

KRAS Mutations and Epidermal Growth Factor Receptor Inhibitor Therapy in Metastatic Colorectal Cancer



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Executive Summary

Background

Cetuximab (Erbix[®], ImClone Systems) and panitumumab (Vectibix[®], Amgen) are monoclonal antibodies that bind to the epidermal growth factor receptor (EGFR), preventing binding and activation of downstream signaling pathways vital for cancer cell proliferation, invasion, metastasis, and stimulation of neovascularization.

Cetuximab and panitumumab are approved by the U.S. Food and Drug Administration (FDA) in the treatment of metastatic colorectal cancer 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 colorectal cancer have tumors that harbor a somatic *KRAS* mutation that may affect tumor response to EGFR inhibitors.

Objective

This Assessment evaluates and summarizes the evidence of using tumor cell *KRAS* mutational status as a predictor of nonresponse to EGFR-targeted therapy with monoclonal antibodies cetuximab and panitumumab in patients with metastatic colorectal cancer.

Search Strategy

A MEDLINE[®] search (via PubMed) was performed through October 2008 to obtain references to original reports on anti-EGFR therapy and *KRAS* mutation analysis in metastatic colorectal cancer, using keywords “EGFR,” “epidermal growth factor receptor,” “*KRAS*,” “cetuximab,” “panitumumab,” and “metastatic colorectal cancer.” The electronic search was limited to English-language studies of human subjects. Review articles provided background information. The bibliographies of retrieved articles were consulted to identify references that may have been overlooked by the electronic search. The electronic search was supplemented with online abstracts from the 2008 American Society of Clinical Oncology (ASCO) annual meeting. Manufacturers and other vendor websites were consulted for information on commercial laboratory assays and drug package inserts.

Selection Criteria

Studies were selected for inclusion in the Assessment if they were full-length, peer-reviewed articles published in an English-language journal and studied metastatic colorectal cancer and patient response to anti-EGFR antibodies in relation to tumor *KRAS* mutational status. To provide more complete information, data from phase II and III randomized trials presented at the 2008 American Society of Clinical Oncology (ASCO) meeting were included if full presentation slides of the study were available online.



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Main Results

Five randomized, controlled trials have performed nonconcurrent subgroup analyses of the efficacy of EGFR inhibitors in patients with wild-type versus mutated *KRAS* in metastatic colorectal cancer. The data have consistently shown a lack of clinical response to cetuximab and panitumumab in patients with mutated *KRAS*, with tumor response and prolongation of progression-free and overall survival observed only in wild-type *KRAS* patients. One of the randomized trials showed decreased progression-free survival in patients with mutated *KRAS* who received cetuximab.

Five single-arm studies that have retrospectively analyzed *KRAS* mutation status and tumor response rate in patients with metastatic colorectal cancer have shown a consistent lack of response to cetuximab or panitumumab in patients with a *KRAS* mutation. Two of these 5 studies have also shown progression-free and overall survival benefit with the use of EGFR inhibitors is limited to patients with wild-type *KRAS*.

These data are sufficient to show the clinical validity of *KRAS* mutation testing and its clinical utility in guiding therapy selection for patients with metastatic colorectal cancer. The analytic validity of *KRAS* mutation testing by polymerase-chain reaction (PCR) methods is established as a commercially available laboratory test in CLIA-licensed laboratories.

Author's Comments and Conclusions

The data show that the clinical benefit of using EGFR inhibitors in treating metastatic colorectal cancer, either as monotherapy or in combination with other treatment regimens, is not seen in patients with *KRAS*-mutated tumors. These data support knowing a patient's tumor mutation status before consideration of use of an EGFR inhibitor in the treatment regimen. Identifying patients whose tumors express mutated *KRAS* will avoid exposing patients to ineffective drugs, avoid exposure to unnecessary drug toxicities, and expedite the use of the best available alternative therapy.

Based on the available evidence, the Blue Cross and Blue Shield Association Medical Advisory Panel made the following judgments about whether use of *KRAS* mutation analysis to predict nonresponse to anti-EGFR monoclonal antibodies cetuximab and panitumumab to treat metastatic colorectal cancer meets the Blue Cross and Blue Shield Association Technology Evaluation Center (TEC) criteria.

1. The technology must have final approval from the appropriate governmental regulatory bodies.

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 FDA is not required when the assay is performed in a laboratory that is licensed by CLIA for high-complexity testing.

2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.

The evidence compiled from 5 randomized trials and 5 single-arm studies is sufficient to conclude that patients with mutated *KRAS* tumors in the setting of metastatic colorectal cancer do not respond to anti-EGFR monoclonal antibody therapy, do not derive survival benefit, and may experience decreased progression-free survival.

3. The technology must improve the net health outcome; and

4. The technology must be as beneficial as any established alternatives.

There is sufficient evidence to permit conclusions regarding the use of *KRAS* mutation analysis when the use of an EGFR inhibitor is a consideration in the management of a patient with metastatic colorectal cancer.

5. The improvement must be attainable outside the investigational settings.

The improvement in health outcomes in testing for a KRAS mutation in a patient with metastatic colorectal cancer prior to treatment with an anti-EGFR monoclonal antibody can be attained outside of the investigational setting.

Based on the above, use of KRAS mutation analysis to predict nonresponse to the anti-EGFR monoclonal antibodies cetuximab and panitumumab to treat metastatic colorectal cancer meets the TEC criteria.

