KRAS, NRAS, and BRAF Mutation Analysis in Metastatic Colorectal Cancer

Policy Number: 2.04.53  Last Review: 5/2017  
Origination: 1/2011  Next Review: 5/2018

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for KRAS mutation analysis in metastatic colorectal cancer when it is determined to be medically necessary because the criteria shown below are met.

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

When Policy Topic is covered
KRAS mutation analysis may be considered medically necessary for patients with metastatic colorectal cancer to predict nonresponse prior to planned therapy with anti-EGFR monoclonal antibodies cetuximab or panitumumab.

NRAS mutation analysis may be considered medically necessary for patients with metastatic colorectal cancer to predict nonresponse prior to planned therapy with anti-EGFR monoclonal antibodies cetuximab or panitumumab.

When Policy Topic is not covered
KRAS mutation analysis is considered investigational if the criterion is not met.

BRAF mutation analysis is considered investigational to predict nonresponse to anti-EGFR monoclonal antibodies cetuximab and panitumumab in the treatment of metastatic colorectal cancer.

Description of Procedure or Service

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
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<tr>
<td>Individuals:</td>
<td>Interventions of interest are:</td>
<td>Comparators of interest are:</td>
<td>Relevant outcomes include:</td>
</tr>
<tr>
<td>• With metastatic colorectal</td>
<td>• KRAS mutation testing to guide</td>
<td>• No KRAS mutation testing to guide</td>
<td>• Overall survival</td>
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<tr>
<td>cancer</td>
<td>treatment</td>
<td>treatment</td>
<td>• Disease-specific survival</td>
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<td>• Change in disease status</td>
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<td>• Medication use</td>
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<td>• Resource utilization</td>
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The epidermal growth factor receptor (EGFR) is overexpressed in colorectal cancer (CRC). EGFR-targeted therapy with monoclonal antibodies cetuximab and panitumumab has shown clear survival benefit in patients with metastatic CRC, however, this benefit depends on lack of mutations in certain genes in the signaling pathway downstream from EGFR. This review summarizes the evidence for using tumor cell KRAS, NRAS, and BRAF mutational status as a predictor of nonresponse to anti-EGFR monoclonal antibody therapy.

For individuals who have metastatic CRC who receive KRAS mutation testing to guide treatment, the evidence includes multiple systematic reviews including a TEC Assessment. Relevant outcomes are overall survival, disease-specific survival, change in disease status, medication use, resource utilization, and treatment-related morbidity. Mutation testing of tumor tissue performed in prospective and retrospective analyses of randomized controlled trials (RCTs) has consistently shown that the presence of a KRAS mutation predicts nonresponse to cetuximab and panitumumab, either as monotherapy or in combination with other treatment regimens, and supports the use of KRAS mutation analysis of tumor DNA before considering a treatment regimen. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

For individuals who have metastatic CRC who receive NRAS mutation testing to guide treatment, the evidence includes prospective and retrospective analyses of RCTs. Relevant outcomes are overall survival, disease-specific survival, change in disease status, medication use, resource utilization, and treatment-related morbidity. Pooled analyses of RAS mutations beyond the common KRAS exon 2 mutations have been shown to predict nonresponse to cetuximab and panitumumab, and support the use of NRAS mutation 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
For individuals who have metastatic CRC who receive BRAF mutation testing to guide treatment, the evidence includes 2 meta-analyses of prospective and retrospective analyses of RCTs. Relevant outcomes are overall survival, disease-specific survival, change in disease status, medication use, resource utilization, and treatment-related morbidity. The meta-analyses showed 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 not been consistently demonstrated in the literature. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Background**

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

The RAS-RAF-MAP kinase pathway is activated in the EGFR cascade. RAS proteins are G proteins that cycle between active (RAS-GTP) and inactive (RAS-GDP) forms, in response to stimulation from a cell surface receptor such as EGFR, and act as a binary switch between the cell surface EGFR and downstream signaling pathways. The KRAS gene can harbor oncogenic mutations that result in a constitutively activated protein, independent of EGFR ligand binding, rendering antibodies to the upstream EGFR ineffective. KRAS mutations are found in approximately 30% to 50% of CRC tumors and are common in other tumor types. Another proto-oncogene that acts downstream from KRAS–NRAS harbors oncogenic mutations in codons 12, 13, or 61 that result in constitutive activation of the EGFR mediated pathway. These mutations are relatively rare compared with KRAS, detected in perhaps 2% to 7% of CRC specimens. It is unclear whether NRAS mutations predict poor response to anti-EGFR monoclonal antibody therapy or are 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 and is a principal downstream effector of KRAS. BRAF mutations occur in less than 10% to 15% of CRCs and appear to be a marker of poor prognosis. KRAS and BRAF mutations are considered to be mutually exclusive.

