Genetic Testing for Lynch Syndrome

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➲ Terms and Conditions

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Policy Summary

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Overview

This policy guideline limits Lynch syndrome (LS) genetic testing to a stepped approach for Microsatellite Instability and Immunohistochemistry (MSI/IHC) screening, BRAF gene mutation, MLH1 gene promoter hypermethylation and targeted mismatch repair (MMR) germ-line gene testing to all patients with colorectal cancer (CRC) and endometrial cancer regardless of age, or a multi-gene NGS or other multi-analyte methodology that is inclusive of MSI microsatellite loci, and MLH1, MSH2, MSH6 and PMS2 genes. MSI/MMR testing is also covered for adult and pediatric patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options, or colorectal cancer that has progressed following treatment with fluoropyrimidine, oxaliplatin, and irinotecan.

Lynch Syndrome

Most colorectal cancer is caused by non-hereditary somatic mutations. Individuals with LS (a.k.a. Hereditary nonpolyposis colorectal cancer (HNPCC)) are predisposed to cancer due to having inherited or de novo germ-line mutations in DNA repair genes, that result in an accelerated accumulation of somatic mutations. LS, the most common hereditary cause of colorectal cancer, accounts for 2-3% of all colorectal cancers, followed by familial adenomatous polyposis (FAP) which accounts for <1% of colorectal malignancies and MUTYH-associated polyposis (MAP) whose frequency of occurrence is very rare.

LS is an autosomal dominant familial cancer syndrome caused by mutations in multiple susceptibility genes (e.g., MLH1, MSH2, MSH6, PMS2, EPCAM), and is associated with an increased lifetime risk for colorectal cancer (CRC) and other malignancies within the tumor spectrum including at least endometrial, ovarian, gastric, small bowel, urothelial, hepatobiliary tract, sebaceous and pancreatic cancers. Current literature suggests LS annually affects 28,000 individuals. In individuals with LS, the lifetime risk of colon cancer may be as high as 75% by the age of 70 years, with an average age onset of 45 years in

MLH1 and MSH2 mutation carriers. While the incidence of adenomas in individuals with LS is similar to that in the general population, the high rate of colorectal cancer is due to an acceleration of the adenoma to carcinoma sequence.

Cancer risks associated with LS are largely derived from family studies. Mutations in MLH1 and MSH2 account for 70-90% of families with LS. The risk of colon and endometrial cancer is less in MSH6 and PMS2 mutation carriers, although the cancer risk may not be lower for MSH6 carriers if one takes the data out to age 80. While individuals with a single MLH1, MSH2, MSH6 and PMS2 mutation develop cancers in mid-life, individuals with biallelic MLH1, MSH2, MSH6 and PMS2 mutations have a distinctive phenotype and tumor spectrum, and often develop cancer as early as the first decade of life.

First-degree relatives of mutation carriers have a 50% probability of having the same germ-line mutation. Despite the high penetrance of CRC and endometrial cancer and recommendations of consideration for screening unaffected first-degree relatives following diagnosis of a LS proband, testing of genetic carriers who are unaffected with a Lynch related cancer is statutorily excluded from coverage.

Testing Strategy for Patients with Personal History of Colorectal and Endometrial Cancer

There are two methods available to determine the presence of defective mismatch repair, i.e. microsatellite instability testing (MSI) and detection of loss of the protein product of the mismatch repair genes involved in DNA mismatch repair (MLH1, MSH2, MSH6 and PMS2) by immunohistochemistry (IHC). MSI testing and IHC are about equally sensitive (~95%) for detecting defective mismatch repair (MMR). Some authors advocate testing all tumors by both methods to ensure correct classification, while others prefer MSI testing if other biomarkers are being evaluated. This policy guideline does not dictate the use of one method or another. However, if IHC is done first and is abnormal, MSI testing is not warranted. If IHC is normal, MSI is warranted.

Step 1: Immunohistochemistry (IHC) testing for LS Screening

The use of IHC to detect loss of DNA mismatched repair (MMR) protein expression complements MSI to screen patients for defective MMR (dMMR), including both sporadic dMMR and LS dMMR. IHC allows detection of loss of protein expression for the MLH1, MSH2, MSH6 and PMS2 genes. Loss of MMR protein expression is detected by the absence of nuclear staining in the tumor cells and the presence of nuclear staining in lymphocytes and normal colon crypt epithelial cells.

The MMR proteins are present as heterodimers (MLH1 pairs with PMS2, and MSH2 pairs with MSH6). Knowledge of MMR protein expression loss patterns allows a logical and cost effective “directed” testing appropriate for germ-line mutation analysis. As a general rule, loss of expression of MLH1 or MSH2 is associated with loss of their partners. For example, mutation of the MLH1 gene generally leads to loss of expression of both the MLH1 and PMS2 proteins. However, loss of PMS2 or MSH6 due to a germ-line mutation is associated only with loss of the mutated protein. For example, mutation of the PMS2 gene leads to loss of expression of only the PMS2 protein.