Contents			
Assessment Objective	4	Discussion	14
Introduction	4	Summary of Application of the Technology Evaluation Criteria	14
Methods	6	References	16
Formulation of the Assessment	7	Appendix	18
Review of Evidence	7		

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Assessment Objective

Cetuximab (Erbix[®], ImClone Systems) and panitumumab (Vectibix[®], Amgen) are monoclonal antibodies that bind to the epidermal growth factor receptor (EGFR), preventing binding and activation of downstream signaling pathways vital for cancer cell proliferation, invasion, metastasis, and stimulation of neovascularization.

Cetuximab and panitumumab are approved by the U.S. Food and Drug Administration (FDA) in the treatment of metastatic colorectal cancer 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 metastatic colorectal cancer have tumors that harbor a somatic *KRAS* mutation that may affect tumor response to EGFR inhibitors.

The objective of this Assessment is to evaluate tumor-cell *KRAS* mutational status as a predictor of nonresponse to EGFR-targeted therapy with the monoclonal antibodies cetuximab and panitumumab in patients with metastatic colorectal cancer, thereby aiding in the selection of the most effective treatment regimen for each patient.

Introduction

Metastatic Colorectal Cancer Therapy

Colorectal cancer is the third most commonly diagnosed cancer in men and women in the U.S., and the third leading cause of cancer death (Ng et al. 2008). In 2008, there will be an estimated 108,070 new cases and 49,960 deaths from colon cancer in the U.S. (Physician Data Query [PDQ] National Cancer Institute [NCI] 2008). Up to 20% of patients with colorectal cancer will present with metastases, with 5-year survival less than 10% (Ng et al. 2008). Supportive care alone provides a median survival of approximately 6 months for patients with metastatic colorectal cancer (Jackson et al. 2008).

For more than 40 years, 5-fluorouracil (5-FU) has been the primary agent in chemotherapeutic regimens in the treatment of metastatic colorectal cancer, with single agent response rate of 20–25% in advanced-stage disease (Wilson et al. 2007). In the past decade, the

introduction of newer cytotoxic agents such as irinotecan and oxaliplatin, when used in combination with 5-FU have increased the response rate to 40–50% (Wilson et al. 2007) and have been shown to prolong progression-free survival (PFS) and overall survival (OS) to 20–24 months (Jackson et al. 2008).

More recent progress has been made with the use of targeted biologic therapies, such as the monoclonal antibodies that target the epidermal growth factor receptor (EGFR) or that inhibit vascular endothelial growth factor (VEGF). The VEGF inhibitor bevacizumab (Avastin[®], Genentech) was the first such therapy to demonstrate clinical benefit in metastatic colorectal cancer, prolonging overall survival by 5 months in patients with metastatic colorectal cancer when used in combination with conventional chemotherapeutic agents (Ng et al. 2008).

The anti-EGFR monoclonal antibodies cetuximab and panitumumab are presently approved for use by the FDA in metastatic colorectal cancer for refractory disease. Cetuximab is an immunoglobulin (Ig)G1 human-murine, chimeric, monoclonal antibody that binds with high affinity to the external cell surface domain of EGFR, competitively inhibiting binding of natural ligands to EGFR (Lee et al. 2007). This binding by cetuximab blocks receptor phosphorylation and downstream growth signaling, which induces receptor internalization and reduction in the level of EGFR expression on the cell surface (Lee et al. 2007). Cetuximab also exerts antitumor effect by inducing cell-cycle arrest and apoptosis, and it is thought to possibly activate immune-mediated mechanisms such as antibody-dependent and/or complement-dependent cellular cytotoxicity (Lee et al. 2007). Panitumumab is a fully humanized IgG2 antibody that, like cetuximab, binds to EGFR with high affinity, inhibiting downstream signaling by the same mechanisms. However, unlike cetuximab, panitumumab is not thought to mediate its antitumor effects via immunologic mechanisms (Lee et al. 2007).

Toxicities are associated with the use of these monoclonal antibodies. Some of the most frequently reported adverse events in patients with advanced colorectal cancer treated with cetuximab monotherapy were (ImClone 2007):

- acneform rash/desquamation (89%)
- fatigue (89%)
- abdominal pain (59%)

- dyspnea (48%)
- constipation (46%)
- diarrhea (39%)
- vomiting (37%)
- infection (35%)
- fever (30%)
- stomatitis (25%)
- infusion reactions (20%)

The most common grade 3/4 adverse events (graded using National Cancer Institute [NCI] Common Toxicity Criteria [CTC] v. 2.0, grade scale 0–4) with cetuximab monotherapy included:

- fatigue (35%)
- dyspnea (16%)
- infection (15%)
- acneform rash/desquamation (12%)

A randomized, controlled trial of 229 patients with metastatic colorectal cancer who received panitumumab monotherapy (Amgen 2008) reported:

- dermatologic toxicities (90%; severe in 16%)
- ocular toxicities (15%)
- and other toxicities including stomatitis, mucositis, infectious complications subsequent to the development of the dermatologic toxicities, and infusion reactions

Several studies have demonstrated the efficacy of anti-EGFR monoclonal antibodies as monotherapy or in combination with other chemotherapies, as first-line or second- and subsequent-line treatment in metastatic colorectal cancer

First-Line Therapy. The CRYSTAL trial (Van Cutsem et al. 2007a), reported as an abstract, randomized 1,198 patients to receive either cetuximab and FOLFIRI (irinotecan, leucovorin, 5-FU) or FOLFIRI alone as first-line therapy for metastatic colorectal cancer. A statistically significant improvement in progression free survival (PFS) was seen in the population that received combination therapy, with a rate of 34% at 1 year versus 23% in the patients who received FOLFIRI only (hazard ratio [HR]=0.85; $p=0.048$). Tumor response rate was 47% (95% CI: 43–51%) with FOLFIRI plus cetuximab versus 39% (95% CI: 35–43%) with FOLFIRI alone ($p=0.038$).

