



Louisiana

KRAS, NRAS and BRAF Variant Analysis in Metastatic Colorectal Cancer

Policy # 00233

Original Effective Date: 12/17/2008

Current Effective Date: 02/21/2018

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When Services Are Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider *KRAS* variant analysis for patients with metastatic colorectal cancer (mCRC) to predict nonresponse prior to planned therapy with anti-epidermal growth factor receptor (EGFR) monoclonal antibodies cetuximab and panitumumab to be **eligible for coverage**.

Based on review of available data, the Company may consider *NRAS* variant analysis for patients with mCRC to predict nonresponse prior to planned therapy with anti-EGFR monoclonal antibodies cetuximab or panitumumab to be **eligible for coverage**.

Based on review of available data, the Company considers *BRAF* variant analysis for patients with mCRC who are found to be wild-type on *KRAS* and *NRAS* variant analysis to guide management decisions to be **eligible for coverage**.

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers *KRAS*, *NRAS*, and *BRAF* variant analysis for all other indications to be **investigational**.*

Policy Guidelines

There is support from the evidence and clinical input to use *BRAF* V600 variant testing for prognostic stratification. Clinical input suggests that patients who are positive for this variant may be considered for clinical trials.

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It is uncertain whether the presence of a *BRAF* V600 variant in patients with mCRC who are wild-type on *KRAS* and *NRAS* variant analysis is predictive of response to anti-EGFR therapy. Furthermore, there is mixed opinion in clinical guidelines and clinical input on the use of *BRAF* variant analysis to predict response to treatment.

GENETICS NOMENCLATURE UPDATE

Human Genome Variation Society (HGVS) nomenclature is used to report information on variants found in deoxyribonucleic acid (DNA) and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). HGVS nomenclature is recommended by HGVS, the Human Variome Project, and the HUman Genome Organization (HUGO).

The American College of Medical Genetics and Genomics (ACMG) and Association for Molecular Pathology (AMP) standards and guidelines for interpretation of sequence variants represent expert opinion from ACMG, AMP, and the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology—"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"—to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

Background/Overview

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

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The RAS-RAF-MAP kinase pathway is activated in the EGFR cascade. The Ras proteins are G proteins that cycle between active (RAS guanosine triphosphate) and inactive (RAS guanosine diphosphate) forms in response to stimulation from a cell surface receptor, such as EGFR, and they act as a binary switch between the cell surface EGFR and downstream signaling pathways. The *KRAS* gene can harbor oncogenic variants that result in a constitutively activated protein, independent of EGFR ligand binding, rendering antibodies to the upstream EGFR ineffective. Approximately 40% of colorectal cancer (CRC) have *KRAS* variants in codons 12 and 13 in exon 2. Another proto-oncogene that acts downstream from *KRAS-NRAS* harbors oncogenic variants in codons 12, 13, or 61 that result in constitutive activation of the EGFR-mediated pathway. These variants are less common compared with *KRAS*, detected in 2% to 7% of CRC specimens. It is unclear whether *NRAS* variants predict poor response due to anti-EGFR monoclonal antibody therapy, or are a prognostic of poor CRC outcome in general. A third proto-oncogene, *BRAF*, encodes a protein kinase and is involved in intracellular signaling and cell growth; *BRAF* is also a principal downstream effector of *KRAS*. *BRAF* variants occur in fewer than 10% to 15% of CRCs and appear to be a marker of poor prognosis. *KRAS* and *BRAF* variants are considered to be mutually exclusive.

Cetuximab and panitumumab have marketing approval from the U.S. Food and Drug Administration (FDA) for treatment of metastatic CRC in the refractory disease setting. FDA approval for panitumumab indicates that panitumumab is not indicated for the treatment of patients with *KRAS* or *NRAS* variant-positive disease in combination with oxaliplatin-based chemotherapy.

FDA or Other Governmental Regulatory Approval **U.S. Food and Drug Administration (FDA)**

Approved Companion Diagnostic Tests for *KRAS* Variant Analysis

Companion diagnostic tests for the selection of cetuximab and panitumumab have been approved by FDA through the premarket approval process, specifically:

“The cobas[®] KRAS Mutation Test, for use with the cobas[®] 4800 System, [which] is a real-time PCR [polymerase chain reaction] test for the detection of seven somatic mutations in codons 12 and 13 of the *KRAS* gene in DNA derived from formalin-fixed paraffin-embedded (FFPE) human CRC tumor tissue. The test is intended to be used as an aid in the identification of CRC patients for whom treatment with Erbitux (cetuximab) or with Vectibix (panitumumab) may be indicated based on a no mutation detected result.”

“The theascreen[®] KRAS RGQ PCR Kit is a real-time qualitative PCR assay used on the Rotor-Gene Q MDx instrument for the detection of seven somatic mutations in the human *KRAS* oncogene, using DNA extracted from FFPE, CRC tissue. The theascreen KRAS RGQ PCR Kit is intended to aid in the identification of CRC patients for treatment with Erbitux (cetuximab) and Vectibix (panitumumab) based on a *KRAS* no mutation detected test result.”

Laboratory-Developed Tests for *KRAS*, *NRAS*, and *BRAF* Variant Analysis

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory

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Improvement Amendments. *KRAS*, *NRAS*, and *BRAF* variant analyses using PCR methodology are available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer LDTs must be licensed under the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, FDA has chosen not to require any regulatory review of this test.

Centers for Medicare and Medicaid Services (CMS)

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Rationale/Source

Validation of the clinical use of any genetic test focuses on 3 main principles: (1) analytic validity, which refers to the technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent; (2) clinical validity, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and (3) clinical utility (ie, how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes). The following is a summary of the key literature.

A large body of literature has shown that mCRC tumors with a variant in exon 2 (codon 12 or 13) of the *KRAS* gene do not respond to cetuximab or panitumumab therapy. More recent evidence has shown that variants in *KRAS* outside exon 2, in exons 3 (codons 59 and 61) and exon 4 (codons 117 and 146), and variants in *NRAS* exon 2 (codons 12 and 13), exons 3 (codons 59 and 61), and exon 4 (codons 117 and 146) also predict a lack of response to these monoclonal antibodies. Variant testing of these exons outside the *KRAS* exon 2 is referred to as extended *RAS* testing.

***KRAS* VARIANT TESTING FOR METASTATIC CRC**

Clinical Context and Test Purpose

The purpose of *KRAS* variant testing in individuals with metastatic CRC is to determine *KRAS* variant status to guide treatment decisions with EGFR–targeted therapy with the monoclonal antibodies cetuximab and panitumumab.

The question addressed in this evidence review is: In individuals with metastatic CRC, does the use of *KRAS* variant testing improve health outcomes?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest includes individuals with metastatic CRC.