If IHC is done first and is abnormal, MSI testing is not warranted. Often IHC is done first because of its rapid turn-around and minimal amount of tissue required. If IHC demonstrates loss of protein expression for the MLH1, MSH2, MSH6 and PMS2 genes, the following test results direct further testing:

- MLH1 loss by IHC, test for BRAF gene mutation (Step 3) or test for MLH1 promoter, (Step 4)
- MSH2/MS6 loss by IHC, perform MSH2 germ-line testing (Step 5)

If IHC test results are normal, there remains a small chance of high levels of microsatellite instability (MSI-H), so both IHC and MSI would be needed to rule out LS in a clinically suspicious setting.

Step 2: Microsatellite Instability (MSI) and/or Deficient Mismatch Repair (MMR) by Immunohistochemistry (IHC) Analysis for LS Screening

MSI analysis for screening LS microsatellites are short repeated segments of DNA spread throughout the genome. Under normal conditions, the MMR gene complex (MLH1, MSH2, MSH6 and PMS2 genes) corrects mismatched base pairs that occur during the final stage of DNA replication. When the MMR complex is functioning normally, all cells show an identical pattern of microsatellite lengths. When the MMR complex is non-functioning, due to two hits of any type, random mutations accumulate in microsatellites, leading to differences in microsatellite lengths (microsatellite instability, MSI). Therefore, MSI indicates loss-of-function defects in a MMR protein, which may be due to somatic mutations, germ-line MMR gene mutations, allelic loss, or to

epigenetic down-regulation. MSI is usually associated with absence of protein expression of one or more of the MMR proteins (MLH1, MSH2, MSH6M and PMS2).

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

Levels of MSI in colon tumors are classified as:
- MSI-H>-30% or more of a tumor's markers are unstable;
- MSI-L-> one but < 30% of a tumor's markers are unstable;
- MSS-no loci are unstable.

MSI-L and MSS indicates the MMR mechanism is functioning adequately. Virtually all CRC tumors from individuals with LS demonstrate MSI-H. However, MSI-H is NOT diagnostic of LS as MSI-H can be observed in roughly 15% of sporadic colorectal cancers. In other Lynch tumors, the percentage level of MSI-H is less consistent and is inadequately studied.

As indicated above, MSI testing is not necessary if IHC demonstrates loss of protein expression for the MLH1, MSH2, MSH6 and PMS2 genes. If IHC test results are normal, there remains a small chance of high levels of microsatellite instability (MSI-H), so both IHC and MSI should be performed to rule out LS in a clinically suspicious setting such as meeting a Revised Bethesda guideline. Additionally, some individuals with 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.

Definitive Molecular Testing for Lynch Syndrome

Next generation sequencing (NGS "hotspot") testing platforms:
- Molecular testing for MLH1, MSH2, MSH6 and PMS2 genes by NGS is covered as medically acceptable for the identification of LS by this contractor. BRAF V600E and MLH1 promoter methylation may not be included in NGS panel hereditary colon cancer panels. If MLH1 is abnormal for MMR by IHC, BRAF codon 600 reflex testing may be performed. If BRAF is negative, reflex MLH1 promoter methylation may be performed. Reflex EpCAM testing is indicated when EpCAM is not included in a hereditary colon cancer panel by NGS and IHC shows a loss of MSH2.

Non-NGS testing platforms:
- Molecular testing for MLH1, MSH2, MSH6 and PMS2 genes by non-NGS must be based upon IHC and/or MSI preliminary test results according to the following stepped approach:

Steps 3 and/or 4 apply only for tumors that are negative for MLH1 protein expression by IHC.

Step 3: BRAF V600E (BRAF) Mutation Testing

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

Step 4: MLH1 Promoter Hypermethylation (MLH1 PHM)

The combination of MLH1 PHM and a BRAF mutation in tumors rules out LS and no further molecular analysis is warranted. Tumors with MLH1 PMH identify dMMR which will most often be sporadic, but its presence does not fully rule out LS. However, there have been rare reports of MLH1 hypermethylation as a second hit in LS and there are new reports of constitutional MLH1 methylation. As a rule, discovery of MLH1 PHM indicates the tumor is not due to Lynch syndrome.

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

- If MKH1 is hypermethylated, germline MLH1 is not medically necessary.
- If the MLH1 promoter is hypermethylated and modified Amsterdam Criteria ACII is fulfilled, germ-line MLH1 may still be considered (2nd hit scenario).
- If the MLH1 promoter is normally methylated, and BRAF is negative for mutation then germ-line MLH1 testing is medically indicated.

Note: There is variability in laboratory preference for BRAF and MLH1 promoter testing sequence. Although BRAF is generally cheaper and faster, some labs test MLH1 PHM first because it is more sensitive for detection of sporadic dMMR.

In a study by Gausachs (2012), when MLH1 PHM testing is used in conjunction with BRAF mutation testing, the cost per additional mutation detected when using hypermethylation analysis was lower than that of BRAF and germinal MLH1 mutation analysis. Somatic hypermethylation of MLH1 is an accurate and cost-effective pre-screening method in the selection of patients that are candidates for MLH1 germ-line analysis when LS is suspected and MLH1 protein expression is absent.

