

MEDICAL POLICY

SUBJECT: GENOTYPING – RAS MUTATION ANALYSIS IN METASTATIC COLORECTAL CANCER (KRAS/NRAS)	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
POLICY NUMBER: 2.02.41 CATEGORY: Laboratory	PAGE: 1 OF: 6
<ul style="list-style-type: none">• <i>If a product excludes coverage for a service, it is not covered, and medical policy criteria do not apply.</i>• <i>If a commercial product (including an Essential Plan product) or a Medicaid product covers a specific service, medical policy criteria apply to the benefit.</i>• <i>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.</i>	

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 Genotyping - Epidermal Growth Factor Receptor (EGFR) for Patients with 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.

<p>SUBJECT: GENOTYPING - RAS MUTATION ANALYSIS IN METASTATIC COLORECTAL CANCER (KRAS/NRAS)</p> <p>POLICY NUMBER: 2.02.41</p> <p>CATEGORY: Laboratory</p>	<p>EFFECTIVE DATE: 02/19/09</p> <p>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</p> <p>PAGE: 2 OF: 6</p>
-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

Cetuximab (Erbix®[®], 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.

<p>SUBJECT: GENOTYPING - RAS MUTATION ANALYSIS IN METASTATIC COLORECTAL CANCER (KRAS/NRAS)</p> <p>POLICY NUMBER: 2.02.41</p> <p>CATEGORY: Laboratory</p>	<p>EFFECTIVE DATE: 02/19/09</p> <p>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</p> <p>PAGE: 3 OF: 6</p>
-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

CODES: Number Description

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:	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)

Copyright © 2018 American Medical Association, Chicago, IL

HCPCS: No specific code(s)

ICD10:	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

REFERENCES:

Allegra CJ, et al. Extended RAS Gene Mutation Testing in Metastatic Colorectal Carcinoma to Predict Response to Anti-Epidermal Growth Factor Receptor Monoclonal Antibody Therapy: American Society of Clinical Oncology Provisional Clinical Opinion Update 2015. *J Clin Oncol*. 2016 Jan 10;34(2):179-85.

*Amado RG, et al. Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. *J Clin Oncol* 2008 Apr 1;26(10):1626-34.

*Ashraf N, et al. Predictive biomarkers for anti-epidermal growth factor receptor therapy: beyond KRAS testing. *J Natl Compr Canc Netw* 2014 Oct;12(1):1433-42.

*Behl AS, et al. Cost-effectiveness analysis of screening for KRAS and BRAF mutations in metastatic colorectal cancer. *J Natl Cancer Inst* 2012 Dec 5;104(23):1785-95.

*Blons H, et al. Prognostic value of KRAS mutation in stage III colon cancer: post hoc analysis of the PETACC8 phase III trial dataset. *Ann Oncol* 2014 Dec;35(12):2378-85.

BlueCross BlueShield Association. KRAS mutation analysis in metastatic colorectal cancer. Medical Policy Reference Manual Policy #2.04.53. 2017 Nov 09.

*BlueCross BlueShield Association TEC Assessments. KRAS mutations and epidermal growth factor receptor inhibitor therapy in metastatic colorectal cancer. 2008.

<p>SUBJECT: GENOTYPING - RAS MUTATION ANALYSIS IN METASTATIC COLORECTAL CANCER (KRAS/NRAS)</p> <p>POLICY NUMBER: 2.02.41</p> <p>CATEGORY: Laboratory</p>	<p>EFFECTIVE DATE: 02/19/09</p> <p>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</p> <p>PAGE: 4 OF: 6</p>
-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

*Benvenuti S, et al. Oncogenic activation of the RAS/RAF signaling pathway impairs the response of metastatic colorectal cancers to anti-epidermal growth factor receptor antibody therapies. Cancer Res 2007 Mar 15;67(6):2643-8.

*Chen D, et al. BRAFV600E mutation and its association with clinicopathological features of colorectal cancer: a systematic review and meta-analysis. PLoS One 2014 Mar 3;9(3):e90607.