Cetuximab and panitumumab have FDA marketing approval for treatment of metastatic CRC in the refractory disease setting, and ongoing studies are investigating the use of these EGFR inhibitors as monotherapy and as part of combination therapy in first, second, and subsequent lines of therapy.

KRAS, NRAS, and BRAF mutation analyses using polymerase chain reaction methodology are commercially available as laboratory-developed tests. Such tests are regulated under the Clinical Laboratory Improvement Amendments (CLIA).
Premarket approval from FDA is not required when the assay is performed in a laboratory that is licensed by CLIA for high-complexity testing.

Rationale
This evidence review was created in October 2008 and has been updated regularly with reviews of the MEDLINE and EMBASE databases. The most recent literature review was performed through March 24, 2016.

A large body of literature has shown that metastatic colorectal cancer (CRC) tumors with a mutation 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 mutations in Kras outside exon 2, in exons 3 (codons 59 and 61) and exon 4 (codons 117 and 146) and mutations 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. Mutation testing of these exons outside the Kras exon 2 is referred to as extended RAS testing.

Kras Mutations
This evidence review is based, in part, on a 2008 TEC Assessment. Additional evidence is available 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 epidermal growth factor receptor (EGFR) inhibitors in patients with wild-type versus 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 progression-free survival (PFS) observed only in wild-type Kras patients.

Amado et al performed a subgroup analysis of Kras tumor mutations in a patient population that had previously been randomly assigned to panitumumab versus best supportive care as third-line therapy for chemotherapy-refractory metastatic CRC. The original study was designed as a multicenter, RCT but 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 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 study, 427 (92%) were included in the Kras subgroup mutation analysis. A central laboratory performed the Kras mutational analysis in a blinded fashion, using formalin-fixed, paraffin-embedded (FFPE) tumor sections and a validated Kras mutation kit (Dxs, Manchester, England)
that identifies 7 somatic mutations located in codons 12 and 13 using real-time polymerase chain reaction (PCR). *KRAS* mutation status could not be determined in 36 patients because tumor samples were not available or DNA was insufficient or poor quality for analysis. Forty-three percent of the *KRAS*-evaluable patients had *KRAS*-mutated tumors, with similar distribution of *KRAS* mutation types between treatment arms.

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 mutant group.

### Table 1. *KRAS* Status and Efficacy of Panitumumab as Monotherapy in the Treatment of Chemotherapy-Refractory Metastatic Colorectal Cancer

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>KRAS WT (n=243 [57%])</th>
<th>KRAS MT (n=184 [43%])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample (N=427)</td>
<td>P (n=124)</td>
<td>BSC (n=119)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P (n=84)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BSC (n=100)</td>
</tr>
<tr>
<td>Median progression-free survival, wk</td>
<td>12.3</td>
<td>7.3</td>
</tr>
<tr>
<td></td>
<td>7.4</td>
<td>7.3</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.45 (0.34 to 0.59)</td>
<td>0.99 (0.73 to 1.36)</td>
</tr>
<tr>
<td>Response rate, %</td>
<td>17</td>
<td>0</td>
</tr>
</tbody>
</table>

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

Given the crossover design of the study and the fact that most of the best supportive care (BSC) 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 end points are limited. However, of the 168 BSC patients who crossed over to 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, in which 1198 patients with metastatic CRC were randomly assigned to receive either cetuximab in combination with folinic acid (leucovorin), 5-flourouracil (5-FU), and irinotecan (FOLFIRI) or FOLFIRI alone for first-line treatment, a subgroup analysis of response rate and PFS according to *KRAS* mutational status was performed. 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).

Of the original 1198 patients, 540 had KRAS-evaluable, archival material. KRAS testing was performed from genomic DNA isolated from archived FFPE 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. KRAS mutations 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 by computed tomography scan 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)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>ITT&lt;sup&gt;a&lt;/sup&gt;</th>
<th>KRAS WT (n=348 [64%]&lt;sup&gt;b&lt;/sup&gt;)</th>
<th>KRAS MT (n=192 [36%]&lt;sup&gt;b&lt;/sup&gt;)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C+F</td>
<td>F</td>
<td>C+F</td>
</tr>
<tr>
<td>N</td>
<td>599</td>
<td>599</td>
<td>172</td>
</tr>
<tr>
<td>RR, %</td>
<td>46.9%</td>
<td>38.7%</td>
<td>59.3%</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(42.9 to 51.0)</td>
<td>(34.8 to 42.8)</td>
<td>(51.6 to 66.7)</td>
</tr>
<tr>
<td>mPFS, mo&lt;sup&gt;c&lt;/sup&gt;</td>
<td>8.9</td>
<td>8.0</td>
<td>9.9</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>0.68 (p=0.017)</td>
<td>1.07 (p=0.47)</td>
<td>1.07 (p=0.47)</td>
</tr>
</tbody>
</table>

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.

