
C50.812	Malignant neoplasm of overlapping sites of left female breast
C50.821	Malignant neoplasm of overlapping sites of right male breast
C50.822	Malignant neoplasm of overlapping sites of left male breast
C50.911	Malignant neoplasm of unspecified site of right female breast
C50.912	Malignant neoplasm of unspecified site of left female breast
C50.921	Malignant neoplasm of unspecified site of right male breast
C50.922	Malignant neoplasm of unspecified site of left male breast
C56.1	Malignant neoplasm of right ovary
C56.2	Malignant neoplasm of left ovary
C57.01	Malignant neoplasm of right fallopian tube
C57.02	Malignant neoplasm of left fallopian tube
D05.01	Lobular carcinoma in situ of right breast
D05.02	Lobular carcinoma in situ of left breast
D05.11	Intraductal carcinoma in situ of right breast
D05.12	Intraductal carcinoma in situ of left breast
D05.81	Other specified type of carcinoma in situ of right breast
D05.82	Other specified type of carcinoma in situ of left breast
D05.91	Unspecified type of carcinoma in situ of right breast
D05.92	Unspecified type of carcinoma in situ of left breast
Z85.3	Personal history of malignant neoplasm of breast
Z85.43	Personal history of malignant neoplasm of ovary

Group 4 Paragraph: CPT 81235

Group 4 Codes:

ICD-10 Codes	Description
C33	Malignant neoplasm of trachea
C34.01	Malignant neoplasm of right main bronchus
C34.02	Malignant neoplasm of left main bronchus
C34.11	Malignant neoplasm of upper lobe, right bronchus or lung
C34.12	Malignant neoplasm of upper lobe, left bronchus or lung
C34.2	Malignant neoplasm of middle lobe, bronchus or lung
C34.31	Malignant neoplasm of lower lobe, right bronchus or lung
C34.32	Malignant neoplasm of lower lobe, left bronchus or lung
C34.81	Malignant neoplasm of overlapping sites of right bronchus and lung
C34.82	Malignant neoplasm of overlapping sites of left bronchus and lung
C34.91	Malignant neoplasm of unspecified part of right bronchus or lung
C34.92	Malignant neoplasm of unspecified part of left bronchus or lung
C38.4	Malignant neoplasm of pleura
C45.0	Mesothelioma of pleura

Group 5 Paragraph: CPT codes 81270 and 81403 (that meet coverage criteria for JAK2 testing).

Group 5 Codes:

ICD-10 Codes	Description
C88.8	Other malignant immunoproliferative diseases
C91.00	Acute lymphoblastic leukemia not having achieved remission
C91.10	Chronic lymphocytic leukemia of B-cell type not having achieved remission
C91.11	Chronic lymphocytic leukemia of B-cell type in remission
C91.12	Chronic lymphocytic leukemia of B-cell type in relapse
C92.00	Acute myeloblastic leukemia, not having achieved remission
C92.10	Chronic myeloid leukemia, BCR/ABL-positive, not having achieved remission
C92.40	Acute promyelocytic leukemia, not having achieved remission
C92.50	Acute myelomonocytic leukemia, not having achieved remission
C92.60	Acute myeloid leukemia with 11q23-abnormality not having achieved remission
C92.A0	Acute myeloid leukemia with multilineage dysplasia, not having achieved remission
C94.40	Acute panmyelosis with myelofibrosis not having achieved remission
C94.41	Acute panmyelosis with myelofibrosis, in remission
C94.42	Acute panmyelosis with myelofibrosis, in relapse
C94.6	Myelodysplastic disease, not classified
D45	Polycythemia vera
D46.Z	Other myelodysplastic syndromes
D46.9	Myelodysplastic syndrome, unspecified
D47.1	Chronic myeloproliferative disease
D47.3	Essential (hemorrhagic) thrombocythemia
D47.Z9	Other specified neoplasms of uncertain behavior of lymphoid, hematopoietic and related tissue
D47.9	Neoplasm of uncertain behavior of lymphoid, hematopoietic and related tissue, unspecified
D48.9	Neoplasm of uncertain behavior, unspecified
I82.0	Budd-Chiari syndrome

