KRAS Mutation Analysis in Non-Small Cell Lung Cancer (NSCLC)

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Next Review: 5/2015

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will not provide coverage for KRAS mutation analysis in non-small cell lung cancer (NSCLC) this is considered investigational.

Note: Genetic testing may be excluded in some contracts. Verify benefits prior to review of Medical Necessity.

When Policy Topic is covered
Not Applicable

When Policy Topic is not covered
Analysis of somatic mutations of the KRAS gene is considered investigational 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.

Description of Procedure or Service
The epidermal growth factor receptor (EGFR), a receptor tyrosine kinase (TK), is frequently 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, 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.

Background
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 U.S. in 2005, it continued to be used elsewhere in the world, and a 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 U.S. (1) All of the patients had advanced or metastatic disease and had been previously treated with at least 1 platinum-containing regimen and were randomly assigned to receive either gefitinib or docetaxel. Of the 1,466 patients, 1,433 were evaluable. Objective tumor response rates and progression-free survival (PFS) and overall survival (OS) were similar for the two groups; however, gefitinib was associated with lower rates of treatment-related adverse events than docetaxel. The authors stated that based on their findings, they are hopeful that gefitinib can return as a treatment for lung cancer in the U.S.

Because gefitinib is currently in very limited use in the U.S., 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.

**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. (2) 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. (3) Although several of the studies outlined in this policy 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 policy.

**Rationale**

This policy was originally created in 2009 and was updated annually with searches of the MEDLINE database. The most recent literature search was performed on January 19, 2014.

**KRAS and EGFR TKIs**

Data on the role of KRAS mutations in NSCLC and response to erlotinib are available from post hoc analyses of 2 phase 3 trials of TKIs in patients with wild-type (nonmutated) versus KRAS-mutated lung tumors; phase 2 trials; a large prospective study; retrospective single-arm studies; and 2 meta-analyses.

Pao et al (2005) were the first to suggest that patients with KRAS-mutated lung tumors were nonresponsive to treatment with EGFR TKIs. (4) Thirty-six patients with bronchioloalveolar carcinoma underwent KRAS mutation analysis; 9 (25%) were found to harbor KRAS mutations. Response was by a single radiologist, who was blinded to patient outcome, using RECIST (Response Evaluation Criteria in Solid Tumors). None of 9 patients with KRAS-mutated tumors responded to erlotinib (p=0.553).

Zhu et al (2008) performed a post hoc subgroup analysis of KRAS mutations in patients with advanced NSCLC who had failed standard chemotherapy and had been previously randomized to receive erlotinib or placebo. (5) The original phase 3 trial (National Cancer Institute of Canada Clinical Trials Group Study BR.21; 2005) was the first to demonstrate a significant survival advantage with the use of an EGFR TKI in previously treated NSCLC patients. (6) In post hoc analysis, 206 (28%) of the original 731 tumors were tested for KRAS mutations, which were identified in 30 patients (15%). Among the
206 tested patients, 118 (57%) were assessable for response to erlotinib. Of 98 patients with wild-type KRAS, 10 (10.2%) responded to erlotinib; of 20 patients with mutated KRAS, 1 patient (5.0%) responded (hazard ratio [HR] [erlotinib vs placebo] in patients with mutated KRAS, 1.67; 95% confidence interval [CI], 0.62 to 4.50; p=0.31); HR in wild-type patients, 0.69; 95% CI, 0.49 to 0.97; p=0.03). In Cox regression, the interaction between KRAS mutation status and treatment was not statistically significant (p=0.09).

Eberhard et al (2005) performed a post hoc subgroup analysis of KRAS mutations in previously untreated patients with advanced NSCLC who had been randomly assigned to receive chemotherapy with or without erlotinib.(7) The original phase 3 trial (TRIBUTE; 2005) randomly assigned patients to carboplatin plus paclitaxel either with or without erlotinib.(8) Of the original 1079 patients, tumor DNA from 274 patients (25%) was sequenced for KRAS mutations. Baseline demographics between patients with available tumor DNA and those without were balanced. KRAS mutations were detected in 55 of 274 patients (21%). Response rate for patients with wild-type KRAS was 26%, regardless of treatment received. In patients with KRAS-mutated tumors, response rate was 8% for those receiving chemotherapy with erlotinib and 23% for those receiving chemotherapy alone (p=0.16; 95% CI for difference: -5% to 35%); median OS was 4.4 months (95% CI, 3.4 to 12.9) in patients who received erlotinib and 13.5 months (95% CI, 11.1 to 15.9) in those who received chemotherapy alone (p=0.019).