Interventions

The relevant intervention of interest is *KRAS* variant testing.

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Comparators

The relevant comparator of interest is no *KRAS* variant testing to guide treatment.

Outcomes

The beneficial outcomes of interest include progression-free survival (PFS) and overall survival (OS).

Timing

The time frame for outcomes measures varies from several months to several years.

Setting

Patients with metastatic CRC are actively managed by oncologists.

Analytic Validity

Analytic validity is the technical accuracy of the test in detecting a variant that is present, or in excluding a variant that is absent. The FDA Summary of Safety and Effectiveness Data documents have described the analytic validity of the theascreen *KRAS* RGQ PCR Kit and cobas *KRAS* Mutation Test, which were approved through the premarket approval process. Both FDA-approved tests are real-time PCR tests intended to detect somatic variants in *KRAS* genes and have documented analytic validity including concordance studies between the test and Sanger sequencing, the limits of detection for both variants detected, cross-reactivity to interference by substances such as hemoglobin, albumin, and blood preservatives, and reproducibility. These results have shown that both tests have high analytic sensitivity and specificity compared with Sanger sequencing, high reproducibility, sufficient levels of detection and limits of blank (ie, highest analyte concentration expected to be detected when blank samples are tested), and low cross-reactivity. No published studies are available demonstrating the analytic validity of LDTs for *KRAS* variants.

Section Summary: Analytic Validity

Evidence for the analytic validity of the theascreen *KRAS* RGQ PCR Kit and cobas *KRAS* Mutation Test include FDA Summary of Safety and Effectiveness Data for both tests. There is a lack of published evidence on the analytic validity of LDTs to detect *KRAS* variants. However, it is expected that the analytic validity will be high when testing is performed according to optimal laboratory standards.

Clinical Validity

This evidence review has been informed, in part, by a 2008 TEC Assessment. Additional evidence derives from randomized controlled trials (RCTs) and single-arm studies, organized and outlined below.

Randomized Controlled Trials

RCTs have performed nonconcurrent subgroup analyses of the efficacy of EGFR inhibitors in patients with wild-type vs mutated *KRAS* in metastatic CRC. Data from these trials have consistently shown a lack of clinical response to cetuximab and panitumumab in patients with mutated *KRAS*, with tumor response and prolongation of PFS observed only in wild-type *KRAS* patients.

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Amado et al (2008) performed a subgroup analysis of *KRAS* tumor variants in a patient population that had previously been randomized to panitumumab or to best supportive care as third-line therapy for chemotherapy-refractory metastatic CRC. The original 2007 study, designed as a multicenter RCT, was not blinded because of expected skin toxicity related to panitumumab administration. Patients were randomized 1:1 to panitumumab or to best supportive care. Random assignment was stratified by Eastern Cooperative Oncology Group (ECOG) Performance Status (0 or 1 vs 2) and geographic region. Crossover from best supportive care to the panitumumab arm was allowed in patients who experienced disease progression. Of the 232 patients originally assigned to best supportive care alone, 176 crossed over to the panitumumab arm, at a median time to crossover of 7 weeks (range, 6.6-7.3 weeks).

Of the 463 patients in the original trial, 427 (92%) were included in the *KRAS* subgroup variant analysis. A central laboratory performed the *KRAS* variant analysis in a blinded fashion, using FFPE tumor sections and a validated *KRAS* variant kit (DxS) that identifies 7 somatic variants located in codons 12 and 13 using real-time PCR. *KRAS* variant status could not be determined in 36 patients because tumor samples were not available or DNA was of insufficient or of poor quality for analysis. Forty-three percent of the *KRAS*-evaluable patients had *KRAS*-mutated tumors, with a distribution similar to *KRAS* variant types between treatment arms.

Patient demographics and baseline characteristics were balanced between the wild-type and mutated groups for the panitumumab and best supportive care groups including patient age, sex, and ECOG Performance Status. The interaction between variant status and PFS was examined, controlling for randomization factors. PFS and tumor response rate were assessed radiographically every 4 to 8 weeks until disease progression using Response Evaluation Criteria in Solid Tumors criteria by blinded, central review. In the *KRAS*-assessable population, 20% of patients had a treatment-related grade 3 or 4 adverse events. As shown in Table 1, the relative effect of panitumumab on PFS was significantly greater among patients with wild-type *KRAS* than 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 that group.

Table1. *KRAS* Status and Efficacy of Panitumumab as Monotherapy in the Treatment of Chemotherapy-Refractory Metastatic Colorectal Cancer (n=427)

Outcomes	<i>KRAS</i> WT (n=243 [57%])		<i>KRAS</i> MT (n=184 [43%])	
	P (n=124)	BSC (n=119)	P (n=84)	BSC (n=100)
Median progression-free survival, wk	12.3	7.3	7.4	7.3
Hazard ratio (95% CI)	0.45 (0.34 to 0.59)		0.99 (0.73 to 1.36)	
Response rate, %	17		0	

Adapted from Amado et al (2008).

BSC: best supportive care; CI: confidence interval; MT: mutated; P: panitumumab; WT: wild-type.

Given the crossover trial design and the fact that most of the best supportive care patients crossed over to the panitumumab arm early in the trial, conclusions of the effect of *KRAS* variant status on PFS and tumor response rate end points are limited. However, of the 168 best supportive care patients who crossed over to



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panitumumab after disease progression (119 with wild-type *KRAS*, 77 with mutated *KRAS*), PFS was significantly longer among patients with wild-type *KRAS* (median PFS: 16.4 weeks for wild-type vs 7.9 weeks for mutated; hazard ratio [HR], 0.32; 95% confidence interval [CI], 0.22 to 0.45).

After completion of the CRYSTAL trial (detailed below), in which 1198 patients with metastatic CRC were randomized to cetuximab in combination with folinic acid (leucovorin), 5-fluorouracil, and irinotecan (FOLFIRI) or to FOLFIRI alone for first-line treatment, a subgroup analysis of response rate and PFS according to *KRAS* variant status was performed by Van Cutsem et al (2009). 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.

Of the original 1198 patients, 540 had *KRAS*-evaluable, archival material. *KRAS* testing was performed using genomic DNA isolated from archived FFPE tissue, using quantitative PCR to detect the *KRAS* variant status of codons 12 and 13. It was not stated whether the *KRAS* variant analysis was performed blinded. *KRAS* variants were present in 192 (35.6%) patients. 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. PFS and tumor response rate were assessed by a blinded, independent review committee using computed tomography scans every 8 weeks. A multivariate analysis performed for PFS according to patient characteristics showed a trend for PFS favoring the cetuximab plus FOLFIRI combination. The patients with wild-type *KRAS* who received cetuximab plus FOLFIRI showed a statistically significant improvement in median PFS and tumor response rate, whereas the mutated *KRAS* population did not, as summarized in Table 2.