Group 6 Paragraph: CPT code 81381 when meeting coverage criteria

Group 6 Codes:

ICD-10 Codes	Description
B20	Human immunodeficiency virus [HIV] disease
Z21	Asymptomatic human immunodeficiency virus [HIV] infection status

Group 7 Paragraph: Multiple codes exist for the various molecular tests for lymphoma and leukemia. The appropriate code should be selected from the most current manual. The following diagnosis codes meet coverage criteria as indications for molecular testing of lymphoma and leukemia, so long as documentation of medical necessity for the specific test in question is present in the medical record, as noted elsewhere in this LCD. 81206, 81207, 81208 and 81403 (that meet coverage criteria as indications for testing for BCR/ABL fusion gene).

Group 7 Codes:

ICD-10 Codes	Description
C82.00	Follicular lymphoma grade I, unspecified site
C82.01	Follicular lymphoma grade I, lymph nodes of head, face, and neck
C82.02	Follicular lymphoma grade I, intrathoracic lymph nodes
C82.03	Follicular lymphoma grade I, intra-abdominal lymph nodes
C82.04	Follicular lymphoma grade I, lymph nodes of axilla and upper limb
C82.05	Follicular lymphoma grade I, lymph nodes of inguinal region and lower limb
C82.06	Follicular lymphoma grade I, intrapelvic lymph nodes
C82.07	Follicular lymphoma grade I, spleen
C82.08	Follicular lymphoma grade I, lymph nodes of multiple sites
C82.09	Follicular lymphoma grade I, extranodal and solid organ sites
C82.11	Follicular lymphoma grade II, lymph nodes of head, face, and neck
C82.12	Follicular lymphoma grade II, intrathoracic lymph nodes
C82.13	Follicular lymphoma grade II, intra-abdominal lymph nodes
C82.14	Follicular lymphoma grade II, lymph nodes of axilla and upper limb
C82.15	Follicular lymphoma grade II, lymph nodes of inguinal region and lower limb
C82.16	Follicular lymphoma grade II, intrapelvic lymph nodes
C82.17	Follicular lymphoma grade II, spleen

