

## Evidence Based Guideline

# KRAS Mutation Analysis in Cancer

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### Description of Procedure or Service

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#### **KRAS Mutation Analysis in Metastatic Colorectal Cancer**

Cetuximab (Erbix®<sup>®</sup>, ImClone Systems) and panitumumab (Vectibix®<sup>®</sup>, 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.

The RAS-RAF-MAP kinase pathway is activated in the 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 KRAS gene can harbor oncogenic mutations that result in a constitutively activated protein, independent of EGFR ligand binding, rendering antibodies to the upstream EGFR ineffective. KRAS mutations are found in approximately 30%–50% of colorectal cancer (CRC) tumors and are common in other tumor types

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.

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.

This guideline summarizes the evidence for using tumor cell KRAS mutational status as a predictor of non-response to EGFR-targeted therapy with monoclonal antibodies cetuximab and panitumumab in patients with metastatic CRC.

#### **KRAS Mutation Analysis in Non-small Cell Lung Cancer (NSCLC)**

The epidermal growth factor receptor (EGFR), a receptor tyrosine kinase (TK), is frequently overexpressed and activated in non-small cell lung cancer (NSCLC). Two EGFR tyrosine kinase inhibitor (TKI) drugs, erlotinib and gefitinib, block intracellular receptor phosphorylation, dampening signal transduction through pathways downstream to the EGF receptor, such as the RAS/RAF/MAPK cascade. RAS proteins are G-proteins that cycle between active and inactive 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 important in cancer cell proliferation, invasion, metastasis, and stimulation of neovascularization.

The KRAS gene (which encodes for the RAS proteins) can harbor oncogenic mutations that result in a constitutively activated protein, independent of signaling from the EGF receptor, possibly rendering a tumor

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resistant to therapies that target the EGF receptor (e.g., TKIs). KRAS mutations are found in approximately 15%–30% of lung adenocarcinomas.

Erlotinib (Tarceva®) received approval from the U.S. Food and Drug Administration (FDA) in November 2004 as salvage therapy for advanced NSCLC, based on results of a phase III clinical trial that demonstrated a modest survival benefit: 6.7 months median survival compared to 4.7 months in the placebo group. Gefitinib (Iressa®) was approved by the FDA in 2003 through the agency's accelerated approval process, based on the initially promising results of phase II trials. The labeled indication was limited to patients with NSCLC who had failed 2 or more prior chemotherapy regimens. However, in December 2004, results of phase III trials became available, suggesting that gefitinib was not associated with a survival benefit. In May 2005, the FDA revised the labeling of gefitinib to further limit its use to patients who were currently benefiting from the drug, or who had benefited in the past, and that no new patients were to be given the drug.

Although gefitinib fell out of use in the United States in 2005, it continued to be used elsewhere in the world, and a recent study was published (“Iressa in NSCLC Trial Evaluating Response and Survival vs Taxotere,” or “INTEREST” trial) that involved 1,466 patients from 24 countries outside of the United States. (1) All of the patients had advanced or metastatic disease and had been previously treated with at least 1 platinum-containing regimen, and were randomized to receive either gefitinib or docetaxel. Of the 1,466 patients, 1433 were evaluable. Objective tumor response rates and progression-free and overall survival were similar for the 2 groups; however, gefitinib was associated with lower rates of treatment-related adverse events than docetaxel. The authors state that based on their findings, they are hopeful that gefitinib can return as a treatment for lung cancer in the United States.

Because gefitinib is currently in very limited use in the United States, and only as part of a special access program, this policy will only address studies that assess the response to erlotinib in relation to the presence or absence of KRAS mutations in NSCLC.

KRAS mutation analysis is commercially available to test NSCLC from Genzyme Genetics and Medical Solutions™.

Several studies have reported that somatic mutations in the EGFR gene TK ATP-binding domain predict sensitivity to these targeted therapies.

**\*\*\*Note: The Evidence Based Guideline on KRAS Mutation Analysis is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.**

### Evidence Based Guideline for KRAS Mutation Analysis

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KRAS mutation analysis may be appropriate to predict nonresponse to anti-EGFR monoclonal antibodies cetuximab and panitumumab in the treatment of metastatic colorectal cancer.

### Medical Evidence regarding KRAS Mutation Analysis indicates it is not recommended in the following situations:

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- A. KRAS mutation analysis is not recommended for indications not listed above.
- B. Analysis of somatic mutations of the KRAS gene is not recommended as a technique to predict treatment response to erlotinib in non-small cell lung carcinoma.

## Benefits Application

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Please refer to certificate for availability of benefit. This guideline relates only to the services or supplies described herein. Benefits may vary according to benefit design; therefore certificate language should be reviewed before applying the terms of the policy.

## Billing/Coding/Physician Documentation Information

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This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at [www.bcbsnc.com](http://www.bcbsnc.com). They are listed in the Category Search on the Medical Policy search page.

*Applicable codes: S3713*

## Medical Term Definitions

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### **epidermal growth factor receptor**

protein found on the surface of some cells and to which epidermal growth factor binds, causing the cells to divide. It is found at abnormally high levels on the surface of many types of cancer cells, so these cells may divide excessively in the presence of epidermal growth factor.

### **monoclonal antibody**

a highly specific antibody produced in large quantity by the clones of single hybrid cell formed in the laboratory by the fusion of a B cell (lymphocyte) with a tumor cell.

### **vascular endothelial growth factor**

a soluble factor that acts through specific cell-surface receptors on endothelial cells to critically regulate new blood vessel formation.

## Scientific Background and Reference Sources

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BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.53, 10/07/08

BCBSA TEC Assessment [Electronic Version]. October 2008

Karapetis CS, Khambata-Ford S, Jonker DJ, et al. K-ras Mutations and Benefit from Cetuximab in Advanced Colorectal Cancer. *N Engl J Med* 2008;359:1757-1765

Khambata-Ford S, Garrett CR, Meropol NJ, 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; 25(22):3230-7

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

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National Comprehensive Cancer Network (NCCN). Clinical practice guidelines in oncology: Non-small cell lung cancer. v.2.2009. Retrieved 3/13/09 from [http://www.nccn.org/professionals/physician\\_gls/PDF/](http://www.nccn.org/professionals/physician_gls/PDF/)

## Policy: KRAS Mutation Analysis in Cancer

nscl.pdf.

Senior Medical Director - 3/2009

Specialty Matched Consultant Advisory Panel - 8/2009

### Policy Implementation/Update Information

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- 1/12/09 New Evidence Based Guideline entitled; KRAS Mutation Analysis in Metastatic Colorectal Cancer.
- 4/13/09 Policy name changed from KRAS Mutation Analysis in Metastatic Colorectal Cancer to KRAS Mutation Analysis in Cancer. Updated the "Description" of KRAS mutation analysis in metastatic colorectal cancer. Added information in the "Description" section specific to KRAS Mutation Analysis in Non-Small Cell Lung Cancer (NSCLC). Added the following statement to the "When Not Recommended" section; "Analysis of somatic mutations of the KRAS gene is not recommended as a technique to predict treatment response to erlotinib in non-small cell lung carcinoma." Senior Medical Director reviewed 3/16/2009. References added. (btw)
- 10/12/09 Specialty Matched Consultant Advisory Panel review 8/28/09. No changes to evidence based guideline. Added new HCPCS code "S3713" to the "Billing/Coding" section. (btw)

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Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.