<sup>a</sup> ITT in the original CRYSTAL trial assessing C+F versus F alone as first-line therapy for metastatic CRC.

<sup>b</sup> 540 patients had available archival pathology material for the KRAS mutation subset analysis.

<sup>c</sup> 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 randomly assigned to cetuximab and folinic acid (leucovorin), 5-FU, oxaliplatin (FOLFOX) versus FOLFOX alone in the first-line treatment of metastatic CRC. A 10% higher response rate (assessed by independent reviewers) was observed in the population treated with C, but no difference in PFS was seen between the 2 groups. The researchers then reevaluated the efficacy in the 2 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. 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 study showed that the
addition of C 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)

<table>
<thead>
<tr>
<th></th>
<th>KRAS WT (n=134 [58%])</th>
<th>KRAS MT (n=99 [42%])</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>C+Fx</td>
<td>Fx</td>
</tr>
<tr>
<td><strong>n (KRAS evaluable)</strong></td>
<td>61</td>
<td>73</td>
</tr>
<tr>
<td><strong>RR, % (95% CI)</strong></td>
<td>60.7 (47.3 to 72.9)</td>
<td>37.0 (26.0 to 49.1)</td>
</tr>
<tr>
<td><strong>p value</strong></td>
<td>0.011</td>
<td>0.106</td>
</tr>
<tr>
<td><strong>Odds ratio (95% CI)</strong></td>
<td>2.54 (1.24 to 5.23)</td>
<td>0.51 (0.22 to 1.15)</td>
</tr>
<tr>
<td><strong>mPFS, mo</strong></td>
<td>7.7</td>
<td>7.2</td>
</tr>
<tr>
<td><strong>p value</strong></td>
<td>0.016</td>
<td>0.019</td>
</tr>
<tr>
<td><strong>Hazard ratio</strong></td>
<td>0.57</td>
<td>1.83</td>
</tr>
</tbody>
</table>

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

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

In the CAIRO2 study, Tol et al analyzed tumor samples from 528 of 755 previously untreated patients with metastatic CRC who were randomly assigned to receive capecitabine, oxaliplatin, and bevacizumab (CB regimen, n=378), or the same regimen plus cetuximab (CBC regimen, n=377). A KRAS mutation was found in 40% of tumors (108 from patients in the CB group, 98 from the CBC group). Patients with KRAS mutations treated with cetuximab had significantly shorter PFS than the wild-type KRAS patients who received cetuximab (8.1 months vs 10.5 months, respectively, p=0.04). In addition, patients who had mutated KRAS tumors who received cetuximab had significantly shorter PFS than patients with mutated KRAS tumors who did not receive C (8.1 months vs 12.5 months, respectively, p=0.003) and overall survival (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 2 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 analyzed tumor samples from 394 (69%) of 572 patients with CRC who were randomly assigned to receive C plus BSC (n=287) versus BSC alone (n=285) for KRAS mutations and assessed whether mutation status was associated with survival. The patients had advanced CRC, had failed chemotherapy and had no other standard anticancer therapy available. Of the tumors that were evaluated (198 from the C group, 196 from the BSC group), 41% and 42% had a KRAS mutation, respectively. In OS (median, 9.5 months vs 4.8 months, respectively; HR for death, 0.55; 95% confidence interval [CI], 0.41 to 0.74; p<0.001) and PFS (median, 3.7 months vs 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 C versus BSC alone with respect to OS (HR=0.98, p=0.89) or PFS (HR=0.99, p=0.96).

Douillard et al reported 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 randomly assigned 1:1 to receive panitumumab plus FOLFOX4 versus 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 randomly assigned. 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 versus 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 versus the FOLFOX4 arm (HR=1.29; 95% CI, 1.04 to 1.62; p=0.02), and median OS was 15.5 months versus 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 study demonstrated that panitumumab plus FOLFOX4 was well-tolerated and significantly improved PFS in patients with wild-type KRAS tumors.