ICD-10 Codes	Description
C82.18	Follicular lymphoma grade II, lymph nodes of multiple sites
C82.19	Follicular lymphoma grade II, extranodal and solid organ sites
C82.23	Follicular lymphoma grade III, unspecified, intra-abdominal lymph nodes
C82.27	Follicular lymphoma grade III, unspecified, spleen
C82.28	Follicular lymphoma grade III, unspecified, lymph nodes of multiple sites
C82.29	Follicular lymphoma grade III, unspecified, extranodal and solid organ sites
C82.31	Follicular lymphoma grade IIIa, lymph nodes of head, face, and neck
C82.32	Follicular lymphoma grade IIIa, intrathoracic lymph nodes
C82.33	Follicular lymphoma grade IIIa, intra-abdominal lymph nodes
C82.34	Follicular lymphoma grade IIIa, lymph nodes of axilla and upper limb
C82.35	Follicular lymphoma grade IIIa, lymph nodes of inguinal region and lower limb
C82.36	Follicular lymphoma grade IIIa, intrapelvic lymph nodes
C82.37	Follicular lymphoma grade IIIa, spleen
C82.38	Follicular lymphoma grade IIIa, lymph nodes of multiple sites
C82.39	Follicular lymphoma grade IIIa, extranodal and solid organ sites
C82.41	Follicular lymphoma grade IIIb, lymph nodes of head, face, and neck
C82.42	Follicular lymphoma grade IIIb, intrathoracic lymph nodes
C82.43	Follicular lymphoma grade IIIb, intra-abdominal lymph nodes
C82.44	Follicular lymphoma grade IIIb, lymph nodes of axilla and upper limb
C82.45	Follicular lymphoma grade IIIb, lymph nodes of inguinal region and lower limb
C82.46	Follicular lymphoma grade IIIb, intrapelvic lymph nodes
C82.47	Follicular lymphoma grade IIIb, spleen
C82.48	Follicular lymphoma grade IIIb, lymph nodes of multiple sites
C82.49	Follicular lymphoma grade IIIb, extranodal and solid organ sites
C82.61	Cutaneous follicle center lymphoma, lymph nodes of head, face, and neck
C82.62	Cutaneous follicle center lymphoma, intrathoracic lymph nodes
C82.63	Cutaneous follicle center lymphoma, intra-abdominal lymph nodes
C82.64	Cutaneous follicle center lymphoma, lymph nodes of axilla and upper limb
C82.65	Cutaneous follicle center lymphoma, lymph nodes of inguinal region and lower limb
C82.66	Cutaneous follicle center lymphoma, intrapelvic lymph nodes
C82.67	Cutaneous follicle center lymphoma, spleen
C82.68	Cutaneous follicle center lymphoma, lymph nodes of multiple sites
C82.69	Cutaneous follicle center lymphoma, extranodal and solid organ sites
C82.81	Other types of follicular lymphoma, lymph nodes of head, face, and neck
C82.82	Other types of follicular lymphoma, intrathoracic lymph nodes
C82.83	Other types of follicular lymphoma, intra-abdominal lymph nodes
C82.84	Other types of follicular lymphoma, lymph nodes of axilla and upper limb
C82.85	Other types of follicular lymphoma, lymph nodes of inguinal region and lower limb
C82.86	Other types of follicular lymphoma, intrapelvic lymph nodes
C82.87	Other types of follicular lymphoma, spleen
C82.88	Other types of follicular lymphoma, lymph nodes of multiple sites
C82.89	Other types of follicular lymphoma, extranodal and solid organ sites
C82.91	Follicular lymphoma, unspecified, lymph nodes of head, face, and neck
C82.92	Follicular lymphoma, unspecified, intrathoracic lymph nodes
C82.93	Follicular lymphoma, unspecified, intra-abdominal lymph nodes
C82.94	Follicular lymphoma, unspecified, lymph nodes of axilla and upper limb
C82.95	Follicular lymphoma, unspecified, lymph nodes of inguinal region and lower limb
C82.96	Follicular lymphoma, unspecified, intrapelvic lymph nodes
C82.97	Follicular lymphoma, unspecified, spleen
C82.98	Follicular lymphoma, unspecified, lymph nodes of multiple sites
C82.99	Follicular lymphoma, unspecified, extranodal and solid organ sites
C83.11	Mantle cell lymphoma, lymph nodes of head, face, and neck
C83.12	Mantle cell lymphoma, intrathoracic lymph nodes
C83.13	Mantle cell lymphoma, intra-abdominal lymph nodes
C83.14	Mantle cell lymphoma, lymph nodes of axilla and upper limb
C83.15	Mantle cell lymphoma, lymph nodes of inguinal region and lower limb
C83.16	Mantle cell lymphoma, intrapelvic lymph nodes
C83.17	Mantle cell lymphoma, spleen