Chiu JW, et al. Molecular profiling of patients with advanced colorectal cancer: Princess Margaret Cancer Centre experience. Clin Colorectal Cancer. 2018 Mar;17(1):73-79.

*Corcoran RB. New therapeutic strategies for BRAF mutant colorectal cancers. J Gastrointest Oncol 2015 Dec;6(6):650-9.

*Dahabreh IJ, et al. Systematic review: anti-epidermal growth factor receptor treatment effect modification by KRAS mutations in advanced colorectal cancer. Ann Intern Med 2011;154:37-49.

*Derbel O, et al. Impact of KRAS, BRAF and PIK3CA mutations in rectal carcinomas treated with neoadjuvant radiochemotherapy and surgery. BMC Cancer 2013 Apr 23;13:200.

*De Roock W, et al. KRAS wild-type state predicts survival and is associated to early radiological response in metastatic colorectal cancer treated with cetuximab. Ann Oncol 2008 Mar;19(3):508-15.

*De Stefano A, et al. Beyond KRAS: predictive factors of the efficacy and anti-EGFR monoclonal antibodies in the treatment of metastatic colorectal cancer. World J Gastroenterol 2014 Aug 7;20(29):9732-43.

*Di Fiore F, et al. Clinical relevance of KRAS mutation detection in metastatic colorectal cancer treated by Cetuximab plus chemotherapy. Br J Cancer 2007 Apr 23;96(8):1166-9.

*Di Nicolantonio F, et al. Wild-type BRAF is required for response to panitumumab or cetuximab in metastatic colorectal cancer. J Clin Oncol 2008;26:5705-12.

Freidrich T, et al. Beyond RAS and BRAF: a target rich disease that is ripe for picking. J Gastrointest Oncol 2016;7(5):705-12.

Gelsomino F, et al. The evolving role of microsatellite instability in colorectal cancer: a review. Cancer Treat Rev 2016 Dec;51:19-26.

*Goncalves A, et al. A polymorphism of EGFR extracellular domain is associated with progression free-survival in metastatic colorectal cancer patients receiving cetuximab-based treatment. BMC Cancer 2008 Jun 10;8:169.

Gong J, et al. RAS and BRAF in metastatic colorectal cancer management. J Gastrointest Oncol 2016 Oct;7(5):687-704.

*Heinemann V, et al. Targeted therapy in metastatic colorectal cancer – an example of personalized medicine in action. Cancer Treat Rev 2013 Oct;39(6):592-601.

*Kalady MF, et al. BRAF mutations in colorectal cancer are associated with distinct clinical characteristics and worse prognosis. Dis Colon Rectum 2012 Feb;55(2):128-33.

*Karapetis CS, et al. PIK3CA, BRAF, and PTEN status and benefit from cetuximab in the treatment of advanced colorectal cancer- results from NCIC CTG/AGITG CO. 17. Clin Cancer Res 2014 Feb 1;20(3):744-53.

*Karapetis CS, et al. K-ras mutations and benefit from cetuximab in advanced colorectal cancer. N Engl J Med 2008 Oct 23;359(17):1757-65.

*Khambata-Ford S, et al. Expression of epiregulin and amphiregulin and K-ras mutation status predict disease control in metastatic colorectal cancer patients treated with cetuximab. J Clin Oncol 2007 Aug 1;25(22):3230-7.

*Lin JS, et al. Systematic review of pharmacogenetic testing for predicting clinical benefit to anti-EGFR therapy in metastatic colorectal cancer. Am J Cancer Res 2011 May 15;1(5):650-62.

<p>SUBJECT: GENOTYPING - RAS MUTATION ANALYSIS IN METASTATIC COLORECTAL CANCER (KRAS/NRAS)</p> <p>POLICY NUMBER: 2.02.41</p> <p>CATEGORY: Laboratory</p>	<p>EFFECTIVE DATE: 02/19/09</p> <p>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</p> <p>PAGE: 5 OF: 6</p>
-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

*Lievre A, et al. KRAS mutations as an independent prognostic factor in patients with advanced colorectal cancer treated with cetuximab. J Clin Oncol 2008 Jan 20;26(3):374-9.