The CRYSTAL trial 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 metastatic CRC that was wild-type KRAS, compared with chemotherapy alone. An updated analysis of CRYSTAL reported increased follow-up time and an increased number of patients evaluable for tumor KRAS status and considered the clinical significance of the tumor mutation status of BRAF in the expanded population of patients with wild-type KRAS tumors. Subsequent to the initial published analysis, which had a cutoff for OS of December 2007, and an associated overall median duration of follow-up of 29.7 months, additional tumor analysis allowed for the typing of an additional 523 tumors for KRAS mutation 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 mutations detected in 37% of tumors. The updated analysis of OS 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 mutation status was confirmed as a powerful predictive biomarker for the efficacy of cetuximab plus FOLFIRI. BRAF V600E mutations were detected in 60 (6%) of 999 tumor samples evaluable for both BRAF and KRAS. In all but 1 case, BRAF mutations were identified in tumors
that were wild type for \textit{KRAS}. The impact of \textit{BRAF} tumor mutation status in relation to the efficacy of cetuximab plus FOLFIRI was examined in the population of patients with wild-type \textit{KRAS} disease (n=625). No evidence was reported for an independent treatment interaction by tumor \textit{BRAF} mutation status. The authors concluded that \textit{BRAF} mutation status was not predictive of treatment effects of cetuximab plus FOLFIRI but that \textit{BRAF} tumor mutation was a strong indicator of poor prognosis for all efficacy end points compared with those whose tumors were wild type.

Peeters et al reported the results of a phase 3 study in which 1186 patients with metastatic CRC were randomized to receive panitumumab with FOLFIRI versus FORFIRI alone as second-line treatment.\textsuperscript{11} The study end points were PFS and OS, which were independently tested and prospectively analyzed by \textit{KRAS} status. \textit{KRAS} status was available for 91\% of patients: 597 (55\%) with wild-type \textit{KRAS} tumors and 486 (45\%) with mutated \textit{KRAS} tumors. In the wild-type \textit{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 versus 3.9 months for FOLFIRI. A nonsignificant trend toward increased OS was observed; median OS was 14.5 months versus 12.5 months, respectively (HR=0.85, 95\% CI, 0.70 to 1.04; p=0.12); response rate was improved to 35\% versus 10\% with the addition of panitumumab. In patients with mutated \textit{KRAS}, no difference was reported in efficacy. Adverse events were comparable across arms. The authors concluded that panitumumab plus FOLFIRI significantly improved PFS and is well-tolerated as second-line treatment in patients with wild-type \textit{KRAS} metastatic CRC (mCRC).

Maughan et al reported 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 and fluoropyrimidine chemotherapy (arm A) or the same combination plus cetuximab.\textsuperscript{12} The comparison between arms A and B (for which the primary outcome was OS) was in patients with wild-type \textit{KRAS} tumors. Baseline characteristics were well-balanced between the trial groups. Analysis was by ITT and treatment allocation was not masked. Further analysis with respect to other mutations, including \textit{BRAF}, was done; 1630 patients were randomly assigned to treatment groups (815 to standard therapy, 815 to the addition of cetuximab). Tumor samples from 1316 (81\%) of patients were used for somatic mutation analyses; 43\% had \textit{KRAS} mutations. In patients with wild-type \textit{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). \textit{BRAF} mutations were detected in 8\% of patients; \textit{BRAF} did not show any evidence of a benefit from the addition of cetuximab. Contrary to other trials that have assessed \textit{KRAS} mutation status and the benefit of the addition of cetuximab to the regimen of wild-type \textit{KRAS} patients, this trial did not show a benefit of the addition of cetuximab to oxaliplatin-based chemotherapy.
Systematic Reviews
Qiu et al conducted a meta-analysis of 22 studies on the predictive and prognostic value of KRAS mutations in metastatic CRC patients treated with cetuximab. The overall KRAS mutation rate was 38% (829/2188 patients). The results of the meta-analysis were consistent with previous reports on the use of cetuximab and KRAS mutation status, that patients with tumors that harbor mutant-type KRAS are more likely to have a worse response, PFS and OS when treated with cetuximab when compared with those with wild-type KRAS.

Dahabreh et al conducted a systematic review of RCTs that assessed the use of KRAS mutation testing as a predictive biomarker for treatment of advanced CRC with cetuximab and panitumumab. The authors concluded that, compared with patients with wild-type KRAS, KRAS mutations are 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 pooled analysis of the CRYSTAL and OPUS RCT data was performed to further investigate the findings of these trials in patients with wild-type KRAS tumors, using extended survival data and following an enhancement in the ascertainment rate of KRAS and BRAF tumor mutation status. Pooled individual patient data from each study were analyzed for OS, PFS and best objective response rate (ORR) in patients evaluable for KRAS and BRAF mutation status. Treatment arms were compared according to mutation 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 improvement in OS (HR= 0.81; p=0.006), PFS (HR=0.66; p<0.001), and ORR (OR=2.16; p<0.001). BRAF mutations were detected in 70 (8.8%) of 800 evaluable tumors. No significant differences were found in outcome between the treatment groups in these patients. However, prognosis was worse in each treatment arm for patients with BRAF tumor and OPUS studies confirms the consistency of the benefit obtained across all efficacy end points from adding cetuximab to first-line chemotherapy in patients with wild-type KRAS median CRC. It further suggests that BRAF mutation does not appear to be a predictive biomarker in this setting, but is a marker of poor prognosis.

