Clinical Policy Title: Viral oncogene mutation

Clinical Policy Number: 05.01.01

Effective Date: March 1, 2014
Initial Review Date: November 20, 2013
Most Recent Review Date: November 16, 2017
Next Review Date: November 2018

Related policies:

CP# 05.01.04 Molecular analysis for targeted therapy for lung cancer
CP# 02.01.11 Afirma™ gene expression classifier for indeterminate thyroid nodules
CP# 02.01.08 Familial polyposis gene testing
CP# 02.01.14 Gene expression profile testing for breast cancer
CP# 02.01.02 Genetic testing for breast and ovarian cancer
CP# 13.01.01 Genetic testing for prostate cancer prognosis
CP# 02.01.10 COLARIS® test for Lynch syndrome

Coverage policy

AmeriHealth Caritas considers the one-time use of Kirsten rat sarcoma (KRAS) viral oncogene mutation testing to be clinically proven and, therefore, medically necessary under the following conditions (Tosi 2017, Hayes 2015, Westwood 2014, Barni 2013, Chen 2013, Clancy 2013, Hoyle 2013):

As part of the diagnostic workup for suspected or proven metastatic colorectal carcinoma when anti-epidermal growth factor receptor (EGFR) is indicated as therapy (Hayes 2015, Hoyle 2013, Jiang 2013, Vale 2012).
**Limitations:**

All other uses of KRAS viral oncogene mutation testing are not medically necessary.

**Alternative covered services:**

Fecal occult blood test, flexible sigmoidoscopy, prothrombin time, serum glutamic-oxaloacetic transaminase, stool deoxyribonucleic acid mutation analysis, urine proteinuria levels.

**Background**

Colorectal cancer is cancer in the large intestine and rectum. It is one of the most common malignancies in developed countries and usually develops over a decade from benign lesions, such as polyps. Causes of colorectal cancer are multi-factorial, most likely including (in addition to polyps) family history and diet. Viral oncogenesis of colorectal cancer remains to be clearly defined.

Treatment of colorectal cancer includes surgery, radiotherapy and chemotherapy. Chemotherapy includes targeted therapy against specific molecules involved in tumor growth and progression, such as EGFR or vascular endothelial growth factor (VEGF). Targeted therapies for metastatic colorectal cancer include cetuximab (EGFR), panitumumab (EGFR) and bevacizumab (VEGF), all monoclonal antibodies designed to bind to and inactivate growth factor receptors.

Genetic testing, gene expression testing, or mutation testing includes a variety of laboratory tests (analysis of deoxyribonucleic acid, ribonucleic acid, genes or gene products) for the purposes of diagnosing disease, assisting in treatment decisions, predicting future disease, identifying carriers of disease or for prenatal testing.

Viral oncogene mutation tests are used to select patients for EGFR or VEGF therapies. One gene of particular interest in colorectal cancer is the KRAS mutated tumor as it apparently inhibits the therapeutic response of these tumors to anti-EGFR treatment. Randomized controlled trials and systematic reviews tabulated below demonstrate the deleterious effects on tumor response rates when the KRAS mutation is present.

**Searches**

AmeriHealth Caritas searched PubMed and the databases of:

- UK National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality’s National Guideline Clearinghouse and other evidence-based practice centers.
- The Centers for Medicare & Medicaid Services.
We conducted searches on October 11, 2017. The search terms were “viral oncogene mutation test” and “colorectal cancer.”

We included:

- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.

- **Guidelines based on systematic reviews.**

- **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

**Findings**

The American Society of Clinical Oncology (ASCO, 2009) recommended that patients with metastatic colorectal carcinoma who were candidates for anti-EGFR therapy have their tumors tested for KRAS mutations because tumors with these mutations will not respond to therapy. Limiting therapy to tumors without mutations will reserve treatment for those most likely to benefit while avoiding unnecessary costs and harms to those who would not.

In February 2016, the National Comprehensive Cancer Network (NCCN) updated their guidelines for colon cancer to recommend that KRAS and other sequence variant testing of suspected or proven sites of metastasis should be part of the pretreatment work-up for all patients diagnosed with metastatic synchronous adenocarcinoma. In addition, the NCCN Guidelines state that the EGFR inhibitors cetuximab and panitumumab are now recommended only for patients with tumors that do not have sequence variants in the KRAS gene.

Hayes (2015) found that the potential patient population for viral oncogene mutation testing is all patients under consideration for treatment with anti-EGFR monoclonal antibodies (cetuximab and panitumumab) for metastatic colorectal cancer. Clinical evidence suggests that the benefit from these drugs is limited to a subgroup of up to 60 percent of colorectal carcinoma patients. Hayes also noted that the cost of genetic testing for KRAS sequence variants is reported to be a one-time $500 to $1000 expenditure while the treatment-duration monthly costs of cetuximab and panitumumab are $10,000 and $8,000, respectively.