Step 5: Targeted MMR (MLH1, MSH2, MSH6 and PMS2 gene) Germ-line and EpCAM Testing

Step 5A: MLH1 Testing

When IHC shows loss of both MLH1 and PMS2, further genetic testing of PMS2 is not indicated, as no cases have been reported of a PMS2 germ-line mutation when IHC showed a loss of both MLH1 and PMS2. PMS2 mutations have only been detected when IHC shows a loss of PMS2 only. If MLH1 gene mutation is positively identified, then LS is diagnosed, and further testing of the patient is not medically necessary.

Step 5B: MSH2 Testing

When IHC shows loss of MSH2 and MSH6, genetic testing should start with analysis of the MSH2 gene, given its frequency of germ-line mutation in LS. If MSH2 germ-line mutation is identified, then LS is diagnosed, and further testing of the patient is not medically necessary.

However, if genetic testing for germ-line mutations in MSH2 is negative, analysis for deletion in the EpCAM gene should be performed (Step 6). If EpCAM is also negative, genetic testing of MSH6 should be performed (Step 5C). The presence of MSI and the loss of MSH2/MSH6 strongly indicate a MMR germ-line defect.

Step 5C: MSH6 Testing

When IHC shows loss of just MSH6, it suggests a germ-line mutation in MSH6 and genetic testing of that gene is indicated. As previously noted, MSH6 CRC tumors can be MSI-H, MSI-L or MSS. This pitfall illustrates the utility of IHC for MMR protein expression. If MSH6 germ-line mutation is identified, then LS is diagnosed, and further testing of the patient is not medically necessary.

Step 5D: 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 6: EpCAM Testing

Recently, deletions in a portion of the EpCAM gene were found in a subset of families with LS with a loss of MSH2 by IHC. A common deletion in the 3' region of EpCAM causes somatic hypermethylation of MSH2, as the 2 genes are adjacent to one another on chromosome 2. Approximately 20% of patients with absence of MSH2 and MSH6 protein expression by IHC, but without MSH2 or MSH6 mutation, will have germ-line deletions in EpCAM. Early estimates suggest that germ-line mutations in EpCAM may account for approximately 6% of LS cases and possibly as high as 30% when IHC shows a loss of MSH2.

Note: Many labs incorporate EpCAM detection their MSH2 dup/deletion analysis.

Indications of Coverage

Coverage is based upon the existing Local Coverage Determination (LCD) for the jurisdiction in which the procedure is performed.

IHC and/or MSI Testing

LS tumor screening with IHC or MSI is considered medically necessary and covered for the following indications:

- All individuals with colorectal cancer regardless of age or
- Individuals with endometrial cancer

*Hereditary nonpolyposis colorectal cancer (HNPCC)-related tumors include colorectal, endometrial, gastric, ovarian, pancreas, ureter and renal pelvis, biliary tract, brain (usually glioblastomas as seen in Turcot syndrome), small intestinal cancers, and sebaceous gland adenomas and keratoacanthomas as seen in Muir-Torre syndrome

- For patients with unresectable or metastatic solid tumors, either MSI or IHC or a multigene NGS or other multi-analyte methodology panel inclusive of MSI microsatellite loci, and MLH1, MSH2, MSH6 and PMS2 genes is medically reasonable and necessary.

For coverage, the treating physician/pathologist is expected to follow the stepped approach outlined for LS screening and targeted MMR testing in this policy guideline. 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 policy guideline, 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 from patient with CRC or endometrial cancer
- Diagnosis of any Lynch-associated cancer prior to Medicare eligibility and tumor sample no longer available and meets either Revised Bethesda guidelines or has at least a personal 5% estimated likelihood to be mutation positive, as calculated by an established available risk model (e.g., PREMM, MMRpredict, MMRpro)

If targeted gene testing is not possible, testing of the four MMR genes can be performed concurrently followed by testing for EPCAM, or per a testing strategy deemed appropriate by the physician.

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 policy guideline does not imply that testing family members of a known familial variant is not medically warranted. The scope of the benefit requires the member 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

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

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 policy guideline is non-covered.

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...". Furthermore, 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".

Documentation Requirements

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.

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this guideline does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

CPT Code	Description
0158U	MLH1 (mutL homolog 1) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) mRNA sequence analysis (List separately in addition to code for primary procedure)
0159U	MSH2 (mutS homolog 2) (e.g., hereditary colon cancer, Lynch syndrome) mRNA sequence analysis (List separately in addition to code for primary procedure)
0160U	MSH6 (mutS homolog 6) (e.g., hereditary colon cancer, Lynch syndrome) mRNA sequence analysis (List separately in addition to code for primary procedure)
0161U	PMS2 (PMS1 homolog 2, mismatch repair system component) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) mRNA sequence analysis (List separately in addition to code for primary procedure)
81210	BRAF (B-Raf proto-oncogene, serine/threonine kinase) (e.g., colon cancer, melanoma), gene analysis, V600 variant(s) (See also the Medicare Advantage Policy Guideline titled Molecular Pathology/Molecular Diagnostics/Genetic Testing)
81288	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; promoter methylation analysis
81292	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81293	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
81294	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
81295	MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81296	MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
81297	MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
81298	MSH6 (mutS homolog 6 [E. coli]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81299	MSH6 (mutS homolog 6 [E. coli]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
81300	MSH6 (mutS homolog 6 [E. coli]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
81301	Microsatellite instability analysis (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) of markers for mismatch repair deficiency (e.g., BAT25, BAT26), includes comparison of neoplastic and normal tissue, if performed (List separately in addition to code for primary procedure) (See also the Medicare Advantage Policy Guideline titled Molecular Pathology/Molecular Diagnostics/Genetic Testing)