Single-Arm Studies (Cetuximab or Panitumumab)
In addition to the 3 randomized trials outlined here, a number of single-arm studies retrospectively evaluated KRAS mutational status and treatment response in patients with metastatic CRC. Overall they showed similar nonresponse to anti-EGFR monoclonal antibodies in patients with mutated KRAS tumors. Two of these single-arm studies also reported a difference in PFS and OS.

NRAS Mutations

Randomized Controlled Trials
RCTs have performed nonconcurrent subgroup analyses of the efficacy of EGFR inhibitors in patients with wild-type versus mutated RAS in metastatic CRC.
In 2015, Peeters et al reported the influence of RAS mutation status in a prospective/retrospective analysis of a randomized, multicenter phase 3 trial of panitumumab plus FOLFIRI versus FOLFIRI alone as second-line therapy in patients with metastatic CRC. If a tumor was wild-type KRAS exon 2, extended RAS mutations beyond KRAS exon 2 was performed (KRAS exons 3 and 4; NRAS exons 2, 3, and 4; BRAF exon 15). Primary end points were PFS and OS. RAS mutations were obtained in 85% of the specimens from the original trial; 18% of wild-type KRAS exon 2 tumors harbored other RAS mutations. For PFS and OS, the HR for panitumumab plus FOLFIRI versus FOLFIRI alone more strongly favored panitumumab in the wild-type RAS population than in the wild-type KRAS exon 2 population (PFS HR= 0.70; 95% CI, 0.54 to 0.91; p=0.007 vs PFS HR=0.73; 95% CI, 0.59 to 0.90; p=0.004; OS HR=0.81; 95% CI, 0.63 to 1.03; p=0.08 vs OS HR=0.85; 95% CI, 0.70 to 1.04; p=0.12). Patients with RAS mutations were unlikely to benefit from panitumumab. Among RAS wild-type patients, the ORR was 41% in the panitumumab plus FOLFIRI group and 10% in the FOLFIRI group.

In 2015, van Cutsem et al reported results of a prospective/retrospective extended RAS mutation analysis in tumor samples from the randomized phase 3 CRYSTAL trial, which compared FOLFIRI to FOLFIRI plus cetuximab in wild-type KRAS exon 2 patients. Mutation status was available in 430 (64.6%) of 666 patients from the trial. A pooled analysis of RAS mutations, 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=NS) and median OS (16.4 months vs 17.7 months; p=NS). Patients with tumors that had no RAS mutations 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<.05) with the addition of cetuximab to chemotherapy.

Douillard et al performed a prospective/retrospective analysis of RAS mutations (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 mutations in exon 2 had mutations in other RAS exons, including NRAS (exons 2 or 4) and KRAS (exons 3 and 4). Among the wild-type KRAS exon 2 patients (n=656), OS was significantly better with panitumumab added to FOLFOX4 (n=325; median, 23.8 months) versus FOLFOX4 alone (n=331; median, 19.4 months; p=0.03). Among patients with no KRAS exon 2 mutation but with 1 type of RAS mutation, 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 suggest mutation in a RAS gene exon other than KRAS exon 2 negatively affects anti-EGFR therapy. However, the investigators do not discriminate specific types of RAS mutations, 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 an RCT were analyzed using massively parallel multigene sequencing (next-generation sequencing) to investigate whether EGFR pathway mutations predicted response to monotherapy with panitumumab compared with BSC. This analysis showed that NRAS was 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 BSC. 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 a hypothesis that NRAS mutations may limit the efficacy of anti-EGFR therapy. However, because the prevalence of NRAS mutations is low, their true predictive or prognostic value is unclear.

A retrospective consortium analysis reported results of centrally performed high-throughput mass spectrometric mutation profiling of CRC specimens gathered from 11 centers in 7 European countries.25 Patients had been treated with panitumumab alone, cetuximab alone, or cetuximab plus chemotherapy. Among 747 of 773 samples with data, KRAS was mutated in 299 (40%), including codons 12, 13, 61, and 146. By contrast, NRAS mutations were identified in 17 (2.6%) of 644 samples with data, primarily in codon 61. KRAS and NRAS mutations were mutually exclusive. Among wild-type KRAS samples from patients treated with cetuximab plus chemotherapy, NRAS mutation was associated with an ORR of 7.7% (1/13) compared with wild-type NRAS (ORR=38%, p=0.013). However, there were no significant differences between NRAS mutants and wild-type in median PFS (14 weeks vs 26 weeks, p=0.055) or OS (38 weeks vs 50 weeks, p=0.051). Similar to the results previously reported, the results for this analysis show a very low prevalence of NRAS mutations and are inconclusive as to whether NRAS mutation is predictive of nonresponse to anti-EGFR therapy or is a prognostic indicator of poor outcomes of CRC.