Westwood (2014) studied in a systematic review the various tests that are available to identify the KRAS mutations in the 17 percent of colorectal cancers that metastasize to the liver. Five studies were included in the review: two studies provided data on the accuracy of KRAS mutation testing for predicting response to treatment in patients treated with cetuximab plus standard chemotherapy, and others provided data on the clinical effectiveness of cetuximab plus standard chemotherapy compared
with that of standard chemotherapy in patients with KRAS wild-type tumors. There were no clear differences in the treatment effects reported by different studies, regardless of which KRAS mutation test was used to select patients. There was no strong evidence that any one KRAS mutation test was more effective or cost-effective than any other test.

Policy updates:

A systematic review (Tosi 2017) studied the predictive capability of mutations in patients with colorectal cancer liver metastases who undergo complete liver resection. Meta-analysis revealed that Kirsten rat sarcoma viral oncogene homolog mutation was negatively associated with overall survival. (hazard ratio [HR], 1.674; 95% confidence interval [CI], 1.341-2.089; P < .001) and relapse-free survival (HR, 1.529; 95% CI, 1.287-1.817; P < .001). Meta-analysis of overall survival in b-viral oncogene homolog B1 mutation also demonstrated a negative association with overall survival (HR, 3.055; 95% CI, 1.794-5.204; P < .001). The authors concluded that the data support integration of mutational status into a combined predictive score for prospective assessment of outcome after resection of colorectal cancer liver metastases in clinical studies.

Summary of clinical evidence:

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
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<tbody>
<tr>
<td>Tosi (2017)</td>
<td><strong>Key points:</strong></td>
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| Effect of KRAS and BRAF Mutations on Survival of Metastatic Colorectal Cancer After Liver Resection: A Systematic Review and Meta-Analysis. | - A systematic review studied the predictive capability of mutations in patients with colorectal cancer liver metastases who undergo complete liver resection.  
- Meta-analysis revealed that KRAS viral oncogene homolog mutation was negatively associated with overall survival. (hazard ratio [HR], 1.674; 95% confidence interval [CI], 1.341-2.089; P < .001) and relapse-free survival (HR, 1.529; 95% CI, 1.287-1.817; P < .001).  
- Meta-analysis of overall survival in b-viral oncogene homolog B1 mutation also demonstrated a negative association with overall survival (HR, 3.055; 95% CI, 1.794-5.204; P < .001).  
- The authors concluded that the data support integration of mutational status into a combined predictive score for prospective assessment of outcome after resection of colorectal cancer liver metastases in clinical studies. |
| NCCN (2016)                   | **Key points:**                                                                                  |
| Clinical practice guidelines in oncology: Colon Cancer | - NCCN updated their guidelines for both colon and rectal cancer.  
- Recommends KRAS sequence variant testing of either the primary colonic tumor or site of metastasis.  
- Added that the EGFR inhibitors cetuximab and panitumumab are appropriate only for patients with tumors that do not have sequence variants in the KRAS gene. |
<p>| Hayes (2015)                  | <strong>Key points:</strong>                                                                                  |
| KRAS Sequence Variant Analysis | - Found that the potential patient population for viral oncogene mutation testing is all |</p>
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| (Colorectal Cancer) | patients under consideration for treatment with anti-EGFR monoclonal antibodies.  
- Clinical evidence suggests that the benefit from these drugs is applicable to a subgroup of up to 60 percent of colorectal cancer patients.  
- Noted that the cost of genetic testing for KRAS sequence variants is far less than ongoing monthly costs of cetuximab and panitumumab (approximately $10,000 and $8,000, respectively). |
| Westwood (2014) | Key points:  
- Systematic review of various tests to identify KRAS mutation.  
- Five studies were included in the review:  
  - Two studies provided data on the accuracy of KRAS mutation testing for predicting response to treatment in patients treated with cetuximab plus standard chemotherapy  
  - Three studies provided data on the clinical effectiveness of cetuximab plus standard chemotherapy compared with that of standard chemotherapy in patients with KRAS wild-type tumors.  
- There were no clear differences in the treatment effects reported by different studies, regardless of which KRAS mutation test was used to select patients.  
- There was no strong evidence that any one KRAS mutation test was more effective or cost-effective than any other test. |
| Barni (2013) | Key points:  
- Evaluation of cetuximab/irinotecan-chemotherapy in KRAS wild-type pretreated metastatic colorectal cancer  
- Studies enrolled pre-treated patients for second-line intervention or beyond; 2007 – 12  
- Overall response was 31.1%; survival was 12.5 months, progression-free survival was six months.  
- Response rates and survival were similar in second-line intervention and beyond. |
| Chen (2013) | Key points:  
- Evaluation of cetuximab/irinotecan-chemotherapy in KRAS wild-type pretreated metastatic colorectal cancer  
- Relevant studies (no design restrictions), — July 2012.  
- Seven studies (2,802 patients).  
- Greater response in codon 13 mutation patients than other KRAS mutation. |
| Clancy (2013) | Key points:  
- Evaluation KRAS mutation does not predict neo-adjuvant chemo-radiotherapy in rectal cancer.  
- Relevant published studies, no design restrictions.  
- Eight case series (696 patients); KRAS mutations in mean 33.2±11.8%.  
- KRAS mutations associated with decreased pathological complete response, tumor down-staging, and with increased mortality. |
<p>| Hoyle (2013) | Key points: |</p>
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| Cetuximab, bevacizumab, and panitumumab for metastatic colorectal cancer | - Review of trials (2005-10) found identification of KRAS mutation does not predict neo-adjuvant chemo-radiotherapy response in rectal cancer  
- Interventions included cetuximab, bevacizumab, or panitumumab in patients with EGF-expressing KRAS wild-type metastatic colorectal cancer that progressed after first-line therapy.  
- Authors performed an economic model with sensitivity analyses for third- and further-line treatment.  
- Cetuximab and panitumumab are clinically beneficial vs. supportive care but poor value for money |
| Hoyle (2013a) | Key points:  
- Evaluation of KRAS testing cost-effectiveness with regard to cetuximab; cetuximab + irinotecan; and panitumumab for third and further lines of treatment for KRAS wild-type metastatic colorectal cancer:  
- Results over 10 years; cetuximab cost £28,860 and produced 0.6 QALYs; + irinotecan, 0.7 QALYs and £59,348; panitumamab, 0.52 and £35,213; supportive care, 0.36 QALYs, £6,256.  
- Monoclonal antibody-based treatments unlikely to be cost effective but contingent on thresholds. |
| Jiang (2013) | Key points:  
- Systematic review of 13 studies (1,669 patients) KRAS EGFR gene copy number as a prognostic marker in patients treated with cetuximab or panitumumab:  
- Increased copy number associated with increased survival, independent of KRAS status. |
| Lawrence (2013) | Key points:  
- Economic analysis of bevacizumab, cetuximab and panitumamab with fluoropyrimidine-based chemotherapy as first-line treatment of KRAS wild-type metastatic colorectal cancer (mCRC):  
- Probably most cost effective: bevacizumab + fluoropyrimidine-based chemotherapy |
| Mao (2013) | Key points:  
- Economic analysis KRASp.G13D and codon 12 mutations in predicting outcomes with cetuximab in metastatic colorectal cancer  
- Relevant studies without design restriction. — October 2011.  
- 10 studies (1,487 patients).  
- KRASp.GG13D mutation patients appear to benefit more with cetuximab than those with codon 12 mutations but methods limitations argue for cautious interpretation. |
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<tr>
<td><strong>Zhang (2013)</strong></td>
<td><strong>Key points:</strong></td>
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</table>
| Treatment related severe and fatal adverse events with cetuximab in colorectal cancer patients: a meta-analysis | • Severe and fatal adverse events with cetuximab:  
  • Trials, 2000 – 2012.  
  • Nine trials (8,520 patients with metastatic colorectal carcinoma: severe adverse event rate higher in cetuximab than controls but no evidence of higher fatality rate. |
| **Behl (2012)**     | **Key points:**                    |
| Cost-effectiveness analysis of screening for KRAS and BRAF mutations in metastatic colorectal cancer | • Cost effectiveness of screening for KRAS and BRAF mutations in metastatic colorectal cancer.  
  • Decision analysis: screening for KRAS and BRAF in context of cetuximab treatment.  
  • Cohort of 50,000 patients simulated 10,000 times using randomly assigned attributes from study distributions.  
  • Screening for both mutations compared to base strategy of no anti-EFG therapy: increased expected overall survival by 0.034 years at cost of $22,033.  
  • Incremental cost-effectiveness ratio = $635,000/ additional year of life.  
  • Vs. anti-EFG therapy without screening: adding KRAS test saved $7,500/patient; adding BRAF saved.  
  • $1,013; with little reduction in survival.  
  • Mutation screening improves cost effectiveness but incremental ratio still above generally acceptable level of $100,000/QALY. |
| **Vale (2012)**     | **Key points:**                    |
| Does anti-EGF therapy improve outcome in advanced colorectal cancer? A systematic review and meta-analysis | • Cost effectiveness of screening does anti-EGF therapy improve outcomes in advanced colorectal cancer?  
  • 10 trials (8,782 patients).  
  • Clear benefits for KRAS wild-type patients with advanced disease.  
  • No benefit for KRAS mutation patients. |
| **Chen (2013)**     | **Key points:**                    |
| Incidence and risk of hypomagnesemia in advanced cancer patients treated with cetuximab: a meta-analysis | • Systematic review of ten trials inclusive of 7,045 patients studied hypomagnesaemia with cetuximab:  
  • Cetuximabsignificantly increased risk of grade ¾ hypomagnesaemia RR, 8.60 (CI, 5.08 – 14.54). |
| **Zhou (2012)**     | **Key points:**                    |
| No survival benefit from adding cetuximab or panitumumab to oxaliplatin-based chemotherapy in the first-line treatment of metastatic colorectal cancer in KRAS wild type patients: a meta-analysis | • Four trials (1,270 patients) evaluated survival benefit from adding cetuximab or panitumumab to oxaliplatin-based chemotherapy in first-line treatment of KRAS wild-type metastatic colorectal cancer  
  • Addition of monoclonal antibodies did not improve survival or response rate. |
<p>| Petrelli (2012)      | <strong>Key points:</strong>                    |</p>
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| Risk of venous and arterial thromboembolic events associated with anti-EGFR agents: a meta-analysis of randomized clinical trials | • Phase II and III trials, no date restrictions.  
• Anti-EGFs associated with significant risk of vascular events. |
| NICE (2011) | Key points:  
• Diagnosis and management of colorectal cancer is not influenced by direct reference to mutation testing or genotyping |
| EGAPP (2009) | Key points:  
• Posed question “Can UGT1A1 genotyping reduce morbidity and mortality in patients with metastatic colorectal cancer treated with irinotecan?”  
• Found insufficient evidence to draw conclusion. |
| NICE (2009) | Key points:  
• Trial studied cetuximab as first-line treatment for KRAS wild-type metastatic colorectal cancer  
• Effectiveness of cetuximab + folinic acid (FOL) + fluorouracil (F) and irinotecan (IRI) was superior to FOLFIRI alone.  
• Recommendations:  
  - Cetuximab + FOLFOX (5-flurouricil, folinic acid and oxaliplatin) is recommended as first-line treatment for metastatic colorectal cancer only when:  
    • The primary colorectal tumor has been resected or is potentially operable.  
    • Metastases are confined to the liver and unresectable.  
    • Manufacturer rebates 16% of cetuximab cost per patient. |
| ASCO (2009) | Key points:  
• Recommended that patients with metastatic colorectal carcinoma who were candidates for anti-EGFR therapy have their tumors tested for KRAS mutations  
• Tumors with these mutations will not respond to therapy.  
• Limiting therapy to tumors without mutations will reserve treatment for those most likely to benefit while avoiding unnecessary costs and harms to those who would not. |

