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Medical Policy Manual

Topic: KRAS and BRAF Mutation Analysis in Colorectal Cancer

Date of Origin: January 27, 2011

Section: Genetic Testing

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IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Cetuximab (Erbitux®) and panitumumab (Vectibix®) are monoclonal antibodies that bind to the epidermal growth factor receptor (EGFR), preventing binding and activation of downstream signaling pathways vital for cancer cell proliferation, invasion, metastasis, and stimulation of neovascularization.

The KRAS gene can harbor oncogenic mutations that may result in tumor resistance to therapies that target the epidermal growth factor receptor (EGFR). KRAS mutations are found in approximately 30–50% of colorectal cancer tumors and are common in other tumor types.

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 10–15% of colorectal cancers.

It has been shown that patients with a KRAS mutant tumor do not respond to cetuximab or panitumumab. However, there are still patients with KRAS wild-type tumors that do not respond to these agents, suggesting that other factors, such as alterations in other EGFR effectors could drive resistance to anti-EGFR therapy, and therefore, BRAF mutations are now increasingly being

investigated in metastatic colorectal cancer. KRAS and BRAF mutations are considered to be mutually exclusive.

KRAS and BRAF mutation analyses using PCR methodology are commercially available as laboratory-developed tests. Such tests are regulated under the Clinical Laboratory Improvement Amendments (CLIA). Premarket approval from the U.S. Food and Drug Administration (FDA) is not required when the assay is performed in a laboratory that is licensed by CLIA for high-complexity testing.

MEDICAL POLICY CRITERIA

I. KRAS mutation analysis may be considered **medically necessary** to predict nonresponse to anti-EGFR monoclonal antibodies cetuximab (Erbitux®) and panitumumab (Vectibix®) in the treatment of metastatic, unresectable, or advanced colorectal cancer.

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

SCIENTIFIC EVIDENCE

The focus of the scientific evidence is on evidence related to the ability of test results to:

- Guide decisions in the clinical setting related to either treatment, management, or prevention, and
- Improve health outcomes as a result of those decisions.

KRAS

Technology Assessments

BlueCross BlueShield Association Technology Evaluation Center (TEC) Assessment

The 2008 BlueCross BlueShield Association TEC Assessment concluded the following:[1]

- The data are sufficient to demonstrate both the analytical and clinical validity of KRAS mutation testing.
- The evidence from five randomized trials and five single-arm studies is sufficient to conclude that metastatic colorectal cancer patients with mutated KRAS tumors do not respond to anti-EGFR monoclonal antibody therapy (either as monotherapy or in combination with other treatment regimens), do not derive survival benefit, and may experience decreased progression-free survival.
- Identifying patients whose tumors express mutated KRAS avoids exposing them to ineffective drugs, avoids exposure to unnecessary drug toxicities, and expedites the use of the best available alternative therapy.

Agency for Healthcare Research and Quality (AHRQ) Technology Assessment[2]

In 2010, AHRQ carried out a systematic review of the published evidence on KRAS mutation testing and its ability to predict patient response to treatment with the anti-EGFR antibodies cetuximab and panitumumab. 47 publications of KRAS mutation testing met the eligibility criteria and were included in the review (45 in metastatic setting and 2 in neo-adjuvant setting). The review of evidence identified both small, retrospective studies and randomized controlled trials (RCT). The assessment concluded the following:

- There is substantial and consistent evidence that KRAS testing can predict response to anti-EGFR therapy in colorectal cancer patients.
- "For all outcomes assessed, patients with KRAS mutations were less likely to experience benefit with anti-EGFR antibody treatment, compared to patients whose tumors were wild-type for KRAS mutations. The direction of the association is consistent for overall mortality, disease progression and treatment failure by radiologic imaging."

