Protocol

KRAS, NRAS, BRAF Variant Analysis (Including Liquid Biopsy) in Metastatic Colorectal Cancer

(20453)

Medical Benefit		**Effective Date**: 08/01/20	**Next Review Date**: 05/21
Preauthorization	Yes	**Review Dates**: 05/12, 05/13, 05/14, 05/15, 05/16, 07/16, 05/17, 05/18, 05/19, 09/19, 05/20	

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
Individuals: • With metastatic colorectal cancer	Interventions of interest are: • KRAS, NRAF, and BRAF variant analysis using circulating tumor DNA or circulating tumor cell testing (liquid biopsy)	Comparators of interest are: • Using tissue biopsy to guide treatment	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity • Morbid events • Medication use

DESCRIPTION

The epidermal growth factor receptor (EGFR) is overexpressed in colorectal cancer (CRC). EGFR-targeted therapy

combined 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 to predict nonresponse to anti-EGFR monoclonal antibody therapy. Typically, the evaluation of RAS mutation status requires tissue biopsy. Circulating tumor DNA or circulating tumor cell testing (also known as a liquid biopsy) is proposed as a non-invasive alternative.

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. The relevant outcomes are overall survival (OS), 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 randomized controlled trials 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 randomized controlled trials and retrospective cohort studies. The relevant outcomes are OS, 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 the 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 treatment, the evidence includes two meta-analyses of prospective and retrospective analyses of randomized controlled trials. The relevant outcomes are OS, disease-specific survival, change in disease status, medication use, resource utilization, and treatment-related morbidity. The meta-analyses have shown that anti-EGFR monoclonal antibody therapy did not improve survival in patients with RAS wild-type or 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.

Clinical input obtained in 2017 supports that the following indication provides a clinically meaningful improvement in net health outcome and is consistent with generally accepted medical practice.

- Use of BRAF V600E variant analysis in individuals with metastatic CRC who are found to be wild-type on KRAS and NRAS variant analysis to guide management decisions.

Thus, the above indication may be considered medically necessary considering the suggestive evidence and clinical input support.

For individuals with metastatic CRC who receive circulating tumor DNA or circulating tumor cell testing (liquid biopsy) to guide treatment, the evidence includes observational studies. The relevant outcomes are OS, disease-specific survival, test validity, morbid events, and medication use. Given the breadth of methodologies available to assess circulating tumor DNA and circulating tumor cell, the clinical validity of each commercially available test must be established independently. The clinical validity of the OncoBEAM RAS CRC Assay has been studied in multiple observational studies. When compared to tissue biopsy, sensitivity ranged from 70% (51% to 84%) to

96% (95% confidence interval 87% to 100%) and specificity ranged from 83% (95% confidence interval 71% to 92%) to 94% (82% to 98%). FoundationOne Liquid has been compared to tissue biopsy with the Foundation ACT assay in one observational study; positive percent agreement was 80% overall and 90% when tissue and liquid biopsy were collected less than 270 days apart. Clinical validity studies were limited by unclear reporting of blinding, use of convenience rather than consecutive samples, and variation in the timing of sample collection. There are no published studies reporting clinical outcomes or clinical utility. There are no published studies reporting clinical outcomes or clinical utility. 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.

KRAS, NRAF, and BRAF variant analysis using circulating tumor DNA or circulating tumor cell testing (liquid biopsy) to guide treatment for patients with metastatic colorectal cancer is considered **investigational**.

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

The Human Genome Variation Society 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 review updates starting in 2017 (see Table PG1). The Society's nomenclature is recommended by the Human Variome Project, the HUman Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to 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.

The oncology (gastrointestinal neuroendocrine tumors), real-time PCR expression analysis of 51 genes, utilizing whole peripheral blood, algorithm reported as a nomogram of tumor disease index for its use in treating neuroendocrine tumors is considered **not medically necessary**.