ICD-10 Codes	Description
C83.18	Mantle cell lymphoma, lymph nodes of multiple sites
C83.19	Mantle cell lymphoma, extranodal and solid organ sites
C83.31	Diffuse large B-cell lymphoma, lymph nodes of head, face, and neck
C83.32	Diffuse large B-cell lymphoma, intrathoracic lymph nodes
C83.33	Diffuse large B-cell lymphoma, intra-abdominal lymph nodes
C83.34	Diffuse large B-cell lymphoma, lymph nodes of axilla and upper limb
C83.35	Diffuse large B-cell lymphoma, lymph nodes of inguinal region and lower limb
C83.36	Diffuse large B-cell lymphoma, intrapelvic lymph nodes
C83.37	Diffuse large B-cell lymphoma, spleen
C83.38	Diffuse large B-cell lymphoma, lymph nodes of multiple sites
C83.39	Diffuse large B-cell lymphoma, extranodal and solid organ sites
C85.21	Mediastinal (thymic) large B-cell lymphoma, lymph nodes of head, face, and neck
C85.22	Mediastinal (thymic) large B-cell lymphoma, intrathoracic lymph nodes
C85.23	Mediastinal (thymic) large B-cell lymphoma, intra-abdominal lymph nodes
C85.24	Mediastinal (thymic) large B-cell lymphoma, lymph nodes of axilla and upper limb
C85.25	Mediastinal (thymic) large B-cell lymphoma, lymph nodes of inguinal region and lower limb
C85.26	Mediastinal (thymic) large B-cell lymphoma, intrapelvic lymph nodes
C85.27	Mediastinal (thymic) large B-cell lymphoma, spleen
C85.28	Mediastinal (thymic) large B-cell lymphoma, lymph nodes of multiple sites
C85.29	Mediastinal (thymic) large B-cell lymphoma, extranodal and solid organ sites
C91.00	Acute lymphoblastic leukemia not having achieved remission
C91.01	Acute lymphoblastic leukemia, in remission
C91.02	Acute lymphoblastic leukemia, in relapse
C91.10	Chronic lymphocytic leukemia of B-cell type not having achieved remission
C91.11	Chronic lymphocytic leukemia of B-cell type in remission
C91.12	Chronic lymphocytic leukemia of B-cell type in relapse
C91.30	Prolymphocytic leukemia of B-cell type not having achieved remission
C91.31	Prolymphocytic leukemia of B-cell type, in remission
C91.32	Prolymphocytic leukemia of B-cell type, in relapse
C91.50	Adult T-cell lymphoma/leukemia (HTLV-1-associated) not having achieved remission
C91.51	Adult T-cell lymphoma/leukemia (HTLV-1-associated), in remission
C91.52	Adult T-cell lymphoma/leukemia (HTLV-1-associated), in relapse
C91.60	Prolymphocytic leukemia of T-cell type not having achieved remission
C91.61	Prolymphocytic leukemia of T-cell type, in remission
C91.62	Prolymphocytic leukemia of T-cell type, in relapse
C91.A0	Mature B-cell leukemia Burkitt-type not having achieved remission
C91.A1	Mature B-cell leukemia Burkitt-type, in remission
C91.A2	Mature B-cell leukemia Burkitt-type, in relapse
C91.Z0	Other lymphoid leukemia not having achieved remission
C91.Z1	Other lymphoid leukemia, in remission
C91.Z2	Other lymphoid leukemia, in relapse
C91.90	Lymphoid leukemia, unspecified not having achieved remission
C91.91	Lymphoid leukemia, unspecified, in remission
C91.92	Lymphoid leukemia, unspecified, in relapse
C92.00	Acute myeloblastic leukemia, not having achieved remission
C92.01	Acute myeloblastic leukemia, in remission
C92.02	Acute myeloblastic leukemia, in relapse
C92.10	Chronic myeloid leukemia, BCR/ABL-positive, not having achieved remission
C92.11	Chronic myeloid leukemia, BCR/ABL-positive, in remission
C92.12	Chronic myeloid leukemia, BCR/ABL-positive, in relapse
C92.20	Atypical chronic myeloid leukemia, BCR/ABL-negative, not having achieved remission
C92.21	Atypical chronic myeloid leukemia, BCR/ABL-negative, in remission
C92.22	Atypical chronic myeloid leukemia, BCR/ABL-negative, in relapse
C92.30	Myeloid sarcoma, not having achieved remission
C92.31	Myeloid sarcoma, in remission
C92.32	Myeloid sarcoma, in relapse
C92.40	Acute promyelocytic leukemia, not having achieved remission
C92.41	Acute promyelocytic leukemia, in remission