In a 2007 phase 2, multicenter, open-label study, Jackman et al evaluated treatment response to erlotinib in chemotherapy-naïve patients 70 years of age or older who had advanced NSCLC.(9) Of 80 patients eligible for treatment, 41 (51%) had KRAS mutation analysis; 6 patients (15%) were mutation-positive, none of whom responded to erlotinib. Five (14%) of 35 patients with wild-type KRAS had a partial response.

In a 2008 phase 2 trial, Miller et al assessed response to erlotinib in 101 patients with lung bronchioloalveolar carcinoma (n=12) or adenocarcinoma, bronchioloalveolar subtype (n=89), according to KRAS mutational status.(10) Eighteen patients (18%) had KRAS-mutated tumors, and none of them responded to erlotinib (95% CI, 0% to 19%; p<0.01). In patients without a KRAS mutation, response rate was 32%. Median OS in patients with KRAS-mutated tumor was 13 months versus 21 months in patients with KRAS wild-type tumor (p=0.30).

In a 2006 phase 2 trial, Giaccone et al studied response to erlotinib in 53 chemotherapy-naïve patients with advanced NSCLC.(11) Histologic material was available to assess KRAS mutational status from 29 patients, 10 of whom (34%) had mutations. All 10 were nonresponders to erlotinib (p=0.125).

In 2009, Boldrini et al reported on the association between KRAS and EGFR mutation status and several clinical variables in 411 patients with lung adenocarcinoma, and presented a subgroup analysis of tumor response in patients treated with erlotinib or gefitinib.(12) KRAS mutations were observed in 17.9% of all patients. The subset analysis comprised 21 women with stage IV disease who received a TKI as second- or third-line therapy and were assessed for radiographic tumor response using RECIST. Mean age of this subpopulation at the time of diagnosis was 60.8 years (range, 40-86). Nineteen (90%) of 21 women were KRAS wild-type, and of those, 8 (42%) showed partial response, 4 (21%) had stable disease, and 7 (37%) had progressive disease. Two patients with KRAS mutations had progressive disease.

Schneider et al (2008) reported on the relationship between clinical benefit and putative tumor markers in a subgroup of patients participating in a global open-label, single-arm study of erlotinib in advanced NSCLC, involving 7043 patients in 52 countries (the TRUST study).(13) The subgroup in this publication was from German centers and comprised 311 patients with stage IIIIB/IV disease who were treated with erlotinib because they had failed or were not medically suitable for standard first-line chemotherapy. Tumor response was assessed using RECIST. Seventeen patients (15%) had KRAS mutations, and none had a response to erlotinib; 2 patients had stable disease. The impact of KRAS mutation status on OS (p=0.06) and PFS (p value not reported) was of borderline statistical significance. The authors concluded that current data did not support selection of patients for treatment
with erlotinib on the basis of tumor molecular characteristics and that further studies were needed to determine definitively whether patients with KRAS mutations can derive survival benefit from erlotinib.

Two meta-analyses on the relationship between KRAS mutations and response to EGFR TKI therapy follow. Data were insufficient to make a determination about an association between KRAS mutation status and PFS or OS in these meta-analyses.

Linardou et al (2008) performed a meta-analysis of 17 studies with 1008 patients, 165 (16.4%) of whom had a KRAS mutation. (14) Eligible studies reported response (complete or partial) stratified by KRAS mutational status. Primary end points were sensitivity and specificity of KRAS testing, defined as KRAS mutation carriers showing no response to erlotinib (stable disease or progressive disease) and KRAS wild-type patients showing a response, respectively. Sensitivity and specificity were assessed overall and in subgroups defined by TKI received (gefitinib and/or erlotinib), response criteria (RECIST or World Health Organization), possible selection bias, and previous chemotherapy, if any. There was no significant difference in sensitivity or specificity across subgroups. The presence of a KRAS mutation was associated with a lack of response to TKIs (sensitivity, 0.21; 95% CI, 0.16 to 0.28; specificity, 0.94; 95%, 0.89 to 0.97; positive likelihood ratio, 3.52; negative likelihood ratio, 0.84). (For the analysis, likelihood ratios were calculated by using pooled estimates for sensitivity and specificity.) The authors concluded that KRAS mutations conferred a high level of resistance to anti-EGFR therapies; however, this conclusion is tentative due to limitations of the study, such as lack of individual patient data. Prospective validation is needed. Furthermore, incomplete reporting of survival data precluded meaningful assessment of the effect of KRAS mutation on survival. Other limitations included heterogeneity of response end points, treatment regimens, and patient selection criteria, and the retrospective design of included studies.