CPT Code	Description
81317	PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81318	PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
81319	PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
88341	Immunohistochemistry or immunocytochemistry, per specimen; each additional single antibody stain procedure (List separately in addition to code for primary procedure) (See also the Medicare Advantage Policy Guideline titled Molecular Pathology/Molecular Diagnostics/Genetic Testing)
88342	Immunohistochemistry or immunocytochemistry, per specimen; initial single antibody stain procedure (See also the Medicare Advantage Policy Guideline titled Molecular Pathology/Molecular Diagnostics/Genetic Testing)
Multi-Gene Panel	
0101U	Hereditary colon cancer disorders (e.g., Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis), genomic sequence analysis panel utilizing a combination of NGS, Sanger, MLPA, and array CGH, with MRNA analytics to resolve variants of unknown significance when indicated (15 genes [sequencing and deletion/duplication], EPCAM and GREM1 [deletion/duplication only])
0130U	Hereditary colon cancer disorders (e.g., Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis), targeted mRNA sequence analysis panel (APC, CDH1, CHEK2, MLH1, MSH2, MSH6, MUTYH, PMS2, PTEN, and TP53) (List separately in addition to code for primary procedure)
0162U	Hereditary colon cancer (Lynch syndrome), targeted mRNA sequence analysis panel (MLH1, MSH2, MSH6, PMS2) (List separately in addition to code for primary procedure)
0238U	Oncology (Lynch syndrome), genomic DNA sequence analysis of MLH1, MSH2, MSH6, PMS2, and EPCAM, including small sequence changes in exonic and intronic regions, deletions, duplications, mobile element insertions, and variants in non-uniquely mappable regions (Effective 01/01/2021)
81435	Hereditary colon cancer disorders (e.g., Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis); genomic sequence analysis panel, must include sequencing of at least 10 genes, including APC, BMPR1A, CDH1, MLH1, MSH2, MSH6, MUTYH, PTEN, SMAD4, and STK11
81436	Hereditary colon cancer disorders (e.g., Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis); duplication/deletion analysis panel, must include analysis of at least 5 genes, including MLH1, MSH2, EPCAM, SMAD4, and STK11

Diagnosis Code	Description
For DOS on or after 04/08/2020, for CPT codes 81292, 81293, and 81294	
C16.0	Malignant neoplasm of cardia
C16.1	Malignant neoplasm of fundus of stomach
C16.2	Malignant neoplasm of body of stomach
C16.3	Malignant neoplasm of pyloric antrum
C16.4	Malignant neoplasm of pylorus
C16.5	Malignant neoplasm of lesser curvature of stomach, unspecified
C16.6	Malignant neoplasm of greater curvature of stomach, unspecified
C16.8	Malignant neoplasm of overlapping sites of stomach
C16.9	Malignant neoplasm of stomach, unspecified

Diagnosis Code	Description
For DOS on or after 04/08/2020, for CPT codes 81292, 81293, and 81294	
C17.0	Malignant neoplasm of duodenum
C17.1	Malignant neoplasm of jejunum
C17.2	Malignant neoplasm of ileum
C17.3	Meckel's diverticulum, malignant
C17.8	Malignant neoplasm of overlapping sites of small intestine
C17.9	Malignant neoplasm of small intestine, unspecified
C18.0	Malignant neoplasm of cecum
C18.1	Malignant neoplasm of appendix
C18.2	Malignant neoplasm of ascending colon
C18.3	Malignant neoplasm of hepatic flexure
C18.4	Malignant neoplasm of transverse colon
C18.5	Malignant neoplasm of splenic flexure
C18.6	Malignant neoplasm of descending colon
C18.7	Malignant neoplasm of sigmoid colon
C18.8	Malignant neoplasm of overlapping sites of colon
C18.9	Malignant neoplasm of colon, unspecified
C19	Malignant neoplasm of rectosigmoid junction
C20	Malignant neoplasm of rectum
C21.0	Malignant neoplasm of anus, unspecified
C21.1	Malignant neoplasm of anal canal
C21.2	Malignant neoplasm of cloacogenic zone
C21.8	Malignant neoplasm of overlapping sites of rectum, anus and anal canal
C22.0	Liver cell carcinoma
C22.1	Intrahepatic bile duct carcinoma
C22.2	Hepatoblastoma
C22.3	Angiosarcoma of liver
C22.4	Other sarcomas of liver
C22.7	Other specified carcinomas of liver
C22.8	Malignant neoplasm of liver, primary, unspecified as to type
C22.9	Malignant neoplasm of liver, not specified as primary or secondary
C24.0	Malignant neoplasm of extrahepatic bile duct
C24.9	Malignant neoplasm of biliary tract, unspecified
C25.0	Malignant neoplasm of head of pancreas
C25.1	Malignant neoplasm of body of pancreas
C25.2	Malignant neoplasm of tail of pancreas
C25.3	Malignant neoplasm of pancreatic duct
C25.4	Malignant neoplasm of endocrine pancreas
C25.7	Malignant neoplasm of other parts of pancreas
C25.8	Malignant neoplasm of overlapping sites of pancreas
C25.9	Malignant neoplasm of pancreas, unspecified
C45.1	Mesothelioma of peritoneum