The OPUS trial (Bokemeyer et al. 2007), reported as an abstract, randomized 337 patients to either cetuximab and FOLFOX (oxaliplatin, leucovorin, 5-FU) or FOLFOX

alone. Overall tumor response rate in the cetuximab plus FOLFOX group was 45.6% versus 35.7% in the FOLFOX-only arm (odds ratio [OR] 1.516; $p=0.064$). No difference in progression-free survival was observed between the two groups.

Second- and Subsequent-line Therapy. The BOND study (Cunningham et al. 2004) randomized 329 patients with irinotecan-refractory metastatic colorectal cancer to cetuximab monotherapy or cetuximab plus irinotecan (second-, third-line treatment). The response rate in the combination therapy group (22.9%; 95% CI: 17.5–29.1%) was significantly higher than the monotherapy group (10.8%; 95% CI: 5.7–18.1%). The median time to progression was significantly longer in the combination-therapy group (4.1 vs. 1.5 months; $p<0.001$).

A trial using cetuximab versus best supportive care as third-line therapy randomized 572 patients and showed improved PFS and OS in the cetuximab group (Jonker et al. 2007). Compared with best supportive care, cetuximab treatment was associated with a significant improvement in OS (HR for death 0.77; 95% CI: 0.64–0.92; $p=0.005$) and in PFS (HR for disease progression or death 0.68; 95% CI: 0.57–0.80; $p<0.001$). Median OS in the cetuximab group was 6.1 months versus 4.6 in the best-supportive-care group.

A study of third-line therapy for metastatic colorectal cancer randomized 463 patients to either panitumumab or best supportive care (Van Cutsem et al. 2007b). Patients who received panitumumab showed a mean (standard error) PFS time of 13.8 (± 0.8) weeks versus 8.5 (± 0.5) with best supportive care. Median PFS was 8 weeks (95% CI: 7.9–8.4) with panitumumab versus 7.3 (95% CI: 7.1–7.7). Objective response rates were 10% for panitumumab versus 0% for best supportive care ($p<0.0001$).

As some of these studies assessing the efficacy and safety of anti-EGFR monoclonal antibodies in metastatic colorectal cancer treatment were completed, differences in tumor response rate and survival among patients prompted investigators to reevaluate these parameters after stratifying patients by *KRAS* mutational status. The discovery that patients with colorectal tumors harboring *KRAS* mutations did not appear to respond to anti-EGFR monoclonal antibodies has contributed to a recent paradigm

shift in the management of colorectal cancer, with increasing emphasis on individualized treatment strategies (Wilson et al. 2007).

EGFR Inhibition in the Treatment of Metastatic Colorectal Cancer

EGFR belongs to the ErbB family of receptor tyrosine kinases, which are stimulated upon ligand binding. The receptor is composed of three domains: an extracellular binding, trans-membrane and intracellular tyrosine kinase (Ponz-Sarvisé et al. 2007; Spano et al. 2008). Binding of a ligand by EGFR initiates a complex cascade of events that can switch on several pathways that result in cellular responses such as cell proliferation, migration, and survival.

A majority of human epithelial cancers are marked by functional activation of growth factors and receptors of the EGFR family (Ciardiello et al. 2008), and EGFR is overexpressed in more than 85% of tumors in patients with metastatic colorectal cancer (Lee et al, 2007).

KRAS

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 tumors and are common in other tumor types (Amado et al. 2008).

FDA Status. *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 FDA is not required when the assay is performed in a laboratory that is licensed by CLIA for high-complexity testing.

Methods

Search Methods

A MEDLINE® search (via PubMed) was performed through October 2008 to obtain references to original reports on anti-EGFR therapy and *KRAS* mutation analysis in metastatic colorectal cancer, using keywords “EGFR,” “epidermal growth factor receptor,” “KRAS,” “cetuximab,” “panitumumab,” and “metastatic colorectal cancer.” The electronic search was limited to English-language studies of human subjects. Review articles provided background information. The bibliographies of retrieved articles were consulted to identify references that may have been overlooked by the electronic search. The electronic search was supplemented with online abstracts from the 2008 American Society of Clinical Oncology (ASCO). Manufacturers and other vendor websites were consulted for information on commercial laboratory assays and drug package inserts.

Study Selection

Studies were selected for inclusion in the Assessment if they were full-length, peer-reviewed articles published in an English-language journal and studied metastatic colorectal cancer and patient response to anti-EGFR antibodies in relation to tumor *KRAS* mutational status. To provide more complete information, data from phase II and III randomized trials presented at the 2008 ASCO meeting were included if full presentation slides of the study were available online.

Medical Advisory Panel Review

This Assessment was reviewed by the Blue Cross and Blue Shield Association Medical Advisory Panel (MAP) on September 16, 2008. In order to maintain the timeliness of the scientific information in this Assessment, literature searches were performed subsequent to the Panel’s review (see “Search Methods”). If the search updates identified any additional studies that met the criteria for detailed review, the results of these studies were included in the tables and text where appropriate. There were no studies that would change the conclusions of this Assessment.

Formulation of the Assessment

Patient Indications

Patient indications included in this review of evidence are individuals with metastatic colorectal cancer treated with anti-EGFR antibody therapies cetuximab or panitumumab with or without chemotherapy who have undergone *KRAS* mutational status testing.

