

## Evidence Based Guideline

### KRAS Mutation Analysis in Cancer

**File Name:** kras\_mutation\_analysis\_in\_cancer  
**Origination:** 1/2009  
**Last CAP Review:** 8/2011  
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**Last Review:** 11/2011

#### 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. These proteins 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 BRAF encodes a protein kinase and is involved in intracellular signaling and cell growth and is a principal downstream effector of KRAS. BRAF mutations occur in less than 10–15% of colorectal cancers and appear to be a marker of poor prognosis.

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. . It has been shown that patients with a KRAS mutant tumor do not respond to cetuximab or panitumumab. However, there are still patients with KRAS wild-type tumors that do not respond to these agents, suggesting that other factors, such as alterations in other EGFR effectors could drive resistance to anti-EGFR therapy, and therefore, BRAF mutations are now increasingly being investigated in metastatic colorectal cancer. KRAS and BRAF mutations are considered to be mutually exclusive.

KRAS and BRAF mutation analyses using polymerase chain reaction (PCR) methodology are 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 and BRAF mutational status as a predictor of nonresponse 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

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overexpressed and activated in non-small cell lung cancer (NSCLC). Anti-EGFR drugs that target EGFR include the tyrosine kinase inhibitors (TKIs) and monoclonal antibodies. These targeted therapies 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. These proteins 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 resistant to therapies that target the EGF receptor.

## **TKIs**

### **Two TKIs are used to treat NSCLC: erlotinib and gefitinib.**

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. 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 two 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 guideline will only address studies that assess the response to erlotinib in relation to the presence or absence of KRAS mutations in NSCLC.

## **Anti-EGFR monoclonal antibodies**

Anti-EGFR monoclonal antibodies include cetuximab and panitumumab. Recent conclusive evidence has shown that patients with metastatic colorectal cancer whose tumors harbor KRAS mutations do not respond to EGFR monoclonal antibodies, as summarized in a TEC Assessment. Cetuximab is used in combination with chemotherapy in patients with advanced or recurrent NSCLC as first-line and maintenance therapy.

KRAS mutation analysis is commercially available to test NSCLC, and laboratories performing the test include Genzyme Genetics and Medical Solutions™.

Several studies have shown that EGFR and KRAS mutations are mutually exclusive. Although

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several of the studies outlined in this guideline that analyzed KRAS mutations also tested for other markers in NSCLC (e.g., EGFR mutations), only the data from each study as they relate to KRAS are presented in the guideline.

**\*\*\*Note: This Evidence Based Guideline 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 in Metastatic Colorectal Cancer**

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

Clinical trial data show that patients with KRAS-mutated metastatic colorectal cancer 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 expedites the use of alternative therapies

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

Not applicable.

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

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

KRAS mutation analysis is not recommended for indications not listed above.

BRAF mutation analysis is not recommended to predict nonresponse to anti-EGFR monoclonal antibodies cetuximab and panitumumab in the treatment of metastatic colorectal cancer.

The data for patients with metastatic colorectal cancer and a BRAF mutation have shown consistently that a BRAF mutation is a poor prognostic marker, as it is associated with shorter PFS and OS regardless of treatment. However, the data for a BRAF mutation predicting response to anti-EGFR therapy are limited by small numbers of patients and conflicting results among studies, with recent data (currently unpublished) from the CRYSTAL trial suggesting that patients with KRAS WT/BRAF mutant tumors may respond to anti-EGFR therapy. Nonconcurrent subgroup analyses of BRAF mutations in patients previously randomized in the large trials in which KRAS mutations predicted nonresponsiveness to anti-EGFR therapy are necessary to confirm the current data available for BRAF mutations.

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

Analysis of somatic mutations of the KRAS gene is not recommended as a technique to predict treatment non-response to anti-EGFR therapy with the tyrosine-kinase inhibitor erlotinib and the anti-EGFR monoclonal antibody cetuximab in non-small cell lung carcinoma. No recommendation for KRAS testing is made in the NCCN guidelines as to the use of cetuximab in patients with NSCLC.

In treating NSCLC, the data on KRAS mutation status and non-response to EGFR TKI therapy have been

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based on retrospective reviews with small sample sizes and heterogeneous treatment settings, contributing to the ambiguity of the predictive value of this marker. Although studies have shown that a KRAS mutation in patients with NSCLC confers a high level of resistance to TKIs, data are insufficient to make a determination about an association between KRAS mutation status and survival in these patients.