References

Professional society guidelines/other:


**Peer-reviewed references:**


**CMS National Coverage Determination (NCDs):**

No NCDs identified as of the writing of this policy.

**Local Coverage Determinations (LCDs):**

Commonly submitted codes

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
<th>Comment</th>
</tr>
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<tbody>
<tr>
<td>81235</td>
<td>EGRF (epidermal growth factor receptor) gene analysis, common variants</td>
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<tr>
<td>81275</td>
<td>KRAS gene analysis, variants in codons 12 and 13.</td>
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<thead>
<tr>
<th>ICD-10 Code</th>
<th>Description</th>
<th>Comment</th>
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<tbody>
<tr>
<td>C18.0</td>
<td>Malignant neoplasm of cecum</td>
<td></td>
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<tr>
<td>C18.2</td>
<td>Malignant neoplasm of ascending colon</td>
<td></td>
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<tr>
<td>C18.3</td>
<td>Malignant neoplasm of hepatic flexure</td>
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<tr>
<td>C18.4</td>
<td>Malignant neoplasm of transverse colon</td>
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<tr>
<td>C18.5</td>
<td>Malignant neoplasm of splenic flexure</td>
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<tr>
<td>C18.6</td>
<td>Malignant neoplasm of descending colon</td>
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<tr>
<td>C18.8</td>
<td>Malignant neoplasm of overlapping sites of colon</td>
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<tr>
<td>C18.9</td>
<td>Malignant neoplasm of colon, unspecified</td>
<td></td>
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<tr>
<td>C19</td>
<td>Malignant neoplasm of rectosigmoid junction</td>
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<thead>
<tr>
<th>HCPCS Level II Code</th>
<th>Description</th>
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