Technologies to Be Compared

The technology of interest is *KRAS* mutation analysis accuracy in predicting nonresponse to anti-EGFR therapy in patients with metastatic colorectal cancer. The key comparison is the lack of clinical response to anti-EGFR therapy observed in patients whose tumor samples carry somatic *KRAS* gene mutations versus the clinical response in patients with tumors that have the wild-type *KRAS* gene.

Health Outcomes

Health outcomes of interest include overall survival (where available), avoiding ineffective treatment and drug toxicities, and preventing delay of best available alternative therapy.

Specific Assessment Questions

This Assessment uses a conceptual evaluation framework that examines the clinical validity, clinical utility, and analytic validity of genetic tests, as defined by the U.S. National Human Genome Research Institute, National Institutes of Health (<http://www.genome.gov/10002404>) and the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group (<http://www.geneticsinmedicine.org/pt/re/gim/pdfhandler.00125817-900000000-99948.pdf>). The clinical validity of a genetic test defines its ability to detect or predict the presence or absence of the phenotype, which in the case of this review is defined as clinical response to treatment with anti-EGFR monoclonal antibodies. The clinical utility of a genetic test refers to the likelihood that using the test results to help make management decisions will lead to an improved health outcome. The analytical validity of a genetic test defines its ability to accurately and reliably measure the genotype of interest in blood or tissue samples. This framework is used to assess the overall value of tumor cell *KRAS* gene mutation analysis to identify those patients unlikely to respond to anti-EGFR therapy with cetuximab or panitumumab.

1. What is the clinical validity of *KRAS* gene mutation analysis to predict nonresponse to anti-EGFR monoclonal antibodies in metastatic colorectal cancer?
2. What is the clinical utility of *KRAS* gene mutation analysis to predict nonresponse to anti-EGFR monoclonal antibodies in metastatic colorectal cancer?
3. What is the analytic validity of *KRAS* gene mutation analysis to predict nonresponse to anti-EGFR monoclonal antibodies in metastatic colorectal cancer?

Review of Evidence

In this section, evidence supporting the use of tumor cell *KRAS* gene mutation analysis to identify patients with metastatic colorectal cancer who are not expected to respond to anti-EGFR monoclonal antibody therapy is evaluated.

1. What is the clinical validity of *KRAS* gene mutation analysis to predict nonresponse to anti-EGFR monoclonal antibodies in metastatic colorectal cancer?

Patients from 5 randomized, controlled trials using cetuximab or panitumumab for metastatic colorectal cancer have been re-evaluated for tumor response rate (in 4 of the studies), PFS and OS (in 2 of the studies), according to *KRAS* mutational status. Currently, data from two of these trials are available in full-length manuscript form (Amado et al. 2008; Karapetis et al. 2008), and three as full presentation slides (Van Cutsem et al. 2008; Bokemeyer et al. 2008; Punt et al. 2008). Quality ratings for the 5 randomized, controlled trials are available in the Appendix. Five single-arm studies provide data on *KRAS* mutations in tumor samples from patients with metastatic colorectal cancer and tumor response rates, with 2 of the 5 providing additional data on PFS and OS. The studies administered cetuximab with or without chemotherapy, or panitumumab as monotherapy.

Randomized, Controlled Trials (Cetuximab or Panitumumab)

Amado et al. (2008). Amado et al. (2008) performed a subgroup analysis of *KRAS* tumor mutations in a patient population that had been previously randomized to panitumumab versus best supportive care as third-line

therapy for chemotherapy-refractory metastatic colorectal cancer (Van Cutsem et al. 2007b). The design of the original study was that of a multicenter, randomized, controlled trial, that was not blinded because of expected skin toxicity related to panitumumab administration. Patients were randomly assigned 1:1 to receive panitumumab or best supportive care. Random assignment was stratified by ECOG performance status (0 or 1 vs. 2) and geographic region. Crossover from best supportive care to the panitumumab arm was allowed after disease progression. One-hundred seventy-six of the 232 patients originally assigned to best supportive care alone crossed over to the panitumumab arm (median time to cross over was 7 weeks [range 6.6–7.3]).

Of the 465 patients in the original study, 427 (92%) were included in the *KRAS* subgroup analysis. *KRAS* status could not be determined in 36 patients because of unavailable tumor sample or samples with insufficient or poor quality DNA. Forty-three percent of the *KRAS*-evaluable patients had *KRAS*-mutated tumors, and the distribution of *KRAS* mutations was similar between treatment arms. A central laboratory performed the *KRAS* mutational analysis in a blinded fashion, using formalin-fixed, paraffin-embedded tumor sections using a validated *KRAS* mutation kit (DxS Ltd, Manchester, U.K.) that identifies 7 somatic mutations located in codons 12 and 13 using real-time PCR.

Patient demographics and baseline characteristics were balanced between the wild-type and mutated groups for panitumumab versus best supportive care including patient age, sex and ECOG performance status. The interaction between mutational status and PFS was examined controlling for randomization factors. PFS and tumor response rate was assessed radiographically every 4 to 8 weeks until disease progression using Response Evaluation Criteria

in Solid Tumors (RECIST) criteria by blinded, central review. In the *KRAS*-assessable population, 20% of patients had a treatment-related grade 3 or 4 adverse event. As shown in Table 1, the relative effect of panitumumab on PFS was significantly greater among patients with wild-type *KRAS*, compared with patients with mutated *KRAS* in whom no benefit from panitumumab was observed. No responders to panitumumab were identified in the mutated group, indicating a 100% positive predictive value for nonresponse in the mutated group.

