APPLICATION STATEMENT

The application of the Clinical Coverage Guideline is subject to the benefit determinations set forth by the Centers for Medicare and Medicaid Services (CMS) National and Local Coverage Determinations and state-specific Medicaid mandates, if any.

DISCLAIMER

The Clinical Coverage Guideline (CCG) is intended to supplement certain standard WellCare benefit plans and aid in administering benefits. Federal and state law, contract language, etc. take precedence over the CCG (e.g., Centers for Medicare and Medicaid Services [CMS] National Coverage Determinations [NCDs], Local Coverage Determinations [LCDs] or other published documents). The terms of a member’s particular Benefit Plan, Evidence of Coverage, Certificate of Coverage, etc., may differ significantly from this Coverage Position. For example, a member’s benefit plan may contain specific exclusions related to the topic addressed in this CCG. Additionally, CCGs relate exclusively to the administration of health benefit plans and are NOT recommendations for treatment, nor should they be used as treatment guidelines. Providers are responsible for the treatment and recommendations provided to the member. The application of the CCG is subject to the benefit determinations set forth by the Centers for Medicare and Medicaid Services (CMS) National and Local Coverage Determinations and state-specific Medicaid mandates, if any. All links are current at time of approval by the Medical Policy Committee (MPC) and are subject to change prior to the annual review date. Lines of business (LOB) are subject to change without notice; current LOBs can be found at www.wellcare.com. All guidelines can be found at this site as well but selecting the Provider tab, then “Tools” and “Clinical Guidelines”.

BACKGROUND

Genetic testing for KRAS (Kirsten Rat Sarcoma) sequence variants is generally performed using polymerase chain reaction (PCR) amplification followed by confirmation using sequencing of variants. Most assays detect the presence of sequence variants in codons 12 and 13 of the KRAS gene, where the majority of variants are found. The potential patient population is all patients under consideration for treatment with anti-EGFR monoclonal antibodies (cetuximab and panitumumab) for CRC.¹

KRAS Sequence Variant Analysis for Metastatic Colorectal Cancer

Policy Number: HS-137

Original Effective Date: 10/15/2009

 Colon and rectal cancer are collectively known as colorectal cancer (CRC). It is the third most common cancer in the United States. The morbidity and mortality associated with CRC are significant, with an estimated 49,960 deaths caused by CRC in 2008. The 5-year survival rate for those diagnosed with CRC is 64% over all stages; however, this drops to 11% in those with metastatic disease. Treatment of CRC through surgery is the usual approach for cancers that have not metastasized, and is often curative. Before or following surgery, chemotherapy, sometimes with radiotherapy, is given to patients with stage III or IV cancer.\(^3,^4\)

Cetuximab (Erbitux\(^\text{®}\); Imclone Systems/Bristol-Myers Squibb) and panitumumab (Vectibix\(^\text{®}\); Amgen Inc.) are anti–epidermal growth factor receptor (EGFR) monoclonal antibodies that are generally used for second- or third-line treatment in patients with metastatic disease following failure of first-line chemotherapy. Clinical evidence suggests that the benefit from these drugs is limited to a subgroup of up to 60% of CRC patients (Van Custem, Kohne, Lang, Folprecht, Nowacki, Cascinu, & et al., 2011). Accordingly, biomarkers are needed to help select those patients who will benefit from treatment with EGFR inhibitors. One of the biomarkers that have been investigated as a predictive indicator is the presence of sequence variants in the KRAS viral oncogene homolog gene. KRAS sequence variants are found in 27% to 42% of patients with CRC and are generally absent in normal controls.\(^1,^2\)

In April 2012, the NCCN updated their guidelines for both colon and rectal cancer to recommend that KRAS sequence variant testing of either the primary tumor or a site of metastasis should be part of the pretreatment work-up for all patients diagnosed with metastatic CRC. 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.\(^3,^4\)

The cost of genetic testing for KRAS sequence variants is reported to be $500 to $1000. In contrast the monthly costs of cetuximab and panitumumab are $10,000 and $8,000, respectively.\(^1\)

### Position Statement

**Applicable To:**
- Medicaid – Hawaii
- Medicare – Easy Choice Health Plan, Hawaii

**Note:** For all other lines of business, please refer to the current contracted vendor for Lab Management requests.

### Exclusions

KRAS sequence variant analysis is considered experimental and investigational for all other indications other than metastatic colorectal cancer.

