**Protocol**

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

(20453)

<table>
<thead>
<tr>
<th>Medical Benefit</th>
<th>Effective Date: 07/01/17</th>
<th>Next Review Date: 05/18</th>
</tr>
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<tbody>
<tr>
<td>Preauthorization</td>
<td>Yes</td>
<td>Review Dates: 05/12, 05/13, 05/14, 05/15, 05/16, 07/16, 05/17</td>
</tr>
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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.

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
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<tr>
<td>Individuals: • With metastatic colorectal cancer</td>
<td>Interventions of interest are: • KRAS mutation testing to guide treatment</td>
<td>Comparators of interest are: • No KRAS mutation testing to guide treatment</td>
<td>Relevant outcomes include: • Overall survival • Disease-specific survival • Change in disease status • Medication use • Resource utilization • Treatment-related morbidity</td>
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<tr>
<td>Individuals: • With metastatic colorectal cancer</td>
<td>Interventions of interest are: • NRAS mutation testing to guide treatment</td>
<td>Comparators of interest are: • No NRAS mutation testing to guide treatment</td>
<td>Relevant outcomes include: • Overall survival • Disease-specific survival • Change in disease status • Medication use • Resource utilization • Treatment-related morbidity</td>
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<tr>
<td>Individuals: • With metastatic colorectal cancer</td>
<td>Interventions of interest are: • BRAF mutation testing to guide treatment</td>
<td>Comparators of interest are: • No BRAF mutation testing to guide treatment</td>
<td>Relevant outcomes include: • Overall survival • Disease-specific survival • Change in disease status • Medication use • Resource utilization • Treatment-related morbidity</td>
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**Description**

The epidermal growth factor receptor (EGFR) is overexpressed in colorectal cancer (CRC). EGFR-targeted therapy with monoclonal antibodies cetuximab and panitumumab has shown clear survival benefit in patients with metastatic CRC, however, this benefit depends on lack of mutations in certain genes in the signaling pathway downstream from EGFR. This protocol summarizes the evidence for using tumor cell KRAS, NRAS, and BRAF mutational status as a predictor of nonresponse to anti-EGFR monoclonal antibody therapy.
Summary of Evidence

For individuals who have metastatic CRC who receive KRAS mutation 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. Mutation testing of tumor tissue performed in prospective and 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 CRC who receive NRAS mutation testing to guide treatment, the evidence includes 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. 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 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 qualitatively that the technology results in a meaningful improvement in the net health outcome.

For individuals who have metastatic CRC who receive BRAF mutation testing to guide treatment, 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 showed 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 not been consistently demonstrated in the literature. The evidence is insufficient to determine the effects of the technology on health outcomes.

Policy

KRAS mutation 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 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.

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

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
• 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 (Erbitux®, ImClone Systems) and panitumumab (Vectibix®, Amgen) are monoclonal antibodies that bind to the 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-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. Approximately 40% of CRC have KRAS mutations in codons 12 and 13 in exon 2. 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 less common compared with KRAS, detected in 2% to 7% of colorectal cancer (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 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 mutation-positive disease in combination with oxaliplatin-based chemotherapy.1

Regulatory Status

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 mutation analyses using polymerase chain reaction methodology are available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration 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.


46. Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000), Revision Effective Date for services performed on or after 02/01/2017.