Given the crossover design of the study, and that the majority of best supportive care patients crossed over to the panitumumab arm early in the trial, conclusions of the effect of *KRAS* mutational status on PFS and tumor response rate endpoints are limited. However, of the 168 best supportive care patients that crossed over to panitumumab after disease progression (119 with wild type and 77 with mutated *KRAS*), a significant prolongation of PFS was only seen in patients with wild-type *KRAS* (mPFS 16.4 weeks for wild type versus 7.9 weeks for mutated; HR 0.52; 95% CI: 0.22–0.45).

Van Cutsem et al. (2008). After completion of the previously described CRYSTAL trial, in which 1,198 patients with metastatic colorectal cancer were randomized to receive either cetuximab (C) in combination with FOLFIRI or FOLFIRI alone for first-line treatment (Van Cutsem et al. 2007a), the authors then performed a subgroup analysis of response rate and PFS according to *KRAS* mutational status. The original trial design consisted of a central stratified permuted block randomization procedure with geographic regions and ECOG performance status as randomization strata. Two interim assessments of safety data were conducted by an independent data safety monitoring board (DSMB).

Table 1. *KRAS* Status and Efficacy of Panitumumab as Monotherapy in the Treatment of Chemotherapy-Refractory Metastatic Colorectal Cancer (Amado et al. 2008)

Total n=427	<i>KRAS</i> Wild Type		<i>KRAS</i> Mutated	
	Panitumumab n=124	Best Supportive Care n=119	Panitumumab n=84	Best Supportive Care n=100
Wild Type: Mutated 243 (57%): 184 (43%)				
mPFS	12.3 weeks (HR 0.45; 95% CI: 0.34–0.59)	7.3 weeks	7.4 weeks (HR 0.99; 95% CI: 0.73–1.36)	7.3 weeks
Response rate	17%		0%	

mPFS: median progression-free survival

Of the original 1,198 patients, 540 had *KRAS*-evaluable, archival material. *KRAS* mutations were present in 192 patients (35.6%). *KRAS* testing was performed from genomic DNA isolated from archived formalin-fixed, paraffin-embedded tissue, using quantitative PCR to detect the *KRAS* mutation status of codons 12 and 13. It is not stated whether the *KRAS* mutation analysis was performed blinded; however, the data available are from a video/slide presentation only. No differences were found in patient demographics or baseline characteristics between the mutated and wild type populations, including age, sex, ECOG performance status, involved disease sites, and liver-limited disease, and a multivariate analysis performed for PFS according to patient characteristics showed a trend for PFS favoring the cetuximab plus FOLFIRI combination. PFS and tumor response rate were assessed by a blinded, independent review committee by CT scan every 8 weeks. The patients with wild-type *KRAS* who received cetuximab with FOLFIRI showed a statistically significant improvement in mPFS and tumor response rate, whereas the *KRAS*-mutant population did not, as summarized in Table 2.

Bokemeyer et al. (2008). The intention-to-treat (ITT) population in the randomized, phase II OPUS trial (Bokemeyer et al. 2008) consisted of 337 patients randomized to cetuximab and FOLFOX versus FOLFOX alone in the first-line treatment of metastatic colorectal cancer. A 10% higher response rate was observed in the population treated with cetuximab, but no difference in PFS was seen between the two

groups. Response rate was assessed by independent reviewers. The researchers re-evaluated the efficacy in the two treatment arms with consideration of *KRAS* mutational status of the patients' tumors. Of the original ITT population, 233 subjects had evaluable material for *KRAS* testing, and 99 (42%) were *KRAS* mutant. There was no difference in demographics or baseline characteristics between the wild type and mutated groups, including patient age, sex, ECOG performance status, involved disease sites and liver-limited disease. The study showed that the addition of cetuximab to FOLFOX resulted in a significant improvement in response rate and PFS only in the wild-type *KRAS* group. The study findings are summarized in Table 3.

Karapetis et al. (2008). Karapetis et al. (2008) performed a subgroup analysis of *KRAS* mutational status in a patient population that had been previously randomized to cetuximab plus best supportive care versus best supportive care alone as second- or subsequent-line therapy for advanced colorectal cancer (Jonker et al. 2007). In the original study, patients were randomized at a 1:1 ratio to cetuximab (n=287) or supportive care (n=285). Random assignment was stratified according to center and ECOG performance status (0 or 1 versus 2). Of the original patients, tumor samples for analysis were available from 394 of 572 (68.9%, 198 from the cetuximab group and 196 from the supportive care group). Baseline characteristics, including ECOG performance status and other variables associated with survival, were

Table 2. *KRAS* Status and Efficacy in the First-Line Therapy of Metastatic Colorectal Cancer Treated with FOLFIRI with or without Cetuximab (the CRYSTAL Trial; Van Cutsem et al. 2008)

ITT*	<i>KRAS</i> Wild Type n=348** (64.4%)		<i>KRAS</i> Mutated n=192** (35.6%)			
	C + F	F	C + F	F		
n	599	599	172	176	105	87
Response rate (%)	46.9 (95% CI: 42.9–51.0)	38.7 (95% CI: 34.8–42.8)	59.3 (95% CI: 51.6–66.7%)	43.2 (95% CI: 35.8–50.9%)	36.2 (95% CI: 27.0–46.2%)	40.2 (95% CI: 29.9–51.3%)
p value	0.0025		0.46			
mPFS (months)***	8.9	8.0	9.9 (HR 0.68; p=0.017)	8.7	7.6 (HR 1.07; p=0.47)	8.1

*ITT in the original CRYSTAL trial assessing C+F versus F alone as first-line therapy for metastatic colorectal cancer.

