FEP 2.04.53 *KRAS*, *NRAS*, and *BRAF* Variant Analysis in Metastatic Colorectal Cancer

Effective Date: April 15, 2018

Related Policies: 5.21.84 Erbitux (cetuximab)
5.21.85 Vectibix (panitumamab)

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

Description

The epidermal growth factor receptor (EGFR) is overexpressed in colorectal cancer (CRC). EGFR-targeted therapy, with monoclonal antibodies cetuximab and panitumumab, has shown a clear survival benefit in patients with metastatic CRC. However, this benefit depends on a lack of variants in certain genes in the signaling pathway downstream from the EGFR. It has been hypothesized that knowledge of tumor cell *KRAS, NRAS*, and *BRAF* variant status might be used as a predictor of nonresponse to anti-EGFR monoclonal antibody therapy.

FDA REGULATORY STATUS

Approved Companion Diagnostic Tests *for KRAS* Variant Analysis

Companion diagnostic tests for the selection of cetuximab and panitumumab have been approved by FDA through the premarket approval process, specifically:

> "The cobas® KRAS Mutation Test, for use with the cobas® 4800 System, [which] is a real-time PCR [polymerase chain reaction] test for the detection of seven somatic mutations in codons 12 and 13 of the KRAS gene in DNA derived from formalin-fixed paraffin-embedded human colorectal cancer (CRC) tumor tissue. The test is intended to be used as an aid in the identification of CRC patients for whom treatment with Erbitux® (cetuximab) or with Vectibix® (panitumumab) may be indicated based on a no mutation detected result."[2]

> "The therascreen® KRAS RGQ PCR Kit is a real-time qualitative PCR assay used on the Rotor-Gene Q MDx instrument for the detection of seven somatic mutations in the human KRAS oncogene, using DNA extracted from formalin-fixed paraffin-embedded (FFPE), colorectal cancer (CRC) tissue. The therascreen KRAS RGQ PCR Kit is intended to aid in the identification of CRC patients for treatment with Erbitux (cetuximab) and Vectibix (panitumumab) based on a KRAS no mutation detected test result."[2]

Laboratory-Developed Tests for *KRAS, NRAS*, and *BRAF* Variant Analysis

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. *KRAS*, *NRAS*, and *BRAF* variant analyses using polymerase chain reaction methodology are available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed under the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, FDA has chosen not to require any regulatory review of this test.

POLICY STATEMENT

KRAS variant 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 variant 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.

POLICY GUIDELINES

There is support from the evidence and clinical input to use *BRAF* V600 variant testing for prognostic stratification. Clinical input suggests that patients who are positive for this variant may be considered for clinical trials.

It is uncertain whether the presence of a *BRAF* V600 variant in patients with metastatic colorectal cancer who are wild-type on *KRAS* and *NRAS* variant analysis is predictive of response to anti-epidermal growth factor receptor therapy. Furthermore, there is mixed opinion in clinical guidelines and clinical input on the use of *BRAF* variant analysis to predict response to treatment.

Genetics Nomenclature Update

Human Genome Variation Society (HGVS) nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). HGVS nomenclature is recommended by HGVS, the Human Variome Project, and the HUman Genome Organization (HUGO).

The American College of Medical Genetics and Genomics (ACMG) and Association for Molecular Pathology (AMP) standards and guidelines for interpretation of sequence variants represent expert opinion from ACMG, AMP, and the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology—“pathogenic,” “likely pathogenic,” “uncertain significance,” “likely benign,” and “benign”—to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

GENETIC COUNSELING

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

BENEFIT APPLICATION

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient's existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

RATIONALE

Summary of Evidence

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 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.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

National Comprehensive Cancer Network

National Comprehensive Cancer Network guidelines on the treatment of colon cancer recommend that tumor tissue should be genotyped for *RAS* (*KRAS* and *NRAS*) and *BRAF* variants for all patients with metastatic colon cancer (v.2.2017).[45] Testing should be performed 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 appropriate only for patients with a tumor that expresses wild-type *KRAS* and *NRAS* genes. The guidelines also state that the presence of the *BRAF* V600E variant makes response to panitumumab and cetuximab highly unlikely.