Table 2. *KRAS* Status and Efficacy in the First-Line Therapy of Metastatic Colorectal Cancer Treated With FOLFIRI With or Without Cetuximab (CRYSTAL Trial) (N=540)

Outcomes	ITT ^a		<i>KRAS</i> WT (n=348 [64%] ^b)		<i>KRAS</i> MT (n=192 [36%] ^b)	
	C+F	F	C+F	F	C+F	F
n	599	599	172	176	105	87
RR (95% CI), %	46.9 (42.9 to 51.0)	38.7 (34.8 to 42.8)	59.3 (51.6 to 66.7)	43.2 (35.8 to 50.9)	36.2 (27.0 to 46.2)	40.2 (29.9 to 51.3)
mPFS, mo ^c	8.9	8.0	9.9	8.7	7.6	8.1
Hazard ratio			0.68 (p=0.017)		1.07 (p=0.47)	

Adapted from Van Cutsem et al (2009).

C: cetuximab; CI: confidence interval; F: FOLFIRI; HR: hazard ratio; ITT: intention-to-treat; mPFS: median progression-free survival; MT: mutated; RR: response rate; WT: wild-type.

^a ITT in the original CRYSTAL trial assessing C+F vs F alone as first-line therapy for metastatic colorectal cancers.

^b 540 patients had available archival pathology material for the *KRAS* variant subset analysis.

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

In a third trial, the randomized, phase 2 OPUS trial, the intention-to-treat (ITT) population consisted of 337 patients randomized to cetuximab and folinic acid (leucovorin), 5-fluorouracil, and oxaliplatin (FOLFOX) or to FOLFOX alone in the first-line treatment of mCRC. A 10% higher response rate (assessed by independent



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reviewers) was observed in the population treated with cetuximab, but no difference in PFS was seen between the groups. The researchers then reevaluated the efficacy in the 2 treatment arms based on the *KRAS* variant status of patients' tumors. Of the original ITT population, 233 subjects had evaluable material for *KRAS* testing, and 99 (42%) were *KRAS* variants. The demographics or baseline characteristics were similar between the wild-type and mutated groups, including patient age, sex, ECOG Performance Status, involved disease sites, and liver-limited disease. The trial 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.

Table 3. *KRAS* Status and Efficacy in the First-Line Therapy of Metastatic Colorectal Cancer Treated With FOLFOX With or Without Cetuximab (OPUS Study) (n=233)

Outcomes	<i>KRAS</i> WT (n=134 [58%])		<i>KRAS</i> MT (n=99 [42%])	
	C+Fx	Fx	C+Fx	Fx
n (<i>KRAS</i> -evaluable)	61	73	52	47
RR (95% CI), %	60.7 (47.3 to 72.9)	37.0 (26.0 to 49.1)	32.7 (20.3 to 47.1)	48.9 (34.1 to 63.9)
p	0.011		0.106	
Odds ratio (95% CI)	2.54 (1.24 to 5.23)		0.51 (0.22 to 1.15)	
mPFS, mo ^a	7.7	7.2	5.5	8.6
p	0.016		0.019	
Hazard ratio	0.57		1.83	

Adapted from Bokemeyer et al (2009).

C: cetuximab; CI: confidence interval; Fx: FOLFOX; MT: mutated; mPFS: median progression-free survival; RR: response rate; WT: wild-type.

^a Confidence intervals for mPFS were not provided in presentation slides.

In the CAIRO2 study, Tol et al (2009) analyzed tumor samples from 528 of 755 previously untreated patients with metastatic CRC who were randomized to capecitabine, oxaliplatin, and bevacizumab (CB regimen, n=378), or to the same regimen plus cetuximab (CBC regimen, n=377). *KRAS* variant was found in 40% of tumors (108 from patients in the CB group, 98 from the CBC group). Patients with *KRAS* variants treated with cetuximab had a significantly shorter PFS (8.1 months) than the wild-type *KRAS* patients who received cetuximab (10.5 months; p=0.04). In addition, patients who had mutated *KRAS* tumors who received cetuximab had a significantly shorter PFS and OS than patients with mutated *KRAS* tumors who did not receive cetuximab (PFS: 8.1 months vs 12.5 months, respectively, p=0.003; OS: 17.2 months vs 24.9 months, respectively, p=0.03). For patients with wild-type tumors, no significant PFS differences were reported between the groups. Overall, patients treated with cetuximab who had tumors with a mutated *KRAS* gene had significantly decreased PFS compared with cetuximab-treated patients with wild-type *KRAS* tumors or patients with mutated *KRAS* tumors in the CB group.

Karapetis et al (2008) analyzed tumor samples from 394 (69%) of 572 patients with CRC who were randomized to cetuximab plus best supportive care (n=287) or to best supportive care alone (n=285) for *KRAS* variants and assessed whether variant status was associated with survival. The patients had advanced CRC had failed chemotherapy and had no other standard anticancer therapy available. Of the tumors evaluated (198 from the cetuximab group, 196 from the best supportive care group), 41% and 42%



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had a *KRAS* variant, respectively, and these groups reported a median OS 9.5 months and 4.8 months, respectively (HR for death, 0.55; 95% CI, 0.41 to 0.74; $p < 0.001$) and a median PFS of 3.7 months and 1.9 months, respectively (HR for progression to death, 0.40; 95% CI, 0.30 to 0.54; $p < 0.001$). For patients with mutated *KRAS* tumors, no significant differences were reported between those treated with cetuximab and best supportive care alone with respect to OS (HR=0.98, $p=0.89$) or PFS (HR=0.99, $p=0.96$).

Douillard et al (2010) reported on the results of a multicenter, phase 3 trial in which patients with no prior chemotherapy for metastatic CRC, ECOG Performance Status of 0 to 2, and available tissue for biomarker testing were randomized 1:1 to panitumumab plus FOLFOX4 or to FOLFOX4. The primary end point was PFS; OS was a secondary end point. Results were prospectively analyzed on an ITT basis by tumor *KRAS* status. *KRAS* results were available for 93% of the 1183 patients randomized. In the wild-type *KRAS* group, panitumumab plus FOLFOX4 significantly improved PFS compared with FOLFOX4 alone (median PFS, 9.6 months vs 8.0 months, respectively; HR=0.80; 95% CI, 0.66 to 0.97; $p=0.02$). A nonsignificant increase in OS was also observed for panitumumab plus FOLFOX4 vs FOLFOX4 (median OS, 23.9 months vs 19.7 months, respectively; HR=0.83; 95% CI, 0.67 to 1.02; $p=0.072$). In the mutant *KRAS* group, PFS was significantly reduced in the panitumumab plus FOLFOX4 arm compared with the FOLFOX4 arm (HR=1.29; 95% CI, 1.04 to 1.62; $p=0.02$), and median OS was 15.5 months vs 19.3 months, respectively (HR=1.24; 95% CI, 0.98 to 1.57; $p=0.068$). Adverse event rates were generally comparable across arms with the exception of toxicities known to be associated with anti-EGFR therapy. The trial demonstrated that panitumumab plus FOLFOX4 was well-tolerated and significantly improved PFS in patients with wild-type *KRAS* tumors.