ICD-10 Codes	Description
C92.42	Acute promyelocytic leukemia, in relapse
C92.50	Acute myelomonocytic leukemia, not having achieved remission
C92.51	Acute myelomonocytic leukemia, in remission
C92.52	Acute myelomonocytic leukemia, in relapse
C92.60	Acute myeloid leukemia with 11q23-abnormality not having achieved remission
C92.61	Acute myeloid leukemia with 11q23-abnormality in remission
C92.62	Acute myeloid leukemia with 11q23-abnormality in relapse
C92.A0	Acute myeloid leukemia with multilineage dysplasia, not having achieved remission
C92.A1	Acute myeloid leukemia with multilineage dysplasia, in remission
C92.A2	Acute myeloid leukemia with multilineage dysplasia, in relapse
C92.Z0	Other myeloid leukemia not having achieved remission
C92.Z1	Other myeloid leukemia, in remission
C92.Z2	Other myeloid leukemia, in relapse
C92.90	Myeloid leukemia, unspecified, not having achieved remission
C92.91	Myeloid leukemia, unspecified in remission
C92.92	Myeloid leukemia, unspecified in relapse
C93.00	Acute monoblastic/monocytic leukemia, not having achieved remission
C93.01	Acute monoblastic/monocytic leukemia, in remission
C93.02	Acute monoblastic/monocytic leukemia, in relapse
C93.10	Chronic myelomonocytic leukemia not having achieved remission
C93.11	Chronic myelomonocytic leukemia, in remission
C93.12	Chronic myelomonocytic leukemia, in relapse
C93.30	Juvenile myelomonocytic leukemia, not having achieved remission
C93.31	Juvenile myelomonocytic leukemia, in remission
C93.32	Juvenile myelomonocytic leukemia, in relapse
C93.Z0	Other monocytic leukemia, not having achieved remission
C93.Z1	Other monocytic leukemia, in remission
C93.Z2	Other monocytic leukemia, in relapse
C93.90	Monocytic leukemia, unspecified, not having achieved remission
C93.91	Monocytic leukemia, unspecified in remission
C93.92	Monocytic leukemia, unspecified in relapse
C95.00	Acute leukemia of unspecified cell type not having achieved remission
C95.01	Acute leukemia of unspecified cell type, in remission
C95.02	Acute leukemia of unspecified cell type, in relapse
C95.10	Chronic leukemia of unspecified cell type not having achieved remission
C95.11	Chronic leukemia of unspecified cell type, in remission
C95.12	Chronic leukemia of unspecified cell type, in relapse
C95.90	Leukemia, unspecified not having achieved remission
C95.91	Leukemia, unspecified, in remission
C95.92	Leukemia, unspecified, in relapse
D72.828	Other elevated white blood cell count
D72.89	Other specified disorders of white blood cells

ICD-10 Codes that DO NOT Support Medical Necessity
Group 1 Paragraph: NA

Group 1 Codes: N/A

ICD-10 Additional Information

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General Information

Associated Information

Documentations Requirements

Documentation does not need to be sent in with the initial claim unless you receive an additional documentation Request, (ADR). Documentation must be adequate to verify that coverage guidelines listed in this LCD have been met. The documentation, which must be made available upon request from the laboratory or billing provider, must include personal and family history information consistent with this policy.

The laboratory or billing provider must have on file the physician requisition which sets forth the diagnosis or condition (diagnosis code) that warrants the test. The documentation must be made available from the billing provider (i.e. the laboratory) upon request by the contractor.

