MedStar Health, Inc.
POLICY AND PROCEDURE MANUAL

Policy Number: MP.088.MH
Last Review Date: 05/19/2016
Effective Date: 07/01/2016

MP.884.MH – Colorectal Cancer, Mutation Testing for Treatment

This policy applies to the following lines of business:
- ✓ MedStar Employee (Select)
- ✓ MedStar MA – DSNP – CSNP
- ✓ MedStar CareFirst PPO

MedStar Health considers **Mutation Testing for Treatment of Colorectal Cancer (CRC)** medically necessary for the following indications:

KRAS mutation testing is considered medically necessary for a diagnosis of CRC when it is used in predicting nonresponse to anti-epidermal growth factor receptor (EGFR) monoclonal antibodies (cetuximab and panitumumab) in the treatment of metastatic colorectal carcinoma from either primary tumor or metastatic tumor tissue.

Limitations
KRAS mutation testing for CRC not listed above is considered not medically necessary.

Background
Over 108,000 cases of colon and 40,700 cases of rectal cancer are expected to occur annually in the United States. CRC is the third leading cause of cancer-related deaths in the United States. The American Cancer Society (ACS) states that the risk of CRC increases with age, with over 90% of the diagnoses in patients over 50 years of age. The 5-year survival rate for those diagnosed with CRC is 67% over all stages; however, this drops to 12% in those with metastatic disease.

Cetuximab (Erbitux; Imclone Systems/Bristol-Myers Squibb) and panitumumab (Vectibix; Amigen Inc.) are anti-EGFR monoclonal antibodies used for treatment in patients with metastic disease. To determine benefit from this treatment, biomarkers are needed to select the potential patient population. The KRAS (v-Ki-ras2 Kirsten rat sarcoma) mutation test is to identify those individuals who are unlikely to respond to treatment with anti-EGFR monoclonal antibodies. The KRAS mutation assay detects mutations at codons 12 and 13 of the KRAS gene and these mutations have been associated with lack of response to EGFR targeted therapies.

On July 17, 2009, the Food and Drug Administration (FDA) made class labeling changes to the product labels of cetuximab (Erbitux) and panitumumab (Vectibix) to indicate the drugs are now not recommended for the treatment of colorectal cancer for patients with KRAS mutation.

MP.088.MH – Colorectal Cancer, Mutation Testing for Treatment

Policy Number: MP.088.MH
Last Review Date: 05/19/2016
Effective Date: 07/01/2016

Codes:

CPT Codes / HCPCS Codes / ICD-10 Codes	
Code	Description
CPT Codes	
81275	KRAS (v-Ki-ras2 Kirsten rat sarcoma viral oncogene)(e.g. carcinoma) gene analysis, variants in codons 12 and 13
CPT Codes (Medicare Only)	
81210	BRAF (v-raf murine sarcoma viral oncogene homolog B1) (eg, colon cancer), gene analysis, V600E variant
81479	Unlisted molecular pathology
ICD-9 codes covered if selection criteria are met:	
152.0-152.9	Malignant neoplasm of small intestine including duodenum
153.0-154.8	Malignant neoplasm of colon, rectum, and anus
197.5	Secondary malignant neoplasm of large intestine and rectum
230.3-230.6	Carcinoma in situ anus, colon, or rectum
ICD-10 codes covered if selection criteria are met:	
C17.0-C17.9	Malignant neoplasm of small intestine
C18.0-C18.9	Malignant neoplasm of colon
C19-C21.8	Malignant neoplasm of rectum and anus
C78.5	Secondary malignant neoplasm of large intestine and rectum
D01.0-D01.3	Carcinoma in situ of colon, rectum, and anus

Variations

Medicare (see LCD L35396):

The following testing will be covered for Medicare members for the condition of Colorectal Cancer:

- KRAS (12/13) – PRED of resistance to anti-EGFR agent (81275)
- KRAS codon 61 – PRED of resistance to anti-EGFR agent (81276)
- KRAS codon 146 – PRED of resistance to anti-EGFR agent (81276)
- NRAS – PRED of resistance to anti-EGFR agent (81311)
- BRAF – PRED of resistance to an anti-EGFR agent + DX (sporadic vs. Lynch syndrome) (81210)

- PIK3CA – PRED of resistance to an anti-EGFR agent + PROG for local recurrence (81479)
- MSI by PCR – PRED of 5-FU resistance + DX (81301)
- MLHI promoter hypermethylation – PRED of 5-FU resistance + DX (81292, 81293, 81294)

DX = Diagnosis; PROG = prognostic; and/or PRED = predictive

Medicare Members in Maryland:

Local Medicare coverage of such biomarkers must be predicated upon four fundamental principles:

1. First, the biomarkers must have proven clinical validity/utility (CVU).

2. Second, to support the medical necessity of the service, there must be acceptance/uptake of specific testing into patient management. **It is essential that physicians be familiar enough with all specific biomarkers, which they order, such that all test results may become clinically actionable.**

Note: Off-label chemotherapeutic agents, corresponding genotypic testing, which is designed to better help guide therapy, is also coverable.

3. Third, providers managing oncological conditions must demonstrate that the use of biomarkers will be used to assist in the management/treatment of the beneficiary.

4. Peer-reviewed full manuscript evidence is required to support combination panels for multiple biomarkers, particularly regarding their alleged composite clinical validity/utility. For example; such potential billing for multiple, diverse biomarkers (e.g., diagnostic/monitoring/prognostic/predictive) can only achieve medical necessity when it is clearly evident how each requested biomarker can be individually contributory.