### Coverage

KRAS sequence variant analysis is considered medically necessary if ALL of the following criteria are met:

- Member has a diagnosis of metastatic colorectal cancer.
- The KRAS test is used to predict response to treatment with anti-EGFR monoclonal antibodies (cetuximab and panitumumab monotherapy, and for combination therapy of cetuximab with irinotecan or oxaliplatin).

### Coding

**CPT\(^\text{®}\) Codes**

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<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>81275</td>
<td>KRAS (v-Ki-ras2 Kirsten rat sarcoma viral oncogene) (eg, carcinoma) gene analysis, variants in codons 12 and 13</td>
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<tr>
<td>81276</td>
<td>KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; additional variant(s) (eg., codon 61, codon 146)</td>
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<td>81405</td>
<td>Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons) KRAS (v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog)(eg, Noonan syndrome), full gene sequence</td>
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<td>88363</td>
<td>Examination and selection of retrieved archival (ie, previously diagnosed) tissue(s) for molecular analysis</td>
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Strength: Strongly supported.

*Note:* Onset of benefit and duration of benefit from cetuximab and panitumumab are not known.

**Original Effective Date:** 10/15/2009
KRAS SEQUENCE VARIANT ANALYSIS FOR METASTATIC COLORECTAL CANCER
HS-137

(e.g., KRAS mutational analysis)

HCPCS Level II © Codes – No applicable codes.

ICD-10-PCS – No applicable codes.

Covered ICD-10-CM Diagnosis Codes – These codes may not be all inclusive

The following primary cancer codes are covered when the above criteria has been met:

C18.0 Malignant neoplasm of cecum
C18.1 Malignant neoplasm of appendix
C18.2 Malignant neoplasm of ascending colon
C18.3 Malignant neoplasm of hepatic flexure
C18.4 Malignant neoplasm of transverse colon
C18.5 Malignant neoplasm of splenic flexure
C18.6 Malignant neoplasm of descending colon
C18.7 Malignant neoplasm of sigmoid colon
C18.8 Malignant neoplasm of overlapping sites of colon
C18.9 Malignant neoplasm of colon, unspecified
C19 Malignant neoplasm of rectosigmoid junction
C20 Malignant neoplasm of rectum
C21.2 Malignant neoplasm of cloacogenic zone
C21.8 Malignant neoplasm of overlapping sites of rectum, anus and anal canal

The following Metastatic Sites Secondary to Colorectal Cancer must be documented and billed:

C77.2 Secondary and unspecified malignant neoplasm of intra-abdominal lymph nodes
C77.5 Secondary and unspecified malignant neoplasm of intrapelvic lymph nodes
C78.00 Secondary malignant neoplasm of lung, unspecified side
C78.6 Secondary malignant neoplasm of retroperitoneum and peritoneum
C78.7 Secondary malignant neoplasm of liver and intrahepatic bile duct
C79.31 Secondary malignant neoplasm of brain
C79.51 Secondary malignant neoplasm of bone
C79.60 Secondary malignant neoplasm of ovary


REFERENCES


MEDICAL POLICY COMMITTEE HISTORY AND REVISIONS

<table>
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<td>7/6/2017</td>
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<td>7/7/2016</td>
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<td>10/3/2013</td>
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<tr>
<td>10/4/2012</td>
<td>Approved by MPC. Updated efficacy (p.2) from 10-30% to “up to 60%” due to new reference from 2011. No other changes.</td>
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<td>12/1/2011</td>
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