Third-party Additional Documentation Request (IOM 100-08) 3.2.3.3:
We will *request information from the billing provider/supplier. The treating physician, another clinician, provider, or supplier should submit the requested documentation. However, because the provider selected for review is the one whose payment is at risk, it is this provider who is ultimately responsible for submitting, within the established timelines, the documentation requested.*

Special Provisions for Lab Additional Documentation Requests (IOM 100-08, 3.2.3.7)
The following documentation shall be requested from the billing lab:

- *The order for the service billed (including sufficient information to allow the reviewer to identify and contact the ordering provider);*
- *Verification of accurate processing of the order and submission of the claim; and*
- *Diagnostic or other medical information supplied to the lab by the ordering provider, including any ICD-10 codes or narratives.*

The contractor shall deny the claim if a benefit category, statutory exclusion, or coding issue is in question, or send an ADR to the ordering provider in order to determine medical necessity. The contractor shall review information from the lab and find it insufficient before the ordering provider is contacted. The contractor shall send an ADR to the ordering provider that shall include sufficient information to identify the claim in question.

If the documentation received does not demonstrate that the service was reasonable and necessary, the contractor shall deny the claim. Beneficiaries cannot be held liable for these denials unless they have received proper liability notification before services were rendered.

The medical record must contain documentation that the testing is expected to influence treatment of the condition toward which the testing is directed. Providers are also reminded that all such claims may be subject to post pay review.

Documentation will be requested for BRCA1, BRCA2 (breast cancer 1 and 2) full sequence analysis and full duplication/deletion analysis. The documentation should support that a **full** sequence and a **full** duplication/deletion analysis was performed.

Utilization Guidelines

Genetic testing is considered a screening test for unaffected patients. **Medicare does not cover** these **screening tests**. Predictive and pre-symptomatic genetic tests and services are not covered.

A specific genetic test may only be performed **once in a lifetime** per beneficiary for inherited conditions; however, when medically reasonable and necessary, genetic testing may be done on acquired conditions such as malignancies (including separate malignancies developing at different times) as they are treated and are being followed, in order to assess response or other relevant clinical criteria. **Likewise**, there are situations where medical record and literature documentation are able to demonstrate that serial testing can be reasonably predicted to provide additional clinically useful information. When the record documents that this information, such as confirmed significant response to current therapy, is likely to assist in modifying treatment, serial testing can be considered reasonable and necessary and eligible for coverage.

Sources of Information and Basis for Decision

Chin, K., Wessler, B., Chew, P., & et al. (January, 2006) Technology assessment, genetic tests for cancer; Agency for Healthcare Research and Quality (AHRQ).

Genetic counseling, and genetic testing for BRCA-related cancer in women: U.S. preventive services task force

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Judkins, T., Rosenthal, E., Arnell, C., & et al. (April, 2012). Clinical significance of large rearrangements in BRCA1 and BRCA2. *Cancer*, 5210-5216.

Nelson, H., Huffman, L., Fu, R., & et al (September, 2005). Genetic risk assessment and BRCA mutation testing for breast and ovarian cancer susceptibility: evidence synthesis.

Palma, M., Domchek, S., Stopfer, J., & et al, (2008). The relative contribution of point mutations and genomic rearrangements in BRCA1 and BRCA2 in high-risk breast cancer families. *Cancer Research*. 68(17):7006-14.

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Smith, L., Tesoriero, A., Wong, E., & et al. (2011). Contribution of large genomic BRCA1 alterations to early-onset breast cancer selected for family history and tumour morphology: a report from The Breast Cancer Family Registry. *Breast Cancer Research*, 13(1):R14.