Finally, it is quite useful to categorize oncology biomarkers into functional clusters which reflect both (1) The predominant intent of testing (with the caveat that individual assays may cross over into more than one category) and (2) The relative evidentiary expectations:

1. Oncology Biomarkers Used for Diagnosis/Classification/Monitoring/Surveillance: These types of assays are supportable by case-control sensitivity/specificity studies, with appropriate designs in place to minimize the extent of bias and confounding.

2.Oncology Biomarkers Used for Prognosis/Prediction: Oncology biomarkers used for prognosis/prediction (i.e., a predictive biomarker is associated with response [benefit] or lack of response to a particular therapy, relative to other available therapy, whereas a prognostic biomarker provides information on the likely outcome of the disease in an untreated individual).

MOLECULAR TESTS

Covered clinical types of application(s) are identified below as diagnostic (DX), prognostic (PROG) and/or predictive (PRED).

1. Colorectal Cancer

KRAS (12/13) - PRED of resistance to an anti-EGFR agent
KRAS codon 61 - PRED of resistance to an anti-EGFR agent
KRAS codon 146 - PRED of resistance to an anti-EGFR agent

References

1. Allegra CJ, Jessup JM, Somerfield MR, et al. American Society of Clinical Oncology Provisional Clinical Opinion, Testing for KRAS gene mutations in patients with metastatic colorectal carcinoma to predict response to anti-epidermal growth factor receptor monoclonal antibody therapy. J Clin Oncol. 2009 Apr; 27(12): 2091-2096. http://jco.ascopubs.org/content/27/12/2091.full.pdf+html
2. American College of Pathologists. The Pathologist's Message. KRAS Mutation Testing for Colorectal Cancer (CRC). Last updated: Dec. 17, 2010. http://www.cap.org/apps/cap.portal?_nfpb=true&cntvwrPtlt_actionOverride=%2Fportlets%2FcontentViewer%2Fshow&_windowLabel=cntvwrPtlt&cntvwrPtlt%7BactionForm.contentReference%7D=committees%2Ftechnology%2FKRAS_Mutation.html&_state=maximized&_pageLabel=cntvwr
3. Carethers JM. DNA testing and molecular screening for colon cancer. Clin Gastroenterol Hepatol. 2014 Mar;12(3):377-381. doi: 10.1016/j.cgh.2013.12.007. Epub 2013 Dec 17. http://www.cghjournal.org/article/S1542-3565(13)01933-2/abstract
4. Centers for Medicare and Medicaid Services (CMS). Local Coverage Determination (LCD) No. L35396 - Biomarkers for Oncology. (Contractor: Novitas Solutions, Inc.). Revision Effective Date: 01/22/2016. https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=35396&ver=50&Date=&DocID=L35396&bc=iAAAAAgAAAAAAA%3d%3d&
5. Centers for Medicare and Medicaid Services (CMS). Local Coverage Article: Biomarkers for Oncology (A52986). (Contractor: Novitas Solutions, Inc.).

Effective 10/01/2015. https://www.cms.gov/medicare-coverage-database/details/article-details.aspx?articleId=52986&ver=26&ContrId=324&ContrVer=1&CoverageSelection=Both&ArticleType=All&PolicyType=Final&s=Maryland&KeyWord=Biomarkers&KeyWordLookUp=Title&KeyWordSearchType=And&bc=gAAAABAAAAAAAA%3d%3d&

6. General Electric Healthcare: Clarient Diagnostic Services, Inc., *Colorectal Cancer Testing* ©2015, Clarient Diagnostic Services, Inc. http://clarient.gehealthcare.com/Diagnostic-Services/Colorectal-Cancer-Testing
7. Hayes Genetic Testing Evaluation. KRAS Sequence Variant Analysis for Predicting Response to Colorectal Cancer Drug Therapy. Annual Review May 27, 2015.
8. National Comprehensive Cancer Network (NCCN): NCCN Clinical Practice Guidelines in Oncology- Colon Cancer Version 3.2014. J Natl Compr Canc Netw 2014; 12: 1028-1059. http://www.jnccn.org/content/12/7/1028.abstract
9. Plesec TP, Hunt JL. KRAS mutation testing in colorectal cancer. Adv Anat Pathol. 2009 Jul; 16(4): 196-203. http://www.ncbi.nlm.nih.gov/pubmed/19546608
10. Quest Diagnostics®. Test Center: KRAS Mutation Analysis. Content reviewed: 03.2014 . ©2000-2014, Quest Diagnostics, Inc. http://www.questdiagnostics.com/testcenter/testguide.action?dc=TS_KRAS
11. United States Food and Drug Administration: Cetuximab (Erbitux) and Panitumumab (Vectibix). Page Last Updated: 01/11/2010. http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm172905.htm

Disclaimer:
MedStar Health medical payment and prior authorization policies do not constitute medical advice and are not intended to govern or otherwise influence the practice of medicine. The policies constitute only the reimbursement and coverage guidelines of MedStar Health and its affiliated managed care entities. Coverage for services varies for individual members in accordance with the terms and conditions of applicable Certificates of Coverage, Summary Plan Descriptions, or contracts with governing regulatory agencies.

MedStar Health reserves the right to review and update the medical payment and prior authorization guidelines in its sole discretion. Notice of such changes, if necessary, shall be provided in accordance with the terms and conditions of provider agreements and any applicable laws or regulations.