The CRYSTAL trial (2009) demonstrated that the addition of cetuximab to FOLFIRI statistically significantly reduced the risk of disease progression and increased the chance of response in patients with wild-type *KRAS* metastatic CRC compared with chemotherapy alone. An updated analysis of CRYSTAL (2011) reported on longer follow-up and more patients evaluable for tumor *KRAS* status and considered the clinical significance of the *BRAF* variant tumor status in the expanded population of patients with wild-type *KRAS* tumors. Subsequent to the initial published analysis, which had an OS cutoff of December 2007, and an associated overall median duration of follow-up of 29.7 months, additional tumor analysis allowed for the typing of another 523 tumors for *KRAS* variant status, representing an increase in the ascertainment rate from 45% of ITT population patients in the original analysis to 89% (540 to 1063) in the current analysis, with variants detected in 37% of tumors. The updated OS analysis was carried out with a new cutoff date of May 2009, giving an overall median duration of follow-up of 46 months. The addition of cetuximab to FOLFIRI in patients with wild-type *KRAS* disease resulted in significant improvements in OS (median, 23.5 months vs. 20.0 months; HR=0.796; $p=0.009$), PFS (median, 9.9 months vs 8.4 months; HR=0.696; $p=0.001$), and response rate (57.3% vs 39.7%; odds ratio [OR], 2.069; $p < 0.001$) compared with FOLFIRI alone. Significant interactions between *KRAS* status and treatment effect were noted for all key efficacy end points. *KRAS* variant status was confirmed as a powerful predictive biomarker for the efficacy of cetuximab plus FOLFIRI. *BRAF* V600E variants were detected in 60 (6%) of 999 tumor samples evaluable for both *BRAF* and *KRAS*. In all but a single case, *BRAF* variants were identified in tumors wild-type for *KRAS*. The impact of *BRAF* tumor variant status in relation to the efficacy of cetuximab plus FOLFIRI was examined in the population of patients with wild-type *KRAS* disease ($n=625$). No evidence was reported for an

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independent treatment interaction by tumor *BRAF* variant status. The trialists concluded that *BRAF* variant status was not predictive of treatment effects of cetuximab plus FOLFIRI but that *BRAF* tumor variant was a strong indicator of poor prognosis for all efficacy end points compared with those whose tumors were wild-type.

Peeters et al (2010) reported on the results of a phase 3 study in which 1186 patients with metastatic CRC were randomized to panitumumab plus FOLFIRI or to FOLFIRI alone as a second-line treatment. The study end points were PFS and OS, which were independently tested and prospectively analyzed by *KRAS* status. *KRAS* status was available for 91% of patients: 597 (55%) had wild-type *KRAS* tumors and 486 (45%) had mutated *KRAS* tumors. In the wild-type *KRAS* subpopulation, when panitumumab was added to chemotherapy, a significant improvement in PFS was observed (HR=0.73; 95% CI, 0.59 to 0.90; p=0.004); median PFS was 5.9 months for panitumumab plus FOLFIRI and 3.9 months for FOLFIRI. A nonsignificant trend toward increased OS was observed; median OS was 14.5 months and 12.5 months, respectively (HR=0.85, 95% CI, 0.70 to 1.04; p=0.12); response rates were improved to 35% and 10%, respectively, with the addition of panitumumab. In patients with mutated *KRAS*, no difference was reported in efficacy. Adverse events were comparable across arms. The authors concluded that panitumumab plus FOLFIRI significantly improved PFS and was well-tolerated as second-line treatment in patients with wild-type *KRAS* metastatic CRC.

Maughan et al (2011) reported on the results of a phase 3, multicenter trial (MRC COIN trial), which randomized patients with advanced CRC who had not received previous chemotherapy to oxaliplatin plus fluoropyrimidine chemotherapy (arm A) or to the same combination plus cetuximab (arm B). The comparison between arms A and B (for which the primary outcome was OS) was in patients with wild-type *KRAS* tumors. Baseline characteristics were well-balanced between groups. Analysis was by ITT and treatment allocation was not masked. Further analysis of other variants, including *BRAF*, was done; 1630 patients were randomized to treatment groups (815 to standard therapy, 815 to the addition of cetuximab). Tumor samples from 1316 (81%) of patients were used for somatic variant analyses; 43% had *KRAS* variants. In patients with wild-type *KRAS* tumors, OS did not differ between treatment groups (median survival, 17.9 months in the control group vs 17.0 months in the cetuximab group; HR=1.04; 95% CI, 0.87 to 1.23; p=0.67). *BRAF* variants were detected in 8% of patients; *BRAF* did not show any evidence of a benefit from the addition of cetuximab. Contrary to other trials that have studied *KRAS* variant status and the benefit of adding cetuximab to the regimen of wild-type *KRAS* patients, this trial did not show a benefit of adding cetuximab to oxaliplatin-based chemotherapy.

Systematic Reviews

Qiu et al (2010) conducted a meta-analysis of 22 studies on the predictive and prognostic value of *KRAS* variants in metastatic CRC patients treated with cetuximab. The overall *KRAS* variant rate was 38% (829/2188 patients). The results of the meta-analysis were consistent with previous studies on the use of cetuximab and *KRAS* variant status, in that patients with tumors harboring mutant-type *KRAS* were more likely to have a worse response, PFS, and OS when treated with cetuximab than those with wild-type *KRAS*.

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KRAS, NRAS and BRAF Variant Analysis in Metastatic Colorectal Cancer

Policy # 00233

Original Effective Date: 12/17/2008

Current Effective Date: 02/21/2018

Dahabreh et al (2011) conducted a systematic review of RCTs that assessed the use of *KRAS* variant testing as a predictive biomarker for treatment of advanced CRC with cetuximab and panitumumab. Reviewers concluded that, compared with patients who had wild-type *KRAS*, *KRAS* variants were consistently associated with reduced OS and PFS and increased treatment failure rates among patients with advanced CRC who are treated with anti-EGFR antibodies.