A lack of response to the EGFR monoclonal antibodies has been established in metastatic colorectal cancer, and the use of these drugs is mostly restricted to patients with wild-type KRAS. The expectation that KRAS mutation status would also be an important predictive marker for cetuximab use in NSCLC has not been shown. In two randomized trials with nonconcurrent subgroup analyses of KRAS mutation status and the use of cetuximab with chemotherapy, KRAS mutations did not appear to identify patients who would not benefit from anti-EGFR antibodies, as the outcomes observed with cetuximab were regardless of KRAS mutational status.

## Benefits Application

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This evidence based guideline relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this guideline.

## Billing/Coding/Physician Documentation Information

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This guideline 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: 81210, 81275, 81403, 88363, S3713*

## Scientific Background and Reference Sources

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

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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

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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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Specialty Matched Consultant Advisory Panel – 8/2011

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BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.55, 1/12/2012

## 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  | Guideline 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)  |
| 6/22/10  | Policy Guideline Number(s) removed (amw)   |
| 1/4/11   | Added new 2011 CPT code, 88363 to "Billing/Coding" section. (btw)  |
| 4/12/11  | Updated "Description" section. Scientific evidence added to the "When Recommended" section indicating; "Clinical trial data show that patients with KRAS-mutated metastatic colorectal cancer 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 expedites the use of alternative therapies." Added the following information regarding BRAF to the "When Not Recommended" section; "BRAF mutation analysis is not recommended to predict nonresponse to anti-EGFR monoclonal antibodies cetuximab and panitumumab in the treatment of metastatic colorectal cancer. The data for patients with metastatic colorectal cancer and a BRAF mutation have shown consistently that a BRAF mutation is a poor prognostic marker, as it is associated with shorter PFS and OS regardless of treatment. However, the data for a BRAF mutation predicting response to anti-EGFR therapy are limited by small numbers of patients and conflicting results among studies, with recent data (currently unpublished) from the CRYSTAL trial suggesting that patients with KRAS WT/BRAF mutant tumors may respond to anti-EGFR therapy. Nonconcurrent subgroup analyses of |

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BRAF mutations in patients previously randomized in the large trials in which KRAS mutations predicted nonresponsiveness to anti-EGFR therapy are necessary to confirm the current data available for BRAF mutations.” Also added the following related to non-small cell lung cancer; “Analysis of somatic mutations of the KRAS gene is not recommended as a technique to predict treatment non-response to anti-EGFR therapy with the tyrosine-kinase inhibitor erlotinib and the anti-EGFR monoclonal antibody cetuximab in non-small cell lung carcinoma. No recommendation for KRAS testing is made in the NCCN guidelines as to the use of cetuximab in patients with NSCLC. In treating NSCLC, the data on KRAS mutation status and non-response to EGFR TKI therapy have been based on retrospective reviews with small sample sizes and heterogeneous treatment settings, contributing to the ambiguity of the predictive value of this marker. Although studies have shown that a KRAS mutation in patients with NSCLC confers a high level of resistance to TKIs, data are insufficient to make a determination about an association between KRAS mutation status and survival in these patients. A lack of response to the EGFR monoclonal antibodies has been established in metastatic colorectal cancer, and the use of these drugs is mostly restricted to patients with wild-type KRAS. The expectation that KRAS mutation status would also be an important predictive marker for cetuximab use in NSCLC has not been shown. In two randomized trials with nonconcurrent subgroup analyses of KRAS mutation status and the use of cetuximab with chemotherapy, KRAS mutations did not appear to identify patients who would not benefit from anti-EGFR antibodies, as the outcomes observed with cetuximab were regardless of KRAS mutational status.” Reviewed with Medical Director 3/23/2011. References added. (btw)

- 9/30/11 Specialty Matched Consultant Advisory Panel review 8/31/11. No change to Evidence Based Guideline. References added. (btw)
- 1/1/12 Added new 2012 CPT code, 81275, to “Billing/Coding” section. (btw)
- 1/24/12 Added new 2012 CPT code, 81210, to Billing/Coding section (btw)
- 3/30/12 Removed deleted HCPCS code S3713 from Billing/Coding section. (btw)
- 4/17/12 Added CPT code 81403 and HCPCS code S3713 to Billing/Coding section. Reference added. (btw)

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