Diagnosis Code	Description
For DOS on or after 04/08/2020, for CPT codes 81292, 81293, and 81294	
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
C68.0	Malignant neoplasm of urethra
C68.1	Malignant neoplasm of paraurethral glands
C68.8	Malignant neoplasm of overlapping sites of urinary organs
C68.9	Malignant neoplasm of urinary organ, unspecified
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

Diagnosis Code	Description
For DOS on or after 04/08/2020, for CPT codes 81292, 81293, and 81294	
C71.4	Malignant neoplasm of occipital lobe
C71.5	Malignant neoplasm of cerebral ventricle
C71.6	Malignant neoplasm of cerebellum
C71.7	Malignant neoplasm of brain stem
C71.8	Malignant neoplasm of overlapping sites of brain
C71.9	Malignant neoplasm of brain, unspecified
C78.5	Secondary malignant neoplasm of large intestine and rectum
D12.0	Benign neoplasm of cecum
D12.1	Benign neoplasm of appendix
D12.2	Benign neoplasm of ascending colon
D12.3	Benign neoplasm of transverse colon
D12.4	Benign neoplasm of descending colon
D12.5	Benign neoplasm of sigmoid colon
D12.6	Benign neoplasm of colon, unspecified
K63.5	Polyp of colon
L85.3	Xerosis cutis
Z15.04	Genetic susceptibility to malignant neoplasm of endometrium
Z15.09	Genetic susceptibility to other malignant neoplasm
Z80.0	Family history of malignant neoplasm of digestive organs
Z85.00	Personal history of malignant neoplasm of unspecified digestive organ
Z85.038	Personal history of other malignant neoplasm of large intestine
Z85.048	Personal history of other malignant neoplasm of rectum, rectosigmoid junction, and anus
Z85.42	Personal history of malignant neoplasm of other parts of uterus
Z85.43	Personal history of malignant neoplasm of ovary
Z85.53	Personal history of malignant neoplasm of renal pelvis
Z85.54	Personal history of malignant neoplasm of ureter
Z85.59	Personal history of malignant neoplasm of other urinary tract organ
Z85.841	Personal history of malignant neoplasm of brain
Z86.010	Personal history of colonic polyps

Non-Covered Diagnosis Code
Non-Covered Diagnosis Codes List This list contains diagnosis codes that are never covered when given as the primary reason for the test. If a code from this section is given as the reason for the test and you know or have reason to believe the service may not be covered, call UnitedHealthcare to issue an Integrated Denial Notice (IDN) to the member and you. The IDN informs the member of their liability for the non-covered service or item and appeal rights. You must make sure the member has received the IDN prior to rendering or referring for non-covered services or items in order to collect payment.

Definitions

Close Blood Relatives: Are defined as follows:

- First degree relatives include parents, siblings, and offspring
- Second degree relatives include half-brothers/sisters, aunts/uncles, grandparents, grandchildren and nieces/nephews affected on the same side of the family

- Third degree relatives include first cousins, great-aunts/uncles, great-grandchildren and great grandparents affected on same side of family

Lynch Syndrome-Associated Cancer: Colorectal, endometrial, gastric, ovarian, pancreatic, ureter and renal pelvis, brain (usually glioblastoma), biliary tract, small intestinal cancers, sebaceous adenomas, sebaceous carcinomas and keratoacanthomas as seen in Muir-Torre syndrome.

Multi-Gene Panel: Genetic tests that use next-generation sequencing to test multiple genes simultaneously. Also called multigene test, Multiple-Gene Panel test and multiple-gene test.

PREMM: PREdiction Model for gene Mutations. The PREMM model estimates the overall cumulative probability of having an MLH1, MSH2, MSH6, PMS2, and EPCAM gene mutation.

