Medical Policy

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

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- Coding Information
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Policy Number: 104
BCBSA Reference Number: 2.04.53
NCD/LCD:
- Local Coverage Determination (LCD): K-ras Testing Required before Epidermal Growth Factor Receptor Antibody Use in Colorectal Cancer (L33434)
- Local Coverage Determination (LCD): MolDX: NRAS Genetic Testing (L35073)

Related Policies
None

Policy
Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity

KRAS variant 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 variant 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.

BRAF variant analysis is considered MEDICALLY NECESSARY for patients with metastatic colorectal cancer who are found to be wild-type on KRAS and NRAS variant analysis to guide management decisions.

Medicare HMO BlueSM and Medicare PPO BlueSM Members

Medical necessity criteria and coding guidance for Medicare Advantage members living in Massachusetts can be found through the links below.

Local Coverage Determination (LCD): K-ras Testing Required before Epidermal Growth Factor Receptor Antibody Use in Colorectal Cancer (L33434)
Local Coverage Determination (LCD): MolDX: NRAS Genetic Testing (L35073)

For medical necessity criteria and coding guidance for Medicare Advantage members living outside of Massachusetts, please see the Centers for Medicare and Medicaid Services website for information regarding your specific jurisdiction at https://www.cms.gov.

Prior Authorization Information

Inpatient
- For services described in this policy, precertification/preauthorization IS REQUIRED for all products if the procedure is performed inpatient.

Outpatient
- For services described in this policy, see below for products where prior authorization might be required if the procedure is performed outpatient.

<table>
<thead>
<tr>
<th>Product Type</th>
<th>Prior Authorization Required</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commercial Managed Care (HMO and POS)</td>
<td>Not required.</td>
</tr>
<tr>
<td>Commercial PPO and Indemnity</td>
<td>Not required.</td>
</tr>
<tr>
<td>Medicare HMO BlueSM</td>
<td>Not required.</td>
</tr>
<tr>
<td>Medicare PPO BlueSM</td>
<td>Not required.</td>
</tr>
</tbody>
</table>

CPT Codes / HCPCS Codes / ICD Codes

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The above medical necessity criteria MUST be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

CPT Codes

<table>
<thead>
<tr>
<th>CPT codes</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>81275</td>
<td>KRAS Kirsten rat sarcoma viral oncogene homolog (eg. carcinoma) gene analysis; variants in exon 2 (eg. codons 12 and 13)</td>
</tr>
<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>
</tr>
<tr>
<td>81311</td>
<td>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)</td>
</tr>
<tr>
<td>88363</td>
<td>Examination and selection of retrieved archival (i.e., previously diagnosed) tissue(s) for molecular analysis (e.g., KRAS mutational analysis)</td>
</tr>
</tbody>
</table>

The following ICD Diagnosis Codes are considered medically necessary when submitted with the CPT codes above if medical necessity criteria are met:
ICD-10 Diagnosis Codes

<table>
<thead>
<tr>
<th>ICD-10-CM diagnosis codes:</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>C18.0</td>
<td>Malignant neoplasm of cecum</td>
</tr>
<tr>
<td>C18.1</td>
<td>Malignant neoplasm of appendix</td>
</tr>
<tr>
<td>C18.2</td>
<td>Malignant neoplasm of ascending colon</td>
</tr>
<tr>
<td>C18.3</td>
<td>Malignant neoplasm of hepatic flexure</td>
</tr>
<tr>
<td>C18.4</td>
<td>Malignant neoplasm of transverse colon</td>
</tr>
<tr>
<td>C18.5</td>
<td>Malignant neoplasm of splenic flexure</td>
</tr>
<tr>
<td>C18.6</td>
<td>Malignant neoplasm of descending colon</td>
</tr>
<tr>
<td>C18.7</td>
<td>Malignant neoplasm of sigmoid colon</td>
</tr>
<tr>
<td>C18.8</td>
<td>Malignant neoplasm of overlapping sites of colon</td>
</tr>
<tr>
<td>C18.9</td>
<td>Malignant neoplasm of colon, unspecified</td>
</tr>
<tr>
<td>C19</td>
<td>Malignant neoplasm of rectosigmoid junction</td>
</tr>
<tr>
<td>C20</td>
<td>Malignant neoplasm of rectum</td>
</tr>
<tr>
<td>C21.2</td>
<td>Malignant neoplasm of cloacogenic zone</td>
</tr>
<tr>
<td>C21.8</td>
<td>Malignant neoplasm of overlapping sites of rectum, anus and anal canal</td>
</tr>
<tr>
<td>C78.5</td>
<td>Secondary malignant neoplasm of large intestine and rectum</td>
</tr>
</tbody>
</table>

The above medical necessity criteria MUST be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

CPT Codes

<table>
<thead>
<tr>
<th>CPT codes:</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>81210</td>
<td>BRAF (Raf proto-oncogene serine/threonine kinase) (eg, colon cancer, melanoma), gene analysis, V600E variant(s)</td>
</tr>
</tbody>
</table>

**Description**

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. 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.¹

**Summary**

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 overall survival, 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 randomized controlled trials (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 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 overall survival, 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 overall survival, disease-specific survival, change in disease status, medication use, resource utilization, and treatment-related morbidity. The meta-analyses have shown 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 been inconsistent. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Policy History**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>10/2016</td>
<td>BCBSA National medical policy review. 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. Effective 10/1/2016.</td>
</tr>
<tr>
<td>1/2016</td>
<td>Clarified coding information.</td>
</tr>
<tr>
<td>5/2014</td>
<td>Updated Coding section with ICD10 procedure and diagnosis codes, effective 10/2015.</td>
</tr>
<tr>
<td>1/2014</td>
<td>BCBSA National medical policy review.</td>
</tr>
</tbody>
</table>
Language on KRAS testing clarified.


2/2011 Updated policy statement to clarify ongoing non-coverage of BRAF mutation analysis.


10/2009 Updated HCPCS Level II.


Information Pertaining to All Blue Cross Blue Shield Medical Policies
Click on any of the following terms to access the relevant information:
- Medical Policy Terms of Use
- Managed Care Guidelines
- Indemnity/PPO Guidelines
- Clinical Exception Process
- Medical Technology Assessment Guidelines

References
12. Peeters M, Price TJ, Cervantes A, et al. Randomized phase III study of panitumumab with fluorouracil, leucovorin, and irinotecan (FOLFIRI) compared with FOLFIRI alone as second-line