BACKGROUND

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 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 cancers (CRCs) 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 com-

pared 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 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 the 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 variant-positive disease in combination with oxaliplatin-based chemotherapy.[1]

DETECTING CTDNA AND CIRCULATING TUMOR CELLS

Typically, the evaluation of RAS mutation status requires tissue biopsy. Circulating tumor DNA (ctDNA) testing is proposed as a non-invasive alternative.

Detection of ctDNA is challenging because ctDNA is diluted by nonmalignant circulating DNA and usually represents a small fraction (<1%) of total cfDNA. Therefore, more sensitive methods than the standard sequencing approaches (e.g., Sanger sequencing) are needed.

Highly sensitive and specific methods have been developed to detect ctDNA, for both single nucleotide variants (e.g., BEAMing [which combines emulsion polymerase chain reaction with magnetic beads and flow cytometry] and digital polymerase chain reaction) and copy-number variants. Digital genomic technologies allow for enumeration of rare variants in complex mixtures of DNA.

Approaches to detecting ctDNA can be considered targeted, which includes the analysis of known genetic mutations from the primary tumor in a small set of frequently occurring driver mutations, which can impact therapy decisions or untargeted without knowledge of specific variants present in the primary tumor, and include array comparative genomic hybridization, next-generation sequencing, and whole exome and genome sequencing.

CTC assays usually start with an enrichment step that increases the concentration of CTCs, either by biologic properties (expression of protein markers) or physical properties (size, density, electric charge). CTCs can then be detected using immunologic, molecular, or functional assays.

A number of liquid biopsy tests related to targeted treatment of metastatic colorectal cancer have been developed (Table 1).

Table 1. Examples of Liquid Biopsy Tests Related to Targeted Treatment of Metastatic Colorectal Cancer

Manufacturer	Test	Type of Liquid Biopsy
Biocept	Target SElector ctDNA EGFR Kit	ctDNA
CellMax Life	CellMax-CRC Colorectal Cancer Early Detection Test	CTC
Cynvenio	ClearID Solid Tumor Panel	ctDNA and CTC
Foundation Medicine	FoundationOne Liquid (Previously FoundationAct)	ctDNA
Guardant Health	Guardant360®	ctD
IV Diagnostics	Velox™	CTC
Pathway Genomics	CancerIntercept® Detect	ctD
Personal Genome Diagnostics	PlasmaSELECT	ctD
Sysmex Inostics	OncoBEAM	ctD
Circulogene	Theranostics	ctD

CTC: circulating tumor cell; ctDNA: circulating tumor DNA.

REGULATORY STATUS

APPROVED COMPANION DIAGNOSTIC TESTS FOR KRAS VARIANT ANALYSIS TO SELECT CETUXIMAB AND PANITUMUMAB IN METASTATIC COLORECTAL CANCER

Companion diagnostic tests for the selection of cetuximab and panitumumab have been approved by the FDA through the premarket approval process (Table 2):

Table 2. Companion Diagnostic Tests for the Selection of Cetuximab and Panitumumab for Metastatic Colorectal Cancer

Diagnostic Name	PMA/510(k)/HDE	Description	Approval Date	Diagnostic Manufacturer
FoundationOne CDx	P170019	Next Generation Sequencing Oncology Panel, Somatic Or Germline Variant Detection System	11/30/2017	Foundation Medicine, Inc.
Praxis Extended RAS Panel	P160038	Next Generation Sequencing Oncology Panel, Somatic Or Germline Variant Detection System	06/29/2017	Illumina, Inc.
cobas KRAS Mutation Test	P140023	Somatic Gene Mutation Detection System		Roche Molecular Systems, Inc
therascreen KRAS RGQ PCR Kit	P110030 P110027	Somatic Gene Mutation Detection System	5/23/2014	Qiagen Manchester, Ltd.
Dake EGFR pharmDx Kit	P030044/S002	Immunohistochemistry Assay, Antibody, Epidermal Growth Factor Receptor	9/27/2006	Dako North America, Inc.

Source: U.S. Food and Drug Administration (2019)[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, the FDA has chosen not to require any regulatory review of this test.

LIQUID BIOPSY

No liquid biopsy test is currently FDA approved to select treatment for patients with metastatic colorectal cancer.

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

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

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