Revised Bethesda guidelines:
- 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

References

CMS National Coverage Determinations (NCDs)

NCD 90.2 Next Generation Sequencing (NGS)

CMS Local Coverage Determinations (LCDs) and Articles

LCD	Article	Contractor	Medicare Part A	Medicare Part B
L35349 MolDX: Genetic Testing for Lynch Syndrome	A56882 Billing and Coding: MolDX: Genetic Testing for Lynch Syndrome	CGS	KY, OH	KY, OH
	A56106 Billing and Coding: MolDX: Microsatellite Instability-High (MSI-H) and Mismatch Repair Deficient (dMMR) Biomarker for Patients with Unresectable or Metastatic Solid Tumors			
L32912 Genetic Testing for Lynch Syndrome	A57450 Billing and Coding: Genetic Testing for Lynch Syndrome	First Coast	FL, PR, VI	FL, PR, VI
	A55126 Genetic testing for Lynch syndrome revision to the Part A and Part B LCD			
	A57439 Genetic testing for lynch syndrome revision to the Part A and Part B LCD			
L36370 MolDX: Genetic Testing for Lynch Syndrome	A54995 Billing and Coding: MolDX: Genetic Testing for Lynch Syndrome	Noridian	AS, CA, GU, HI, MP, NV	AS, CA, GU, HI, MP, NV

LCD	Article	Contractor	Medicare Part A	Medicare Part B
	A56103 Billing and Coding: MolDX: Microsatellite Instability-High (MSI-H) and Mismatch Repair Deficient (dMMR) Biomarker for Patients with Unresectable or Metastatic Solid Tumors			
L36374 MolDX: Genetic Testing for Lynch Syndrome	A54996 Billing and Coding: MolDX: Genetic Testing for Lynch Syndrome	Noridian	AK, AZ, ID, MT, ND, OR, SD, UT, WA, WY	AK, AZ, ID, MT, ND, OR, SD, UT, WA, WY
	A56104 Billing and Coding: MolDX: Microsatellite Instability-High (MSI-H) and Mismatch Repair Deficient (dMMR) Biomarker Billing and Coding Guidelines for Patients with Unresectable or Metastatic Solid Tumors			
L35024 MolDX: Genetic Testing for Lynch Syndrome	A54987 Billing and Coding: MolDX: Genetic Testing for Lynch Syndrome	Palmetto	AL, GA, NC, SC, TN, VA, WV	AL, GA, NC, SC, TN, VA, WV
	A56072 Billing and Coding: MolDX: Microsatellite Instability-High (MSI-H) and Mismatch Repair Deficient (dMMR) Biomarker for Patients with Unresectable or Metastatic Solid Tumors			
L36793 MolDX: Genetic Testing for Lynch Syndrome	A55135 Billing and Coding: MolDX: Genetic Testing for Lynch Syndrome	WPS	AK, AL, AR, AZ, CA, CO, CT, DE, FL, GA, HI, IA, ID, IL, IN, KS, KY, LA, MA, MD, ME, MI, MO, MS, MT, NC, ND, NE, NH, NJ, NM, NV, OH, OK, OR, PA, RI, SC, SD, TN, TX, UT, VA, VT, WA, WI, WV, WY	IA, IN, KS, MI, MO, NE
	A56501 Billing and Coding: MolDX: Microsatellite Instability-High (MSI-H) and Mismatch Repair Deficient (dMMR) Biomarker for Patients with Unresectable or Metastatic Solid Tumors			
L35062 Biomarkers Overview	A56541 Billing and Coding: Biomarkers Overview	Novitas	AR, CO, DC, DE, LA, MD, MS, NJ, NM, OK, PA, TX	AR, CO, DC, DE, LA, MD, MS, NJ, NM, OK, PA, TX
L35396 Biomarkers for Oncology	A52986 Billing and Coding: Biomarkers for Oncology	Novitas	AR, CO, DC, DE, LA, MD, MS, NJ, NM, OK, PA, TX	AR, CO, DC, DE, LA, MD, MS, NJ, NM, OK, PA, TX
L34519 Molecular Pathology Procedures	A57451 Billing and Coding: Molecular Pathology Procedures	First Coast	FL, PR, VI	FL, PR, VI
	A57440 Molecular pathology procedures revision to the Part A and Part B LCD			