A 2012 pooled analysis of wild-type *KRAS* tumors from the CRYSTAL and OPUS trial data assessed extended survival data and enhancement in the ascertainment rate of *KRAS* and *BRAF* tumor variant status. Pooled individual patient data from each trial were analyzed for OS, PFS, and best objective response rate (ORR) in patients evaluable for *KRAS* and *BRAF* variant status. Treatment arms were compared by variant status using log-rank and Cochran-Mantel-Haenszel tests. In 845 patients with wild-type *KRAS* tumors, adding cetuximab to chemotherapy led to a significant improvements in OS (HR=0.81; p=0.006), PFS (HR=0.66; p<0.001), and ORR (OR=2.16; p<0.001). *BRAF* variants were detected in 70 (8.8%) of 800 evaluable tumors. No significant differences were found in outcomes between treatment groups. However, prognosis was worse in each treatment arm for patients with *BRAF* tumors, and OPUS trials confirmed the consistency of the benefit obtained from all efficacy end points from adding cetuximab to first-line chemotherapy in patients with wild-type *KRAS* metastatic CRC. It further suggested that *BRAF* variants do not appear to be predictive biomarkers in this setting, but are markers of poor prognosis.

Single-Arm Studies (Cetuximab or Panitumumab)

In addition to the 3 randomized trials discussed here, a number of single-arm studies have retrospectively evaluated *KRAS* variant status and treatment response in patients with metastatic CRC. Overall they have shown similar nonresponse rates to anti-EGFR monoclonal antibodies in patients with mutated *KRAS* tumors. Two of these single-arm studies have also reported differences in PFS and OS.

Section Summary: Clinical Validity

Evidence for the clinical validity *KRAS* variants in predicting nonresponse to anti-EGFR monoclonal antibody therapy consists of multiple systematic reviews, including a TEC Assessment, and RCTs. The evidence has demonstrated that the presence of a *KRAS* variant predicts nonresponse to treatment while *KRAS* wild-type status predicts response to anti-EGFR monoclonal antibody therapy.

Clinical Utility

Cetuximab and panitumumab are anti-EGFR monoclonal antibodies indicated for the treatment of patients with wild-type *KRAS* metastatic CRC. Cetuximab and panitumumab are not indicated for the treatment of patients when *KRAS* variants are present or when *KRAS* variant status is unknown.

Section Summary: Clinical Utility

Direct evidence for the clinical utility of *KRAS* variant testing includes RCTs. RCTs supporting FDA approvals for cetuximab and panitumumab has demonstrated that the presence of *KRAS* variants is predictive of nonresponse to anti-EGFR monoclonal antibody therapy. Documentation of *KRAS* wild-type status is required before patients are eligible for treatment with cetuximab or panitumumab.

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KRAS, NRAS and BRAF Variant Analysis in Metastatic Colorectal Cancer

Policy # 00233

Original Effective Date: 12/17/2008

Current Effective Date: 02/21/2018

NRAS VARIANT TESTING FOR METASTATIC CRC

Clinical Context and Test Purpose

The purpose of *NRAS* variant testing in individuals with metastatic CRC is to determine *NRAS* variant status to guide treatment decisions with EGFR-targeted therapy with the monoclonal antibodies cetuximab and panitumumab.

The question addressed in this evidence review is: In individuals with metastatic CRC, does the use of *NRAS* variant testing improve health outcomes?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest includes individuals with metastatic CRC.

Interventions

The relevant intervention of interest is *NRAS* variant testing.

Comparators

The relevant comparator of interest is no *NRAS* variant testing to guide treatment.

Outcomes

The beneficial outcomes of interest include PFS and OS.

Timing

The time frame for outcomes measures varies from several months to several years.

Setting

Patients with metastatic CRC are actively managed by oncologists.

Analytic Validity

No published studies are available demonstrating the analytic validity of LDTs for *NRAS* variants in CRC samples.

Section Summary: Analytic Validity

There is a lack of published evidence on the analytic validity of LDTs to detect *NRAS* variants in CRC samples. However, it is expected that analytic validity will be high when testing is performed according to optimal laboratory standards.

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KRAS, NRAS and BRAF Variant Analysis in Metastatic Colorectal Cancer

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Clinical Validity

Prospective-Retrospective Analyses of Randomized Controlled Trials

RCTs have analyzed nonconcurrent subgroups for the efficacy of EGFR inhibitors in patients with wild-type and mutated *RAS* genes in metastatic CRC.

In 2015, Peeters et al reported on the influence of *RAS* variant status in a prospective-retrospective analysis of a randomized, multicenter phase 3 trial comparing panitumumab plus FOLFIRI with FOLFIRI alone as second-line therapy in patients with metastatic CRC. If a tumor was classified as wild-type *KRAS* exon 2, extended *RAS* variant testing beyond *KRAS* exon 2 was performed (*KRAS* exons 3 and 4; *NRAS* exons 2, 3, and 4; *BRAF* exon 15). Primary endpoints were PFS and OS. *RAS* variants were obtained in 85% of the specimens from the original trial; 18% of wild-type *KRAS* exon 2 tumors harbored other *RAS* variants. The PFS and OS HRs for panitumumab plus FOLFIRI vs FOLFIRI alone are summarized in Table 4. The HRs more strongly favored panitumumab in the wild-type *RAS* population.

Table 4. Hazard Ratios of Panitumumab Plus FOLFIRI vs FOLFIRI Alone Based on *RAS* Status

<i>RAS</i> Status	PFS HR (95% CI)	p	OS HR (95% CI)	p
Wild-type <i>RAS</i>	0.70 (0.54 to 0.91)	0.007	0.81 (0.63 to 1.03)	0.08
Wild-type <i>KRAS</i> exon 2	0.73 (0.59 to 0.90)	0.004	0.85 (0.70 to 1.04)	0.12

CI: confidence interval; HR: hazard ratio; OS: overall survival; PFS: progression-free survival.

For *RAS* wild-type patients, the ORR was 41% when they were treated with panitumumab plus FOLFIRI vs 10% when treated FOLFIRI alone. Therefore, *RAS* wild-type status predicted likely response to panitumumab and overall benefit from treatment. In contrast, the presence of *RAS* variants predicted nonresponse to panitumumab and unlikely benefit from treatment.

In 2015, Van Cutsem et al reported on results of a prospective-retrospective extended *RAS* variant analysis of tumor samples from the randomized phase 3 CRYSTAL trial, which compared FOLFIRI with FOLFIRI plus cetuximab in wild-type *KRAS* exon 2 patients. Variant status was available in 430 (64.6%) of 666 patients from the trial. A pooled analysis of *RAS* variants, other than *KRAS* exon 2, found a lack of benefit from the addition of cetuximab to FOLFIRI for median PFS (7.4 months vs 7.5 months; $p=0.47$) and median OS (16.4 months vs 17.7 months; $p=0.64$). Patients with tumors without *RAS* variants experienced significant benefit in median PFS (9.9 months vs 8.4 months; $p<0.05$) and median OS (23.5 months vs 20 months; $p<0.05$) with the addition of cetuximab to chemotherapy.