Mao et al (2010) performed a meta-analysis of 22 studies in 1470 patients with NSCLC (1335 [91%] evaluable for response), 231 (17%) of whom had KRAS mutations.(15) Studies were heterogeneous in patient populations (smoking history, tumor histology, stage, ethnicity, treatment received) and response criteria. The primary end point was objective response rate, defined as the sum of complete and partial response. Objective response rates for patients with mutated KRAS and wild-type KRAS were 3% and 26%, respectively. Incomplete reporting of survival data precluded meaningful assessment of the effect of KRAS status on survival in NSCLC patients treated with EGFR TKIs. Data for PFS and OS stratified by KRAS status were available in 8 studies. Median PFS in KRAS-mutated and wild-type patients was 3.0 months and 3.9 months, respectively. Median OS in KRAS-mutated and wild-type patients was 4.7 months and 10.7 months, respectively. However, only 2 studies presented hazard ratios with 95% confidence intervals for PFS and OS, and therefore, pooled analysis to derive an overall HR was not performed.

Guan et al (2013) reported on 1935 consecutive patients with NSCLC who were treated at a single institution in China.(16) Patients with mutated KRAS were random matched on tumor, node, metastasis (TNM) stage, time of first visit within 1 year, and histology, to both EGFR mutation-positive and KRAS/EGFR wild-type patients. Seventy patients (4%) received EGFR TKI therapy. In this group, median PFS was 11.8 and 2.0 months in patients with EGFR and KRAS mutations, respectively, and 1.9 months in wild-type patients; in comparison with wild-type patients, PFS was statistically longer in patients with EGFR mutations (p<0.001) but no different in patients with KRAS mutations (p=0.48). The authors observed that “the presence of an EGFR mutation, but not a KRAS mutation, was predictive of responsiveness to EGFR TKI treatment.”

Fiala et al (2013) reported on a retrospective analysis of patients with squamous cell NSCLC who underwent EGFR, KRAS, and PIK3CA (phosphatidylinositol-3-kinase catalytic subunit-alpha) mutation testing.(17) Of 215 patients tested, 16 (7.4%) had mutated KRAS. Of 174 tested patients who were treated with an EGFR TKI (erlotinib or gefitinib), median PFS in 14 KRAS-mutated patients was 1.3 months versus 2.0 months in KRAS wild-type patients (n=160 [92%]); the difference was not statistically significant (Kaplan-Meier log-rank test, p=0.120). Median OS in this treated group was 5.7 months in KRAS-mutated patients versus 8.2 months in KRAS wild-type patients, a statistically
significant difference (Kaplan-Meier log-rank test; p=0.039). The authors concluded that KRAS mutation status may have a negative prognostic role but a predictive role was not confirmed. “Patients with squamous cell NSCLC harboring these mutations could benefit from targeted treatment and should not be excluded from treatment with EGFR TKIs.”

Two reviews published in 2013 concluded that, in comparison with KRAS mutation testing, EGFR mutation status is the preferred predictive marker for response to EGFR TKIs in patients with NSCLC.(18,19)

**KRAS and Anti-EGFR Monoclonal Antibodies**

Two phase 3 trials, BMS-099 and FLEX, investigated platinum-based chemotherapy with and without cetuximab in the first-line setting for advanced NSCLC. Subsequently, investigations of KRAS mutation status and cetuximab treatment were performed for both trials.

In the multicenter phase 3 BMS099 trial (2010), 676 chemotherapy-naïve patients with stage IIIIB/IV NSCLC were assigned to taxane and carboplatin with or without cetuximab.(20) The primary end point was PFS; secondary end points were overall response rate, OS, quality of life, and safety. The addition of cetuximab did not significantly improve PFS; however, there was a statistically significant improvement in overall response rate in the cetuximab group. There was a trend in OS favoring cetuximab; however, this was not statistically significant. A post hoc correlative analysis of this trial was conducted to identify molecular markers for the selection of patients most likely to benefit from cetuximab. (21) Of the original 676 enrolled patients, 202 (29.9%) had tumor samples available for KRAS testing. KRAS mutations were present in 35 patients (17%). Among patients with wild-type KRAS, OS was similar between the cetuximab-containing arm (n=85) and the chemotherapy alone arm (n=82) (HR=0.93; 95% CI, 0.67 to 1.30; p=0.68; median survival, 9.7 and 9.9 months, respectively). Among patients with KRAS mutations, OS was similar between the cetuximab-containing arm (n=13) and the chemotherapy-alone arm (n=22) (HR=0.91; 95% CI, 0.45 to 2.07; p=0.93; median survival, 16.8 and 10.8 months, respectively). Overall, the study showed no significant treatment-specific interactions between the presence of KRAS mutations and outcomes evaluated; treatment differences favoring the addition of cetuximab in the KRAS-mutated subgroup were consistent with those observed in the wild-type KRAS subgroup and in the overall study population. The authors concluded that the results do not support an association between KRAS mutation and lack of cetuximab benefit similar to that observed in patients with KRAS-mutated metastatic colorectal cancer. However, results should be interpreted with caution due to small subgroup sample sizes and retrospective nature of the analysis.