Loree JM, et al. Current companion diagnostics in advanced colorectal cancer; getting a bigger and better piece of the pie. J Gastrointest Oncol 2017 Feb;8(1):199-212.

*Lupini L, et al. Prediction of response to anti-EGFR antibody-based therapies by multigene sequencing in colorectal cancer patients. BMC Cancer 2015 Oct 27;15:808.

Modest DP, et al. Outcome according to KRAS-, NRAS- and BRAF-mutation as well as KRAS mutation variants: pooled analysis of five randomized trials in metastatic colorectal cancer by the AIO colorectal cancer study group. Ann Oncol 2016 Sep;27(9):1746-53.

*Modest DP, et al. The influence of KRAS and BRAF mutations on the efficacy of cetuximab-based first-line therapy of metastatic colorectal cancer: an analysis of the AIO KRK-0104-trial. Int J Cancer 2012 Aug 15;131(4):980-6.

Mody K and Bekaii-Saab T. Clinical trials and progress in metastatic colon cancer. Surg Oncol Clin N Am. 2018 Apr;27(2):349-365.

Morris V, et al. Progression-free survival remains poor over sequential lines of systemic therapy in patients with BRAF-mutated colorectal cancer. Clin Colorectal Cancer 2014 Sep;13(3):164-71.

National Comprehensive Cancer Network (NCCN). Practice Guidelines in Oncology v.2.2018. Colon Cancer. [http://www.nccn.org/professionals/physician_gls/pdf/colon.pdf] accessed 4/5/18.

National Comprehensive Cancer Network (NCCN). Practice Guidelines in Oncology v.1.2018. Rectal Cancer. [http://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf] accessed 4/5/18.

*Ogino S, et al. Predictive and prognostic analysis of PIK3CA mutation in stage III colon cancer intergroup trial. J Natl Cancer Inst 2013 Dec 4;105(23):1789-98.

Paleari L, et al. PIK3CA mutation, aspirin use after diagnosis and survival of colorectal cancer. A systematic review and meta-analysis of epidemiological studies. Clin Oncol (R Coll Radiol) 2016 May;28(5):317-26.

Pietrantonio F, et al. Predictive role of BRAF mutations in patients with advanced colorectal cancer receiving cetuximab and panitumumab: A meta-analysis. Eur J Cancer 2015;51(2):587-94.

*Saridaki Z, et al. BRAFV600E mutation analysis in patients with metastatic colorectal cancer (mCRC) in daily clinical practice: correlations with clinical characteristics, and its impact on patients' outcomes. PloS One 2013 Dec 18;8(12):e84604.

Seligmann JF, et al. Investigating the poor outcomes of BRAF-mutant advanced colorectal cancer: analysis from 2530 patients in the randomized clinical trials. Ann Oncol 2017 Mar 1;28(3):562-568.

Sepulveda AR, et al. Molecular Biomarkers for the Evaluation of Colorectal Cancer: Guideline From the American Society for Clinical Pathology, College of American Pathologists, Association for Molecular Pathology, and the American Society of Clinical Oncology. J Clin Oncol 2017 May 1;35(13):1453-1486.

*Therkildsen C, et al. The predictive value of KRAS, NRAS, BRAF, PIK3CA, and PTEN for anti-EGFR treatment in metastatic colorectal cancer: a systematic review and meta-analysis. Acta Oncol 2014 Jul;53(7):852-64.

*Van Cutsem E, et al. KRAS status and efficacy in the first-line treatment of patients with metastatic colorectal cancer (mCRC) treated with FOLFIRI with or without cetuximab: The CRYSTAL experience. J Clin Oncol 2008; 26(15 Suppl):abstract 2. Presented at 2008 annual meeting of the American Society of Clinical Oncology; Chicago, IL.

* key article

SUBJECT: GENOTYPING - RAS MUTATION ANALYSIS IN METASTATIC COLORECTAL CANCER (KRAS/NRAS)	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
POLICY NUMBER: 2.02.41 CATEGORY: Laboratory	PAGE: 6 OF: 6

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=79&CtrctrSelected=298*1&Ctrctr=298&s=41&DocType=Active&bc=AggAAAIbAAAA&