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

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- Policy: Commercial
- Policy: Medicare
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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 mutation analysis may be considered MEDICALLY NECESSARY for patients with metastatic colorectal cancer to predict nonresponse prior to planned therapy with anti-epidermal growth factor receptor (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.

BRAF mutation analysis is INVESTIGATIONAL to predict non-response to anti-EGFR monoclonal antibiotics cetuximab and panitumumab in the treatment of metastatic colorectal cancer.

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 link 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
Pre-service approval is required for all inpatient services for all products.
See below for situations where prior authorization may be required or may not be required.
Yes indicates that prior authorization is required.
No indicates that prior authorization is not required.
N/A indicates that this service is primarily performed in an inpatient setting.

<table>
<thead>
<tr>
<th>Outpatient</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Commercial Managed Care (HMO and POS)</td>
<td>No</td>
</tr>
<tr>
<td>Commercial PPO and Indemnity</td>
<td>No</td>
</tr>
<tr>
<td>Medicare HMO BlueSM</td>
<td>No</td>
</tr>
<tr>
<td>Medicare PPO BlueSM</td>
<td>No</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-9 Diagnosis coding

<table>
<thead>
<tr>
<th>ICD-9-CM diagnosis codes:</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>153.0</td>
<td>Malignant neoplasm of hepatic flexure</td>
</tr>
<tr>
<td>153.1</td>
<td>Malignant neoplasm of transverse colon</td>
</tr>
</tbody>
</table>
Malignant neoplasm of descending colon
Malignant neoplasm of sigmoid colon
Malignant neoplasm of cecum
Malignant neoplasm of appendix vermiformis
Malignant neoplasm of ascending colon
Malignant neoplasm of splenic flexure
Malignant neoplasm of other specified sites of large intestine
Malignant neoplasm of colon, unspecified site
Malignant neoplasm of rectosigmoid junction
Malignant neoplasm of rectum
Malignant neoplasm of other sites of rectum, rectosigmoid junction, and anus
Secondary malignant neoplasm of large intestine and rectum

ICD-10 Procedure Codes

<table>
<thead>
<tr>
<th>ICD-10-PCS procedure 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>

According to the policy statement above, the following CPT code is considered investigational for the conditions listed 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>
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<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-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. Approximately 40% of CRC have *KRAS* mutations in codons 12 and 13 in exon 2. 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 less common compared with *KRAS*, detected in 2% to 7% of colorectal cancer (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 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* mutation-positive disease in combination with oxaliplatin-based chemotherapy.1

**Summary**

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 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-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.
Policy History

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
</tr>
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<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. Language on KRAS testing clarified.</td>
</tr>
<tr>
<td>2/2011</td>
<td>Updated policy statement to clarify ongoing non-coverage of BRAF mutation analysis.</td>
</tr>
<tr>
<td>10/2009</td>
<td>Updated HCPCS Level II.</td>
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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


43. Evaluation of Genomic Applications in P, Prevention Working G. Recommendations from the EGAPP Working Group: can testing of tumor tissue for mutations in EGFR pathway downstream effector