In the open-label, randomized, phase 3 FLEX trial, 1125 chemotherapy-naïve patients with stage III/IV, NSCLC were randomly assigned to receive either chemotherapy (cisplatin and vinorelbine) plus cetuximab (n=557) or chemotherapy alone (n=568).(22) The primary end point was OS. Patients who received chemotherapy plus cetuximab survived longer than those who received chemotherapy only (median OS, 11.3 months vs 10.1 months, respectively; HR for death, 0.87; 95% CI, 0.76 to 1.00; p=0.04). Subsequently, KRAS mutation testing was performed on archival tumor tissue of 395 (35%) of 1125 patients. (23) KRAS mutations were detected in 75 tumors (19%). Among patients with mutated KRAS, OS in the cetuximab-containing (n=38) and chemotherapy-alone arms (n=37) was similar (median OS, 8.9 months vs 11.1 months, respectively; HR=1.00; 95% CI, 0.60 to 1.66; p=1.0). Among patients with wild-type KRAS, OS in the cetuximab-containing (n=161) and chemotherapy-alone arms (n=159) was similar (median OS, 11.4 months vs 10.3 months, respectively; HR=0.96; 95% CI, 0.75 to 1.23; p=0.74). PFS also was similar in cetuximab-containing and chemotherapy-alone arms in patients with mutated (HR=0.97; 95% CI, 0.76 to 1.24) and wild-type (HR=0.84; 95% CI, 0.50 to 1.40) KRAS. Response rates in the cetuximab-containing arm in patients with KRAS-mutated and wild-type tumors were 36.8% and 37.3%, respectively (p=0.96). Overall, there was no indication that KRAS mutation status was predictive of cetuximab effect in NSCLC.
KRAS and EGFR TKIs

A phase 3 trial is currently actively assessing OS with the combination regimen of ARQ 197 (tivantinib, a novel MET inhibitor) plus erlotinib versus placebo plus erlotinib for the treatment of locally advanced or metastatic nonsquamous, non-NSCLC in patients who have received 1 or 2 prior systemic anticancer therapies (NCT01244191). EGFR and KRAS mutation status will be collected prior to randomization. Estimated enrollment is 988, with an estimated study completion date of July 2014.

KRAS and EGFR Monoclonal Antibodies

A phase 3 trial is currently recruiting patients to assess PFS and secondarily (OS) with dacomitinib, another selective tyrosine kinase inhibitor, compared with erlotinib for the treatment of advanced NSCLC in patients who have received one or more prior anticancer therapies (NCT01360554). KRAS mutation status will be collected at baseline. Estimated enrollment is 800, with an estimated study completion date of August 2014.

KRAS and MAPK Kinase (MEK) Inhibitors

A phase 2 trial is currently recruiting participants to assess the effect of AZD6244 (a mitogen-activated protein kinase inhibitor) with and without erlotinib in patients who have not responded to previous therapy for NSCLC (NCT01229150). KRAS mutation status will be assessed and utilized to stratify patients into treatment groups. Half of KRAS wild-type and KRAS-mutated patients will receive AZD6244 + erlotinib. Remaining wild-type patients will receive erlotinib alone, and remaining KRAS-mutated patients will receive AZD6244 alone. Outcomes of interest are PFS, clinical response rate, adverse events, and OS. Expected enrollment is 100 participants, with an estimated completion date of September 2014. Another phase 2 study recruiting several types of cancer patients, including advanced NSCLC patients, will treat KRAS-mutated patients with the MEK inhibitor, AZD6244 (NCT01306045). Expected enrollment in this study is 600 patients, with an estimated completion date of January 2017.