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Revision History Information

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

Revision History Date	Revision History Number	Revision History Explanation	Reason(s) for Change
01/01/2016	R8	01/01/2016- Code update- Added new codes 81276 & 81162 ; 81162 was added to paragraph 3 dx codes: C45.1, C48.0, C48.1, C48.8, C50.011, C50.012, C50.021, C50.022, C50.111, C50.112, C50.121, C50.122, C50.211, C50.212, C50.221, C50.222, C50.311, C50.312, C50.321, C50.322, C50.411, C50.412, C50.421, C50.422, C50.511, C50.512, C50.521, C50.522, C50.611, C50.612, C50.621, C50.622, C50.811, C50.812,C50.821,C50.822, C50.911, C50.912, C50.921, C50.922, C56.1,C56.2,C57.01, C57.02, D05.01, D05.02, D05.11, D05.12, D05.81, D05.82,D05.91,D05.92, Z85.3, Z85.43& added to the Documentation section: Documentation will be requested for BRCA1, BRCA2 (breast cancer 1 and 2) full sequence analysis and full duplication/deletion analysis. The documentation should support that a full sequence and a full duplication/ deletion analysis was performed Short description change to codes 81275, 88341 & 88342, removed CAC information.	• Revisions Due To CPT/HCPCS Code Changes • Other
10/01/2015	R7	10/01/2015- Annual Review completed 09/03/2015; reformatted references, changed level 2 to tier 2 under Group 1 Paragraph, no change in coverage.	• Other (Annual Review)
10/01/2015	R6	01/01/2015-Code update-removed deleted codes G0461, G0462 & added 88341, 88342.	• Revisions Due To CPT/HCPCS Code Changes
10/01/2015	R5	11/01/2014-Removed broken link and underlining in the source of information section.	• Other

Revision History Date	Revision History Number	Revision History Explanation	Reason(s) for Change
10/01/2015	R4	10/01/2014-Removed G0461 & G0462 from ICD-9 Codes that Support Medical Necessity in paragraph 2; Added dx codes C18.0-C18.9 to list of covered diagnosis codes for 81301; typos corrected, Annual Review-09/10/2014.	• Other
10/01/2015	R3	08/01/2014-Removed CPT code 88342 – Not valid for Medicare purposes effective 01/01/2014; Added G0461 & G0462; 81405 description change-effective 07/01/2014.	• Revisions Due To CPT/HCPCS Code Changes • Other
10/01/2015	R2	06/01/2014- Added BRAF V600 Testing - covered for unresectable or metastatic melanoma and plan on using vemurafenib, dabrafenib and trametinib. Added C43.0, C43.11, C43.12, C43.21, C43.22, C43.31, C43.39, C43.4, C43.51, C43.52, C43.59, C43.61, C43.62, C43.71, C43.72, C43.8, D03.0, D03.11, D03.12, D03.21, D03.22, D03.39, D03.4, D03.51, D03.52, D03.59, D03.61, D03.62, D03.71, D03.72, D03.8 to CPT 81210.	• Other
10/01/2015	R1	05/01/2014- Long CPT description code changes noted in MCD. Added 81215 to the Group 1 listing of CPT/HCPCs codes; CPT 81215 had been listed in ICD-9 Group 3 Paragraph: No change in coverage made.	• Other

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Associated Documents

Attachments Billing and Coding Guidelines (PDF - 22 KB)

Related Local Coverage Documents N/A

Related National Coverage Documents N/A

Public Version(s) Updated on 12/22/2015 with effective dates 01/01/2016 - N/A Updated on 09/16/2015 with effective dates 10/01/2015 - 12/31/2015 Updated on 12/19/2014 with effective dates 10/01/2015 - N/A Updated on 10/22/2014 with effective dates 10/01/2015 - N/A Updated on 09/17/2014 with effective dates 10/01/2015 - N/A Updated on 07/25/2014 with effective dates 10/01/2015 - N/A Updated on 05/21/2014 with effective dates 10/01/2015 - 09/30/2015 Updated on 04/16/2014 with effective dates 10/01/2015 - N/A Updated on 03/04/2014 with effective dates 10/01/2015 - N/A Back to Top

Keywords

N/A Read the **LCD Disclaimer** Back to Top