MEDICAL POLICY

MEDICAL POLICY DETAILS	
Medical Policy Title	**GENOTYPING – RAS MUTATION ANALYSIS IN METASTATIC COLORECTAL CANCER (KRAS/NRAS)**
Policy Number	**2.02.41**
Category	**Laboratory**
Effective Date	**02/19/09**
Revised Date	**04/22/10, 04/21/11, 03/15/12, 03/21/13, 02/20/14, 03/19/15, 05/26/16, 05/18/17, 05/17/18, 07/18/19**
Product Disclaimer	• *If a product excludes coverage for a service, it is not covered, and medical policy criteria do not apply.* • *If a commercial product (including an Essential Plan product) or a Medicaid product covers a specific service, medical policy criteria apply to the benefit.* • *If a Medicare product covers a specific service, and there is no national or local Medicare coverage decision for the service, medical policy criteria apply to the benefit.*

POLICY STATEMENT

I. Based on our criteria and peer-reviewed literature, including National Comprehensive Cancer Network (NCCN) clinical guidelines, RAS mutation analysis (KRAS and NRAS) of tumor tissue is considered **medically appropriate** to predict non-response to anti-EGFR monoclonal antibodies cetuximab and panitumumab in the treatment of *metastatic Stage IV* colorectal cancer.

II. Based on our criteria and peer-reviewed literature, including National Comprehensive Cancer Network (NCCN) clinical guidelines, genotyping of tumor tissue for BRAF mutations is considered **medically appropriate** to predict non-response to anti-EGFR monoclonal antibodies cetuximab and panitumumab in the treatment of *metastatic Stage IV* colorectal cancer.

III. Based on our criteria and peer-reviewed literature, PIK3CA status, HER2 amplification, and PTEN expression mutation analysis to predict non-response to anti-EGFR monoclonal antibodies cetuximab and panitumumab in the treatment of *metastatic* colorectal cancer is considered **investigational**.

Refer to Corporate Medical Policy # 2.02.35 regarding Molecular Analysis for Targeted Therapy of Non-Small Cell Lung Cancer (NSCLC).

Refer to Corporate Medical Policy #11.01.03 regarding Experimental and Investigational Services.

POLICY GUIDELINES

The Federal Employee Health Benefit Program (FEHBP/FEP) requires that procedures, devices or laboratory tests approved by the U.S. Food and Drug Administration (FDA) may not be considered investigational and thus these procedures, devices or laboratory tests may be assessed only on the basis of their medical necessity.

DESCRIPTION

The RAS-RAF-MAP kinase pathway is activated in the epidermal growth factor receptor (EGFR) cascade. RAS proteins are G-proteins that cycle between active (RAS-GTP) and inactive (RAS-GDP) forms, in response to stimulation from a cell surface receptor such as EGFR, and act as a binary switch between the cell surface EGFR and downstream signaling pathways. The most common RAS mutations seen in 30-50% of colorectal cancer (CRC) tumors are activating mutations of KRAS exon 2 at codons 12 and 13. These KRAS gene mutations result in a constitutively activated protein, independent of EGFR ligand binding which can render antibodies to the upstream EGFR ineffective. Consequently patients with KRAS mutations will exhibit resistance to EGFR inhibitors.

Another RAS gene is the neuroblastoma RAS viral (v-ras) oncogene homolog, or (NRAS). NRAS mutations are found in 3-5% of CRCs and occur most commonly in codon 61 rather than codon 12 or 13. NRAS mutations are mutually

exclusive from KRAS and NRAS mutation testing should be performed when KRAS is wild-type. The presence of NRAS mutations is associated with lack of response to cetuximab therapy.

Approximately 5% to 9% of colorectal cancers are characterized by the BRAF V600E gene. BRAF mutations are for the most part, mutually exclusive of KRAS mutations. Activation of the protein product of the BRAF occurs downstream of the KRAS protein in the EGFR pathway and if the BRAF gene is mutated, inhibition of EGFR is bypassed. The BRAF V600E mutation is also associated with lack of response to cetuximab therapy.

Cetuximab (Erbitux®, ImClone Systems) and panitumumab (Vectibix®, Amgen) are monoclonal antibodies that bind to the epidermal growth factor receptor (EGFR), preventing intrinsic ligand binding and activation of downstream signaling pathways vital for cancer cell proliferation, invasion, metastasis, and stimulation of neovascularization. Cetuximab and panitumumab are approved in the treatment of metastatic CRC in the refractory disease setting, and ongoing studies are investigating the use of these EGFR inhibitors as monotherapy and as part of combination therapy in first, second, and subsequent lines of therapy. A proportion of patients with CRC have tumors that harbor a somatic KRAS mutation that may affect tumor response to EGFR inhibitors.

RATIONALE

KRAS mutation analysis using PCR methodology is commercially available as a laboratory-developed test. Such tests are regulated under the Clinical Laboratory Improvement Amendments (CLIA). Premarket approval from the U.S. Food and Drug Administration (FDA) is not required when the assay is performed in a laboratory that is licensed by CLIA for high-complexity testing.