LCD	Article	Contractor	Medicare Part A	Medicare Part B
L35000 Molecular Pathology Procedures	A56199 Billing and Coding: Molecular Pathology Procedures	NGS	CT, IL, MA, ME, MN, NH, NY, RI, VT, WI	CT, IL, MA, ME, MN, NH, NY, RI, VT, WI
L36021 MolDX: Molecular Diagnostic Tests (MDT)	A56973 Billing and Coding: MolDX: Molecular Diagnostic Tests (MDT)	CGS	KY, OH	KY, OH
	A54191 (Billing and Coding: MolDX: FDA-Approved BRAF Tests)			
L35160 MolDX: Molecular Diagnostic Tests (MDT)	A57526 Billing and Coding: MolDX: Molecular Diagnostic Tests (MDT)	Noridian	AS, CA, GU, HI, MP, NV	AS, CA, GU, HI, MP, NV
	A54418 Billing and Coding: MolDX: FDA-Approved BRAF Tests			
L36256 MolDX: Molecular Diagnostic Tests (MDT)	A57527 Billing and Coding: MolDX: Molecular Diagnostic Tests (MDT)	Noridian	AK, AZ, ID, MT, ND, OR, SD, UT, WA, WY	AK, AZ, ID, MT, ND, OR, SD, UT, WA, WY
	A54420 Billing and Coding: MolDX: FDA-Approved BRAF Tests			
L35025 MolDX: Molecular Diagnostic Tests (MDT)	A56853 Billing and Coding: MolDX: Molecular Diagnostic Tests (MDT)	Palmetto	AL, GA, NC, SC, TN, VA, WV	AL, GA, NC, SC, TN, VA, WV
	A54018 Billing and Coding: MolDX: FDA-Approved BRAF Tests			
L36807 MolDX: Molecular Diagnostic Tests (MDT)	A57772 Billing and Coding: MolDX: Molecular Diagnostic Tests (MDT)	WPS	AK, AL, AR, AZ, CA, CO, CT, DE, FL, GA, HI, IA, ID, IL, IN, KS, KY, LA, MA, MD, ME, MI, MO, MS, MT, NC, ND, NE, NH, NJ, NM, NV, OH, OK, OR, PA, RI, SC, SD, TN, TX, UT, VA, VT, WA, WI, WV, WY	IA, IN, KS, MI, MO, NE
	A55161 Billing and Coding: MolDX: FDA-Approved BRAF Tests			
L38274 MolDX: Repeat Germline Testing	A57141 Billing and Coding: MolDX: Repeat Germline Testing	CGS	KY, OH	KY, OH
L38351 MolDX: Repeat Germline Testing	A57331 Billing and Coding: MolDX: Repeat Germline Testing	Noridian	AS, CA, GU, HI, MP, NV	AS, CA, GU, HI, MP, NV
L38353 MolDX: Repeat Germline Testing	A57332 Billing and Coding: MolDX: Repeat Germline Testing	Noridian	AK, AZ, ID, MT, ND, OR, SD, UT, WA, WY	AK, AZ, ID, MT, ND, OR, SD, UT, WA, WY

LCD	Article	Contractor	Medicare Part A	Medicare Part B
L38274 MolDX: Repeat Germline Testing	A58017 Billing and Coding: MolDX: Repeat Germline Testing	Palmetto	AL, GA, NC, SC, TN, VA, WV	AL, GA, NC, SC, TN, VA, WV
L38429 MolDX: Repeat Germline Testing	A57100 Billing and Coding: MolDX: Repeat Germline Testing	WPS	AK, AL, AR, AZ, CA, CO, CT, DE, FL, GA, HI, IA, ID, IL, IN, KS, KY, LA, MA, MD, ME, MI, MO, MS, MT, NC, ND, NE, NH, NJ, NM, NV, OH, OK, OR, PA, RI, SC, SD, TN, TX, UT, VA, VT, WA, WI, WV, WY	IA, IN, KS, MI, MO, NE
N/A	A57910 Billing and Coding: MolDX: Testing of Multiple Genes	CGS	KY, OH	KY, OH
N/A	A58120 Billing and Coding: MolDX: Testing of Multiple Genes	Noridian	AS, CA, GU, HI, MP, NV	AS, CA, GU, HI, MP, NV
N/A	A58121 Billing and Coding: MolDX: Testing of Multiple Genes	Noridian	AK, AZ, ID, MT, ND, OR, SD, UT, WA, WY	AK, AZ, ID, MT, ND, OR, SD, UT, WA, WY
N/A	A57503 Billing and Coding: MolDX: Testing of Multiple Genes	Palmetto	AL, GA, NC, SC, TN, VA, WV	AL, GA, NC, SC, TN, VA, WV
N/A	A57880 Billing and Coding: MolDX: Testing of Multiple Genes	WPS	AK, AL, AR, AZ, CA, CO, CT, DE, FL, GA, HI, IA, ID, IL, IN, KS, KY, LA, MA, MD, ME, MI, MO, MS, MT, NC, ND, NE, NH, NJ, NM, NV, OH, OK, OR, PA, RI, SC, SD, TN, TX, UT, VA, VT, WA, WI, WV, WY	IA, IN, KS, MI, MO, NE

CMS Benefit Policy Manual

Chapter 15; § 80.1–80.1.3 Clinical Laboratory Services

CMS Claims Processing Manual

Chapter 12; § 60 Payment for Pathology Services
Chapter 16, § 10.2 General Explanation of Payment; § 20 Calculation of Payment Rates-Clinical Laboratory Test Fee Schedules; § 40 Billing for Clinical Laboratory Tests

UnitedHealthcare Commercial Policy

Genetic Testing for Hereditary Cancer

Other(s)

CMS Clinical Laboratory Fee Schedule, CMS Website
Palmetto GBA MolDx Website
Tests Subject to CLIA Edits

Guideline History/Revision Information

Revisions to this summary document do not in any way modify the requirement that services be provided and documented in accordance with the Medicare guidelines in effect on the date of service in question.