The rarity of NRAS mutations reported in the studies previously outlined in this evidence review is also shown in a study that used PCR and pyrosequencing (Qiagen, Valencia, CA) 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.26 Among 225 CRC specimens, NRAS mutations were identified in 5 (2.2%). Because of the low frequency of NRAS mutations, they were not associated with any clinical or pathologic features or with patient survival.

A 2014 meta-analysis evaluated the predictive value of NRAS mutations on clinical outcomes of anti-EGFR therapy in CRC.27 The meta-analysis included data from 3 studies included in this evidence review.23-25 The investigators suggested that the pooled analyses showed a trend toward poor odds ratio (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 mutations, permitting no conclusions as to whether NRAS mutations have an effect on anti-EGFR therapy.
**BRAF Mutations**

A 2015 meta-analysis identified 9 phase 3 trials that compared cetuximab or panitumumab with standard therapy or BSC. The analysis included 463 patients with metastatic CRC and BRAF mutations. 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 to the control arms.

A 2011 meta-analysis of BRAF mutation 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. A total of 11 studies reported sample sizes ranging from 31 to 259 patients. All studies 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 mutational status was unknown) totaling 546 patients, for whom 520 were assessable for tumor response. In the unselected population, a BRAF mutation 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 mutational status was performed on 376 wild-type KRAS tumors. BRAF mutation was detected in 10.6% (n=40) of primary tumors. Among the 376 analyzed, all patients were assessable for tumor response. ORR of patients with mutant BRAF 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, a pooled analysis was not performed. The authors conclude that although the meta-analysis provided evidence that BRAF mutation is associated with lack of response to anti-EGFR monoclonal antibodies in wild-type KRAS metastatic CRC, the number of studies and number of patients included in the meta-analysis were relatively small and that large studies are 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 also assessed BRAF V600E mutation and resistance to anti-EGFR monoclonal antibodies in patients with metastatic CRC. The same 11 studies were selected. Seven included unselected patients, and 4 included only patients with wild-type KRAS. The primary end point was ORR. In the 7 studies with unselected patients, BRAF mutational status was performed successfully on 546 mCRC. BRAF mutation was detected in 8.8% of primary tumors. The ORR of median CRC patients with median CRC with mutant BRAF was 29.2% versus 33.5% in patients with wild-type BRAF. In the 4 studies that included patients with wild-type KRAS, BRAF mutational status was performed successfully on 376 wild-type KRAS median CRC. BRAF mutations were detected in 10.6% of primary tumors. The ORR of patients with mutant BRAF was 0.0%, whereas it was 36.3% in patients with wild-type. The authors concluded that the results of their meta-analysis provided evidence that BRAF mutation is associated with lack of response in wild-type KRAS median CRC treated with anti-EGFR monoclonal antibodies.
Phillips et al analyzed the data from 4 studies that reported tumor response and survival in patients with median CRC treated with anti-EGFR monoclonal antibodies related to \textit{BRAF} mutational status.\textsuperscript{40} Di Nicolantonio et al looked retrospectively at 113 patients with median CRC who had received cetuximab or panitumumab.\textsuperscript{31} None of the \textit{BRAF}-mutated tumors (0/11) responded to treatment, whereas 32.4\% (22/68) of the wild-type \textit{BRAF} WT did. Loupakis et al retrospectively assessed 87 patients receiving irinotecan and cetuximab.\textsuperscript{34} Of the 87 patients in the study, \textit{BRAF} was mutated in 13 cases and none responded to chemotherapy, compared with 32\% (24/74) with wild-type \textit{BRAF} who did. In the CAIRO2 study, a retrospective analysis of \textit{BRAF} mutations was performed in 516 available tumors from patients previously randomized to CB regimen or the same regimen plus cetuximab (CBC regimen).\textsuperscript{39} A \textit{BRAF} mutation was found in 8.7\% (n=45) of the tumors. Patients with a \textit{BRAF} mutation had a shorter median PFS and OS compared with wild-type \textit{BRAF} tumors in both treatment arms. The authors concluded that a \textit{BRAF} mutation is a negative prognostic marker in patients with median CRC and that this effect, in contrast with \textit{KRAS} mutations, is not restricted to the outcome of cetuximab treatment. In the CRYSTAL trial, Van Cutsem et al randomized 1198 patients with untreated median CRC to FOLFIRI with or without cetuximab.\textsuperscript{5} A 2014 analysis of \textit{BRAF} mutations in this patient population and the influence on outcome was presented at the 2010 American Society of Clinical Oncology Gastrointestinal Cancers Symposium.\textsuperscript{41} The authors showed that, of the wild-type \textit{KRAS} and \textit{BRAF}-mutated patients, the OS rates for cetuximab plus FOLFIRI and FOLFIRI alone were 14.1 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 \textit{KRAS} and \textit{BRAF}-mutant patients may benefit from anti-EGFR therapy. This unpublished analysis is the first to show a possible benefit of anti-EGFR therapy in patients with \textit{BRAF}-mutant tumors.