American College of Medical Genetics and Genomics

An evidence review published in 2013 by the American College of Medical Genetics and Genomics, *Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group*, has stated that evidence is insufficient to support the clinical validity or utility of testing colorectal cancer specimens for *NRAS* variants to guide patient management.[46] That same review further found no guidelines on *NRAS* testing from any other U.S. group.

American Society of Clinical Oncology

In 2017, American Society of Clinical Oncology along with American Society for Clinical Pathology, College of American Pathologists, and the Association for Molecular Pathology published guidelines on Molecular Biomarkers for the Evaluation of Colorectal Cancer.[47]

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Table 1. Summary of Recommendations

Guideline Statements	Type	SOE	QOE
Colorectal carcinoma patients being considered for anti-EGFR therapy must receive RAS mutational testing. Mutational analysis should include KRAS and NRAS codons 12, 13 of exon 2; 59, 61 of exon 3; and 117 and 146 of exon 4 ("expanded" or "extended" RAS)	Recommendation	Convincing/ adequate, benefits outweigh harms	High/intermediate
BRAF p.V600 (BRAF c. 1799 (p.V600) mutational analysis should be performed in colorectal cancer tissue in patients with colorectal carcinoma for prognostic stratification	Recommendation	Adequate/inadequate, balance of benefits and harms	Intermediate/low
BRAF p.V600 mutational analysis should be performed in deficient MMR tumors with loss of MLH1 to evaluate for Lynch Syndrome risk. Presence of a BRAF mutation strongly favors a sporadic pathogenesis. The absence of BRAF mutation does not exclude risk of Lynch syndrome	Recommendation	Adequate/inadequate, balance of benefits and harms	Intermediate/low
Clinicians should order mismatch repair status testing in patients with colorectal cancers for the identification of patients at high risk for Lynch syndrome and/or prognostic stratification	Recommendation	Adequate/inadequate, balance of benefits and harms	Intermediate/low
There is insufficient evidence to recommend BRAF c.1799 p.V600 mutational status as a predictive molecular biomarker for response to anti-EGFR inhibitors	No recommendation	Insufficient, benefits/harms balance unknown	Insufficient

EGFR: epidermal growth factor receptor; QOE: quality of evidence; SOE: strength of evidence.

The American Society of Clinical Oncology published a provisional clinical opinion update in 2016 on extended *RAS* variant testing in metastatic colorectal cancer to predict response to anti-EGFR monoclonal antibody therapy.[48] The opinion was based on evidence from 13 articles on *KRAS* variants (11 systematic reviews, 2 health technology assessments) and 2 articles on *NRAS* testing. The opinion stated that subgroup analyses of patients with any of the less common *RAS* variants are small, and there is inadequate evidence to provide a definitive opinion on the lack of benefit for the use of anti-EGFR antibodies for patients whose cancer harbors any specific *RAS* variant other than the exon 2 *KRAS* variant. The Society considered the less common *RAS* variants as a group, and a pooled analysis seemed to confer the same lack of benefit with anti-EGFR therapy as seen with the more common variants in exon 2 of *KRAS*.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

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POLICY HISTORY

Date	Action	Description
March 2012	New Policy	
March 2013		Policy updated with literature review, Reference 14 added, policy statements unchanged.
March 2014		Policy updated with literature review. No references added. Policy statements unchanged except for minor wording change in statement on KRAS testing.
March 2015		Policy updated with literature review. References 20-24, 38 added. Title change indicate inclusion of NRAS testing to the policy; NRAS testing policy statement added as investigational to predict nonresponse to anti-EGFR monoclonal antibodies cetuximab panitumumab in the treatment of metastatic colorectal cancer.
March 2018		Policy updated with literature review through June 2, 2017; reference 1, 2-4, 21-22, 28, and 42-43 and 46 added. Policy revised with updated genetics nomenclature. 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. Policy statement revised to indicate that *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. KRAS policy statement unchanged. Title changed to "*KRAS*, *NRAS*, and *BRAF* Variant Analysis in Metastatic Colorectal Cancer".