Douillard et al (2013) performed a prospective-retrospective analysis of *RAS* variants (*KRAS*, *NRAS*) in tumor samples from patients enrolled in the Panitumumab Randomized Trial in Combination with Chemotherapy for Metastatic Colorectal Cancer to Determine Efficacy (PRIME) RCT. A total of 108 (17%) of 641 tumor specimens that did not harbor *KRAS* variants in exon 2 had variants in other *RAS* exons, including *NRAS* (exons 2 or 4) and *KRAS* (exons 3 and 4). For patients with wild-type *KRAS* exon 2 variant ($n=656$), OS was significantly better with panitumumab plus FOLFOX4 ($n=325$; median, 23.8 months) than with FOLFOX4 alone ($n=331$; median, 19.4 months; $p=0.03$). For patients with no *KRAS* exon 2 variant but

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with 1 type of *RAS* variant, median OS with panitumumab plus FOLFOX4 was shorter (n=51; median, 17.1 months) than with FOLFOX4 alone (n=57; median, 17.8 months) (p=0.01). These data would suggest variants in a *RAS* gene exon other than *KRAS* exon 2 negatively affect anti-EGFR therapy. However, the investigators do not discriminate specific types of *RAS* variants, so it is not possible to relate *NRAS* to these results. Furthermore, the numbers of patients involved are very small, further limiting conclusions.

Tumor specimens (288 of 320) from a 2007 RCT were analyzed using massively parallel multigene sequencing (next-generation sequencing) to investigate whether EGFR pathway variants would predict response to monotherapy with panitumumab compared with best supportive care. This 2013 analysis showed that *NRAS* had mutated in 14 (5%) of 282 samples with available data. Among patients with wild-type *KRAS* (codons 12, 13, and 61) and wild-type *NRAS* (n=138), treatment with panitumumab was associated with improved PFS (HR=0.39; 95% CI, 0.27 to 0.56; p<0.001) compared with best supportive care. Among those with wild-type *KRAS* but mutated *NRAS* (n=11), treatment with panitumumab was no longer associated with longer PFS (HR=1.94; 95% CI, 0.44 to 8.44; p=0.379). A treatment interaction analysis was suggestive but not significantly indicative of an interaction between the presence of mutated *NRAS* and poorer outcome (p=0.076). The authors suggested their data were consistent with the hypothesis that *NRAS* variants may limit the efficacy of anti-EGFR therapy. However, because the prevalence of *NRAS* variants was low, the degree of predictive or prognostic value is more uncertain.

Retrospective Cohort Studies

A 2010 retrospective consortium analysis reported results of centrally performed high-throughput mass spectrometric variant profiling of CRC specimens gathered from 11 centers in 7 European countries. Patients had been treated with panitumumab alone, cetuximab alone, or cetuximab plus chemotherapy. Among 747 of 773 samples with data, *KRAS* had mutated in 299 (40%), including codons 12, 13, 61, and 146. By contrast, *NRAS* variants were identified in 17 (2.6%) of 644 samples with data, primarily in codon 61. *KRAS* and *NRAS* variants were mutually exclusive. Among wild-type *KRAS* samples from patients treated with cetuximab plus chemotherapy, the *NRAS* variant was associated with an ORR of 7.7% (1/13) compared with 38% for the wild-type *NRAS* (p=0.013). However, there were no significant differences between *NRAS* mutant and wild-type genes in median PFS (14 weeks vs 26 weeks, p=0.055) or OS (38 weeks vs 50 weeks, p=0.051). Similar to results previously reported, the results of this analysis showed a very low prevalence of *NRAS* variants and were inconclusive as to whether *NRAS* variants are predictive of nonresponse to anti-EGFR therapy or are prognostic indicators of poor outcomes of CRC.

The rarity of *NRAS* variants reported in the studies previously discussed was also shown in 2010 a study that used PCR and pyrosequencing (Qiagen) to assess tumor samples from individuals who developed CRC and were identified within the databases of 2 prospective cohort studies: the Nurses' Health Study and the Health Professionals Follow-Up Study. Among 225 CRC specimens, *NRAS* variants were identified in 5 (2.2%). Because of the low frequency of *NRAS* variants, they were not associated with any clinical or pathologic features or with patient survival.

A 2014 systematic review evaluated the predictive value of *NRAS* variants on clinical outcomes of anti-EGFR therapy in CRC. The meta-analysis included data from 3 studies included in this evidence review.

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Reviewers suggested that the pooled analyses showed a trend toward a poor OR based on 17 events, but significant effects on PFS (HR=2.30; 95% CI, 1.30 to 4.07) and OS (HR=1.85; 95% CI, 1.23 to 2.78) among patients with wild-type *KRAS*. These results are limited by the small pool of variants, permitting no conclusions whether *NRAS* variants have an effect on anti-EGFR therapy.

Section Summary: Clinical Validity

Evidence for the clinical validity of *NRAS* variants in predicting nonresponse to anti-EGFR monoclonal antibody therapy includes prospective-retrospective analyses of RCTs. Subgroup analyses of *KRAS* wild-type patients who did not respond to anti-EGFR monoclonal antibody therapy have suggested that variants in *NRAS* are predictive of nonresponse. However, because of the low prevalence of *NRAS* variants, the predictive value of *NRAS* variants is uncertain.

Clinical Utility

Documentation of *KRAS* wild-type status is required prior to treatment with cetuximab or panitumumab. Documentation of *NRAS* variant status is not required but has been recommended to identify patients who are predicted to be nonresponders to anti-EGFR monoclonal antibody therapy.

Section Summary: Clinical Utility

Direct evidence for the clinical utility of *NRAS* variant testing includes prospective-retrospective analyses of RCTs and retrospective cohort studies. *NRAS* variant testing has potential clinical utility in predicting nonresponse to anti-EGFR monoclonal antibody therapy in patients with documented *KRAS* wild-type status. However, the direct evidence is limited for *NRAS* variant testing due to low prevalence *NRAS* variants in CRC.

BRAF VARIANT TESTING FOR METASTATIC CRC

Clinical Context and Test Purpose

The purpose of *BRAF* variant testing in individuals with metastatic CRC is to determine *BRAF* variant status to guide management decisions.

The question addressed in this evidence review is: In individuals with metastatic CRC, does the use of *BRAF* variant testing improve health outcomes?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest includes individuals with metastatic CRC who are found to be wild-type on *KRAS* and *NRAS* variant analysis.

Interventions

The relevant intervention of interest is *BRAF* variant testing.