De Roock et al reported the effects of 4 mutations, including \textit{BRAF}, on the efficacy of cetuximab and chemotherapy in chemotherapy-refractory metastatic CRC in 773 primary tumor samples.\textsuperscript{25} Tumor samples were from fresh frozen or FFPE tissue, and the mutation status were compared with retrospectively collected clinical outcomes including ORR, PFS, and OS. \textit{BRAF} mutations were found in 36 (4.7\%) of 761 tumors. In patients with wild-type \textit{KRAS}, carriers of \textit{BRAF} mutations had a significantly lower response rate (8.3\% \[2/24\] patients) than \textit{BRAF} WT (38.0\% \[124/326\] patients; OR=0.15; 95\% CI, 0.02 to 0.51; p=0.001). PFS for \textit{BRAF}-mutated versus wild-type was a median of 8 weeks versus 26 weeks, respectively (HR=3.74; 95\% CI, 2.44 to 5.75; p<0.001), and OS median 26 weeks versus 54 weeks, respectively (HR=3.03; 95\% CI, 1.98 to 4.63; p<0.001).

An updated analysis of the CRYSTAL trial reported increased follow-up time and an increased number of patients evaluable for \textit{KRAS} tumor status and considered the clinical significance of the tumor mutation status of \textit{BRAF} in the expanded population of patients with wild-type \textit{KRAS} tumors.\textsuperscript{10} The impact of \textit{BRAF} tumor mutation 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 independent treatment interaction by BRAF tumor mutation status. The authors concluded that BRAF mutation status was not predictive of treatment effects of cetuximab plus FOLFIRI but that BRAF tumor mutation was a strong indicator of poor prognosis for all efficacy end points compared with those whose tumors were wild type.

**Ongoing and Unpublished Clinical Trials**
Some currently unpublished trials that might influence this review are listed in Table 4.

### Table 4 Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td>Treatment Strategies in Colorectal Cancer Patients With Initially Unresectable Liver-only Metastases (CAIRO5)</td>
<td>640</td>
<td>Jul 2025</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

**Summary of Evidence**
For individuals who have metastatic colorectal cancer (CRC) who receive KRAS mutation testing to guide treatment, the evidence includes multiple systematic reviews including a TEC Assessment. Relevant outcomes are overall survival, disease-specific survival, change in disease status, medication use, resource utilization, and treatment-related morbidity. Mutation testing of tumor tissue performed in prospective and retrospective analyses of randomized controlled trials (RCTs) has consistently shown that the presence of a KRAS mutation predicts nonresponse to cetuximab and panitumumab, either as monotherapy or in combination with other treatment regimens, and supports the use of KRAS mutation analysis of tumor DNA before considering a treatment regimen. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

For individuals who have metastatic CRC who receive NRAS mutation testing to guide treatment, the evidence includes prospective and retrospective analyses of RCTs. Relevant outcomes are overall survival, disease-specific survival, change in disease status, medication use, resource utilization, and treatment-related morbidity. Pooled analyses of RAS mutations beyond the common KRAS exon 2 mutations have been shown to predict nonresponse to cetuximab and panitumumab, and support the use of NRAS mutation 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 qualitatively that the technology results in a meaningful improvement in the net health outcome.

For individuals who have metastatic CRC who receive BRAF mutation testing to guide treatment, the evidence includes 2 meta-analyses of prospective and
retrospective analyses of RCTs. Relevant outcomes are overall survival, disease-specific survival, change in disease status, medication use, resource utilization, and treatment-related morbidity. The meta-analyses showed that anti-epidermal growth factor receptor 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 not been consistently demonstrated in the literature. The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information

Practice Guidelines and Position Statements

National Comprehensive Cancer Network
The National Comprehensive Cancer Network (NCCN) guidelines on the treatment of colon cancer strongly recommend that KRAS and NRAS tumor gene status testing be performed for all patients with metastatic colon cancer (v.2.2016). Testing should be performed on archived specimens of primary tumor or a metastasis at the time of diagnosis of metastatic disease. The guidelines indicate that cetuximab and panitumumab are appropriate only for patients with a tumor that expresses wild-type KRAS and NRAS genes. The guidelines further state that if the tumor harbors wild-type KRAS and NRAS mutations, the clinician should consider testing for BRAF mutation status.

