

Protocol

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

(20453)

(Formerly KRAS, NRAS, and BRAF Mutation Analysis in Metastatic Colorectal Cancer)

Medical Benefit		Effective Date: 07/01/18	Next Review Date: 05/19
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Preauthorization is required.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

Populations	Interventions	Comparators	Outcomes
Individuals: • With metastatic colorectal cancer	Interventions of interest are: • KRAS variant testing to guide treatment	Comparators of interest are: • No KRAS variant testing to guide treatment	Relevant outcomes include: • Overall survival • Disease-specific survival • Change in disease status • Medication use • Resource utilization • Treatment-related morbidity
Individuals: • With metastatic colorectal cancer	Interventions of interest are: • NRAS variant testing to guide treatment	Comparators of interest are: • No NRAS variant testing to guide treatment	Relevant outcomes include: • Overall survival • Disease-specific survival • Change in disease status • Medication use • Resource utilization • Treatment-related morbidity
Individuals: • With metastatic colorectal cancer	Interventions of interest are: • BRAF variant testing to guide treatment	Comparators of interest are: • No BRAF variant testing to guide treatment	Relevant outcomes include: • Overall survival • Disease-specific survival • Change in disease status • Medication use • Resource utilization • Treatment-related morbidity

DESCRIPTION

The epidermal growth factor receptor (EGFR) is overexpressed in colorectal cancer (CRC). EGFR-targeted therapy, with monoclonal antibodies cetuximab and panitumumab, have 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.

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 two 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

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 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.

POLICY GUIDELINES

There is support from the evidence 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 protocol 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.

MEDICARE ADVANTAGE

For Medicare Advantage the following gene analysis is considered **medically necessary** in patients with colorectal cancer when needed to determine if a Medicare approved therapy is a reasonable option given the individual's specific clinical presentation.

- KRAS gene analysis, variants in codons 12 and 13 and KRAS (Kirsten rat sarcoma viral oncogene homolog) (e.g., carcinoma) gene analysis; additional variant(s) (e.g., codon 61, codon 146)
- NRAS (neuroblastoma RAS viral [v-ras] oncogene homolog) (e.g., colorectal carcinoma), gene analysis, variants in exon 2 (e.g., codons 12 and 13) and exon 3 (e.g., codon 61)

For Medicare Advantage BRAF gene analysis is considered **medically necessary** in patients with metastatic colorectal cancer when needed to determine if a Medicare approved therapy is a reasonable option given the individual's specific clinical presentation.

BACKGROUND

Cetuximab (Erbix; 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

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 thescreen[®] 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 thescreen 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 (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). 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 LDTs must be licensed under the CLIA for high-complexity testing. To date, FDA has chosen not to require any regulatory review of this test.

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

REFERENCES

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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