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Original Effective Date: 12/17/2008

Current Effective Date: 02/21/2018

Comparators

The relevant comparator of interest is no *BRAF* variant testing to guide management.

Outcomes

The beneficial outcomes of interest include PFS and OS.

Timing

The time frame for outcomes measures varies from several months to several years.

Setting

Patients with metastatic CRC are actively managed by oncologists.

Analytic Validity

No published studies are available demonstrating the analytic validity of LDTs for *BRAF* variants in CRC samples.

Section Summary: Analytic Validity

There is a lack of published evidence on the analytic validity of LDTs to detect *BRAF* variants in CRC samples. However, it is expected that analytic validity will be high when testing is performed according to optimal laboratory standards.

Clinical Validity

Systematic Reviews

A 2015 meta-analysis identified 9 phase 3 trials that compared cetuximab or panitumumab with standard therapy or best supportive care. The analysis included 463 patients with metastatic CRC and *BRAF* variants. The addition of an EGFR inhibitor did not improve PFS (HR=0.88; 95% CI, 0.67 to 1.14; p=0.33) or ORR (RR=1.31; 95% CI, 0.83 to 2.08; p=0.25) compared with the control arms.

A 2011 meta-analysis of *BRAF* variants and resistance to anti-EGFR monoclonal antibodies in patients with metastatic CRC was performed. The primary end point of eligible studies was ORR, defined as the sum of complete and partial tumor response. Eleven studies reported sample sizes ranging from 31 to 259 patients. All were conducted retrospectively (1 study was a nonconcurrent analysis of response in a population previously randomized). Anti-EGFR therapy was given as first-line treatment in 1 study and as second-line or greater in the other 10. In 2 studies, the anti-EGFR monoclonal antibody was given as monotherapy, and in 9 studies, patients received various chemotherapies. Seven studies were performed in unselected patients (ie, *KRAS* variant status was unknown) totaling 546 patients, for whom 520 were assessable for tumor response. In the unselected population, a *BRAF* variant was detected in 8.8% of patients, and the ORR for patients with mutant *BRAF* was 29.2% (14/48) and for wild-type *BRAF* was 33.5% (158/472; p=0.048). Four studies were performed in patients with wild-type *KRAS* metastatic CRC. *BRAF* variant status was performed on 376 wild-type *KRAS* tumors. *BRAF* variant was detected in 10.6% (n=40) of primary tumors. Among the 376 analyzed, all patients were assessable for tumor response. The

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ORR of patients with a mutant *BRAF* gene was 0% (0/40), whereas the ORR of patients with wild-type *BRAF* was 36.3% (122/336). Only 3 studies presented data on PFS and OS and, therefore, pooled analysis was not performed. Reviewers concluded that, although the meta-analysis provided evidence that *BRAF* variant was associated with lack of response to anti-EGFR monoclonal antibodies in wild-type *KRAS* metastatic CRC, the number of studies and number of patients analyzed were relatively small and that large studies would be needed to confirm the results of the meta-analysis using homogenous metastatic CRC patients with assessors blinded to the clinical data.

Mao's meta-analysis (2011) also assessed *BRAF* V600E variant and resistance to anti-EGFR monoclonal antibodies in patients with metastatic CRC. The same 11 studies were selected. Seven included unselected patients, and 4 studies included only patients with wild-type *KRAS*. The primary end point was ORR. In the 7 studies with unselected patients, *BRAF* variant status was performed successfully on 546 metastatic CRC. *BRAF* variants were detected in 8.8% of primary tumors. The ORR of metastatic CRC patients with mutant *BRAF* was 29.2% and 33.5% in patients with wild-type *BRAF*. In the 4 studies that included patients with wild-type *KRAS*, *BRAF* variant status was performed successfully on 376 wild-type *KRAS* metastatic CRC. *BRAF* variants were detected in 10.6% of primary tumors. The ORR of patients with mutant *BRAF* genes was 0.0%, whereas it was 36.3% in patients with wild-type. Reviewers concluded that their results provided evidence that the *BRAF* variant is associated with lack of response in wild-type *KRAS* metastatic CRC treated with anti-EGFR monoclonal antibodies.

Retrospective Studies

Di Nicolantonio et al (2008) retrospectively analyzed 113 patients with metastatic CRC who had received cetuximab or panitumumab. None of the *BRAF*-mutated tumors (0/11) responded to treatment, whereas 32.4% (22/68) of the wild-type *BRAF* did. Loupakis et al (2009) retrospectively assessed 87 patients receiving irinotecan and cetuximab. Of the 87 patients in the study, *BRAF* was mutated in 13 patients, and none of whom responded to chemotherapy, compared with 32% (24/74) of patients with wild-type *BRAF* who did. In the CAIRO2 study (2009), retrospective analysis of *BRAF* variants was performed in 516 available tumors from patients previously randomized to the CB regimen or to the CBC regimen. A *BRAF* variant was found in 8.7% (n=45) of the tumors. Patients with a *BRAF* variant had a shorter median PFS and OS compared with wild-type *BRAF* tumors in both treatment arms. The authors concluded that a *BRAF* variant was a negative prognostic marker in patients with metastatic CRC and that this effect, in contrast with *KRAS* variants, was not restricted to the outcome of cetuximab treatment. In the CRYSTAL trial, Van Cutsem et al (2009) randomized 1198 patients with untreated metastatic CRC to FOLFIRI with or without cetuximab. A 2014 analysis of *BRAF* variants in this patient population and the influence of *BRAF* variant status showed that, for the wild-type *KRAS* and *BRAF*-mutated patients, OS for cetuximab plus FOLFIRI and FOLFIRI alone was 14.1 months and 10.3 months, respectively ($p=0.744$). Although this difference was not statistically significant, it showed a trend toward improved OS, PFS, and response, suggesting that wild-type *KRAS*- and *BRAF*-mutant patients might benefit from anti-EGFR therapy.

De Roock et al (2010) reported on the effects of 4 variants, including *BRAF*, on the efficacy of cetuximab and chemotherapy in chemotherapy-refractory metastatic CRC in 773 primary tumor samples. Tumor samples were from fresh frozen or FFPE tissue, and the variant status was compared with retrospectively

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Original Effective Date: 12/17/2008

Current Effective Date: 02/21/2018

collected clinical outcomes including ORR, PFS, and OS. *BRAF* variants were found in 36 (4.7%) of 761 tumors. In patients with wild-type *KRAS*, carriers of *BRAF* variants had a significantly lower response rate (8.3% [2/24] patients) than wild-type *BRAF* (38.0% [124/326] patients; OR=0.15; 95% CI, 0.02 to 0.51; $p=0.001$). PFS for *BRAF*-mutated vs wild-type patients was a median of 8 weeks vs 26 weeks, respectively (HR=3.74; 95% CI, 2.44 to 5.75; $p<0.001$), and median OS was 26 weeks vs 54 weeks, respectively (HR=3.03; 95% CI, 1.98 to 4.63; $p<0.001$).