NCCN guidelines also state that patients with a BRAF V600E mutation appear to have a poorer prognosis. However, evidence is insufficient to guide the use of anti-EGFR therapy in the first-line setting with active chemotherapy based on BRAF V600E mutation status, and testing for BRAF is currently optional but not necessary part of decision-making on use of anti-EGFR agents. Limited evidence suggests lack of antitumor activity with anti-EGFR monoclonal antibodies in the presence of a BRAF V600E mutation when used after a patient has progressed on first-line therapy.

American College of Medical Genetics and Genomics
An evidence review published in 2013 by the American College of Medical Genetics and Genomics, Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group, states that evidence is insufficient to support the clinical validity or utility of testing CRC specimens for NRAS mutations to guide patient management. In the same review, EGAPP found no guidelines on NRAS testing from any other U.S. group.

American Society of Clinical Oncology
The American Society of Clinical Oncology (ASCO) published a provisional clinical opinion update in 2016 on extended RAS mutation testing in metastatic CRC to predict response to anti-EGFR monoclonal antibody therapy. The opinion was based on evidence from 13 articles on KRAS mutations (11 systematic reviews, 2 health technology assessments) and 2 articles on NRAS testing. The opinion stated that subgroup analyses of patients with any of the less common RAS mutations
are small, and there is inadequate evidence to provide a definitive opinion on the lack of benefit for the use of anti-EGFR antibodies for patients whose cancer harbors any specific RAS mutation other than the exon 2 KRAS mutation. ASCO considered the less common RAS mutations as a group, and a pooled analysis seemed to confer the same lack of benefit with anti-EGFR therapy as seen with the more common mutations in exon 2 of KRAS.

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

References


**Billing Coding/Physician Documentation Information**

**81210** BRAF (v-raf murine sarcoma viral oncogene homolog B1) (eg, colon cancer), gene analysis, V600E variant

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

**81276** KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; additional variant(s) (eg, codon 61, codon 146) (new code 1/1/2016)

**81311** NRAS (neuroblastoma RAS viral [v-ras] oncogene homolog) (eg, colorectal carcinoma), gene analysis, variants in exon 2 (eg, codons 12 and 13) and exon 3 (eg, codon 61) (new code 1/1/2016)
81403  Molecular pathology procedure, Level 4 (eg, analysis of single exon by DNA sequence analysis, analysis of > 10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons) ABL1 (c-abl oncogene 1, receptor tyrosine kinase) (eg, acquired imatinib tyrosine kinase inhibitor resistance), variants in the kinase domain DAZ/SRY (deleted in azoospermia and sex determining region Y) (eg, male infertility), common deletions (eg, AZFa, AZFb, AZFc, AZFd) GJB1 (gap junction protein, beta 1) (eg, Charcot-Marie-Tooth X-linked), full gene sequence JAK2 (Janus kinase 2) (eg, myeloproliferative disorder), exon 12 sequence and exon 13 sequence, if performed KRAS (v-Ki-ras2 Kirsten rat sarcoma viral oncogene) (eg, carcinoma), gene analysis, variant(s) in exon 2 MPL (myeloproliferative leukemia virus oncogene, thrombopoietin receptor, TPOR) (eg, myeloproliferative disorder), exon 10 sequence VHL (von Hippel-Lindau tumor suppressor) (eg, von Hippel-Lindau familial cancer syndrome), deletion/duplication analysis VWF (von Willebrand factor) (eg, von Willebrand disease types 2A, 2B, 2M), targeted sequence analysis (eg, exon 28)

81404  Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)

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

ICD10 Codes
C18.0-  Malignant neoplasm of colon code range
C18.9
C19  Malignant neoplasm of rectosigmoid junction
C20  Malignant neoplasm of rectum
C78.5  Secondary malignant neoplasm of large intestine and rectum

Additional Policy Key Words
N/A

Policy Implementation/Update Information
1/1/11  New policy; may be considered medically necessary
5/1/11  No policy statement changes.
5/1/12  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; KRAS policy statement unchanged.
5/1/13  No policy statement changes.
5/1/14  No policy statement changes.
5/1/15  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. KRAS testing not meeting criteria changed from not medically necessary to investigational.

5/1/16  No policy statement changes.
12/1/16  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.

5/1/17  No policy statement changes.

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