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

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. The 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.

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy

BCBSNC will provide coverage for KRAS, NRAS, and BRAF mutation analysis and related treatment in metastatic colorectal cancer when it is determined to be medically necessary because the medical criteria and guidelines noted below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit
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design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When KRAS, NRAS, BRAF Mutation Analysis and Related Treatment in Metastatic Colorectal Cancer 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.

Cetuximab (Erbitux®) is considered medically necessary for the treatment of patients with:

Colorectal Cancer
  - K-Ras wild-type, EGFR-expressing, metastatic colorectal cancer, anal adenocarcinoma and small bowel adenocarcinoma as determined by FDA-approved tests:
    a. In combination with FOLFIRI for first line treatment;
    b. In combination with irinotecan in patients who are refractory to irinotecan-based chemotherapy;
    c. As a single agent in patients who have failed oxaliplatin-and irinotecan-based chemotherapy or who are intolerant to irinotecan and cannot tolerate intensive therapy.

Head and Neck Cancer
  - Locally or regionally advanced squamous cell carcinoma of the head and neck in combination with radiation therapy, OR
  - Recurrent locoregional disease or metastatic squamous cell carcinoma of the head and neck in combination with platinum-based therapy, OR
  - Recurrent or metastatic squamous cell carcinoma of the head and neck progressing after platinum-based therapy.

Panitumumab (Vectibix®) is considered medically necessary for the treatment of patients as a single agent for the treatment of metastatic colorectal carcinoma (mCRC) with disease progression on or following fluoropyrimidine, oxaliplatin, and irinotecan chemotherapy regimens.

When KRAS, NRAS, BRAF Mutation Analysis and Related Treatment in Metastatic Colorectal Cancer is not covered

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

Policy Guidelines

EGFR (epidermal growth factor receptor) is overexpressed in colorectal cancer. EGFR–targeted therapy with monoclonal antibodies cetuximab and panitumumab has shown clear survival benefit in patients with metastatic colorectal cancer, however, this benefit is dependent upon 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 non-response to anti-EGFR monoclonal antibody therapy.
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For individuals who have metastatic colorectal cancer who receive KRAS mutation testing to guide treatment, the evidence consists of 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-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 colorectal cancer who receive NRAS mutation testing to guide treatment, the evidence consists of prospective-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 has been strong support from NCCN and ASCO recommending 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 colorectal cancer who receive BRAF mutation testing to guide treatment, the evidence consists of 2 meta-analyses of prospective-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/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.

Use of Cetuximab (Erbitux) is not recommended for the treatment of colorectal cancer with KRAS mutations in codon 12 or 13.

Panitumumab (Vectibix) is not indicated for the treatment of patients with KRAS mutation-positive mCRC or for whom KRAS mCRC status is unknown.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

*Applicable service codes: 81210, 81275, 81276, 81311, 81403, 81404, 88363, J9055, J9303, S0353, S0354

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

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


Sr. Medical Director review 5/2016


U.S. Food and Drug Administration (FDA). Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/125147s200lbl.pdf

U.S. Food and Drug Administration (FDA). Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/125147s169lbl.pdf


Medical Director review 8/2016


Specialty Matched Consultant Advisory Panel 8/2017

Policy Implementation/Update Information

For Policy Titled “KRAS, NRAS, and BRAF Mutation Analysis in Metastatic Colorectal Cancer

12/30/15 New policy issued. 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 is considered investigational to predict nonresponse to anti-EGFR monoclonal antibodies cetuximab and panitumumab in the treatment of metastatic colorectal cancer. BRAF mutation analysis is considered investigational to predict nonresponse to anti-EGFR monoclonal antibodies cetuximab and panitumumab in the treatment of metastatic colorectal cancer. Information on KRAS previously included in Corporate Medical Policy “Molecular Analysis for Targeted Therapy of Non-Small-Cell Lung Cancer.” Added CPT codes 81276 and 81311 to Billing/Coding section effective 1/1/2016. Reference added. (lpr)

7/1/16 Added covered indication for NRAS under “When Covered” section: “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.” Revised Policy Guidelines section. Deleted HCPCS code S3713 from Billing/Coding section. Reference added. Sr. Medical Director review 5/2016. (lpr)

9/30/16 Specialty Matched Consultant Advisory Panel review 8/31/2016. No change to policy statement. Added Panitumumab and Cetuximab indications to “When Covered” section. Medical Director review 8/2016. (lpr)
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For Policy Re-Titled “KRAS, NRAS, BRAF Mutation Analysis and Related Treatment in Metastatic Colorectal Cancer”

12/30/16 Notification given 12/30/16 for effective date 4/1/17. (lpr)

9/29/17 Specialty Matched Consultant Advisory Panel review 8/30/2017. No change to policy statement. Reference added. (lpr)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.