A 2008 BlueCross BlueShield Association TEC Assessment concluded that clinical trial data show that patients with KRAS-mutated metastatic CRC do not benefit from cetuximab or panitumumab, either as monotherapy or in combination with other treatment regimens. These data support the use of KRAS mutation analysis of tumor DNA before considering use of cetuximab or panitumumab in a treatment regimen. Identifying patients whose tumors express mutated KRAS will avoid exposing patients to ineffective drugs and unnecessary drug toxicities, and expedite the use of alternative therapies. Thus, KRAS mutation analysis may be considered medically necessary to predict nonresponse to anti-EGFR monoclonal antibodies cetuximab and panitumumab in the treatment of metastatic CRC.

The Molecular Biomarkers for the Evaluation of Colorectal Cancer Guidelines from the American Society for Clinical Pathology, College of American Pathologists, Association for Molecular Pathology, and the American society of Clinical Oncology (2017) recommend RAS mutational testing for colorectal carcinoma patients being considered for anti-EGFR therapy. Mutational analysis should include KRAS and NRAS codons 12, 13 of exon 2; 59, 61 of exon 3; and 117 and 146 of exon 4 (“expanded” or “extended” RAS) (Strength of evidence: convincing/adequate. Quality of evidence: high/intermediate). BRAF p.V600 (BRAF c. 1799 (p.V600) mutational analysis should be performed in colorectal cancer tissue in patients with colorectal carcinoma for prognostic stratification. (Strength of evidence: adequate/inadequate. Quality of evidence: intermediate/low).

An American Society of Clinical Oncology (ASCO) provisional clinical opinion (PCO) (Updated 2015), states all patients with mCRC who are candidates for anti-EGFR antibody therapy should have their tumor tested in a Clinical Laboratory Improvement Amendments–certified laboratory for mutations in both *KRAS* and *NRAS* exons 2 (codons 12 and 13), 3 (codons 59 and 61), and 4 (codons 117 and 146). The weight of current evidence indicates that anti-EGFR MoAb therapy should only be considered for treatment of patients whose tumor is determined to not have mutations detected after such extended *RAS* testing.

A significant number of patients with KRAS exon 2 wild-type metastatic colorectal cancer experience no response to anti-EGFR therapy. Thus other mutations in the RAS-RAF-MAP kinase pathway were explored that may show a response similar to KRAS gene mutations. One such mutation is NRAS, another member of the *RAS* family of protooncogenes, which can harbor mutations in codons 12, 13, and 61. Thus, the NRAS oncogene also may have an impact on outcomes of anti-EGFR treatments for CRC. Compared with KRAS, NRAS mutations are extremely rare. Although NRAS mutations account for approximately 15% of all *RAS* mutations, they are found in perhaps 2% to 7% of all CRC.

In 2016 the National Comprehensive Cancer Network (NCCN) guidelines for both colon and rectal cancer were updated to include genotyping FOR RAS (KRAS and NRAS) and BRAF mutations in all patients with metastatic colorectal cancer. Patients with known KRAS mutation (exon 2 or non-exon 2) or NRAS mutation should not be treated with either cetuximab or panitumumab. Evidence increasingly suggests that BRAF V600E mutation makes response to panitumumab or cetuximab, as single agents or in combination with cytotoxic chemotherapy, highly unlikely.

CODES

- *Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract.*
- *CODES MAY NOT BE COVERED UNDER ALL CIRCUMSTANCES. PLEASE READ THE POLICY AND GUIDELINES STATEMENTS CAREFULLY.*
- *Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.*

CPT Codes

Code	Description
81210	BRAF (v-raf murine sarcoma viral oncogene homolog B1) (eg, colon cancer), gene analysis, V600E variant(s)
81275	KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; variants in exon 2 (eg, codons 12 and 13)
81276	KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; additional variant(s) (eg, codon 61, codon 146)
81311	NRAS (neuroblastoma RAS viral [v-ras] oncogene homolog) (eg, colorectal carcinoma), gene analysis, variants in exon 2 (eg, codons 12 and 13) and exon 3 (eg, codon 61)
81321	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; full sequence analysis (E/I for listed diagnosis codes)
88363	Examination and selection of retrieved archival (ie, previously diagnosed) tissue(s) for molecular analysis (eg, KRAS mutational analysis)
0111U	Oncology (colon cancer), targeted KRAS (codons 12, 13, and 61) and NRAS (codons 12, 13, and 61) gene analysis utilizing formalin-fixed paraffin-embedded tissue (Praxis (TM) Extended RAS Panel by Illumina) (effective 10/1/2019)
0069U	miR-31now™, GoPath Laboratories, GoPath Laboratories (*effective 10/1/18*)

HCPCS Codes

Code	Description
No specific code(s)	

ICD10 Codes

Code	Description
C18.0-C21.8	Malignant neoplasm of colon, rectosigmoid junction, rectum, and anus and anal canal (code range)
C78.5	Secondary malignant neoplasm of large intestine and rectum

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*Key Article

KEY WORDS

Anti-EGFR monoclonal antibodies, KRAS, NRAS, BRAF, cetuximab, colorectal cancer**,** panitumumab.

CMS COVERAGE FOR MEDICARE PRODUCT MEMBERS

There is currently a Local Coverage Determination (LCD) for Molecular Pathology Procedures. Please refer to the following LCD website for Medicare members: https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=35000&ver=128&CntrctrSelected=298*1&Cntrctr=298&s=41&DocType=Active&bc=AggAAAIBAAAA&