**540 patients had available archival pathology material for the *KRAS* mutation subset analysis.

***Confidence intervals for mPFS were not provided in the presentation slides.

C: cetuximab; F: FOLFIRI; mPFS: median progression free survival; HR: hazard ratio

balanced between the wild type and mutated patient groups. Tumor response or progression was evaluated every 8 weeks by radiologic imaging and defined according to the RECIST criteria. *KRAS* testing was performed in a blinded fashion, using formalin-fixed, paraffin-embedded tumor samples to detect *KRAS* mutation status of codons 12 and 13. A *KRAS* mutation was detected in 40.9% of tumor specimens in the cetuximab group, and 42.3% in the supportive-care group. The patients with wild-type *KRAS* who received cetuximab showed a statistically significant objective tumor response with prolonged progression-free and overall survival, whereas the *KRAS*-mutated population showed no significant difference between treatment with cetuximab versus supportive care, as summarized in Table 4.

Punt et al. (2008). Punt et al. performed a subgroup analysis of *KRAS* mutational status in a patient population that had been previously randomized to capecitabine, oxaliplatin and bevacizumab with or without cetuximab. The original study was a randomized, Phase III, multicenter trial involving 755 patients with surgically unresectable colorectal cancer who had not received previous systemic therapy

for advanced disease. Median follow-up was 18.7 months. The findings of the original study were that the combination of both monoclonal antibodies (bevacizumab and cetuximab) to capecitabine and oxaliplatin resulted in a significant decrease in PFS compared to the addition of only bevacizumab.

Of the original study group, 501 patients were analyzed by quantitative PCR for *KRAS* mutations. There were no significant differences in baseline characteristics between patients with and without *KRAS* mutations. In patients with mutated *KRAS*, the addition of cetuximab to chemotherapy and bevacizumab resulted in a significantly decreased PFS, as summarized in Table 5.

Single-Arm Studies (Cetuximab or Panitumumab)

In addition to the 5 randomized trials outlined above, several single-arm studies retrospectively evaluated *KRAS* mutational status and treatment response, and showed similar non-response to anti-EGFR monoclonal antibodies in patients with mutated *KRAS* tumors in metastatic colorectal cancer. These studies are summarized in Table 6.

Table 3. *KRAS* Status and Efficacy in the First-Line Therapy of Metastatic Colorectal Cancer Treated with FOLFOX with or without Cetuximab (OPUS Study, Bokemeyer et al. 2008)

	<i>KRAS</i> Wild Type n=134 (58%)		<i>KRAS</i> Mutated n=99 (42%)	
	C + Fx	Fx	C + Fx	Fx
n (KRAS evaluable)	61	73	52	47
Response rate (%)	60.7%	37.0%	32.7%	48.9%
	(95% CI: 47.3–72.9%)	(95% CI: 26.0–49.1%)	(95% CI: 20.3–47.1)	(95% CI: 34.1–63.9%)
p value	p=0.011		p=0.106	
odds ratio	2.54 (95% CI: 1.24–5.23)		0.51 (95% CI: 0.22–1.15)	
mPFS (months)*	7.7	7.2	5.5	8.6
p value	p=0.016		p=0.019	
hazard ratio	0.57		1.83	

*Confidence intervals for mPFS were not provided in the presentation slides.

C: cetuximab; Fx: FOLFOX; mPFS: median progression-free survival

Table 4. KRAS Status and Efficacy of Cetuximab as Monotherapy as Second- or Subsequent-Line Therapy in the Treatment of Advanced Colorectal Cancer (Karapetis et al. 2008)

Total n=394	KRAS Wild Type		KRAS Mutated	
	Cetuximab n=117	Best Supportive Care n=113	Cetuximab n=81	Best Supportive Care n=83
Wild Type: Mutated 230 (58.4%): 164 (41.6%)				
mOS	9.5 months	4.8 months	4.5 months	4.6 months
p value	p=0.01 for interaction between KRAS mutation status and assigned treatment			
One-year overall survival rate	28.3% [hazard ratio for death in cetuximab group versus supportive care, 0.55; 95% CI, 0.41 to 0.74; p<0.001]	20.1%	13.2% [hazard ratio for death in cetuximab group versus supportive care, 0.98; 95% CI, 0.70 to 1.37; p=0.89]	19.6%
mPFS	3.7 months (hazard ratio for progression or death in the cetuximab versus supportive care group, 0.40; 95% CI: 0.30–0.54; p<0.001)	1.9 months	1.8 months (hazard ratio for progression or death in the cetuximab versus supportive care group, 0.99; 95% CI: 0.73–1.35; p=0.96)	1.8 months
Response rate	12.8%	0%	1.2%	0%

mOS: median overall survival; mPFS: median progression-free survival

Table 5. KRAS Status and Efficacy in the Treatment of Advanced Colorectal Cancer with Capecitabine, Oxaliplatin and Bevacizumab, with or without Cetuximab (CAIRO 2 Study, Punt et al. 2008)

ITT	KRAS Wild Type n=305 (61%)		KRAS Mutated n=196 (39%)			
	CapOx + Bev	CapOx + Bev + C	CapOx + Bev	CapOx + Bev + C	CapOx + Bev	CapOx + Bev + C
n	368	368	152	153	103	93
mPFS (months)	10.7 (95% CI 9.7–12.5)	9.6 (95% CI 8.5–10.7)	10.7	10.5	12.5	8.6
p value	0.018		0.10		0.04	
mOS (months)	20.4 (95% CI 18.1–26.1)	20.3 (95% CI 17.9–21.6)	23.0	22.2	24.9	19.1
p value	0.21		0.49		0.35	