An updated analysis of the CRYSTAL trial (2011) reported on longer follow-up and larger numbers of patients with evaluable for *KRAS* tumor status and considered the clinical significance of *BRAF* tumor variant status in the expanded population of patients with wild-type *KRAS* tumors. The impact of *BRAF* tumor variant status on the efficacy of cetuximab plus FOLFIRI was examined in the population with wild-type *KRAS* disease ($n=625$). No evidence was reported for an independent treatment interaction by *BRAF* tumor variant status. The authors concluded that *BRAF* variant status was not predictive of the treatment effects of cetuximab plus FOLFIRI but that *BRAF* tumor variant was a strong indicator of poor prognosis for all efficacy end points compared with those whose tumors were wild-type.

Section Summary: Clinical Validity

Evidence for the clinical validity *BRAF* variants in predicting nonresponse to anti-EGFR monoclonal antibody therapy includes 2 meta-analyses of prospective and retrospective analyses of RCTs. Subgroup analyses of *KRAS* wild-type and *NRAS* wild-type patients who did not respond to anti-EGFR monoclonal antibody therapy suggested that *BRAF* variants might be predictive of nonresponse. However, because of the low prevalence of *BRAF* variants, the true predictive value of *BRAF* variants is unclear.

Clinical Utility

Documentation of *KRAS* wild-type status is required prior to treatment with cetuximab or panitumumab. Documentation of *BRAF* variant status is not required but has been suggested to identify patients who are predicted to be nonresponders to anti-EGFR monoclonal antibody therapy.

Section Summary: Clinical Utility

Direct evidence for the clinical utility of *BRAF* variant testing includes meta-analyses of prospective and retrospective analyses of RCTs. *BRAF* variant testing has potential clinical utility in predicting nonresponse to anti-EGFR monoclonal antibody therapy in patients with documented *KRAS* wild-type and *NRAS* wild-type status. However, the direct evidence is limited for *BRAF* variant testing due to the low prevalence *BRAF* variants in CRC.

SUMMARY OF EVIDENCE

For individuals with metastatic CRC who receive *KRAS* variant testing to guide treatment, the evidence includes multiple systematic reviews including a TEC Assessment. Relevant outcomes are OS, disease-specific survival, change in disease status, medication use, resource utilization, and treatment-related morbidity. Variant testing of tumor tissue performed in prospective and retrospective analyses of RCTs has consistently shown that the presence of a *KRAS* variant predicts nonresponse to cetuximab and panitumumab, either as monotherapy or in combination with other treatment regimens, and supports the

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use of *KRAS* variant analysis of tumor DNA before considering a treatment regimen. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals with metastatic CRC who receive *NRAS* variant testing to guide treatment, the evidence includes prospective-retrospective analyses of RCTs and retrospective cohort studies. Relevant outcomes are OS, disease-specific survival, change in disease status, medication use, resource utilization, and treatment-related morbidity. Pooled analyses have shown that *NRAS* variants (beyond the common *KRAS* exon 2 variants) predict nonresponse to cetuximab and panitumumab, and support the use of *NRAS* variant analysis of tumor DNA before considering a treatment regimen. In addition, there is strong support from the National Comprehensive Cancer Network and American Society of Clinical Oncology for *NRAS* and *KRAS* testing in patients with metastatic CRC. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals with metastatic CRC who receive *BRAF* variant testing to guide management decisions, the evidence includes 2 meta-analyses of prospective and retrospective analyses of RCTs. Relevant outcomes are OS, disease-specific survival, change in disease status, medication use, resource utilization, and treatment-related morbidity. The meta-analyses have shown that anti-EGFR monoclonal antibody therapy did not improve survival in patients with *RAS* wild-type and *BRAF*-mutated tumors; however, the individual studies have been small, and the results have been inconsistent. The evidence is insufficient to determine the effects of the technology on health outcomes.

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Policy # 00233

Original Effective Date: 12/17/2008

Current Effective Date: 02/21/2018

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Original Effective Date: 12/17/2008

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Policy History

Original Effective Date: 12/17/2008

Current Effective Date: 02/21/2018

12/03/2008	Medical Director review
12/17/2008	Medical Policy Committee approval. New policy.
12/04/2008	Medical Director review
12/16/2008	Medical Policy Committee approval. No change to coverage.
12/01/2010	Medical Policy Committee review
12/15/2010	Medical Policy Implementation Committee approval. No change to coverage.
12/08/2011	Medical Policy Committee review

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Current Effective Date: 02/21/2018

12/21/2011 Medical Policy Implementation Committee approval. Title changed to indicate inclusion of BRAF testing to the policy. BRAF testing policy statement added as investigational to predict nonresponse to anti-EGFR monoclonal antibodies cetuximab and panitumumab in the treatment of metastatic colorectal cancer.

12/06/2012 Medical Policy Committee review

12/19/2012 Medical Policy Implementation Committee approval. No change to coverage.

03/04/2013 Coding revised

12/12/2013 Medical Policy Committee review

12/18/2013 Medical Policy Implementation Committee approval. No change to coverage.

01/01/2015 Coding Update

04/02/2015 Medical Policy Committee review

04/20/2015 Medical Policy Implementation Committee approval. Title changed to indicate inclusion of NRAS testing to the policy. NRAS testing policy statement added as investigational to predict nonresponse to anti-EGFR monoclonal antibodies cetuximab and panitumumab in the treatment of metastatic colorectal cancer.

08/03/2015 Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.

01/01/2016 Coding update

04/07/2016 Medical Policy Committee review

04/20/2016 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

06/30/2016 Medical Policy Committee review

07/20/2016 Medical Policy Implementation Committee approval. Policy statement revised to indicate that NRAS testing policy statement added as medically necessary to predict nonresponse to anti-EGFR monoclonal antibodies cetuximab and panitumumab in the treatment of metastatic colorectal cancer.

01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes

09/07/2017 Medical Policy Committee review

09/20/2017 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

02/01/2018 Medical Policy Committee review

02/21/2018 Medical Policy Implementation Committee approval. Title changed from "KRAS, NRAS, and BRAF Mutant Analysis in Metastatic Colorectal Cancer" to "KRAS, NRAS, and BRAF Variant Analysis in Metastatic Colorectal Cancer". BRAF variant analysis changed from investigational to eligible for coverage. Policy revised with updated genetic nomenclature.

Next Scheduled Review Date: 02/2019

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HCPCS	No codes
ICD-10 Diagnosis	C18.0-C18.9 C19 C20 C21.0-C21.2 C21.8

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

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- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
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- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

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