Other Studies

Studies published after the TEC and AHRQ assessments, including a meta-analysis and systematic review, continue to support the above findings.[3-9]

BRAF

The data for patients with metastatic colorectal cancer and a BRAF mutation have shown consistently that a BRAF mutation is a poor prognostic marker, as it is associated with shorter progression-free survival and overall survival regardless of treatment. The data for a BRAF mutation predicting response to anti-EGFR therapy are limited by small numbers of patients and conflicting results among studies.[6,10-17]

An updated analysis of the CRYSTAL trial reported increased follow-up time and an increased number of patients evaluable for tumor KRAS status and considered the clinical significance of the tumor mutation status of BRAF in the expanded population of patients with KRAS wild-type tumors.[6] The impact of BRAF tumor mutation status in relation to the efficacy of cetuximab plus folinic acid [leucovorin], 5-FU, and irinotecan (FOLFIRI) was examined in the population of patients with KRAS wild-type disease (n=625). There was no evidence of an independent treatment interaction by tumor BRAF mutation status. The authors concluded that BRAF mutation status was not predictive of treatment effects of cetuximab plus FOLFIRI but that BRAF tumor mutation was a strong indicator of poor prognosis for all efficacy end points compared with those whose tumors were wild-type.

Clinical Practice Guidelines

The 2014 National Comprehensive Cancer Network (NCCN) guidelines on the treatment of colon cancer[18]recommend that tumor KRAS gene status testing be performed for all patients with metastatic colon cancer, on archived specimens of primary tumor or a metastasis, at the time of diagnosis of metastatic disease. The guidelines indicate that cetuximab and panitumumab are only indicated for patients with tumors that express the WT KRAS gene.

The guidelines state that patients with a BRAF V600E mutation appear to have a poorer prognosis. Data are insufficient to guide the use of anti-EGFR therapy in the first-line setting with active chemotherapy based on BRAF V600E mutation status. Limited data suggest lack of antitumor activity from anti-EGFR

monoclonal antibodies in the presence of a BRAF V600E mutation when used after a patient has progressed on first-line therapy.

Summary

Clinical trial data show that patients with KRAS-mutated metastatic colorectal cancer do not benefit from cetuximab or panitumumab, either as monotherapy or in combination with other treatment regimens. These data support the use of KRAS mutation analysis of tumor DNA before considering use of cetuximab or panitumumab in a treatment regimen. Identifying patients whose tumors express mutated KRAS will avoid exposing patients to ineffective drugs and unnecessary drug toxicities, and expedite the use of alternative therapies. Thus, KRAS mutation analysis may be considered medically necessary to predict nonresponse to anti-EGFR monoclonal antibodies in the treatment of metastatic colorectal cancer.

The data for patients with metastatic colorectal cancer and a BRAF mutation have shown consistently that a BRAF mutation is a poor prognostic marker, as it is associated with shorter progression-free survival and overall survival regardless of treatment. However, the data for a BRAF mutation predicting response to anti-EGFR therapy are limited by small numbers of patients and conflicting results among studies. Thus, BRAF mutation analysis is considered investigational to predict nonresponse to anti-EGFR monoclonal antibodies in the treatment of metastatic colorectal cancer.

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CROSS REFERENCES

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Analysis of Human DNA in Stool Samples as a Technique for Colorectal Cancer Screening, Genetic Testing, Policy No. 12

Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20

BRAF Gene Mutation Testing To Select Melanoma Patients for BRAF Inhibitor Targeted Therapy, Genetic Testing, Policy No. 41

CODES	NUMBER	DESCRIPTION
CPT	81210	BRAF (v-raf murine sarcoma viral oncogene homolog B1) (eg, colon cancer), gene analysis, V600E variant
	81275	KRAS (v-Ki-ras2 Kirsten rat sarcoma viral oncogene) (eg, carcinoma) gene analysis, variants in codons 12 and 13
	81403	Molecular pathology procedure, Tier 2 Level 4
	88363	Examination and selection of retrieved archival (ie, previously diagnosed) tissue(s) for molecular analysis (eg, KRAS mutational analysis)
HCPCS	None	