CapOx= capecitabine plus oxaliplatin; Bev=bevacizumab; C=cetuximab; mPFS= median progression-free survival; mOS= median overall survival

Table 6. Single-Arm Studies Showing Objective Response Rate (n [%]) to Anti-EGFR Monoclonal Antibodies in Chemotherapy Refractory Metastatic Colorectal Cancer

Study	Treatment	Total Patients (Wildtype: Mutated)	Wild Type n (%)	Mutated n (%)
Lievre et al. 2008	C ± CT	89 (65:24)	26 (40)	0 (0)
De Roock et al. 2008	C ± CT	108 (66:42)	27 (41)	0 (0)
Khambata-Ford et al. 2007	C	80 (50:30)	5 (10)	0 (0)
Di Fiore et al. 2007	C + CT	59 (43:16)	13 (28)	0 (0)
Benvenuti et al. 2007	P or C or C + CT	48 (32:16)	10 (31)	1 (6)

C: cetuximab; CT: chemotherapy; P: panitumumab

Two of these single-arm studies also reported a difference in PFS and OS as summarized in Table 7.

***KRAS* Mutational Status and Prognosis.**

A putative predictive marker may also be prognostic, however, several of the randomized, controlled studies of cetuximab and panitumumab presented above, suggest a lack of a prognostic effect of a *KRAS* mutation in metastatic colorectal cancer. In the trial by Amado et al. (2008), in which patients received best supportive care or panitumumab, there was no difference in PFS in the patients who received best supportive care only (both were 7.3 weeks), regardless of their mutation status. In the trial by Karapetis et al. (2008), in which patients received cetuximab or best supportive care, in the supportive care group there was no significant difference in overall survival between patients with wild type and mutated tumors. In the CRYSTAL trial (Van Cutsem et al. 2008), there was no difference in tumor response rate or PFS between the wild type and mutated *KRAS* groups that received FOLFIRI alone. Therefore, available evidence indicates that *KRAS* mutational status in metastatic colorectal cancer is fundamentally predictive.

2. What is the clinical utility of *KRAS* gene mutation analysis to predict nonresponse to anti-EGFR monoclonal antibodies in metastatic colorectal cancer?

KRAS testing of patients with metastatic colorectal cancer will identify patients who will not respond to anti-EGFR antibody therapy, and, therefore, should not receive this therapy. Identifying patients who should not receive these drugs will avoid the administration of

ineffective treatment and unnecessary exposure to the drug and its associated toxicities. In addition, identifying those patients who are not expected to respond to anti-EGFR monoclonal antibodies will minimize a delay in administering potentially effective alternative therapy.

3. What is the analytic validity of *KRAS* gene mutation analysis to predict nonresponse to anti-EGFR monoclonal antibodies in metastatic colorectal cancer?

Usual components of analytic validity include analytic sensitivity (how often the marker of interest is detected when it is present), analytic specificity (how often the marker is not detected when it is absent), assay performance when potentially interfering substances are present in the specimen, and assay variability. Assay variability is usually examined within an assay run; between runs; across reagent lot numbers; and across operators, automated instruments, and laboratories (where applicable).

KRAS gene mutation analysis is commercially available as a laboratory-developed test under CLIA regulation through several laboratories including Genzyme Genetics (<http://www.genzyme-genetics.com>), Clariant, Inc (<http://www.clariantinc.com>), Caris Dx (<http://www.carisdxc.com>) and Targeted Molecular Diagnostics (<http://www.tmdl.com>). Assessment of test technical performance characteristics is desirable to determine the accuracy and reliability of results in clinical practice. Information on the analytic performance of the procedures used by the aforementioned laboratories was not available, however, the methods used in the studies compiled in this Assessment concur with current, widespread clinical laboratory

Table 7. Single-Arm Studies of Treatment of Metastatic Colorectal Cancer with Anti-EGFR Monoclonal Antibodies and KRAS Mutational Status with PFS and OS

Study/Year	Description	Results			
		Outcome	Wild Type	Mutated	p value
De Roock et al. 2008	113 patients with irinotecan (I) -refractory metastatic CRC treated with cetuximab (C) with or without I (5 patients dropped out) Wild Type: Mutated 67 (59.3%): 46 (40.7%)	Overall response (n=108), C+I and C	27/66 (41%)	0/42 (0%)	p=0.00001 (C+I) p=0.126 (C alone)
		mPFS (C+I)	34 weeks (95% CI: 28.5–40.0)	12 weeks (95% CI: 5.4–18.7)	p=0.016
		mPFS (C)	12 weeks (95% CI: 4.2–20.0)	12 weeks (95% CI: 7.0–17.0)	p=0.351
		mOS (C+I)	44.7 weeks (95% CI: 28.4–61.0)	27.3 weeks (95% CI: 9.5–45.0)	p=0.003
		mOS (C)	27 weeks (95% CI: 8.9–45.1)	25.3 weeks (95% CI: 0.0–70.0)	p=0.330
Lievre et al. 2008	89 patients treated with C monotherapy after treatment failure with I Wild Type: Mutated 65 (73%): 24 (27%)	Response rate	40%	0%	p<0.001
		mPFS	31.4 weeks (95% CI: 19.4–36)	10.1 weeks (95% CI: 8–16)	p=0.0001
		mOS	14.3 months (95% CI: 9.4–20)	10.1 months (95% CI: 5.1–13)	p=0.026

C: cetuximab; I: irinotecan; mPFS: median progression-free survival; mOS: median overall survival

use consisting of PCR assays to detect the most common mutations in codons 12 and 13 (and rarely 61) of the *KRAS* gene, using formalin fixed paraffin-embedded or frozen tumor tissue. Results are reported as positive (presence of a mutation) or negative (no mutation detected).