KRAS and Heat Shock Protein 90 (HSP90) Inhibitors

A phase 2 trial is currently recruiting patients with advanced NSCLC who have failed 2 or more previous lines of chemotherapy (NCT01124864). Patients will be assessed for EGFR, KRAS, and EML4-ALK mutations and treated with AUY922, a HSP90 inhibitor that degrades mutated EGFR. Outcomes of interest are treatment efficacy and OS. Expected enrollment is 150 participants, with an estimated completion date of November 2014.

Guidelines and Position Statements

National Comprehensive Cancer Network Guidelines(24)

Current NCCN guidelines (version 2.2014) state that KRAS mutations are associated with primary resistance to TKI therapy, and KRAS gene sequencing may be useful for selecting patients as candidates for TKI therapy. The guidelines make no specific recommendations for testing. NCCN guidelines make no recommendation for KRAS testing for the use of cetuximab in patients with NSCLC.

College of American Pathologists (CAP) Joint Guideline(25)
In 2013, CAP, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology published evidence-based guidelines for molecular testing to select patients with lung cancer for treatment with EGFR and alkaline phosphatase TKI therapy. Based on good quality evidence (category B), KRAS mutation testing is not recommended as a sole determinant of EGFR TKI therapy. The guideline authors state, “The significance of KRAS mutational analysis may become increasingly important with the further development of new therapies targeting downstream RAS pathways, such as PI3K/AKT/mTOR and RAS/RAF/MEK, but at this time, the absence of a KRAS mutation does not add clinically useful information to the EGFR mutation result and should not be used as a determinant of EGFR TKI therapy.”

Summary

It remains unclear whether assessment of KRAS mutation status will be clinically useful with regard to anti-epidermal growth factor receptor (EGFR) therapy in the treatment of non-small-cell lung cancer (NSCLC).

KRASand EGFR tyrosine kinase inhibitors

Data on the role of KRAS mutations in NSCLC and response to erlotinib are available from post hoc analysis of 2 phase 3 trials that compared TKI efficacy in patients with wild-type (nonmutated) versus KRAS-mutated lung tumors; phase 2 trials; a large prospective study; retrospective single-arm studies; and 2 meta-analyses. Although studies have shown that KRAS mutations in patients with NSCLC confer a high level of resistance to tyrosine kinase inhibitors (TKIs), data are insufficient to assess any association between KRAS mutation status and survival in these patients.

KRASand anti-EGFR Monoclonal Antibodies

A lack of response to EGFR monoclonal antibodies has been established in metastatic colorectal cancer, and use of these drugs is largely restricted to patients with wild-type KRAS. The expectation that KRAS mutation status also would be an important predictive marker for cetuximab response in NSCLC has not been shown. In 2 randomized trials with post hoc analyses of KRAS mutation status and use of cetuximab with chemotherapy, KRAS mutations did not identify patients who would not benefit from anti-EGFR antibodies, as outcomes with cetuximab were similar regardless of KRAS mutation status.

Future Challenges

A 2010 editorial(26) highlighted the challenges in biomarker testing and validation in patients with NSCLC, as summarized here. First, the purest evaluation of a biomarker would be from a study of treatment compared with observation or placebo, allowing for assessment of the prognostic importance of the marker in the untreated control arm and assessment of the predictive effect by comparing treated and untreated arms. However, it is not feasible to conduct placebo-controlled studies in first-, second-, or third-line treatment of NSCLC because agents of proven benefit are available. Therefore, studies must compare targeted agents with another treatment or must add targeted therapy to standard therapy. A further confounding factor is that the effect of standard therapy also may differ in biomarker subsets. Finally, many studies of targeted therapies suffer from crossover at the time of disease progression, impairing the assessment of overall survival.

Results of ongoing phase 3 trials may guide future management of NSCLC with TKIs and anti-EGFR monoclonal antibodies according to KRAS mutation status.

References


Billing Coding/Physician Documentation Information

81275  KRAŠ (v-Ki-ras2 Kirsten rat sarcoma viral oncogene) (eg, carcinoma) gene analysis, variants in codons 12 and 13

81403  Molecular pathology procedure, Level 4 (eg, analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)

88363  Examination and selection of retrieved archival (ie, previously diagnosed) tissue(s) for molecular analysis (eg, KRAS mutational analysis)

Code S3713 (KRAS mutation analysis testing) was deleted in 2012.

Additional Policy Key Words

N/A

Policy Implementation/Update Information

1/1/11  New policy; considered investigational.
5/1/11  No policy statement changes.
9/1/11  Policy statement revised to indicate that testing to predict non-response to anti-EGFR monoclonal antibody (cetuximab) is also investigational.
5/1/12  No policy statement changes.
5/1/14  No policy statement changes.

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