Date	Summary of Changes
04/14/2021	Policy Summary *Overview* Definitive Molecular Testing for Lynch Syndrome • Replaced language indicating "molecular testing for MLH1, MSH2, MSH6 and PMS2 genes by Next Generation Sequencing (NGS) is covered as medically acceptable for the identification of Lynch Syndrome (LS) by *UnitedHealthcare*" with "molecular testing for MLH1, MSH2, MSH6 and PMS2 genes by NGS is covered as medically acceptable for the identification of LS by *this contractor*" *Indications of Coverage* • Added language to indicate coverage is based upon the existing Local Coverage Determination (LCD) for the jurisdiction in which the procedure is performed IHC and/or MSI Testing • Replaced language indicating "Lynch Syndrome (LS) tumor screening with immunohistochemistry (IHC) or Microsatellite Instability (MSI) is considered medically necessary and covered *by UnitedHealthcare* for the indications [listed in the policy]" with "LS tumor screening with IHC or MSI is considered medically necessary and covered for the indications [listed in the policy]" MMR Germline Gene Mutation Testing Exception • Replaced language indicating "if a lab is unable to perform the stepped testing approach outlined in this policy guideline, multiple germ-line gene testing will be covered *by UnitedHealthcare* only for one or more of the findings [listed in the policy]" with "if a lab is unable to perform the stepped testing approach outlined in this policy guideline, multiple germ-line gene testing will be covered only for one or more of the findings [listed in the policy]" • Revised coverage criteria for multiple germ-line gene testing; replaced criterion requiring "diagnosis of any Lynch-associated cancer prior to eligibility" with "diagnosis of any Lynch-associated cancer prior to *Medicare* eligibility" *Limitations* • Replaced language indicating "molecular testing for LS to identify carrier status or family studies is not a *covered* benefit" with "molecular testing for LS to identify carrier status or family studies is not a *Medicare* benefit" *Documentation Requirements* • Replaced language indicating "*UnitedHealthcare expects* the ordering/treating physician or pathologist to obtain sufficient clinical and family history to warrant first-line testing (IHC/MSI), and subsequent targeted mismatched repair (MMR) germ-line testing or for germ-line mutation exceptions [listed in the policy]" with "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 [listed in the policy]" • Removed language indicating: ○ 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)

Date	Summary of Changes
	○ When MSI/IHC testing cannot be performed or is contradictory, claims for MMR germ-line testing exemptions will require the addition of the KX modifier with the billing CPT code **Applicable Codes** • Added CPT codes: ○ 0158U, 0159U, 0160U, and 0161U (previously listed as *Multi-Gene Panel* only) ○ 0238U (for *Multi-Gene Panel*) **Definitions** • Updated definition of "Lynch Syndrome-Associated Cancer" **Supporting Information** • Updated *References* section to reflect the most current information • Archived previous policy version MPG385.01

Purpose

The Medicare Advantage Policy Guideline documents are generally used to support UnitedHealthcare Medicare Advantage claims processing activities and facilitate providers' submission of accurate claims for the specified services. The document can be used as a guide to help determine applicable:

- Medicare coding or billing requirements, and/or
- Medical necessity coverage guidelines; including documentation requirements.

UnitedHealthcare follows Medicare guidelines such as NCDs, LCDs, LCAs, and other Medicare manuals for the purposes of determining coverage. It is expected providers retain or have access to appropriate documentation when requested to support coverage. Please utilize the links in the References section below to view the Medicare source materials used to develop this resource document. This document is not a replacement for the Medicare source materials that outline Medicare coverage requirements. Where there is a conflict between this document and Medicare source materials, the Medicare source materials will apply.

Terms and Conditions

The Medicare Advantage Policy Guidelines are applicable to UnitedHealthcare Medicare Advantage Plans offered by UnitedHealthcare and its affiliates.

These Policy Guidelines are provided for informational purposes, and do not constitute medical advice. Treating physicians and healthcare providers are solely responsible for determining what care to provide to their patients. Members should always consult their physician before making any decisions about medical care.

Benefit coverage for health services is determined by the member specific benefit plan document* and applicable laws that may require coverage for a specific service. The member specific benefit plan document identifies which services are covered, which are excluded, and which are subject to limitations. In the event of a conflict, the member specific benefit plan document supersedes the Medicare Advantage Policy Guidelines.

Medicare Advantage Policy Guidelines are developed as needed, are regularly reviewed and updated, and are subject to change. They represent a portion of the resources used to support UnitedHealthcare coverage decision making. UnitedHealthcare may modify these Policy Guidelines at any time by publishing a new version of the policy on this website. Medicare source materials used to develop these guidelines include, but are not limited to, CMS National Coverage Determinations (NCDs), Local Coverage Determinations (LCDs), Medicare Benefit Policy Manual, Medicare Claims Processing Manual, Medicare Program Integrity Manual, Medicare Managed Care Manual, etc. The information presented in the Medicare Advantage Policy Guidelines is believed to be accurate and current as of the date of publication and is provided on an "AS IS" basis. Where there is a conflict between this document and Medicare source materials, the Medicare source materials will apply.

You are responsible for submission of accurate claims. Medicare Advantage Policy Guidelines are intended to ensure that coverage decisions are made accurately based on the code or codes that correctly describe the health care services provided. UnitedHealthcare Medicare Advantage Policy Guidelines use Current Procedural Terminology (CPT®), Centers for Medicare and Medicaid Services (CMS), or other coding guidelines. References to CPT® or other sources are for definitional purposes only and do not imply any right to reimbursement or guarantee claims payment.

*For more information on a specific member's benefit coverage, please call the customer service number on the back of the member ID card or refer to the Administrative Guide.