Laboratory-developed tests performed by laboratories licensed for high complexity testing under the Clinical Laboratory Improvement Amendments (CLIA) do not require FDA clearance. Current FDA labeling for cetuximab and panitumumab does not include companion *KRAS* gene mutation testing.

Discussion

A convincing body of evidence from 5 randomized, controlled trials with nonconcurrent *KRAS* mutational status subgroup analysis and 5 single-arm studies has shown a consistent correlation between the presence of a *KRAS* mutation in metastatic colorectal cancer and nonresponse to anti-EGFR monoclonal antibodies. In addition, several of these studies have shown improved PFS and OS with the use of these monoclonal antibodies only in patients with wild type *KRAS* tumors, and one study showed a decrease in PFS in patients with mutated *KRAS* in whom cetuximab was a part of the therapeutic regimen. Although the *KRAS* findings were done as subgroup analyses in the randomized trials, the analyses were sufficiently powered and prespecified in a statistical analysis prior to knowledge of *KRAS* status. These findings support the clinical validity of *KRAS* mutation testing to predict which patients will not respond to cetuximab or panitumumab or derive incremental benefit to the addition of an anti-EGFR monoclonal antibody to other therapies for metastatic colorectal cancer.

Based on clinical validity of *KRAS* mutation testing to predict nonresponse to EGFR inhibitors, the clinical utility can be inferred to guide treatment decisions in patients with metastatic colorectal cancer. The data support testing of a tumor for a *KRAS* mutation when use of an anti-EGFR antibody is under consideration in this patient population, regardless of line of therapy.

Large, phase III trials that are currently underway assessing different combinations

of chemotherapeutic regimens with monoclonal antibodies in various lines of order in metastatic colorectal cancer and in the adjuvant setting are being amended to incorporate *KRAS* mutational status. The C80405 trial (FOLFIRI or FOLFOX plus cetuximab, bevacizumab or both), is being amended for *KRAS* mutation testing, and mutated patients will not be eligible (Eckhardt et al. 2008). S0600 (irinotecan plus cetuximab with or without bevacizumab) is also under amendment, as is a trial assessing anti-EGFR monoclonal antibodies in the adjuvant setting (N0147, FOLFOX with or without cetuximab).

Application of *KRAS* testing to other EGFR-driven tumors will require validation within each disease setting. Factors likely to influence such studies will include the percentage of tumors in each disease setting with *KRAS* mutations, as well as how accessible tumor material is for testing. For example, in non-small-cell lung cancer (NSCLC), *KRAS* mutations are only present in 20–30% of tumors and the prevalence within the group of NSCLC is dependent upon tumor histology, patient ethnicity and history of tobacco smoking (Aviel-Ronen et al. 2006).

Summary of Application of the Technology Evaluation Criteria

Based on the available evidence, the Blue Cross and Blue Shield Association Medical Advisory Panel made the following judgments about whether use of *KRAS* mutation analysis to predict nonresponse to anti-EGFR monoclonal antibodies cetuximab and panitumumab to treat metastatic colorectal cancer meets the Blue Cross and Blue Shield Association Technology Evaluation Center (TEC) criteria.

1. The technology must have final approval from the appropriate governmental regulatory bodies.

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.

2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.

The evidence compiled from 5 randomized trials and 5 single-arm studies is sufficient to conclude that patients with mutated *KRAS* tumors in the setting of metastatic colorectal cancer do not respond to anti-EGFR monoclonal antibody therapy, do not derive overall survival benefit, and may experience decreased progression-free survival.

- 3. The technology must improve the net health outcome; and**
4. The technology must be as beneficial as any established alternatives.

There is sufficient evidence to permit conclusions regarding the use of *KRAS* mutation analysis when the use of an EGFR inhibitor is a consideration in the management of a patient with metastatic colorectal cancer.

5. The improvement must be attainable outside the investigational settings.

The improvement in health outcomes in testing for a *KRAS* mutation in a patient with metastatic colorectal cancer prior to treatment with an anti-EGFR monoclonal antibody can be attained outside of the investigational setting.

Based on the above, use of *KRAS* mutation analysis to predict nonresponse to the anti-EGFR monoclonal antibodies cetuximab and panitumumab to treat metastatic colorectal cancer meets the TEC criteria.

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Appendix

Study Quality for 4 Randomized, Controlled Trials of Cetuximab or Panitumumab for Metastatic Colorectal Cancer

Study	Initial Assembly Comparable Groups	<80% Loss to Follow-up, Maintain Comparable Groups	Measurements Reliable, Valid, Equal	Intervention Comparable/Clearly Defined	Appropriate Analysis of Results	Quality Rating
Amado et al. (2008)	Y	N*	Y	Y	Y	Fair
Van Cutsem et al. (2008)	Y	Y	Y	Y	Y	Good
Bokemeyer et al. (2008)	Y	Y	Y	Y	Y	Good
Karapetis et al. (2008)	Y	Y	Y	Y	Y	Good
Punt et al. (2008)	Y	Y	Y	Y	Y	Good

* due to cross over



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